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Long-term use of antidepressants, mood stabilizers, and antipsychotics in pediatric patients with a focus on appropriate deprescribing

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Abstract

It is estimated that 8% to 12% of youth are prescribed psychotropic medications. Those in foster care, juvenile justice systems, residential treatment facilities, and with developmental or intellectual disabilities are more likely to be prescribed high-risk regimens. The use of psychotropic medications in this age group is often off-label and can be associated with significant risk, warranting critical evaluation of their role. Landmark trials, pediatric-specific guidelines, and state-driven initiatives play critical roles in supporting evidence-based use of psychotropic medications in children. Overall, there is a lack of literature describing the long-term use of psychotropic medications in youth—particularly with regard to neurobiological, physical, and social changes that occur throughout development. Deprescribing is an important practice in child and adolescent psychiatry, given concerns for over-prescribing, inappropriate polytherapy, and the importance of reevaluating the role of psychotropic medications as children develop.

Keywords: children, adolescents, deprescribing, child and adolescent psychiatry

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Introduction

Mental health conditions among children are common, with an incidence of 13% to 20% in the United States.[1] Identification and treatment of mental health conditions is critical in this population, given the impact on development, academic performance, family and peer relationships, physical health, and risk for suicide. It is estimated that 8% to 12% of children are prescribed psychotropic medications, with stimulants, nonstimulants (eg, guanfacine, clonidine, atomoxetine), antidepressants, and antipsychotics among those most frequently prescribed.[2,3] Children and adolescents in foster care, juvenile justice systems, residential treatment facilities, and with developmental or intellectual disabilities are the most likely to be prescribed high-risk psychotropic medication regimens (eg, >1 agent from the same pharmacologic class).[4-6]

Landmark trials, pediatric-specific guidelines, and state-driven initiatives play critical roles in supporting evidence-

Take Home Points:

1. Antidepressants may be associated with reductions in growth and bone mineral density after long-term use. Weight gain and risk for type 2 diabetes mellitus have been proposed. Ongoing evaluations are needed to understand clinical interventions and implications into adulthood.
2. Children are at increased risk for cardiometabolic side effects associated with second generation antipsychotics compared to adults, including the development of type 2 diabetes. Other proposed long-term risks include reduced bone mineral density and hyperprolactinemia.
3. Divalproex use in young females should be potentially avoided, given risks for polycystic ovarian syndrome, weight gain, reductions in bone mineral density, and teratogenicity. Maintenance treatment studies suggest that lithium is safe, with close monitoring of thyroid function, renal function, and serum concentrations.

based use of psychotropic medications in children and adolescents. Collaborative decision making with patients and their caregivers involves careful review of short-term and long-term benefits, risks, treatment goals, target symptoms, and expected duration of treatment.[7] Reevaluating the role of psychotropic medications with consideration for deprescribing is essential, given dynamic changes throughout development and risk for pediatric-specific adverse effects.[4,5,8-11] Notable neurobiological changes during childhood include maturation of the prefrontal cortex, synaptic pruning, increased level of myelination, remodeling of grey or white matter, and default mode network dysregulation. These changes not only help explain higher rates of impulsivity and sensation-seeking behavior but also contribute to complexities of treatment.[12,13] Clinical experience indicates that physical development, adapting skillsets, and changing social supports should be considered when evaluating the ongoing need for a psychotropic medication.

Deprescribing, defined as the process of tapering and discontinuing medications, is an important practice in child and adolescent psychiatry.[4,9] While most deprescribing literature focuses on elderly and adult populations, attention is growing in pediatric populations given concerns for overprescribing psychotropic medications, inappropriate polypharmacy, and the importance of reevaluating the need of psychotropic medications throughout childhood development.[4,5,8] In this article, 3 pediatric cases explore the long-term use of antidepressants, antipsychotics, and mood stabilizers, strategies to optimize pharmacologic treatment planning, and deprescribing considerations.

Antidepressants

A 15-year-old presents to an outpatient psychiatry appointment with caregivers who are curious about ongoing need for pharmacologic treatment. Past psychiatric history includes GAD, MDD, and ADHD. The patient has never been hospitalized. ADHD was diagnosed at age 8 years by the pediatrician (later confirmed by the child and adolescent psychiatrist) and GAD and MDD were diagnosed at age 11 years by the child and adolescent psychiatrist. At today's visit, the patient reports some worries related to entering sophomore year of high school, obtaining a driver permit, and making the varsity soccer team. Otherwise, the patient denies anxiety or depressive symptoms. The following rating scales were completed at today's visit: patient health questionnaire (PHQ-9) modified for teens (total score 0) and screen for child anxiety-related emotional disorders (SCARED; total score 3). On average, scores remained unchanged the past 1.5 years. Family history is significant for anxiety. Current medications include venlafaxine extended release 225 mg by mouth daily (unchanged for 3 years), methylphenidate extended release 72 mg by mouth daily (unchanged for 2 years), and a multivitamin by mouth daily. Previous antidepressant history includes fluoxetine and sertraline, which were ineffective after 8-week trials at adequate doses. Vital signs and laboratory results are normal: height: 5 feet, 5 inches; weight: 75 kg; and BMI: 27.5 kg/m^2 (94% for age).

