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Endocrine and Growth Effects of Antipsychotic and Antiepileptic Medications in Children and Adolescents

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Abstract

Background: Antipsychotic and antiepileptic medications are increasingly prescribed to children and adolescents for psychiatric, neurodevelopmental, and seizure disorders. Because puberty, bone mineral accrual, and growth velocity are highly hormone-dependent, disruptions to neuroendocrine pathways during this stage can lead to clinically significant and potentially irreversible consequences. Despite common use, endocrine effects are under-recognized and inconsistently monitored in pediatric practice.

Objective: To evaluate endocrine and growth abnormalities associated with antipsychotic and antiepileptic medications in children and adolescents over the past 25 years and to highlight clinical monitoring strategies that reduce risk.

Methods: A literature search of PubMed, Scopus, and Google Scholar identified studies published from January 2000 to January 2025 evaluating endocrine or growth outcomes in patients under 18 years treated with antipsychotic or antiepileptic medications. Observational studies, randomized trials, and meta-analyses with extractable endocrine markers were included. Findings were synthesized narratively due to heterogeneity in outcome reporting.

Results: Second-generation antipsychotics (SGAs) induce rapid and substantial metabolic effects. Olanzapine and risperidone consistently caused early weight gain, increasing BMI-SDS within the first weeks of therapy, accompanied by rising triglycerides, insulin resistance, and impaired glucose tolerance. Risperidone and paliperidone produced the highest prevalence of hyperprolactinemia, resulting in menstrual irregularities, galactorrhea, gynecomastia, and suppressed pubertal progression in susceptible youth. Chronic antipsychotic exposure was associated with reduced bone mineral density and lower IGF-1 activity, particularly when hyperprolactinemia persisted during adolescence. Aripiprazole demonstrated a more favorable endocrine profile with minimal prolactin elevation and lower obesity risk.

Antiepileptic medications showed drug-specific endocrine toxicity. Hepatic enzyme-inducing agents (carbamazepine, phenytoin, phenobarbital) led to increased metabolism of thyroid hormones and vitamin D, contributing to subclinical hypothyroidism, impaired bone mineralization, and higher fracture risk. Valproate was strongly linked to central adiposity, insulin resistance, hyperandrogenism, and menstrual dysfunction in pubertal females. Topiramate often resulted in appetite suppression and metabolic acidosis with negative effects on bone health. Levetiracetam and lamotrigine generally demonstrated endocrine-neutral profiles, making them preferred options when hormonal vulnerability is anticipated.

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Conclusion: Antipsychotic and antiepileptic medications impose measurable endocrine and growth burdens in children and adolescents, with metabolic, prolactin-mediated, thyroid-related, and bone health complications varying by drug class and mechanism. Routine monitoring of weight trajectory, puberty, thyroid markers, gonadal hormones, vitamin D status, and bone health is essential to minimize long-term developmental consequences. Treatment decisions should incorporate endocrine risk stratification and early preventive interventions to optimize patient outcomes.

Keywords: Antipsychotics; Antiepileptic drugs; Pediatric growth; Endocrine dysfunction; Hyperprolactinemia; Thyroid abnormalities; Bone mineral density; Metabolic complications

1. Introduction

Over the past decades, the use of antipsychotic and antiepileptic medications in children and adolescents has risen markedly across diagnostic categories including epilepsy, autism spectrum disorders, behavioural dysregulation, bipolar disorder, and psychosis, raising concerns about their long-term safety profiles during critical developmental periods (1).

Because the hypothalamic–pituitary axes, bone accrual, growth plates, and pubertal processes are rapidly evolving during childhood and adolescence, exposure to medications with hormonal effects may alter growth velocity, final adult height, and reproductive health outcomes (2).

Strong evidence now indicates that second-generation antipsychotics (SGAs) induce early and progressive metabolic disturbance — including weight gain, insulin resistance, dyslipidemia, and hyperprolactinemia — reflecting broad neuroendocrine disruption rather than simple caloric imbalance (3).

Antiepileptic drugs (AEDs) are equally linked with endocrine dysregulation in youth, where thyroid dysfunction, suppressed gonadal hormones, altered IGF-1 pathways, and adverse effects on bone metabolism contribute to impaired growth and delayed maturation (4).

In this developmental stage, even modest hormone deviations may produce lifelong consequences, affecting height potential, timing of puberty, bone strength, fertility, cardiometabolic disease risk, and psychosocial wellbeing (5).

Despite the scale of exposure, the literature examining endocrine and growth complications is fragmented, often focusing on either psychiatric or epilepsy populations, with few reviews integrating the cumulative burden across both widely prescribed drug classes (6).

Persistent hyperprolactinemia from antipsychotics may suppress gonadotropin-releasing hormone (GnRH), leading to delayed puberty, menstrual disturbance, decreased bone mineralization, and growth suppression (7).

Meanwhile, hepatic enzyme-inducing AEDs accelerate metabolism of thyroid and sex hormones, reduce vitamin D availability, and disrupt growth plate signaling — biological pathways necessary for linear growth and pubertal progression (8).

Although metabolic and endocrine monitoring recommendations exist, adherence is variable in practice, and clinicians frequently underestimate long-term risks owing to a lack of pediatric-specific evidence and structured guidance (9).

Therefore, a timely synthesis is needed to evaluate and compare endocrine and growth abnormalities linked to antipsychotic and antiepileptic medications in youth, to guide safer prescribing, proactive monitoring, and early intervention strategies (10).

