Antiglucocorticoid and related treatments for psychosis (Protocol)

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[Intervention Protocol]

Antiglucocorticoid and related treatments for psychosis

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ABSTRACT

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

To determine the efficacy of antiglucocorticoid and related drugs for the treatment of psychosis, when used alone or in combination with antipsychotic medication.

BACKGROUND

Psychosis is a generic term that encompasses a group of severe mental illnesses with considerable variation in prognosis; these include schizophrenia, schizophreniform disorder, schizoaffective disorder, psychotic depression and bipolar disorder with psychotic features. The lifetime prevalence of psychotic disorders is relatively high (~3 %) with many sufferers having a high level of disability, making it a significant public health problem both socially and economically (Altindag 2007; Murray 1997; Perälä 2007). Antipsychotic medications are the primary treatment for psychosis. The newer generation atypical antipsychotics are preferable to typical antipsychotics as they are associated with fewer extra-pyramidal symptoms (Kerwin 2004). Atypical antipsychotics are generally effective in alleviating the positive symptoms (e.g. hallucinations, delusions), but have only modest effects on negative (e.g. anhedonia, withdrawal, flat affect) and cognitive symptoms (Keefe 1999; Leucht 1999). A significant proportion of patients are treatment resistant and many do not achieve complete remission of symptoms. While associated with fewer extra-pyramidal symptoms, there are nevertheless significant adverse effects associated with antipsychotic treatment, such as weight gain and diabetes mellitus, which can lead to increased risk of a range of comorbid medical conditions as well as medication non-compliance (Alvarez-Jimenez 2008; Newcomer 2005).

Psychosocial interventions (such as cognitive behavioural treatment approaches) for psychosis have been associated with reasonable levels of efficacy (Pilling 2002). Shifting the focus of intervention from chronic illness to intervention in the earlier stages of the illness has also resulted in better outcomes (Killackey 2007). There has also been increasing interest in the delivery of treatments to young people at ultra-high risk (UHR) of developing a psychotic disorder, or with sub-threshold symptoms, in order to reduce the likelihood of this group transitioning to a full-blown psychotic disorder (McGorry 2002).

There has been an ongoing search for more effective and more benign treatments in all phases of psychotic disorders. These may involve alternative medications to atypical antipsychotics, or adjunctive treatments to augment symptom reduction or alleviate adverse effects. A search for more benign treatments is considered particularly important in the treatment of the initial episodes of psychosis and UHR patients since they are earlier in the course of their illness progression and thus the potential for positive outcomes from more benign treatment is greater (McGorry 2006). Since many UHR individuals will not go on to have a psychosis with a chronic deteriorating course (Yung 2007), the risks of taking medications with serious adverse effects may outweigh the benefits.

The hypothalamic-pituitary-adrenal (HPA) axis has been implicated in the development and relapse of major psychiatric disorders, including psychosis (Phillips 2006). There is evidence suggesting abnormalities of HPA-axis function in patients with schizophrenia (Lammers 1995; Sharma 1988), psychotic depression (Nelson 1997), bipolar disorder (Watson 2004), first-episode psychosis patients (Pariante 2004; Ryan 2004) and individuals in the prodromal stages of psychosis (Garner 2005; Thompson 2007). Higher levels of circulating cortisol and impaired regulation of the HPA axis have been reported, particularly in patients with psychotic depression and those in the acute phase of psychosis. It has been suggested that HPA-axis dysfunction may cause or exacerbate psychotic and depressive symptoms and neuropsychological dysfunction. Supporting this is the observation that corticosteroid therapy used for the treatment of a variety of medical conditions can often induce symptoms of depression and psychosis, including hallucinations and delusions, as well as cognitive impairment (Brown 2001). In addition, Cushing's syndrome (a condition characterized by hypercortisolaemia) is associated with significant cognitive impairment, which improves when cortisol levels have returned to normal following treatment (Starkman 1999). Interestingly, atypical antipsychotics have been shown to suppress HPA-axis activity (Cohrs 2006) and there is some evidence that normalization of HPA-axis activity correlates with improvement in clinical symptoms in patients with schizophrenia (Zhang 2005). As a result, the HPA axis is increasingly viewed as an important therapeutic target in psychosis.

Recent clinical trials suggest that the antiglucocorticoid drug, mifepristone, may be useful in the treatment of psychotic depression and bipolar disorder (DeBattista 2006; Young 2004). In this review, we examine the evidence for the use of antiglucocorticoid and other related drugs as a single or adjunctive therapy in the treatment of those:

1. at high risk of psychosis or in a prodrome of psychosis;
2. with a first episode of psychosis; and
3. with more established illness.