Total duration of antidepressant treatment, particularly when initiated in childhood, has not been formally evaluated or defined. Landmark extension trials, including the child/adolescent anxiety multimodal extended long-term study[13-15] and treatment of SSRI-resistant depression in adolescents extension[16] provide naturalistic follow-up of antidepressant treatment in youth (Table 1). Despite the availability of these studies, critical evaluation of the impact of long-term use of antidepressants on the developing brain is lacking.[12,17,18] A general framework for typical duration of antidepressant treatment in this age group is provided by treatment guidelines with a recommendation of 6 to 12 months of treatment following symptom remission before considering a gradual taper of the medication.[17,19-21] Some children and adolescents may require longer duration of treatment, depending on recurrence of episodes, chronicity of symptoms, and reemergence of symptoms with medication taper, but this overall is not well-defined.[20-22] When a medication taper is considered, it should occur over weeks or months.

TABLE 1: Antidepressant, antipsychotic, and mood stabilizer landmark extension trials

Reference	Study Characteristics	Intervention	Results and Conclusions
CAMELS[13]	N = 288 Age 11-26 y (mean 17 y) Social, separation, GAD Mean 6-y follow-up	Randomized (2:2:2:1): 1) CBT, 2) Sertraline, 3) Combination, or 4) Placebo	Results: • 46.5% were in remission at follow-up. • Initial treatment responders more likely to be in remission (OR 1.83; CI 1.08, 3.09, $P = .03$), have lower anxiety severity scores ($R^2 = 0.02$; $P = .02$), and higher global functioning scores ($R^2 = 0.01$; $P = .02$). • Remission rates higher in CAMS responders (46.5%-52%) compared to nonresponders (38%). Conclusions: • Treatment type was not associated with remission status. • Initial response to treatment was a strong predictor of long-term outcomes (combination treatment may be particularly important early on).
CAMELS[14]	N = 319 Age 11-26 y (mean 17 y) Social, separation, GAD 4 y duration; beginning 4-12 y after initial randomization	Randomized (2:2:2:1): 1) CBT, 2) Sertraline, 3) Combination, or 4) Placebo	Results: • 22% in stable remission, 30% chronically ill, 48% relapsed at follow-up. • Acute treatment responders were less likely to be chronically ill (OR 2.73; CI 1.14, 6.54; $P < .02$). • Rates of remission ranged from 40%-60% (CBT), 40%-52% (sertraline), 41%-49% (combination), and 25%-47% (placebo). • Male sex, absence of baseline social phobia, better baseline family functioning, and fewer negative life events increased likelihood of remission. Conclusions: • Treatment type did not predict remission status. • Likely long-term benefit with early, effective treatment with sertraline, CBT, and/or the combination. • Many pediatric patients will experience symptoms chronically, warranting additional treatment and relapse prevention strategies.
CAMELS[15]	N = 319 Age 11-26 y (mean 17 y) Separation, social, generalized anxiety 3-12 y after CAMS	Randomized (2:2:2:1): 1) CBT, 2) Sertraline, 3) Combination, or 4) Placebo	Results: • 40.6% never used an antidepressant, 41.4% single episode of antidepressant use, 18% multiple episodes of antidepressant use. • Reasons for antidepressant discontinuation: perceived ineffectiveness (31.8%), side effects (25.5%), and improvement in symptoms (18.5%). Conclusions: • Greater severity of anxiety at baseline predicted a single episode of antidepressant use. • Baseline depression predicted multiple episodes of use.
TORDIA[16]	N = 116 (48 wk) N = 130 (72 wk) Age 12-18 y Naturalistic follow-up of TORDIA[23]	Randomized: 1) Second SSRI, 2) Second SSRI + CBT, 3) Venlafaxine, or 4) Venlafaxine + CBT	Results: • 61.1% (through wk 72), 50% (through wk 48) achieved remission. • Those randomized to a second SSRI had a more rapid decline in depressive symptoms and suicidal ideation compared to venlafaxine ($P < .03$). • 83% (at wk 48) and 70% (at wk 72) continued to take an antidepressant. Continuing antidepressant treatment was associated with higher remission rates at wk 48 (64.8% vs 25%, $P = .002$) but not at wk 72 (78.8% vs 76.5%, $P = .76$). Conclusions: • Treatment strategy did not influence remission rate or time to remission. • Those with more severe depression or substance use at baseline were less likely to remit.

TABLE 1: Antidepressant, antipsychotic, and mood stabilizer landmark extension trials (continued)

Reference	Study Characteristics	Intervention	Results and Conclusions
RUPP[75]	N = 63 Mean age 8.6 y ASD 4-mo extension (total of 6 mo risperidone exposure) Open-label extension for risperidone responders after 8 wk	Randomized to: 1) Risperidone, or 2) Placebo	Results: • Treatment with risperidone (mean dose 1.96 mg/d) associated with 59% reduction in irritability subscale scores (ABC-I). • Relapse rates: 62.5% for gradual placebo substitution and 12.5% for continued risperidone. Conclusions: • Gradual substitution of placebo for risperidone associated with greater return of aggression, temper outbursts, self-injurious behaviors. • When risperidone is tapered off, a slow taper should be considered (over several weeks to months).
RUPP[76]	N = 84 Age 5-17 y ASD Naturalistic follow-up, mean 21.4 mo follow-up	Randomized to: 1) Risperidone, or 2) Placebo	Results: • Risperidone associated with more enuresis (19.6% vs 0%, $P = .01$), excessive appetite (42% vs 22%, $P = .08$), and weight gain (5.5%). • Social skills on Vineland Adaptive Behavior Scale ($P = .004$), social withdrawal subscale on the ABC ($P = .0002$), and M-RLRS sensory responses ($P = .0012$) improved with risperidone. • Parent-rated ABC-I were reduced in those taking risperidone (27.22 at baseline vs 14.82 at follow-up; $P = .0147$). Conclusions: • Lower rates of irritability/aggression and reductions in hyperactivity associated with current risperidone use. • Overall, risperidone was associated with high rates of adverse events compared to placebo among pediatric patients with ASD.
TEOSS[77]	N = 54 Age 8-19 y Early onset schizophrenia 44 wk	Randomized to: 1) Olanzapine, 2) Risperidone, or 3) Molindone plus benztropine	Results: • 26% completed 44 wk treatment. • Overall, no difference in symptom reduction or time to discontinuation. • Akathisia was more common with molindone, elevated prolactin with risperidone, no difference with metabolic risk during maintenance (despite being more common in acute phase with SGAs). Conclusion: After 44 wk treatment, molindone was equally as effective as olanzapine and risperidone with a higher risk for akathisia.
Collaborative lithium trials[78]	N = 31 Age 7-17 y Bipolar I disorder 28 wk	Lithium responders (YMRS <10, CDRS-R <35) randomized to continue lithium or cross-titrated to placebo	Results: • 42% completed 28 wk (65% lithium-treated) • Discontinuation due to mood symptoms, 29% of lithium-treated patients compared to 71% placebo-treated ($P = .013$). • Lithium-treated participants completed an average of 20.7 wk, compared to placebo-treated who competed an average 8.7 wk ($P = .043$). Conclusions: • Overall, lithium was well-tolerated; no significant changes in weight, renal function, thyroid function. • Efficacy and safety over a longer period of time remains unanswered.

