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Effects of pioglitazone on metabolic abnormalities, psychopathology, and cognitive function in schizophrenic patients treated with antipsychotic medication: A randomized double-blind study☆,☆☆,★,★★

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ABSTRACT

Background: Schizophrenic patients treated with antipsychotic drugs (AP) have an increased frequency of glucose–lipid metabolic abnormalities and diabetes. Pioglitazone has been shown to be effective in the treatment of glucose and lipid abnormalities in diabetes and decreasing longer-term conversion of impaired glucose tolerance to frank diabetes. Some studies also suggest possible pro-cognitive and antidepressant effects of pioglitazone. We studied the effects of pioglitazone on potential metabolic, symptomatic and cognitive benefits in schizophrenic patients treated with AP.

Methods: 54 schizophrenic patients with at least both a)impaired glucose and b) triglycerides ≥120 mg/dL and/or low HDL levels, participated in a double-blind placebo controlled study of 3 month treatment with Pioglitazone (30–45 mg/day) or matched placebo, at 5 sites (4 U.S., 1 China). Fasting glucose and lipid parameters, and psychopathology (PANSS scale) were assessed monthly, and patients had a glucose tolerance test and cognitive testing (RBANS and CPT) at baseline and at the end of study. Statistical analysis used mixed model repeated measures analysis, supplemented by completer and LOCF analysis.

Results: In the total sample there was an overall effect (P's<.05 to <.01) of pioglitazone on preventing deterioration in fasting glucose and improving HDL and PANSS depression scores; in the pioglitazone group comparison of baseline vs 3 month values also showed significant (P<.05) decreases in fasting insulin, 2 h glucose in GTT and insulin resistance (HOMA-IR). However there were marked differences between the responses of patients in the U.S. sites vs the China site. In the U.S. sample, patients treated with pioglitazone, when compared to placebo treated patents, had significantly lower fasting glucose ($F=3.99$, $P=0.02$), improved insulin sensitivity (lower H0MA-IR, $F=6.24$, $P=.002$), lower triglycerides ($F=2.68$, $P=.06$) and increased HDL ($F=6.50$, $P=.001$). By the end of the study 52% of the pioglitazone treated patients compared to 15% of the placebo patients had fasting glucose in the normal range (Fisher's exact test $P=.02$). Pioglitazone also significantly improved PANSS depression factor scores ($F=2.82$, $P=0.05$). It did not improve cognitive performance on the RBANS or CPT tasks. Pioglitazone did not increase weight or produce any other significant side-effects. In the small mainland China site sample, pioglitazone treatment, as compared to placebo, did not show greater improvement in metabolic parameters or psychopathology ratings.

☆ When this work was done, Drs. Smith and Dwivedi were also associated with Manhattan Psychiatric Center, New York, New York.

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★ Clinical Trial Registration: NCT00231894, Clinical Trials.gov.

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Conclusions: In the sample of patients from the U.S., pioglitazone was an efficacious and safe treatment for glucose and lipid metabolic abnormalities in schizophrenic patients treated with AP, and it may also have beneficial effects on depressive symptoms. It may be particularly useful in patients whose weight gain effects from antipsychotics have plateaued and where weight loss is not the primary goal. The risk vs. benefits of longer term treatment with pioglitazone has to be carefully evaluated for individual patients.

1. Introduction

Drug treatments that could reduce or prevent the progression of glucose and lipid metabolic changes occurring during treatment with second generation antipsychotics (APs) might permit patients to continue to receive the benefits of these APs with reduced drug-induced comorbidity. Pioglitazone (PIO)is an antidiabetic drug, in the thiazolidinedione class (TZDs), which is thought to act through its effect on increasing insulin sensitivity and decreasing hepatic glucose utilization (Parker, 2002; Stumvoll and Herring, 2002), and a case series suggested that PIO might improve hyperglycemia in schizophrenics (Edlinger et al., 2007). Preliminary data also suggest possible antidepressant and pro-cognitive effects of PIO in major depressive disorder or early Alzheimer's patients (Kemp et al., 2009; Sato et al., 2011). This background led us to design a double-blind study of the effects of pioglitazone on glucose and lipid metabolism, psychopathology, and cognition in schizophrenic patients.

