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Clozapine-induced weight gain predicts improvement in psychopathology

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Abstract

Background: Some, but not all, previous studies have indicated that weight gain is associated with greater improvement in psychopathology during clozapine treatment. Possible reasons for the inconsistent results include failure to adjust for initial body weight and level of psychopathology, differences in trial duration, outcome measures, reliability of assessment, concomitant medications and clozapine dosage. The purpose of this study was to test the hypothesis that clozapine-induced weight gain is related to antipsychotic efficacy at 6 weeks and 6 months after adjusting for initial body weight and severity of illness. *Methods*: Weight and psychopathology were determined in 74 patients with schizophrenia or schizoaffective disorder at baseline and after 6 weeks and 6 months of open treatment with clozapine monotherapy. The primary measures of psychopathology were the Brief Psychiatric Rating Scale (BPRS) Total and Positive symptoms subscales, Schedule for Assessment of Negative Symptoms (SANS), Schedule for Assessment of Positive Symptoms (SAPS) and Global Assessment of Function Scale (GAFS). *Results*: Significant improvement in the key measures of psychopathology was noted at 6 weeks and 6 months. Mean weight gains at 6 weeks and 6 months were 3.7 ± 5.7 S.D. and 7.3 ± 7.9 S.D. kg, respectively, with the increase between 6 weeks and 6 months being significant. Age, but not gender, initial body weight, clozapine dosage or plasma levels predicted weight gain at both time points. At 6 weeks and 6 months, after adjustment for age, initial weight and level of psychopathology, the percentage change in weight significantly predicted the improvement in the BPRS Total and Positive symptoms subscale, the SANS Global score, as well as other measures of psychopathology. *Conclusions*: Increase in weight with clozapine predicted improvement in psychopathology. This suggests that effects of clozapine on neurotransmitters which influence weight gain, e.g. 5-HT_{2C} and 5-HT_{1a} antagonism, in association with individual variations in these receptors and others molecules, e.g. peptides and transporters, due to polymorphisms or post-translational editing of mRNAs, may also contribute to the improvement in psychopathology.

Keywords: Clozapine; Weight gain; Serotonin

1. Introduction

Clozapine is an atypical antipsychotic drug which has been reported to be superior in efficacy to typical antipsychotic drugs for both positive and negative

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symptoms in neuroleptic–refractory patients with schizophrenia (Kane et al., 1988; Leucht et al., 1999). Despite other advantages, including minimal extrapyramidal side effects (EPS), lack of tardive dyskinesia, lack of hyperprolactinemia, improvement in cognitive function and a possible effect to decrease suicidality, its use has been limited by side effect liability, especially agranulocytosis, seizures and weight gain (Baldessarini and Frankenburg, 1991; Meltzer, 1992, 1997).

While agranulocytosis and seizures are much more common with clozapine than other atypical antipsychotic drugs, olanzapine produces weight gain equivalent to that of clozapine; risperidone and quetiapine produce smaller increases; and ziprasidone has no net effect on weight (Allison et al., 1999). Marked weight gain with the atypical antipsychotic drugs is to be associated with increased risk of diabetes mellitus and cardiovascular disease as well as other undesirable consequences (Allison et al., 1999).

The weight gain associated with clozapine may be one of the major reasons for the reluctance to use it more extensively and for discontinuation, but there are no reliable data concerning how important a factor is in these two matters. However, there is considerable, if controversial, evidence that weight gain is also related to the improvement in psychopathology during treatment with clozapine. Such a relationship was first suggested by Leadbetter et al. (1992), who reported a significant correlation between weight gain and improvement in the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), total, as well as negative symptom score, in 21 patients with schizophrenia or schizoaffective disorder in a 16-week clozapine trial. Subsequently, Lamberti et al. (1992) reported a nearly significant correlation between the decrease in BPRS Total score and weight gain in 36 schizophrenic patients treated with clozapine for 6 months. Thirdly, Bustillo et al. (1996), in a study of 19 schizophrenic patients treated with clozapine for 10 weeks, also found an inverse relationship between the percentage change in BPRS Total score and weight gain. However, in 33 patients treated with open-label clozapine for 1 year, no significant correlation between these measures was observed. Finally, Bai et al. (1999) studied 96 schizophrenic patients treated with clozapine for 14 months and found a significant correlation between weight gain and change in the Clinical Global Impression Scale (CGI) (Guy, 1976) scores in female but not in male patients.

On the other hand, Umbricht et al. (1994) failed to find a significant correlation between weight gain and improvement in BPRS Total score in a study of 64, 45 and 19 schizophrenic patients treated with clozapine for 4, 8 and 12 weeks, respectively. However, they examined this relationship by classifying patients into responders and non-responders at each of these time periods, which would be expected to reduce the power to find a relationship. Subsequently, Hummer et al. (1995) found no correlation between improvement in psychopathology and weight gain in 31 patients treated with clozapine for 12 weeks. The initial level of psychopathology was not included as a covariate in the analysis. Ganguli (1999) has concluded that the relationship between weight gain and response to antipsychotic drugs is unclear. In summary, studies which examined the relationship between weight gain and response to clozapine in the first 10–12 weeks of treatment found no or modest relationships between the response to clozapine and weight gain, whereas two studies of this relationship with a duration of 4–6 months and one study of 14 month's duration reported a significant association.

The purpose of the present study was to test the hypothesis that clozapine-induced weight gain is related to its antipsychotic efficacy using multiple regression to control for initial severity of illness since clinical response in this population is often a function of initial level of psychopathology (Thompson et al., 1994). Studies which only utilize percent change in one or another psychopathology measure as a criterion of response have a greater chance of a type-II error for this reason (Thompson et al., 1994). We also examined the possibility that initial body weight and gender might influence the relationship between change in weight with clozapine and improvement in psychopathology. We predicted that weight change and improvement in psychopathology would be directly related, i.e. that patients who gained the most weight would show the greatest improvement after adjustment for initial weight and severity of psychopathology. We also considered whether basal metabolic index (BMI) might provide results different from those with weight alone.