



The Burden of Antipsychotic-Induced Weight Gain and Metabolic Syndrome in Children

Mark R. Libowitz and Erika L. Nurmi*

Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, Los Angeles, CA, United States

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*Correspondence:

Erika L. Nurmi
enurmi@g.ucla.edu

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Antipsychotic medications are critical to child and adolescent psychiatry, from the stabilization of psychotic disorders like schizophrenia, bipolar disorder, and psychotic depression to behavioral treatment of autism spectrum disorder, tic disorders, and pediatric aggression. While effective, these medications carry serious risk of adverse events—most commonly, weight gain and cardiometabolic abnormalities. Negative metabolic consequences affect up to 60% of patients and present a major obstacle to long-term treatment. Since antipsychotics are often chronically prescribed beginning in childhood, cardiometabolic risk accumulates. An increased susceptibility to antipsychotic-induced weight gain (AIWG) has been repeatedly documented in children, particularly rapid weight gain. Associated cardiometabolic abnormalities include central obesity, insulin resistance, dyslipidemia, and systemic inflammation. Lifestyle interventions and medications such as metformin have been proposed to reduce risk but remain limited in efficacy. Furthermore, antipsychotic medications touted to be weight-neutral in adults can cause substantial weight gain in children. A better understanding of the biological underpinnings of AIWG could inform targeted and potentially more fruitful treatments; however, little is known about the underlying mechanism. As yet, modest genetic studies have nominated a few risk genes that explain only a small percentage of the risk. Recent investigations have begun to explore novel potential mechanisms of AIWG, including a role for gut microbiota and microbial metabolites. This article reviews the problem of AIWG and AP metabolic side effects in pediatric populations, proposed mechanisms underlying this serious side effect, and strategies to mitigate adverse impact. We suggest future directions for research efforts that may advance the field and lead to improved clinical interventions.

Keywords: child psychiatry, pediatrics, antipsychotics, antipsychotic-induced weight gain, adverse drug effects, metabolic syndrome

INTRODUCTION

In the 1950s the first antipsychotic (AP) medication, chlorpromazine, became available for adults. These first-generation antipsychotic (FGAs) drugs made it possible to stabilize severe mental illness that previously required long-term institutionalization. While FGAs revolutionized the practice of psychiatry, serious motor adverse effects were common (1). This prompted the introduction of the first atypical antipsychotic (second-generation antipsychotic, SGA), clozapine, in 1990. SGA

prescriptions soon dominated due to their reduced motor side effects and benefit in treating negative symptoms compared to FGAs (2, 3). SGAs also cause considerable morbidity, however, predominantly through antipsychotic-induced weight gain (AIWG) and metabolic dysfunction (1). Nevertheless, SGAs continue to represent the standard of care (93% of AP prescriptions as of 2008) (4), including for children and adolescents (age ≤ 19) (5).

The already dire prevalence of pediatric obesity and metabolic syndrome (6) is compounded by increasing global trends in pediatric AP prescribing, with children potentially accumulating risk over decades of pharmacotherapy. The mechanisms underlying these adverse effects are poorly understood, and consequently, few mitigating or alternative options are available to clinicians. This review will first outline AP exposure in the pediatric population, metabolic health consequences of pediatric AP treatment, and moderators of risk for adverse events (AEs). Next, an overview of proposed mechanistic pathways will be provided. Finally, we will summarize strategies to mitigate adverse impacts of these necessary therapeutics and synthesize a decision support algorithm for clinicians. We will conclude with future directions for research and treatment. An understanding of the biological underpinnings of metabolic AP effects is crucial to preventing negative physical and mental outcomes of youth in need of AP therapy and to designing new targeted treatments without burdensome side effects.

SEARCH STRATEGY, SELECTION CRITERIA, AND DEFINITION OF TERMS

In this narrative review, we attempted to limit bias and ensure comprehensiveness through broad search strategies. We searched PubMed, using the search terms “antipsychotic-induced weight gain,” “metabolic syndrome,” “cardiometabolic,” “pediatric OR adolescents OR child OR children,” “obesity,” “diabetes,” “second generation antipsychotics,” “neurohormone,” and “neuroendocrine.” Our search included articles published on PubMed through October 30th 2020. Publications were selected based on relevance, with priority given to publications from human research on antipsychotic-induced weight gain and metabolic effects from the past 10 years. We prioritized data from pediatric populations and provided adult data when this was lacking. With regard to treatment studies, we prioritized randomized controlled trials, systematic reviews and meta-analyses. With regard to genetic studies, we prioritized unbiased genome-wide studies. We also searched the reference list from articles and reviews identified by this strategy to select additional relevant titles. We supplemented the search with reviewer recommendations.

We use the following terms as defined by the American Association of Child and Adolescent Psychiatry (AACAP): “child” or “children” will refer to patients ages 5 to 12 years (or zero to 12 when specified), “adolescent(s)” to those between the ages of 13–17 years (inclusive) and “youth” to patients between ages 5 and 18 (7).

ANTIPSYCHOTIC EXPOSURE IN YOUTH

Prescription rates of psychotropic medications vary by country, with US utilization exceeding that in Europe (8). A 2019 analysis of international data revealed that the highest prevalence estimates ($\sim 3\%$) for AP prescriptions in children and adolescents (age ≤ 19) occur in Taiwan and the US (9). A 2014 survey revealed that AP prescription rates are higher in publicly (2%) vs. privately (0.7%) insured US children and adolescents (0–19 years) (10). In the outpatient setting, the SGA most frequently prescribed to children aged 0–13 is risperidone (42.1%), followed by aripiprazole (28.0%), quetiapine (19.2%), and olanzapine (4.4%) (11).

Despite their name and primary use in treating psychosis, AP treatment is supported by evidence for a range of psychiatric disorders. Aggression, and not psychosis, is the most common symptom targeted by AP administration to youth (12–17). The National Ambulatory Medical Care Survey reported that from 2005–2009, APs were prescribed in 31.3% of outpatient visits for youth (age ≤ 20 , $n = 527$) with mood disorders (11). The Food and Drug Administration has approved SGAs for use in children and adolescents with schizophrenia, type I and II bipolar disorder, Tourette disorder, and irritability related to autism spectrum disorder. Prescribing trends have shown an increase in SGA prescriptions for younger children (5, 18–24), including off-label use for childhood ADHD and depression for which AP therapy has limited evidence-base (22).

The typical reported duration of pediatric AP treatment varies. In a cohort of Australian patients <15 years of age prescribed APs ($n = 901$), the average duration of overall AP use was 2.4 years (25). The AP with the longest duration of use for this cohort was haloperidol followed by risperidone, chlorpromazine, olanzapine, quetiapine, aripiprazole, and lastly amisulpride. The most prescribed AP for this age group, risperidone, had a mean use of 2.25 years. In a Canadian Cohort of pediatric patients prescribed an SGA the most common diagnosis was ADHD, Mood Disorder, Conduct Disorder, or Psychotic Disorder. The median duration of risperidone, the most prescribed SGA for this cohort, was 179, 334, and 408 days for children aged 1–6 ($n = 1,341$), 7–12 ($n = 17,356$), and 13–18 ($n = 32,604$), respectively (26). A Medicaid-insured birth cohort examining trends in psychotropic prescription rates and medication use found that among 7-year-old children prescribed APs, 50.6% continued use for 6 months or more (27). Median duration of AP use increased with age, from 57 days in children aged 3 ($n = 9$) to 193 days in children aged 7 ($n = 193$). In this cohort only 15% of those prescribed an AP had a diagnosis of autism spectrum disorder, schizophrenia or bipolar disorder, revealing a trend of off-label AP prescriptions.

Weight gain is commonly reported by patients and physicians as an important factor in non-adherence (28–30). Discontinuation of pediatric AP treatment is common and determining the long-term severity of AEs after discontinuation is a concern (28–33). Both a naturalist study of (29) first-episode psychosis ($n = 110$, age range = 9–17, mean age = 15.3) treated with olanzapine, clozapine, or quetiapine and a controlled study (28) of early-onset schizophrenia spectrum disorder ($n = 116$,

age range = 8–19) treated with olanzapine, risperidone, or molindone found that discontinuation of AP use within 12 months is the norm. In both studies, the main reasons cited by patients for discontinuation were insufficient response and AEs such as weight gain.

