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[Intervention Review]

Pharmacological treatments for psychosis-related polydipsia

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ABSTRACT

Background

Polydipsia is the intake of more than three litres of fluids per day. Primary polydipsia occurs when excessive drinking cannot be explained by an identified medical condition, and is not secondary to polyuria. The prevalence of this problem in psychiatric inpatients has been estimated at between 6 and 17%. It can hinder standard care and be a highly disabling, even life-threatening condition.

Objectives

To review the effect of pharmacological interventions for the treatment of psychosis-related polydipsia.

Search methods

We searched the Cochrane Schizophrenia Group's Register (January 2002 and February 2005) which is compiled by up-to-date methodical searches of BIOSIS, The Cochrane Library, CINAHL, Dissertation abstracts, EMBASE, LILACS, MEDLINE, PSYINDEX, PsycINFO, RUSSMED and Sociofile and is supplemented with hand searching of relevant journals and numerous conference proceedings. References of all identified studies were also searched for further trials.

Selection criteria

We included all randomised controlled trials involving people with a psychotic illness and secondary polydipsia, which evaluated drug treatments, and measured clinically meaningful outcomes.

Data collection and analysis

Working independently, we inspected citations, ordered papers, and then re-inspected and quality assessed the studies and extracted data. For homogeneous dichotomous data, we calculated the relative risk (RR), 95% confidence interval (CI), and, where appropriate, the number needed to treat (NNT) and the number needed to harm (NNH), on an intention-to-treat basis. We assumed that people who left the study early or who were lost to follow-up had no improvement. We calculated weighted mean differences (WMD) for continuous data. We excluded data if loss to follow-up was greater than 50%.

Main results

We identified two small trials (Alexander 1991 and Nishikawa 1996) which fulfilled the inclusion criteria, (total n=17, duration 3-6 weeks). Few data were reported and, because of inappropriate use of crossover methodology, we could not include all of the data in this review. For the few chronically ill people in these trials, neither the 'active' tetracycline bacteriostatic agent, oral demeclocycline, nor the opiate antagonist naloxone, nor placebo, gave any suggestion of serious adverse effects for a period of up to six weeks. The studies did not report any useful data on measures of polydipsia, physical symptoms secondary to increased fluid intake, mental state, general functioning or economic outcomes.

Authors' conclusions

The trials offer little useful data to the clinician hoping to treat psychosis-related polydipsia with drugs, except that further evaluative studies need to be conducted in this area. Treatment of any sort for psychosis related polydipsia might only be informative within a well designed, conducted and reported randomised study. The two pioneering studies suggest that larger trials, though difficult, would not be impossible with adequate support and co-ordination.

PLAIN LANGUAGE SUMMARY

Pharmacological treatments for psychosis-related polydipsia

Schizophrenia is a serious, chronic and relapsing mental illness with a worldwide lifetime prevalence of about one percent. An uncommon but serious complication of psychotic illness is polydipsia, the intake of more than three litres of fluids per day. Although the exact reason for any one person developing polydipsia is unclear, effective treatment is essential as if untreated, such a high intake of fluids can lead to hyponatraemia which in turn can lead to coma or even death. It is estimated that between 6% and 17% of psychiatric inpatients suffer from polydipsia, and even if this is an over estimate it is a common and serious enough condition to merit clinical concern.

We systematically searched and evaluated randomised controlled trials investigating the effectiveness of drug treatment for polydipsia. We found two short trials (n=17, duration 3-6 weeks) that were too small and short to be informative. Data reporting was also poor with no pre crossover data available for analysis. The only data available were for adverse effects and neither the active treatments nor placebo produced any serious side effects. The studies did not report any useful data on measures of polydipsia, physical symptoms secondary to increased fluid intake, mental state, general functioning or economic outcomes.

Clinicians hoping to treat people with psychosis-related polydipsia are unable to gain any useful information from these trials and treatment of any sort might only be informative within a well-designed study. More research is needed and these two trials, although unable to provide much data, do show this type of research is possible.

