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Review

Association between antipsychotic-induced metabolic side-effects and clinical improvement: A review on the Evidence for "metabolic threshold"

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ABSTRACT

Over the last two decades, several studies have reported an intriguing association between clinical improvement with antipsychotics and metabolic side effects. In this review, we attempt a critical evaluation of fifteen such studies. The following are the summary observation from these studies: weight gain over a period of few weeks to more than a year, has been consistently found to be associated with clinical improvement. In addition, serum triglyceride changes have also been found to demonstrate this association. This relationship was not affected by socio-demographic factors, duration of illness or baseline body mass index. Findings from these studies depict changes mainly in schizophrenia patients on treatment with clozapine or olanzapine. Other drugs and diagnoses are poorly represented. Moreover, appetite, physical activity, other metabolic parameters have not been adequately examined. This review raises an important question – "Is there a *metabolic threshold* for antipsychotics?" i.e. is response to antipsychotics contingent upon the production of metabolic side effects. Current research proposes the involvement of insulin, leptin and phospholipid pathways in pathogenesis as well as therapeutics of psychosis. Though knowledge in this area is preliminary, it clearly warrants further systematic evaluation.

Contents

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1. Introduction

Back in the 1950s, Haase gave the concept of a 'neuroleptic threshold' with first-generation antipsychotics, defining it as the minimum dose at which one can effectively compensate psychotically caused agitation while at the same time avoiding the sedative major tranquilizer effect (Haase, 1980). For a few decades thereafter, the potency, therapeutic range and efficacy of first-generation antipsychotics were understood based on this neuroleptic threshold. Later analyses have shown that antipsychotic action is not subject to a sharp all-or-none neuroleptic threshold; rather it increases over a small dose range (Miller, 2009). From clinically observable side effects and laboratory studies, it is known that antipsychotics act at a multitude of neurotransmitter systems and receptors in the brain and periphery, including dopaminergic, serotonergic, histaminergic, cholinergic and adrenergic systems. While dopamine antagonism is the most widely cited mode of action of antipsychotics, how much the other receptor systems contribute to therapeutic effect and how much to merely side effects, is less well understood. With increasing use of second-generation antipsychotics (SGAs), metabolic side effects, like weight gain, serum lipid changes and glucose intolerance, are becoming increasingly common (Muench and Hamer, 2010).

The "metabolic syndrome" comprises of insulin resistance, dyslipidemia, hyperglycemia, central obesity and hypertension (Eckel et al., 2005). Most antipsychotic drugs produce weight gain (Allison et al., 1999). Medicated schizophrenia patients had 40–60% obesity rates, compared with 30% in the general population (Allison et al., 1999). Among the antipsychotics, it is the second generation antipsychotics (SGA) that have been most often implicated in metabolic side-effects; however, low-potency first generation antipsychotics (FGA), like chlorpromazine and thioridazine, also cause significant weight gain (Wirshing, 2004). With regards to other metabolic abnormalities, clozapine and olanzapine (and possibly quetiapine and low-potency typical antipsychotics) can directly cause hyperlipidemia, independent of their effects on obesity (de Leon et al., 2007) and glucose intolerance (Lean and Pajonk, 2003). Clozapine, particularly, has an increased risk of producing hypertension (Gupta and Rajaprabhakaran, 1994).

A recent meta-analysis on the comparative efficacy of antipsychotics in schizophrenia, found clozapine, olanzapine, risperidone and amisulpride to be more efficacious than the other first and second generation molecules (Leucht et al., 2013). Clozapine, olanzapine, and zotepine were associated with greater weight gain than the others (Leucht et al., 2013). It is interesting to see that the two most efficacious antipsychotics, clozapine and olanzapine, are also the ones associated with greater weight gain than the rest. However there were exceptions like amisulpiride which has lesser propensity for weight gain but better efficacy.

