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Evidence-Based Best Practices for the Use of Second Generation Antipsychotics (SGAs) in Pediatric Primary Care in South Carolina

Complete a mental health evaluation, including assessment for substance abuse, prior to initiating an antipsychotic or any other psychotropic medication

- Psychosocial therapy is first-line for most childhood mental health conditions
- Consider safer alternatives before prescribing an antipsychotic for clearly identified mental health condition(s) or target symptom(s)
- Before considering an antipsychotic for target symptoms, treat the primary condition first (e.g., ADHD, anxiety), as it may resolve the targeted symptoms (e.g., aggression)
- Consult a psychiatric specialist prior to initiating long-term use of antipsychotics as long-term effectiveness and safety are not established in children and adolescents

Assess the effectiveness of and continued need for antipsychotics on a regular basis

- Identify child-specific treatment goals to monitor effectiveness, using validated tools when available
- Remember that aggression is just a symptom, not a diagnosis – continue to monitor for underlying condition
- If the child does not respond to an antipsychotic as expected, review adequacy of: medication trial (i.e., dose, duration, adherence); original patient assessment including substance abuse; and treatment plan
- Do not combine antipsychotics if response is insufficient – taper and switch to a different one
- Treatment duration varies based on the severity of symptoms, natural course of the condition being treated, and psychosocial settings

Routinely monitor for weight gain, metabolic changes and other antipsychotic medication side effects

- Pediatric patients are even more sensitive than adults to adverse metabolic effects (e.g., weight gain, increased lipids); one-third can become overweight after only 3 months of treatment
- Track weight and body mass index (BMI) changes on growth chart at every visit for the first 3 - 6 months after initiation of an antipsychotic
- Extrapyramidal side effects, EPS, (e.g., akathisia, dystonic reactions) occur frequently in children and adolescents
- Use standardized rating scales (e.g., Abnormal Involuntary Movement Scale [AIMS] for tardive dyskinesia) at baseline and routinely during treatment to identify movement disorders

Engage with family, child and other key people (e.g., other healthcare professionals, teachers, caregivers) involved with child

University of South Carolina | Medical University of South Carolina
843-792-5915 | www.sccp.sc.edu/SCORxE | SCORxE@sccp.sc.edu

Routine Monitoring Parameters For Second Generation Antipsychotics

Monitoring Parameters (i) Assess more frequently if: risk factors for specific adverse events are identified by personal/family history; on a medication requiring more frequent monitoring; or other abnormalities present.	**Frequency**						
	Baseline	**Every Visit for Initial 3 – 6 Months**	**At 3 Months**	**Quarterly**	**Every 6 – 12 Months**	**Annually**	**If Abnormal Lab or Symptomatic**
Personal/Family History	√					√	
Lifestyle Behaviors e.g., diet, exercise, sleep hygiene, tobacco/substance use	√	√		√			
Height, Weight, BMI adjusted for age & sex (ii)	√	√ (iii)		√			
Blood Pressure and Pulse	√		√			√	
Fasting Lipid Profile & Plasma Glucose	√		√		√		
Prolactin e.g., breast enlargement/pain, galactorrhea, pubertal development delay, amenorrhea, oligomenorrhea (i[d])							√
Extrapyramidal Symptoms (EPS) (iv) (v) **Akathisia** e.g., inner restlessness, inability to sit still **Dystonia** i.e., sustained, involuntary muscle contractions **Pseudoparkinsonism** e.g., akinesia (difficulty initiating movement), tremor, cogwheel rigidity, postural abnormalities **Tardive dyskinesia** i.e., abnormal involuntary movements, sometimes irreversible. Often late onset, beginning with orofacial movements	√		√			√	
WBC & ANC (clozapine only) WBC ≥ 3500/mm^3; ANC ≥ 2000/mm^3	Weekly x 6 months, then q 2 weeks x 6 months, then q 4 weeks ad infinitum						√

Key: ANC = absolute neutrophil count **BMI** = body mass index **WBC** = white blood cell count

