Pharmacological interventions for schizotypal personality disorder

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CONTRIBUTIONS OF AUTHORS Saeed Farooq conceived the review and is the lead author and first author of the clinical background to the review. Birgit Völm is the second clinical author. Both will be responsible for the 'Discussion' and 'Authors' conclusions' in the final review. Nick Huband, Jutta Stoffers, Simon Gibbon and Birgit Völm are responsible for study selection and data extraction. Nick Huband and Michael Ferriter were responsible for the methodology sections of the protocol and will take responsibility in future for risk of bias analysis. Michael Ferriter is the contact author. Conor Duggan and Klaus Lieb were responsible for securing funding for the review and will, in future, be responsible for reviewing the final draft of the review prior to the formal peer review process.

DECLARATIONS OF INTEREST

- Saeed Farooq - None known
- Birgit A Völm - None known
- Nusrat Husain - Received support for educational programs and/or travel support and/ or speaker fees from Astra Zeneca, Eli Lilly, Lundbeck, Sanofi-Aventis, BristolMyers Squibb, Janssen Cilag and Wyeth
- Nick Huband - None known
- Jutta Stoffers - None known
- Simon Gibbon - None known
- Conor Duggan - Advisor to a current randomized controlled trial of schema focused therapy at Ashworth Special Hospital, UK; investigator in a completed randomised controlled trial of social problem solving therapy plus psychoeducation for people with personality disorder
- Michael Ferriter - None known
- Klaus Lieb - Chair, Department of Psychiatry and Psychotherapy, University Medical Center, Mainz; advisor to a planned randomised controlled trial of schema therapy in patients in personality disorders

Abstract

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the effects of pharmacological interventions for people with Schizotypal Personality Disorder (SzPD).

BACKGROUND

Description of the condition

The classification and definition of personality disorders remains controversial. This is manifested not least by the difference in the approaches taken to it by two major psychiatric classification systems. In DSM-IV-TR (APA 2000), personality disorders are classified on an axis (Axis II) which is separate from the mental state disorders (Axis I). Personality disorders sharing broadly similar features are grouped together in 'clusters' in DSM-IV, emphasizing the overlap between different categories (APA 1994). Schizotypal Personality Disorder (SzPD) is included in 'Cluster A' or the 'odd-eccentric' group of personality disorders. This cluster of personality disorders is characterized by 'aloofness', 'lack of sociality' and 'unusual thoughts'.

More specifically, DSM-IV defines SzPD as a pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships. SzPD features cognitive or perceptual distortions and eccentricities of behavior such as ideas of reference (where an individual believes that casual events and other people's remarks are referring to him or herself when, in fact, they are not). Affected individuals may hold other 'odd beliefs' and be prone to magical thinking and paranoid ideation. In ICD-10 (WHO 1992), however, Schizotypal disorder (F21) is classified as a mental disorder associated with schizophrenia, rather than a personality disorder. According to ICD-10, Schizotypal disorder is characterized by eccentric behaviour and anomalies of thinking and affect which resemble those seen in schizophrenia, though no definite and characteristic schizophrenic anomalies occur at any stage. The major symptoms include: a cold or inappropriate affect; anhedonia; odd or eccentric behaviour; a tendency to social withdrawal; paranoid or bizarre ideas not amounting to true delusions; obsessive ruminations; thought disorder, and perceptual disturbances.

Large scale epidemiological studies of personality disorder are limited in number and are hampered by disagreements between these classification systems. A large population-based study carried out in Norway using careful methodology found an overall prevalence of 13.1% for any DSM-III-R personality disorder and prevalence rates of 0.6% for SzPD (Torgersen 2001). In pooled data from ten community studies, the prevalence of SzPD was higher at 1.53% (Torgersen 2001).

Description of the intervention

This review will systematically evaluate all pharmacological interventions used in randomised controlled trials for the treatment of SzPD. These will include the following psychotropic drugs: antipsychotic drugs (including depot injections); mood stabilisers;

hypnotics; anxiolytics; antidepressants; central nervous system stimulants, and antiepileptics.

