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# Antipsychotic induced metabolic changes & treatment response: A prospective study

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ABSTRACT

*Background:* Metabolic side effects of antipsychotics contribute to morbidity and non-compliance in treatment of psychosis. Multiple studies suggest that metabolic side effects correlate with response to antipsychotic treatment. However, few studies have systematically looked at this. We conducted an exploratory, naturalistic, prospective, trans-diagnostic study to examine this association.
*Methods:* 100 patients with psychosis, initiated on antipsychotic treatment alone, were assessed on Brief Psychiatric Rating Scale (BPRS), visual analog scale for appetite, anthropometric measurements (weight, waist circumference, body mass index), and fasting serum lipid and glucose profiles at baseline, 2–4 weeks ($n = 71$) and 8–12 weeks ($n = 39$).
*Results:* Subjects who dropped out at first/second follow-ups did not differ from those who followed-up, in age, sex, illness duration and BPRS scores. On forward stepwise multiple linear regression analysis, early (2–4 weeks) increase in appetite and triglyceride levels ($R^2 = 0.257$; $p = 0.003$) together predicted 26% variance in treatment response (BPRS score reduction) at first follow-up. At second follow-up 16% of variance in treatment response was predicted by early (2–4 weeks) increase in triglyceride levels ($R^2 = 0.169$; $p = 0.009$).
*Conclusions:* Early appetite and triglyceride changes predicted antipsychotic treatment response. Involvement of dopaminergic, serotonergic and histaminergic neural pathways could explain the association between appetite and treatment response. Insulin signaling pathways have been implicated in lipid changes with antipsychotics. Study findings suggest metabolic side effects may be early predictors of antipsychotic response. These findings warrant further examination to elucidate the interaction between metabolic pathways and psychotic illnesses, and possibly mechanism of action of antipsychotics beyond dopamine blockade.



## 1. Introduction

Antipsychotics have changed the outcome of and the outlook on severe mental illnesses like schizophrenia; however, antipsychotic medications have the propensity to produce significant side effects that can impede long-term care. The occurrence of these side effects can be understood by the pharmacodynamic profiles of these molecules (Stahl, 2008). Multiple observations show that use of antipsychotics has been associated with a tremendous rise in prevalence of obesity, diabetes, and other metabolic derangements, both in adults and children. Medicated schizophrenia patients had 40–60% obesity rates, compared with 30% in the general population (Allison et al., 1999). In the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) (Lieberman et al., 2005), significant weight and BMI increases were noted at 8 weeks on olanzapine, risperidone and quetiapine, in a prospective, second-generation-antipsychotic-naïve sample.

Given the existing literature on metabolic syndrome, both in drug-naïve and treated patients, antipsychotics may either be causative or may exacerbate pre-existing metabolic abnormalities

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(Keck and McElroy, 2003). Antipsychotics are known to affect all components of the metabolic syndrome. Weight gain can range from 1 to 10 kg over a 1-year period (Newcomer and Haupt, 2006). Total cholesterol and triglyceride levels are probably the earliest and most sensitive indices of the metabolic abnormalities associated with olanzapine and other antipsychotics (de Leon and Diaz, 2007). Clozapine is the only oral antipsychotic that appears to be consistently associated with increased risk of hypertension, an association more likely in patients with prior history of hypertension or borderline blood pressure readings at baseline (Gupta and Rajaprabhakaran, 1994).

Antipsychotics vary in their propensity to produce metabolic side effects, with clozapine being the most likely and ziprasidone the least (clozapine > olanzapine > risperidone > quetiapine > aripiprazole > ziprasidone). This is elucidated by the average weight gain over a 1 year period with antipsychotics: clozapine and olanzapine 4–10 kg, Risperidone and quetiapine 2–3 kg, aripiprazole and ziprasidone <1 kg (Newcomer and Sernyak, 2007). Interestingly, antipsychotics graded according to their efficacy also follow the same hierarchy i.e. clozapine > olanzapine > risperidone > quetiapine = aripiprazole = ziprasidone (Girgis et al., 2008). Several studies over the last two decades have reported an association between antipsychotic induced metabolic side effects and clinical response (Ascher-Svanum et al., 2008; Bai et al., 2006; Bustillo et al., 1996; Czobor et al., 2002; Dursun et al., 1999; Gupta et al., 1999; Hermes et al., 2011; Kinon et al., 2005; Lamberti et al., 1992; Lane et al., 2003; Leadbetter et al., 1992; Meltzer et al., 2003; Procyshyn et al., 2007; Sharma et al., 2010; Umbricht et al., 1994). These studies looked mainly at patients with schizophrenia and schizoaffective disorder. While second-generation antipsychotics (clozapine and olanzapine, more than risperidone and quetiapine) have shown this association more consistently, Hermes et al. found this association with low-potency first generation antipsychotics like perphenazine also (Hermes et al., 2011). Recently, the relevant literature in this area has been reviewed and it has been postulated that response to antipsychotics (at least partially) might be contingent upon the production of metabolic side effects – a concept provocatively termed as 'metabolic threshold' (Sharma et al., 2013).