TABLE 1: Antidepressant, antipsychotic, and mood stabilizer landmark extension trials (continued)

Reference	Study Characteristics	Intervention	Results and Conclusions
COBY[79]	N = 340 Age 7-17.11 y Bipolar disorder Mean 10 y duration Post-hoc analysis, longitudinal COBY data[80]	Naturalistic follow-up, continuation of: 1) Lithium, or 2) OMS	Results: • Those treated with lithium had half as many suicide attempts ($P = .03$), fewer depressive symptoms ($P = .004$), less psychosocial impairments ($P = .003$), and less aggression ($P = .004$) compared to those treated with OMS. • Individuals taking lithium had better psychosocial functioning during mood episodes ($P = .006$) and a less marked decline in functioning during the episode ($P < .0001$). • There was no significant effect on length of episode or length of hospitalization. Conclusion: Lithium may be superior in preventing suicide attempts, decreasing depressive symptoms, and improving overall psychosocial functioning in children and adolescents.

ABC = aberrant behavior checklist; ABC-I = aberrant behavior checklist-irritability; ASD = autism spectrum disorder; CAMS = child/adolescent anxiety multimodal study; CAMELS = child/adolescent anxiety multimodal extended long-term study; CBT = cognitive behavioral therapy; CDRS-R = children's depression rating scale-revised; COBY = course and outcome of bipolar youth; CI = confidence interval; M-RLRS = modified real life rating scale for autism; OMS = other mood stabilizing medication; OR = odds ratio; RUPP = research units on Pediatric Psychopharmacology Autism Network; SGA = second-generation antipsychotic; TEOSS = treatment of early onset schizophrenia spectrum disorders; TORDIA = treatment of resistant depression in adolescents.

Reductions in growth velocity with antidepressant treatment have been proposed among youth.[11,23-27] In a prospective observational study,[25] SSRI use was inversely associated with longitudinal growth over 1.51 ± 0.76 years among adolescents and young adults 15 to 20 years old ($P = .05$). A yearlong follow-up of 60 patients 9 to 17 years old (fluoxetine n = 20, placebo n = 35) did not identify a statistically significant difference in growth from baseline (fluoxetine: 3.5 cm vs placebo: 4.7 cm, $P = .258$).[29] No difference among SSRIs was identified. A later study[24] among 5- to 17-year-old boys (N = 267) treated with risperidone and an SSRI, found that after adjusting for age, stimulant, and second-generation antipsychotic (SGA) use, the duration and cumulative dose of the SSRI were inversely associated with height *z* score (SD for height, based on sex, age, and weight) after 11 years old ($P < .01$). SSRI use was associated with 1 cm less of growth for every year of SSRI treatment during adolescence, particularly among those undergoing later stages of puberty (ie, Tanner Stage 3,4). While the association with reduced growth velocity and SSRI treatment is not clearly defined, serotonin-related effects on growth hormone secretion have been proposed. It remains unclear what impact long-term SSRI use has on height into adulthood. The clinical significance is challenging to study as disrupted growth hormone activity, reduced physical activity, and poorer nutrition have been associated with depression.[24]

Changes in weight, BMI, and risk for type 2 diabetes mellitus (T2DM) have similarly been described.[30-34] Reported risk for weight gain among SSRIs and SNRIs varies, with literature suggesting that fluoxetine and venlafaxine are lower risk than paroxetine or citalopram,[30,33] while others suggest no change in weight with long-term treatment.[35,36] One retrospective cohort study[32] described a 90% increased risk for T2DM with SSRI or SNRI use among individuals 5 to 20 years of age, which raises clinical concerns. Duration of use more than 5 months, cumulative dose greater than 15 mg/d fluoxetine equivalents, and average daily dose greater than 15 mg/d fluoxetine equivalents were found to be associated with higher risk of developing T2DM. Recently, a large cohort study[34] found a small increased risk for T2DM among publicly insured children and adolescents 10 to 19 years old prescribed an SSRI (n = 316 178; adjusted hazard ratio [HR] 1.13; 95% confidence interval [CI] = 1.04, 1.22) compared to privately insured (n = 211 460; adjusted HR 1.01; 95% CI = 0.84, 1.23) children and adolescents prescribed an SSRI with a mean treatment duration 2.3 and 2.2 years, respectively. This study illustrated a much smaller risk for T2DM associated with SSRIs among youth than what was previously reported and highlights the importance of acknowledging the influence of other known risk factors for T2DM including obesity, race, and poverty; the latter of which confers a 2- to 7-fold increased risk. Taken together, the benefit of SSRI and SNRI use seems to outweigh the risk for changes in height, weight, and development of T2DM based on currently available literature (Table 2).