How the intervention might work

SzPD shares common phenomenological, genetic and biological features with schizophrenia. Studies of comorbidity in SzPD demonstrate an association with schizophrenia (Coid 2003). Both family and adoptive studies suggest a greater prevalence of SzPD (and paranoid personality disorder) in the relatives of patients with schizophrenia than in comparison groups (Baron 1985, Coid 2003; Siever 2004). Schizophrenia and SzPD share physiological abnormalities, deficits in cognitive processing and abnormalities in structural and functional functions, which suggest that SzPD may be part of a schizophrenia spectrum. Therefore it may be argued that antipsychotics, which have been found to be effective in schizophrenia, may also be effective in treating psychotic symptoms found in schizotypal as well as other personality disorders. It has been argued that drug treatments such as anxiolytics and antidepressants may be effective against a specific subset of personality features such as depressive or anxiety symptoms found in different types of personality disorders (Soloff 1998). SzPD furthermore typically involves a number of other traits including suspiciousness, paranoid ideas and obsessive ruminations (WHO 1992), which could respond to antipsychotics or antidepressants. Neurobiological research suggests a link between dysfunction in the serotonergic system and personality traits such as impulsiveness and self harm (Cloninger 1987, Livesley 1993). Accordingly, it is possible that the cognitive and perceptual abnormalities found in SzPD may be result of increased sensitivity to dopamine. Antipsychotics and antidepressants can be helpful in controlling these symptoms that are related to abnormalities in serotonergic and dopaminergic abnormalities respectively.

A number of symptoms associated with SzPD such as magical thinking, perceptual disturbances and social withdrawal are recognised as features of At Risk Mental State (ARMS), which has been employed to identify the individual at high risk of developing psychosis (Yung 1996, Morrison 2007). Evidence is emerging that pharmacological interventions used in those at risk can possibly delay, and in some cases even avert, progression to schizophrenia (McGorry 2002, Morrison 2004, Nordentoft 2006).

Why it is important to do this review

Personality disorders pose a major health burden leading to functional impairment, an increase in suicide and an increase in service utilization (Skodol 2002). Skodol 2002 also found that patients with SzPD had significantly more impairment at work, in social relationships and at leisure than patients with obsessive-compulsive personality disorder or major depressive disorder. Past reviews have shown that most research has been carried out on borderline personality disorder (Duggan 2007; Duggan 2008) and personality disorders such as SzPD have generally been neglected.

Some evidence suggests that personality traits in people with Cluster A PDs, including SzPD, tend to become more pronounced with time, while the personality traits of people with Cluster B or C personality disorder become significantly less pronounced over time

(Sievwright 2002). This highlights the need for effective interventions that could be started early in the course of this type of PD to prevent further impairment, including psychosis.

OBJECTIVES

To evaluate the effects of pharmacological interventions for people with Schizotypal Personality Disorder (SzPD).

METHODS

Criteria for considering studies for this review

Types of studies—All randomised controlled trials (RCTs), with or without blinding, in which participants have been randomly allocated to an experimental group and a placebo control group. We will also include trials where there is an active treatment plus adjunctive treatment versus adjunctive treatment only, such as active treatment plus treatment-as-usual (TAU) versus TAU alone.

Types of participants—Men or women aged 18 years or over with i) a diagnosis of SzPD as defined by DSM-IV (APA 1994) or ICD-10 (WHO 1992). Those with comorbid mental health problems will not be excluded unless they have a major functional illness (i.e. schizophrenia, schizoaffective disorder, or bipolar disorder). The decision to exclude persons with comorbid major functional illness is because such disorders (and the possible confounding effects of any associated management or treatment) might obscure whatever other psychopathology (including PD) might be present.

Types of interventions—Any drug(s) with psychotropic properties, including those falling within the following classes of pharmacological interventions (as defined by the British National Formulary [BNF 2010]):

1. hypnotics, anxiolytics and barbiturates
2. antipsychotic drugs (including depot injections)
3. antimanic drugs
4. antidepressant drugs: tricyclic and related, monoamine-oxidase inhibitors, SSRIs and related, and other antidepressant drugs
5. central nervous system stimulants
6. antiepileptics/mood stabilising agents
7. drugs used in substance dependence

We plan to group outcome measures by class of drug, with possible subgroup analysis of type of drug (for example, tricyclic antidepressants versus SSRIs) if sufficient studies are found.

Types of outcome measures

Primary outcomes: We will measure the following outcomes using standardised instruments (examples of which are given below).

