

Metformin for Antipsychotic-Related Metabolic Syndrome in Children: Fact or Fiction?

Ahmed Naguy¹, Dalal El-Sori²

¹Al-Manara CAP Centre, Kuwait Centre for Mental Health, Shuwaikh, State of Kuwait

²Paediatrics Department, Cleveland Clinic Children's, Cleveland, Ohio, USA

Use of atypical antipsychotics (AAPs) in child/adolescent psychiatry (CAP) population is rife to address a wide array of indications. Apart from the Food and Drug Administration approval in schizophrenia, bipolar mood disorders, irritability in autism spectrum disorder, and Tourette's syndrome, AAPs are commonly prescribed off-label for aggression in intellectual disability or attention-deficit/hyperactivity disorder, augmentation in depression and obsessive-compulsive disorder, borderline personality disorder, anorexia nervosa, posttraumatic stress disorder, insomnia, etc.

Initial enthusiasm about AAPs benign (neurologic) side effect profile has been tempered by emergence of metabolic syndrome (MetS). CAP population, by virtue of age, is at a heightened risk compared to adult counterparts. MetS increases the risk of type 2 diabetes mellitus by 5–6 times and that of coronary artery disease by 3–6-folds. MetS is tied to weight gain and insulin resistance (IR).

AAPs induce weight gain by H1 blockade and 5HT_{2C} antagonism actions on proopiomelanocortin neurones. Pancreatic M3 blockade might be contributory. Heat shock protein-72 (HSP-72) is a molecular chaperone that protects against IR; AAPs were shown to reduce HSP-72. Clozapine and olanzapine are very notorious in this regard.

Strategies to mitigate MetS include judicious use of metabolic-friendly AAPs (e.g., aripiprazole), dietary and life-style modifications, and pharmacologic interventions.

One such pharmacologic maneuver that gained popularity lately is add-on use of metformin, a biguanide oral hypoglycemic agent, which is also used in polycystic ovary disease. Most adult data are derived from Chinese randomized controlled trials (RCTs), supporting the use of metformin not only for AAP-induced weight gain but also for AAP-induced hyperlipidemia.^[1,2] Metformin also helps in antipsychotic-induced hyperprolactinemia.^[3] Interestingly,

metformin was shown in a 24-week RCT to possess antidepressant and precognitive actions in diabetics.^[4] Metformin is not metabolized by hepatic microsomal enzymes, hence no pharmacokinetic interactions can be expected.

Evidence in CAP comes from two open-label trials and three RCTs (two positive and one negative). One 12-week open-label trial by Morrison *et al.*^[5] enrolled 19 patients, age group of 10–18 years, and was positive. Another 12-week open-label trial involving 11 patients aged 10–18 years by Shin *et al.*^[6] confirmed safety and tolerability in improving triglyceride level but with nonsignificant weight loss. One positive 16-week RCT by Klein *et al.*^[7] enrolled 39 patients, age group of 10–17 years and metformin was dosed at 850 mg bid. Another 12-week RCT by Arman *et al.*^[8] of using metformin 1000 mg for weight gain associated with initiation of risperidone in children and adolescents below 20 ($n = 49$) years old but was negative. Recently, Anagnostou *et al.*^[9] conducted a 16-week RCT, involving 61 patients of autistic population and including children as young as 6 years of age, which was positive without gastrointestinal tolerability issues that are commonly overrepresented in this population.

Of note, as metformin decreases insulin-like growth factor-1, which has been shown to be deficient in antipsychotic-naïve schizophrenics, cases of psychotic exacerbations by metformin have been reported.^[10,11]

Monitoring of metabolic screen during AAPs use is then mandatory and instituting effective measures to ameliorate MetS, arguably from the outset, might curtail long-term drastic sequelae.

Address for correspondence: Dr. Ahmed Naguy,
Al-Manara CAP Centre, Kuwait Centre for Mental Health, Jamal
Abdul-Nassir Street, Shuwaikh, State of Kuwait
E-Mail: ahmednaguy@hotmail.co.uk

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