



Much ado about small differences

JOSEPH P. McEVoy

Duke University Medical Center, Durham, NC, USA

Fleischhacker and Goodwin note that “meta-analyses and systematic reviews have often delivered discrepant messages” regarding comparisons across antipsychotic medications; they refer to these discrepancies as “mutually contradictory”. A more parsimonious explanation is that, when only a small difference exists between one drug and another, and numerous studies compare the two drugs, some, but not all, of the studies “detect” the difference. If no difference exists, only a rare, anomalous study “detects” a difference. These are fundamental tenets of probability.

Fleischhacker and Goodwin also state that “where the results of efficacy trials are positive and an effectiveness trial is negative, one should not necessarily prefer the effectiveness trial – it may simply have failed”. Others have cautioned that one should not necessarily prefer the efficacy trials – they may simply be biased (1,2). “Failed” implies that a trial was done so poorly that it was incapable of detecting a difference between treatments when a difference exists. “Failed” is fighting words. The use of such a pejorative term is usually accompanied by detailed delineation of the trial’s purported deficits.

Regarding CATIE, the authors state that “this type of staged design may en-





courage early treatment discontinuation in Phase I, as it allows graduation into a second phase of the investigation". Investigators and patients involved in single phase trials have financial incentives to continue on assigned treatments when they would otherwise switch; payment from sponsors to investigators and free care for patients cease when treatment is discontinued. By having subsequent phases available we did not "encourage" discontinuation; we simply avoided discouraging discontinuation. The CATIE design resembles usual clinical care, wherein alternative treatments are readily available and switches are common. The CATIE survival curves correspond closely to the antipsychotic switch curves in large administrative databases.

Fleischhacker and Goodwin also question whether the selection of perphenazine in CATIE "fairly represented the classical antipsychotic group". This is a puzzling comment. Should we have selected haloperidol to maximize extrapyramidal side effects, or thioridazine to maximize weight gain and anticholinergic side effects? We chose perphenazine because we believed it offered the best package of therapeutic benefit relative to side effects among the classical antipsychotic agents (3,4). Should one insist that ziprasidone most fairly represents the second-generation antipsychotic medications?

Finally, Fleischhacker and Goodwin state that in CATIE "only about 40% of all patients in Phase I received the maximally allowed doses". They seem to imply that the randomized and blinded design of CATIE somehow restricted clinicians from increasing doses. CATIE clinicians could adjust dose at their discretion, just as they could utilize adjunctive medications (e.g., mood stabilizers or antidepressants) and concomitant medications (e.g., anti-parkinson drugs or anti-hypertensive agents) at their discretion. We surmise that these clinicians saw no reason to increase dose in patients who did well, or who developed dose-related side effects, at low doses. Should everyone have been pushed to the highest available dose irrespective of such indicators?

Fleischhacker and Goodwin fault

CUtLASS because "the perception of clinicians may have favoured 'atypicals' and it was difficult to persuade clinicians to use the older (and more 'typical') antipsychotics". This same concern about clinician biases must, of course, be applied to the EUFEST results, where un-blinded clinicians were quicker to discontinue haloperidol than atypical comparators, even though no differences in Positive and Negative Syndrome Scale (PANSS) outcomes were apparent across the drugs. The equivalent survival curves for haloperidol and risperidone in large blinded first episode trials (5,6) are noteworthy.

An over-arching view of all available comparisons (many of which are poorly characterized by an "efficacy/effectiveness" dichotomy) across antipsychotic medications suggest that any therapeutic advantages for second-generation antipsychotic medications (other than clozapine) are small (compared to their differential pricing) and restricted to amisulpride, olanzapine, and perhaps risperidone; any therapeutic advantages of these drugs must be weighed against their potentials for producing metabolic abnormalities and/or prolactin elevations.

Many patients have excellent therapeutic outcomes, and avoid metabolic side effects and prolactin elevations, if treated with inexpensive, low-dose perphenazine (or loxitane, or thiothixene).

The under-utilization of such agents reflects marketing rather than evidence.

References

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