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How to compare doses of different antipsychotics: A systematic review of methods

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ABSTRACT

Background: The ability to calculate equivalent dosage is important when comparing or switching between doses of different antipsychotics in the treatment of schizophrenia. It is also necessary when designing antipsychotic comparator trials which control for dosage.
Method: A systematic review to identify and critically evaluate the methods available for the estimation of antipsychotic dose equivalence was conducted. Electronic searches were carried out using Medline and PubMed and additional information was requested from pharmaceutical companies. The identified methods were evaluated against specific criteria regarding scientific rigour, quality of source data underpinning the method, clinical applicability and utility.
Results: Eleven articles were identified that described methodologies for antipsychotic dose equivalence. Seven of these referred to calculated methods, including chlorpromazine equivalence, maximum dose and daily-defined dose, and relied on an evidence base from both fixed and flexible dosing data. The remaining four described consensus methods which were based on the knowledge and experience of experts. Chlorpromazine was used as the standard comparator drug in the majority of the calculated equivalence studies, whereas risperidone was used for most consensus methods.
Conclusions: Comparison of methods for calculating antipsychotic dose equivalence suggests that different methods yield different equivalencies and the evidence is not sufficiently robust for any of these to be considered as a gold standard method. Thus, choice of method may introduce bias, either an over or underestimate of equivalent dosage, when designing head-to-head, antipsychotic, fixed-dose trials. Consequently, clinical trial reports should routinely include justification of the choice of method for calculating dose equivalence.

1. Introduction

Antipsychotic medications are commonly used for the pharmacological treatment of schizophrenia and related psychotic illnesses. While all of these medications share dopamine D2 receptor antagonist properties, they also have varying receptor binding profiles. Despite this pharmacological heterogeneity, with the exception perhaps of clozapine, the differences in efficacy are modest and must be weighed against larger differences in liability for particular side effects (McCue et al., 2006; Leucht et al., 2009a,b). Switching between antipsychotics is commonplace in routine clinical practice (Bitter et al., 2008; Taylor et al., 2008). To minimise any disruptive effects and maximise the likelihood of success, the clinician must choose an appropriate target dose for the new antipsychotic. This is perhaps commonly selected on the basis of dose equivalency data (Lambert, 2007) or by titrating to the dose that produces maximum effectiveness and then stopping the titration when tolerance to emergent side effects is no longer maintained.

An understanding of antipsychotic dosing in terms of equivalent efficacy is also necessary in clinical research. Drug dose comparisons are necessary in pharmacoepidemiological drug utilisation studies and clinical trials. This is particularly true in randomised controlled trials (RCTs) conducted pre-licensing to demonstrate the superiority of a new antipsychotic over placebo and/or non-inferiority to the current 'gold standard' comparator antipsychotic, although choice and dose of a comparator antipsychotic can vary between studies. For most head-to-head clinical trials comparing antipsychotic medication, clinically equivalent dosages are chosen in order to control for dosage. For example, interpretation of the relative efficacy of the antipsychotics tested in one large, pragmatic clinical trial, the CATIE study, was partly confounded by the use of relatively high doses of olanzapine and/or relatively low doses of risperidone (Rosenheck et al., 2009).

Antipsychotic dose comparison is important both in clinical practice and for research purposes. For example, assessment of the quality of antipsychotic prescribing practice will include the identification of high-dose prescribing and polypharmacy (Paton et al., 2008; Lin et al.,

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2010; Suzuki, 2011). As it is not realistic to expect all antipsychotics to be compared with one another in fixed-dose RCTs and across the various illness phases, a method for calculating or otherwise extrapolating equivalent doses is required. However, the development of valid and reliable methods of dose comparison is yet to be fully realised. Consequently, we aimed to conduct a systematic review to identify and critically evaluate the methods currently available to compare the doses of individual antipsychotic drugs.

2. Method

2.1. Search strategy

A systematic electronic search was conducted using Medline and PubMed in March 2012. For Medline, keywords were used, mapped to MeSH headings as appropriate, for the following terms: 1. 'antipsychotic' OR 'neuroleptic'; 2. 'dose' OR 'dosage' OR 'dosing'; 3. 'equivalen*'; 4. 'consensus'. Combinations were then conducted to form term 5 from '1 AND 2' as well as term 6 from '3 OR 4'. The final combination was formed from '5 AND 6'. For PubMed, an identical search strategy was used other than term 3 being constructed with the key words of 'equivalents' or 'equivalency' or 'equivalence'. The resultant abstracts were then examined for duplication and independently reviewed by two authors. The primary inclusion criteria were provision of a description of a method for antipsychotic dose comparison in humans and publication in English. If a method for antipsychotic dose comparison was described in several articles, then the earliest article only was included. Where no initial, definitive, agreed decision could be made on the basis of the abstract alone, the full article was examined and disagreement between the two reviewers was resolved with subsequent discussion. In order to check for other eligible methods, six pharmaceutical companies known to be working in the field of psychosis were contacted to request information regarding which dose comparison method, if any, was referred to when selecting the dose(s) of an active comparator drug in antipsychotic phase II/III clinical trials.

