Olanzapine and Weight Loss in Early-Onset Schizophrenia

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Olanzapine use is plagued with resultant metabolic syndrome. Children and adolescents, by virtue of age, are at a heightened vulnerability. This is the case of a patient with early-onset schizophrenia maintained on olanzapine who experienced significant weight loss. The working differential, purported mechanisms, and pertinent therapeutic issues are briefly discussed.

Case Report

A 15-year-old Kuwaiti boy with early-onset schizophrenia maintained on olanzapine 20 mg/d was admitted to our inpatient facility. His father was concerned that his son had recently experienced diminished appetite and weight loss (7 kg [15 lb] over 2 weeks) as well as terminal insomnia. On mental status examination, the patient had marginal grooming and self-hygiene with an unkempt, disheveled appearance and a musty odor. He was skinny and detached with bland facial expression and was slavering at times. He had an *attitude d'impénétrabilité* with a flat affect. He was taciturn with laconic hesitant speech and sterile thought content.

Effect of Atypical Antipsychotics on Weight

The child and adolescent population is at a heightened risk to develop atypical antipsychotic–related metabolic syndrome compared to their adult counterparts. Atypical antipsychotics induce weight gain by H_1 blockade and 5-HT_{2C} antagonism actions on proopiomelanocortin neurons. Pancreatic M3 blockade might be contributory. Heat shock protein-72 (HSP-72) is a molecular chaperone that protects against insulin resistance; atypical antipsychotics were shown to reduce HSP-72.[1] Clozapine and olanzapine are notorious in this regard. Additional mechanisms have also been reported including reduced glucagon-like peptide-1 and biochemical hypothyroidism (especially with quetiapine and clozapine).[2]

For some individuals, however, clozapine use has been associated with significant weight loss (13.5%–50% of body weight). The observed weight loss in these groups of patients has not been attributed to any underlying diagnosable physical disorders. A few cases have been published with this phenomenon, which seems to be contrary to what is expected when clozapine is prescribed.[3] From the currently published cases, 3 groups emerge: those who lost weight simply by taking clozapine; those who lost weight due to improved mental state, engaging in diet and increased exercise; and those for whom weight loss was a sign of a poor response to clozapine.[3] Similarly, this could be the case with olanzapine in our patient, although we failed to locate relevant literature on olanzapine-related weight loss. Some genetic variations could be at play.

In our experience, these aforementioned groups remain the exception rather than the rule. In cases like that presented here, we would strongly suggest expansion of the working differential to include the following[4]:

- Paranoid delusions (eg, food is poisoned, anorexia mirabilis): check on compliance and ultrarapid metabolizer genotype to optimize antipsychotic treatment.
- Negative symptom domain (deficit state): look for other A's (**a**ffective flattening, **a**logia, **a**volia, **a**bulia, **a**nhedonia, **a**sociality, and **a**ttentional impairment). Use the Scale for the Assessment of Negative Symptoms (SANS).[5]
- Depressive presentation (and possibly implicit suicidality): use the Calgary Depression Rating Scale.[6]
- Substance use disorder: urinary toxicology screen.
- Catatonic presentation: use the Bush-Francis Catatonia Rating Scale.[7]
- Comorbid eating disorder: assess for conditions such as avoidant restrictive food intake disorder.[8]
- Physical presentation: assess for diabetes, thyrotoxicosis, parasitic infestation, and poor dental hygiene. Olanzapine-associated "diabesity" remains a possibility.

Case Report, Continued

The laboratory workup came back within normal limits, apart from vitamin D deficiency (he received

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supplementation) and a hemoglobin level of 12 mg/dL (he was started on an iron supplement). The urine toxicology screen was negative. A dental checkup was done with a negative yield. No catatonic signs were noted on examination. No delusional material was detected on serial mental status examinations. He self-rated his mood as 5 out of 10 for no particular reason for the past couple of weeks, but this was coupled with flat affective display, lack of rapport, and occasional mirthless laughter. He denied suicidal ideation or deliberate self-harm. He scored 20 on the 4-item Negative Symptom Assessment (NSA-4),[9] reflecting prominent negative symptoms (which affects approximately 40% of patients with schizophrenia[10]).

Inpatient psychosocial treatment, including rehabilitation, social skills training, and cognitive remediation, was provided by our occupational therapy staff. Dietary advice was summoned. Over the 6-week hospital stay, his weight plateaued, and he gained only a half kilo (1 lb) throughout.

Cosmetic psychopharma. This case was discussed in our hospital grand rounds, and a trial of shifting the patient from olanzapine (Zydis) to a regular formulation was suggested based on a 1-year open-label prospective study[11] wherein patients incurred an average weight loss of 2.7 ± 0.7 kg ($P = .001$) after switching from olanzapine standard oral tablets to olanzapine orally disintegrating tablets at 12 months. Peak weight loss was observed at 6 months; however, significant weight loss was seen as early as 3 months.[11] This shift to regular formulation resulted in gaining an extra half kilo (1 lb) in 2 weeks. Add-on mirtazapine, albeit off label, was then suggested for our patient, and his parents' consent was obtained beforehand. It was titrated up to 60 mg/d over 4 weeks. Clinical improvement in the negative symptom domain was seen on the NSA-4 (down to 7). Better interpersonal socialization was noted as was engagement with occupational therapy. The patient gained 4 kg (9 lb). This outcome was achieved with great tolerability. No significant pharmacokinetic drug interactions were observed.

Discussion

Is it merely antihistaminic action? Mirtazapine, an atypical noradrenergic (NE) and specific serotonergic antidepressant, has a unique mode of action. It seems that boosting NE drive by mirtazapine with subsequent disinhibition of dopaminergic projections to the dorsolateral prefrontal cortex corrects the dopamine hypofrontality underlying the negative symptoms. Moreover, decreased NE in patients with chronic schizophrenia is well documented in the literature, and psychotropics acting primarily to increase NE (eg, milnacipran) were reported to mitigate negative symptoms.[12] Similarly, mirtazapine efficacy against negative symptoms has been documented in a meta-analysis.[13]

Mirtazapine has been successfully used to counteract anorexogenic effects of stimulants in children with attention-deficit/hyperactivity disorder.[14] This might be attributed to H_1 and M_1 blockade. But this unusual dose (60 mg/d) is more adrenergic, and weight gain might simply reflect improvement in the negative symptom domain. We believe both mechanisms can be contributory.

Quick take. Early-onset schizophrenia is notorious for poor prognostication and treatment refractoriness. Although the positive symptom domain is the most vivid and conspicuous symptom profile of schizophrenia and the chief cause of referral for treatment, the negative symptom domain is pervasive but sometimes invisible—and especially difficult to treat. Weight loss in these cases has a broad differential diagnosis. Mirtazapine, by virtue of antidepressant, orexigenic, and procognitive actions, in addition to boosting NE tone, remains a viable option in these complicated clinical scenarios.

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