(i) Additional monitoring considerations lacking clinical consensus:
- (a) for olanzapine: LFTs at baseline, at 3 – 6 months and at 1 year;
- (b) for all antipsychotics, particularly clozapine, iloperidone and ziprasidone: EKG at baseline and as clinically indicated in patients with a family history of cardiac abnormalities or sudden death, or a personal history of syncope, palpitations, or cardiovascular abnormalities; serum K & serum Mg in patients at risk for electrolyte disturbances;
- (c) for quetiapine: TSH levels at baseline, at 3 months and at 1 year, plus every 3 months if TSH is elevated;
- (d) for olanzapine and risperidone: prolactin at baseline, at 3 months, 6 months and at 1 year.

(ii) Free growth charts available at: www.cdc.gov/growthcharts. Though more difficult to interpret in growing youth, may consider monitoring waist circumference using age & sex-adjusted percentile tables available at: www.idf.org/webdata/docs/Mets_definition_children.pdf.

(iii) May consider weekly monitoring during initial phase of treatment to identify patients who gain weight rapidly.

(iv) Validated rating scales can be used, such as: the Extrapyramidal Symptom Rating Scale (ESRS) or Simpson Angus Rating Scale (SAS) for movement side effects; and the Abnormal Involuntary Movement Scale (AIMS), www.cqaimh.org/pdf/tool_aims.pdf, for tardive dyskinesia.

(v) Also monitor during titration for akathisia, dystonia, and pseudoparkinsonism.

References: 8, 14, 18, 19, 21, 31, 45-48, 53

Select Side Effects of Second Generation Antipsychotics (i)

Side Effect	Onset	Dose Dependency	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone	Side Effect Management/ Considerations/ Comments (ii)
Akathisia	Early/Mid	+++	++	+	+	+	+	+	+	+	+ (iii)	+	↓ dose; switch AP; add beta-blocker or benzodiazepine
Anticholinergic (e.g., dry mouth, dry eyes, constipation)	Early	++	0	0	+++ (iv)	+	0	++	0	0/+	0	0	Use sugar-free gum/candy, oral lubricants, maintain oral hygiene; use artificial tears; ↑ fluid & bulk intake; ↓ dose, switch AP
Dyslipidemia	Early/Mid	0?	0/+	0	+++	++	0	+++	+	+/++	+	0/+	Diet/exercise program; switch AP; consider adding lipid lowering agent
Dystonia	Early	+++	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+ (iii)	0/+	Add antihistamine or anticholinergic; ↓ dose; switch AP
Glucose Dysregulation	Late	0?	0/+	+	+++	+	+	+++	+	++	+	0/+	Diet/exercise program; switch AP; add metformin
Neutropenia/ Agranulocytosis	First 6 mo	+?	0/+	0/+	++	0/+	0/+	0/+	0/+	0/+	0/+	0/+	Repeat labs; hold or discontinue AP; switch AP after resolution
Orthostatic Hypotension	Early/ Titration	+++	0/+	+	+++	+++	+	++	+	++	+	0	Provide patient education; slow down titration; ↑ hydration; ↓ dose; switch AP
Prolactin Increase MD (ng/mL)	Early	+++	0 -4.1	+	0	+	+	+/++ 11.5	+++	0 NSD	+++ 22.6	+	Wait if asymptomatic. If persistent & symptomatic: reduce dose; switch AP; refer to specialist
Pseudoparkinsonism	Early	+++	+	+	0	+	+	+	++	0	++ (iii)	+	↓ dose; switch AP; add anticholinergic
QTc Prolongation	Early/ Titration	+?	0/+	+	+	++	0	0/+	+	+	+	++	If 450 – 500 Msecs: ↓ dose; consult cardiology; switch AP. If > 500 Msecs: discontinue AP; consult cardiology; switch AP
Sedation/Somnolence NNH	Early	+++	0/+ 10	++	+++	+	++	++ NSD	+	++ 4	+ 4	0/+ 7	Give HS; ↓ dose; discontinue other sedating medications; switch AP
Seizures	Titration	+++	0/+	0/+	++ (v)	0/+	0/+	0/+	0/+	0/+	0/+	0/+	Get EEG; consult neurology; ↓ dose; switch AP; add anticonvulsant
Tardive Dyskinesia	Late	++	0/+	0/+	0	0/+	0/+	0/+	0/+	0/+	0/+	0/+	Consult neurology; replace with non-AP if possible; ↑ dose (to mask)
Weight Gain MD (kg) NNH (vi) **AP naïve patients** (kg) NNH (vii)	First 3 – 6 mo	0?	+ 0.77 12 4.4 5	+	+++	++	+	+++ 4.6 3 8.5 2	+/++	++ 1.78 9 6.1 3	++ 1.79 6 5.3 2	+ NSD	Diet/exercise program; switch AP; consider adding metformin

