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HIV prevention advice for people with serious mental illness

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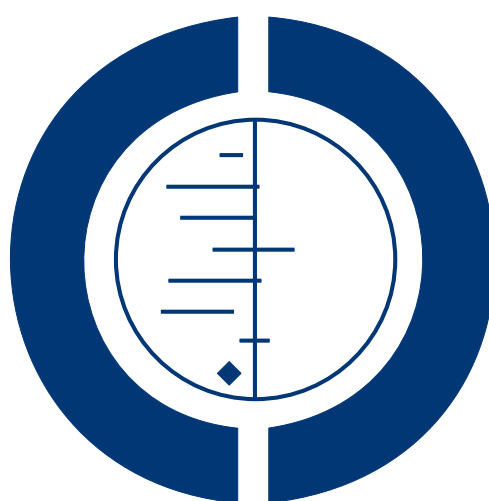
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HIV prevention advice for people with serious mental illness (Protocol)

Wright N, Akhtar A, Tosh G, Clifton A



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[Intervention Protocol]

HIV prevention advice for people with serious mental illness

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ABSTRACT

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

To review the effects of HIV prevention advice for people with SMI.

BACKGROUND

Description of the condition

The definition of severe mental illness with the widest consensus is that of the US National Institute of Mental Health (NIMH) (Schinnar 1990) and is based on diagnosis, duration and disability (NIMH 1987). People with serious mental illness (SMI) have conditions such as schizophrenia or bipolar disorder, over a protracted period of time resulting in erosion of functioning in day to day life. A European survey put the total population-based annual prevalence of serious mental illness at approximately two per thousand (Ruggeri 2000). Evidence suggests that those with SMI have rates of HIV infection which are higher than expected in the general population in the same demographic area (Hughes 2009). The current prevalence rate of HIV infection for the general population in North America is 0.3%, which is marginally lower than Europe (prevalence 0.4% - UNAIDS 2010). In contrast, studies from the USA report prevalence rates of between 9% and 19%, while in Europe five percent prevalence rates have been reported for people with serious mental illness (Cournos 1991; Grassi 1999; Susser 1993). Despite this higher than expected prevalence, UK national strategies around sexual health and HIV prevention do not state that people with SMI are a high risk group. However, a significant proportion in this group are sexually active and engage in HIV-risk behaviours including having multiple sexual partners, infrequent use of condoms and trading sex for money or drugs (Rosenberg 2001). Additionally, during relapse, symptoms of SMI may lead people to engage in practices they would not engage in if functioning at their optimum level (Carey 2004).

Description of the intervention

HIV health advice can take many forms, depending on environmental and socioeconomic factors. Advice is the active provision of preventative information; it has an educative component and is delivered in a gentle non-patronising manner (Stott 1990). Therefore HIV health advice could be defined as any advice about HIV health from a healthcare profession.

How the intervention might work

Advice from a healthcare professional can have a positive impact on behaviour (Kreuter 2000; Russell 1979) and may motivate people to seek further support and treatment (Sutherland 2003). Given the evidence of increased rates of potentially preventable health problems in people with serious mental illness (Cournos 2005; Dixon 1999; Robson 2007), and the suggestion that methodologically robust, healthy living interventions give “promising outcomes” in people with schizophrenia (Bradshaw 2005), we believe that appropriate HIV health advice could improve the quality of

life and increase life expectancy for sufferers of serious mental illness. HIV healthcare advice from a healthcare professional may encourage those with serious mental illness to be sexually abstinent, delay the initiation of sexual activity, decrease the numbers of sexual partners, use condoms consistently and correctly if they are sexually active and engage in harm reduction and needle exchange programmes.

Why it is important to do this review

People with SMI are some of the most vulnerable and socially excluded members of society; the same could be said for those with HIV. Therefore, the combination of both debilitating illnesses could have a profound social, psychological and economic impact on individuals, their families and friends (Hughes 2009). It has been identified that fewer than one in five people at risk of HIV currently have access to infection prevention (The Global HIV Prevention Working Group 2006). Given the effects of SMI and the difficulties this population have in accessing general healthcare advice (Tosh 2010), it is important that appropriate targeted advice is given to this group. It is important to complete this review because there is no cure or vaccination for HIV; the only way to prevent infection is by the adoption of safer sexual and injection behaviours. We are not aware of any systematic review which compares HIV advice-giving interventions to standard care for people with SMI.

