META-ANALYSIS OF ANTIPSYCHOTIC DRUGS IN SCHIZOPHRENIA

COMPARATIVE EFFICACY, ACCEPTABILITY AND TOLERABILITY OF 15 ANTIPSYCHOTIC DRUGS IN SCHIZOPHRENIA: A MULTIPLE TREATMENT META-ANALYSIS

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PROTOCOL

BACKGROUND

Schizophrenia is a usually chronic psychiatric disorder which afflicts approximately 1% of the population world-wide with little gender differences. Its typical manifestations are positive symptoms such as fixed, false beliefs (delusions) and perceptions without cause (hallucinations), negative symptoms such as apathy and lack of drive, disorganisation of behaviour and thought, and catatonic symptoms such as mannerisms and bizarre posturing (Carpenter 1994). The degree of suffering and disability of afflicted people is considerable. 80% - 90% do not have a job (Marvaha 2004) and up to 10% commit suicide (Tsuang 1978).

Antipsychotic drugs are the mainstay of treatment of schizophrenia, but there is no consensus about which antipsychotic drug should be used first-line. For example, there is a debate about the benefits of newer, usually expensive, second-generation (atypical) antipsychotic drugs (SGAs) compared with first-generation antipsychotic drugs (FGAs). Systematic reviews of different research groups have found evidence from meta-analyses of individual trials that the same SGAs (amisulpride, clozapine, olanzapine, risperidone) are more efficacious than FGAs (Geddes et al. 2000, Davis et al. 2003, Cochrane Reviews – Adams et al. 2008; summarized in Leucht et al. 2009a), but the interpretation differed because of varying perceptions of the methodological weaknesses of the primary trials. The most recent review included important independent trials and confirmed the efficacy findings of the previous reviews, but also found important differences in the relative side-effects of SGAs compared to FGAs. High-potency and low-potency FGAs also have markedly different clinical properties, and the authors therefore suggested abandoning the confusing classification (Leucht et al. 2009b). A systematic review of head-to-head comparisons of SGAs revealed an efficacy pattern which was in part compatible with the meta-analyses comparing SGAs with FGAs (i.e. some of the SGAs that were more efficacious than FGAs were also more effective than other SGAs in the head-to-head analysis, Leucht et al. 2009c).

However, the main limitation of these reviews is that they do not allow for establishing a clear hierarchy of the efficacy, acceptability and tolerability of the available agents. When indirect evidence (SGAs versus FGAs) is used for evaluating the relative efficacy and tolerability of SGAs, there are multiple possible confounders. The matrix of the direct evidence (SGAs versus SGAs) is not complete and leaves out important FGAs which are still frequently used.

Multiple treatment meta-analysis (MTM) is a statistical technique that allows both direct and indirect comparisons to be undertaken, even when two of the treatments have not been directly compared (Salanti et al., 2008; Higgins et al., 1996; Hasselblad et al., 1998; Lumley, 2002). In other words, it is a generalisation of standard pair-wise meta-analysis for A vs B trials, to data structures that include, for example, A vs B, B vs C, and A vs C trials.

The mixed treatment comparison might have advantages over other approaches of indirect comparisons such as a "naïve approach" (comparing the average from baseline of different drugs, Tandon et al. 2005), meta-regression (Geddes et al. 2000), comparing point estimates, comparing 95% confidence intervals, performing statistical tests on summary estimates, indirect comparison using a single common comparator, because it is not reliant on a single common comparator and can incorporate the results of direct and indirect comparisons into the analysis (Glenny et al. 2005).

MTM (also known as *network meta-analysis*) can summarise RCTs of several different treatments providing point estimates (together with 95% confidence intervals [CIs]) for their association with a given endpoint, as well as an estimate of incoherence (that is, a measure of how well the entire network fits together, with small values suggesting better internal agreement of the model). MTM has already been used successfully in other fields of psychiatry (Cipriani et al. 2009) and medicine (Psaty et al., 2003; Elliott et al., 2007) and two fruitful roles for MTM have been identified (Lu & Ades, 2004):

(i)   to strengthen inferences concerning the relative efficacy of two treatments, by including both direct and indirect comparisons to increase precision and combine both direct and indirect evidence;

(ii)   to facilitate simultaneous inference regarding all treatments in order for example to select the best treatment. Considering how important comparative efficacy could be for clinical practice and policy making, it is useful to use all the available evidence to estimate potential differences in efficacy among treatments.