Scale: **?** = inconclusive; **0** = none; **0/+** = minimal; **+** = mild; **++** = moderate; **+++** = severe (Most data extrapolated from adult populations. Data for asenapine, iloperidone & lurasidone from different sources of only adult data and may not be directly comparable.)

Key: AP = antipsychotic **HS** = at bedtime **MD** = mean difference (95% CI) between treatment and control groups **mo** = months **NNH** = number needed to harm **NSD** = not statistically different **NR** = not reported **RR** = relative risk (data are from pediatric populations)

(i) Rule out neuroleptic malignant syndrome (NMS) in patients presenting with fever, tachycardia, rigidity, and mental status change as several cases have been reported in pediatrics. **(ii)** Most management strategies based on clinical consensus as controlled data are limited. **(iii)** Increased risk with doses > 10 mg daily. **(iv)** Excess drooling reported. **(v)** Increased risk with doses > 300mg. **(vi)** > 7% weight gain. **(vii)** BMI z-score ↑ > 0.5.

References: 1, 15-19, 21, 34, 35, 45, 51

Over Five Years of Age
- ✓ General psychosocial screen (e.g., PSC, SDQ) at health maintenance visits
- ✓ Suicidality - screen at-risk patients when age appropriate (i)
- ✓ Substance use/abuse screen in adolescents (e.g., CRAFFT) at health maintenance visits

Tobacco Use Screen
to promote
good health
in adolescents

When a risk for a mental health concern is identified above, target further diagnosti
personal history (including patient, parents and school/work input when

Target Symptoms/ Conditions *Relative Prevalence*	Select Rating Tools Web Link	When to Consider an SGA (ii)
Bipolar *Rare*	Mood Disorder Questionnaire (MDQ) – ages 12+ years (free) www.cqaimh.org/pdf/tool_mdq.pdf Parent version of the Young Mania Rating Scale (P-YMRS) (free) www.thereachinstitute.org/rating-scales.html	One of the primary treatments
Schizophrenia *Children: Very Rare Adolescents: Rare*	——	Primary treatment
Aggression/Irritability *Common*	Modified Overt Aggression Scale (MOAS) – developed for adults but used in adolescents (free) www.thereachinstitute.org/rating-scales.html	If very severe aggression or if insufficient response to psychotherapy or for treatment of underlying condition
Autism *Rare*	Modified Checklist for Autism in Toddlers (M-CHAT) and M-CHAT Follow-Up Interview – ages 16-30 months (free) http://www2.gsu.edu/~psydlr/Diana_L._Robins,_Ph.D..html Aberrant Behavior Checklist (ABC) – ages 6+ ($) www.stoeltingco.com/stoelting/2257/1467/1497/Psychological/Aberrant-Behavior-Checklist-ABC Autism Treatment Evaluation Checklist (ATEC) - ages 5-12 years old (free) www.autismeval.com/ari-atec/atec_form.pdf	For challenging and repetitive behaviors (iii)
Tics *Transient Tics: Common Chronic Tics: Infrequent TS: Rare*	Yale Global Tics Severity Scale (YGTSS) – ages 5+ years (free) www.excellenceforchildandyouth.ca/support-tools/measures-database	Usually reserved for tics causing severe impairment or if insufficient response to other treatments (iv)
Eating disorders *Adolescent Girls: Rare to Infrequent Adolescent Boys: Rare*	Eating Disorder Examination Questionnaire (EDE-Q) – adolescents www.rcpsych.ac.uk/pdf/EDE-Q.pdf	Role not established (v)
ADHD *Frequent*	Vanderbilt – ages 6-12 years (free) www.nichq.org/adhd_tools.html	NO ROLE
Anxiety *Common*	Self-Report for Childhood Anxiety Related Emotional Disorders (SCARED) – ages 8+ years (free) http://psychiatry.pitt.edu/research/tools-research/assessment-instruments	NO ROLE
Depression *Children:Infrequent Adolescents: Frequent*	Children's Depression Inventory (CDI) – ages 7-17 years ($) www.mhs.com PHQ-9 – developed for adults but preliminary validity in ages 13-17 (free) www.phqscreeners.com PHQ-9 Modified for adolescents – not validated (free) www.thereachinstitute.org/rating-scales.html	NO ROLE (vii)
Sleep Difficulties *Common*	Epworth Sleepiness Scale – Revised for Children (free) www.peds.ufl.edu/divisions/pulmonary/ess_children.pdf	NO ROLE

