Prescribing Antipsychotics to Pediatric Patients

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Asenapine: approved for pediatric use in 2015

Trends in use of antipsychotics (APs): increasingly prescribed by nonpsychiatrists; primarily prescribed for disruptive behavior disorders (DBD; eg, attention-deficit/hyperactivity disorder, oppositional defiant disorder)

Data on use of APs for DBDs: primarily sponsored by pharmaceutical industry; studies tend to be of insufficient duration or have inadequate controls

Side effects: primary concerns — weight gain; hyperlipidemia; diabetes; sedation (extremely common); agent-specific concerns — cardiovascular complications; agranulocytosis; hepatic dysfunction; prolactin elevation; gynecomastia; reduced seizure threshold; movement disorders; extrapyramidal symptoms (EPS); neuroleptic malignant syndrome; cataracts (associated with quetiapine in animals)

Screening recommendations from American Diabetes Association: family history; body mass index; vital signs; plasma glucose; fasting lipid profile; hemoglobin A1c; recheck variables 12 wk after starting AP, and annually thereafter (if patient seems stable)

Recommmendations from American Academy of Child and Adolescent Psychiatry: use APs only in context of careful diagnostic assessment and thorough discussion of potential risks and benefits; follow latest relevant scientific evidence about dosing and indication; in absence of specific indications approved by Food and Drug Administration (FDA) and empirical support for use of APs with other problems (eg, DBDs), clinicians should consider other pharmacologic or psychosocial treatment modalities with more established efficacy and safety profiles; since almost no data on second-generation APs available for preschool-aged children, exercise extreme caution before prescribing to this population; document personal and family history of diabetes, seizures, and cardiac abnormalities; obtain vital signs and laboratory studies; avoid polypharmacy (multiple medications from multiple categories); use of >1 AP not recommended or supported by literature; monitor metabolic status and movement disorders (using structured measures [eg. Abnormal Involuntary Movement Scale]) at baseline and regular intervals thereafter (even during tapering); electrocardiography may be appropriate with some APs; indefinite use should not be assumed, and continued need should be regularly assessed; recommended as component of first-line therapy for primary indications (eg, adolescent with clear psychotic symptoms)

Other recommendations: start at lowest dose possible; maintain dose at low level for amount of time sufficient for determining effectiveness; add family-based interventions

Study (Rettew et al, 2015): only ≈50% of prescriptions for APs followed best practice recommendations (lack of metabolic monitoring identified as primary issue); only ≈25% of prescriptions written for FDA-approved indications; APs primarily prescribed for aggression and mood instability; ≈40% of clinicians prescribing AP did not initiate prescription; although most clinicians tried other therapies or medications before APs, they often failed to provide evidence-based treatments; in many cases, clinicians unaware of modalities tried previously (highlights importance of medication history, particularly for patients subject to frequent relocation)

Study (Office of Inspector General, 2015): problems with quality of care found in >66% children receiving APs; based on Medicaid claims for children 10 to 12 yr of age, only 25% had glucose screening and 10% had lipid screenings

Speaker’s final recommendations: primary care physicians should avoid prescribing APs without copious input from other professionals; in many cases of aggression and irritability, other types of medications (eg, α-adrenergic agents, stimulants, selective serotonin reuptake inhibitors) can substitute for APs; always assess whether irritable and explosive adults may be responsible for similar behavior among children (in which case entire family should receive help); when “inheriting” prescriptions for APs, find out why AP originally started and consider slow taper or family-based interventions

Suggested Reading

Educational Objectives

The goal of this program is to improve the clinician’s ability to manage psychotic disorders in all types of patient populations. After hearing and assimilating this program, the clinician will be better able to:

1. Ensure adherence to guidelines and recommendations which help prevent serious side effects associated with the use of antipsychotic (AP) medications in pediatric populations.
2. Provide alternative medications or interventions for pediatric patients who have been given an AP to treat a disruptive behavior disorder, or other psychiatric illness.
3. Weigh the risks associated with long-term use of APs against potential harms associated with untreated or relapsing psychosis.
4. Compare the potential treatment benefits and side effects of older APs to newer atypical antipsychotics.
5. Incorporate newer APs and formulations which can improve adherence and efficacy, while potentially reducing side effects.

