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Pharmacological interventions for those who have sexually offended or are at risk of offending

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Abstract

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

To evaluate the effects of pharmacological interventions on target sexual behaviour for people who have been convicted or at risk of sexual offending.

BACKGROUND

Description of the condition

Sexual offending is a legal construct which overlaps, but is not entirely congruent with, the clinical constructs of disorders of sexual preference as described in the *ICD-10 Classification of Mental and Behavioural Disorders* (WHO 1992) or paraphilias as described in the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition-Revised) (APA 1994). Most but not all sexual offences are disorders of sexual preference and most but not all disorders of sexual preference are sexual offences. For instance, clinically defined sexual behaviours such a paedophilia, voyeurism, frotteurism, exhibitionism, zoophilia and necrophilia also meet the rubric for sexual offences but, for instance, fetishism and transvestic fetishism do not, in many jurisdictions. Crimes such as rape, and incest with consenting adult participants are not of themselves classified as disorders of sexual preference or paraphilias.

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CONTRIBUTIONS OF AUTHORS: OK was responsible for the clinical background to the protocol and MF was responsible for the methodology section of the protocol. Jo Abbott will run the searches. Two authors (NS and NH) will inspect the identified citations for inclusion and exclusion with a third adjudicating where there is disagreement (OK). Full papers of the included citation will be obtained and reviewed by two authors (MF, NS) with a third reviewer adjudicating (OK) if there is disagreement. Data extraction will be carried out by two reviewers (OK and MF) with a third adjudicating (NH). Risk of bias tables will be completed by two reviewers (OK, NH) with a third adjudicating (NS). Data entry will be completed by NS and checked by MF. OK will be responsible for writing the discussion and conclusions.

DECLARATIONS OF INTEREST: None known.

Sexual offending is both a social problem and a public health issue (Laws 1999). People who have committed a sexual offence represent nearly one quarter of the total population in state prisons in the USA (McGrath 2003). Victim surveys illustrate high incidence and prevalence levels and it is commonly accepted that there is a high proportion of hidden sexual victimization (Chapman 2004,Edwards 2003, Hood 2002). A number of surveys have reported high levels of psychiatric morbidity in survivors of sexual offences (McCauley 1997, Mchichi 2004, Molnar 2001, Swanston 2003,Chapman 2004, Hill 2000).

Sexual offending has therefore become a major challenge for social policy. The electorate and the media expect policy makers to be accountable for the effects of their responses to sexual offending. In the UK, provisions in the Sexual Offences Act 2003 include substantial increases in sentence length for many sexual offences and increased state control, in terms of notification requirements and supervision, for up to ten years after a sentence has been spent (Great Britain 2003). In the USA, such concerns led to Megan's Law in 1996, which allows private and personal information on those registered as sex offenders against children to be made available to the community (About Megan's 2007). Exaggerating the danger that sexual offenders pose is problematic and may increase public fear, stigmatise and hinder rehabilitation of offenders who have changed their lifestyles, while wasting valuable resources on unnecessary surveillance (Soothill 2000).

Quantifying the prevalence of sexual offending is problematic because of variations in definitions of what constitutes sexual abuse, changes in true rates over time and between cultures and countries, and cultural and age related variations in the survivors willingness to disclose abuse. Quantifying its consequences is problematic where an association is not necessarily proof of a causative relationship.

Description of the intervention

A companion review of psychological interventions for those who have sexually offended or are at risk of offending is currently being updated (Bilby 2008) and it is important to note the underlying difference between psychological and the anti-libidinal approaches with which this review is concerned (see below). The objective of psychological interventions is, in general, to change the sexual behaviour of the offender while leaving libido intact, principally, though not exclusively, from child to adult sexual partners and/or from non-consenting to consenting sexual activity. In contrast anti-libidinal interventions such as the pharmacological interventions reviewed here seek to greatly diminish or altogether eradicate sexual desire and capacity (Abel 2000). Surgical approaches to anti libidinal interventions such as orchiectomy/orchidectomy (male castration) or neurosurgery will be the subject of a separate review.

Medication—Anti-libidinal medications broadly fall within two categories, namely those medications that have a testosterone suppressing effect, and those medications that affect libido through other mechanisms

The three main classes of testosterone suppressing drugs (TSDs) used today include progestogens, anti-androgens, and Gonadotropin releasing Hormone (GnRH) analogues.

Prior to the 1960s, oestrogens were prescribed in North America to treat sexually aggressive men but this practice has been discontinued (Grubin 2008).