METABOLIC EFFECTS OF ANTIPSYCHOTICS IN YOUTH

Metabolic syndrome is a cluster of signs and symptoms, including insulin resistance, dyslipidemia, and hypertension, that increases subsequent risk of type 2 diabetes, heart disease, and stroke (Figure 1). APs can adversely impact metabolic function through direct effects on lipids and insulin sensitivity and indirect effects on these parameters as a result of AIWG and obesity (34–36). AIWG can be substantial, with average weight gain over a 12-month period measured at 5 kg, corresponding to a BMI increase by 1.5 in children and adolescents (mean age = 12, age range = 6–18, $n = 200$) (37). Importantly, AIWG increases the risk of obesity, which is predictive of both adult type 2 diabetes and adult metabolic syndrome (38). The International Childhood Cardiovascular Cohort Consortium consisting of 5,803 participants found a 2.4-fold increased risk for adult metabolic syndrome in children that are overweight with metabolic metrics above the 75th percentile from 5 years of age onward (39). Additionally, this study found increased risk (risk ratio = 2.6–4.1) for type 2 diabetes for children 8 years and older that were overweight and met 2 metabolic syndrome criteria.

Several studies have indicated that SGAs are associated with increased risk for metabolic symptoms. Results of a 2018 systematic review of 126 studies report AEs of APs in pediatric populations showed that compared to placebo, SGAs were associated with elevated triglyceride levels, weight gain, increased risk of type 2 diabetes, and unfavorable lipid changes (34). While this included only subjects under 18 years of age, the mean age across the studies was > 8 years, reducing its applicability to younger children. The SATIETY cohort (age range 4–19, mean age = 13.9, $n = 205$) study observed mean level increases in serum total cholesterol (15.6 mg/dL: both low-density lipoprotein, high density lipoprotein) and triglyceride (24.3 mg/dL) levels to increase with just a median of 10.8 weeks of exposure to SGAs (40). Further, patients developed dyslipidemia (17.1%), insulin resistance (8.6%), and metabolic syndrome (1.6%). In a mixed diagnosis comparison study of metabolic changes in adolescents ($N = 179$, age range = 12–18, mean age = 15.8) vs. adults ($N = 4,280$) receiving at least 24 weeks of olanzapine treatment, adolescents were found to have greater mean increases in fasting total cholesterol, LDL and triglyceride levels as compared to adults, while increases in fasting glucose levels were similar (41). Despite greater vulnerability, children and adolescents are less likely than adults to have their metabolic parameters monitored during AP treatment (37).

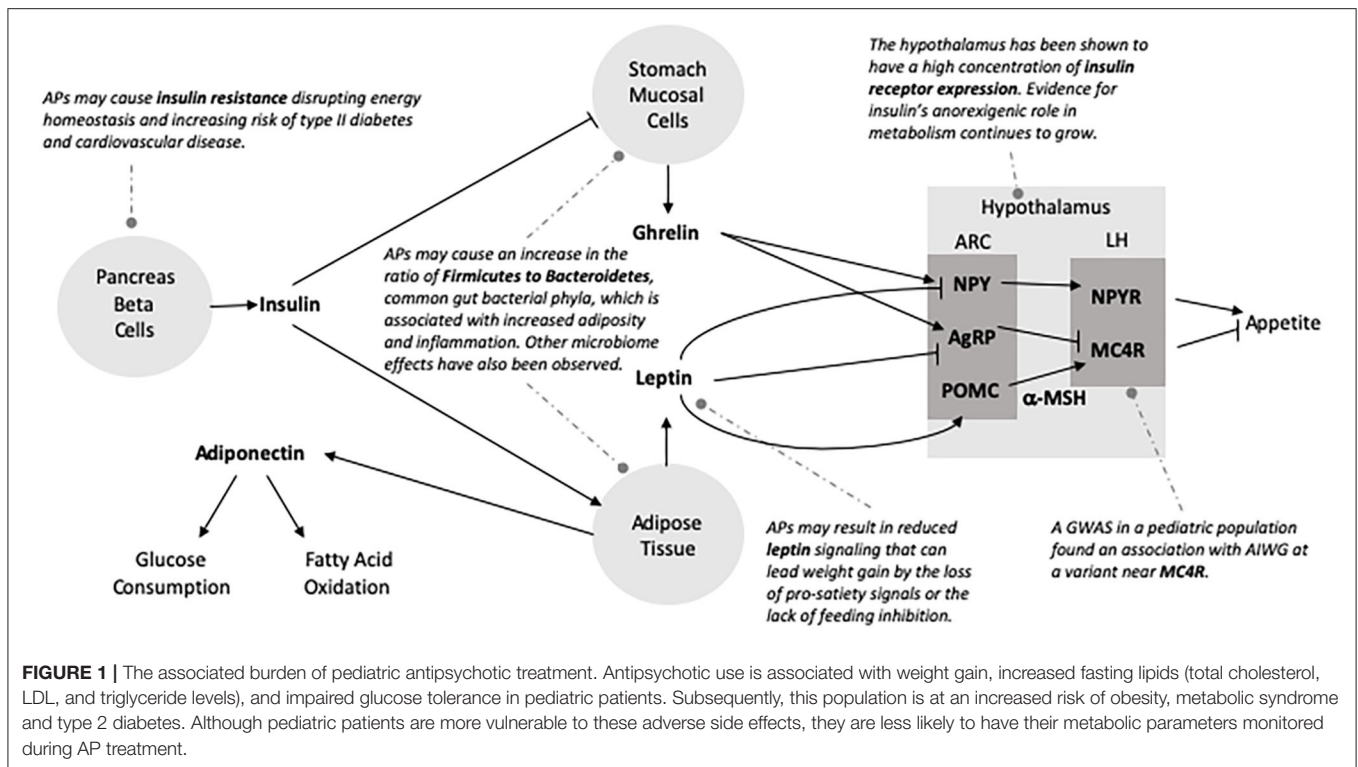
Type 2 diabetes has been implicated as a long-term AE of AP treatment in children and adolescents (42–45), as well as in adults (42, 43, 46). Studies examining this association are inconsistent. A retrospective study (47) evaluated South Carolina medical

and pharmacy claims of children/adolescents receiving AP monotherapy ($n = 30$) or AP plus antidepressant treatment ($n = 274$) with type 2 (or misclassified type 1) diabetes did not attribute psychotropic medication as an explanatory factor of diabetes; however, causality cannot be inferred with a retrospective design and final group sizes are underpowered for most comparisons. Another retrospective cohort study (48) of outpatients (mean age 41.9, $SD = 21.5$) administered SGAs ($n = 10,265$), FGA ($n = 4,607$), antidepressants ($n = 60,856$), or antibiotics ($n = 59,878$) and a systematic review ($n = 258,597$ aged 0–5, $n = 294,722$ aged 6–11, and 331,339 aged 12–17) attributed risk of diabetes to non-specific factors given similar rates of diabetes with both APs and antidepressants (48, 49). A final retrospective national cohort study (age range = 10–18, 59.8% age 10–14, 40.2% age 15–18, $n = 107,551$) of youth receiving AP treatment reported higher risk of type 2 diabetes when antidepressants are used concomitantly with APs (45). Studies are also contradictory with regard to the relationship between risk for diabetes and age, with some reporting greater risk in older adolescents (44, 50) and others in younger patients (42). Although, there have been inconsistent findings for pediatric AP treatment and subsequent type 2 diabetes, data is strong enough to warrant regular physician monitoring of glucose levels (42, 44, 51).

RISK FOR ANTIPSYCHOTIC-RELATED METABOLIC EFFECTS

Negative metabolic consequences and AIWG affect up to 60% of patients receiving APs, with the highest risk to children (40, 52–57). A multicenter naturalistic observational study (ETAPE) performed a 12-month follow up of AEs for 200 youth (mean age = 12, 92% prescribed SGAs) and found that the overall AE incidence rate was 11.52 AEs per person-years (37). For the AEs attributable to APs, 12.2% were related to metabolic or neuroendocrine parameters and included elevated cholesterol (>170 mg/dl) and triglycerides (≥ 100 mg/dl) (36.3%), hyperprolactinemia (>25 ng/ml) (38.5%), vitamin D deficiency (<30 ng/mL) (36.6%), hyperphagia (67.4%), and diabetes (7%). For the AEs recorded, more than half had incidence during the first 3 months of treatment. Moreover, children are more vulnerable to both the adverse physical and emotional effects of SGAs (24). As a result of this increased vulnerability, non-adherence in youth is prompted by changes in their physical appearance leading to body image issues (58) and negative peer perception (59).

Studies have shown that adverse health effects in youth increase with duration of treatment (60, 61) and that a younger age of AP use is associated with increased AIWG vulnerability (62), as well as AEs associated with obesity such as cardiovascular and metabolic complications (62–65). As research shows that most pediatric AIWG occurs within the first 12 weeks of administration (40, 65, 66), even relatively short-term treatment can result in considerable weight gain. First-episode psychosis is also a risk factor for greater weight gain, likely due to multiple factors (40, 67–69) such as younger age, lack of previous antipsychotic exposure, and less established



participation in psychiatric treatment. Regular monitoring of adverse cardiometabolic effects for pediatric patients prescribed APs is standard of care (21, 70–77). Given accumulating risk over time and earlier age of initiation, longitudinal studies for pediatric AP use are highly warranted.