Faculty Disclosure

In adherence to ACCME Standards for Commercial Support, Audio Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. The following has been disclosed: Dr. Rettew receives royalties from WW Norton and Psychology Today. In their lectures, Drs. Rettew and Hu present information related to the off-label or investigational use of a therapy, product, or device. The planning committee reported nothing to disclose.
Update on Psychopharmacology for Psychotic Disorders

Rona Hu, MD, Clinical Associate Professor of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Palo Alto, CA

Risks vs benefits of APs: typical APs have additive risk for tardive dyskinesia (TD; increasing by 4%/yr); although this risk relates to dose, discontinuing AP may not resolve symptoms; atypical antipsychotics (AAP) cause greater weight gain (varies among agents); early studies found 80% of patients would relapse into psychosis within 5 yr of withdrawing from medication; however, those studies only included patients who were rehospitalized; speaker argues relapses actually occur at much higher rates (cases often masked by cultural tendencies and stigmas [eg., patients may be isolated or restrained at home])

Willingness to diagnose schizophrenia (SZ): some clinicians remain hesitant to make diagnosis because of its ominous prognosis and social stigma; this hesitance may deny patients and families access to appropriate treatment, knowledge about disorder, and social support services

Changes to SZ in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition:eliminated special treatment for bizarre delusions and “special hallucinations” (eg, Capgras and Fregoli delusions); delusions now treated based on their effect on patient; diagnosis of SZ may not be made in absence of psychotic symptoms; deletion of specific subtypes of SZ; disambiguation of schizo-affective diagnosis; catatonia recognized as symptom that occurs in multiple disorders (eg, depression, bipolar disorder [BD])

Neurotoxicity hypothesis: repeated episodes of BD and SZ harm brain (similar to kindling in seizures); contradicted by some papers; speaker argues psychosis causes harm even if it does not cause neurotoxicity, since episodes frighten patients and their families, tend to disable patients at vulnerable point in life, and may cause patients to harm themselves (or, less frequently, others); supporting evidence—over 5-yr period, patients with SZ showed greater loss of brain matter than controls (particularly in important cortical and subcortical areas); linear correlation established between number of hospitalizations and volume of gray matter lost (cause undetermined)

Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE; Lieberman et al, 2005): when compared with perphenazine (typical AP), AAPs showed somewhat different levels of efficacy and marked differences in side effects; all-cause discontinuation rates—olanzapine (64%; most efficacious agent in phase I); perphenazine (75%); ziprasidone (Geodon; 79%; probably underdosed, and not always given with food [important]); side effects—olanzapine strongly associated with weight gain and metabolic effects (≈33% of patients gained >7% of body weight); despite avoiding its use in patients with history of TD, perphenazine showed highest rates of EPS (17%; caused discontinuation in 8% of patients); 9% of patients on olanzapine discontinued because of weight gain

Study (Ascher-Svanum et al, 2006): when assessing all-cause discontinuation, patients remained on olanzapine for median of 20 mg

Update on clozapine: monitoring of total white cell counts no longer required; instead, clinicians should focus on absolute neutrophil count (ANC); in speaker’s experience, patients with extremely low levels of eosinophils may not experience long-term side effects; benign ethnic neutropenia—occurs in some patients of African or Asian ancestry; causes ANC count to decrease below acceptable levels, and although this decrease may linger, it typically remains stable; dose reduction—weekly for 6 mo, then every other week for 6 mo, and eventually monthly; risk for decreased ANC—elevated with certain human leukocyte antigen subtypes; modest increase seen in elderly and female patients; myocarditis—most problematic during first month of treatment (monitor troponin and C-reactive protein levels during this period)

Update on risperidone: now available in quick-dissolving tablets, generic and liquid formulations, and long-acting injection (Risperdal Consta); some pharmacies can provide long-acting injections on site (significantly improves accessibility); side effects—prolactin elevation; increased mortality in elderly; moderate weight gain

