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Letter to the Editor

H_1-histamine Receptor Affinity Predicts Short-term Weight Gain for Typical and Atypical Antipsychotic Drugs

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Sir

In their report, Kroeze *et al* (2003) conclude that antipsychotic-induced weight gain is mainly due to H_1 receptor antagonism. They suggest that 'The next generation of antipsychotic drugs be screened to avoid H_1-histamine receptors'. This major conclusion is based on statistical analyses relating weight gain indices for 17 antipsychotics to their affinities for 12 receptors. These analyses suggested that 'Affinity for the H_1 receptor is the best single predictor of a drug's propensity to induce weight gain'. If valid, this important conclusion will drive drug discovery. However, a number of issues raised by Kroeze *et al*'s (2003) paper merit consideration before these conclusions are accepted uncritically. The weight gain data used in the relevant analyses are all cited as taken from a meta-analysis conducted by Allison *et al* (1999). Some authors reviewing the literature on antipsychotic-induced weight gain have concluded that meta-analysis is not appropriate in this context (Taylor and McAskill, 2000). However, even if we ignore this specific problem, the following issues arise.

Firstly, Kroeze *et al* (2003) cite weight gain data for the novel antipsychotic aripiprazole. However, Allison *et al* (1999) did not include aripiprazole in their meta-analysis at all, since this drug was not marketed until very recently. Secondly, data are presented for quetiapine as weight gain in kg/10 weeks of treatment (as for all drugs), despite the fact that Allison *et al* (1999) reported that 'Insufficient data were available to evaluate quetiapine at 10 weeks'. The data reported for quetiapine were actually for 6 weeks of treatment.

Thirdly, Allison *et al* (1999, Table 4) reported four different indices of weight gain: (i) weight gain derived from a fixed effects model when duration of treatment was not considered; (ii) weight gain derived from a random effects model when duration of treatment was not considered; (iii) estimated weight gain after 10 weeks of treatment derived from a fixed effects model; and (iv) estimated weight change after 10 weeks of treatment derived from a random effects model. Allison *et al* (1999) stressed the importance of using a random effects model, and concluded that the 'most reasonable estimates' were the estimated weight changes after 10 weeks of treatment derived from a random effects model. However, rather surprisingly, *none* of the weight gain data cited by Kroeze *et al* (2003, Table 1) were derived from this specific recommended index. Instead, some data were derived from index (i), for example data for loxapine and molindone; some from index (ii), for example data for risperidone and thioridazine; and some from index (iii), for example data for chlorpromazine and clozapine. The reason(s) why different indices were used for different drugs were not explained, despite the fact that the use of different indices can lead to very different estimates of weight gain. For example, for chlorpromazine, the four indices were 6.19, 4.19, 2.10, and 2.58 kg, respectively. The index actually used (2.10 kg) was clearly substantially smaller than the highest possible index (6.19 kg). Given that the critical indices of weight gain used in the analyses reported by Kroeze *et al* (2003) remain unclear, we suggest that the very provocative conclusions they draw from their analyses should be considered with some care at present.

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