BACKGROUND

Polydipsia is the intake of more than three litres of fluids per day (Mercier-Guidez 2000). Primary polydipsia occurs when the excessive drinking cannot be explained by an identified medical condition and is not secondary to polyuria. It may be measured directly by fluid intake or indirectly by urine or plasma analysis. Though there have been many proposed causes, the exact reason for primary polydipsia remains unclear, and probably varies between individuals. It has been described as a form of compulsive behaviour, a means of stress reduction, a disturbance of homeostatic mechanisms, or as secondary to the 'positive' symptoms of schizophrenia or medication adverse effects (Kruse 2001). There is also increasing evidence of a genetic link to the cause of primary polydipsia (Ouyang 2001).

Polydipsia, even when not severe, is a problematic behaviour that can hinder standard treatment of the underlying condition. Severe polydipsia is very difficult to manage as a major focus of the person's efforts is on consumption of large amounts of fluid. Hyponatraemia may follow polydipsia, and untreated, this may lead to coma and even death. Death is caused by a combination of renal and heart failure. Vieweg 1985 reported that almost 20% of deaths under the age of 50 in a state psychiatric hospital could have been associated with self-induced water intoxication. It has long been recognised that there is an increased prevalence of primary polydipsia in people with mental illness, with, for example, a prevalence of between 6 and 17% in psychiatric inpatients (De Leon 1994). Primary polydipsia may be particularly associated with chronic illness, male gender, smoking, schizophrenia and Caucasian race (De Leon 1994). The lack of precise validated criteria for diagnosis, however, has led to considerable difficulty in accurately gauging the magnitude of the problem (Tracy 1997).

Along with behavioural strategies, various drug treatments, some based on aetiological theories and others discovered fortuitously, may be effective in managing polydipsia. These include: clonidine and enalapril (Greendyke 1998), clozapine (Spears 1996), propranolol (Kishi 1998), naloxone (Nishikawa 1992), lithium (Khamnei 1984), demeclocycline (Vieweg 1988), risperidone and olanzapine (Kruse 2001). With so many approaches, none can be expected to work very well, but this review summarises the best available evidence of the effects of these pharmacological treatments.

OBJECTIVES

To review the effects of pharmacological interventions for the treatment of psychosis-related polydipsia.

METHODS

Criteria for considering studies for this review

Types of studies

We included all relevant randomised controlled trials. Where a trial was described as 'double-blind', but it was implied that the study was randomised, we included the trial 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 analysed 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.

Types of participants

We included people diagnosed with a psychotic illness and having polydipsia secondary to this. We included trials however polydipsia was defined or measured. We did not include trials where polydipsia was secondary to polyuria or other medical conditions, or occurred as an adverse effect of lithium or carbamazepine treatment. We did not exclude trials due to age, nationality or gender of participants.

Types of interventions

We only included pharmacological interventions. Where there was doubt as to whether a drug belonged to a particular class, we consulted the British National Formulary. We included studies whatever dose or route of administration was used.

We considered the following drugs:

1. Antipsychotics
For example clozapine, olanzapine and risperidone.
2. Antidepressants
For example, mianserin.
3. Beta adrenergic receptor blockers
For example, propranolol.
4. Angiotensin converting enzyme (ACE) inhibitors
For example, captopril and enalapril.
5. Mood stabilisers
For example, lithium.
6. Angiotensin II receptor-blocking agents
For example, irbesartan.
7. Anticonvulsants
Only phenytoin was considered as it suppresses central release of vasopressin. Other antiepileptic drugs were not considered.
8. Tetracycline bacteriostatic agents
Only demeclocycline was considered.
9. Opiate antagonists
For example, naloxone.
10. Alpha adrenergic receptor blockers
For example, clonidine.
11. Placebo

We excluded interventions consisting of treatment with more than one class of drug simultaneously. We also excluded trials if, in addition to pharmacological treatment, behavioural interventions also varied between the groups studied.

Types of outcome measures

We reported all outcomes for the immediate term (within 24 hours) short term (up to one week), medium term (eight days to one month), and long term (more than one month).