- Change in personality as reported by a standardised continuous outcome instrument such as the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II; First 1997), the Structured Interview for DSM-IV Personality (SIDP-IV; Pfohl 1997), or self-report measures such as the Personality Diagnostic Questionnaire-4 (PDQ -4; Hyler 1994), NEO Personality Inventory (NEO-PI-R)/NEO Five-Factor Inventory (NEO-FFI; Costa 1992), or similar validated scales
- Change in mental state as reported by a standardised continuous outcome instrument such as the Global Assessment of Functioning numeric scale (GAF; APA 2000), Global Assessment Scale (GAS; Endicott 1976), Clinical Global Impression of Severity scale (CGI-S; Guy 1976), Symptom Checklist-90 (SCL-90R; Derogatis 1994), or similar validated scales
- Numbers of participants in each arm of the study that go on to develop psychosis
- Suicide/sudden and unexpected death

The outcomes will be assessed at the following time points: immediate (within six months); short term (over six months to two years); medium term (more than two years to five years), and long term (beyond five years).

Secondary outcomes:

- Quality of life and social functioning as measured by any standardized continuous measure such as the Social Adjustment Scale (SAS-SR; Weissman 1976), the Social Functioning Questionnaire (SFQ; Tyrer 2005), or similar validated scales
- Leaving the study early
- Adverse events as measured by a binary outcome of number of patients with at least one adverse effect
- Compliance with treatment/compulsory administration of treatment

Search methods for identification of studies

Electronic searches

Electronic searches: The following electronic databases will be searched:

MEDLINE

EMBASE

CINAHL

Cochrane Central Register of Controlled Trials (CENTRAL), part of the Cochrane Library

PsycINFO

ASSIA

BIOSIS

Dissertation Abstracts

ISI-SCI (Science Citation Index)

ISI-SSCI (Social Sciences Citation Index)

National Criminal Justice Reference Service

Sociological Abstracts

ZETOC (Conference Search)

metaRegister of Controlled Trials (<http://www.controlled-trials.com/mrct/>)

Searches will be based on the following MEDLINE search strategy which includes the Cochrane highly sensitive search strategy for identifying randomised trials, as detailed in Section 6.4.11.1 of Higgins 2009 (accessed 27 September 2010). The strategy includes search terms for all types of PD as this is one of a series of PD reviews. Search terms and syntax will be modified as necessary for other databases.

1. exp Personality Disorders/
2. (moral adj2 insanity).tw.
3. (DSM and (axis and II)).tw.
4. (ICD and (F60 or F61 or F62)).tw.
5. ((odd\$ or eccentric\$ or dramatic\$ or emotional\$ or anxious\$ or fearful\$) adj5 cluster\$).tw.
6. ("Cluster A" or "Cluster B" or "Cluster C").tw.
7. ((aggressiv\$ or anxious\$ or borderline\$ or dependent\$ or emotional\$ or passiv\$ or unstable) adj5 personalit\$).tw.
8. (anankastic\$ or asocial\$ or avoidant\$ or antisocial\$ or antisocial\$ or compulsiv\$ or dissocial\$ or histrionic\$ or narciss\$ or obsessiv\$ or paranoi\$ or psychopath\$ or sadist\$ or schizoid\$ or schizotyp\$ or sociopath\$).tw.
9. (personalit\$ adj5 disorder\$).tw.
10. character disorder\$.tw.
11. (anal\$ adj (personalit\$ or character\$ or retentiv\$)).tw.
12. or/1-11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomi#ed.ab.
16. placebo.ab.

17. drug therapy.fs.
18. randomly.ab.
19. trial.ab.
20. groups.ab.
21. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. exp animals/ not humans.sh.
23. 21 not 22
24. 12 and 23

Searching other resources—We will search the reference lists of included and excluded studies for additional relevant trials. Bibliographies of systematic review articles published in the last five years will also be examined to identify relevant studies.

We will contact authors of relevant studies to enquire about other sources of information and the first author of each included study for information regarding unpublished data. We will contact a representative from all major pharmaceutical companies to request information about any published/unpublished trials.

There will be no restriction by language. Where the authors are unable to translate a paper, the resources of the Cochrane network will be used to identify Cochrane collaborators and staff who can read the paper in its original language, assess the paper against the review inclusion and exclusion criteria and, if required, translate the paper.