Propensity for weight gain and metabolic effects varies among AP agents. A 2018 network meta-analysis of 28 studies of pediatric AIWG (mean age = 14.41, 58% male) (78) found that molindone, lurasidone, and ziprasidone were relatively benign while clozapine, quetiapine, and olanzapine resulted in the greatest weight gain. Paralleling the adult literature, clozapine demonstrated both the greatest efficacy and side effect burden in youth. Importantly, medications touted to be weight neutral in adults behave differently in children. Aripiprazole, for example, has been noted to produce weight gain equivalent to or greater than risperidone in 2 pediatric studies (79, 80). The relationship of AP dose to AIWG remains unclear and may vary with time and across specific APs (81–83). Concomitant medications can also alter risk in either direction; for example, stimulants have been associated with attenuated (83) and mood stabilizers with compounded (84) risk for AIWG.

Diagnostic differences in weight gain have also been examined. A systematic review of children receiving AP treatment ($n = 3,048$) found that children diagnosed with autism spectrum disorder had higher propensity for weight gain, but this could be a result of younger age at treatment or lack of previous exposure to APs (66). Additionally, in a cohort of youth with schizophrenia or schizoaffective disorder, the Treatment of Early-Onset Schizophrenia Spectrum Disorders Study found

that schizoaffective diagnosis predicted greater weight gain for risperidone prescribed youth ($n = 119$, age range = 8–19, $p = 0.004$) (85).

Considerable variability in weight gain and metabolic effects exists between individuals (86), though this variability is poorly understood. As previously discussed, young and antipsychotic-naïve patients are at particularly high risk, gaining 3–4-fold more weight irrespective of the specific AP (67). Few other patient-specific moderators of AIWG have been confirmed. Both higher and lower baseline BMI have been reported to predict AIWG in children (83, 87), which is complicated by confounding with age, AP exposure, and the expectation that extreme BMI values will regress toward the mean (83, 88). Reports of sex effects are also inconsistent, with studies claiming female (46, 89–91), male (63, 92), or equal (80) predominance of weight gain; though boys are prescribed APs more frequently than girls, paralleling male preponderance of many indications for AP administration (autism, Tourette, aggression). While AIWG and metabolic AEs appear to be a worldwide phenomenon, ethnicity and socioeconomic status may influence risk magnitude (92–94). APs are disproportionately prescribed more frequently to those in foster care (95) and to those with public insurance (96, 97).

Only a few studies have addressed the reversibility of AIWG (30–33). Two of these studies reported that AIWG in children and/or adolescents was reversible but are limited by small sample size ($n = 14$, mean age = 11.5; and $n = 18$, mean age = 9.68) and the inclusion of subjects who did not gain weight during AP treatment (31, 33). More moderately-sized studies showed contradicting results (30, 32). In a secondary analysis of AIWG

in a pediatric placebo-controlled, cross-over study (age range = 5–17, mean age = 11.1, $n = 527$) of risperidone treatment of disruptive behavior disorders, those receiving placebo after 12 weeks of treatment underwent an average decrease of 0.2 kg ($SD = 2.2$ kg) over 6-months compared to an average of 3.2 kg ($SD = 2.49$ kg) gained during the treatment period (32). Upadhyay et al. (30) performed the most robust study to date, which showed only a fraction of weight gained during AP treatment is lost (average of +7.85 kg during treatment and –3.39 kg after 12-months discontinuation). This study limited its analysis to individuals who experienced any weight gain after AP treatment for a bipolar diagnosis before the age of 18 ($n = 146$). To date, it is unclear the extent to which pediatric AIWG is reversible. It is essential that future studies investigate the persistence of long-term metabolic outcomes in the context of AP discontinuation.

MECHANISMS UNDERLYING ANTIPSYCHOTIC-RELATED METABOLIC SYNDROME AND AIWG

Multiple mechanisms have been hypothesized to influence pediatric AIWG and metabolic effects of APs. It is likely that AEs are due to a combination of these mechanisms including AP influence on neurohormone receptor signaling and hormone mediation of APs, predisposition due to genetic risk factors, and AP effects on the gut microbiome. This review will summarize the main aspects of these mechanisms, as each has been thoroughly reviewed by other authors.

Neurotransmitter Receptor Signaling

APs bind, with various affinities, to serotonin (5-HT), dopamine, histamine, adrenergic, and muscarinic cholinergic receptors (98–102). Several extensive reviews are available on neurotransmitter signaling as a potential mechanism in AIWG (Table 1) and metabolic effects of APs (101, 102, 112).

Serotonin Signaling

Compared to FGAs, SGAs have greater affinity for 5-HT receptors than for dopamine receptors, conferring their reduced extrapyramidal side effects and superior efficacy in treating negative psychotic symptoms (2, 3) leading to preferential use in children (101, 113). Of the 5-HT receptors, SGA blockade of the serotonin 2C receptor (5-HT_{2C}R) has been the most comprehensively studied. Rat models have shown reduced mRNA expression of 5-HT_{2C}Rs in the hypothalamus, striatum, nucleus accumbens and amygdala with long-term clozapine administration (114). SGAs have shown high 5-HT receptor occupancy in neuroimaging studies (115), and there is longstanding evidence for the association of increased 5-HT levels and satiety (116). SGAs act to block 5-HT receptors including those in the hypothalamus, which play a central role in satiety signaling, and thus have been implicated as a candidate mechanism in AIWG (102, 112). Olanzapine and clozapine act as inverse agonists at the 5-HT_{2C}R (117, 118) with lower affinity than aripiprazole, a partial agonist (119), but show greater AIWG

(101). This evidence highlights the likely complex role of multiple mechanisms in AIWG.

Histamine Signaling

Three histamine receptors are expressed in the brain (H1, H2, and H3). Histaminergic neurons originating in the posterior hypothalamus project throughout the brain and the H1 receptor, specifically, has been described to have a role in feeding behavior. In a study screening FGAs and SGAs, AP binding to the H1 receptor was most strongly associated with weight gain (99). In animal studies investigating clozapine and olanzapine, weight gain is associated with H1 receptor blockade, whereas agonist such as betahistine reduced olanzapine-induced weight gain (120, 121). Further, H1 antagonism by olanzapine and clozapine is proportional to the activation of AMP-activated protein kinase (AMPK) (122, 123), which has been shown to reduce the anorexigenic effects of leptin (124). These associations should be interpreted with caution, as both clozapine and olanzapine have high affinity for multiple receptors.

Other Neurotransmitter Signaling

SGAs result in lower occupancy of dopamine D2 receptors (D2R) as compared to FGAs but still bind these receptors as antagonists (98–100, 125). AP administration results in decreased striatal D2R availability (102, 126) and it has been hypothesized that overeating compensates for reduction of D2-regulated reward circuits resulting in increased caloric intake (126–128). SGAs also act as antagonists at D4 and agonists at D1 receptors (98). Many APs have strong affinity for adrenergic receptors which have been more heavily implicated in metabolic effects of APs due to $\alpha 1$ and $\alpha 2$ receptor association with glucose control (101) and the ratio of $\alpha 2$ to $\beta 3$ in adipocyte hyperplasia (129, 130). SGAs have high affinity for cholinergic muscarinic receptors and blockade of M3 has been proposed to disrupt insulin homeostasis (131), but there is lack of data for a role in AIWG. Of the early hypotheses related to AP effects on neurohormone signaling based on genetic candidate gene data, none of the genetic associations with AIWG have been strengthened by concurrent evidence from unbiased genome studies.

Neuroendocrine Signaling

Metabolic effects associated with APs could result from direct changes to neuroendocrine signaling or occur secondary to weight gain. AP effects on adiponectin, ghrelin, insulin, and leptin (Figure 2) have been examined as potential mediators of AP-related changes in energy homeostasis (132). These signaling molecules impact various levels of energy balance including appetite and feeding, energy expenditure and metabolic rate. Insulin and leptin modulate expression of neuropeptides in the hypothalamus, which regulate feeding behavior and are considered the most important agents in regulating weight gain and energy homeostasis (133).

Leptin Signaling

A review published by Endomba et al. (134) provides an excellent overview of the potential influence of APs on leptin metabolism. In brief, leptin acts on neurons of the lateral arcuate

TABLE 1 | Second generation antipsychotic neurotransmitter receptor binding profiles.

