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Pharmacological interventions for paranoid personality disorder

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CONTRIBUTIONS OF AUTHORS Birgit Völlm conceived the review and is the lead author and first author of the clinical background to the review. Saeed Farooq is the second clinical author. Both will be responsible for the 'Discussion' and 'Authors' conclusions' in the final review. Jutta Stoffers, Simon Gibbon, Birgit Völlm, Hannah Jones and Najat Khalifa 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. 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. Jane Dennis (as author support) edited the protocol and will screen and select studies for inclusion in the review.

DECLARATIONS OF INTEREST

- Birgit A Völlm - None known
- Saeed Farooq - None known
- Hannah Jones - None known
- Michael Ferriter - None known
- Simon Gibbon - None known
- Jutta Stoffers - None known
- Conor Duggan - Advisor to a current randomised 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
- 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

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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 paranoid personality disorder (PPD).

BACKGROUND

Description of the condition

The Diagnostic and Statistical Manual of Mental Disorders (fourth edition, text revision, more commonly known as DSM-IV-TR (APA 1980)) uses a multiaxial system of classification of psychiatric diagnoses. Axis I includes major mental disorders such as depression or schizophrenia. Axis II describes personality disorders and mental retardation. Personality disorders (PD) are characterised by "an enduring pattern of inner experience and behaviour that deviates markedly from the expectations of the culture of the individual who exhibits it". They cause difficulties with functioning fully in social, vocational and other important areas of an individual's life.

Within Axis II, personality disorders are categorised within three clusters. Cluster 'A' or 'odd eccentric' personality disorders are characterised by aloofness, asociality and unusual thoughts. This group includes paranoid, schizoid and schizotypal personality disorders.

Paranoid personality disorder (PPD) is characterised by a pervasive distrust and suspicion of others such that their motives are interpreted as malevolent, beginning by early adulthood and present in a variety of contexts (DSM-IV-TR; APA 1980). According to DSM-IV-TR, at least four of the following criteria have to be fulfilled:

- suspects, without sufficient basis, that others are exploiting, harming, or deceiving him or her;
- is preoccupied with unjustified doubts about the loyalty or trustworthiness of friends or associates;
- is reluctant to confide in others because of unwarranted fear that the information will be used maliciously against him or her;
- reads benign remarks or events as threatening or demeaning;
- persistently bears grudges, i.e., is unforgiving of insults, injuries, or slights;
- perceives attacks on his or her character or reputation that are not apparent to others and is quick to react angrily or to counterattack;
- has recurrent suspicions, without justification, regarding fidelity of spouse or sexual partner.

The symptoms should not occur exclusively during the course of schizophrenia, a mood disorder with psychotic features or another psychotic disorder and should not be due to physiological effects of a general medical condition.

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Individuals with PPD often have difficulties in interpersonal relationships and work settings due to their suspicious, rigid and critical nature. They may therefore fail to achieve meaningful relationships or employment, adapt poorly to life challenges and have a poor quality of life. Substance misuse problems are common.

Individuals with PPD do not typically seek treatment as they do not see themselves as having a problem. When in treatment, healthcare professionals are often faced with significant difficulties in developing a therapeutic relationship with people with PPD.

PPD was first described by Kraepelin in 1921 (as cited in Bernstein 1995) and was incorporated in the DSM classification in 1980 (APA 1994). Kraepelin considered the disorder to be part of a "schizophrenia spectrum" based on observations that individuals with paranoid personalities often developed paranoid psychoses later on. This conceptualisation has continued until today, raising issues regarding the boundaries between PPD and other Axis II disorders (for example, schizotypal personality disorder) and Axis I disorders (for example, delusional disorder, schizophrenia) with which it shares certain characteristics.

Comorbidity between PPD and other mental disorders is common. Individuals with PPD have an increased risk for substance misuse disorders, major depressive disorder, agoraphobia and obsessive-compulsive disorder (Bienenfeld 2010). Among the Axis II disorders, schizoid, schizotypal, narcissistic, borderline, avoidant and passive-aggressive personality disorders most commonly co-occur with PPD (Bernstein 1995). While antisocial and borderline PD are the most prevalent personality disorders in forensic-psychiatric settings, PPD has also been found to be associated with violent behaviour (Stone 2007).