Primary outcomes

1. Death
2. Lack of improvement in polydipsia, to a clinically significant degree, however measured within the trial
3. Not any alleviation of polydipsia
4. Leaving the study early, for specific or general reasons
5. Symptomatic visceral oedema

Secondary outcomes

1. Emergence or worsening of physical symptoms secondary to increased fluid intake
 - 1.1 Symptomatic cerebral oedema
 - 1.2 Significantly impaired renal function
 - 1.3 Dilatation of gastrointestinal or urinary tracts
 - 1.4 Osteoporosis
2. Deterioration in mental state
 - 2.1 Clinically significant worsening of psychosis, however measured within the trial
 - 2.2 Average score or change in psychosis scoring, however measured within the trial
 - 2.3 Reported deterioration in well-being
 - 2.4 Need for additional medication for mental state
3. General functioning
 - 3.1 Reduced level of functioning, to a clinically significant degree, however measured within the trial
 - 3.2 Average score or change in functioning scoring, however measured within the trial
4. Reduced acceptability of treatment
 - 4.1 Reduced compliance
5. Adverse effects of interventions
 - 5.1 General adverse effects
 - 5.2 Specific adverse effects
6. Economic outcomes

Search methods for identification of studies

Electronic searches

1. Update search of 2005

We searched the Cochrane Schizophrenia Group's Trials Register (February 2005) using the phrase:

`[(((*drink* OR *water int* OR *polydipsi* OR *fluid int* OR *water con* OR *fluid con*) in REFERENCE )and ((fluid* in Outcome OR *polydipsia* in Health Care Condition) in STUDY))]`

This register is compiled by systematic searches of major databases, hand searches and conference proceedings (see Group Module).

2 Search for the first version of this review 2002

We searched the Cochrane Schizophrenia Group's Register (January 2002) using the phrase:

`(*water intoxication* or *drinking behav* or *polydipsi* or *excessive drink*) in REFERENCE`

This register is compiled by up-to-date methodical searches of BIOSIS, The Cochrane Library, CINAHL, Dissertation abstracts,

EMBASE, LILACS, MEDLINE, PSYINDEX, PsycINFO, RUSSMED, Sociofile, and is supplemented with hand searching of relevant journals and numerous conference proceedings (see Group Module).

Searching other resources

1. Reference searching

We also inspected the references of all identified studies for more studies.

2. Personal contact

We contacted the first author of each included study for information regarding unpublished trials.

3. We repeated the electronic search (September 2005) in order to identify additional relevant studies.

Data collection and analysis

1. Study selection

The principal reviewer (GB) inspected all reports and these were re-inspected by reviewer AA, to ensure reliable selection. Where disagreement occurred we resolved this by discussion or, if doubt remained, we acquired the full article for further inspection. Once the full articles were obtained we (GB and AA,) again working independently, decided whether they met the criteria for inclusion. Again, when disputes arose, we attempted resolution by discussion but if this was not possible we did not enter data and allocated the trial to the list of those awaiting assessment whilst we contacted the authors.

2. Assessment of methodological quality

We allocated trials to three quality categories, as described in the Cochrane Collaboration Handbook (Higgins 2005). When disputes arose as to which category a trial was allocated, again, we attempted resolution by discussion. When this was not possible and further information was necessary to clarify into which category to allocate the trial, we did not enter data and the trial was allocated to the list of those awaiting assessment. We only included trials in Category A or B in the review.

3. Data collection

Working independently we extracted data from selected trials. When disputes arose resolution was attempted by discussion. When this was not possible and further information was necessary to resolve the dilemma, we did not enter data and we added this outcome of the trial to the list of those awaiting assessment.

4. Data synthesis

4.1 Incomplete data.

We felt that attrition of > 50% would call into question the value of the study and we therefore excluded studies losing more than 50% of people when reporting relevant outcomes.

4.2 Dichotomous - yes/no - data.

4.2.1 Statistics: For binary outcomes, for example, target behaviour significantly reduced or not, relative risk, random effects (RR), with the 95% confidence interval (CI) was estimated. Where possible, we calculated the number needed to treat or harm (NNT/H).

4.2.2 Intention to treat: Where possible, we presented data on a 'once-randomised-always-analyse' basis. Where people were lost to follow up it was assumed, with the exception of death, that they

had a poor outcome. This assumption was tested in a sensitivity analysis.

4.3 Continuous data

4.3.1 Intention to treat: In the case of continuous data we presented 'completer' analysis.

4.3.2 Normal data: Mental health continuous data is often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data we applied the following standards to all continuous data before inclusion: i. standard deviations or standard errors and means were reported in the paper or were obtainable from the authors; ii. when a continuous measure starts from a finite number (such as 0), the standard deviation, when multiplied by two, is less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution - [Altman 1996](#)). Endpoint scores on scales often have a finite start and end point and this rule was applied to them. We did not present data not meeting the second standard within the RevMan graphs as the calculator assumes a normal distribution. We reported these data in the 'Other data types' of the results section if they had been analysed with appropriate non-parametric tests.