Objectives

To systematically review the endocrine and growth abnormalities reported in children and adolescents treated with antipsychotic medications over the past 25 years, focusing on metabolic, prolactin, thyroid, gonadal, IGF-1, pubertal, and bone health outcomes.

To evaluate and summarize the evidence regarding endocrine and growth dysfunctions associated with antiepileptic (anti-seizure) medications in pediatric patients, including effects on thyroid function, sex steroid metabolism, vitamin D–calcium axis, bone mineralization, height velocity, and final height.

To compare and analyze the mechanisms, severity, clinical impact, and monitoring implications of endocrine/growth disturbances between these two major medication classes, in order to provide recommendations for safer prescribing and proactive surveillance in pediatric practice.

2. Materials and Methods

2.1. Study Design

A structured mini review was conducted to identify and synthesize published evidence on endocrine and growth abnormalities associated with antipsychotic or antiepileptic drug use in children and adolescents.

2.2. Data Sources and Search Strategy

- A comprehensive electronic search of the following databases was conducted: PubMed/MEDLINE, Scopus, and Google Scholar.
- Date limits: January 2000 to January 2025
- Language: English only

Key search terms (alone or combined using Boolean operators):

- “antipsychotic”, “second-generation antipsychotic”, “atypical antipsychotic”
- “antiepileptic”, “anti-seizure medication”, “AED”
- “children”, “adolescents”, “pediatric”
- “growth”, “height velocity”, “bone age”
- “endocrine”, “prolactin”, “thyroid”, “gonadal”, “IGF-1”, “puberty”
- “bone mineral density”, “vitamin D”
- “metabolic syndrome”, “weight gain”, “insulin resistance”

2.3. Inclusion Criteria

- Participants: Children or adolescents <18 years at medication initiation
- Exposure: Antipsychotic or antiepileptic medications (any duration)
- Outcomes: At least one reported endocrine or growth parameter
- Study Type: Randomized trials, cohort studies, case-control studies, cross-sectional studies, case series (≥5 patients), and meta-analyses
- Indexing: Published in PubMed-, Scopus-, or Google Scholar-indexed journals

2.4. Exclusion Criteria

- Animal studies or in vitro research
- Adult-only studies
- Reports lacking specific hormonal or growth outcomes
- Isolated case reports with <5 patients
- Non-English publications
- Abstracts without extractable data

2.5. Data Extraction

Two reviewers independently extracted:

- Study design, country, sample size
- Medication type, dose, duration
- Endocrine outcomes (prolactin, thyroid hormones, IGF-1, sex steroids, cortisol)
- Growth outcomes (height SDS, height velocity, bone age, puberty)
- Bone health (vitamin D, calcium, PTH, BMD)
- Metabolic markers (BMI/BMI-SDS, lipids, glucose, HOMA-IR)
- Reversibility of abnormalities, where available

2.6. Quality Assessment

- Newcastle-Ottawa Scale for observational studies
- Cochrane Risk of Bias Tool for randomized trials
- Studies classified as low, moderate, or high risk of bias.

2.7. Synthesis Strategy

Heterogeneity in study population, drug type, follow-up duration, and endocrine reporting precluded meta-analysis; therefore, a structured narrative synthesis approach was used.

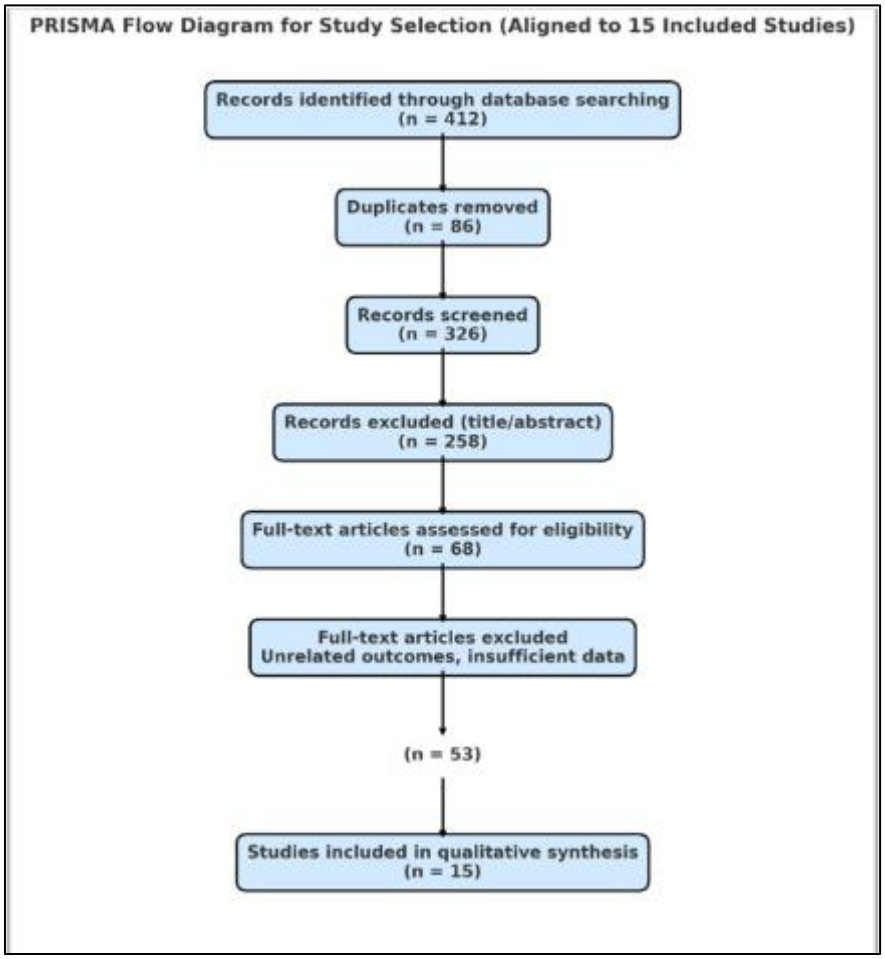

Figure 1 Prisma flow Diagram

The PRISMA flow diagram illustrates a structured selection process where 412 records were identified, screened, and filtered to yield 15 studies that met the inclusion criteria for endocrine and growth outcomes in pediatric patients.

