הצעת מחקר איגוד פסיכיאטרי של הילד והמתבגר

Metformin treatment and dietary intervention for treating weight gain induced by atypical antipsychotic medications in children: A naturalistic study

מטפורמין והתערבות דיאטנית להשמנה כתוצאה מטיפול בתרופות אנטיפסיכוטיות בילדים: מחקר נטוראליסטי

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חוקרות ראשיות:

דר' מריאלה מושבה, מתמחה בפסיכיאטריה ופסיכיאטריה של הילד, מרכז רפואי שיבא, תל השומר

דר' אירנה קוסוב, מנהלת מחלקת ילדים, מרכז לבריאות הנפש נס ציונה.

חוקרים נוספים:

דר' יעל לוי, אנדוקרינולוגית ילדים, היחידה לאנדוקרינלוגיה ילדים, מרכז רפואי שיבא, תל השומר

מור שלו, דיאטנית, החטיבה לפסיכיאטריה של הילד והמתבגר, המרכז הרפואי שיבא, תל השומר

קרן שינה, דיאטנית, מחלקת ילדים, מרכז לבריאות הנפש נס ציונה

Background

Over the last decade, atypical antipsychotics (AAPs) medications have been increasingly prescribed for children and adolescents.[1] Indications include severe behavioral disturbances, psychotic disorders and ADHD, which is the most common indication for prescribing risperidone in children and adolescents.[2,3] Nonetheless, there is established increased risk that exposure to AAPs can cause severe adverse metabolic effects including weight gain, hyperlipidemia, and increased risk of type 2 diabetes.[4,5]

Children and adolescents are suggested to have a greater risk than adults for AAP related weight gain.[6] Antipsychotic-induced weight gain is a major management concern for clinicians. A large naturalistic cohort study showed that 85% of patients treated with olanzapine, 65% of

patients treated with risperidone, and 60% of patients treated with aripiprazole gained >7% of weight during the first 3 months of AAPs treatment.[7]

Weight gain during childhood is associated with increased risk for a variety of negative outcomes including asthma, orthopedic problems, adverse cardiovascular and metabolic outcomes. The risk of heart disease is tenfold higher in obese youth compared with healthy-weight peers.[8] Obese youth may also experience psychological distress related to being bullied, leading to poor self-image and depression.[9] Moreover, childhood obesity predicts obesity during adulthood and is related to reduced quality of life and poor drug compliance.[10]

Metformin enhances the action of insulin in the liver and thereby decreases the rate of hepatic glucose production. Metformin also increases peripheral glucose utilization and suppresses appetite. Therefore, it is recommended as first line treatment in type 2 diabetes in children.[11] It is also used off-label to treat obesity also without diabetes.[12]

Previous studies have demonstrated the safety and tolerability of metformin for pediatric population.[13] Furthermore, studies in children and adolescents treated with antipsychotics have shown a reduction of weight and BMI z-score as well as improvement of glucose metabolism during treatment with metformin for 12-16 weeks.[14–18] A recent 16‑week RCT, consisting of 61 patients with ASD as young as 6 years of age (mean age 12.8 years), showed positive results.[19] An open label 16 week extension trial to this study, found that participants maintained prior decreases in weight but did not have additional weight loss.[20]

Nonpharmacological lifestyle interventions of dietary counseling, exercise programs and cognitive and behavioral strategies has demonstrated efficacy to reduce obesity or to prevent weight gain induced by AAPs.[21] In adults, metformin treatment plus lifestyle intervention was found to be superior to each intervention alone for AAP induced weight gain in a12—week RCT trial.[16] However, to our knowledge, dietary-lifestyle intervention studies in pediatric population are currently lacking.

Research objectives

1. To evaluate efficacy and safety of metformin and dietary intervention alone and in combination for AAPs induced weight gain in children aged 6-12 years. We will use a multicenter naturalistic trial design.

2. Identify possible clinical and laboratory factors predicting weight gain induced by AAP in young children.

Methods

Participants

Inclusion criteria: Children age 6 to 12 years diagnosed with psychotic disorders, affective disorders, autism, ODD and ADHD with severe aggressive behavior for whom the psychiatrist recommended an initiation of AAP medication.

Exclusion criteria: any medical condition or concomitant treatment that may influence body weight such as endocrine disorders e,g, diabetes type 1, genetic disorders e.g, Prader Willi syndrome.

