Interaction between Weight and Medications in Psychological Illnesses of Children

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Abstract
Psychiatric medications have many implications on weight and growth. Stimulant medications may produce appetite loss and thus affect growth. Second-generation antipsychotics which are widely used for psychosis and many other indications may cause weight gain and subsequent metabolic disease. Weight loss such as that seen in anorexia nervosa may severely interfere with the efficacy of antidepressant agents.

Psychological illnesses are among the most common serious and chronic disorders in childhood and adolescence. The development of modern psychotropic medications has given new hope to many of these sufferers; however, these agents are not without side effects and thus the pediatrician needs to be informed about the potential benefits and drawbacks involved in these therapies. The present chapter will deal with the effects of some of the drugs involved focusing on adverse reactions involving weight and growth.

More specifically, the focus will be on weight loss due to the use of stimulants for attention-deficit disorder and hyperactivity (ADHD) and weight gain due to the use of antipsychotics. In addition, we will also discuss a reverse effect where weight loss as seen in anorexia nervosa interferes with the use of antidepressant medications in adolescent mood disorder patients.

Attention Deficit Disorder and Hyperactivity

The diagnosis of ADHD and consequently treatment with ritalin have been on the rise during the last three decades. Thus, already in 1999 the Surgeon General reported that 8% of prepubertal boys and 2% of prepubertal girls suffered from ADHD as did
4% of male and 1% of female adolescents. Adult rates were 3% males and 1% females [Am Acad Pediatr 2000;105;1,158–1,170]. Most modern authorities would probably set even higher rates in recent times. Thus, the overall prevalence of ADHD in school-aged children is thus estimated to be 8–10%.

Although once considered to be limited to children with natural remission in adolescence, it is now generally felt that the majority of children with ADHD continue to exhibit symptoms of the disorder throughout their lifespan.

Stimulant therapy continues to be the most widely prescribed and effective treatment for ADHD and the use of these medicines in adolescents and young adults continues to expand almost exponentially as the disorder becomes increasingly diagnosed and treated.

According to Sax [1], 15,000 US children were on ritalin in 1975 as compared to six million in 2000 – i.e. 1 of every 8 children in the US.

One postulated mechanism of ADHD is that prefrontal cortex attention and possibly motivation is regulated by noradrenergic and dopaminergic neurotransmission. Thus, the release of noradrenaline (NA) from the presynaptic membrane impinges on alpha-1 and alpha-2a, b and c receptors on the postsynaptic membrane. In ADHD, these signals are weak and inefficient.

All stimulants such as amphetamines, methylphenidate and cocaine-like substances amplify the tonic and phasic release of monoamines, dopamine and NA from the presynaptic receptors. Related drugs such as guanefecine, atomoxetine and modafenil have similar effects. These neurotransmitters then activate the D1 receptors in the postsynaptic membrane of the prefrontal cortex as well as the D2 receptors in the striatum and alpha-2 receptors in the cortex, thus enhancing attention and motivation. As a result, the more motivated and focused child is less hyperactive. Consequently, there is a diminishing of behavioral disturbances, academic problems, and difficulties in social interactions, self-esteem issues, legal issues, substance abuse, injury, accidents and occupational difficulties.

Children receiving stimulants for ADHD may have a slowing of growth in height and weight. Yearly growth slows for the first several years of stimulant therapy, then later resumes at a nearly normal rate. With long-term (2–3 years) stimulant treatment, slowing of growth is usually minimal, though more significant slowing may occur in a subset of patients (perhaps 10%).

This slowing of growth appears to be related to decreased appetite and food intake while on stimulants. It may be greater in prepubertal children than adolescents. It appears to be more severe in boys than girls and children who are taller or overweight at baseline. The phenomenon is more marked in children treated with sustained-release preparations or who use higher drug doses.

Poulton et al. [2] reported a ‘slowing of growth in height and weight on stimulants’ with children dropping about five percentiles over 1–2 years with subsequent recovery which, however, was not always complete.
Wigal et al. [3] showed that on placebo just under 30% of preschool children had appetite suppression as opposed to just over 40% preschool children who received 7.5 mg of ritalin thrice daily.

Swanson et al. [4], for the MTA Cooperative Group, evaluated the effects of stimulant medication on growth rates across 3 years in the MTA follow-up. This multicenter treatment of attention deficit disorder found that growth rates might well be effected in children treated on long-term stimulants and concluded that ‘more work is needed to clarify the effects of continuous treatment from childhood to adulthood’. The problems were especially salient for those children who were on continuous medication for the full 36 months.