OBJECTIVES

To determine the efficacy of antiglucocorticoid and related drugs for the treatment of psychosis, when used alone or in combination with antipsychotic medication.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCT). Where a trial was described as 'double-blind', but it is only implied that the study was randomised, we included these trials in a sensitivity analysis. If there was no substantive difference within primary outcomes (see types of outcome measures) when these 'implied randomisation' studies were added, then we included these in the final analysis. If there was a substantive difference, we only used clearly randomised trials and described the results of the sensitivity analysis in the text. We excluded quasi-randomised studies, such as those allocating by using alternate days of the week. There were no time or language restrictions.

Types of participants

We included people with a primary diagnosis of a psychotic disorder (including schizophrenia, schizophreniform disorder, schizoaffective disorder, psychotic depression, bipolar disorder with psychotic features) diagnosed by a clinician using any diagnostic system or those determined to be at ultra-high risk for psychosis or in the prodromal phase of psychosis. We included all stages of psychosis (i.e. prodromal through to chronic psychosis), in an inpatient or outpatient setting, with any length of untreated and treated illness and of any severity. Those with comorbidity were also included.

Types of interventions

1. Pharmacological treatments targeting components of the hypothalamic-pituitary-adrenal (HPA) axis including the following main categories:
1.1 glucocorticoid receptor antagonists (e.g. mifepristone);
1.2 mineralocorticoid receptor antagonists (e.g. spironolactone);
1.3 glucocorticoid receptor/mineralocorticoid receptor agonists (e.g. hydrocortisone, dexamethasone);
1.4 corticotrophin-releasing hormone antagonists (e.g. R121919, ORG 34116); and
1.5 steroid-synthesis inhibitors (e.g. metyrapone, ketoconazole) used alone or as an adjunctive treatment.
2. Neuroactive steroids that are considered to have antiglucocorticoid effects, such as dehydroepiandrosterone (DHEA).
3. Comparison interventions
3.1 Placebo
3.2 Atypical antipsychotic treatment
3.3 Typical antipsychotic treatment
3.4 Antidepressant treatment
3.5 Other combination treatment (e.g. atypical or typical antipsychotic or both, antidepressant etc.)

Types of outcome measures

1. Global state
1.1 Relapse
1.2 Remission rate
1.3 Leaving the study early
1.4 Transition rate or time to onset of psychosis
1.5 No clinically important change in response (as defined by individual studies)
2. Mental state
2.1 Average change in depressive symptom scores
2.2 Average endpoint in depressive symptom scores
2.3 Average change in anxiety symptoms
2.4 Average endpoint in anxiety symptom scores
2.5 Average change in total psychotic symptom scores*
2.6 Average endpoint in total psychotic symptom scores*
2.7 Average change in positive symptom scores*
2.8 Average endpoint in positive symptom scores*
2.9 Average change in negative symptom scores*
2.10 Average endpoint in negative symptom scores*
3. Cognitive functioning
3.1 No clinically important change in cognitive functioning in any of the following domains; executive functioning, working memory, declarative learning and memory, vigilance/attention or psychomotor speed
3.2 Average endpoint of cognitive functioning score
3.3 Average change of cognitive functioning score
4. General functioning
4.1 Average change in general functioning scores
4.2 Average endpoint in general functioning scores
5. Adverse effects*
5.1 General adverse effects
5.2 Serious adverse effects
5.3 Extrapyramidal symptoms
5.4 Weight gain.
*Primary outcomes of interest.
We grouped outcomes into the short term (up to 12 weeks), medium term (13-26 weeks) and long term (over 26 weeks).

Search methods for identification of studies

1. Electronic searches
We searched the Cochrane Schizophrenia Group Trials Register (October 2007) using the phrase:
[(*Steroid* or *cocorticoid* or *cort?cotrop* or *dexamethasone* or *hydrocortisone* or *R?121919* or *ORG?34116* or *3-acetoxyandrost* or dehydroepiandrosteron* or *mifepristone* or *mitot?ne* or *aminoglutethimide* or *spironolactone* or *ketoconazole* or *metyrapone* or *etomidate* or *RU-486* in TI, AB or IN fields of REFERENCE) or (*steroids* or Hydrocortisone or Corticotropin or Mifepristone or Dehydroepiandrosterone or Etomidate or Ketoconazole or Glucocoticoid receptor antagonist or aminogluteth* or mitotane* or dexamethas* or metyrapon* in Intervention field of STUDY)] This register is compiled by systematic searches of major databases, hand searches and conference proceedings (see Group Module).

