

# TOP Journal Club

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## Validation of the Investigator's Assessment Questionnaire, a new clinical tool for relative assessment of response to antipsychotics in patients with schizophrenia and schizoaffective disorder.

The success of long-term therapy in schizophrenia is contingent upon real-world effectiveness or improvements in several domains, including efficacy, safety and tolerability. This report describes the Investigator's Assessment Questionnaire (IAQ), a new 10-item instrument designed to assess relative effectiveness (efficacy, safety and tolerability) of antipsychotic medications in patients with schizophrenia or schizoaffective disorder. To measure content validity, 300 psychiatrists rated the importance of the IAQ items. Efficacy (i.e., positive and negative symptoms) was considered most important, but importance scores relative to the mean ranged only from 0.87 to 1.18, suggesting similar importance of the items. Cronbach's coefficient alpha values showed that the items were internally consistent. Factor analyses indicated that all IAQ items belong to a single domain. Data from the US Broad Effectiveness Trial of Aripiprazole were used for construct validation. Total IAQ score correlated significantly with time to treatment discontinuation ( $r=-0.50$ ), Clinical Global Impressions-Improvement (CGI-I) score ( $r=0.76$ ) and medication preference of patients ( $r=0.71$ ) or caregivers ( $r=0.70$ ). A one-unit decrease in IAQ score corresponded to an additional 1.35 days in the study and a decrease in CGI-I of 0.21 units. These results provide initial validation of the IAQ as a tool for evaluating antipsychotic response in patients with schizophrenia or schizoaffective disorder.

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## Reversal of Symptomatic Hyperprolactinemia by Aripiprazole

To the Editor: Hyperprolactinemia is a well-recognized complication of treatment with antipsychotics, causing multiple endocrine and sexual

side effects, including the risk for osteoporosis and possibly breast cancer. We report a case of successful treatment of risperidone-induced hyperprolactinemia by the partial dopamine agonist aripiprazole.

Anne was a 17-year-old adolescent diagnosed with schizophrenia complicated by medication noncompliance. She was admitted to the inpatient service while acutely psychotic. She had mild asthma but no other medical problems. Her periods had been normal since menarche. Her maternal grandfather also has schizophrenia but had been asymptomatic for many years while taking haloperidol.

Risperidone was started because of the option for a long-acting formulation. Anne accepted the idea of an intramuscular injection because of her grandfather's history. Her oral dose was titrated up to 4 mg/day over 2 weeks, after which she received her first injection of 25 mg. She reported a decrease in psychotic symptoms but began to complain of bilateral breast pain, swelling, and galactorrhea. Serum prolactin was drawn and found to be elevated, at 119  $\mu\text{g/ml}$  (normal range 0–25  $\mu\text{g/ml}$ ). Aripiprazole (15 mg/day) was added to her drug regimen because of its partial agonism at the dopamine receptor making it a theoretically useful tool in lowering prolactin. Anne remained taking oral risperidone, 4 mg/day, and had a gradual resolution of her breast pain and galactorrhea. Another prolactin level taken 12 days later was 18  $\mu\text{g/ml}$ . Anne was discharged from the hospital much improved while taking a combination of a long-acting intramuscular injection of risperidone, 25 mg every 2 weeks, and aripiprazole, 15 mg/day.

Aripiprazole lowers serum prolactin below placebo when it is used as a single agent. To our knowledge, this is the first case report of aripiprazole used in combination with another antipsychotic expressly to treat symptomatic hyperprolactinemia. Risperidone causes more marked elevations in prolactin than other atypical antipsychotics because it does not fully cross the blood-brain barrier. Dopamine D<sub>2</sub> receptor occupancy is therefore higher at the level of the pituitary than in the striatum. Aripiprazole has a greater affinity for the D<sub>2</sub> receptor than risperidone, with central D<sub>2</sub> receptor occupancy around 90% at a dose of 15 mg/day. The partial agonist property of this compound means that in the presence of dopamine hypoactivity, as induced by risperidone, aripiprazole will function as a dopamine agonist with roughly 30% intrinsic activity at postsynaptic receptors, restoring tonic inhibition to anterior pituitary lactotrophs.

Spontaneous prolactin decline in this case would be unlikely because the time since risperidone exposure was short. However, normalization after longer-term treatment (1 year) has been reported.

It may be advantageous to avoid the use of directly acting dopaminergic agents in psychotic patients because of the risk for worsening psychosis. Whether this risk is really any lower for aripiprazole when combined with a direct D<sub>2</sub> receptor antagonist is not clear and would need to be answered in a controlled trial.

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### **Clozapine-induced hyperlipidemia resolved after switch to aripiprazole therapy.**

**OBJECTIVE:** To report a case of severe clozapine-induced hypercholesterolemia and hypertriglyceridemia that resolved after therapy was switched to aripiprazole. **CASE SUMMARY:** A 42-year-old white man with schizoaffective disorder experienced new-onset hyperlipidemia with the addition of clozapine therapy. Despite treatment with various antihyperlipidemic agents, his total cholesterol level reached 477 mg/dL and his triglyceride level reached 4758 mg/dL. After a decrease in adherence with clozapine and subsequent deterioration, the patient was hospitalized and his antipsychotic therapy was switched to aripiprazole. The patient's lipid levels improved dramatically to the point that antihyperlipidemic treatment was discontinued. Due to lack of adequate symptomatic relief of psychiatric symptoms, the patient was ultimately switched back to clozapine therapy, at which time his lipid levels started to worsen again. **DISCUSSION:** There is a critical scarcity of data that relate to aripiprazole-induced lipid changes. Some studies have suggested that aripiprazole is not associated with the development of hyperlipidemia. Our case indicates that aripiprazole therapy may not have an adverse effect on lipid levels, even in patients who have a history of hyperlipidemia induced by another atypical antipsychotic. **CONCLUSIONS:** Should aripiprazole be found to have a definitive lipid-neutral effect, then clinicians would be wise to factor this finding into overall

benefit-versus-risk considerations in the antipsychotic treatment selection process, especially in a society in which cardiovascular disease continues to be a principal cause of morbidity and mortality.

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### **Drug-induced diabetes mellitus: the exemple of atypical antipsychotics]**

As an example of iatrogenic diabetes, we discuss the problem of diabetes mellitus in patients receiving atypical antipsychotics. The risk of diabetes mellitus appears to be different according to various molecules with, by decreasing order, clozapine, olanzapine, risperidone and quetiapine, and finally amisulpride, aripiprazole and ziprasidone. A careful analysis of published case reports and series indicates the existence of two different problems: 1) the rather common development of impaired glucose tolerance or diabetes mellitus (often associated with metabolic syndrome) related to weight gain in individuals at risk for type 2 diabetes; and 2) the occurrence of rare cases of acute metabolic episodes with severe ketoacidosis and/or pancreatitis whose pathophysiological mechanisms remain largely unknown. Generally speaking, the pathophysiology involves both increased insulin resistance and deficient insulin secretion. Cautious metabolic monitoring of patients receiving atypical antipsychotics is recommended, and the selection of the appropriate drug should be influenced by the metabolic profile of the various molecules and the metabolic risk of the patients who should be treated with atypical antipsychotics.

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