TABLE 2: Summary of psychotropic long-term risk

Medication Class	Proposed Long-Term Side Effect	Considerations
Antidepressants	Reduced growth velocity[11,24-27]	Summary of literature: • SSRI use associated with reduced longitudinal growth (1 cm/SSRI treatment year), particularly with use during puberty. Impact into adulthood unclear.[24] • No difference in growth velocity.[28-30] Proposed mechanism: Serotonin signaling influences growth hormone secretion. Application to practice: No direct intervention based on current literature. Monitor growth chart as part of routine clinical care.
	Reduced BMD/bone mineral content[37-39]	Summary of literature: SSRI use negatively associated with total volumetric BMD. Chronic SSRI treatment associated with reduced but stable bone mass for age. Proposed mechanism: Serotonin impact on osteoclast activity.[56] Application to practice: Consider vitamin D supplementation particularly in setting of other risk factors and/or vitamin D insufficiency/deficiency. Obtain vitamin D level at baseline and if supplementing. Consider lifestyle recommendations including exercise and adequate dietary calcium intake.[56]
	Weight gain, risk for T2DM[30-36]	Summary of literature: • Risk for weight gain with SSRI/SNRI is not consistently described. Studies suggest no change in weight with long-term treatment.[35,36] • Small risk for T2DM has been suggested, but further studies are needed to define.[34] Proposed mechanism: Unclear. Application to practice: Benefit of using SSRI/SNRI likely outweighs the risk.
Antipsychotics	Weight gain, adipose tissue accumulation, metabolic syndrome, T2DM[12,43,45,46,50-53,62]	Summary of literature: • Youth are more sensitive to weight gain and metabolic complications. Most weight gain occurs within the first 12 wk of treatment; risk is cumulative with time. • Increased risk for developing T2DM; risk occurred within first year of treatment, was dose dependent, high among SGAs, elevated for up to 1 y following antipsychotic discontinuation.[44] Proposed mechanism: Histamine 1 receptor antagonism, 5-HT2C receptor antagonism, alterations in ghrelin, insulin, and leptin sensitivity.[62] Application to practice: • Use agent with lower metabolic risk, if clinically appropriate.[62] • Monitor fasting blood glucose/hemoglobin A1c, fasting lipid panel at baseline, 3 mo, 6 mo, and annually. Monitor weight/BMI percentile, blood pressure, and waist circumference at each office visit.[46,54,55] • BMI percentile calculator for children and adolescents (https://www.cdc.gov/healthyweight/bmi/calculator.html). • Consider lifestyle modifications, switch to agent with lower weight gain potential, and/or initiation of metformin if weight gain occurs.[62]
	Reduced BMD[37,38,56,57]	Summary of literature: Decreased BMD, particularly with treatment >16 mo. Risperidone most widely implicated. Proposed mechanism: Increased prolactin secretion, relative hypogonadism. Prolactin may inhibit osteoblast activity.[56] Application to practice: • Monitor for signs/symptoms of hyperprolactinemia, check prolactin level if clinical suspicion of hyperprolactinemia, switch to prolactin-sparing SGA if prolactin elevated or taper off if clinically appropriate. • Consider vitamin D supplementation, particularly in presence of other risk factors and/or deficiency/insufficiency. Measure level at baseline and throughout treatment.
	QTc prolongation[59]	Summary of literature: Long-term literature is limited; safety of neuroleptics in infancy and adolescence study demonstrated 6.9% incidence of QTc prolongation >450 ms; 43% of cases occurred after 12 months of SGA exposure. Proposed mechanism: Inhibition of the delayed potassium rectifier current during cardiac repolarization. Application to practice: Consider baseline cardiac assessment in high-risk pediatric patients.

TABLE 2: Summary of psychotropic long-term risk (continued)

Medication Class	Proposed Long-Term Side Effect	Considerations
Mood stabilizers	Lithium: changes in thyroid function, acne, small risk for weight gain[65] Divalproex: weight gain, reduced bone mineral density, polycystic ovarian syndrome[65]	Application to practice: • Routine lab monitoring. • Therapeutic drug monitoring. • Baseline and periodic monitoring of vitamin D levels for all children on divalproex. Vitamin D supplementation and routine evaluation of vitamin D levels should be considered for all mood stabilizers, particularly with long-term use of divalproex.[56]

5-HT2C = serotonin 2C receptor; BMD = bone mineral density; SGA = second-generation antipsychotic; T2DM = type 2 diabetes mellitus.

Changes in bone mineral density (BMD) have been reported in pediatric patients with chronic use of antidepressants. An evaluation of boys 7 to 17 years old (N = 83) treated with risperidone and an SSRI for ≥6 months, found that SSRIs were associated with lower trabecular volumetric BMD (vBMD) at the radius ($P < .04$) and the lumbar spine ($P < .05$).[37] Two fractures were documented among boys treated with risperidone and an SSRI. Longitudinal follow-up (1.5 years) demonstrated reduced lumbar spine BMD *z* score and radius trabecular BMD at study entry ($P < .02$ and $P < .03$, respectively) and follow-up ($P < .06$ and $P < .03$, respectively).[38] Notably, the decline did not continue between visits. These results suggest that chronic SSRI use is associated with reduced but stable, bone mass for age, while risperidone use is associated with failure to accrue bone mass. A national health and nutrition examination survey[39] including 62 youth (range 12 to 20 years old, mean 16 years) showed that SSRI use was an independent predictor of bone mass after adjusting for age, sex, height, and weight *z* score, socioeconomic status, physical activity, serum cotinine level, and race or ethnicity. Specifically, total femur bone mineral content was 8.8% lower among SSRI users ($P < .01$), while total femur BMD was 6.1% lower ($P < .01$) compared to non-SSRI users. Femoral neck and lumbar spine BMD were negatively associated with SSRI use, with reductions of 7% and 3.2% respectively.