The present review will examine the available randomised evidence for 15 (old and new) antipsychotic drugs in schizophrenia, in order to inform clinical practice and mental health policies. We will use MTM to estimate the comparative efficacy, acceptability and tolerability of 13 second-generation, and two standard first-generation antipsychotic drugs for acute treatment of schizophrenia and related disorders.

OBJECTIVES

To compare individual antipsychotic drugs in terms of:

(1) Overall efficacy, measured by the total score of the Positive and Negative Syndrome Scale (Kay et al. 1993) or the Brief Psychiatric Rating Scale (Overall and Gorham 1962).

(2) Acceptability of treatment, defined as the proportion of patients who left the study early by any cause.

(3) Overall tolerability, defined as the proportion of patients who left the study early for adverse events.

(4) Movement disorders, defined as the proportion of patients who needed at least one dose of antiparkinsonian medication.

(5) Weight gain, defined as the mean change of weight from baseline to endpoint.

METHODS

Criteria for considering studies for this review

Types of participants

Patients aged 18 or older of both sexes with a primary diagnosis of schizophrenia or related disorders (schizophreniform disorder, schizoaffective disorder, delusional disorder) according to the diagnostic criteria used by the study authors. There is no evidence that the latter disorders require substantially different treatment than schizophrenia (Carpenter 1994). Most recent studies are likely to have used DSM-IV (APA 1994) or ICD-10 (WHO 1992) criteria. Older studies may have used ICD-9 (WHO 1978), DSM-III (APA 1980)/DSM-III-R (APA 1987) or other diagnostic systems such as Feighner criteria (Feighner et al. 1972) or Research Diagnostic Criteria (Spitzer et al. 1978). There is no evidence that treatment effects differ depending on the diagnostic criteria used, and clinical criteria will also be accepted. A concurrent secondary diagnosis of another psychiatric disorder will not be considered as exclusion criteria. Studies in which all participants have a diagnosis of resistant schizophrenia (as defined by study authors) or in which all participants suffered from primary negative symptoms (as defined by study authors) or in which all participants were stable at baseline (as defined by study authors) will be excluded. Antipsychotic drug trials in schizophrenia patients with a serious concomitant medical illness as an inclusion criterion will be excluded. Trials that allowed for switching of treatments between groups will be excluded. In the analysis of EPS we will also exclude studies that used prophylactic antiparkinson medication.

Types of interventions

We will include the following antipsychotic drugs in any oral form of administration: amisulpride, aripiprazole, asenapine, chlorpromazine, clozapine, haloperidol, iloperidone, lurasidone, olanzapine, quetiapine, paliperidone, risperidone, sertindole, ziprasidone, zotepine. Haloperidol and chlorpromazine were selected as the most frequently used high- and low-potency antipsychotic drugs. We decided against the inclusion of a midpoteny antipsychotic, because it is difficult to define which drugs fall in this category and that the randomised evidence on this class is limited (e.g. perphenazine Hartung et al. 2005, sulpiride Soares et al. 2000). In flexible-dose studies we assume that the doctors would titrate the medication to find the ideal dose for the individual patient. In studies that examined several fixed doses we will include only the optimum doses as they were found in dose-finding studies or were recommended by guidelines: amisulpride 400-800mg/day (Puech et al. 1998), aripiprazole 10-30mg/day (Kane et al. 2002, Potkin et al. 2003, Study 94292, Study 138001, Modell et al. 2005), asenapine 10-20mg/day (Kane et al. 2008 and Center for Drug Evaluation and Research 2008), chlorpromazine 400-800mg/day (Davis et al. 1989), clozapine ≥ 400mg/day (Simpson et al. 1999), haloperidol 5-20 mg/day (Lehman et al. 2004), iloperidone 12-24 mg/day (studies 3000, 3004, 3005 in Potkin et al. 2008), lurasidone 40-160mg/day (studies 006, 049, 229, 231 and 233 in: Center for Drug Evaluation and Research 2010 and Sunovion data on file), olanzapine 10-20mg/day (Beasley et al. 1996, Beasley et al. 1996b, Beasley et al. 1997, Kinon et al. 2008), quetiapine > 400mg/day (Small et al. 1997, Arvanitis et al. 1997, Kahn et al. 2008, Lindenmayer et al. 2008), paliperidone 6-12mg/day (Kane et al. 2007, Marder et al. 2007, Davidson et al. 2007), risperidone 4-6 mg/day, Marder and Meibach 1994, Chouinard et al. 1993, Peuskens et al. 1995), sertindole 16-24mg/day (van Kammen et al. 1996, Zimbroff et al. 1997, Hale et al. 2000), ziprasidone 120-160mg/day (Keck et al. 1998, Goff et al. 1998, Daniel et al. 1999), zotepine 100-250mg/day (Falkai et al. 2005). In a sensitivity analysis we will address whether unfair dose comparisons affected the results (see below).