Change data are even more problematic as they do not have finite end points - whereas the scale goes from 0-100 the change in that scale may go from -100 to +100. Although most change scores are likely to be skewed, it cannot be proven from the rule outlined above so we presented these in RevMan graphs. Where both endpoint and change data for particular outcomes were available, we presented the former in preference.

4.3.3 Rating scales: A wide range of instruments are available to measure mental health outcomes. These instruments vary in quality and many are not valid, or even ad hoc. For outcome instruments we set some minimum standards. These were: i. the psychometric properties of the instrument should have been described in a peer-reviewed journal; ii. the instrument should either be: a. a self report, or b. completed by an independent rater or relative (not the therapist); and iii. the instrument should be an unmodified global assessment of an area of functioning ([Marshall 2000](#)).

4.3.4 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 intra class 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 intra-class correlation co-efficients of their clustered data and to adjust for these 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 non-cluster randomised study, but adjusted 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](#)).

5. Heterogeneity

As well as inspecting the graphical presentations, we checked whether the differences between results of trials were greater than would be expected by chance alone using tests of heterogeneity (Chi squared). We interpreted a significance level of less than 0.10 as evidence of heterogeneity. When heterogeneity was present, we undertook a sensitivity analysis. We removed outlying studies from the pooled measure if they caused a substantive change in the overall findings and presented and discussed their data separately.

6. Assessing the presence of publication bias

We entered data from all included trials into a funnel graph (trial effect versus trial size or 'precision') in an attempt to investigate the likelihood of overt publication bias. We undertook a formal test of funnel plot asymmetry (suggesting potential publication bias), where appropriate, according to the methods of [Egger 1997](#). Significance levels of $p < 0.1$ were set, a priori, as indication of the presence of asymmetry. Where only three or four studies reported an outcome or there was little variety in sample size (or precision estimate) between studies, tests of asymmetry were not appropriate.

RESULTS

Description of studies

1. Excluded

We excluded two studies. We inspected other citations but these were so clearly not relevant that reporting them here or in the table of excluded studies was not helpful. Both excluded studies investigated the effects of different drugs for people with polydipsia. We excluded [Greendyke 1998](#) as it was not randomised and [Levine 1997](#) for the same reason and also because the polydipsia resulted from lithium treatment rather than being psychosis-related. In this update (September 2005) we identified six potentially relevant studies from the Cochrane Schizophrenia Group Register. However, we excluded these as they did not address the problem of psychosis related polydipsia.

2. Awaiting assessment

No further studies are awaiting assessment.

3. Ongoing studies

None known.

4. Included studies

Only two very small studies (n=17) met the inclusion criteria, [Alexander 1991](#) and [Nishikawa 1996](#).

4.1 Methods

Discussion of randomisation, blinding and description of withdrawal is given below in 'Methodological quality of included studies'. Both of the included studies used a crossover design. This presupposes that i. the condition under investigation, in this case psychosis related polydipsia, is stable, and that ii. any effect of the interventions is free of carryover effects. Both presuppositions

are unlikely. [Alexander 1991](#) was of only three weeks duration and [Nishikawa 1996](#) was six weeks before the crossover took place.

4.2 Participants

Both studies included only inpatients. [Alexander 1991](#) included nine participants (six men, three women), all suffering from either schizophrenia or schizoaffective disorder. All had a history of polydipsia and hyponatraemia. They had been ill for an average of 18 years. [Nishikawa 1996](#) included seven men and one woman with schizophrenia and histories of intermittent hyponatraemia and polydipsia.

4.3 Interventions

[Alexander 1991](#) compared the tetracycline bacteriostatic agent, demeclocycline, given orally at doses of up to 1.2gms/day, with placebo. [Nishikawa 1996](#) compared the opiate antagonist naloxone, given by infusion, with placebo. Participants also had standard diet, and fluid restriction if weight exceeded a threshold. Both studies ensured a stable dose of anti-psychotic medication throughout.