Most of these previous studies have been retrospective or post hoc analyses, and have not systematically examined all metabolic parameters. We conducted an exploratory, naturalistic, prospective, trans-diagnostic study to examine this association. The study objective was to evaluate the relation between the metabolic side effects, [both clinical (weight, BMI, waist circumference, appetite change) and laboratory parameters (lipid profile, blood sugar)] and clinical improvement with antipsychotics, in psychotic illnesses [non-affective psychoses and mania-first episode]. Based on the background literature (as reviewed above), we hypothesized that the magnitude of metabolic changes will have a significant positive correlation with magnitude of clinical improvement.

## 2. Methods

Patients ($n$ = 100) fulfilling the DSM-IV-TR diagnostic criteria for schizophrenia/schizoaffective disorder/schizophreniform disorder/brief psychotic disorder/mania first episode/unspecified psychosis, with diagnosis independently confirmed by two psychiatrists, were recruited for the study, after written informed consent. The National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, ethics committee approved the study. The patients were recruited from May 1st, 2010 till August 1st, 2011. They were all inpatients in the Psychiatry wards at NIMHANS at the time of recruitment into the study and were aged between 15 and 45 years. Patients were excluded if they were: in catatonia/not taking food orally; on treatment with oral antipsychotics for more than 5 days or depot neuroleptics within the past one month; having mental retardation; using substances other than nicotine; Pregnant/lactating/postpartum women; having medical co-morbidity (Diabetes mellitus, Obesity, Dyslipidemia, Hypertension, Ischemic heart disease, Cushing's syndrome, Thyroid disorder, Hepatic or Renal dysfunction, Polycystic ovarian disease); using oral contraceptive pills, steroids, beta-blockers or weight-lowering medication.

100 subjects were recruited into the study at baseline. Of these, 72 could be followed up at Follow-up 1 (2–4 weeks) and 39 at Follow-up 2 (8–12 weeks). A single rater carried out all the assessments.

### 2.1. Assessments

A structured proforma was designed to record information on patients. It included – socio-demographic data, education, age at onset, duration of illness, course, diagnosis, treatment history, family history, substance use, anthropometric data, psychopathology rating scores, current medication, including parenteral, sedatives and electroconvulsive therapy, and blood test results. For rating psychopathology the 24-item Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) was used. We assessed appetite using a visual analog scale (VAS). Operationally a VAS is usually a horizontal line, on which a patient marks the point that he/she feels represents their perception of their current state. With regards its use in appetite assessment, food intake was related to perceptions of hunger and fullness as assessed by VAS in healthy older and young subjects (Parker et al., 2004). A VAS is a useful measurement for subjective characteristics or attitudes that range across a continuum and that cannot be directly measured. As such the assessment is highly subjective. These scales are of most value when looking at change within individuals, and are of less value for comparing across a group of individuals at one time point (Wewers and Lowe, 1990). In our study we asked patients to rate their appetite in the last one week prior to assessment on a scale ranging from −5 to +5, with 0 being their usual appetite. The negative rating, i.e. −5 to 0, was useful for baseline assessments since psychosis can be associated with reduced appetite. Antipsychotic treatment has a restorative effect on biological functions, including appetite. For some individuals antipsychotics can produce increases in appetite beyond their normal appetite. The part of the VAS ranging from 0 to +5 could capture this aspect. For recording other side effects on antipsychotics, we used an adaptation of the LUNSERS (Day et al., 1995) scale. The Indian Diabetes Risk Score (IDRS), a four-item scale developed by the Madras Diabetes Research Foundation (Mohan et al., 2005) was used in our study as an indicator of metabolic risk in a given patient. Anthropometric measures included weight, waist circumference and body mass index (BMI). Blood tests were done on an 8 h fasting sample for blood sugars and serum lipid profile (triglycerides and cholesterol – total, high density, low density and very low density).

### 2.2. Statistical analyses

The Statistical Package for Social Sciences (SPSS) version 13.0 was used for statistical analyses. Pearson's correlation and linear regression were used to study the association between metabolic side effects and clinical improvement with antipsychotics. To look at the effects of confounding variables on clinical improvement and metabolic parameters, the Independent Samples $T$-test, Chi-square test, and One way Analysis of Variance (ANOVA) were used.