Update on olanzapine: long-acting injection formulation (Zyprexa Relprevv) available for several years but remains difficult to use because of potential for postinjection delirium and sedation syndrome (PDSS; appears to occur when mistakenly injected intravenously instead of intramuscularly [IM]); since PDSS may decrease respiratory rates to dangerous levels, injections must be administered in facility with available “crash cart”; however, PDSS rare; side effects—increased weight gain; however, weight gain tends to have rapid onset (without plateausing) in susceptible patients, and does not typically develop in patients whose weight remains stable during initial months of treatment

Update on quetiapine: available in generic formulation, although extended-release (ER) tablet (Seroquel XR) may be better tolerated; increase in mortality among elderly patients may be less than that with other APs; study (Maust et al, 2015)—in patients with dementia, haloperidol (Haldol) had number needed to harm (NNH) of 15, while quetiapine (Seroquel) had NNH of 50; cataract risk—data from CATIE repudiated data suggesting particularly high risks (which had originally been identified in dogs)

Update on ziprasidone: available in generic and fast-acting IM injection formulations; QT interval prolongation—per data from CATIE, changes in QT interval much more significant with quetiapine and older APs

Update on aripiprazole: first agent in class of third-generation dopamine partial agonists; now available as generic, liquid, quick-dissolving orally disintegrating tablet, and ER injectable suspension (Abilify Maintena); side effects—weight gain (modest compared with other AAPs); increased mortality in elderly (comparable to other APs)

Update on paliperidone: active metabolite of risperidone in ER formulation; advantages—metabolized in kidneys (not liver); approved for schizo-affective disorder (in addition to SZ); well-tolerated; paliperidone palmitate (Invega Sustenna)—“game-changer”; injections provided on-site in some pharmacies; new formulation allowing trimonthly dosing (Invega Triniva) now available

Update on iloperidone: approved for acute SZ in adults only; warnings similar to those with other APs (hypotension most frequently reported); long-acting IM formulation under development; requires titration (initial prescription provided in “titration pack”); study (Cutler et al, 2008)—highly effective when compared with ziprasidone and placebo

Update on asenapine: only sublingual AP; placed between cheek and gum (unlike other orally dissolving tablets); swallowing pill prevents uptake of full dose; speaker recommends having patients consume strong-tasting substance (eg, mint) before use to avoid temptation to wash away unpleasant taste soon after dosing; side effects—some weight gain (relative to other newest APs); akathisia (common); reasonably well-tolerated; efficacy—confirmed in comparative trials vs haloperidol and risperidone
Lurasidone: approved for acute treatment of SZ and BD, and maintenance treatment of SZ; pregnancy category B (only AP given this designation, aside from clozapine); may benefit cognition; taken with food (350 kcal sufficient); fared well in comparative trials vs olanzapine

Brexpiprazole (Rexulti): partial dopamine agonist; effective in SZ and as adjunct for depression; warnings similar to those with other APs; associated with akathisia (although less than with similar agents); subject to issues of availability and insurance coverage (because of its relative newness); patient assistance program available

Cariprazine (Vraylor): partial agonist of dopamine D2 and D3 receptors (first in class to affect D3); approved for SZ and BD; associated with akathisia

New formulations: several fast-acting IM injections for inpatients; quick-dissolving orally disintegrating tablets (eg, Zyprexa Zydus, Risperdal M-Tab, Fazaclo); liquids for difficulty swallowing and “cheeking” precautions; ER oral pills; long-acting injections; inhaled loxapine — AP with pharmacodynamic profile closer to AAPs (eg, some affinity for serotonin receptors); effective for SZ and acute agitation in bipolar mania; must be given in enrolled health-care facility; negates issues with needles; onset extremely fast (2 min); indicator light on inhaler confirms patient has properly inhaled dose; may cause bronchospasms

New recommendations: published data support use of long-acting IM injections as first-line agents (even for first-episode psychosis); however, cost varies substantially between older and newer injectables

Neuroleptic malignant syndrome: 24-hr hotline available to provide assistance (call 888-NMS-TEMP)

FDA black box warning on APs: increased risk for death in patients with dementia-related psychosis; no agents have been approved for dementia-related psychosis; studies have shown APs pose higher risks (vs AAPs)

Metabolic issues with APs: mechanism — thought to involve antihistamine effects and effects on serotonin 2c receptors and leptin; clozapine and olanzapine have strongest affinity for 2c receptor (among APs); mice with “knocked out” 2c receptors show increased appetites and gain more weight, even with yoked feeding (because of decreased movement); obesity — affects compliance; switching agents moderately effective