References: 1-7, 9-13, 20, 22, 24-29, 32-34, 38-43, 49-52, 54, 55-60

Health Screening: When and How

Five Years of Age or Less
- ✓ General psychosocial screen (e.g., CBCL, BASC-2) when:
  - Abnormal developmental screen (e.g., ASQ)
  - Abnormal autism screening test (e.g., M-Chat)

All Ages
- ✓ General psychosocial screen (age specific) when:
  - Suspected signs/symptoms present during a visit
  - Life/personal situations detected that place patient at risk

ic work-up to signs/symptoms identified using validated rating tools when available, possible) and clinical examination; or refer to specialist as appropriate.

Overview of Management
• SGA or mood stabilizer monotherapy • If insufficient, combine mood stabilizer and SGA but not 2 SGAs
• Monotherapy with SGA • If insufficient, switch to alternate SGA but do not combine 2 SGAs
• Psychotherapy (e.g., behavioral parent training for younger children; CBT for older children) • Initial medication treatment should target primary or comorbid conditions (e.g., ADHD, anxiety) that may cause or exacerbate aggression
• Early and intensive behavioral and developmental interventions • Initial medication treatment should target coexisting conditions that cause significant impairment or if challenging behaviors (e.g., self-injury, severe aggression, irritability or mood swings)
• Psychoeducation and watch & wait; offer treatment if tics cause impairment • Initial treatment should target coexisting conditions if present • If insufficient, consider behavioral therapy (habit reversal therapy) or medication treatment (alpha2-agonists or SGAs) that targets tics
• Medical stabilization **AND** Nutritional rehabilitation **AND** Psychotherapy (family-based therapy for anorexia nervosa; CBT for bulimia nervosa) • If needed, day-treatment or hospital-based program • Consider SSRIs for bulimia nervosa
• Psychoeducation **AND** Psychotherapy (behavioral parent training for parents of younger children; CBT and social skills therapy for older children) **AND/OR** Stimulants or atomoxetine
• Psychoeducation **AND** Psychotherapy (CBT, may include parent component if parent also anxious) • If insufficient or if moderate-severe anxiety, consider SSRI (vi)
• Psychoeducation and supportive therapy including family and school support x 4 - 6 weeks • If insufficient, add psychotherapy (CBT or IPT) **AND/OR** SSRI if moderate-severe major depressive disorder
• Sleep hygiene **AND** Treatment of underlying health conditions • If insufficient, consider short-term use of sleep medications