Receptor	Second generation antipsychotic								
	ZPD	LRD	APZ	ASN	RSP	PPD	QTP	CLZ	OLZ
5-HT _{1A}	+++	+++	+++	+++	+	+	++	+	-
5-HT _{1B}	+++		+	+++	++	++		+	+
5-HT _{2A}	++++	+++	++	++++	++++	++++	++	++	+++
5-HT_{2C}	++++	+	++	++++	++	++	+	++	++
5-HT ₆	++		+	++++	-	-	+	++	+++
D1	+	+		+++	+	+	+	+	++
D2	+++	+++	+++	+++	+++	+++	+	+	++
D3	+++		+++	++++	+++	+++	+	+	++
D4	++		+	+++	+++	+++		++	++
M1							+	+++	++
M3	-	-	-		-	-	+	++	++
H1	++	-	++	+++	+++	++	+++	+++	+++
H2				+++	+	+		+	++
H3									+
α1	++	++	++	+++	+++	+++	++	+++	++
α2A	+	++	++	+++	++	+++	+	++	+
α2B	++		++	++++	++	+++	+	++	++
α2C	++	+++	++	+++	+++	+++	++	++	++

Antipsychotic-Induced Weight gain

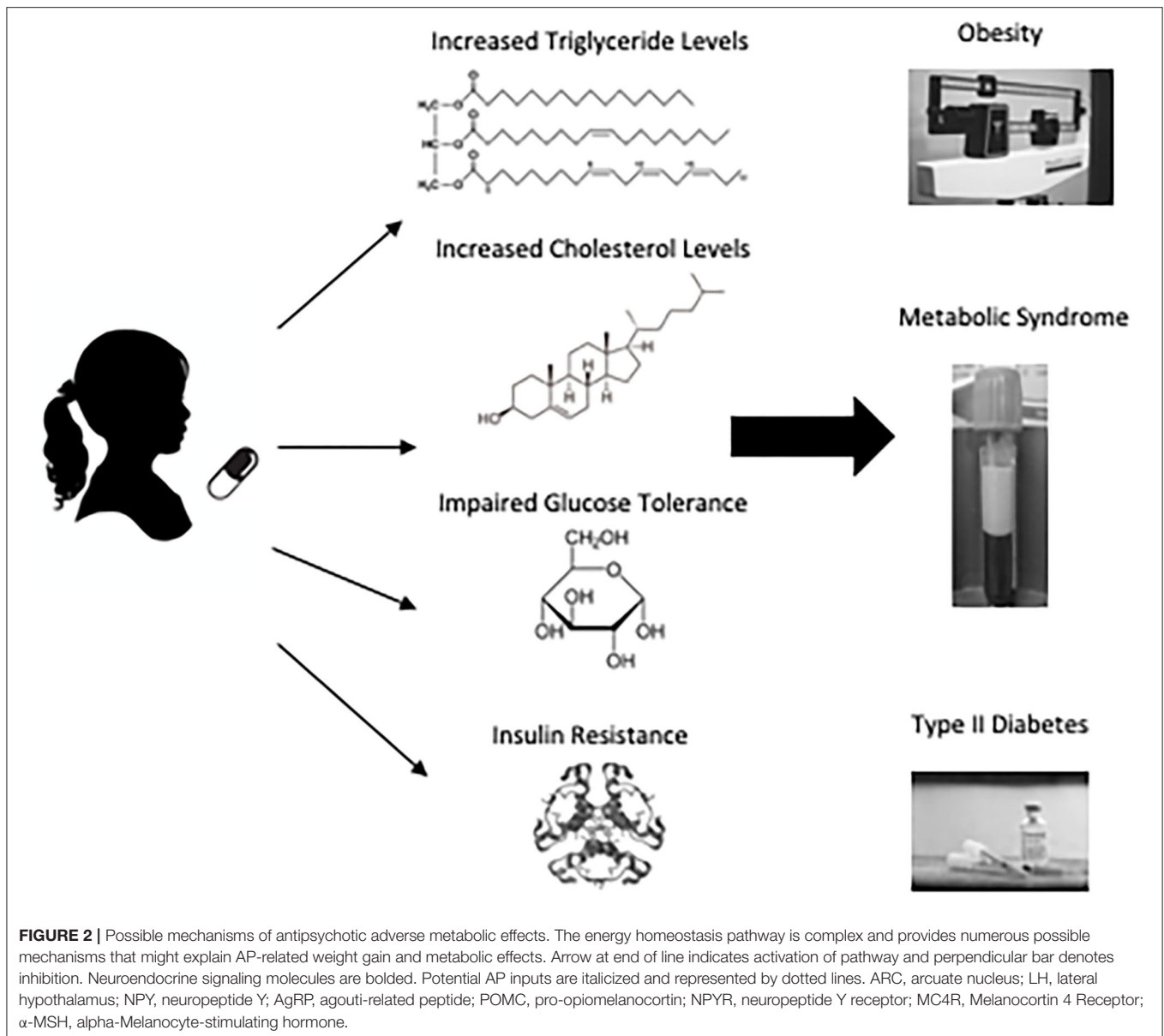
Inhibition constants (K_i) indicated as follows: +++++ (1 > K_i), +++ (1 < K_i < 10), ++ (10 < K_i < 100), + (100 < K_i < 1,000), -(1,000 < K_i), gray box indicates lack of data; data derived from (98–100, 103–111). Second Generation Antipsychotics are listed from left-to-right in order of increasing antipsychotic-induced weight gain; data derived from (78). This table does not provide an exhaustive receptor profile but focusses on receptors hypothesized to relate to metabolic effects. Those with the most evidence are bolded. ZPD, ziprasidone; LRD, lurasidone; APZ, aripiprazole; ASN, asenapine; RSP, risperidone; PDD, paliperidone; QTP, quetiapine; CLZ, clozapine; OLZ, olanzapine.

nucleus within the hypothalamus inhibiting the expression of neuropeptide Y (NPY) and agouti-related peptide (AgRP) and stimulating proopiomelanocortin (POMC) (135–137). POMC is modified to α-melanocyte-stimulating hormone, which can then stimulate melanocortin receptor 3 (MC3R) and 4 (MC4R), suppressing food intake (137). Mouse models have shown that structural MC4R alterations and decreased MC3R expression are associated with leptin resistance and obesity (137, 138). In addition to NPY and AgRP, leptin also acts to inhibit neurons in the ventromedial arcuate nucleus that express gamma-amino butyric acid (GABA), which induce feeding (139). Thereby, reduced leptin signaling can lead to obesity by the loss of pro-satiety signals or the lack of feeding inhibition (135). Yet, the overall effects of APs on leptin remain unclear despite extensive investigation. For example, increased leptin levels have been associated with SGA treatment in patients with schizophrenia (140). It has been proposed that leptin metabolism can be affected by AP treatment independent of AIWG (141–146), or conversely, only secondary to AIWG rather than by direct effects (147–152).

Insulin Signaling

APs have been shown to increase insulin resistance (40). Insulin is produced in the pancreas by beta cells and binds to receptors in the arcuate nucleus aiding in energy homeostasis. Insulin resistance occurs when the activity of insulin is blunted in liver, muscle and adipose tissue and is linked to intra-abdominal fat

(153). Childhood-onset insulin resistance increases risk for type 2 diabetes and cardiovascular disease (154, 155). AP actions on histamine and muscarinic receptors have been shown to reduce acetylcholine-induced insulin secretion (156, 157) and result in the failure of leptin signaling (158), which may contribute to insulin resistance. More recently, the hypothalamus has been shown to have a high concentration of insulin receptor expression and insulin concentration *in vitro* (159). In post-mortem studies receptor expression has been revealed to be greatest in the cerebellum and hypothalamus (160). Insulin has been shown to play an anorexigenic role in the brain and brain imaging studies have revealed a reduced neural response in patients with obesity upon exogenous insulin administration (160, 161). Insulin produced by the pancreas enters the brain via the bloodstream through an insulin-receptor mediated pathway initiating the phosphoinositide 3-kinase pathway that plays a crucial role in controlling metabolism (160). Additionally, insulin is involved in the stimulation of leptin secretion (162), and reciprocally, leptin plays a role in the regulation of circulating insulin (153). Human imaging studies have revealed that central insulin modulates the activity of mesocorticolimbic dopaminergic circuitry (163–165). In psychiatric patients, the development of type 2 diabetes and adverse metabolic effects may be facilitated by insulin resistance in the brain (166). **Figure 2** depicts aspects of insulin's role in the CNS. For a more comprehensive review of the role insulin plays in the



central nervous system as it relates to metabolism see Kullmann et al. (160).