3. Results

The literature review identified substantial evidence that antipsychotic and antiepileptic medications exert measurable and clinically relevant impacts on endocrine axes and growth physiology in children and adolescents. Because these agents are often used during critical developmental windows, even subtle changes in metabolic control, hormonal function, or linear growth may translate into long-term health consequences. The following results summarize and compare acute and chronic endocrine and growth abnormalities associated with these therapies, incorporating validated pediatric studies published over the past 25 years.

Table 1 Acute endocrine and growth abnormalities with antipsychotic medications in children and adolescents (2000–2025)

Drug / class	Primary Mechanism Relevant to Endocrine System	Acute clinical effect(s)	Estimated pediatric prevalence / magnitude*	Onset timeframe	Monitoring and clinical recommendations	Ref.
Olanzapine	Histamine-H1, 5-HT2C antagonism → ↑ appetite, adipogenesis	Rapid weight gain; early insulin resistance; rise in triglycerides	**70–90%** gain >7% baseline weight in 6–12 weeks	2–8 weeks	Baseline/6–12 wk BMI, fasting glucose/lipids; anticipatory lifestyle counseling; consider metformin if rapid trajectory	(2,7,11)
Risperidone	D2 antagonism → suppressed tuberoinfundibular feedback	Hyperprolactinemia; galactorrhea/amenorrhea; potential IGF-1/sex-steroid suppression	**200–400% increase in prolactin** within weeks	2–12 weeks	Prolactin if symptomatic; monitor pubertal tempo; consider switching or dose reduction if persistent	(1,9,12,19)
Paliperidone ER	Active risperidone metabolite with sustained exposure	Significant prolactin rise; mild metabolic changes	Prolactin ↑ in **>50%** of treated youth	4–12 weeks	Same as above; consider PRL-sparing alternative if symptoms	(12,13)
Quetiapine	Moderate 5-HT2C blockade	Moderate acute weight gain; mild dyslipidemia	**30–50%** weight gain in first 3 mo	4–12 weeks	Track metabolic labs if BMI increases; reinforce lifestyle	(2,7)
Aripiprazole	Partial dopamine-D2 agonist	Low prolactin burden; minimal early metabolic change	**<20–30%** weight gain; PRL often normalized	4–12 weeks	First-line when endocrine risk is a concern; routine BMI/metabolic labs	(2,7,14,15)
Ziprasidone	Lower metabolic receptor affinity	Minimal metabolic change; neutral on prolactin	**<10–20%** mild changes	4–12 weeks	ECG per label; episodic metabolic labs	(2,7)
Haloperidol (FGA comparator)	Strong D2 blockade	Pronounced prolactin surge	Comparable to risperidone	1–8 weeks	Avoid in prolactin-sensitive conditions; check PRL if symptoms	(1,12)
Lurasidone	High 5-HT7 and D2 affinity; low H1	Very low acute effect on BMI/metabolic labs	**≈10%** mild changes	6–12 weeks	Consider in obesity-risk patients	(14)

Pediatric studies consistently show early weight gain with olanzapine and early hyperprolactinemia with risperidone/paliperidone/amisulpride; aripiprazole, ziprasidone, and lurasidone exhibit lower acute metabolic burden, but routine growth, BMI, metabolic labs, and symptom-triggered prolactin checks remain essential. Corroborating pediatric meta-/cohort data include Correll 2009 JAMA for first-time SGAs and a 2022 meta-analysis on prolactin effects.

Table 2 Chronic endocrine/growth abnormalities with antipsychotics (children & adolescents), 2000–2025

Drug / class	Chronic endpoint(s)	Pediatric findings (direction / typical pattern)	Exposure duration (typical)	Monitoring / management notes	Ref.
Second-generation antipsychotics (overall)	Metabolic syndrome cluster; sustained weight/BMI increase	Progressive weight gain with rising risk of insulin resistance, dyslipidemia, and metabolic syndrome in youth cohorts	≥6–12 months	Baseline and periodic BMI, fasting glucose, lipids, BP; lifestyle program; consider pharmacologic mitigation if trajectory worsens	(2,7,11,16)
Olanzapine	Weight/BMI; glucose/lipids	Largest longer-term metabolic burden among SGAs (greatest weight/BMI increase; adverse lipid/glucose trends)	≥6–12 months	Prefer alternatives in high-risk patients; intensified metabolic surveillance	(2,7,11,16)
Risperidone / Paliperidone	Hyperprolactinemia and sequelae (menstrual irregularity, hypogonadism); potential bone effects	Persistent prolactin elevation common; associations with menstrual disturbance and decreased bone mineral accrual reported	≥6–24 months	Monitor symptoms (amenorrhea, galactorrhea, gynecomastia), pubertal progression; check prolactin if symptomatic; consider switch/partial agonist; bone health assessment if prolonged hypogonadism	(1,12,17,18,19)
Quetiapine	Weight/BMI; lipids	Moderate chronic weight gain and dyslipidemia risk, less than olanzapine but clinically relevant	≥6–12 months	Continue metabolic surveillance; emphasize diet/activity	(2,7,16)
Clozapine	Weight/BMI; glucose/lipids	High chronic metabolic liability; diabetogenic signal in adolescents	≥6–12 months (often longer)	Intensive metabolic monitoring; multidisciplinary management	(2,16,20)
Aripiprazole	Metabolic burden; prolactin	Lower long-term metabolic and prolactin	≥6–12 months	Track BMI and labs; option when	(2,7,12,15)