Types of studies

Double-blind or single-blind RCTs comparing one drug with another within the group of 15 antipsychotic drugs as oral monotherapy in the acute phase treatment of schizophrenia will be included. Trials in which antipsychotic drugs were used as an augmentation strategy will be excluded. Quasi-randomized trials (such as those allocating by using alternate days of the week) will be excluded. For trials which have a crossover design only results from the first randomisation period will be considered to avoid carry-over effects which are very likely in schizophrenia. Only at least single-blind studies will be included, because it has been shown that lack of blinding can be a source

of bias in this area (Leucht et al. 2009b). For example, the open, randomised European First Episode of Schizophrenia Treatment study (EUFEST) showed more pronounced differences between antipsychotic drugs than previous double-blind evidence (Kahn et al. 2008).

Outcome measures

(1) Overall efficacy of antipsychotic treatment

Overall efficacy is primarily measured as the mean change of the total score of the Positive and Negative Syndrome Scale (PANSS, Kay et al. 1994) from baseline to endpoint. If PANSS results are not available, we will use the mean change from baseline to endpoint of the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham 1962), or if again not available the mean values at endpoint of either scale.

(2) Acceptability of treatment

Treatment discontinuation (acceptability) is defined as the proportion of patients who leave the study early for any reason, out of the total number of patients randomly assigned to each antipsychotic drug.

(3) Overall tolerability

Overall tolerability is defined as the proportion of patients who leave the study early for adverse events, out of the total number of patients randomly assigned to each antipsychotic drug.

(4) Movement disorders

Movement disorders (extrapyramidal side-effects) include side-effects such as dystonias, dyskinesia, tremor, akinesia, rigor and other parkinson-like symptoms. The number of patients who used antiparkinson medication (e.g. biperiden) at least once during the trial will be analysed as a proxy measure for these adverse events.

(5) Weight gain

Weight will be assessed as the mean change in kg from baseline to study endpoint.

Search strategy

All published and unpublished randomized controlled, blinded trials that compared oral doses of at least two of the above mentioned antipsychotic drugs with another or placebo in the treatment of schizophrenia or related disorders will be identified. For this, we will mainly build on the results of seven previous systematic reviews (SGA vs FGA, Leucht et al. 2009b; SGA vs SGA, Leucht et al. 2009c; SGA vs placebo, Leucht et al. 2009d; haloperidol versus chlorpromazine, Leucht C. et al. 2008; paliperidone versus other antipsychotic drugs, Nussbaum and Stroup 2009; haloperidol versus placebo, Joy et al. 2006; chlorpromazine versus placebo, Adams et al. 2007) for which the Cochrane

Schizophrenia Group Controlled Trials Register was searched. The CSG register is compiled using regular methodical searches in various electronic databases supplemented by the hand searching of relevant journals and conference proceedings (for details see Group Module of the Cochrane Schizophrenia Group, Adams et al. 2008). We will make update searches for all these reviews (search terms: a) ["amisulprid*, aripiprazol*, asenapin*, clozapin*, olanzapin*, paliperidon*, quetiapin*, risperidon*, sertindol*, ziprasidon*, zotepin*]; b) [haloperidol AND chlorpromazine*]; c) [(haloperidol OR chlorpromazine*) AND placebo]). There will be new searches for asenapine, iloperidone and lurasidone which have recently been registered by the FDA (search terms [iloperidon*, asenapin*, lurasidon*]). All relevant authors and principal manufacturers will be contacted to supplement the incomplete report of the original papers. We will also check clinicaltrials.gov, the FDA website, and the websites of these manufacturers for further studies.

