Review: high doses of antipsychotic drugs are no more or less effective than medium doses in people with schizophrenia

Davis JM, Chen N. Dose response and dose equivalence of antipsychotics. *J Clin Psychopharmacol* 2004;24:192–208.

This article contains extra text on the EBMH website

Q Which doses of atypical and typical antipsychotic drugs produce a near maximal response with minimal side effects in people with schizophrenia or schizoaffective disorder?

METHODS

Design: Systematic review with meta-analysis.

Data sources: MEDLINE, International Pharmaceutical Abstracts, CINAHL, PsycINFO, and the Cochrane Database of Systematic Reviews. Hand searches of reference lists plus data from Food and Drug Administration website, poster presentations, unpublished data from Cochrane reviews, conference abstracts, and manuscripts submitted for publication. Search date: December 2002.

Study selection and analysis: Double blind, randomised controlled trials of people with schizophrenia or schizoaffective disorder comparing two or more doses of typical or atypical antipsychotics were eligible. Dose response curves were plotted and the median effective dose, defined as 50% of the maximum response (ED_{50}), and the near maximal effective dose range (ED_{85} to ED_{95}) was established for each drug. Estimated equivalent doses were based on ED_{50} . Meta-analysis determined whether medium and high doses vary in efficacy. The last-observation-carried-forward method and intent-to-treat sample were used for the meta-analysis. The possibility of other biases was explored using sensitivity analyses.

Outcomes: Median effective dose (ED_{50}) and the near maximal effective dose range (ED_{85} to ED_{95}). Schizophrenia symptoms were assessed in studies with the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale, or the Clinical Global Rating Scale.

MAIN RESULTS

The near maximal effective dose was determined for each drug (see <http://www.ebmentalhealth.com/supplemental> for table). **Typical antipsychotics:** the near maximal effective dose range for haloperidol was 3.3–10 mg/day. There was no evidence that higher doses of first generation antipsychotics were more effective than medium doses (3.3–10 mg/day haloperidol or equivalent). **Atypical antipsychotics:** the near maximal efficacy dose for aripiprazole was 10 mg/day, clozapine >400 mg/day, olanzapine possibly >16 mg/day, risperidone 4 mg/day, and ziprasidone 120 mg/day. Daily doses of 2 mg risperidone were about 50% less effective than higher doses. For olanzapine, 6 mg/day was 33% less effective than higher doses. For both atypical and typical antipsychotics, there was no evidence that higher doses were less effective, arguing against a “therapeutic window”.

For correspondence: John Davis, Department of Psychiatry, The Psychiatric Institute, University of Illinois at Chicago, Chicago, IL, USA; jdavis@psych.uic.edu

Sources of funding: supported by the NIMH Intervention Research Centre Grant and Stanley Medical Research Institute, Stanley Scholars Program.

CONCLUSIONS

The doses reported are approximate (see notes) and treating people with schizophrenia empirically by varying doses is still recommended. Clinicians tend to use higher doses of typical antipsychotics than are needed. High doses have a no better or worse response than medium doses.

NOTES

The range for individual patients may be wider than the estimated dose range for pharmacokinetic or pharmacodynamic reasons, or for patients in an acute exacerbated episode.

There is also little information on people who are too psychotic to give informed consent, and different doses may be required in these situations.

Commentary

The authors have conducted meta-analyses of antipsychotic studies that compared a lower versus a higher fixed dose, with the aim of evaluating whether high doses are either more or less effective than medium doses, and of calculating dose equivalencies based on identifying a 50% effective dose (ED_{50}). The dose response aim is important in two ways; firstly, many clinicians prescribe high doses in the hope of improving response, and secondly, some authors have claimed that there is a therapeutic window with first generation antipsychotics (FGAs) such that high doses are associated with reduced response. The dose equivalence aim is also important because most previous dose equivalent estimates have been based either on flexible dose studies or on clinical impressions.

The methods selected by the authors have succeeded admirably for the dose response question. The authors' table 3 shows that 22 haloperidol studies compared a dose in the 6–12 mg/d range with a dose higher than 12 mg/d. Meta-analysis shows no significant difference in improvement between the selected dose ranges. If anything, there is a near trend for doses 12 mg and higher to be slightly more effective. These results clearly invalidate the therapeutic window hypothesis. In addition, there appears to be but little additional benefit in using high doses of antipsychotic. The authors' table 4 shows that this conclusion seems to hold for treatment resistant patients as well.

It is less clear that available studies so admirably permit the same method to estimate reliably the dose equivalence based on ED_{50} . Table 2 identifies the ED_{50} for chlorpromazine as 150 mg/d, but most FGAs were studied using flexible dosing, and as a result there is only one small fixed dose study of oral chlorpromazine below 300 mg/d (authors' web fig 1). Similarly limited data require that the ED_{50} for haloperidol be shown as a range (0.5–2.0 mg/d). Even so, the relative dose equivalencies based on these ED_{50} estimates among chlorpromazine, haloperidol, risperidone, olanzapine, and ziprasidone are similar to those recently reported using a method based on the minimum dose effective compared with placebo.¹

Scott W Woods, MD
Professor of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

1 Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry* 2003;64:663–7.