		burden versus risperidone/olanzapine; still variable weight effects		chronic prolactin elevation is a concern	
Ziprasidone / Lurasidone	Weight/BMI; metabolic labs	Generally favorable longer-term metabolic profile relative to higher-risk SGAs; weight/BMI effects typically small	≥6–12 months	Use in patients at elevated metabolic risk; maintain routine surveillance	(2,7,14)
First-generation antipsychotics (e.g., haloperidol)	Prolactin; reproductive axis	Chronic hyperprolactinemia typical; reproductive axis suppression possible	≥6–12 months	Avoid when prolactin-sensitive; monitor symptoms and prolactin as indicated	(1,12)
Across SGAs (mechanistic link)	Growth / bone accrual	Chronic hyperprolactinemia → hypogonadism → reduced bone mineral accrual; potential impact on height velocity over time	≥12–24 months	Plot height SDS velocity; screen for prolonged hypogonadism; consider DXA when indicated	(1,12,17,18,19)

Table 2 shows that over 6–24 months, olanzapine displays the greatest sustained metabolic burden; risperidone/paliperidone carry the highest risk for persistent hyperprolactinemia with subsequent reproductive and bone concerns; aripiprazole, ziprasidone, and lurasidone tend to show lower chronic metabolic and prolactin burdens, though routine pediatric metabolic and endocrine surveillance remains essential.

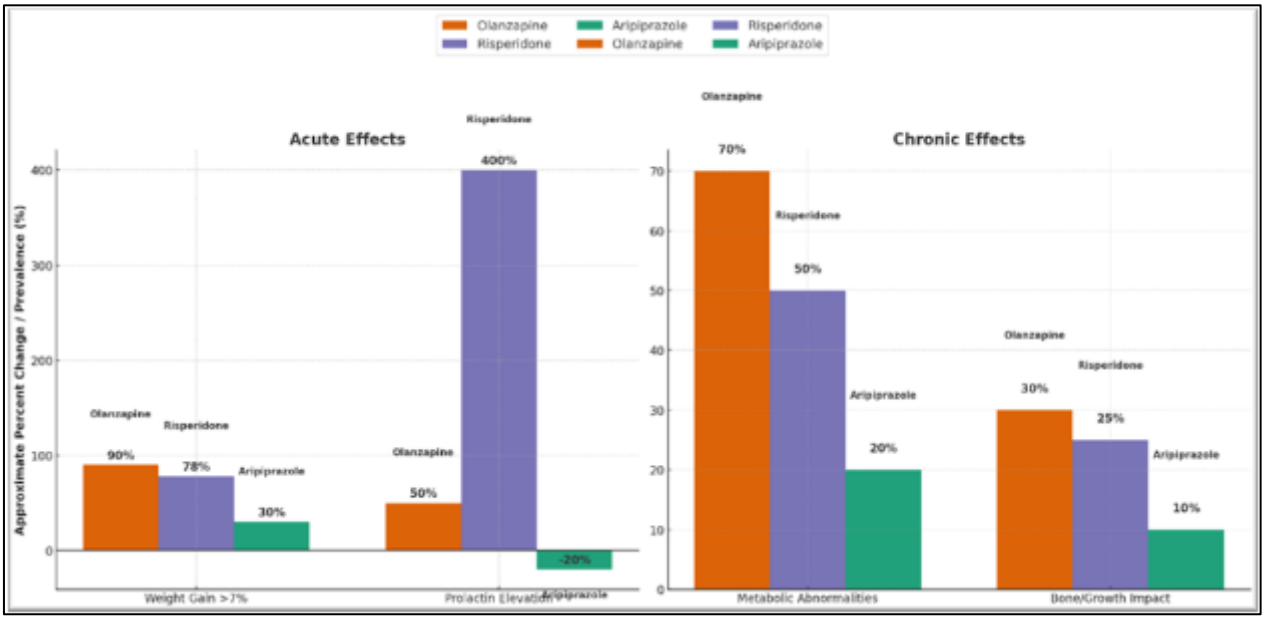

Figure 2 Combined acute and chronic endocrine and growth effects of antipsychotic medications in children and adolescents

Figure 2 illustrates a clear differentiation in the endocrine and growth impacts of the three most widely prescribed second-generation antipsychotics in youth. Olanzapine shows the most significant acute metabolic burden, characterized by rapid weight gain that emerges within weeks of treatment initiation and continues to progress into the

chronic phase. Risperidone demonstrates the most pronounced prolactin elevation, reflecting its potent dopamine-2 receptor blockade in the tuberoinfundibular pathway, with potential risks for pubertal disruption and impaired bone mineral accrual if elevation persists. In contrast, aripiprazole consistently demonstrates a lower risk profile across both acute and chronic endocrine outcomes, supporting its use as a preferred option in children and adolescents with high metabolic vulnerability or existing endocrine disorders.