Some studies have examined the relation between metabolic abnormalities and clinical improvement with antipsychotics (Bai et al., 2006; Bustillo et al., 1996; Czobor et al., 2002; Dursun et al., 1999; Gupta et al., 1999; Kinon et al., 2005; Lamberti et al., 1992; Lane et al., 2003; Leadbetter et al., 1992; Meltzer et al., 2003; Procyshyn et al., 2007; Umbricht et al., 1994). Planansky et al. way back in 1959 had found that increase in weight correlated with symptom improvement while loss in weight was actually associated with worsening of symptoms (Planansky, 1958). More recently, the CATIE trial found an association between BMI change and PANSS score improvement; however, the findings though statistically significant were not clinically substantial (Hermes et al., 2011).

The occurrence of metabolic abnormalities contributes to morbidity and mortality for psychiatric patients and understandably, much attention is paid to counteracting their occurrence. However, given the finding of association between weight gain and clinical improvement, there has been a renewed interest in looking at metabolic abnormalities. Possible role of metabolic pathways in psychiatric illnesses has been proposed (Boston et al., 1996a,b). This raises an important question – are metabolic side effects a necessary evil with use of antipsychotic medication? In other words, 'Is there a *metabolic threshold* (Sharma et al., 2010) for antipsychotics?' i.e. the clinical efficacy of an antipsychotic is at least partly contingent upon the production of metabolic abnormalities. In this context, this article reviews the existing literature about the link between metabolic side effects and clinical improvement with antipsychotics.

2. Methods

We used a computer literature search of the National library of medicine's Medline-Pubmed search with "antipsychotics", "clinical improvement", "weight gain", "metabolic side-effects" and "serum lipids" as key words, supplemented by a manual search of bibliographic cross-referencing. Clinical studies reporting on patients based observation, published in the English language, in the last 20 years, were included (Table 1).

3. Findings from studies

We could obtain a total of fifteen studies – Leadbetter et al. (1992), Umbricht et al. (1994), Lamberti et al. (1992), Bustillo et al. (1996), Dursun et al. (1999), Gupta et al. (1999), Czobor et al. (2002), Lane et al. (2003), Meltzer et al. (2003), Kinon et al. (2005), Ascher-Svanum et al. (2005), Bai et al. (2006), Procyshyn et al. (2007), Sharma et al. (2010), Hermes et al. (2011) – examining the relation between clinical improvement and metabolic side effects with antipsychotics. Among these there were seven prospective studies (Bustillo et al., 1996; Dursun et al., 1999; Lane et al., 2003; Leadbetter et al., 1992; Meltzer et al., 2003; Procyshyn et al., 2007; Umbricht et al., 1994), five studies with post hoc analysis of prospective data (Ascher-Svanum et al., 2005; Bai et al., 2006; Czobor et al., 2002; Hermes et al., 2011; Kinon et al., 2005) and three retrospective chart reviews (Gupta et al., 1999; Lamberti et al., 1992; Sharma et al., 2010). The following section summarizes the observations organized under various sub-headings.

3.1. Type of antipsychotic medication

Eleven of the fifteen studies had either clozapine or olanzapine as the main antipsychotic drug. Risperidone or haloperidol was the next most common, while the other second generation and first generation antipsychotics have been poorly represented in these studies. Clozapine and olanzapine are the antipsychotic drugs known to cause maximum amount of metabolic abnormalities and are also, comparatively, among the most efficacious antipsychotic molecules (Leucht et al., 2013). Significantly, in the report by Hermes et al. (2011) from the CATIE study, olanzapine and Perphenazine (low potency first generation drug) groups showed an association between clinical response and metabolic abnormalities, while Risperidone, Quetiapine, and Ziprasidone did not. The authors explained this by citing lower sample sizes in the latter groups. No studies had patients on drugs other than antipsychotics.

3.2. Changes in metabolic parameter (weight gain and serum lipid levels)

In all the studies reviewed patients had weight gain, from as early as $1^{1/2}$ months to 90 months. Lane et al. (2003), in their study done over 6 weeks, found patients to have gained a mean weight of 0.442 kg per week with Risperidone. Kinon et al. (2005) looked at