The commonly used TSDs include Medroxyprogesterone acetate (MPA), Cyproterone acetate (CPA), Triptorelin and Goserelin. Medications which affect libido through means other than via testosterone-suppression, includes antipsychotics and serotonergic antidepressants (SSRI) (Baldwin 2003) and these medications are the most commonly used for this purpose. SSRIs have been associated with reduced libido and delayed orgasm in 60-70% of people taking them (Montejo 2001).

How the intervention might work

1.1 Testosterone suppressing drugs—Testosterone production in men is controlled by the hypothalamus, anterior pituitary and the gonads. Gonadotrophin releasing hormone (GnRH) is released from the hypothalamus in a pulsatile manner which stimulates the secretion of the gonadotrophins, Luteinizing Hormone and Follicle Stimulating Hormone (LH and FSH), from the anterior pituitary. LH acts on Leydig cells in the testes resulting in the production and secretion of testosterone which in turn has a negative feedback effect on the anterior pituitary and hypothalamus.

Testosterone has been linked to sexual development and drive in man (Grubin 2008). Testosterone has both organisational and activational effects on the nervous system. The former is associated with structural development of the brain and the latter with the effect of testosterone on the organised brain (Sisk 2006). The effect of testosterone on sexual interest and arousal appears to be one of maintaining a spontaneous level of functionality as opposed to being stimulus bound (Bancroft 1989). These effects are not immediate and take several weeks to occur after a change in plasma testosterone levels (Bancroft 2005).

The direct relationship between testosterone and sexual behaviour is, however, confounded by the link between testosterone and aggressive behaviour (Book 2001). In addition, there is evidence that behaviour may itself result in changes in plasma testosterone levels and that testosterone levels may be more closely associated with dominance (Mazur 1980).

GnRH analogues appear to be more effective than CPA and MPA in producing long term castration levels of testosterone (McEvoy 1999). However, there are few if any studies addressing the issue of reversibility after long term use of greater than two years. GnRH analogues and MPA have been shown to produce histological changes, such as reduced Leydig cell numbers, in the testes of animals (McEvoy 1999, Rao 1998, Avari 1992).

All three agents are associated with potential adverse effects Reilly 2000 such as precipitation or aggravation of cardiac conditions (de Voogt 1986, Pierce 1995). CPA has been associated with fatal liver toxicity (Roila 1993, Parys 1991).

An established consequence of low testosterone, osteoporosis, (Schot 2006, Stepan 1989), is a potentially serious and difficult to manage side effect of testosterone suppression, and is more likely to occur with long term use of GnRH agonists. Other side effects of testosterone

suppressing drugs include hot flushes, feminisation, depression, weight gain and gynaecomastia (enlargement of male breast tissue) (Grubin 2008).

1.2 Drugs which decrease libido via mechanisms unrelated to testosterone suppression—Although the exact mechanisms are unclear, animal studies suggest that mesolimbic dopamine has an activating effect on sexual arousal and that serotonin has the opposite effect (Hull 2004). In addition, dopamine antagonism may result in prolactin elevation which may have an effect on libido (Bancroft 2005).

Both classes of medication in this category, although widely used, have potentially troublesome side effects. The adverse effects of antipsychotics include tardive dyskinesia (Kane 2006), weight gain (Allison 2003), and impaired glucose tolerance (Haddad 2004) SSRIs are generally considered to have a more benign side effect profile. However, SSRIs are associated with restlessness, agitation, and suicidallity, particularly in the under 30 age group (CSM Working Group 2004) and they are also associated with an increased risk of bleeding (Paton 2005).

Why it is important to do this review

Both the prevalence of sexual offending and the association between victimisation and subsequent mental health problems means that these offences make a significant contribution to mental health morbidity. There is therefore strong social and political pressure to address this problem, not just in terms of helping the victims but in preventing sexual recidivism (Hanson 2000).

An early Cochrane review (White 1998) looked at all types of interventions for sexual offending; it was partially updated in 2003 in a review which considered only psychological interventions (Kenworthy 2003). The older review identified only one small trial (n=21) that compared anti-androgen medication (MPA) plus a psychological intervention versus the same psychological intervention and identifiable no significant difference between the two groups (McConaghy 1988). The reviewers concluded that there were too few data to come to any conclusion about the effectiveness of MPA.

Adi 2002 reviewed the clinical effectiveness and cost-consequences of selective serotonin reuptake inhibitors (SSRIs) in the treatment of sex offenders but identified no RCTs and only nine case series with a total of 225 participants. The authors concluded that there was insufficient data of high enough quality to come to any conclusion.