Key:
ADHD = attention-deficit/hyperactivity disorder
ASQ = Ages and Stages
BASC-2 = Behavior Assessment System for Children, 2nd Edition
CBCL = Child Behavior Checklist
CBT = cognitive behavioral therapy
CRAFFT = Car, Relax, Alone, Forget, Friends, Trouble
IPT = interpersonal therapy
ODD = oppositional defiant disorder
PSC = Pediatric Symptom Checklist
SDQ = Strengths and Difficulties Questionnaire
SGA = second generation antipsychotic
SSRI = selective serotonin reuptake inhibitor
TS = Tourette's syndrome

(i) If suicide screen is positive, assess risk (intent, motivation, method - including lethality and access); risk factors (e.g., history of self-harm, mental health conditions, victimization, family history of suicide/attempts) and protective factors. Provide crisis stabilization if active thoughts. Treat any underlying psychiatric condition(s).
(ii) Refer to mental health specialist before initiating maintenance therapy with an SGA.
(iii) Best evidence supports risperidone and aripiprazole.
(iv) Best evidence supports risperidone.
(v) Controversial benefits with olanzapine in anorexia nervosa.
(vi) Except for posttraumatic stress disorder (PTSD).
(vii) Consider adding an SGA to antidepressant only if psychotic symptoms, although vague or mild psychotic symptoms may respond to antidepressant alone.

Relative Prevalence:
Very rare: ≤ 0.5%
Rare: 0.6 - 1%
Infrequent: 2 - 5%
Frequent: 6 - 10%
Common: ≥ 11%

Second Generation Antipsychotic (SGA) Oral Medication Dosing Guidelines (i)

Initiate SGA at a low dose and titrate slowly to lowest effective dose. (ii) When possible taper SGA to discontinue, even if switching. (iii)

Medication (Brand Name)	Initial Dose (iv)	Recommended Administration	Maximum Daily Dose	Pediatric Strength of Evidence for Use	FDA-Approved Indications (age in years): Maximum Daily Dose
Aripiprazole (Abilify®)	Children: 2 mg Adolescents: 2 mg	Once daily	Children: 15 mg Adolescents: 30 mg	Bipolar ●●○ PDDs ●○○ Schizophrenia ●●○	Bipolar mania/mixed (10-17): 30 mg Schizophrenia (13-17): 30 mg Irritability with autism (6-17): 15 mg
Asenapine (Saphris®)	Insufficient evidence	N/A	Insufficient evidence	Insufficient evidence	No pediatric approval
Clozapine (Clozaril®) (v)	Children: 6.25 – 12.5 mg Adolescents: 6.25 – 25 mg	HS or BID	Children: 150 – 300 mg Adolescents: 600 mg	——	No pediatric approval
Iloperidone (Fanapt®)	Insufficient evidence	N/A	Insufficient evidence	Insufficient evidence	No pediatric approval
Lurasidone (Latuda®)	Insufficient evidence	N/A	Insufficient evidence	Insufficient evidence	No pediatric approval
Olanzapine (Zyprexa®)	Children: 2.5 mg Adolescents: 2.5 – 5 mg	Once daily	Children: 12.5 mg Adolescents: 20 mg	Bipolar ●●○ Schizophrenia ●●○	Bipolar mania/mixed (13-17): 20 mg Schizophrenia (13-17): 20 mg
Paliperidone (Invega®)	Children: Insufficient evidence Adolescents: 3 mg	Once daily	Children: Insufficient evidence Adolescents: < 51 kg: 6 mg ≥ 51 kg: 12 mg	Schizophrenia ●●○	Schizophrenia (12-17): < 51 kg: 6 mg ≥ 51 kg: 12 mg
Quetiapine (Seroquel®) (vi)	Children: 12.5 – 25 mg Adolescents: 25 – 50 mg	BID or HS	Children: 400 mg Adolescents: 800 mg	Bipolar ●●○ Schizophrenia ●●○	Bipolar mania (10-17): 600 mg Schizophrenia (13-17): 800 mg
Risperidone (Risperdal®)	Children: 0.25 mg Adolescents: 0.5 mg	Once daily or BID	Children: 3 mg Adolescents: 6 mg	Bipolar ●●○ DBDs ●●○ PDDs ●○○ Schizophrenia ●●○ Tics ●●○	Bipolar mania/mixed (10-17): 6 mg Schizophrenia (13-17): 6 mg Irritability with autism (5-16): 3 mg
Ziprasidone (Geodon®)	Children: 5-10 mg Adolescents: 20 mg	BID, with food (vii)	Children: 80 mg Adolescents: 160 mg	Bipolar ●●○ Tics ●●○	No pediatric approval