Other Neurohormone Signaling

Adiponectin is secreted by adipose tissue and increases fatty acid oxidation and glucose uptake in muscle thereby contributing to weight regulation (167). Decreased adiponectin serum levels have been associated with insulin resistance, dyslipidemia, obesity and type 2 diabetes (168, 169). Meta-analysis found that SGA-treatment in patients with schizophrenia was associated with decreased levels of adiponectin (170). Ghrelin is a peptide hormone secreted in the stomach that has orexigenic effects by increasing food intake and fat deposits. Insulin has been evidenced to decrease ghrelin levels (171). Paradoxically, meta-analysis has provided some evidence that

olanzapine-associated weight gain is associated with reduced ghrelin levels but associations with increased ghrelin in the context of SGA treatment has been reported as well (172–174). The circadian and immune regulator, melatonin, also plays a role in energy metabolism (175). Increased weight and visceral adiposity in olanzapine-treated rats is inversely proportional to nocturnal circulating melatonin (176) and daily melatonin supplementation ameliorates this effect (176, 177). More longitudinal studies with greater sample size are necessary to determine the relationship of AP treatment and these neurohormones.

Genetic Predisposition

Genetic risk factors likely play an important role in the extent to which an individual experiences AIWG. In a study of

monozygotic twins and siblings receiving SGAs, the influence of genetic factors on AIWG was reported to be between 60 and 80% (178). Candidate gene studies have focused on neurotransmitter receptors including 5-HT_{2C}R (*HTR2C*) (142, 148, 179–183), D2R (*DRD2*) (184–188), α 2-adrenergic receptor (*ADRA2A*) (189–193) and cannabinoid 1 receptor (*CNR1*) (194–197); energy balance regulators including *MC4R* (198–201), leptin (*LEP*) (145, 202–205) and transcription factor *SREBP* (206–209); and growth and synaptic genes like brain-derived neurotrophic factor (*BDNF*) (210–215) and synaptosomal associated protein *SNAP25* (216). For a comprehensive review of the candidate gene studies associated with AIWG and metabolic effects of APs see Li et al. (217).

Candidate gene studies have exploratory value but are weakened as they are based on functional hypotheses with inherent bias (218–220). The genetics field has agreed that candidate gene studies should be interpreted with extreme caution (221). Large unbiased genome-wide studies, such as genome wide association studies (GWAS), are thus necessary to reveal replicable genetic risk factors for complex phenotypes. The common variation model postulates that susceptibility to complex disease is driven by a combination of common alleles that each carry a small disease risk, such as can be revealed in large-scale GWAS analyses. For example, genetic risk for AIWG at *MC4R* was first identified in the only GWAS study of weight gain in pediatric patients (age \leq 19, $n = 139$) taking quetiapine, risperidone, olanzapine, or aripiprazole for any diagnosis (222). This GWAS study revealed a single nucleotide polymorphism (SNP) at locus rs489693 located downstream from the *MC4R* gene. Independent studies investigating SNPs near *MC4R* subsequently replicated this finding (198–201). *MC4R* plays a central role in energy balance. As described above, leptin stimulates hypothalamic POMC neurons, resulting in the production of α -MSH, which in turn stimulates anorexigenic effects by binding *MC4R* and inhibiting AgRP, an *MC4R* antagonist (102). 5-HT_{2C}R has upstream inputs to this pathway (223), and *BDNF* has been suggested to have effects downstream of *MC4R*, as its infusion in *MC4R*-deficient mouse models reduces food intake (224).

Several GWAS of AIWG have been performed in adult samples receiving APs to treat schizophrenia. Two studies utilized data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (225), both failing to detect genome-wide significant signals. The first also reported trends in SNPs upstream of opioid growth factor receptor *OGFRL1* (226), and the second highlighted enrichment of nominally associated SNPs in energy balance pathway genes by hypothesis-driven pathway enrichment analysis (227). A SNP (rs10977144) located in the protein tyrosine phosphatase, receptor type D gene (*PTPRD*) (228) was associated with AIWG in a GWAS of Chinese patients with schizophrenia ($n = 524$, mean age = 26.4). *PTPRD* deficient mice were shown to have insufficient weight gain postnatally due to feeding difficulties, arguing for a role in energy balance (229). A replication GWAS of European and African ancestry ($n = 201$, mean age = 37) treated primarily with clozapine or olanzapine did not confirm the lead SNP, which may be explained by unmatched ancestry,

but notably did detect nominal significance at other SNPs within the *PTPRD* gene (230). This same GWAS found only marginal association ($p < 0.05$) at a SNP located near the *MC4R* gene. In an additional study of this cohort, a SNP (rs1525085) in the lipid biosynthesis gene, diacylglycerol kinase beta (*DGKB*), was found to be significantly associated with AIWG (231). The study notes that *DGKB* variants have been associated with insulin clearance (232) and, by interaction with insulin secretion, increased risk for type 2 diabetes (233). When limiting analyses to the European subset, a SNP (rs62097526) downstream of *CIDEA*, a regulator of lipolysis and thermogenesis in mice, was nominally associated with AIWG (231). *CIDEA* variants have also been shown to associate with metabolic syndrome in Swedish, Japanese and Chinese population cohorts as well as obesity risk in a Han-Chinese cohort (234, 235). The most recent GWAS (236) examining AIWG analyzed 339 subjects (Age Range = 15–45, mean age = 26.4) with first-episode psychosis derived from The Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE) (237) cohort. This study identified the intergenic SNP rs78310016 near *SEPP1*, a hepatic protein involved in selenium transport, and growth hormone receptor (GHR) that was significantly associated with AIWG but not replicated in follow-up analyses. Providing face validity to this finding, *SEPP1* and GHR have been implicated in metabolic phenotypes (238–243). Another possible functional link was identified by *in silico* analysis, which predicted a chromatin interaction of the lead SNP with the HMG-CoA synthase 1 gene (*HMGCS1*). *HMGCS1* is highly expressed in the brain and liver and involved in the regulation of cholesterol biosynthesis (244).

Overall, while candidate gene studies may provide mechanistic clues in pediatric AIWG and metabolic effects of APs, large GWAS studies are required to definitively identify risk genes. Currently, a few GWAS samples exist but are underpowered and difficult to harmonize given different ages and ancestries. Moreover, only one study examined pediatric participants (222). Existing studies are derived almost entirely from treatment studies of schizophrenia, which due to time and expense are generally limited to hundreds of patients. Sample sizes consisting of thousands of patients will be necessary to comprehensively capture genetic contributions of common variants to AIWG. Data from electronic medical records, national registries, and commercial genetic profile industries may represent fruitful avenues for future study.

The Microbiome

SGAs have been associated with perturbations of the gut microflora that may contribute to weight gain (245–248). The mechanism underlying alterations in the microbiome during SGA treatment and the link between these changes and weight gain are only beginning to be explored.

Several distinct observations have emerged from recent work including evidence that microbiome changes are necessary for AIWG rather than the reverse. AP administration in rodents and humans (249–252) results in an increase in the ratio of *Firmicutes* to *Bacteroidetes* (F:B), two common bacterial phyla. This observation parallels findings in obesity; however, systematic reviews in pediatric (253) and adult (254) populations identify

inconsistencies. Preclinical studies have demonstrated that gut bacteria are necessary for AIWG (245, 249–251). In fact, AIWG is absent in germ-free mice but can be induced by microbiome transplant (251). Similar F:B changes, increased adiposity, and inflammation were reported in olanzapine-treated rats (249). In a follow-up study, these effects could be prevented by co-administration of an antibiotic cocktail that effectively sterilized the gut (250). Similarly, mice receiving risperidone developed AIWG, an effect that was mediated by decreased energy expenditure and transferrable by fecal transplant (245). Small studies investigating risperidone treated children substantiated these preclinical findings. Risperidone treated children ($n = 18$, age range = 9–15, mean age = 12.2) were observed, cross-sectionally, to have an elevated F:B ratio and a host of differences in the metabolic potential of the gut microbiota (252). In an independent longitudinal study published in the same report, children ($n = 5$, age range = 9–13, mean age = 11.7) were enrolled within days (mean = 3.2, $SD = 5.2$) of starting risperidone (252). Within 1–3 months of risperidone initiation, the F:B ratio had begun to increase, appearing to plateau by about 5–6 months. Importantly, the F:B ratio was positively correlated with the magnitude of AIWG. An overall increase in putative “obese gut microbiota” was seen for these adolescents, and interestingly an enrichment in microbiota genes related to serotonin signaling and short chain fatty acid metabolism was reported.

Additional microbiota alterations associated with AP treatment include changes in *Actinobacteria*, although both increases (245, 255) and decreases (249) in the phylum has been reported. Risperidone-treated mice display increased abundance of the *Erysipelotrichaceae* (256) family and *Mollicutes* (257) class but decreases in *Alistipes* and *Akkermansia* species, which are considered lean gut microbiota (258, 259). Reduced diversity and stability of the microbiome of children compared to adults could explain the increased sensitivity to AIWG seen in youth (65, 260, 261). Lower microbiota species diversity is associated with obesity (255) dysbiosis in youth may mediate subsequent adult obesity (65). Childhood microbiota composition has also been shown to be instrumental for brain and immune system development and function (262). Therefore, given their lower baseline microbiota population diversity, long-term disturbance of brain and immune system development as a result of SGA-associated with changes in gut microbiota should be examined. Lastly, a study that investigated 117 adult patients with bipolar disorder ($n = 49$ treated with an AP, $n = 68$ non-treated) a greater AP-related reduction in bacterial diversity was seen in females vs. males treated with an AP (263), suggesting that sex differences must also be considered.