OBJECTIVES

To review the effects of HIV prevention advice for people with SMI.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider all relevant randomised controlled trials (RCTs), and economic evaluations conducted alongside included RCTs. We will exclude quasi-randomised studies, such as those allocating by using alternate days of the week. When we encounter trials described in some way so as to suggest or imply that the study was randomised and where the demographic details of each group's participants are similar, we will include them and undertake sensitivity analysis to evaluate the effect of the presence or absence of these data.

Types of participants

We will require that a majority of participants should be within the age range 18 to 65 years and suffering from SMI, preferably as defined by National Institute of Mental Health (NIMH 1987), but in the absence of that, from diagnosed illness such as schizophrenia, schizophrenia-like disorders, bipolar disorder, or serious affective disorders. If the trials include participants with a range of serious mental illnesses we will include them if the majority have schizophrenia, we will not include trials that only randomise people with bipolar or serious affective disorders. We will not consider substance abuse to be SMI in its own right, however we do feel that studies should remain eligible if they deal with people with dual diagnoses, i.e. those with SMI plus substance abuse. We will not include studies focusing on dementia, personality disorder and mental retardation, as they are not covered by our definition of SMI. Despite the fact that personality disorder is now included in the NIMH definition we plan to exclude it from this review on the basis that the diagnosis of personality disorders has low interrater reliability (Zimmerman 1994); the duration of treatment can be assessed much more precisely than duration of illness (Schinnar 1990); insufficient information is given on how to operationalise the disability criterion in both the original NIMH (NIMH 1987) definition and in the further work of Schinnar 1990.

Types of interventions

1. HIV prevention advice

We have found it difficult to find a useful definition of 'advice'. In the context of this review we will define 'advice' as preventative information (Greenlund 2002) or counsel (OED) that leaves the recipient to make the final decision. Advice may be directional but not paternalistic in its delivery. It is not a programmed or training approach, focusing on the acquisition of knowledge, skills and competencies as a result of formal teaching sessions. The effects of programmes and/or training approaches for HIV prevention in people with SMI will not be considered in this review, they will be considered in a future review.

2. Standard care

Care in which HIV advice is not specifically emphasised above and beyond care that would be expected for people suffering from SMI.

Types of outcome measures

For the purposes of this review we will divide outcomes into four time periods: i. immediate (within one week); ii. short term (one week to six months); iii. medium term (six months to one year); and iv. long term (more than one year).

Primary outcomes

1. HIV infection (any time period)

2. Risk taking behaviour (short-term)

- 2.1 Unprotected sex
- 2.2 Sexual promiscuity
- 2.3 Sharing needles for drug use

Secondary outcomes

1. Adverse events

- 1.1 Number of participants with at least one adverse effect
- 1.2 Clinically important specific adverse events (cardiac events, death, movement disorders, prolactin increase and associated effects, weight gain, effects on white blood cell count)
- 1.3 Average endpoint specific adverse events score
- 1.4 Average change in specific adverse events score
- 1.5 Death - natural or suicide

2. Service use

- 2.1 Hospital admission
- 2.2 Emergency medical treatment
- 2.3 Use of emergency services

3. Financial dependency

- 3.1 Claiming unemployment benefit
- 3.2 Claiming financial assistance because of a physical disability

4. Social

- 4.1 Unemployment
- 4.2 Social isolation as a result of preventable incapacity
- 4.3 Increased burden to caregivers

5. Quality of life

- 5.1 Loss of independence
- 5.2 Loss of activities of daily living (ADL) skills
- 5.3 Loss of earnings
- 5.4 Loss of social status
- 5.5 Healthy days

6. Economic

- 6.1 Increased costs of health care
- 6.2 Days off sick from work
- 6.3 Reduced contribution to society
- 6.4 Family claiming care allowance

7. Leaving the study early (any reason, adverse events, inefficacy of treatment)

8. Global state

- 8.1 Clinically important change in global state (as defined by individual studies)
- 8.2 Relapse (as defined by the individual studies)