4.4 Outcomes

Both [Alexander 1991](#) and [Nishikawa 1996](#) reported on leaving the study early and major adverse effects before the point of crossover. The two studies also reported weight gain, but these data are not used in this review as we are unconvinced that the proposed mechanisms of action of each of the interventions is sufficiently understood to involve no carry over effects. [Alexander 1991](#) also reported on serum sodium but pre-crossover data were absent.

Risk of bias in included studies

1. Randomisation

Both studies simply state that allocation was random without giving further details.

2. Blindness

The two trials report that they were double-blind to minimise observation bias, but do not describe how this was achieved or tested.

3. Description of withdrawal before conclusion of the study

The included studies were both of short duration and no participants were lost to follow up.

4. Overall

The quality of reporting in these two small studies was poor and no pre-crossover data were available, suggesting that the effect of the experimental treatments may have been over estimated.

Effects of interventions

1. The search

The structured search of the Cochrane Schizophrenia Group's Register produced only four trials. Being rather untrusting of this search, we undertook an unsystematic trawl of MEDLINE and, despite every effort, did not find any additional relevant study. Subsequent searches of the Cochrane Schizophrenia Group's Register in February and September 2005 revealed no additional relevant studies.

2. COMPARISON 01: DRUG TREATMENT versus PLACEBO

2.1 Death

No deaths were reported in these short studies.

2.2 Leaving the study early

Both included studies were short ([Alexander 1991](#), three weeks, [Nishikawa 1996](#), six weeks) and neither study lost anyone to follow up. Neither did anyone withdraw early for any reason.

2.3 Adverse effects

Both studies stated that adverse effects were sought and none were found.

2.4 Missing outcomes

We had hoped to find data on measures of fluid intake, physical symptoms secondary to increased fluid intake, mental state, general functioning and economic outcomes. None were identified or usable.

DISCUSSION

1. General

1.1 Interventions used

In [Alexander 1991](#) people were randomised to the tetracycline bacteriostatic agent, demeclocycline given orally at doses of up to 1.2gms/day, or placebo. Demeclocycline is a drug that may be used in the treatment of hyponatraemia resulting from inappropriate secretion of antidiuretic hormone. It is thought to act by directly blocking the renal tubular effect of antidiuretic hormone. The doses given in the trial were standard.

[Nishikawa 1996](#) compared the opiate antagonist naloxone, given by infusion, with placebo. Opioid antagonists have been found to be effective in attenuating drinking behaviour in genetically polydipsic mice ([Ukai 1988](#)). Any effect is thought to be via the hypothalamic thirst centre which may show an increase in endogenous opioid effects ([Greendyke 1998](#)).

2. COMPARISON 01: DRUG TREATMENT versus PLACEBO

2.1 Death, adverse effects, leaving the study early

Data from the studies gave no suggestion that drug treatment increases death, numbers leaving the study early, or occurrence of serious adverse effects. These results however are based on poorly reported data from two small studies and the effect or lack of effects found in these studies cannot be confirmed until more data are available.

2.2 Measures of polydipsia, physical symptoms secondary to increased fluid intake, mental state, general functioning and economic outcomes.

The two small studies do not report any useful data for the above outcomes and again, more research and useful data is needed to assess the effects of drug treatment for people with polydipsia.

3. Lack of data

In this review we attempted to identify all randomised trials for drug treatments of psychosis related polydipsia. Even if the estimated prevalence of polydipsia of between 6% and 17% in psychiatric inpatients ([De Leon 1994](#)) is an over estimate, it is a common enough, and a serious enough condition to merit considerable clinical concern. This concern has not been adequately addressed in the research community.

Undertaking randomised controlled trials in this area must be difficult and accrual of adequate numbers problematic. Nevertheless two pioneering research groups have shown that studies are possible. Many more of these studies, or, better still,

a well-organised multi-centre trial, could begin to address the problem of evaluation of drug treatments for polydipsia.

4. Methodology

The crossover design is not indicated for this area of research. We know how it can be used to increase the power of the investigation, but doubling the number of included participants from 8 - 16 is still unlikely to give a meaningful result (Nishikawa 1996). Besides this, the mode of action of either of these drugs in this area is ill understood and it is feasible that the start of any drug action could have been delayed until after their pharmacological half-lives had passed. Further complicating matters, is the condition polydipsia is not likely to be very stable. If the behaviour reflects that of the psychoses then it is unstable and could easily fluctuate from week to week in a fashion unrelated to treatment.