Study (Constantine et al, 2015): some patients benefitted from remaining on 2 different APs; Joint Commission standards still require justification for ≥2 APs

Acute inpatient psychiatry update: Meredith rule requires additional hearing for patients to be given medication after refusal (even if Riese hearing has been held); under Health Insurance Portability and Accountability Act rules, physicians may talk to families of patients who refuse treatment, so long as this may be considered in patient’s best interest (tenet may not hold true in California)

Adherence vs efficacy: risk-benefit ratios demonstrate AP efficacy cannot be sacrificed to reduce side effects

Suggested Reading


Acknowledgments

Dr. Rettew spoke at the Ninth Annual Child Psychiatry in Primary Care conference, held May 15, 2015, in Colchester, VT, and sponsored by the University of Vermont College of Medicine. For information on the 10th Annual Child Psychiatry in Primary Care Conference, please visit uvm.edu/medicine/cme. Dr. Hu spoke at the Emerging and Innovative Trends in Psychiatry and Behavioral Health: Adult and Adolescent Topics, held October 3-4, 2015, in Stanford, CA, and sponsored by the Stanford University School of Medicine. To learn about upcoming conferences sponsored by Stanford University School of Medicine, please visit med.stanford.edu. The Audio Digest Foundation thanks the speakers and the sponsors for their cooperation in the production of this program.

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ANTIPSYCHOTIC REVIEW

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1. Which of these medications was approved by the Food and Drug Administration for pediatric use in 2015?
   (A) Asenapine  (B) Iloperidone  (C) Paliperidone  (D) Lurasidone

2. The majority of new prescriptions for antipsychotic (AP) medications given to pediatric patients are intended to treat which of the following conditions?
   (A) Bipolar disorder  (B) Autism spectrum disorders  (C) Schizophrenia  (D) Disruptive behavior disorders

3. Which of the following statements about the use of APs in pediatric patients is most accurate?
   (A) Most patients who have been taking APs will need them indefinitely
   (B) Initiation of treatment with APs should be at the lowest dose possible
   (C) Monitoring for movement disorders can be discontinued if APs are being tapered
   (D) APs are not considered first-line therapy for any condition in children or adolescents

4. In a 2015 study of pediatric patients receiving APs, which of the following practice recommendations was followed LEAST frequently and identified as a primary concern?
   (A) Monitoring for movement disorders
   (B) Obtaining electrocardiography
   (C) Metabolic monitoring
   (D) Obtaining complete medical and family history

5. Following changes in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, schizophrenia may no longer be diagnosed in the absence of which of the following?
   (A) Psychotic symptoms  (B) Negative symptoms  (C) Social-occupational dysfunction  (D) All the above

6. Patients are substantially more likely to discontinue medications for reasons related to efficacy than for reasons related to side effects.
   (A) True  (B) False

7. In the later phases of the Clinical Antipsychotic Trials of Intervention Effectiveness, which of the following medications showed substantial superiority over every other typical and atypical AP available at that time?
   (A) Olanzapine  (B) Risperidone  (C) Perphenazine  (D) Clozapine

8. In patients taking clozapine, monitoring of which of the following parameters is most crucial?
   (A) Total white cell count  (B) Absolute neutrophil count  (C) Prolactin levels  (D) QT interval

9. Although AP medications are generally contraindicated in elderly patients, which of the following agents has been associated with less significant increases in mortality rates, compared with the others?
   (A) Clozapine  (B) Risperidone  (C) Olanzapine  (D) Quetiapine

10. Which of the following medications is classified as pregnancy category B by the Food and Drug Administration?
   (A) Ziprasidone  (B) Aripiprazole  (C) Lurasidone  (D) Asenapine

Answers to Audio Digest Psychiatry Volume 44, Issue 23: 1-B, 2-A, 3-D, 4-C, 5-A, 6-C, 7-B, 8-B, 9-A, 10-D

Attention, CME/CE Participants

The cutoff date for logging 2015 credits is December 31, 2015. Test forms received after that date will be accrued to 2016.