9. Mental state (with particular reference to the positive and negative symptoms of schizophrenia)

- 9.1 Clinically important change in general mental state score
- 9.2 Average endpoint general mental score
- 9.3 Average change in general mental state score
- 9.4 Clinically important change in specific symptoms (positive symptoms of schizophrenia, negative symptoms of schizophrenia)
- 9.5 Average endpoint specific symptom score
- 9.6 Average change in specific symptom score

10. Risk taking behaviour

- 10.1 Unprotected sex (not short-term)
- 10.2 Sexual promiscuity (not short-term)
- 10.3 Sharing needles for drug use (not short-term)
- 10.4 STI incidences
- 10.5 Knowledge of HIV transmission routes

11. Health behaviours

- 11.1 Behavioural intentions
- 11.2 Behavioural intentions re safe needle practices

Search methods for identification of studies

Electronic searches

1. Cochrane Schizophrenia Group Trials Register

We will search the register using the phrase:

[(*physical* or *cardio* or *metabolic* or *weight* or *HIV* or *AIDS* or *Tobacc* or *Smok* or *sex* or *medical* or *dental* or *alcohol* or *oral* or *vision* or *sight* or *hearing* or *nutrition* or *advice* or *monitor* in title of REFERENCES) AND (*education* OR *health promot* OR *preventi* OR *motivate* or *advice* or *monitor* in interventions of STUDY)]

This register is compiled by systematic searches of major databases, handsearches and conference proceedings (see [group module](#)).

Searching other resources

1. Reference searching

We will inspect the references of all identified studies for other relevant studies.

2. Personal contact

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

Data collection and analysis

Selection of studies

Two review authors (NW, AC) will screen the results of the electronic search. NW will inspect all abstracts of studies identified through screening and identify potentially relevant reports. Once identified, to ensure reliability, GT and AA will inspect a random sample of these abstracts, comprising 10% of the total. Where disagreement occurs, we will resolve this by discussion, and where there is still doubt, we will acquire the full article for further inspection. We will then request the full articles of relevant reports for reassessment and carefully inspect them for a final decision on inclusion (see [Criteria for considering studies for this review](#)). In turn NW and AC will inspect all full reports and independently decide whether they meet inclusion criteria. We will not be blinded to the names of the authors, institutions or journal of publication. Where difficulties or disputes arise, we will ask author GT for help; if it is impossible to decide, we will add these studies to those awaiting assessment and contact the authors of the papers for clarification.

Data extraction and management

1. Extraction

Authors NW and AC will independently extract data from included studies. Again, we will discuss any disagreement, document our decisions and, if necessary, we will contact the authors of studies for clarification. We will extract data presented only in graphs and figures whenever possible, but we will include such data only if two authors independently reach the same result. We will attempt to contact authors through an open-ended request in order to obtain any missing information or for clarification whenever necessary. Where possible, we will extract data relevant to each component centre of multi-centre studies separately.

2. Management

2.1 Forms

NW and AC will extract data onto standard, simple forms.

2.2 Data from multi-centre trials

Where possible the authors will verify independently calculated centre data against original trial reports.

3. Scale-derived data

We will include continuous data from rating scales only if:

- a. the psychometric properties of the measuring instrument have been described in a peer-reviewed journal (Marshall 2000); and
- b. the measuring instrument has not been written or modified by one of the trialists for that particular trial.

Ideally, the measuring instrument should either be i. a self-report or ii. completed by an independent rater or relative (not the therapist).

We realise that this is not often reported clearly, but we will note if this is the case or not in 'Description of studies'.

4. Endpoint versus change data

We prefer to use scale endpoint data, which typically cannot have negative values and are easier to interpret from a clinical point of view. Change data are often not ordinal and are very problematic to interpret. If endpoint data are unavailable, we will use change data.

5. Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we aim to apply the following standards to all data before inclusion: (a) standard deviations and means are reported in the paper or obtainable from the authors; (b) when a scale starts from the finite number zero, 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); (c) if a scale starts from a positive value (such as PANSS which can have values from 30 to 210), we will modify the calculation described above to take the scale starting point into account. In these cases skew is present if $2SD > (S - S_{min})$, where S is the mean score and S min is the minimum score. Endpoint scores on scales often have a finite start and end point and these rules can be applied. When continuous data are presented on a scale which includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not. We will enter skewed data from studies of fewer

than 200 participants in additional tables rather than into an analysis. Skewed data pose less of a problem when looking at means if the sample size is large, and we will enter skewed data from large sample sizes into syntheses.