Spencer [5] conducted a study of 61 children treated for ADHD for 5 years (average age 10–15) and reported that there was a slowing of linear growth during the first 1–2 years of therapy. Atomoxetine, like stimulants, can cause appetite loss and nausea. The initial slowing of growth was followed in years 3–5 by a period of catch-up growth, such that height was usually normal by years 4–5.

Yet another antidepressant with stimulant properties is bupropion a dopaminergic anti-depressant that is also effective for children and adolescents with attentional problems. Anderson et al. [6] showed that this drug caused considerable weight loss (8–10% weight loss from baseline) which was significant (p < 0.05).

The question arises as to whether we can predict which children are likely to experience the greatest appetite suppression when taking ritalin? One approach looked at dopamine-related genotypes and the dose-response effect of ritalin on eating in ADHD youths was described by Leddy et al. [7]. This study explored the relationship between dopamine-related gene polymorphisms and food consumption in ADHD children receiving various doses of ritalin. The conclusions were that DR-D2 A2/A2 children showed a stronger effect of dose when compared with A1/A1 and A1/A2 children combined (p = 0.007).

In summary, one common side effect of stimulants is appetite loss and consequently weight loss and decline in growth rates. Losing weight is a problem particularly among children and adolescents who are in the process of growth. Some children have loss of appetite, severe enough to prompt them to discontinue the medication (with implications for school functioning, social functioning and comorbidity).

Growth-related recommendations for children receiving ADHD medications include the following: height and weight should be measured before beginning medication; obtain prior growth records if available. Remeasure and plot height and weight every 6–12 months while on treatment. If decreased more than 1 SD while on treatment, pediatric endocrine/gastrointestinal consultation is advised to exclude other disorders and obtain recommendation for treatment.

The strategies for minimizing growth and weight deficits on stimulants also include use of the lowest effective dose of drug, medication-free periods, avoid giving short-acting stimulants just before meals, taking ritalin after a nutritious breakfast, and enriching food with high-energy snacks.
Research is needed to determine the best treatment and the best diet for children with ADHD who are treated with stimulants and suffer from loss of appetite.

Weight Gain – Antipsychotics

Obesity is a growing problem in children; however, children and adolescents with psychiatric illness are at an even greater risk for obesity than the general population.

One major reason for this is the increasing use of second-generation antipsychotics (atypical) which are used for diverse indications as well as psychoses such as behavior problems, tic disorders and autistic spectrum disorder. They are also extensively used for bipolar disorder. Some such children need long-term treatment (e.g. autism, schizophrenia, bipolar). Thus, the use of second-generation antipsychotics has increased exponentially over the last decade [8].

Antipsychotic drugs act by blocking dopamine receptors in the mesolimbic system to reduce the so-called positive symptoms of hallucinations and delusions. However, they also block postsynaptic dopamine receptors in the extrapyramidal system causing Parkinson-like side effects and may even lead to permanent movements of the mandibular muscles – ‘tardive dyskinesia. In addition, these drugs do not affect the negative symptoms of schizophrenia such as reduced emotional responsiveness reduced interest and hobbies, reduced social drive, reduced speech, poor grooming and hygiene and limited eye contact.

These limitations led to the introduction of new ‘second-generation’ antipsychotic agents which have fewer extrapyramidal side effects and may be more effective for negative symptoms. As a class these agents have actions on histamine, serotonin 2c receptors and thus directly affect the appetite centers of the brain leading to increased appetite and weight gain. In addition, they have sedating effects which decrease activity and thus have a potentiating effect on the development of overweight.

This excessive weight gain leads in turn to stigmatization and withdrawal, non-compliance with medication and medical morbidity and mortality arising from dyslipidemia, diabetes mellitus, polycystic ovary syndrome, hypertension, sleep apnea and osteoarthritis. This is sometimes called the ‘metabolic syndrome’ and is a constellation of abdominal obesity, dyslipidemia, glucose intolerance and hypertension. The syndrome carries an elevated risk for cardiovascular disease and overt diabetes mellitus and hyperinsulinemia due to insulin resistance underlies the manifestations of the syndrome.