5. Reporting

Better reporting of even the few data in the two studies would have allowed more outcomes to be reported and discussed.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with psychosis and polydipsia and their families

For people who may have polydipsia and psychosis there is little guide to effective drug management, yet the consequences of unmodified polydipsia may be serious physical illness or death. If additional drug treatment on top of standard care is suggested, then it would be sensible to ensure that potential adverse effects and markers of efficacy are closely monitored. It may also be reasonable to suggest that such treatment is only ethical inside a well-designed randomised trial.

2. For clinicians

It is clearly important to manage polydipsia effectively given the potential consequences. Unfortunately there is little good quality evidence to suggest that any particular drug should be preferred. Therefore, if additional drugs are prescribed, markers of improvement and deterioration should be closely monitored and the effects widely reported. One team from Australia (Kruse 2001) has done this. It would also be ethically sound to prescribe this medication as part of a randomised controlled trial. Such trials need not be complex or intrusive (please see below).

3. For funders of research

At present there is a large volume of literature on the subject of psychosis-related polydipsia but this has not provided clinicians with firm guidance for management of the problem. Trials are required to assist clinicians in drawing relevant conclusions. The wide variety of proposed mechanisms for the development of polydipsia and the large number of potential treatments means that several trials would be required to identify the most effective drug. Further research into the aetiology of polydipsia in those with psychosis may help to narrow down the field, but it would be advisable for funders not to support several underpowered trials in preference to one that could potentially adequately answer the question for at least one eligible compound.

4. For policy makers

It is not possible to develop any strong guidance with regard to any one drug treatment for polydipsia in the context of the evidence which is currently available. It would seem reasonable policy to ensure that any treatment regime is closely monitored and reported in order to generate hypotheses.

Implications for research

1. General

Given the paucity of trials in this area, it was disappointing that we were unable to use some of the data from the only two studies which met the inclusion criteria for this review. Future studies should adhere to the recommendations of the CONSORT statement (Moher 2001).

2. Specific

It is apparent that in order to arrive at fairly strong conclusions it is necessary to undertake larger scale trials which are bound to be difficult. Nevertheless networks of interested researchers, with adequate co-ordination and support, should be able to muster adequate numbers of eligible and consenting people with psychosis related polydipsia. Which intervention to investigate first is a difficult choice. Multiple theories spawn multiple recommendations for first line treatments. More aetiological investigation may be informative, although the small pilot studies of demeclocycline and naloxone presented in this review may be as good a starting point as any. For suggested design of future studies see Table 1.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Alexander 1991

Methods	Allocation: randomised. Blindness: double. Design: crossover. Duration: 3 weeks.
Participants	Diagnosis: psychotic illnesses (schizophrenia or schizoaffective disorder). N=9. Age: >18 years. Sex: 6M, 3F. History: polydipsia and hyponatraemia, inpatients, duration illness 11-31years, mean ~18 years.
Interventions	1. Demeclocycline: dose 600mg/day to 1.2g/day by week? 2. Placebo. Everyone had standard diet, fluid restriction added if weight exceeded threshold, stable dose of anti-psychotic medication throughout.
Outcomes	Death Leaving the study early. Adverse effects. Unable to use - Weight: no pre-crossover data. Serum sodium: no pre-crossover data.
Notes	Authors contacted and kindly replied. Seeking additional data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Nishikawa 1996

Methods	Allocation: randomised. Blindness: double. Design: crossover. Duration: 6 weeks.
Participants	Diagnosis: schizophrenia. N=8. Age: >18 years. Sex: 7M, 1F. History: intermittent hyponatraemia and polydipsia, inpatients.
Interventions	1. Naloxone infusion: at 2 weekly intervals on 3 occasions. N=4. 2. Placebo infusion: at 2 weekly intervals on 3 occasions. N=4.
Outcomes	Death Leaving the study early. Adverse effects. Unable to use - Weight gain: no pre-crossover data.
Notes	Authors contacted and awaiting reply. Pre-crossover data not published or available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Greendyke 1998	Allocation: non-randomised crossover trial.
Levine 1997	Allocation: non-randomised crossover trial.