PPD is one of the most common personality disorders in the general population. Data from the National Epidemiologic Survey on Alcohol and Related Conditions (Grant 2004) found a prevalence of 4.4%, with higher rates in women than men. Other studies have described rates ranging from 0.9% to 2.4% (Torgersen 2001; Coid 2006).

Description of the intervention

This review will systematically evaluate the effectiveness of all pharmacological interventions used in the treatment of PPD, including the following psychotropic drugs: antipsychotic drugs (including depot injections); antidepressant drugs; mood stabilisers; hypnotics; anxiolytics; antimanic drugs; central nervous system stimulants, and antiepileptics. While (due to the main characteristics of the disorder) antipsychotic drugs appear to have the greatest face value in PPD, we do not want to exclude the evidence for other possible psychopharmacological interventions that may be used, for example, to target specific or associated symptoms.

How the intervention might work

It has been suggested that personality disorders may be conceptualised as part of a continuum with Axis I clinical disorders (Siever 1991). This notion is supported by the frequent association (comorbidity) of the different psychiatric disorders with their corresponding personality disorder; by the increased prevalence of corresponding Axis I

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disorders in relatives of individuals with personality disorders, and by shared genetic vulnerabilities for both personality disorders and some Axis I disorders (Tyrer 2007). In this model, the personality disorders in Cluster A, including PPD, can be considered as a subsyndrome of schizophrenia. Cluster A personality disorders have many phenomenological, genetic and physiologic features in common with schizophrenia. PPD is more common among relatives of patients with schizophrenia than among relatives of controls (Baron 1985). It may be possible to delay, and in some cases even avert, progression to schizophrenia through the use of evidence-based interventions in individuals suffering from these personality disorders at an early stage (McGorry 2002;Morrison 2004; Nordentoft 2006).

Applying this model to pharmacological interventions for the treatment of personality disorders (Soloff 1998), it can be argued that the likely impact of drugs on the primary PD symptoms can broadly be predicted from drug effects when used in Axis I disorders. On this basis, medication is matched to the primary symptom group, so that antipsychotic medication would be the preferred drug treatment for cognitive-perceptual symptoms, and mood stabilisers and selective serotonin uptake inhibitors (SSRIs) would be indicated for impulsive-behavioural dyscontrol.

For PPD it can be argued that antipsychotic medication may be effective in treating psychotic symptoms found in psychoses as well as personality disorders on the same continuum. Serotonergic agents are now thought to affect not only depressive mood states but to have a wider role in social interaction. Administration of the SSRI paroxetine over four weeks increased cooperation and reduced hostility and negative affect in healthy volunteers (Knutson 1998), while ingestion of the serotonin precursor L-tryptophan enhanced social functioning (Moskowitz 2001). On this basis, it may be hypothesised that serotonergic agents might impact upon negative mood states in PPD, such as hostility.

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 utilisation (Skodol 2002). PPD has been described as one of four personality disorders significantly associated with disability (Grant 2004). Past reviews have shown that most research has been carried out on borderline personality disorder (Duggan 2007; Duggan 2008) and personality disorders such as PPD have generally been neglected.

Some evidence suggests that personality traits in people with Cluster A personality disorders, including PPD, tend to become more pronounced with time, while the personality traits of people with Cluster B or C personality disorder became significantly less pronounced over time (Sievewright 2002). This highlights the need for effective interventions that could be started early in the course of this type of personality disorder to prevent further impairment.

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OBJECTIVES

To evaluate the effects of pharmacological interventions for people with paranoid personality disorder (PPD).

METHODS

Criteria for considering studies for this review

Types of studies—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, such as active treatment plus treatment as usual (TAU) versus TAU.

Types of participants—Men or women aged 18 years or over with i) a diagnosis of paranoid personality disorder as defined by DSM-IV (APA 1980) or ICD-10 (WHO 1992). We will not exclude those with comorbid mental health problems unless they have a major functional illness (schizophrenia, schizoaffective disorder, 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.

If sufficient studies are found, we plan to group outcome measures by class of drug, with possible subgroup analysis with classes of type of drug (for example, tricyclic antidepressants analysed separately from SSRIs).