6. Common measure

To facilitate comparison between trials, we intend to convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

7. Conversion of continuous to binary

Where possible, we will attempt to convert outcome measures to dichotomous data. This could be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. We will generally assume that if there has been a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (Overall 1962) or the Positive and Negative Syndrome Scale (Kay 1986; Kay 1987), this could be considered as a clinically significant response (Leucht 2005; Leucht 2005a). If data based on these thresholds are not available, we will use the primary cut-off presented by the original authors.

8. Direction of graphs

Where possible, we will enter data in such a way that the area to the left of the line of no effect indicates a favourable outcome for HIV advice.

9. Summary of findings table

We anticipate including the following outcomes in a summary of finding table:

9.1 HIV infection (measured by CD4+ count and viral load)

- Not using a condom
- Number of casual sexual partners
- Prevalence of needle sharing

9.2 Quality of life

- Loss of independence
- Loss of activities of daily living (ADL) skills
- Loss of social status
- Healthy days

9.3 Adverse events

- Clinically important specific adverse effects (cardiac effects, death, movement disorders, prolactin increase and associated effects, weight gain, effects on white blood cell count)

9.4 Service use

- Hospital admission

9.5 Leaving the study early

- Increased costs of health care

9.6 Sexual health practices

- STI incidences - knowledge of HIV transmission

9.7 Safer needle practices

- Attitude towards safer needle practice
- Behavioural intentions and safer needle intention

Assessment of risk of bias in included studies

Again review authors NW and AC will work independently to assess risk of bias by using criteria described in the Cochrane Collaboration Handbook (Higgins 2011) to assess trial quality. This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

If the raters disagree, the final rating will be made by consensus, with the involvement of another member of the review group. Where inadequate details of randomisation and other characteristics of trials are provided, authors of the studies will be contacted in order to obtain further information. Non-concurrence in quality assessment will be reported, but if disputes arise as to which category a trial is to be allocated, again, we will resolve by discussion.

The level of risk of bias will be noted in both the text of the review and in the Summary of findings table 1.

Measures of treatment effect

1. Binary data

For binary outcomes we will calculate a standard estimation of the fixed-effect risk ratio (RR) and its 95% confidence interval (CI). It has been shown that RR is more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as

RR by clinicians (Deeks 2000). Within the Summary of Findings table we will assume for calculation of the low risk groups that the lowest control risk applies to all data. We will do the same for the assumption of the highest risk groups. We will use the Summary of Findings table to calculate absolute risk reduction for primary outcomes.

2. Continuous data

For continuous outcomes we will estimate a random-effects mean difference (MD) between groups. We prefer not to calculate effect size measures (standardised mean difference - SMD). However, in the case of where scales were of such similarity to allow, presuming there was a small difference in measurement, we will calculate it and, whenever possible, transform the effect back to the units of one or more of the specific instruments.

Unit of analysis issues

1. Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice) but analysis and pooling of clustered data pose 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 is not accounted for in primary studies, we will present 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-efficient of their clustered data and to adjust for this by using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we will 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 intra class correlation co-efficient (ICC) [Design effect = 1+(m-1)*ICC] (Donner 2002). If the ICC has not been reported, we will assume it to be 0.1 (Ukoumunne 1999).

If cluster studies have been appropriately analysed, taking into account intra class correlation co-efficient and relevant data documented in the report, synthesis with other studies may be possible using the generic inverse variance technique.

2. Cross-over trials

A major concern of cross-over trials is the carryover effect. It occurs if an effect (e.g. pharmacological, physiological or psychological) of

the treatment in the first phase is carried over to the second phase. As a consequence, on entry to the second phase the participants can differ systematically from their initial state despite a wash-out phase. For the same reason, cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both effects are very likely in severe mental illness, we will only use data from the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involves more than two treatment arms, if relevant, we will present the additional treatment arms in comparisons. Where the additional treatment arms are not relevant, we will not reproduce these data.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2009). For any particular outcome should less than 50% of data be unaccounted, we will not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study are lost, but the total loss is less than 50%, we will mark such data with '*' to indicate that such a result may well be prone to bias.