2. Methods

2.1. Participants

Participants were 54 patients with chronic schizophrenia or schizoaffective disorder, currently treated with APs, who participated at 5 sites: 4 in the U.S. (N = 44), and 1 in Shanghai, China (N = 10). Patients entered met the following metabolic criteria: *a*) fasting glucose ≥ 100 mg/dL or 2 h glucose tolerance test ≥ 140 mg/dL or current treatment with oral antidiabetic drugs with hyperglycemia history; and *b*) triglyceride levels ≥ 120 mg/dL and/or HDL levels < 40 mg/dL. Patients signed informed consents for a study approved by IRB's at each site.

2.2. Design and drug dosage

This was a 3-month, double-blind randomized trial of pioglitazone(PIO) and matching placebo. PIO dosage was 30 mg/day with permission to raise to 45 mg/day if glucose control was deemed insufficient (3 patients), or lower to 15 mg/day if side-effects or hypoglycemia developed (no patients). (Mean ± S.D. PIO dose 31.5 ± 4.6 mg). Due to the characteristics of recruitment and/or drop-outs after randomization assignments, there was a slight excess of randomization to pioglitazone (30) vs. placebo (24) in the total subjects considered for analysis. All patients also participated in a manualized diet-exercise program.

2.3. Assessments

Patients had fasting metabolic glucose and lipid and weight assessments at baseline and then monthly with procedures previously described (Smith et al., 2009). They had an oral glucose tolerance (GTT) test at baseline and end of study. They had monthly PANSS psychopathology ratings (Kay et al., 1987), with ratings on a single patient performed by the same rater, and neuropsychological tests of RBANS (Gold et al., 1999) and Vigil CPT (K and AK) (Psychological Corporation, 1988) at baseline and end of study.

2.4. Metabolic assays

Assays for glucose and lipids were performed at each site's clinical laboratories. (Assay procedures are detailed in a web supplement at http://www.rfmh.org/nki/pubs/fulltext/rsmith2012JSchres.pdf.)

Leptin and FFA assays performed at a single research laboratory were described in our previous publications (Smith et al., 2009, 2010).

2.5. Statistical analyses

Statistical analysis was performed with SPSS (13) and SAS (8.2), and with N-Query 3 (Elashoff, 1999) for power analysis. The primary analysis used to compare drug effects over time was a mixed model repeated measures analysis of variance (MMA), described in our prior publications (Smith et al., 2009). Drug and study site were

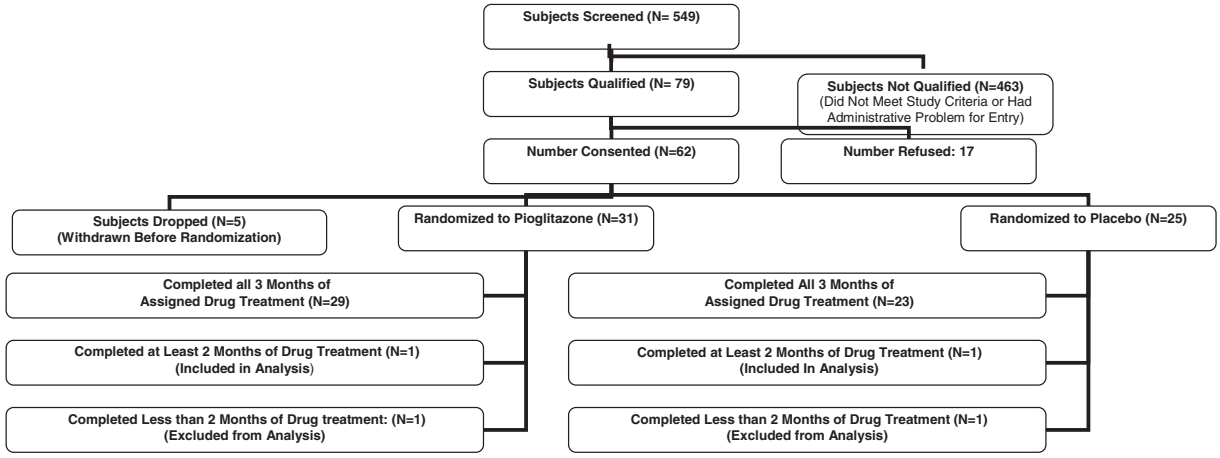

Fig. 1. Subjects flow through the study of metabolic effects of pioglitazone versus placebo. Subjects who were randomized but did not complete the 3 months of study either withdrew consent (N = 2), or had had lab values which on more careful evaluation did not meet the protocol criteria or were grounds for exclusion. Two patients were terminated before two months because of their psychiatric condition which led to non-compliance with protocol procedures (N = 1) or failure to keep study appointments and subsequent loss to study (N = 1).