Agency for Healthcare Research and Quality (AHRQ) Strength of Evidence Scale: ●●● High ●●○ Moderate ●○○ Low

Key: DBDs = disruptive behavior disorders (including oppositional defiant disorder and conduct disorder) **N/A** = not applicable
PDDs = pervasive development disorders (including autism) **RCT** = randomized controlled trial

(i) All are pregnancy FDA Category C except clozapine and lurasidone (Category B); insufficient data available for breastfeeding recommendations. **(ii)** Usual effective doses for some conditions (e.g., irritability with autism, tics) are lower than for bipolar disorder or schizophrenia. **(iii)** Tapering helps minimize withdrawal symptoms. **(iv)** Age-specific dosing is available for some medications. **(v)** Only available through a registry program that requires frequent white blood cell count and absolute neutrophil count monitoring. **(vi)** There is no pediatric FDA approval for Seroquel XR®. **(vii)** Presence of food can increase absorption two-fold.

 References: 22, 23, 25, 28-30, 33, 34, 36, 37, 44, 47-49, 51, 57, 61

Resource Table

Resources Web Link	Provider			Patient & Family			
	Provider Resources	Assessment & Evaluation Tools	Educational Resources Provider Can Offer (i)	Parent/Family/Teen Resources	Online Support	Local Support, Chapters, or Networking	Spanish
Adolescent Health Working Group (AHWG) www.ahwg.net	X		X				X
Bright Futures – at – Georgetown University www.brightfutures.org/mentalhealth/pdf/tools.html	X	X	X				X
Massachusetts General Hospital, School Psychiatry Program & MADI Resource Center – Table of all screening tools & rating scales www2.massgeneral.org/schoolpsychiatry/screeningtools_table.asp	X	X					
Partnership Access Line (Washington) www.palforkids.org/resources/	X	X	X				
The Ontario Centre of Excellence for Child and Youth Mental Health – Measures database www.excellenceforchildandyouth.ca/support-tools/measures-database	X	X					
Treating Maladaptive Aggression (T-MAY) Toolkit www.thereachinstitute.org/tmay.html	X	X					
American Academy of Child and Adolescent Psychiatry www.aacap.org	X	X	X	X	X		X
Autism Speaks www.autismspeaks.org	X	X	X	X	X	X	X
National Alliance on Mental Health (NAMI) www.nami.org	X		X	X	X	X	X
National Initiative for Children's Healthcare Quality www.nichq.org	X	X		X	X		
National Institute of Mental Health www.nimh.nih.gov/index.shtml	X			X	X (ii)		X
Family Connection South Carolina (1-800-578-8750) www.familyconnectionsc.org				X	X	X	X
Federation of Families of South Carolina (1-800-779-0402) www.fedfamsc.org				X		X	X
LUCAS Network www.luluhowle.com				X	X	X	
National Suicide Prevention Lifeline (1-800-273-TALK) www.suicidepreventionlifeline.org				X		X	X
NC State University and A&T State University Cooperative Extension www.ces.ncsu.edu/depts/fcs/pdfs/fcs_504.pdf				X (iii)			
SC Autism Society www.scautism.org				X	X	X	
University of Michigan Health System www.med.umich.edu/yourchild/topics/behave.htm#change				X			X

(i) Websites, books, educational tools. (ii) Only offers to make referrals to local providers. (iii) Handout on aggression.

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