2. Binary

In the case where attrition for a binary outcome is between 0 and 50% and where these data are not clearly described, we will present data on a 'once-randomised-always-analyse' basis (an intention-to-treat analysis). We will assume those lost to follow-up to have the same rates of negative outcome as those who completed, with the exception of the outcome of death. We will undertake a sensitivity analysis testing how prone the primary outcomes are to change when 'completer' data only are compared to the intention-to-treat analysis using the above assumption.

3. Continuous

3.1 Attrition

In the case where attrition for a continuous outcome is between 0 and 50% and completer-only data are reported, we will reproduce these.

3.2 Standard deviations

Where there are missing measures of variance for continuous data but exact standard error and confidence interval are available for

group means, and either P value or T value are available for differences in mean, we will calculate standard deviation value according to method described in Section 7.7.3 of the *Cochrane Handbook* (Higgins 2011). If standard deviations are not reported and can not be calculated from available data, we will ask authors to supply the data. In the absence of data from authors, we will use the mean standard deviation from other studies.

3.3 Last observation carried forward

We anticipate that in some studies the method of last observation carried forward (LOCF) would be employed within the study report. As with all methods of imputation to deal with missing data, LOCF introduces uncertainty about the reliability of the results. Therefore, where LOCF data has been used in the trial, if less than 50% of the data has been assumed, we will reproduce these data and indicate that they are the product of LOCF assumptions.

Assessment of heterogeneity

1. Clinical heterogeneity

To judge clinical heterogeneity, we will consider all included studies, initially without seeing comparison data. We will simply inspect all studies for clearly outlying situations or people which we had not predicted would arise. Should such situations or participant groups arise we will fully discuss these.

2. Methodological heterogeneity

We will consider all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We will simply inspect all studies for clearly outlying methods which we had not predicted would arise. Should such methodological outliers arise we will fully discuss these.

3. Statistical

3.1 Visual inspection

We will visually inspect graphs to investigate the possibility of statistical heterogeneity.

3.2 Employing the I^2 statistic

We will investigate heterogeneity between studies by considering the I^2 method alongside the Chi^2 P value. The I^2 provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depends on i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a confidence interval for I^2).

We will interpret I^2 estimate greater than or equal to 50% accompanied by a statistically significant Chi^2 statistic as evidence of substantial levels of heterogeneity (Section 9.5.2 - Higgins 2011) and explore reasons for heterogeneity. If the inconsistency is high and we find clear reasons, we will present data separately.

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in Section 10 of the *Cochrane Handbook* (Higgins 2011). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We will not use funnel plots for outcomes where there are ten or fewer studies, or where all studies are of similar sizes. In other cases, where funnel plots are possible, we will seek statistical advice in their interpretation.

Data synthesis

Where possible we will employ a fixed-effect model for analyses. We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that different studies are estimating different, yet related, intervention effects. This seems true. Random-effects methods, however, put added weight onto the smaller of the studies - those studies that are likely to carry most bias. This is unfortunate as it seems likely that most studies we will identify will be small. The fixed-effect model is assumption-free and we favour using this model.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

We anticipate no sub-group analyses.

2. Investigation of heterogeneity

2.1 Unanticipated heterogeneity

Should unanticipated clinical or methodological heterogeneity be obvious we will simply state hypotheses regarding these for future reviews or versions of this review. We do not anticipate undertaking analyses relating to these.

2.2 Anticipated heterogeneity

We anticipate some heterogeneity for the primary outcomes, and propose to summate all data but also present them separately.

Sensitivity analysis

1. Implication of randomisation

We aim to include trials in a sensitivity analysis if they are described in some way as to imply randomisation. For the primary outcomes we will include these studies and if there was no substantive difference when we added the implied randomised studies to those with better description of randomisation, we will then employ all data from these studies.

2. Assumptions for lost binary data

Where assumptions have to be made regarding people lost to follow-up (see [Dealing with missing data](#)), we will compare the findings of the primary outcomes where we have used our assumption and compared with completer data only. If there is a substantial difference, we will report results and discuss them, but continue to employ our assumption.

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* Indicates the major publication for the study

HISTORY

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CONTRIBUTIONS OF AUTHORS

Nicola Wright - primary reviewer, protocol writing.

Athfah Akhtar - help with writing the protocol.

Andrew Clifton - help with writing the protocol.

Graeme Tosh - project initiation, screening of search results, editing of protocol.

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None known.

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