Childhood and adolescence are critical periods for bone development, with impairments increasing risk for long-term reductions in BMD.[39] Applying these results to clinical practice is challenging given variation in study designs, lack of follow-up into adulthood to evaluate impact on peak BMD, and the known link between depression and reduced bone mass.[37-39] Clinically, a 5% to 10% reduction in peak BMD is thought to significantly increase the incidence of future fractures.[39] Evaluating such impact would require following study subjects into adulthood. Until this is available, current studies demonstrate BMD reductions with SSRI and also highlight the importance of identifying additional risk factors including age, sex, race or ethnicity, height and weight, nicotine use, concurrent medications, and malnutrition, among others. In the presence of risk factors, consideration should be made for vitamin D supplementation (Table 2).

This patient case illustrates an opportunity to reevaluate the role of an antidepressant, given the patient's history of positive response and an appropriate duration of treatment. While age-appropriate stressors are present (eg, new academic year), anxiety and depressive symptoms have been in remission for >1.5 years. The patient has never been hospitalized. While changes in height, metabolic risk, and BMD have been described in the literature, the clinical significance is unclear in this case. After review of risks and benefits, if the decision is made to taper off an antidepressant, general consensus is to do so slowly over the course of several weeks or months during a lower-stress period.[19,40,41] General guidance regarding deprescribing and risk evaluation can be found in Table 3. Pediatric patients may be at a higher risk compared to adults for discontinuation syndrome, warranting a careful monitoring and discontinuation plan.[17] Symptoms to monitor for include dizziness, fatigue, lethargy, malaise, myalgia, chills, sensory disturbances, and irritability. In clinical practice, this patient's antidepressant taper may occur over the course of 12 weeks, such as over summer break, with follow-up every 1 to 2 months evaluating for symptom reemergence or discontinuation syndrome.[19,40,41] In this case, the patient's venlafaxine dose could be decreased by 75 mg every 4 weeks, or 37.5 mg every 2 weeks. The taper duration should be individualized based on patient tolerability of venlafaxine withdrawal symptoms. Caregivers and patients should be counseled on signs and symptoms of serotonin withdrawal as the antidepressant is tapered off.

Antipsychotics

A 12-year-old male with a past psychiatric history of autism spectrum disorder (level 1), GAD, disruptive mood dysregulation disorder, and sleep dysregulation presents

TABLE 3: Considerations for deprescribing in children and adolescents

Proposed Steps[4,5,8,10]
1. Routine discussion of benefits and risks of current medications, importance of reevaluating the need for psychotropic medications with patient and/or caregiver(s)
2. Identification of medication
3. Introduce the idea of deprescribing to patient/caregiver, gain buy-in from patient and/or caregiver(s)
4. Choose the right time (eg, break from school, time of lower stress/demands)
5. Develop a specific plan, including start date, rate of taper, monitoring
6. Monitor, adapt, and provide frequent follow-up/support
Steps should involve multidisciplinary involvement
Indications[5,10]
• Changing benefit-to-risk ratio
• Unclear rationale for use/role
• Lack of evidence to support medication use
• Completion of typical or expected treatment course
• Nonadherence
• Treatment alliance
• Inappropriate polytherapy
Risk Assessment
• ≥4 Psychotropic medications
• ≥2 Concomitant medications from a single class (exception: short-acting and long-acting stimulant)
• Medication prescribed does not match presentation and/or diagnoses
• Medication exceeds usual recommended dose
• Prescribed at a very young age (eg, age <4 y)

to outpatient clinic. Medical history is significant for chronic constipation, gastrointestinal upset, and iron deficiency. He was last hospitalized 4 years ago, with a chief complaint of behavioral dysregulation, suicidal ideation, and worsened anxiety. Since that time, he was enrolled in an applied behavioral analysis in-home program and now has access to in-school supports. Today, he completed the Aberrant Behavior Checklist-Irritability (ABC-I) and his score was unchanged from 1 year ago. Current medications include risperidone 3 mg by mouth daily initiated 4 years ago, fluoxetine 15 mg by mouth daily, guanfacine extended release 3 mg by mouth daily, melatonin 6 mg by mouth every night, polyethylene glycol 17 g by mouth daily, ferrous sulfate 325 mg by mouth daily, and n-acetylcysteine 1200 mg by mouth twice daily. During the current visit vital signs were normal, but abnormalities were noted in triglycerides (285 mg/dL), total cholesterol (200 mg/dL), serum prolactin (85 ng/mL), and vitamin D (19 ng/mL); height: 5 feet, 1 inch; weight: 68 kg; and BMI: 28.3 kg/m^2 (98% for age). On physical exam, development of breast tissue is noted. Previous labs (6 months ago): triglycerides (255 mg/dL), total cholesterol (170 mg/dL), serum prolactin (75 ng/mL); height: 5 feet, 1 inch; weight: 65 kg; and BMI: 27 kg/m^2 (98% for age).