PHARMACOLOGICAL AND LIFESTYLE INTERVENTIONS TO ADDRESS METABOLIC AEs OF APs

Current strategies to prevent or treat AIWG and the metabolic effects associated with AP use are inadequate. Unfortunately, the two most effective SGAs on the market, clozapine and

olanzapine, also have the highest reported AIWG (78). Clinicians should understand and weigh the benefits and risks of SGA treatment for each individual patient. In some situations, it may be possible to avoid APs if behavioral strategies or medications with less AEs are implemented. Nevertheless, in children with acute psychosis or mania, there are often few other appropriate options. In cases where benefit outweighs risk, it is crucial to warn patients and families about AIWG and metabolic effects and useful to discuss strategies to reduce harm. The most conservative approaches to metabolic side effects, which can also be safely employed for prevention, are non-pharmacologic interventions, which include lifestyle modification and dietary supplementation, including pre- and probiotic supplements. When these approaches are insufficient, switch to an AP with less propensity for weight gain may be warranted or adjunctive medications may be added to manage weight gain. The most effective pharmacologic interventions, however, will likely be supported by a healthy lifestyle.

Non-pharmacological Treatments

There is a paucity of data examining lifestyle interventions for AIWG in children (264). A 52-week study found that standard ($n = 102$) or intense behavioral weight interventions ($n = 103$) did not reduce AEs of APs for adolescents (age range = 13–17, mean age = 15.8) with schizophrenia or bipolar I disorder receiving olanzapine (265). A 16-week intensive weekly family-based behavioral weight loss intervention in AP-treated youth ($n = 19$, mean age = 13.35), compared to treatment as usual, resulted in decreased adiposity ($p = 0.01$) and hepatic fat ($p = 0.04$) that could support beneficial impacts on AIWG with long-term behavioral intervention (266). There is a need for large-scale pediatric studies to determine the most effective lifestyle interventions for weight gain and metabolic symptoms. As childhood obesity continues to present a major health challenge, a robust research literature exists on effective lifestyle interventions for obese youth. A comprehensive review of such integrative approaches was recently published (267) describing potential dietary, physical activity, sleep, and stress management interventions. Nutritional supplements with data in pediatric obesity, though not yet tested in the context of AP treatment, are also reviewed. The interventions with the best support in reducing childhood obesity and subsequent metabolic symptoms include an increased level of physical activity, improved sleep, and a diet consisting of fruits, vegetables, whole grains, and fish oil supplementation (267). Generalizing from healthy populations must be done with caution, however, as psychiatric diagnoses and psychosocial stressors may result in poorer outcomes of lifestyle interventions. Future development of lifestyle programs targeting AIWG should be designed for and tested in relevant psychiatric populations. Mixed data supports the effectiveness of lifestyle interventions in adults receiving AP treatment. A recent meta-analysis, however, reported a significant reduction in body weight after exercise initiation with a large effect size ($SMD = -0.96$), concluding that lifestyle interventions remain the most effective method to improve physical health outcomes in patients with schizophrenia (268). Compared to adults, pediatric patients present some unique

challenges and advantages. Youth may not cognitively appreciate risk, may be less self-motivated to comply with prevention measures, and may be resistant to lifestyle interventions. On the other hand, caregivers are in a position to exercise considerable influence over diet, nutrition, and lifestyle factors.

As SGAs may directly affect gut microbiota populations (245, 249–252, 269, 270) probiotics, prebiotics, and fecal transplants have been proposed as potential therapies to reduce adverse AP effects. Prebiotics have been shown to promote the growth of beneficial microbiota in humans resulting in suppressed appetite in youth ($n = 42$, age range = 7–12) (271), and probiotics are associated with improved gastrointestinal function in patients with schizophrenia (272, 273). While a promising and novel strategy, further research efforts are necessary to explore specific gut microflora that could alleviate AP side effects. Animal models have aided in this effort. Probiotics were able to reverse weight gain and metabolic dysfunction resulting from olanzapine treatment in mice (247). The prebiotic B-GOS prevented weight gain in rats (274), and a prebiotic mixture reduced weight gain and decreased the putative obesogenic F:B ratio in mice (246). Fecal transplants from mice treated with risperidone have also been shown to reduce basal metabolic rate and increase weight gain in control mice (245). Nevertheless, to develop effective and safe interventions, preclinical studies and clinical trials in human subjects will be crucial. An exploratory study comparing children ($n = 30$, age range = 4–17) with extreme risperidone-induced weight gain vs. those without AIWG uncovered bile acid changes resulting from AP treatment and distinct bile acid profiles in subjects with vs. without weight gain (275, 276). Preliminary evidence suggests a potential link between bile acid changes and the gut microbiota. Interestingly, a similar mechanism was suggested by studies of metformin effects in diabetes (277).

Pharmacological Treatments

Metformin, the most commonly used adjunctive medication targeting AIWG, is supported by the strongest evidence, but several other strategies have shown promise including glucagon-like peptide 1 receptor and histamine 1 receptor agonists. Unfortunately, most studies have been small and follow-up periods rarely exceed 6 months. Medications used to treat obesity in the general population have also been tried, and represent reasonable options, but these are often limited by intolerability of unpleasant side effects in psychiatric populations (278). In youth with metabolic abnormalities, insulin resistance, hyperglycemia and dyslipidemia, these medical sequelae are typically managed by a pediatrician or endocrinologist. Studies have shown benefits of standard treatments, such as metformin and statins, in adults with antipsychotic related metabolic syndrome (279).

Metformin

Metformin, an anti-diabetic, has been studied extensively as a potential alleviator of AIWG and metabolic effects. Metformin has been shown to reduce metabolic effects in patients with schizophrenia spectrum disorders by decreasing hepatic gluconeogenesis, insulin resistance (i.e., improving insulin sensitivity) and total cholesterol (264, 268). Regulation

of leptin sensitivity and hypothalamic signaling are also affected by metformin (280). Therefore, metformin may play a role in reducing caloric intake and fat storage (280). A 2014 meta-analysis of 40 studies on pharmacological interventions to combat adverse AP effects concluded that metformin should be the first choice for pharmacological treatment if non-pharmacological interventions have failed and switching to an AP with reduced potential for AIWG is not feasible (281). This meta-analysis was not focused on pediatric populations, but there have been several studies that have examined metformin adjunctive treatment in youth. In the Improving Parameters in Antipsychotic Child Treatment (IMPACT) trial of AIWG interventions, overweight youth ($n = 127$, age range = 8–19, mean age = 13.7) with a primary diagnosis of bipolar spectrum disorder, schizophrenia spectrum disorder, or psychotic depression were randomized to metformin treatment; AP switch to aripiprazole, perphenazine, or molindone; or continued current AP treatment (264). Both the metformin (moderate to large effect size 0.68) and AP switch (large effect size 0.81) group had significant reductions in BMI z-scores compared to the continued treatment control. More gastrointestinal complaints, however, were reported in the metformin group than the AP switch and control groups. Several additional studies support the benefit of metformin for pediatric SGA treatment. A randomized controlled trial ($n = 61$, age range = 6–17, mean age = 12.8) reported that metformin attenuated weight gain but did not affect metabolic measures (282), though given that no metabolic abnormalities were observed in either group, this is not surprising. Two small open label metformin trials reported weight loss in 5 out of 11 (age range = 10–18, mean age = 14) (283) and 15 out of 19 (age range = 10–18, mean age = 14.1) (284) patients. An open-label extension of one of the trials (282) found that this effect on anthropometric measures but not metabolic measures persists over long-term treatment, although they did note a non-significant decrease in hemoglobin A1c in both trial phases (285). One Iranian study failed to demonstrate a significant impact of metformin on AIWG prevention over a 12-week treatment period but did note significant effects over the first 4-weeks of treatment and a positive trend at 12 weeks ($n = 49$, mean age = 10.1) (286). Authors acknowledge that lower doses of metformin were used compared to other studies, which may explain conflicting results. Metformin may be more effective in first-episode psychosis patients in comparison to those receiving chronic treatment (287). Some have proposed that timing is critical and early use of metformin may improve outcomes through prevention rather than correction of weight gain (288). Lessons learned from metformin's modest efficacy may spur the testing and development of new approaches in the future.