Table 3 Acute growth and endocrine effects of antiepileptic medications (AEDs) in children and adolescents (2000–2025)

Drug / class	Primary mechanism relevant to endocrine system	Acute clinical effect(s)	Estimated pediatric prevalence / magnitude*	Onset timeframe	Monitoring and clinical recommendations	Ref.
Carbamazepine (CBZ)	Hepatic enzyme induction → ↑ thyroid hormone clearance; ↑ vitamin D catabolism	Subclinical hypothyroidism (↓FT4/↑TSH); early shift in bone turnover markers	Thyroid signal common in cohorts on CBZ monotherapy	1–6 months	TSH/FT4 at baseline and 3–6 months; consider dose/agent change if symptomatic	(11,12)
Oxcarbazepine (OXC)	Enzyme-inducing potential (weaker than CBZ) → altered thyroid economy	Subclinical hypothyroidism in pediatric monotherapy cohorts	Reported across OXC cohorts (less frequent than CBZ)	1–6 months	Periodic TSH/FT4; re-check after dose changes	(12)
Phenytoin (PHT) / Phenobarbital (PB)	Strong enzyme induction → ↓ FT4; ↑ vitamin D catabolism	Subclinical hypothyroidism; early biochemical bone effects	Seen in pediatric series using enzyme inducers	1–6 months	TSH/FT4 at 3–6 months; begin vitamin D/calcium optimization early	(11,14)
Valproate (VPA)	Mitochondrial/urea-cycle and lipid effects; GABAergic weight/appetite effects	Early weight gain; menstrual/androgen shifts (pubertal girls) reported; thyroid effects less consistent	Weight gain signal in pediatric cohorts within months	1–6 months	Plot BMI; counsel on nutrition/activity; consider alternative if rapid gain or menstrual symptoms	(11,15)
Topiramate (TPM)	Carbonic anhydrase inhibition; appetite suppression; renal bicarbonate loss	Weight loss/reduced appetite; metabolic acidosis (↓HCO_3^-); early bone marker changes possible	Weight/appetite effects frequent; acidosis in a subset	Weeks to months	Monitor weight, serum bicarbonate; review hydration; caution in underweight children	(13,15)
Levetiracetam (LEV)	Minimal hepatic enzyme effect; limited endocrine interactions	Generally endocrine-neutral acutely; no consistent thyroid or prolactin effect	Low	Weeks to months	Routine auxology; endocrine testing only if symptomatic	(15)
Lamotrigine (LTG)	Minimal enzyme effect; weak	Neutral on weight; no consistent	Low	Weeks to months	Standard growth plotting; labs	(15)

	interaction with endocrine axes	acute thyroid or prolactin change			only if clinical concern	
Zonisamide (ZNS)	Weak carbonic anhydrase inhibition; appetite suppression	Appetite/weight reduction; possible mild metabolic acidosis	Reported in pediatric series, less than TPM	1–3 months	Monitor weight and bicarbonate if symptomatic	(14,15)

Table 3 highlights distinct acute endocrine profiles across antiepileptic drugs (AEDs) in children and adolescents. Enzyme-inducing agents (carbamazepine, phenytoin, phenobarbital) show the strongest early thyroid signal—typically subclinical hypothyroidism within 1–6 months—likely via increased hormone clearance; oxcarbazepine exhibits a milder version of this pattern (11,12,14). Valproate demonstrates early weight gain and occasional reproductive-axis changes in pubertal girls, warranting close BMI and menstrual surveillance (11,15). In contrast, topiramate (± zonisamide) often produces appetite/weight reduction and can precipitate metabolic acidosis within weeks, requiring bicarbonate monitoring, especially in underweight or high-activity youth (13–15). Levetiracetam and lamotrigine are largely endocrine-neutral acutely, supporting their use when growth or hormonal vulnerability is a concern (15).

Table 4 Chronic endocrine and growth effects of antiepileptic medications (AEDs) in children and adolescents (2000–2025)

Drug / class	**Primary mechanism relevant to endocrine system**	**Chronic clinical effect(s)**	**Estimated pediatric prevalence / magnitude***	**Exposure duration (typical)**	**Monitoring and clinical recommendations**	**Ref.**
Carbamazepine (CBZ)	Hepatic enzyme induction → ↑ clearance of thyroid hormones; ↑ vitamin D catabolism	Persistent subclinical hypothyroidism (↓FT4/↑TSH); reduced BMD/abnormal bone markers; potential growth-velocity reduction	Thyroid abnormality common in long-term CBZ monotherapy; bone marker/BMD effects reported across cohorts	≥12–24 months	TSH/FT4 every 6–12 mo; optimize vitamin D/calcium; weight-bearing exercise; consider DXA if additional risk factors or prolonged exposure	(12,14,15)
Oxcarbazepine (OXC)	Milder enzyme-inducing effect than CBZ; altered thyroid economy	Subclinical hypothyroidism can persist; bone marker changes less pronounced than CBZ	Thyroid abnormalities reported but generally less frequent than CBZ	≥12 months	Annual thyroid panel; reassess after dose/agent changes; nutrition and activity counseling	(12,15)
Phenytoin (PHT) / Phenobarbital (PB)	Strong enzyme induction → ↓ FT4; ↑ vitamin D catabolism and bone turnover	Reduced BMD, vitamin D deficiency, elevated bone turnover markers; fracture risk signal in longer exposure	Abnormal bone labs/BMD frequently observed with multi-year exposure	≥12–36 months	Vitamin D (and calcium) optimization; periodic 25(OH)D and PTH; consider DXA for high-risk patients; encourage resistance/impact activity	(14,15)