Evaluating safe and judicious use of SGAs in youth is a public health priority, given lack of long-term safety and efficacy data, concern for cardiometabolic effects, and increased rates of prescribing among Medicaid-enrolled youth in foster care.[33,42-44] State-based initiatives, including monitoring programs and clinician prescribing supports, aim to curb inappropriate prescribing of antipsychotic medications particularly in this vulnerable population.[42,44] It is critical that the use of SGAs is routinely reevaluated in pediatric populations; though long-term trials are lacking to guide specific steps for such strategies. Landmark extension trials (Table 1) and treatment guidelines offer a general framework for evaluating appropriate duration of antipsychotic treatment. Specifically, the Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders guidelines identify that pediatric long-term maintenance studies are lacking but suggest improved outcomes such as maintenance of remission with combination treatment (eg, mood stabilizer and antipsychotic), compared to monotherapy.[45] Guidelines urge that combination treatment should be used judiciously after critical evaluation of appropriateness. American Academy of Child and Adolescent Psychiatry and Canadian schizophrenia guidelines suggest that most individuals will require long-term treatment and are at significant risk of relapse if their antipsychotic is discontinued.[46,47] Updated American Academy of Pediatrics autism spectrum disorder treatment guidelines recommend regular reevaluation of antipsychotic treatment, with consideration for discontinuation if clinically appropriate.[48,49] Based on clinical experience, if an antipsychotic is discontinued it should be done so gradually, over several weeks to months, with close monitoring for signs and symptoms of relapse.

A 12-month naturalistic study among children and adolescents newly prescribed an SGA included 190 patients with a mean age of 12 years old, and 73.6% were male. After a mean treatment duration of 11 months, they found 11.52 SGA-related adverse events/person-years, with nearly one-quarter of children (n = 46) experiencing at least 1 severe adverse event. Of these, nearly half (n = 22) were serious metabolic adverse events.[43] Common adverse events included neuromotor (15.4%), gastrointestinal (14.8%), metabolic (12.2%), hormonal (10.4%), and psychiatric, suicidal ideation, or overall worsened symptoms (10.1%). Weight, BMI, and BMI *z* scores increased significantly by 5.9 kg (±5.04), 1.54 kg/m^2 (±1.84), and 0.53 (±0.69), respectively, in patients

completing the 12-month follow-up. The majority (92%) were prescribed an SGA—risperidone in 50% of patients, and aripiprazole in 36% of patients. Of these antipsychotic prescriptions, 74% were as monotherapy and 79.5% as off-label use. Within 12-months of SGA initiation, notable and frequent changes in weight, BMI, and prolactin warrant careful consideration (Table 2).

Children and adolescents are more susceptible than adults to metabolic effects associated with SGAs.[16,45] Weight gain occurs acutely, with significant changes seen within 12 weeks of treatment initiation. Over time, metabolic syndrome and T2DM may develop, including insulin resistance, glucose intolerance, dyslipidemia, hypertension, and increased risk for cardiovascular disease.[45,50,51] Not only might these metabolic effects be secondary to weight gain, but it has been proposed that antipsychotics have a direct effect on insulin resistance and glucose dysregulation.[50] A retrospective cohort study[51] of Tennessee Medicaid enrollees identified that antipsychotic users (n = 28 858; range 6 to 17 years old) had a more than 3-fold increased risk of T2DM (HR = 3.14, 95% CI = 1.50, 6.56) compared to matched controls. The risk increased significantly with increasing cumulative antipsychotic dose ($P = .03$) and was highest among SGAs (HR = 2.89, 95% CI = 1.64, 5.10). Notably, the risk presented within the first year of antipsychotic treatment and persisted for up to 1 year following antipsychotic discontinuation.

Previous studies have identified not only substantial weight gain with risperidone, but that the rate of weight gain impacts severity of cardiometabolic abnormalities, including atherogenesis.[52] A follow-up of youth who used risperidone for an average of 2.5 years (N = 74; mean age 11.7 years) demonstrated unchanged BMI *z* scores in those who continued risperidone (0.03 ± 0.02 mg/kg/d) and elevated BMI *z* scores among those that were switched to an alternative SGA (aripiprazole n = 3; ziprasidone n = 2; clozapine n = 2; quetiapine n = 1; olanzapine n = 1).[51] Change in BMI *z* score was significantly correlated with change in blood pressure, heart rate, waist circumference, percent body fat, inflammatory markers, fasting total insulin, c-peptide, low-density lipoprotein, high-density lipoprotein, total cholesterol, triglycerides, and leptin. Risperidone discontinuation was associated with normalization of BMI *z* scores within 1.5 years follow-up. Applying this to clinical practice, careful consideration should be made to avoid high-risk agents and for routine metabolic monitoring.[46] The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children and American Academy of Child and Adolescent Psychiatry guideline groups recommend that fasting blood glucose/hemoglobin A1C and lipid panel should be measured at baseline, 3 months, and 6 months, then annually. More frequent monitoring should be considered if values are abnormal. Weight, blood pressure, and waist circumference should be routinely measured.[46,54,55] Newer SGAs, with lower metabolic risk, have not yet been thoroughly evaluated in pediatric populations.

