Ask the Expert

SCHIZOPHRENIA

How would you handle the risks of metabolic syndrome in a young person with schizophrenia?

Reply from Christoph U. Correll, M.D.

THE PROBLEM

In psychiatry, the physical health of mentally ill patients and the cardiometabolic risks of psychotropic medications have become a clinical, research and regulatory focus (1). In particular, the cardiometabolic effects of antipsychotics have become a major concern (2, 3). This has been especially the case in pediatric and first episode patients who are at greatest risk for adverse cardiometabolic changes, which include excessive weight gain, obesity and abnormalities in blood lipids (cholesterol, triglycerides), glucose, and blood pressure (3, 4). The metabolic syndrome is defined as a constellation of at least three of the following 5 criteria:

i) abdominal obesity (>40 inches in males and >35 inches in females),
ii) hypertriglyceridemia (≥150 mg/dL),
iii) low HDL-cholesterol (<40 mg/dL in males and <50 mg/dL in females),
iv) hyperglycemia (≥100 mg/dL), and
v) arterial hypertension (≥130/85).

The metabolic syndrome is problematic, as it predicts the development of type 2 diabetes and cardiovascular morbidity and mortality (1). Fortunately, type 2 diabetes, metabolic syndrome and ischemic heart disease morbidity and mortality are less frequent in young patients than in chronically ill, older patients. However, there is great concern about premature cardiovascular aging, in that relative to the general population mentally ill patients and those with medication related weight gain and metabolic burden have metabolic syndrome rates that reach concerning levels at an already very early age (2, 3). This "cardiometabolic progeria" is likely responsible for the 15-25 year mortality gap in seriously mentally ill patients compared with the general population (5). Therefore the delay, attenuation or, even better, prevention of reaching abnormal cardiometabolic health status should be a key concern when treating mentally ill patients, especially those requiring medications with known cardiometabolic risk (2). However, despite the increased cardiometabolic risk in mentally ill and antipsychotic treated patients, metabolic monitoring rates have remained inadequately low (1).

APPROACHING TO THE PROBLEM

Since prevention is the best intervention, all mentally ill patients, even those with normal health status and not treated with cardiometabolically problematic medications, should receive healthy lifestyle counseling. A behavioral, 12-step healthy lifestyle program has been proposed for young people treated with antipsychotics (6). It includes the following steps: 1) Involvement of family members in healthy meal planning and exercise behaviors; 2) Drink water instead of soft drinks; 3) Have 4-6 separate meals/day; 4) Eat breakfast every day; 5) Serve small portions; 6) Eat foods with low glycemic index slowly (www.glycemicindex.com); 7) Reduce/avoid saturated fat intake; 8) Eat at least 25-30 g of soluble

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fiber per day (i.e. fruits instead of fruit juice); 9) Avoid snacking when satiated; 10) Limit fast foods to <1/week; 11) Limit sedentary behaviors to <2 hours/day; and 12) Exercise ≥30-60 minutes daily.

A primary preventive strategy is to chose the cardiometabolically safest medication first whenever psychiatric medications need to be prescribed. This is backed up by the fact that efficacy differences among psychiatric medications are small and difficult to predict while adverse effect differences are much larger and much easier to predict (3).

Patients with already existing, abnormal cardiometabolic health status should receive healthy lifestyle interventions. Recent guidelines from the American Academy of Pediatrics (http://www.ama-assn.org/ama/pub/category/11759.html) describe a three step intervention program. The first step involves recommending 5 servings of fruits, 2 hours or less of screen time daily, greater than one hour of exercise and zero soft drinks. The second step involves more structured and supervised weight reduction interventions, and the third step involves professionals focusing on weight reduction treatments. A meta-analysis of 10 nonpharmacologic intervention studies for antipsychotic induced weight gain (N=482) established the efficacy of healthy lifestyle programs in patients taking antipsychotics. The authors found a combined 2.56 kg (CI: 1.92, 3.20) greater reduction in weight compared with treatment as usual (7). There was no difference between specific techniques, individual and group treatment, and prevention and intervention trials. These data suggest that healthy lifestyle interventions can be useful in patients who are willing and able to participate.

If clinically relevant weight gain or metabolic side effects occur, the healthy lifestyle approach should be reviewed and intensified, and a switch to a potentially cardiometabolically safer medication should be considered. However, switch strategies, especially when switching from an antipsychotic with greater weight gain potential to one with a lower weight gain potential, need to be pharmacologically informed (8). When switching stable patients from a more to a less weight gain producing antipsychotic, there is a risk of potentially destabilizing histaminergic, cholinergic or dopaminergic rebound. This is particularly relevant when switching to aripiprazole and ziprasidone, which is why overlapping switches are proposed as yielding the best switch results. Ideally, an overlapping switch should be performed that involves titrating the less cardiometabolically problematic antipsychotic until target dose and waiting for 4-5 half lives before reducing the dose of the preswitch antipsychotic by 25%–50% about once per week (8).

Finally, if healthy lifestyle counseling or interventions and treatment with a lower cardiometabolic risk agent are insufficient to prevent clinically relevant cardiometabolic health burden, augmentation with a pharmacologic weight loss agent may need to be considered. In a meta-analysis of 15 different pharmacologic strategies (32 studies, n=1,482), only metformin, fenfluramine, sibutramine, topiramate and reboxetine were more effective than placebo regarding antipsychotic related weight gain, reducing the weight gain by 1.5-3.0 kg compared with placebo (9). However, 3 of the 5 effective medications have been removed from the market due to adverse effect concerns (fenfluramine, sibutramine and reboxetine). To date, only metformin (for which the most controlled studies have been conducted) and topiramate are available that have placebo controlled evidence for reducing weight gain associated with antipsychotic treatment, although neither are FDA approved for this purpose. Metformin should only be started if creatinine levels are <1.3 mg/dL. The starting dose in a patient weighing >45 kg is 500 mg with a meal, with weekly increases by 500 mg, divided in two or three daily doses, and with a maximum dose of 2,000 mg/day. Common side effects include nausea, diarrhea and flatulence. Lactic acidosis is only a risk in the elderly and rare. Hypoglycemia is not a problem, as insulin production is not increased, but insulin sensitivity increases, reducing orexigenic insulin levels (10). Topiramate can be started at 25 or 50 mg/day and increased weekly up to 100 mg twice daily. Common side effects include cognitive problems, especially word finding difficulties, but sedation, depression and psychosis have also been described, although no psychotic exacerbations have been reported when given in combination with an antipsychotic medication (10). For metformin and topiramate, both the weight loss effects and the side effects are dose dependent, and the combination of these two agents has also been suggested if one agent is only partially effective, but controlled trials of this strategy are currently absent. In addition, in the only available cotreatment study in antipsychotic treated patients, the combination of metformin plus a healthy lifestyle intervention was superior to either strategy, and metformin alone was more effective than lifestyle intervention alone (11).

Conclusions

Guarding against and reducing cardiometabolic risk factors in young patients with a first episode of a serious mental illness is a key component of integrated medical-psychiatric care. Important strategies include education, regular cardiometabolic

monitoring (1–3), nonpharmacologic healthy lifestyle approaches, choice of the lowest risk medications possible, and, potentially, the addition of medications aimed at reducing excessive body weight or metabolic abnormalities. Whenever medical problems emerge, comanagement with a medical health care provider should be coordinated.

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