Glucagon-Like Peptide 1 Receptor Agonists (GLP1RA)

GLP1RAs, another medication class borrowed from diabetes treatment and associated with weight loss, have been examined as potential adjuncts to reduce AIWG and metabolic dysfunction (289). This approach is supported by evidence that serum GLP1

increases with SGA treatment (290) and is associated with both hyperglycemia as well as insulin resistance (291). A meta-analysis of 3 trials of adults receiving adjunctive GLP1RA along with an AP demonstrated reduced HbA1c, fasting blood glucose and BMI (292). This meta-analysis only consisted of 164 patients, underscoring the need for larger trials. Pediatric trials of efficacy in AIWG are lacking but warranted given promising effects of GL1RA treatment in adolescents with severe obesity (293). Until recently, GLP1RAs have been limited by a subcutaneous formulation, but the 2019 approval of an oral agent, semaglutide, could drive an expanded role for this medication class in the future.

Betahistine

Betahistine, an agonist of the H1 histamine receptor has been shown to reduce or attenuate olanzapine-induced AIWG in adults (121, 294, 295), as discussed previously. Many APs are antagonists at the H1 receptor, especially those with high propensity to cause AIWG. To our knowledge, only one study (296) has included pediatric patients ($n = 12$ of 51 total patients, age range 12-17). In this sample, betahistine tempered weight gain in participants receiving the strongly antihistaminergic APs olanzapine and clozapine, but not for those taking other APs with lower H1 potency. The study found no moderating effect of age (i.e., adolescent vs. adult) but did not analyze the adolescent population separately. Mechanistic queries of protective effects against AIWG conferred by potent H1 antagonists have been explored in several animal models (294, 297–302). The exact mechanism underlying beneficial effects is unclear, however, since adjunctive treatment with betahistine attenuates H1-NPY, H1-AMPK, and H1-POMC signaling and increases H3-mediated release of histamine. Further, in a rat model, betahistine was shown to reverse the upregulated dopamine D2R expression that typically results from olanzapine treatment, while not interfering with AP effects at serotonergic receptors in brain regions associated with AP efficacy (302). Thus, betahistine may reduce the increased D2 sensitivity associated with AP treatment but its potential interference with AP efficacy requires thorough investigation.

Other drugs that have been tested to reduce AIWG, largely in adults, include reboxantine, topiramate, and amantadine. When combined with betahistine, reboxantine, a norepinephrine reuptake inhibitor was shown to be effective in attenuating olanzapine-induced weight gain (294) and appetite (24) in adults. A meta-analysis of 10 studies of adjunctive topiramate (an antiepileptic drug known to reduce appetite) for AIWG, found topiramate mitigated weight gain in AP-treated adults (303). In a medical record review, there was an overall reduction in BMI for 47 child and adolescent psychiatric patients (mean age = 13.4) receiving topiramate and another anticonvulsant, zonisamide (304). Future efforts are needed to investigate these anticonvulsant adjunctive treatments to combat AIWG in pediatric patients.

The “natural,” over-the-counter supplement with the best evidence to mitigate AIWG and metabolic effects is melatonin. As discussed previously, melatonin plays a key role in energy homeostasis as well as central and peripheral insulin action (305).

Reduction in melatonin production has been associated with insulin resistance, glucose intolerance, and metabolic disease (305). A recent meta-analysis of both adult and adolescent studies supported clinical use of melatonin and melatonin receptor agonists as adjuncts to mitigate AIWG and metabolic effects (175). In adolescents ($n = 38$) diagnosed with bipolar disorder receiving olanzapine and lithium combination therapy, melatonin as compared to placebo attenuated increases in cholesterol level and systolic blood pressure (306). In a smaller cohort ($n = 19$, mean age ~ 14), although not reaching significance, melatonin as compared to placebo reduced weight gain in the context of olanzapine and lithium combination therapy (307). Because of its role in the regulation of circadian rhythms (308), it is possible that positive metabolic effects may be secondary to beneficial effects on sleep, which has been shown to play a role in obesity (309). Interestingly, co-administration of melatonin appears more effective with risperidone and quetiapine, agents with intermediate risk of AIWG, compared to olanzapine and clozapine, agents with the highest risk (175). If confirmed in larger studies, melatonin represents a relatively benign pharmacological intervention for youth.

CLINICAL GUIDELINES FOR THE ASSESSMENT, PREVENTION, AND TREATMENT OF METABOLIC ADVERSE EFFECTS OF ANTIPSYCHOTIC MEDICATIONS IN YOUTH

Clinical practice guidelines are published by various groups, organizations, and experts. We present an overview of those guidelines most relevant to pediatric psychiatry, the AACAP Practice Parameters for Schizophrenia (7) and Aggression (14), supplemented with additional recommendations from the American Psychiatric Association (70, 82) and other adult sources (86, 278). The AACAP guidelines emphasize a comprehensive baseline assessment and treatment plan (Figure 3A) followed by responsible regular monitoring and follow-up (Figure 3B).

If initial psychiatric evaluation prompts the consideration of AP therapy, further baseline assessment should include expanded history (personal and family history of diabetes, hyperlipidemia, or previous response or adverse events associated with APs), physical exam (vital signs including blood pressure and heart rate, weight and BMI with determination of pediatric growth chart percentiles, and waist circumferences) and baseline laboratory measurements (fasting lipids, glucose and hemoglobin A1C).

The risks, benefits and alternatives of an AP should be assessed, weighed, and discussed (and informed consent obtained) with the guardian(s) and child/adolescent if possible. Even if an AP is a first-line treatment for the patient's diagnosis, behavioral treatments, psychosocial interventions, and medication alternatives should be considered. Behavioral and psychosocial approaches can improve outcomes and potentially reduce AP burden. Expected duration of therapy may also influence treatment planning, as it may be possible to minimize

A

Decision Support for The Use of Antipsychotics in Youth: INITIAL ASSESSMENT & PLAN

ASSESSMENT

- Conduct psychiatric diagnostic evaluation

Decision Support: Is an AP first-line for the diagnosis?

1. Does the evidence-base strongly support APs as a first-line treatment for the diagnosis?
2. Consider alternative options with less AE potential and weigh risks and benefits:
 - Mania: mood stabilizers, family focused therapy
 - Autism: behavioral treatments, parent-training, stimulants, α 2-agonists, mood stabilizers, SSRIs, others
 - Aggression: behavioral treatments, parent-training, stimulants, α 2-agonists, mood stabilizers, SSRIs, others
 - Tourette: habit reversal therapy, alpha-2 agonists, others

- Conduct expanded baseline health screening if AP will be considered

History	Exam	Labs
<ul style="list-style-type: none"> • Personal history of metabolic dysfunction 	<ul style="list-style-type: none"> • Weight & BMI -> Growth Chart Percentiles 	<ul style="list-style-type: none"> • Fasting glucose & hemoglobin A1C
<ul style="list-style-type: none"> • Family history of metabolic dysfunction 	<ul style="list-style-type: none"> • Waist circumference 	<ul style="list-style-type: none"> • Fasting lipids
<ul style="list-style-type: none"> • Assess other modifiable risk factors (nutrition, exercise, habits) 	<ul style="list-style-type: none"> • Vital signs: Blood pressure & heart rate 	
	<ul style="list-style-type: none"> • Physical exam by pediatrician 	

- Weigh risks versus benefits of AP treatment

Decision Support: Do the benefits of an AP outweigh the risks?

1. Does the child have a high risk for weight gain and metabolic AEs based on personal/family history and baseline exam/labs?
2. Are there viable non-AP alternatives for the diagnosis and specific patient factors?
3. Could APs be used for short-term stabilization with a plan to switch to a safer alternative once stable?
4. Do the patient’s psychosocial situation and level of functioning support the ability to adhere to lifestyle preventive measures?
5. Could an AP with lower propensity for weight gain be prioritized?