We are aware that there are many trials carried out in China (Chakrabarti et al., 2007). However, for many of these studies only incomplete or conflicting information is available and it has been reported many of them do not use appropriate randomisation procedures (Wu et al., 2006). In an effort to avoid the potential biases that may be introduced by including these trials without further information, we will exclude these studies.

Study selection and data extraction

We will use the data that have been extracted for the previous reviews by Leucht and colleagues, but two reviewers will independently re-extract the data of the included studies of Nussbaum and Stroup 2009, Joy et al. 2006 and Adams et al. 2007. Concerning the update search and the newly included antipsychotic drugs, two reviewers will independently review references and abstracts. If both reviewers agree that the trial doesn't meet eligibility criteria, we will exclude it. We will obtain the full text of all remaining articles and use the same eligibility criteria to determine which, if any, to exclude at this stage. Any disagreements will be solved via discussion with a third member of the reviewing team.

Two reviewers will then independently read each article, evaluate the completeness of the data abstraction, and confirm the quality rating. We will design and use a structured data abstraction form to ensure consistency of appraisal for each study. Information extracted will include study characteristics (such as lead author, publication year, risk of bias), participant characteristics (such as diagnostic criteria for schizophrenia, age, sponsorship), intervention details (such as dose ranges, mean doses of study drugs) and outcome measures (see above).

Length of follow up

It is a problem of systematic reviews that usually trials have different durations of follow-up (Edwards & Anderson, 1999; Geddes et al., 2000; Zimmermann et al., 2002). Clinically, the assessment of efficacy after 6 weeks of treatment or after 16 to 24 weeks or more may lead to differences in terms of treatment outcome. Clinicians need to know whether (and to what extent) treatments work within a clinically reasonable period of time. Unfortunately, there is no consensus on what the appropriate duration of an acute phase trial is and different durations have been used. The Cochrane Schizophrenia Group usually defines short-term as a period of up to 12 weeks (Adams et al. 2008). In the present review, acute treatment will be defined as an 4-12 week treatment in all analyses. Study duration will be addressed as a covariate. Longer-term studies will be excluded if they do not provide data for the 4-12 week period. In the present review, acute treatment will be defined as an 6-week treatment in both the efficacy and acceptability analyses. If 6-week data are not available, we will use data ranging between 4 to 12 weeks, the time point given in the original study as the study endpoint is given preference.

Risk of bias

We will assess risk of bias using the tool described in the Cochrane Collaboration Handbook (Higgins and Green 2008). This tool encourages consideration of how the sequence was generated, how allocation was concealed, the integrity of blinding at outcome, the completeness of outcome data, selective reporting and other biases. We will not include studies where sequence generation was at high risk of bias and where allocation was clearly not concealed. We will further more exclude randomised, open-label studies, because lack of blinding has been shown to be a source of bias in this area (Leucht et al. 2009b).

STATISTICAL ANALYSIS

The primary outcome of this review will be the change of the total score of the PANSS or the BPRS. The choice of these total scores of schizophrenia rating scales rather than dichotomous responder rates was made for the following reasons: (i) unfortunately, there is still no consensus on which cut-off should be applied to define response in schizophrenia. (ii) Authors have used a large variety of cut-offs such as at least 20%, 30%, 40% or 50% reduction of the PANSS or BPRS, making comparability difficult. (iii) In recent years, the 20% cut-off which has been shown to be of limited clinical meaningfulness has been frequently used (Leucht et al. 2005a,b). (iv) Finally, it can not be excluded that in some occasions the cut-off has been chosen post-hoc to support the sponsor's compound. Unreported standard deviations will either be obtained from the authors upon request, will

be calculated from other statistics, or will be derived from the average of the other studies (Furukawa et al., 2006).

Dichotomous outcomes will be analysed on an intention-to-treat (ITT) basis: drop-outs will always be included in this analysis. The rule is important for the outcome use of antiparkinson medication at least once. When data on drop-outs are carried forward and included in the evaluation (Last Observation Carried Forward, LOCF), they will be analysed according to the primary studies; when dropouts are excluded from any assessment in the primary studies, we will assume that the dropouts did not receive antiparkinson medication, because it is likely that another assumption (all dropouts have received antiparkinson medication) would overestimate the percentage of people with movement disorders which is relatively low under treatment with the newer antipsychotic drugs.