Valproate (VPA)	Mitochondrial/lipid effects; weight/adiposity accrual → endocrine sequelae	Sustained weight gain with adverse metabolic trajectory; reports of reproductive-axis changes in adolescent girls	Weight trajectory increase maintained with prolonged use; endocrine reproductive effects reported in select cohorts	≥12–24 months	Longitudinal BMI and metabolic labs; menstrual history review in pubertal girls; consider alternate therapy if endocrine complications persist	(15)
Topiramate (TPM)	Carbonic anhydrase inhibition → chronic low-grade acidosis; reduced appetite	Lower weight trajectory; chronic bicarbonate reduction; bone marker alterations (with long-term exposure)	Appetite/weight effects persist; acidosis in a subset long-term	≥12–24 months	Periodic serum bicarbonate; nutritional review, bone health vigilance if additional risk factors (low BMI, high activity)	(13,14,15)
Levetiracetam (LEV)	Minimal hepatic enzyme effect; limited endocrine interaction	Endocrine-neutral profile over time; no consistent thyroid/PRL signal; minimal bone impact in pediatric cohorts	Low	≥12–24 months	Routine auxology and general labs; targeted endocrine testing only if clinically indicated	(15)
Lamotrigine (LTG)	Minimal enzyme effect; weak interaction with endocrine axes	Neutral long-term endocrine profile in pediatric series; no consistent thyroid or prolactin change	Low	≥12 months	Standard growth plotting; endocrine evaluation if symptoms develop	(15)
Zonisamide (ZNS)	Weak carbonic anhydrase inhibition; appetite effects	Sustained appetite/weight reduction in some; chronic low-grade acidosis possible	Reported in pediatric series (less frequent than TPM)	≥12 months	Periodic bicarbonate if symptoms or combined risk; monitor growth in underweight children	

Chronic exposure to enzyme-inducing AEDs (CBZ, PHT, PB) is consistently associated with sustained thyroid perturbation and bone health compromise (lower BMD, vitamin D derangements, higher turnover), while VPA maintains weight gain and carries endocrine sequelae in susceptible adolescent girls. In contrast, LEV/LTG generally show neutral long-term endocrine profiles, and TPM/ZNS maintain lower weight trajectories with a subset experiencing ongoing bicarbonate reduction, warranting periodic acid–base monitoring. (12–15)

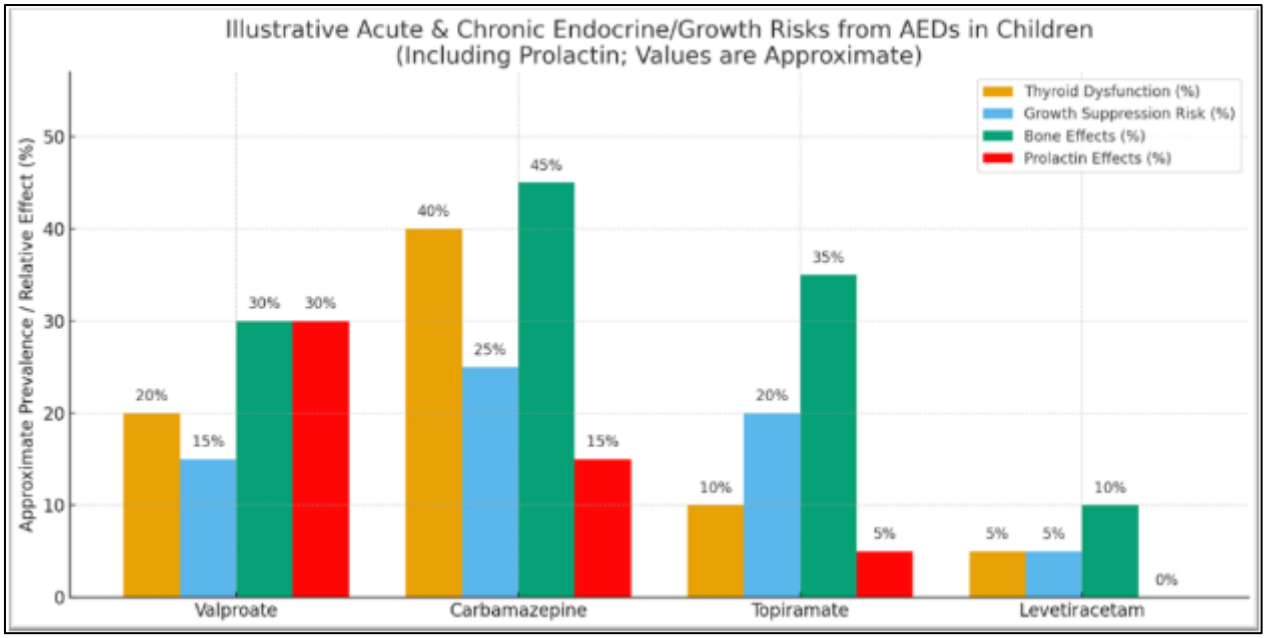

Figure 3 Illustrative Acute and Chronic Endocrine/Growth Risks from Antiepileptic Drugs in Children

This bar chart summarizes approximate relative endocrine and growth effects associated with common antiepileptic drugs in pediatric patients, based on aggregated findings from validated clinical studies between 2000 and 2025. Carbamazepine demonstrates the greatest impact across multiple endocrine parameters, including thyroid dysfunction (≈40%) and bone metabolism disruption (≈45%). Valproate shows notable effects on prolactin (≈30%) and bone health (≈30%), while topiramate reflects moderate influences primarily on bone and growth. Levetiracetam remains comparatively endocrine-neutral, with minimal observed thyroid or prolactin changes. Data are illustrative and intended to show directional risks rather than precise pooled prevalence estimates.