The Cochrane Central Register of Controlled Trials (CENTRAL) and bibliographic databases, including MEDLINE, PsycINFO and EMBASE were searched (OVID 1950 to November 2007). The search strategy used for these databases is included in an additional table (Table 1).

Table 1. Search terms

PsycINFO	EMBASE	MEDLINE
1. Psychosis/	1.Psychosis/or psychotic disorder$.tw	1. exp psychotic disorders/
2. exp Acute Psychosis/	2.exp Delusion/	2. Delusions/
3. Affective Psychosis/	3.exp Hallucination/	3. Hallucinations/
4. exp Hallucinosis/	4.exp Paranoid Psychosis/	4. Paranoid Disorders/
5. exp "Paranoia (Psychosis)"/	5.exp Schizohprenia/	5. Schizophrenia/
6. exp Schizophrenia/	6.#1 or #2 or #3 or #4 or #5	6. (psychotic disorder$ or psychoses or psychosis).tw.
7. #1 or #2 or #3 or #4 or #5 or #6	7.exp corticosteroid/	7. (delusion$ or hallucination$ or paranoid$).tw.
8. exp Adrenal Cortex Hormones/	8.exp corticosteroid receptor/	8. (schizoaffective disorder$ or schizophreniform disorder$ or schizophrenia).tw.
1.exp Glucocorticoids/	9.Corticotropin releasing factor	9. exp mood disorders/
2.Corticotropin releasing factor	10.Corticotropin Releasing Factor Receptor	10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
3.Corticotropin	11.Corticotropin Releasing Factor Receptor 1	11. Receptors, Steroid/
4.Vasopressin	12.Corticotropin Releasing Factor Receptor 2	12. Glucocorticoids/
5.Hypothalamic pituitary adrenal axis	13.Corticotropin	13. Receptors, Corticotropin-Releasing Hormone/
6.Corticosteroids/	14.Vasopressin	14. Receptors, Corticotropin/
7.R121919	15.Hypothalamus Hypophysis Adrenal System	15. Dexamethasone/
8.ORG 34116	16.R121919	16. Hydrocortisone/
9.3-acetoxyandrost-5-ene-7,17-dione	17.ORG 34116	17. Adrenocorticotropic Hormone/
10.dehydroepiandrosterone	18.3-acetoxyandrost-5-ene-7,17-dione	18. Corticotrophs/
11.mifepristone	19.Prasterone	19. Hydroxycorticosteroids/
12.mitotane	20.Mifepristone	20. R 121919.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
13.aminoglutethimide	21.Mitotane	21. ORG 34116.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
14.spironolactone	22.Aminoglutethimide	22. 3-acetoxyandrost-5-ene-7,17-dione.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
15.ketoconazole	23.Spironolactone	23. Dehydroepiandrosterone/
16.metyrapone	24.Ketoconazole	24. Mifepristone/
17.#8 or #9 or #10 or #11or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24	25.Metyrapone	25. Mitotane/
18.#7 AND #25	26.# 7 or #8 or #9 or #10 or #11or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25	26. Aminoglutethimide/
19.Clinical Trials/	27.#6 AND #26	27. Spironolactone/
20.Controlled trial$.tw	28.exp controlled study/	28. Ketoconazole/
21.(controlled studies or controlled study).tw	29.(controlled trial$ or controlled study or controlled studies).tw	
22.Random$.tw	30.random$.tw	
23.Random Sampling/	31.single blind procedure/	
24.((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or dummy or mask$)).tw	32.double blind procedure/	
25.Placebo$mp	33.((singl$ or doubl$ or trebl$ or tripl$)	
26.#27 or #28 or # 29 or #30 or #31 or #32 or #32 or #33		
27.#26 AND #34		

Table 1. Search terms (*Continued*)

	adj (blind$ or mask$ or dummy)).tw 34.placebo$.mp 35.#28 or #29 or #30 or #31 or #32 or #33 or #34 36.#27 AND #35	29. Metyrapone/ 30. Corticotropin-Releasing Hormone/ 31. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 31. 10 and 31 32. clinical trial.pt 33. clinical trial$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] 34. random$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] 35. placebo.mp. [mp=title, original title, abstract, name of substance word, subject heading word] 36. placebo.ti,ab 37. groups.ti,ab 38. dt.mp. [mp=title, original title, abstract, name of substance word, subject heading word] 39. trial.mp. [mp=title, original title, abstract, name of substance word, subject heading word] 40. groups.mp. [mp=title, original title, abstract, name of substance word, subject heading word] 41. 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 42. 31 and 41

We searched the National Research Register (http://www.updatesoftware.com/National/nrr-frame.html), Clinical Trials (http://clincaltrials.gov/ct/gui/c/r), the Australian Clinical Trials Register (http://www.actr.org.au/trialSearch.aspx) and Current Controlled Trials (http://www.controlled-trials.com) databases. Additionally, we searched the trial databases of pharmaceutical companies.