Subsequently, a systematic review by Lösel and Schmucker (Lösel 2005) was produced which, like that by White et al, considered all treatment options for sex offenders but included studies of a larger range of designs. They reported a treatment effect size of 3.08 (95%CI 1.40, 6.79, $p< 0.01$) for anti-libidinal medication based on six identified studies. However, the review does not report sample sizes or study designs for pharmacological interventions and the methodology of the included studies were unclear. There is therefore, an urgent need for an up to date systematic review.

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OBJECTIVES

To evaluate the effects of pharmacological interventions on target sexual behaviour for people who have been convicted or at risk of sexual offending.

METHODS

Criteria for considering studies for this review

Types of studies—Randomised controlled trials with or without blinding will be included. Quasi-randomised trials, such as those where allocation was undertaken on surname, will be excluded.

Types of participants—Adults aged 18 years old and over treated in institutional (prison or psychiatric facility) or community settings for sexual behaviours that have resulted in conviction or caution for sexual offences, offences with a sexual element or violent behaviours with a sexual element (e.g. sexual offences where murder is the index offence), or seeking treatment on a voluntarily basis for behaviours which would be classified as illegal.

We will include studies where behaviours which would be classified as illegal, but where there has been no criminal case reported but where the perpetrator sought treatment or admitted to the behaviours in self report.

Defining what constitutes a sexual offence in the context of the international literature can be problematic as definitions of criminally sexual behaviour differ between jurisdiction, cultures and over time. We will include trials of interventions where the participants have committed a sexual offence which would be accepted by most jurisdictions as crimes, viz. penetrative or non penetrative sexual acts carried out by adults on non consenting adult victims and penetrative or non penetrative sexual acts carried out by adults on consenting or non consenting minors, or adults unable. to give informed consent due to their physical and/or mental disability.

Excluded: Studies of interventions for sex offenders where there is no clear international consensus as to whether the sexual behaviour is a crime or not. Examples include consenting same sex acts between adults, consenting sadomasochistic acts and transvestitism. We will also exclude interventions for sex offenders with learning disability as this is the subject of a separate Cochrane review (Ashman 2008).

Types of interventions—Pharmacological interventions with placebo or standard care (which might include psychological interventions or no treatment).

Types of outcome measures

Primary outcomes: Recidivism as measured by reconviction, caution, or self report.

Secondary outcomes: Suicide or suicide attempts.

Sudden and unexpected death by other causes.

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Side effects.

Leaving treatment early.

Lost to follow up.

Outcomes will be divided into immediate (within 6 months), short term (>6 months - 24 months) and medium term (>24 months - 5 years) and long term (beyond 5 years) during the period at risk e.g. post release from prison or discharge from hospital facility. If the participants were receiving treatment in the community then the period at risk commences from the end of treatment.

Search methods for identification of studies

Electronic searches—The following databases will be searched:

Cochrane Central Register of Controlled Trials

MEDLINE

AMED- Allied and Complementary Medicine

ASSIA - Applied Social Sciences Index and Abstracts

BHI - British Humanities Index

Biosis Previews - Biological Abstracts

CINAHL

COPAC - Consortium of University Research Libraries joint catalogue

Dissertation Abstracts

EMBASE

IBSS - International Bibliography of the Social Sciences

ISI Proceedings

ISI-SCI - Science Citation Index Expanded

ISI-SSCI - Social Sciences Citation Index

National Criminal Justice Reference Service Abstracts Database

Open SIGLE

PsycINFO;

Social Care Online

Sociological Abstracts

UK Clinical Research Network Portfolio Database

ZETOC;

The following strategy will be used to search MEDLINE and modified, where necessary, for the other databases:

1. exp Sex Offenses/
2. exp Paraphilias/
3. exp Sexual Behavior/
4. exp Child Abuse, Sexual/
5. exp “Fetishism (Psychiatric)”/
6. exp Exhibitionism/
7. exp Voyeurism/
8. exp Pedophilia/
9. exp Sadism/
10. exp Masochism/
11. exp Incest/
12. exp Rape/
13. (sex$ adj2 devia$).tw.
14. (public adj2 masturbat$).tw.
15. (child$ adj2 molest$).tw.
16. (child$ adj2 (sex$ or abuse$)).tw.
17. (sex$ adj2 (murder$ or tortur$ or abus$ or fondl$)).tw.
18. (indecen$ adj2 behav$).tw.
19. (child$ adj2 porn$).tw.
20. (lewd$ adj2 (behav$ or act)).tw.
21. bondag$.tw.
22. frotteur$.tw.
23. necrophi$.tw.
24. bugger$.tw.
25. molest$.tw.
26. pederast$.tw.