DATA AND ANALYSES

Comparison 1. DRUG TREATMENTS vs PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (by 3-6 weeks)	2	17	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 demeclocycline orally (tetracycline bacteriostatic agent)	1	9	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 naloxone infusion (opiate antagonist)	1	8	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Leaving the study early (by 3-6 weeks)	2	17	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 demeclocycline orally (tetracycline bacteriostatic agent)	1	9	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 naloxone infusion (opiate antagonist)	1	8	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Adverse effects (by 3-6 weeks)	2	17	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.1 demeclocycline orally (tetracycline bacteriostatic agent)	1	9	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 naloxone infusion (opiate antagonist)	1	8	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 DRUG TREATMENTS vs PLACEBO, Outcome 1 Death (by 3-6 weeks).

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 demeclocycline orally (tetracycline bacteriostatic agent)					
Alexander 1991	0/4	0/5			Not estimable
Subtotal (95% CI)	4	5			Not estimable
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.1.2 naloxone infusion (opiate antagonist)					
Nishikawa 1996	0/4	0/4			Not estimable
Subtotal (95% CI)	4	4			Not estimable
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	8	9			Not estimable
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					
			<div> <div></div> <div>Favours treatment</div> <div>0.1</div> <div>0.2</div> <div>0.5</div> <div>1</div> <div>2</div> <div>5</div> <div>10</div> <div>Favours control</div> </div>		

Analysis 1.2. Comparison 1 DRUG TREATMENTS vs PLACEBO, Outcome 2 Leaving the study early (by 3-6 weeks).

Analysis 1.3. Comparison 1 DRUG TREATMENTS vs PLACEBO, Outcome 3 Adverse effects (by 3-6 weeks).

ADDITIONAL TABLES

Table 1. Suggestions for future trial design

Methods	Participants	Intervention	Outcomes	Notes
Allocation: randomised, with sequence generation and concealment of allocation clearly described. Blindness: single. Duration: 1 month at least. Raters: independent.	People diagnosed with a psychotic illness and having polydipsia secondary to this (polydipsia is defined as >3 litres of water per day). N=300.	<ol style="list-style-type: none"> 1. Antipsychotics For example clozapine, olanzapine and risperidone. 2. Antidepressants For example, mianserin. 3. Beta adrenergic receptor blockers For example, propranolol. 4. Angiotensin converting enzyme (ACE) inhibitors For example, captopril and enalapril. 5. Mood stabilisers For example, lithium. 6. Angiotensin II receptor-blocking agents For example, irbesartan. 7. Anticonvulsants Only phenytoin was considered as it suppresses central release of vasopressin. Other antiepileptic drugs were not considered. 8. Tetracycline bacteriostatic agents Only demeclocycline was considered. 9. Opiate antagonists For example, naloxone. 10. Alpha adrenergic receptor blockers 11. Placebo 	<p>Primary outcomes</p> <p>Death**</p> <p>Lack of improvement in polydipsia, to a clinically significant degree**</p> <p>No alleviation of polydipsia**</p> <p>Leaving the study early, for specific or general reasons**</p> <p>Symptomatic visceral oedema**</p> <p>Emergence or worsening of physical symptoms secondary to increased fluid intake</p> <p>Change in mental state</p> <p>General functioning</p> <p>Acceptability of treatment</p> <p>Adverse effects of interventions</p> <p>Economic evaluations: cost-effectiveness, cost-benefit.</p> <p>Time periods: immediate term (within 24 hours) short term (up to one week), medium term (eight days to one month), and long term (more than one month).</p>	*primary outcome.

WHAT'S NEW

Date	Event	Description
3 May 2012	Amended	Additional table linked to text.

HISTORY

Protocol first published: Issue 1, 2002

Review first published: Issue 3, 2002

Date	Event	Description
31 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Guy Brookes - thought of the review, researched and wrote the protocol, reviewed studies and wrote the final report.

A Ahmed - assisted with the protocol, reviewed studies and commented on the draft review.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Leeds NHS Teaching Hospitals Trust, UK.
- University of Ottawa, Canada.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Drinking [*drug effects]; Psychotic Disorders [*drug therapy] [psychology]

MeSH check words

Humans