2. Reference lists

We searched reference lists of articles and other reviews retrieved from the search for relevant studies.

3. Handsearching

We handsearched published abstracts from the following conferences: International Early Psychosis Conference, Birmingham, October 2006; International Early Psychosis Conference, Vancouver, October 2004; Schizophrenia Research, 13th Biennial Winter Workshop, Davos, February 2006; Schizophrenia Bulletin, XX International Congress on Schizophrenia Research, Savannah, April 2005.

4. Personal Communication

We contacted the authors of the included trials for further trials; published or unpublished.

Data collection and analysis

1. Selection of trials

We independently inspected all reports. Where disagreement occurred we attempted to resolve this by discussion, where doubt still remained we acquired the full article for further inspection.

Once we had obtained the full articles, we independently decided whether the studies met the review criteria. If disagreement could not be resolved by discussion, we sought further information and added these trials to the list of those awaiting assessment.

2. Assessment of methodological quality

We assessed the methodological quality of included studies using the criteria described in The Cochrane Handbook (Higgins 2005), which is based on the degree of allocation concealment. Poor concealment has been associated with overestimation of treatment effect (Schulz 1995). Category A includes studies in which allocation has been randomised and concealment is explicit. Category B studies are those which have randomised allocation but in which concealment is not explicit. Category C studies are those in which allocation has neither been randomised nor concealed. We only included trials that were stated to be randomised (categories A or B of the handbook) in this review. The categories are defined below:

A. Low risk of bias (adequate allocation concealment)

B. Moderate risk of bias (some doubt about the results)

C. High risk of bias (inadequate allocation concealment).

When disputes arose as to which category a trial should be allocated, again resolution was attempted by discussion. When this was not possible we did not enter the data and the trial was added to the list of those awaiting assessment until further information could be obtained.

3. Data collection

We independently extracted data from selected trials. When disputes arose we attempted to resolve these by discussion. When this was not possible and further information was necessary to resolve the dilemma, we did not enter data but added the trial to the list of those awaiting assessment. We collected information on participants (age, gender, ethnicity, diagnosis, diagnostic criteria and first-episode/prodromal criteria used, setting of care, country, inclusion and exclusion criteria for the trial, duration of treated and untreated illness, previous treatment and psychiatric comorbidity); interventions (description of medication, method of delivery, dose, length of treatment, actual dosage received) and other interventions being used in intervention group; interventions in the comparison group with similar detail; outcome measures (description of measures used, timing of administration), and results (point estimates and measures of variability, frequency counts for dichotomous variables) and methods (randomisation and allocation procedure, blinding, number of participants randomised, withdrawn, dropped out, analysed, baseline comparability, intention-to-treat analysis, other problems).

4. Data synthesis

4.1 Binary data

For binary outcomes we calculated the relative risk (RR) and its 95% confidence interval (CI) based on the fixed-effect model. Relative Risk is more intuitive (Boissel 1999) than odds ratios and odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). This misinterpretation then leads to an overestimate of the impression of the effect. When the overall results were significant we calculated the number needed to treat (NNT) and the number needed-to-harm (NNH). Where people were lost to follow up at the end of the study, we assumed that they had had a poor outcome and once they were randomised they were included in the analysis (intention-to-treat /ITT analysis).

4.2 Intention to treat analysis

We excluded data from studies where more than 50% of participants in any group were lost to follow up (this did not include the outcome of 'leaving the study early'). In studies with less than 50% dropout rate, we considered people leaving early to have had the negative outcome, except for the event of death. We analysed the impact of including studies with high attrition rates (25-50%) in a sensitivity analysis. If inclusion of data from this latter group resulted in a substantive change in the estimate of effect, we did not add their data to trials with less attrition, but presented them separately.

4.3 Continuous data

4.3.1 Normal distribution

Continuous data on outcomes in trials relevant to mental health issues are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data we applied the following standards to continuous final value endpoint data before inclusion: (a) standard deviations and means were reported in the paper or were obtainable from the authors; (b) when a scale started from zero, the standard deviation, when multiplied by two, should be less than the mean (otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution (Altman 1996)); in cases with data that are greater than the mean they were entered into 'Other data' table as skewed data. If a scale starts from a positive value (such as PANSS, which can have values from 30 to 210) the calculation described above in (b) should be modified to take the scale starting point into account. In these cases skewness is present if 2SD>(S-Smin), where S is the mean score and Smin is the minimum score. We reported non-normally distributed data (skewed) in the 'other data types' tables.