Synthesis of results

We will generate descriptive statistics for trial and study population characteristics across all eligible trials, describing the types of comparisons and some important variables, either clinical or methodological (such as year of publication, age, severity of illness, sponsorship).

For each pair-wise comparison between antipsychotic drugs, the standardized mean difference Hedges's adjusted g (SMD) will be calculated as the effect size for continuous outcomes and the odds ratio will be calculated for dichotomous outcomes, both with a 95% CI. We will first perform pair-wise meta-analyses by synthesizing studies that compare the same interventions using a random effects model (DerSimonian & Laird, 1986) to incorporate the assumption that the different studies are estimating different, yet related, treatment effects (Higgins & Green, 2008). Visual inspection of the forest plots will be used to investigate the possibility of statistical heterogeneity. This will be supplemented using, primarily, the I-squared statistic. This provides an estimate of the percentage of variability due to heterogeneity rather than a sampling error (Higgins et al., 2003). 95% confidence intervals will be calculated for I-squared, and a P value from a standard test for heterogeneity will be used to assess evidence of its presence.

We will conduct a MTM. MTM is a method of synthesizing information from a network of trials addressing the same question but involving different interventions. For a given comparison, say A versus B, direct evidence is provided by studies that compare these two treatments directly. However, indirect evidence is provided when studies that compare A versus C and B versus C are analyzed jointly. The combination of the direct and indirect into a single effect size can increase precision while randomization is respected. The combination of direct and indirect evidence for any given treatment comparison can be extended when ranking more than three types of treatments according to their effectiveness: every study contributes evidence about a subset of these treatments. We will perform MTM within a Bayesian framework (Ades et al., 2006). This enables us to estimate

the probability for each intervention to be the best for each positive outcome, given the results of the MTM. The analysis will be performed using WinBUGS (MRC Biostatistics Unit, Cambridge, U.K., http://www.mrcbsu cam.ac.uk/bugs/winbugs/contents.shtml).

MTM should be used with caution, and the underlying assumptions of the analysis should be investigated carefully. Key among these is that the network is coherent, meaning that direct and indirect evidence on the same comparisons agree. Joint analysis of treatments can be misleading if the network is substantially incoherent, i.e., if there is disagreement between indirect and direct estimates. So, as a first step, we will calculate the difference between indirect and direct estimates in each closed loop formed by the network of trials as a measure of incoherence and we will subsequently examine whether there are any material discrepancies. In case of significant incoherence we will investigate possible sources of it (dose, study duration, industry sponsorship, publication date, chronicity (mean participant age, duration ill, first episode population), overall dropout rate, sample size, prophylactic antiparkinson medication, study quality). Incoherence may result as an uneven distribution of effect modifiers across groups of trials that compare different treatments. Therefore, we will investigate the distribution of clinical and methodological variables that we suspect may be potential sources of either heterogeneity or incoherence in each comparison-specific group of trials.

Sensitivity and subgroup analyses

We will do sensitivity analyses based on study sponsorship and excluding single-blind trials. Another sensitivity analysis will address whether unbalanced doses affected the results. We will apply a similar approach as that by Gartlehner et al. 2007 and Cipriani et al. 2009 to exclude studies with unfair dose comparisons. For this we put together the roster below in which low- and high doses of the drugs included in the MTM are described (see Table 1). This Table 1 is based on several publications on antipsychotic dose derived from expert opinions (Gardner et al. 2010, Andreasen et al. 2009) and the dose response analysis by Davis and Chen 2004. This roster will be employed to detect inequalities in dosing that could affect comparative effectiveness by excluding studies with low doses of one drug and high doses of the other (or vice-versa). Studies in first-episode and elderly populations will be excluded from this rule, because such participants generally need lower antipsychotic doses. Further analyses to address dose effects will be performed if necessary. Subgroup analyses are not planned.

Table 1:

Drug	low-dose	high-dose
Amisulpride	<300	>700
Aripiprazole	<10	>25
Asenapine	<10	>18
Chlorpromazine	<300	>800
Clozapine	<300	>600
Haloperidol	<5	>15
Iloperidone	<12	>22
Lurasidone	<40	>120
Olanzapine	<=10	>17.5
Paliperidone	<6	>12
Quetiapine	<400	>700
Risperidone	<4	>8
Sertindole	<=12	>22
Ziprasidone	<120	>150
Zotepine	<100	>250

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