Neuropsychopharmacology (2003) 28, 2210–2211

www.neuropsychopharmacology.org

Reply to Andrew J Goudie *et al*

Reply: H1-histamine Receptor Affinity Predicts Short-term Weight Gain for Typical and Atypical Antipsychotic Drugs

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Neuropsychopharmacology (2003) **28,** 2210–2211, advance online publication, 27 August 2003; doi:10.1038/sj.npp.1300292

Sir

We thank the correspondents for their interest in our work (Kroeze *et al*, 2003), and are grateful for the opportunity to respond to their comments. They correctly summarize the major conclusion of our paper, that is, that affinity for the H1-histamine receptor is the *best* predictor of a drug's propensity to induce weight gain. It is not the *only* predictor, however, since affinities for the α-1a adrenergic and the 5-HT2c serotonin receptor, among others, were also statistically related to weight gain propensities. The implication of this conclusion is that those interested in developing new antipsychotic drugs might well consider the possibility that, if the new drug has a high H1 affinity, it may induce weight gain. This statement was not intended to be 'provocative', but rather cautionary, since it could lead to considerable savings in various phases of drug discovery. The notion that H1 receptors have a role in feeding has long been appreciated and has been validated in a replicable fashion by many investigators (see, for example, Orthen-Gambill and Salomon, 1990; Mercer *et al*, 1994). Indeed, these conclusions are already 'driving drug discovery', and have been doing so for many years.

As stated in the paper, the weight gain data were derived from the meta-analysis of Allison *et al* (1999). Despite the possibility that meta-analytic studies may not be ideal, as suggested previously by Taylor and McAskill (2000) and now by Goudie *et al*, it is our conclusion that the report by Allison *et al* (1999) continues to be the most complete study in the field, since it supplies the most data for comparison. Goudie *et al* do point out that the data used by us were incompletely described, and we would like to clarify this point, as follows: Where possible, the weight gain (kg/10 week) data were used. When these data were not available, as for example with quetiapine, the 6-week data were used. When such 'substitute data' were used, we used the lowest estimate of weight gain induced by the drug, in order to retain the most conservative possible conclusions. The aripiprazole data were from a study that had not yet been published at the time of submission of our paper, but is now available (Marder *et al*, 2003).

The key feature of our paper is the discriminant functions analysis shown in Figure 3 and Table 5 and not the correlative data alluded to by Goudie *et al*. The discriminant functions analysis presupposes that weight gain data are not continuous, but rather binary, that is, does the drug induce short-term weight gain or not? Thus, the *degree* of weight gain or whether the data were derived from the fixed or random effects model is not germane to the analysis, although the actual weight gain numbers were included in Table 1 as a convenience to the reader. We also wish to emphasize that the *location* along the discriminant axis is not the appropriate way to understand the data, but that the *classification*, that is, whether or not a drug is predicted to induce weight gain, is the most important outcome of an analysis like this. In our report, 15 of 17 drugs (88.2%) were correctly classified by this analysis, with H1-histamine receptor affinity alone as good a 'predictor' as the entire data set. We do point out in our paper that the method of data extraction from the Allison study, and/or small sample sizes, could be contributing factors in the misclassification of two of the drugs.

Goudie *et al* suggest that the conclusions of our study should be considered with some care, and we agree with this whole-heartedly, since the mechanism by which these drugs induce weight gain remains unknown. Until the mechanism is known, it is our expectation that our study will help guide

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drug development away from drugs with potentially serious side effects, and be beneficial to the field of antipsychotic drug development.

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