

Diabetes Resolution Following Discontinuation of a Second-Generation Antipsychotic: Three Cases

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Introduction

Schizophrenia patients have higher rates of type 2 diabetes mellitus (T2DM) than population comparisons and, in conjunction with highly prevalent obesity and cardiovascular disease, this translates into a 20% reduced life expectancy (1). Unfortunately, despite arguably better outcomes in several psychiatric domains including symptoms, cognition and quality of life, the mortality gap for patients is not narrowing but may indeed be widening (2). Preferential use of second-generation antipsychotics (SGAs) as opposed to older (first-generation antipsychotics, FGAs) antipsychotics may account for the widening mortality gap (3). This is because research has confirmed a link between SGA use and development of T2DM and other metabolic complications (1). Conversely, very little evidence has accumulated that would support a connection between discontinuation of SGAs and diabetes resolution, although implications in the prevailing context would be important. Here, we describe three cases of diabetes onset with SGA treatment and confirmed resolution after switch to an FGA.

Case 1

A 25-year-old, non-diabetic Canadian Aboriginal woman with a three-year history of treatment-resistant DSM-IV schizoaffective disorder was started on clozapine to good clinical response, while experiencing significant weight gain (>7%). Diagnosis of T2DM was made after 6 months on clo-

zapine, following an episode of diabetic ketoacidosis (DKA). T2DM was confirmed with a negative C-peptide test, and hyperlipidemia was present (fasting glucose 36.7 mmol/l [660.6 mg/dl], total cholesterol 7 mmol/l [270.7 mg/dl], triglycerides 2.32 mmol/l [206 mg/dl], LDL-cholesterol 4.94 mmol/l [191 mg/dl]). Thereafter, she required daily insulin injections and oral hypoglycemics for diabetes management. The patient was not reliably compliant with diabetes management and clozapine lab monitoring, and clozapine was discontinued. Clozapine was substituted with a depot first-generation antipsychotic (FGA). Diabetes resolution was noted within two weeks after discontinuation of clozapine with normal glucometer readings off insulin and metformin. Metabolic follow-up continued to be normal two years later (fasting glucose 4.1 mmol/l [73.8 mg/dl], triglycerides 0.98 mmol/l [86.8 mg/dl], LDL-cholesterol 3.45 mmol/l [133.4 mg/dl]). Psychiatric symptoms remained stable.

Case 2

A 45-year-old, black, obese woman, with a ten-year history of schizophrenia, was admitted for a psychotic relapse. Medications prescribed upon admission included olanzapine 30 mg qd, Risperdal Consta 25 mg I/M q2wks. The patient was noted to be hyperglycemic two weeks later; glucose was over 30 mmol/l (540 mg/dl) and required insulin for control, in addition to maximum dose oral hypoglycemics. Olanzapine was discontinued because of difficulty with achieving glycemic control and risperidone due to amenorrhea, and switched to a depot FGA. Lipid and glucometer readings normalized within weeks after discontinuing olanzapine, risperidone and antidiabetes medications, and have continued to be in the healthy range at a six-month routine outpatient follow-up.

Case 3

A 47-year-old single, white, normal-weight woman diagnosed with schizophrenia (DSM-IV) of fifteen years' duration was admitted after her outreach team had docu-

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mented intermittent contact with the patient and treatment refusal. The patient's most recent past antipsychotic regimen (biweekly Risperdal Consta injections) was resumed, but ineffective, and switched to clozapine. Random fasting glucometer testing approximately four weeks after clozapine was started revealed a glucose level of 8.4 mmol/l (151.2 mg/dl), and subsequent confirmatory fasting labwork a fasting glucose of 8 mmol/l (144 mg/dl), along with fasting insulin of 68 pmol/l; new-onset T2DM was diagnosed. Oral antidiabetics were added; however, after further worsening of glucose control and onset of hyperlipidemia over the next few weeks, the patient was switched to an oral FGA. The patient had not gained weight while receiving clozapine. Following the switch, glucose and lipid profile normalized, and metformin was discontinued. Follow-up two months after T2DM diagnosis confirmed that all parameters had returned to within normal limits (fasting glucose 5.6 mmol/l [100 mg/dl], insulin 45 pmol/l). Psychiatric symptoms remained well controlled upon hospital discharge.

Research confirms the connection between schizophrenia, SGAs and the development of T2DM and other metabolic abnormalities but, to date, comparatively little focus has been placed on the potential reversibility of SGA-induced adverse metabolic effects after cessation or switching.

These three presented cases highlight clinically important issues. Research confirms the connection between schizophrenia, SGAs and the development of T2DM and other metabolic abnormalities but, to date, comparatively little focus has been placed on the potential reversibility of SGA-induced adverse metabolic effects after cessation or switching (4). In the few previously reported cases—consistent with our own observations—discontinuation of the SGA led to restoration of normal glucose control (5-9) and lipids.

Because T2DM is a chronic illness with high risk of developing multisystem debilitating complications, the added lifetime burden of a diagnosis of T2DM in an individual with schizophrenia is significant (10). Conversely, in these patients the potential positive impact of diabetes resolution upon switching antipsychotics—while their mental status remains stable—would be considerable. Recent recommendations have started to incorporate antipsychotic switching strategies to improved cardiometabolic risk profiles (11, 12), with the caveat that more research is needed to better assess

the possible connection between potential diabetes resolution—or improvements in other metabolic risk factors, that is—and discontinuation of SGAs.

The presented cases also highlight the importance of frequent metabolic screening and monitoring in this patient population. Metabolic monitoring practices among SGA users still vary widely; metabolic complications are still underrecognized and frequently go undertreated (13-15). Improved awareness among practitioners and early intervention—including potential advantages of switching from certain SGAs—could translate into significant gains in metabolic morbidity and mortality.

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