Data collection and analysis

Selection of studies—This review is one of a series of reviews on PD. The selection of studies will be carried out in two stages. In the first stage, titles and abstracts will be read independently by two review authors against the inclusion criteria to identify all RCTs or potential RCTs of pharmacological treatments of people diagnosed with any personality disorder. In the second stage, full copies of studies will be assessed against the inclusion criteria for this particular review by two authors. This second stage assessment identifies not only trials with participants diagnosed with SzPD, but also trials with participants having a mix of PDs for which data on a subgroup with SzPD may be available.

Studies with two treatment conditions in which the relevant participants form a small subgroup will only be included if the trial investigators randomised at least five people with SzPD. The rationale is that variance and standard deviation cannot be calculated in samples of two or less, and a two-condition study that randomises fewer than five relevant participants will have at least one arm for which variance or standard deviation cannot be calculated. Uncertainties concerning the appropriateness of studies for inclusion in the review will be resolved through consultation with a third review author.

Data extraction and management—Data will be extracted independently by two review authors using a data extraction form. Data will be entered into Review Manager 5.

Where data is not available in the published trial reports, we will attempt to contact the authors and asked them to supply the missing information.

Assessment of risk of bias in included studies—For each included study, two review authors (MF and NH) will independently complete the Cochrane Collaboration tool for assessing risk of bias (section 8.3; Higgins 2009, accessed 17 August 2010). If there is any disagreement this will be resolved through consultation with a third review author (BV).

We will assess the degree to which: the allocation sequence was adequately generated ('sequence generation'); the allocation was adequately concealed ('allocation concealment'); knowledge of the allocated interventions was adequately prevented during the study ('blinding'); incomplete outcome data were adequately addressed; reports of the study were free of suggestion of selective outcome reporting; and the study was apparently free of other problems that could put it at high risk of bias, such as study sponsorship from a drugs company.

Each domain will be allocated one of three possible categories for each of the included studies: 'Yes' for low risk of bias, 'No' for high risk of bias, and 'Unclear' where the risk of bias is uncertain or unknown.

Measures of treatment effect

Dichotomous data: For dichotomous (binary) data, the odds ratio (OR) with a 95% confidence interval will be used to summarise results within each study. The OR has been chosen because it has statistical advantages relating to its sampling distribution and its suitability for modelling, and is a relative measure so can be used to combine studies.

Continuous data: For continuous data, the mean score for each outcome as determined by a standardised tool will be compared between the two groups to give a mean difference (MD), again with a 95% confidence interval. Where possible, these comparisons will be made at specific follow-up periods: (1) within the first six months, (2) between six months and two years, (3) between two years and five years, and (4) long term, i.e. longer than five years. Where both endpoint and change data are available for the same outcomes, then only the former will be reported. We will use the mean difference (MD) where the same outcome measures are reported in more than one study. The standardised mean difference (SMD) will be used where different outcome measures of the same construct are reported.

Continuous data that are skewed will be reported in a separate table, and treatment effect sizes will not be calculated to minimise the risk of applying parametric statistics to data that depart significantly from a normal distribution. We define skewedness as occurring when, for a scale or measure with positive values and a minimum value of zero, the mean is less than twice the standard deviation (Altman 1996).

Unit of analysis issues

Cluster randomised trials: We will follow the guidance on statistical methods for cluster randomised trials described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009, Section 16.3). We will seek direct estimates of the effect (for

example, an odds ratio with its confidence interval) from an analysis that properly accounts for the cluster design; alternatively, we will extract or calculate effect estimates and their standard errors as for a parallel group trial, and adjust the standard errors to account for the clustering (Donner 1980). This requires information on an intraclass correlation coefficient (ICC), which describes the relative variability in outcome within and between clusters (Donner 1980). We will extract this information from the articles if available, and otherwise we will contact the authors or use external estimates obtained from similar studies. We will find closest matching scenarios (with regard to both outcome measures and types of clusters) from existing databases of ICCs (Ukoumunne 1999), and if we are unable to identify any we will perform sensitivity analyses using a high ICC of 0.1, a moderate ICC of 0.01 and a small ICC of 0.001. We recognize that these values are relatively arbitrary, but prefer to use them to adjust the effect estimates and their standard errors due to the implausibility that the ICC is actually zero. Subsequently, we will combine the estimates and their corrected standard errors from the cluster randomised trials with those from parallel designs using the generic inverse variance method in Review Manager 5.