Types of outcome measures—We have listed primary and secondary outcomes below in terms of single constructs. Outcome measures could be either self-rated or interviewer-assessed. We anticipate that a range of outcome measures will have been used in the studies included.

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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.

We will assess outcomes at the following time points: immediate (within six months); short term (more than 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 standardised 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—We will search the following electronic databases:

The Cochrane Central Register of Controlled Trials (CENTRAL)

(*The Cochrane Library*)

MEDLINE

EMBASE

CINAHL

PsycINFO

ASSIA

BIOSIS

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Dissertation Abstracts

ISI-SCI (Science Citation Index)

ISI-SSCI (Social Sciences Citation Index)

National Criminal Justice Reference Service Abstracts

Sociological Abstracts

ZETOC (Conference Search)

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

We will base searches 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 the Cochrane Handbook for Systematic Reviews of Interventions (Lefebvre 2008). The strategy includes search terms for all types of PD as this is one of a series of PD reviews. We will modify search terms and syntax 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.

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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

Handsearching: We will search the reference lists of included and excluded studies for additional relevant trials. We will also examine bibliographies of systematic review articles published in the last five years to identify relevant studies.

Requests for additional data: 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 all major pharmaceutical companies to request information about any published or unpublished trials.

Data collection and analysis

Selection of studies—This review is one of a series of reviews on personality disorders. We will carry out the selection of studies in two stages. In the first stage, two review authors will independently read titles and abstracts 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, we will assess full copies of studies against the inclusion criteria for this particular review. This second stage assessment identifies not only trials with participants diagnosed with PPD, but also trials with participants having a mix of PDs for which data on a subgroup with PPD may be available.

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.

We will include studies with two treatment conditions in which the relevant participants form a small subgroup only if the trial investigators randomised at least five people with PPD. 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.

We will resolve uncertainties concerning the appropriateness of studies for inclusion in the review through consultation with a third review author (CD).

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Data extraction and management—Two review authors will extract data independently using a data extraction form. We will enter data into Review Manager 5 (RevMan 2008). Where data are 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 (BV and JS) will independently complete the Cochrane Collaboration's tool for assessing risk of bias (section 8.3; Higgins 2009, accessed 17 August 2010). If there is any disagreement we will resolve this through consultation with a third review author (CD).

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 ('incomplete outcome data'); reports of the study were free of suggestion of selective outcome reporting ('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 ('other sources of bias').

Each domain will be allocated one of three possible categories for each of the included studies: low risk of bias, high risk of bias, and unclear risk of bias when the risk of bias is uncertain or unknown.

Measures of treatment effect

Dichotomous data: For dichotomous (binary) data, we will use the odds ratio (OR) with a 95% confidence interval to summarise results within each study. We have chosen the OR 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, we will compare the mean score between the two groups for each outcome as determined by a standardised tool to give a mean difference (MD), again with a 95% confidence interval. Where possible, we will make these comparisons 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 we will report only the former. We will use the mean difference (MD) where the same outcome measures are reported in more than one study. We will use the standardised mean difference (SMD) where different outcome measures of the same construct are reported. We will report continuous data that are skewed in a separate table, and will not calculate treatment effect sizes to minimise the risk of applying parametric statistics to data that depart significantly from a normal distribution. We define skewness 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).

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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 OR 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 recognise 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 (RevMan 2008).

Cross-over 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 cross-over point.

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. We will report the standard deviations of the outcome measures for each group in each trial. If these are not given, we plan to impute standard deviations using relevant data (for example, standard

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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^2 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 as ‘moderate’ or higher, 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 they are statistically significant.

In addition, we will draw funnel plots (effect size versus standard error) 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 a plot may indicate publication bias, although it may also represent a true relationship between trial size and effect size. If such a relationship is identified, we will further examine the clinical diversity of the studies 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. We will use random-effects models because studies may include somewhat different treatments or populations; in addition, we will carry out a fixed-effect analysis as a sensitivity analysis, and compare results.

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.

We may undertake subgroup analyses 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. We have planned a priori sensitivity analyses for studies with assessments of 'high risk of bias' for the following criteria:

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

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HISTORY

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