2.2. Classification and analysis

The methods of antipsychotic dose comparison were classified, described and evaluated. As no suitable pre-existing tool existed, the quality assessment criteria used included the type of method used to derive equivalency, source data on which the method was based, the key comparator (baseline antipsychotic drug and dose e.g. chlorpromazine 100 mg) applicability for different antipsychotics with various formulations and for their full dose range, and generalisability across different clinical presentations. For consensus methods, description of the sample of Experts was also examined. Using Web of Knowledge the citation rate of the original source articles for the selected methods, as of October 2012, was recorded. An additional table was constructed that included the equivalent values to the most commonly used first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs), including long-acting injections (LAIs).

3. Results

3.1. Search strategy

The Medline search produced 484 initial articles, of which 27 met the eligibility criteria. These were fully examined including hand-searching of their reference lists, which yielded a further 3 eligible methods. Of these 30 articles, 9 were found to describe for the first time a unique methodology for comparing doses between antipsychotic medications. A tenth article (of the original 30) reported a comparison of two methods to standardize antipsychotic doses including one not described previously (Rijcken et al., 2003). As this article did not provide sufficient information regarding the method, the source book (WHO, 2012a) describing the method was then referred to. Searching on PubMed, 22 out of 422 retrieved articles were found to be relevant, but none described an additional methodology to those identified via Medline. One further eligible method was found following communication with pharmaceutical companies. Overall, a total of 11 original methods for comparing antipsychotics doses were found. Eligible methods were grouped as follows: (i) calculated methods including three on chlorpromazine equivalence (Davis, 1974; Woods, 2003; Andreasen et al., 2010), three using maximum dose (Milton et al., 1995; Yorston and Pinney, 1997; Davis and Chen, 2004), one describing daily defined dose (DDD) (WHO, 2012a); and (ii) four consensus methods (Kane et al., 2003; Buckley, 2005; Simpson et al., 2006; Gardner et al., 2010).

3.2. Calculated methods

3.2.1. Chlorpromazine equivalence

Davis (1974) pioneered dose equivalence methodology for FGAs, using chlorpromazine as the standard comparator, and utilising source data from double-blind trials comparing chlorpromazine with other FGAs. In all studies providing source data, the optimal clinical response was determined by the study physician, and this was used to estimate empirically the efficacy equivalence between drugs. Chlorpromazine equivalents were then developed referring to the dose of an antipsychotic in mg/day that was as effective as 100 mg/day of chlorpromazine [Table 1].

Subsequently, Woods (2003) developed dose equivalency tables for SGAs based on the methodology of Davis (1974). The minimum effective dose, which is the lowest dose that is significantly superior to placebo, was derived from various placebo-controlled and fixed-dose trials. Initially haloperidol equivalencies were estimated, since the minimum effective dose of haloperidol was reported widely in the studies under examination and was considered to be 4 mg. Haloperidol equivalent doses were then converted into chlorpromazine equivalents based on the assumption that "2 mg of haloperidol equals 100 mg of chlorpromazine" (American Psychiatric Association, 1997).

The most recent method for calculating chlorpromazine equivalence was developed by Andreasen et al. (2010). The source data to estimate new dose equivalents were derived from pre-existing consensus guidelines (Kane et al., 2003), where equivalent dosages of FGAs and SGAs to haloperidol or risperidone, respectively, were estimated. From the derived equivalencies it was concluded that "it would probably be possible to generate linear equations to derive equivalency". Thus, a linear regression analysis was conducted in which the dose equivalents of haloperidol and chlorpromazine were used for equivalent values of the other antipsychotics.

3.2.2. Maximum dose

3.2.2.1. Near-effective maximum dose. is defined as the threshold dose eliciting clinical response with the least adverse profile, and can be calculated from dose–response curves which were constructed using data from fixed-dose randomised placebo-controlled studies (Davis and Chen, 2004) [Fig. 1]. Equivalence between antipsychotics is then established by comparing the near-effective doses. Dose equivalence tables have also been calculated on the basis of the median effective dose producing a response in half of the population (ED50) (Davis and Chen, 2004). For trifluoperazine and fluphenazine, a single near-effective dose was not identified due to the lack of sufficient data from fixed-dose and placebo-controlled studies. The best dose–response curves were said to be constructed for risperidone, and for oral and intramuscular olanzapine. A single near-effective maximum dose was reported for aripiprazole and risperidone, whilst for amisulpride the near-effective dose was found by extrapolation. For eight antipsychotics, there was a range of near-effective values provided with as much as a 4-fold variation between the lower and upper range values for quetiapine.