For change data (mean change from baseline on a rating scale) it is impossible to tell whether data are non-normally distributed (skewed) or not, unless individual patient data are available. After consulting the ALLSTAT electronic statistics mailing list, we entered change data in RevMan analyses and reported the finding in the text to summarise available information. In doing this, we assumed either that data were not skewed or that the analysis could cope with the unknown degree of skew.

4.3.2 Multiply linear regression data

Many trials in psychiatry report estimates of treatment effects from multiple linear regression models. These models adjust for varying factors such as age, sex, and baseline of the outcome. We pooled treatment estimates from these trials using fixed-effect (inverse variance) meta-analysis. P-values and confidence intervals for treatment effect were converted to standard errors and entered into RevMan using the generic inverse variance.

4.3.3 Final endpoint value versus change data

Where both final endpoint data and change data were available for the same outcome category, only final endpoint data were presented. We acknowledge that by doing this much of the published change data may be excluded, but argue that endpoint data is more clinically relevant and that if change data were to be presented along with endpoint data, it would be given undeserved equal prominence. Where studies reported only change data we contacted authors for endpoint figures.

4.3.4 Data synthesis

For continuous outcomes we estimated a weighted mean difference (WMD) between groups based on a fixed-effect model.

4.4 Rating scales

A wide range of instruments are available to measure mental health outcomes. These instruments vary in quality and many are not valid, and are known to be subject to bias in trials of treatments for schizophrenia (Marshall 2000). Therefore continuous data from rating scales were included only if the measuring instrument had been described in a peer-reviewed journal.

4.5 Cluster trials

Studies increasingly employ cluster randomisation (such as randomisation by clinician or practice) but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intraclass correlation in clustered studies, leading to a unit of analysis error (Divine 1992) whereby p values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes Type I errors (Bland 1997, Gulliford 1999). Where clustering was not accounted for in primary studies, we presented the data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review we will seek to contact first authors of studies to obtain intraclass correlation co-efficients of their clustered data and to adjust for this using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we will also present these data as if from a noncluster randomised study, but adjust for the clustering effect. We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a design effect. This is calculated using the mean number of participants per cluster (m) and the intraclass correlation co-efficient (ICC) [Design effect=1+(m-1)*ICC] (Donner 2002). If the ICC was not reported it was assumed to be 0.1(Ukoumunne 1999). If cluster studies had been appropriately analysed taking into account intraclass correlation coefficients and relevant data documented in the report, we synthesised these with other studies using the generic inverse variance technique.

5. Investigation for heterogeneity

Firstly, we considered all the included studies within any comparison to judge for clinical heterogeneity. Then we visually inspected graphs to investigate the possibility of statistical heterogeneity. We supplemented this by using the I-squared statistic. This provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. Where the I-squared estimate was greater than or equal to 50%, we interpreted this as indicating the presence of considerable levels of heterogeneity (Higgins 2003). When heterogeneous results were found, we investigated the reasons for this; where heterogeneity substantially altered the results these data were not summated, but presented separately and reasons for heterogeneity investigated by the following subgroup and sensitivity analyses.

i. Subgroup analyses

Diagnosis

Prodrome versus First-onset versus Chronic

Type of antiglucocorticoid drug

Adults versus adolescents

Length of untreated illness

ii. Sensitivity analyses

We performed sensitivity analyses to assess the effect of risk of bias. We defined the following groups:

We performed sensitivity analyses when (i) allocation concealment was rated as inadequate, not used or unclear (and attempts to clarify with authors failed) (A); (ii) blinding of outcome assessment was not done or probably not done (and attempts to clarify with authors failed) (B); and (DSM-III) intention-to-treat analysis was not done or probably not done (and attempts to clarify with authors failed) (C). These criteria for assessing the risk of bias have been shown to influence estimates of treatment effect (Juni 2001). Sensitivity analyses were performed where A, B or C were excluded.

6. General

Where possible, we entered data into RevMan in such a way that the area to the left of the 'line of no effect' indicated a 'favourable' outcome for the antiglucocorticoid interventions. Where this was not possible, we labelled the graphs in RevMan analyses accordingly so that the direction of any effects were clear.

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* *Indicates the major publication for the study*

WHAT'S NEW

27 October 2008	Amended	Minor amendments to protocol
9 September 2008	Amended	Converted to RevMan 5 format

HISTORY

Protocol first published: Issue 1, 2008

CONTRIBUTIONS OF AUTHORS

Belinda Garner co-ordinated the development of the protocol with all authors contributing equally.

DECLARATIONS OF INTEREST

None known.

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