the columns

correspondence

Low dose typical antipsychotics – a brief evaluation

Sir: We read with interest the drug information quarterly by Taylor (*Psychiatric Bulletin*, December 2000, **24**, 465–468) in which the author concluded that "low doses of typical antipsychotics offer no advantages over higher doses". This statement, if true, would be of major clinical importance as it refutes evidence that the apparent advantage of the new 'atypical' antipsychotics, in terms of tolerability, is largely owing to excessive doses of the typical drug being used in the clinical trials (Geddes *et al*, 2000). This statement is, however, opinion rather than evidence-based.

Taylor makes no attempt to review this area systematically, instead relying on the selective citation of a few articles, of variable quality, that support his view. This practice is exemplified on page 466 of the article where, for reasons best known to himself, Taylor cites six isolated 'clinical trials' and neglects to mention the many randomised controlled trials (RCTs) and meta-analyses that cast doubt on the whole thrust of his argument. Taylor measures the tolerability of typical drugs using three indices, hyperprolactinaemia, tardive dyskinesia and placebo levels of extrapyramidal side-effects (EPS). In doing so he biases the article by failing to consider the wide range of potentially distressing side-effects that are associated with antipsychotic treatment. The adoption of hyperprolactinaemia as a proxy for tolerability is particularly confusing as it is accepted that only a proportion of people with it will experience an adverse event. Finally, the receptor binding studies cited in the article in support of Taylor's hypothesis do indeed show that high levels of D2 occupancy are needed for the therapeutic efficacy of typical drugs, but no mention is made of the fact that this may be responsible for early clinical relapse following the withdrawal of 'atypical' drugs (Seeman & Tallerico, 1999).

Taylor does, however, remind us that there is a trend for psychiatrists to use higher doses of typical drugs than can be justified on the basis of the available evidence. Whether such a finding supports Taylor's view or simply indicates that such drugs are used improperly is somewhat debateable. In citing one trial that compares an atypical to haloperidol he also reminds us of the high propensity of this drug to cause EPS even at low doses. To suggest that this fact in itself justifies atypicals as a first-line treatment is as ridiculous as it is to assume that EPS are the only consideration.

Data from well-conducted meta-analyses of RCTs do indeed confirm that 'atypical drugs' are less likely to cause EPS. However, when atypicals are compared to lower doses of 'typicals', efficacy is equal, the burden of total side-effects from both drugs is similar (Kennedy *et al*, 2000) and patients are no more likely to continue taking an atypical drug than an older one (Geddes *et al*, 2000). Taylor's concluding remark flies in the face of almost 50 years of clinical trials and clinical experience in psychiatry. Such 'drug misinformation', if acted upon, would serve only to increase costs with no discernible benefit to patients. Why Taylor should wish for the advantages of atypicals over older drugs to be grossly overstated in this way is a matter for him to clarify.

GEDDES, J. R., FREEMANTLE, N., HARRISON, P., *et al* (2000) Atypical antipsychotics in the treatment of schizophrenia: systematic review and meta-regression analysis. *British Medical Journal*, **321**, 1371–1376.

KENNEDY, E., SONG, F., HUNTER, R., *et al* (2000) Risperidone versus typical antipsychotic medication for schizophrenia. *The Cochrane Database of Systematic Review*. Oxford: Update Software.

SEEMAN, P. & TALLERICO, T. (1999) Rapid release of antipsychotic drugs from dopamine D2 receptors: an explanation for low receptor occupancy and early clinical release upon withdrawal of clozapine or quetiapine. *American Journal of Psychiatry*, **152**, 1210–1212.

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Author's reply: Your correspondents appear to have somewhat misunderstood the main purpose of my review. My intention was to challenge the assertion that low dose typical drugs can be effective without causing 'typical' adverse effects. My final statement (erroneously quoted in your correspondent's letter) relates specifically to this question. I did not, in any way, attempt to address overall tolerability of different groups of drugs; a question well beyond the scope of the article.

Your correspondents cite no data to counter my conclusion that typical drugs produce typical adverse events when used at low but therapeutic doses. Moreover, recent receptor binding studies suggest that it is 'not clinically feasible' to obtain antipsychotic effects of typical drugs without extrapyramidal effects (Kapur & Seeman, 2001).

Your correspondents also aver that I "wish the advantages of atypicals . . . to be grossly overstated". This is demonstrably untrue. Not only did I provide an introduction to the review that gave a balanced view of atypicals, but I am in other respects active in alerting clinicians to the emerging adverse effects of atypical drugs (Taylor & McAskill, 2000; Mir & Taylor, 2001).

KAPUR, S. & SEEMAN, P. (2001) Does fast dissociation from the dopamine D_2 receptor explain the action of atypical antipsychotics? A new hypothesis. *American Journal of Psychiatry*, **158**, 360–369.

MIR, S. & TAYOR, D. (2001) Atypical antipsychotics and hyperglycaemia. *International Clinical Psychopharmacology*, **16**, 63–73.

TAYLOR, D. & MCASKILL, R. (2000) Atypical antipsychotics and weight gain – a systematic review. *Acta Psychiatrica Scandinavica*, **101**, 416–432.

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Antipsychotics in acute agitation

Sir: The pharmacological management of acute agitation, a common clinical problem faced by physicians and psychiatrists, is associated with significant risk. Antipsychotics are frequently used in management but there have been recent reports of dangers associated with some classes of antipsychotics, in particular droperidol and thioridazine. These drugs are associated with QTc interval prolongation, arrhythmia's and sudden death (Reilly *et al*, 2000). In recent months

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