TREATMENT PLAN

- Discuss options with patient/guardian(s) explaining health risks of AP therapy
- Incorporate patient/guardian(s) preferences in treatment decision and obtain informed consent from guardian(s) & ideally child as well
- Prescribe best-evidence AP considering decision support factors above and patient/guardian preference
- Implement preventive measures (healthy lifestyle education and program referrals)
- “Start low & go slow” approach to titration to minimize risk
- Add psychosocial interventions/support and complementary psychotherapy/behavioral approaches to minimize AP use
- Minimize polypharmacy
- Implement regular monitoring plan and follow-up

FIGURE 3 | Continued

B

**Decision Support for The Use of Antipsychotics in Youth:
FOLLOW-UP ASSESSMENT & PLAN**

ASSESSMENT

- Review monitoring metrics

3 Month Follow-up	Quarterly	Annually
Weight & BMI -> Growth Chart Percentiles	Weight & BMI -> Growth Chart Percentiles	Physical exam by pediatrician
Assess lifestyle factors & review preventive plan	Patient/caregiver report of AEs	Consider healthy lifestyle program booster
Exam • Waist circumference • Blood pressure & heart rate	Assess lifestyle & other risk factors	Exam • Waist circumference • Blood pressure & heart rate
Labs • Fasting glucose & hemoglobin A1C • Fasting lipids	Review & troubleshoot preventive plan	Labs • Fasting glucose & hemoglobin A1C • Fasting lipids

- Significant weight gain? (AACAP definition: weight gain exceeding 90th percentile BMI for age or a change of five BMI units in previously obese youth)

Decision Support: Management of AIWG and/or metabolic dysfunction	
Consider	Possible Action
Has the AP been effective for psychiatric symptoms?	Consider alternative treatments
Are there non-AP alternative treatments?	Weigh risks & benefits of switch to a different medication class or psychosocial treatment
Has the preventive plan been followed & what are barriers?	Interventions to enhance effectiveness of non-pharmacologic strategies
Are APs with less potential for AIWG an option?	Weigh risks & benefits of switch to an alternative AP
Is the addition of an adjunctive medication targeting weight gain warranted?	Consider addition of metformin or other evidence-based options as appropriate

- Assess need for continued treatment

Decision Support: Appropriate Treatment Duration
1. Is the diagnosis potentially time-limited (aggression, substance-induced, tics, psychotic depression, acute mania that could be managed with a mood stabilizer in the long-term)? Consider options with less risk.
2. Have the psychosocial factors or comorbidities improved allowing for more conservative medication management? Consider treatment options with less risk.
3. Has the patient been psychiatrically stable for a year or more? Consider careful AP taper if appropriate.

TREATMENT PLAN

- Incorporate patient/guardian(s) preferences in treatment decision and obtain informed consent from guardian(s) & ideally child as well
- Continue regular monitoring plan and follow-up

FIGURE 3 | (A,B) Clinical guideline and decision support for the assessment, prevention, and treatment of metabolic adverse effects of antipsychotic medications in youth. Adapted from the American Academy of Child and Adolescent Psychiatry (7) and American Psychiatric Association and American Diabetes Association Guidelines (70). **(A)** Initial Assessment and Plan. **(B)** Follow-up Assessment and Plan.

long-term AP use by switching to a safer medication or non-pharmacological treatment once an acute crisis has passed. If it is determined that benefits of an antipsychotic outweigh risks, the use of an AP with lower AIWG potential may be appropriate depending on diagnostic and patient-specific factors.

Once an AP is selected, a standard “start low and go slow” approach should be implemented. The administration of multiple concomitant psychotropic medications should be minimized, especially avoiding the concurrent use of multiple APs. Education and counseling on healthy lifestyle choices as preventive measures against weight gain and metabolic effects should be provided. Formal referral to a dietician or healthy lifestyle program may be warranted in higher risk or already overweight patients. An AACAP Facts for Families Sheet on “Weight Gain from Medication: Prevention and Management” is available on the AACAP website at https://www.aacap.org/AACAP/Families_and_Youth/Facts_for_Families/FFF-Guide/Preventing-and-Managing-Medication-Related-Weight-094.aspx.

Given the high risk of AIWG in youth taking APs, frequent monitoring of AEs must occur. Monitoring for AIWG in psychiatric patients using self-reported awareness is less effective than objective measurement (310). AACAP advises following the joint consensus recommendations of the American Diabetes Association and the American Psychiatric Association (**Figure 3B**) to monitor BMI quarterly and blood pressure, fasting blood glucose and fasting lipid profiles at 3 months and then annually thereafter (70). Since BMI distribution varies over typical development, BMI should be normed with respect to age and translated to percentiles. Developmentally normed growth charts can be found at the Center for Disease Control website (www.cdc.gov/growthcharts), and/or percentile calculators can be found online or in mobile app form. Despite strong guidelines, a 2016 review estimates that 70% of patients taking APs in the US fail to be screened or treated for metabolic AEs (311). The continued need for AP treatment should be regularly evaluated, as the appropriateness of long-term use will vary based on the severity of symptoms, psychosocial environment, availability of safer evidence-based options, and the natural course of the illness being treated.

Consideration of weight management interventions and increased regularity of blood glucose and lipid levels should be implemented if AIWG exceeds 90th percentile BMI for age, or a change occurs of 5 BMI units in patients already obese at baseline. Other contributors to weight gain and metabolic syndrome should be explored (312). A review and troubleshooting of lifestyle interventions may be adequate to curb weight gain, but in cases where lifestyle modification is insufficient, 2 main strategies exist for pharmacological intervention. First, a switch from an AP with higher to lower weight gain potential may be appropriate with careful attention to the risk of psychiatric relapse. The effectiveness of the current AP is an important factor. As reviewed previously, an AP switch strategy is supported by studies in both youth (264) and adults (313, 314); however, methodological problems, including high incidence of drug discontinuation and study attrition compounded by the use of per protocol data analysis, confound many of these trials

and limit their application. Prior to switching, patients/families should be informed of the potential risk of relapse. Gradual cross-taper over several weeks is recommended to minimize this risk. If a switch to a lower risk AP is not appropriate or preferred, addition of an evidence-based adjunctive medication is a reasonable option with relatively low risk. As discussed above, metformin is currently the agent with the best support; however, several promising leads and novel alternatives are being developed and tested.

CONCLUSIONS AND FUTURE DIRECTIONS

SGA prescription has become the standard of care for children and adolescents with psychotic disorders as well as a frequent therapeutic employed, both with FDA-approval and off-label, for a range of psychiatric disorders. These APs have proven to be effective to reduce psychiatric symptoms but result in AEs, chiefly AIWG and metabolic effects. Despite robust research efforts to reveal underlying mechanisms, it is unclear how to maintain AP efficacy while reducing serious side effects.

The pharmacological interventions that have been proposed and investigated to date are limited. Interventions such as anti-diabetic and anti-convulsant medications are not biologically targeted treatments but rather repurposed based on incidental observations of weight loss or metabolic improvement when these medications are used for other conditions. Thus, these serendipitous positive effects may simply balance metabolic dysfunction rather than directly correct the underlying lesion driving these AEs. Additionally, drugs targeting obesity in the general population may be relevant to AIWG. Promising drugs that warrant further testing in AIWG include 5-HT_{2C}R agonist lorcaserin (315), fat absorption blocker orlistat (316), and melanin concentrating hormone receptor 1 antagonists (317), as well as combination treatment of naltrexone and bupropion to curb craving (318). While obesity drugs are a Big Pharma priority, lack of mechanistic clarity underlying obesity and frequent prohibitive AEs have stalled progress. Future studies should take care to use high-quality study designs, including randomized controlled trials with intent-to-treat analysis, and provide effect sizes in addition to significance measures to convey the clinical utility of potential treatments.

Efforts to reduce AEs for pediatric patients undergoing SGA treatment will require mechanistic studies that illuminate a clearer, definitive conception of their biological underpinnings. Progress in neuroendocrine, genetic, and microbiome related mechanisms of AIWG lay a foundation for developing interventions to combat unwanted AEs. Manipulation of energy balance pathways in animal models can reveal potential avenues for human translation. Large-scale genomic and microbiome studies in both adult and pediatric patients can also yield links to biology. Further understanding of a healthy gut microbiome and effective manipulation strategies may expand psychotherapeutic modalities. Epigenetic changes produced by

AP exposure, exploration of which remains rudimentary, may also contribute to compounding of genetic and environmental risk. A mechanistic appreciation of metabolic AEs will not only inform interventions to reduce or prevent side effects, but ultimately drive the design of specific therapies that can target psychiatric symptoms without inflicting harm.

The ever-expanding development of new technologies has the potential to considerably advance both discovery and intervention. Computational analysis of electronic medical records and machine learning approaches will generate and test new data-driven hypotheses. Similarly, wearable devices can collect objective data, such as patterns of activity, speech, sleep and biological metrics, that will facilitate clinician monitoring and feed big data approaches. Wearable devices and mobile apps can also be used to enhance patient engagement and motivation with lifestyle interventions and improve treatment adherence.

These diverse approaches can eventually explain the large, individual variability in risk for AIWG and metabolic effects

and fuel precision medicine algorithms. The precision psychiatry model of the future seeks to incorporate demographic, genetic, epigenetic, biomarker, psychosocial, and other information to achieve a molecular diagnosis and a personalized risk assessment. This approach can match the individual patient with a data-driven treatment plan, thus boosting adherence, preventing AEs, and optimizing patient outcomes.

AUTHOR CONTRIBUTIONS

ML performed the primary literature search and prepared the first and final draft of the manuscript, figures, and table. EN defined the scope of the topic, authored the abstract, and edited the manuscript, figures, and tables.

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Conflict of Interest: EN serves on the Medical Advisory Board for the Tourette Association of America and Teva Pharmaceuticals and the Scientific Advisory Board for Myriad Genetics.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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