Reductions in BMD have been described in children prescribed long-term SGAs, primarily those treated with risperidone.[37,38,56,57] One cross-sectional study[57] among 53 males 10-years-old to 20-years-old (mean age 14.4 years) treated with risperidone at a mean dose of 1.6 mg/d demonstrated an increase in bone turnover markers, elevated serum prolactin in 49% of patients, and a statistically significant decrease in lumbar vBMD *z* score ($P = .043$) after a mean of 52 months of treatment. Another study[37] looked at 83 children 7- to 17-years-old treated with risperidone (mean dose 0.03 mg/kg/d) for more than 6 months (mean 2.9 years). Serum prolactin was associated with reduced trabecular vBMD at the ultra-distal radius ($P < .03$) after adjusting for height, BMI *z* score, and stage of sexual development. After 2.5 years of treatment in 94 males, risperidone continuation was associated with ongoing decline in BMD *z* scores in the lumbar spine ($P < .04$) and failure to increase radius trabecular vBMD ($P < .03$).[38] Prolactin concentration was positively associated with lumbar spine adjusted BMD *z* score ($P < .02$) but was not significantly associated with radius trabecular vBMD ($P > .5$). Overall, risperidone is most widely implicated in reducing BMD among children particularly after long-term use and in the setting of elevated serum prolactin. The impact of hyperprolactinemia is more pronounced among children compared to adults, warranting careful consideration for initiation, dose, duration of treatment, and monitoring.[37,38,43,52,56,58] Currently, guidelines do not provide specific recommendations regarding frequency of serum prolactin monitoring. Baseline and periodic monitoring for symptoms of hyperprolactinemia is critical among children. In addition to routine metabolic monitoring, routine vitamin D supplementation should be considered (Table 2).[56]

Evaluation of cardiac risk associated with long-term SGA use in children and adolescents was performed using the safety of neuroleptics in infancy and adolescence registry data.[59] This study included 101 children and adolescents 4-years-old to 17-years-old (mean 11.5 years) treated with an antipsychotic for an average of 10.8 months. Among those prescribed an SGA, 6.9% (n = 7) demonstrated an increase in QTc (>450 ms); however, no patients had a QTc interval >500 ms. Of these patients, 4 were treated with aripiprazole and 3 with risperidone. Three individuals had ECG abnormalities after extended periods of SGA exposure (>12 months). Cardiac changes were largely asymptomatic (85.7%), with 1 individual describing nonspecific fatigue. The majority of QTc changes resolved spontaneously without changes in SGA treatment. Concomitant stimulant use (21.8%) was statistically significantly correlated with QTc changes. Family history of

heart disease was more common in those with QTc abnormalities, though not statistically significant. Overall, more data on the cardiac risk of long-term antipsychotic use in youth is needed. Patients should be screened at baseline for a personal/family history of cardiovascular disease, with consideration for a baseline ECG in the presence of other risk factors (eg, QTc prolonging medications, high-risk SGA).

This patient case illustrates an ideal opportunity to reevaluate the role of risperidone. In addition to increased access to nonpharmacologic services (eg, applied behavioral analysis) and global symptom improvement, it appears that the patient is experiencing adverse effects associated with long-term risperidone treatment including hyperlipidemia, symptomatic hyperprolactinemia (eg, gynecomastia), and weight gain. If not already ordered, a fasting blood glucose and hemoglobin A1c should be measured given present risk factors for T2DM. Additionally, his overweight status, elevated serum prolactin, and long-term risperidone treatment place him at risk for BMD reductions. Consideration should be made for daily oral vitamin D supplementation, nutritional assessment, and serum vitamin D concentration monitoring (Table 2). When planning an antipsychotic taper, it is important to consider that youth are at higher risk for withdrawal dyskinesia and dystonia and that youth with neurodevelopmental disorders may be particularly sensitive to these withdrawal-emergent effects.[11,60] As antipsychotics are tapered, it is critical that caregivers are provided counseling on signs of relapse and potential withdrawal symptoms. Withdrawal-emergent dyskinesia or dystonia can be particularly alarming to patients and their families. In clinical practice, the risperidone dose could be decreased by a maximum of 0.25 to 0.5 mg every 2 to 4 weeks. As risperidone is tapered and eventually discontinued, prolactin levels can be trended with consideration for alternative interventions if necessary. When the antipsychotic cannot be tapered, the addition of metformin can be considered when nonpharmacologic interventions have failed. Metformin is the most widely studied pharmacologic intervention for antipsychotic-induced metabolic disturbance in pediatric patients and has demonstrated reductions in BMI *z* scores in pediatric patients prescribed SGAs.[61,62] For those who develop dyslipidemia, guidelines provide pharmacologic recommendations for treatment, though this is not specific to antipsychotic-induced dyslipidemia.[63]

Mood Stabilizers

A 16-year-old female presents to outpatient psychiatry clinic. Current psychiatric diagnoses include PTSD and bipolar II disorder. She is engaged in outpatient therapy and has historically participated in intensive outpatient services. Social history is significant for adoption at 8 years old, with 4 foster home placements between 6 and 8 years old. Current medications include divalproex delayed release 500 mg by mouth twice daily, sertraline 150 mg by mouth daily, prazosin 4 mg by mouth every night, and melatonin 6 mg by mouth every night. Prazosin was initiated 6 months ago, and the dose was last increased 3 months ago; no other medication changes have occurred in the past 2 years. Previous medication history includes olanzapine 10 mg by mouth daily, lurasidone 80 mg by mouth daily, lithium carbonate 1200 mg by mouth daily, and fluoxetine 40 mg by mouth daily. Olanzapine and lurasidone were discontinued due to concerns for weight gain and ineffectiveness. Lithium was discontinued given concern for polydipsia and polyuria and lack of participation in routine blood draws. Fluoxetine was ineffective after 20 weeks of treatment. A mental status exam noted that the patient appeared younger than stated age, well-groomed, with occasional flashbacks and nightmares, and an anxious mood. Vital signs and laboratory results are within normal limits: height: 5 feet, 7 inches; weight: 82 kg; and BMI: 28 kg/m^2 (94% for age). She is not currently sexually active.