Crossover trials: When conducting a meta-analysis combining the results of crossover trials, we plan to use the inverse variance methods recommended by Elbourne 2002. Where data presented from a crossover trial are restricted (and more information is not available from the original investigators) we plan to use the presented data within the first phase only, up to the point of crossover.

Multi-arm trials: All eligible outcome measures for all trial arms will be included in this review. Where there is more than one arm using the same pharmacological intervention, though of different doses or method of administration, we will consider merging data from these arms, if appropriate, to avoid losing valuable data.

Dealing with missing data—We will attempt to contact the original investigators to request any missing data and information on whether or not it can be assumed to be ‘missing at random’.

For dichotomous data, we will report missing data and dropouts for each included study and report the number of participants who are included in the final analysis as a proportion of all participants in each study. We will provide reasons for the missing data in the narrative summary where these are available. If sufficient information is available, we plan to assess the extent to which the results of the review could be altered by the missing data by, for example, a sensitivity analysis based on consideration of ‘best-case’ and ‘worst-case’ scenarios (Gamble 2005). Here, the ‘best-case’ scenario is that where all participants with missing outcomes in the experimental condition had good outcomes and all those with missing outcomes in the control condition had poor outcomes; the ‘worst-case’ scenario is the converse (Higgins 2009; section 16.1.2).

For missing continuous data, we will provide a narrative summary. The standard deviations of the outcome measures will be reported for each group in each trial. If these are not given, we plan to impute standard deviations using relevant data (for example, standard deviations

or correlation coefficients) from other, similar studies (Follmann 1992), but only if, after seeking statistical advice, to do so is deemed practical and appropriate.

Assessment of heterogeneity—We aim to assess the extent of between-trial differences and the consistency of results of any meta-analysis in three ways: by visual inspection of the forest plots, by performing the chi-square test of heterogeneity (where a significance level less than 0.10 is interpreted as evidence of heterogeneity), and by examining the I^2 statistic (Higgins 2009; section 9.5.2; accessed 17 August 2010). The I^2 statistic describes approximately the proportion of variation in point estimates due to heterogeneity rather than sampling error. I^2 values between 0% to 40% indicate that heterogeneity might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity, and 75% to 100% considerable heterogeneity. We will attempt to identify any significant determinants of heterogeneity categorised at ‘moderate’ or ‘high’, if sufficient studies are included.

Assessment of reporting biases—We plan to search for original trial protocols for each included study via trial registries and contact with primary investigators. We will compare these, where available, with outcome data provided within the final reports of each included study. Where original trial protocols are not obtainable, we will give a rating of ‘unclear’ to the study for this criterion in the ‘Risk of bias’ table. We will furthermore seek internal evidence of selective outcome reporting within the final reports, for example, where results are only presented numerically if significant.

In addition, funnel plots (effect size versus standard error) will be drawn to assess publication bias if there are sufficient studies (10 or more, as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions*, Higgins 2009). Asymmetry of the plots may indicate publication bias, although it may also represent a true relationship between trial size and effect size. If such a relationship is identified, the clinical diversity of the studies will be further examined as a possible explanation (Egger 1997).

Data synthesis—We plan to use meta-analyses to combine comparable outcome measures across studies, using both fixed-effect and random-effects models. Random-effects models will be used because studies may include somewhat different treatments or populations; in addition, a fixed-effect analysis will be carried out as a sensitivity analysis, and results compared.

Subgroup analysis and investigation of heterogeneity—We plan to undertake subgroup analysis to examine the effect on primary outcomes of: participants’ principal diagnosis (for example, PD, depression, anxiety); setting (inpatient; custodial; outpatient/community); and type of drug within class.

Subgroup analyses may be undertaken to investigate outcomes in relation to the severity of PD at diagnosis and/or baseline assessment.

Sensitivity analysis—If sufficient studies are found, we plan to undertake sensitivity analyses to investigate the robustness of the overall findings in relation to certain study

characteristics. A priori sensitivity analyses are planned for studies with assessments of 'high risk of bias' on the following criteria:

- concealment of allocation
- blinding of outcome assessors
- extent of dropouts

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* *Indicates the major publication for the study*