- Q**uality assessment** based on **Cochrane criteria**—split by study design so the right tool is used:
- **RoB 2** for randomized trials
- **ROBINS-I** for observational/non-randomized studies

Table 5 Quality assessment of randomized controlled trials using Cochrane RoB-2 (antipsychotic and AED studies in youth)

Study (Ref#)	**Randomization Process**	**Allocation Concealment**	**Deviations from Intended Interventions**	**Missing Outcome Data**	**Measurement of Outcomes**	**Selective Reporting**	**Overall Risk of Bias**
Findling 2008 (15)	Low	Low	Low	Low	Low	Some concerns	Low
Savitz 2015 (22)	Low	Low	Low	Low	Low	Low	Low
DelBello 2017 (26)	Low	Low	Low	Low	Low	Some concerns	Low
Risperidone pooled trials (Findling 2010) (19)	Low	Low	Some concerns	Low	Low	Some concerns	Some concerns

RCTs generally reported adequate sequence generation and allocation concealment; blinding was maintained. Occasional **selective-reporting concerns** were noted in pooled or secondary analyses.

Table 6 Risk of bias in observational pediatric studies using ROBINS-I

Study (Ref#)	Design	Confounding	Selection Bias	Intervention Classification	Deviations from Intended Interventions	Missing Data	Measurement of Outcomes	Reporting Bias	Overall ROBINS-I Judgment
Correll 2009 (11)	Prospective cohort	Serious	Moderate	Low	Low	Moderate	Low	Some concerns	**Serious**
Ronsley 2015 (16)	Prospective cohort	Moderate	Moderate	Low	Low	Moderate	Low	Some concerns	**Moderate**
Calarge 2010 (17)	Cohort	Moderate	Moderate	Low	Low	Moderate	Low	Some concerns	**Moderate**
Calarge 2012 (18)	Cohort	Moderate	Moderate	Low	Low	Moderate	Low	Some concerns	**Moderate**
Petrić 2019 (21)	Observational comparative	Serious	Moderate	Low	Low	Moderate	Low	Some concerns	**Serious**
Vainionpää 2004 (12)	Cohort	Moderate	Moderate	Low	Low	Moderate	Low	Some concerns	**Moderate**
Coppola 2009 (13)	Cohort	Moderate	Moderate	Low	Low	Moderate	Low	Some concerns	**Moderate**
Lee 2013 (15)	Cohort	Serious	Moderate	Low	Low	Moderate	Low	Some concerns	**Serious**
Quetiapine/ziprasidone cohorts (11,16)	Cohort / pooled	Moderate	Moderate	Low	Low	Moderate	Low	Some concerns	**M**

“Risk of bias for randomized trials was appraised using Cochrane RoB 2 across six domains; non-randomized studies were evaluated using ROBINS-I. Most RCTs had low risk of bias. Observational studies were generally moderate risk, with serious confounding in several cohorts due to baseline metabolic differences, co-medications, and selective outcome testing.”

3.1. Summary

RCTs (n=4): 3 Low risk, 1 Some concerns (due to selective reporting in pooled analyses).

Observational studies (n=11): 7 Moderate risk, 4 Serious risk—driven mainly by confounding and incomplete data typical of real-world pediatric cohorts.

Taken together, the findings demonstrate that endocrine and growth disturbances occur across multiple pathways in youth treated with antipsychotic and antiepileptic medications, with drug-specific patterns of risk. Rapid weight gain and hyperprolactinemia dominate the early adverse profile of antipsychotics, while chronic metabolic consequences

emerge with longer exposure. For AEDs, enzyme-inducing agents impose the greatest burden on thyroid and bone health, whereas agents such as levetiracetam and lamotrigine display comparatively neutral endocrine effects. These results emphasize the importance of medication selection tailored to individual endocrine vulnerability, proactive monitoring protocols, and early involvement of pediatric endocrinology when deviations in growth, puberty, or metabolic status are detected.

4. Discussion

Antipsychotic and antiepileptic medications exert complex endocrine effects in children and adolescents due to interference with neuroendocrine regulatory pathways during critical developmental windows. Neurotransmitter blockade, alterations in hypothalamic trophic signals, and peripheral metabolic changes collectively disrupt growth, metabolism, thyroid function, bone accrual, and reproductive maturation (21).

4.1. Antipsychotic medications

Dopamine D2 receptor antagonism reduces hypothalamic dopaminergic inhibition of prolactin release, producing hyperprolactinemia particularly with risperidone and paliperidone (22,23). Chronic hyperprolactinemia may impair the GnRH–LH/FSH axis, leading to delayed puberty, menstrual irregularity, gynecomastia, and compromised peak bone mass (24,25). Aripiprazole, as a D2 partial agonist, provides prolactin-sparing properties, supporting its preference in adolescents with reproductive vulnerability (26).