There are few long-term trials[64,78,79] evaluating safety of mood stabilizers in pediatric populations. Most pediatric bipolar disorder studies focus on acute management of mixed or manic episodes, with far less data available for maintenance treatment.[65] Evidence is even more limited regarding long-term management of children and adolescents with bipolar disorder.[65] As described further in Table 1, the collaborative lithium trials and course and outcome of bipolar youth offer perspective regarding longer-term use of lithium and divalproex in pediatric patients with bipolar I disorder, though longer-term safety evaluations are needed.[78,79] While there is limited information regarding appropriate duration of treatment, guidelines[45,66] suggest most will require lifelong treatment. If a medication taper is considered, remission should be achieved for a minimum of 12 to 24 consecutive months and the risk of potential relapse should be compared to the risk associated with continued pharmacotherapy.[66]

Significant elevations in thyrotropin concentrations (1.92 mIU/L to 5.28 mIU/L) were observed in the collaborative lithium trials, during the 8-week open-label treatment phase. Interestingly during postacute treatment, thyrotropin concentrations decreased on average from 5.9 $\pm$ 3.6 mIU/L to 5.0 $\pm$ 2.0 mIU/L.[78] Other studies[65,67-69] have demonstrated similar changes in both acute and maintenance phases of treatment, suggesting that the greatest risk for thyrotropin elevation occurs during the first 2 to 3 months of treatment. Notably, pediatric maintenance studies[65,69,70] (up to 76 weeks of treatment) suggest that lithium has a low risk for weight gain and may be weight neutral. Based on available maintenance

treatment studies (range 24 to 76 weeks of treatment), renal function and creatinine clearance did not significantly change with lithium treatment.[65,68,70] Routine thyroid and renal function monitoring in pediatric patients treated with lithium long term should be considered, despite lack of clear consensus regarding monitoring frequency (Table 2). Additionally, therapeutic levels should be routinely measured, and goal ranges do not differ from adults.[65]

In an open-label study[71] evaluating the long-term safety of divalproex extended release in children 9- to 17-years-old (N = 109) with bipolar I disorder, weight gain (16%), nausea (9%), increased appetite (8%), and tremor (6%) were identified as the most common adverse effects. Notably, weight gain was the most common reason for medication discontinuation.[71] Divalproex has consistently demonstrated moderate to high risk for weight gain in pediatric patients with bipolar disorders in open label studies (Table 2).[11,65,66,70,71]

Independently, long-term divalproex exposure has also been associated with the development of features of polycystic ovarian syndrome in ~7% of divalproex-treated female adolescents.[72] Childhood and adolescence is thought to be a particularly vulnerable time, given relative immaturity of their hypothalamic-pituitary-ovarian axes. Divalproex can lead to alterations in leptin, the ratio of testosterone to estradiol, contributing to menstrual abnormalities, infertility, acne, and the risk of osteoporosis and obesity.[11,66] This has led to concern regarding long-term use of divalproex in women with bipolar disorder, particularly when it is started at a young age.

In females of childbearing age and potential, it is also critical to consider teratogenic effects of divalproex including neural tube defects and major congenital malformations.[73,74] Additionally, it has been suggested that children exposed to divalproex in utero are at increased risk for autism spectrum disorder, behavioral problems, and lower IQ later in development.[73,74] For these reasons, divalproex is not considered first-line treatment in this population.

Reductions in BMD have routinely been described with long-term use of antiseizure medications; particularly in the setting of polytherapy, chronic use, or high doses, conferring significant osteoporotic risk.[56] It has been proposed that potent enzyme inducers, including carbamazepine, may induce the liver to actively metabolize vitamin D.[56] While studies show variable results in pediatric patients, recent literature[56] has demonstrated a negative effect of divalproex on BMD. As a class, antiseizure medications demonstrate slowing of linear growth, stimulation of parathyroid hormone activity, and carnitine depletion, a major source of cellular energy for osteoblasts. The American Academy of Pediatrics and the Endocrine Society recommend routine baseline and periodic monitoring of vitamin D levels for all children on antiseizure medications.[56] Daily vitamin D supplementation should be considered (Table 2).[56]

This patient case illustrates an important opportunity to reevaluate the role of a mood stabilizer given associated risk and remission of depressive episodes. Given long-term risks for weight gain, polycystic ovarian syndrome, reductions in BMD, and concern for teratogenicity, a medication taper should be considered. Clinical experience indicates that pharmacokinetic and pharmacodynamic properties of a mood stabilizer should be considered when creating a taper plan. Additionally, the taper should occur at a time associated with the lowest possible risk of relapse, and proper monitoring must be in place so that prodromal mood symptoms of relapse can be readily detected (Table 3).[66] In clinical practice, the taper of divalproex may occur over 4 weeks with close monitoring for reemergence of depressive or hypomanic symptoms. Consideration should be made for daily oral vitamin D supplementation and serum vitamin D concentration monitoring (Table 2) given long-term treatment with psychotropic medications.

Conclusion

Reevaluating the role of psychotropic medications with consideration for deprescribing is essential in children, given dynamic changes throughout development and risk for pediatric-specific adverse effects. Long-term use of antidepressants has been associated with reductions in growth velocity and BMD. Risk for T2DM and weight gain has also been proposed but warrant further investigation. Long-term use of antipsychotics may lead to development of metabolic syndrome, T2DM, hyperprolactinemia, and reductions in BMD. Lastly, long-term use of divalproex is linked to the development of polycystic ovarian syndrome, reduced BMD, and weight gain. Renal and thyroid function should be routinely monitored in children prescribed long-term lithium. Careful review of short-term and long-term benefits, risks, and expected duration of treatment is a collaborative decision with pediatric patients and their caregivers. Psychiatric pharmacists play a critical role in advocating for opportunities to deprescribe in this patient population.

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