Study population: The study will be conducted at the Child Psychiatry Outpatient Clinic at Sheba Medical Center and the Child Psychiatry Inpatient Unit at Ness Ziona Mental Health Center. Only children age 6 to 12 will be recruited. We estimate that both Sheba medical center and Ness Tziona about 75 children initiate AAP per year (total 150 patients). Of them, based on the literature, more than two-thirds (n=100) gain weight during the first weeks of treatment. This patients will naturalistically be randomized.

Screening Assessments

Clinical evaluation: participants and their patents will undergo evaluation to establish relevant medical and psychiatric diagnoses and previous treatment trial with antipsychotics will be documented. Anthropomorphic measures including height, weight, abdominal and hip circumference will be evaluated at each visit.

Laboratory Analysis: liver function tests, BUN, creatinine, electrolytes, bicarbonate, lactate, fasting glucose, HgbA1C, insulin, prolactin, B12, total cholesterol, LDL, HDL, triglycerides, and CBC.

Research plan

The study procedures are summarized in Supplementary A.

First, we will perform a baseline evaluation to all patients starting on AAPs.

After 6 weeks of treatment, all patients will undergo psychiatric examination, physical and laboratory tests. Furthermore, all participants and their parents will encounter dietitian for psychoeducation session and dietary recommendation. Then participants will be randomized

naturalistically by the psychiatrist based on weight gain. Those who gained ≥5% will be randomized to receive metformin in doses based on safety and efficacy findings from previous studies (children aged 6-9 years up to 500mg twice daily and 850mg twice daily for those 10-12 years).[19] The control group will be age matched children treated with AAPs with no intervention.

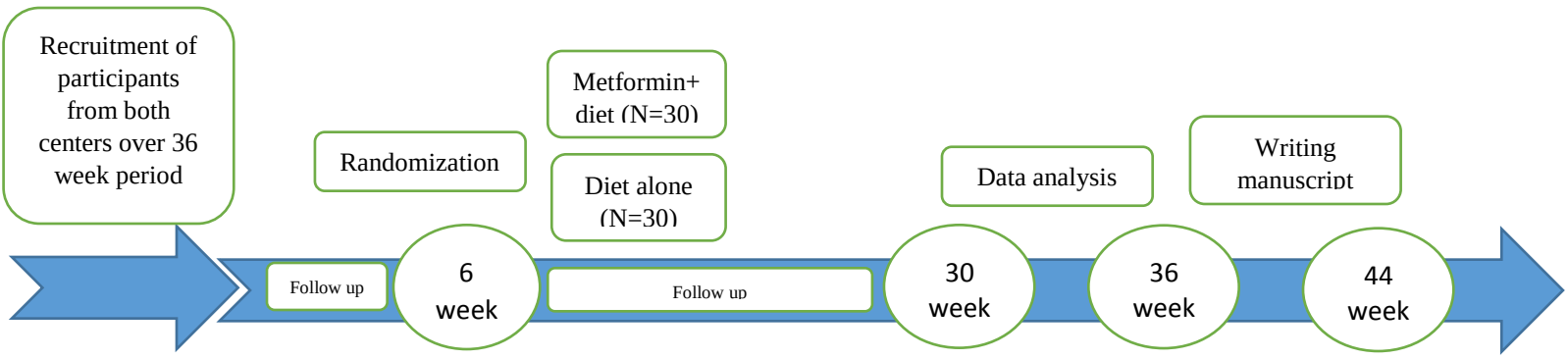
Primary outcome: change in body mass index z-score

Secondary outcomes: changes in fasting metabolic parameters

Statistical analysis

All analyses will be conducted by using the Statistical Package for Social Sciences, version 11.5 (SPSS Inc, Chicago,Illinois). We will use t-tests analysis as appropriate. For comparison of the treatment groups at baseline and follow up ANOVA will be used.

Time schedule



Study significance

Weight gain presents a major concerning side effect of AAP treatment for pediatric population. To our knowledge, this is the first randomized study to evaluate efficacy and safety of metformin and dietary intervention alone and in combination for AAP induced weight gain in young population of children aged 6-12 years. The results of the study will present intervention plan to reduce weight gain with AAP treatment in young children. With tailoring the optimal intervention, we can prevent long-term metabolic abnormalities, improve treatment adherence and improve quality of life of our patients.

Budget

For	**Amount**
Study assistant for the period of the study	25,000 NIS

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