The FDA MedWatch surveillance program received 171 reports of new-onset diabetes associated with clozapine use. In most cases, diabetes appeared within 6 months of starting clozapine. One case appeared after a single accidental ingestion of a 500-mg dose. There were 80 cases of diabetic ketoacidosis or ketosis and 25
patients died [9]. Gothelf et al. [10] studied adolescent schizophrenic patients for
a period of 12 weeks and showed that there is a very significant weight gain with the
two second-generation antipsychotic agents (olanzepine and risperidal) as opposed
to the first-generation haloperidol which induced minimal weight gain. This weight
gain has the potential for setting up a slippery slope [11] down to severe metabolic
and health complications.

In summary, antipsychotic drugs (second-generation) raise the risk of metabolic
syndrome, especially the metabolism of glucose and lipids. Metabolic syndrome and
cardiovascular disease are important factors of morbidity and mortality among men-
tal health patients. Young patient populations, namely children and adolescents, are
the most vulnerable to metabolic syndrome as a result of using atypical antipsychotics
– especially clozapine and olanzapine. These patients develop weight gain and hyper-
glycemia about 8–12 weeks of treatment’s onset.

Efforts to combat this risk have been suggested [12]. It has been shown that the use
of adjuvant metformin can prevent weight gain over a 16-month period. In addition,
young people using these medications require extensive encouragement regarding
diet and exercise. This is difficult with healthy adolescent but all the more so in those
with psychopathology. Further research should take the direction of developing long-
lasting satiety through low-fat drinking yoghurt enriched with high amount of fibers,
low-calorie drinks with green tea extract and caffeine to increase energy expenditure
and adapting commercial weight loss programs for psychiatrically afflicted children
and adolescents.

**Weight Loss Interferes with the Action of Antidepressants – Anorexia Nervosa**

This article has hitherto addressed the issue of weight loss due to psychotropic agents
such as methylphenidate and weight gain due to psychotropic medications such as
the second-generation antipsychotics. However, weight-related issues can also act
in the opposite direction to affect the efficacy of psychotropic agents an example of
which is the interference of weight loss on the action of antidepressants.

The serotonin system has been strongly implicated in affective disorders and the
most common class of antidepressant agents used in children and adolescents are the
selective serotonin reuptake inhibitors (SSRI). These compounds act on presynaptic
receptors at the neural synapse to prevent reuptake of serotonin which has been dis-
charged into the synapse.

There is extensive interest in the question as to whether estrogen enhances the
antidepressant effects of fluoxetine (SSRI)? Thus, perimenopausal women diag-
nosed with major depression were randomly assigned to one of three treatment
conditions: (1) fluoxetine (SSRI) 10–20 mg alone, (2) estradiol patch 0.1–0.2 mg
alone, or (3) the combination of fluoxetine (SSRI) and estradiol patch. The find-
ings were that estrogen can enhance the efficacy of antidepressant medication and
moreover that the adjunctive treatment strategy may be superior to antidepressant or estrogen alone [13].

A trial [14] of short-term combinational therapy of low-dose estrogen with SSRI (fluvoxamine) for oophorectomized women with depressive tendencies showed a significant improvement in Self-Rating Depression Scale scores in the estrogen-replacement therapy plus selective serotonin reuptake inhibitor (ERT + SSRI) combination therapy group between pretreatment and 8 weeks’ post-treatment (McNemar test, \( p = 0.0156 \)).

Similarly, adolescent girls with weight loss due to anorexia nervosa fail to respond to antidepressant treatment when they are depressed [15]. Pharmacological studies have not yet identified a drug that will improve depressive symptoms in anorexia nervosa and the effectiveness of current treatment is unsatisfactory.

Depression among anorectic girls not only causes considerable suffering, but also causes death as a result of suicide and in fact today suicide is the most common cause of mortality. In light of this common phenomenon and its implications, if indeed adding augmentation of estrogen would improve the depressive symptoms among anorectic girls, as expected, then this would be a therapeutic breakthrough for many girls around the world.

**Conclusion**

The interaction between psychology and growth and weight is an enormous topic which necessitates integration between an array of disciplines. The present chapter has restricted itself to a small section of this problem. However, the complex relationship between psychotropic drugs and these factors in childhood is a potentially fruitful but neglected area of collaboration between psychiatrists, gastroenterologists and endocrinologists. Hopefully, this chapter will provide the impetus for such collaborations.

**References**


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