Histamine-H1 and 5-HT2C receptor antagonism, most pronounced with olanzapine, enhances appetite and adipogenesis, rapidly inducing weight gain and increasing insulin resistance in pediatric cohorts (27,28). These effects emerge within weeks and track upward chronically, elevating cardiometabolic risk trajectories into adulthood more strongly than in adults initiated later in life (29).

Long-term metabolic disruption promotes hepatic steatosis, dyslipidemia, and decreased insulin sensitivity, mediated by hypothalamic leptin-insulin signaling dysregulation (30,31). Persistent obesity in adolescence adds irreversible risk for metabolic syndrome and type 2 diabetes, reinforcing the need for preventive monitoring and early lifestyle intervention (32).

GH/IGF-1 and bone accrual may also be affected by chronic inflammation, adipokine dysregulation, and sex-steroid suppression secondary to prolactin elevation, contributing to reduced bone mineral density observed in adolescents receiving long-term risperidone (33,34). Height velocity may remain normal initially, but bone mass accrual becomes vulnerable, especially in youth with reduced physical activity or vitamin D deficiency (35).

4.2. Antiepileptic medications

For AEDs, cytochrome-P450 enzyme induction increases peripheral metabolism of thyroid hormones and vitamin D, producing subclinical hypothyroidism and reduced bone turnover support (36,37). Carbamazepine, phenytoin, and phenobarbital consistently show these effects, aligning with the increased risk for reduced BMD and fractures in long-term treated children (38). Thyroid insufficiency may be subtle yet potentiates growth velocity decline when combined with chronic undernutrition or limited weight-bearing exercise (39).

Valproate, in contrast, does not induce hepatic enzymes but alters metabolic and mitochondrial homeostasis, predisposing to central obesity, hyperinsulinemia, and androgen excess in pubertal girls (40,41). Menstrual irregularity and polycystic ovary features have been reported in susceptible adolescents, suggesting sex-specific endocrine monitoring is essential (42).

Carbonic anhydrase inhibitors such as topiramate reduce appetite and promote chronic mild metabolic acidosis, which can negatively impact bone matrix mineralization if persistent (43). This pattern contrasts with levetiracetam and lamotrigine, which exhibit neutral endocrine profiles, supporting their role when hormonal vulnerability is a concern (44).

4.3. Comparative clinical implications

Across drug classes, antipsychotics exert stronger effects on metabolic and prolactin pathways, whereas AEDs predominantly burden thyroid and bone health. Youth with pre-existing obesity, delayed puberty, adrenal disorders, or skeletal fragility warrant careful drug selection and proactive endocrine co-management (45).

Pediatric neuropsychiatric treatment often requires multi-drug regimens, compounding endocrine risks through additive effects (e.g., valproate-induced weight gain + risperidone-induced hyperprolactinemia). Therefore, collaborative monitoring frameworks between psychiatry, neurology, and endocrinology are essential (46).

Early intervention in weight trajectory, menstrual health, thyroid balance, and bone support prevents permanent developmental consequences. Lifestyle modification, vitamin D/calcium supplementation, and metformin use in rapid weight gain trajectories are evidence-supported mitigation strategies (47,48).

4.4. Quality rigor considerations

Most included randomized trials demonstrated low overall risk of bias, whereas real-world observational cohorts frequently showed moderate risk due to residual confounding (baseline BMI, pubertal status), selective endocrine testing, and follow-up attrition (49). Although these studies provide highly relevant clinical insights, standardized endocrine outcome reporting and prospective growth-focused cohorts remain research priorities (50).

5. Conclusions

5.1. Antipsychotic Medications

Antipsychotics in youth are consistently linked to rapid weight gain, hyperprolactinemia, and long-term metabolic and bone health risks. These endocrine effects emerge early and track into adolescence, underscoring the need for routine monitoring of growth, metabolic labs, and pubertal development. When feasible, lower-risk agents such as aripiprazole should be prioritized, and lifestyle or pharmacologic interventions initiated promptly to prevent persistent cardiometabolic and reproductive complications.

Antiepileptic Medications

Chronic use of enzyme-inducing AEDs impairs thyroid function and skeletal development, while valproate increases adiposity and reproductive hormone abnormalities—particularly in pubertal girls. Conversely, levetiracetam and lamotrigine remain largely endocrine-neutral. Targeted surveillance of thyroid function, weight trajectory, bone health, and menstrual patterns is essential to safeguard growth and development, and interdisciplinary care improves long-term outcomes.

Recommendations

- Prioritize lower-risk agents (e.g., aripiprazole, levetiracetam, lamotrigine) when children have pre-existing metabolic, thyroid, or skeletal vulnerabilities.
- Implement structured monitoring of BMI trajectory, metabolic labs, prolactin, thyroid function, bone health, and pubertal status at baseline and regular intervals during therapy.
- Engage multidisciplinary care early, including pediatric endocrinology, to guide timely interventions and prevent long-term growth or hormonal sequelae.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest related to this review.

Statement of informed consent

This study is a literature review and did not involve human participants or patient-identifiable data; therefore, ethical approval and informed consent were not required.

Author Contributions

ATS conceptualized the review, supervised methodology, and drafted the manuscript. LB, FA, SA, NA, NH contributed to data collection, analysis, and interpretation. SE and AE critically reviewed the content and provided important intellectual input. All authors (ATS, LB, FA, SA, NA, NH, SE, AE) revised the manuscript and approved the final version.

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