27. paedoph$.tw.
28. pedoph$.tw.
29. scatologia.tw.
30. necrophilia.tw.
31. zoophilia.tw.
32. coprophilia.tw.
33. urophilia.tw.
34. partialism.tw.
35. klismaphilia.tw.
36. bestiality.tw.
37. sodom$.tw.
38. molest$.tw.
39. paraphil$.tw.
40. voyeur$.tw.
41. or/1-40

Randomised control filters will also be used where appropriate. No language or date restrictions will be applied. The electronic searches will be constructed taking into account changing terminology and perception of sex offences. We recognise that several of these terms would now be regarded as unacceptable and/or misleading as terms signifying sexual offending. These searches are also being run for a related review (Bilby 2008).

Searching other resources

Hand searching: Reference lists of included studies will be searched for additional relevant trials along with the reference lists of reviews.

Requests for additional data: The first author of each included study and known experts in the field will be contacted for information regarding unpublished data and/or ongoing studies.

Data collection and analysis

Selection of studies—Titles and abstracts of studies identified through searches of electronic databases will be independently read and assessed by two reviewers (NH, MF). Full copies of those papers which appear to meet the inclusion criteria will then be assessed independently by the two reviewers. We will resolve uncertainties concerning the appropriateness of studies for inclusion in the review through consultation with a third reviewer (OK). Reviewers will not be blinded to the name(s) of the study author(s), their institution(s) or publication sources at any stage of the review.

Data extraction and management—Data will be extracted independently by two authors (MF & NH) using a piloted data extraction form. Information on study design and implementation, setting, sample characteristics, intervention characteristics and outcomes will be extracted from all included studies.

Data will be entered into RevMan 5. Where data are not available in the published trial reports, we will contact the authors and ask them to supply the missing information.

Assessment of risk of bias in included studies—For each included study, two authors (NS and HJ) will independently complete the Cochrane Collaboration's tool for assessing risk of bias. This will assess the degree to which:

· the allocation sequence was adequately generated ('sequence generation')

· the allocation was adequately concealed ('allocation concealment')

· knowledge of the allocated interventions was adequately prevented during the study ('blinding')

· incomplete outcome data were adequately addressed

· reports of the study were free of suggestion of selective outcome reporting

Measures of treatment effect—All outcomes are dichotomous and we will use the risk ratio (RR) with a 95% confidence interval to summarize results within each study. Comparisons will be made at specific follow-up periods:

· within the first six months

· between six and twenty four months

· between 24 and five years

· Beyond five years

Unit of analysis issues—Crossover trials may have been undertaken in this area. The method used to utilize data from any crossover trials will be that recommended in the Cochrane Handbook (Higgins 2008) of approximated paired analysis by imputing missing standard deviations.

Dealing with missing data—The original authors will be contacted for any missing data. However, if the data is still unforthcoming and the investigators have not reported conducting their analysis on an intention-to-treat basis, then we will consider recommendations from the Cochrane Handbook (Higgins 2008) for methods for dealing with missing data.

Where the missing data can be assumed to be missing at random (for example, if there is reason to suppose from included studies that participants left the study because they moved from the area or through other evidence that the effects of the intervention were not related to 'drop outs') we will analyse the available data as presented.

Where it cannot be assumed that the data is missing at random we may attempt to impute the missing data with replacement values, whether by 'last observation carried forward' (if the assessment points are not far apart in time) or by using other methods to impute the missing data accounting for the fact that these were imputed with uncertainty and using statistical models to allow for missing data. We will seek the advice of a statistician on which methods of of dealing with missing data are appropriate on a case by case basis.

Assessment of heterogeneity—We will assess the extent of between-trial differences and the consistency of results of any meta-analysis in three ways:

· by visual inspection of the forest plots,

· by performing the Chi squared test of heterogeneity (where a significance level less than 0.10 will be interpreted as evidence of heterogeneity)

· by examining the I^2 statistic (Higgins 2008; section 9.5.2) The I^2 statistic describes approximately the proportion of variation in point estimates due to heterogeneity rather than sampling error. Because heterogeneity may well prove to be a significant problem we will carry out each analysis twice using fixed and random effects models.

Assessment of reporting biases—Funnel plots (effect size versus standard error) will be drawn if sufficient studies are found. We recognize that symmetry of the plots may indicate publication bias, although they may also represent a true relationship between trial size and effect size. If such a relationship is identified, we will examine the clinical diversity of the studies as a possible explanation (Egger 1997).

Data synthesis—We will synthesis data using both a fixed effect and a random effects model.

Meta-analysis will be performed where studies are considered to have sufficiently similar participants, interventions, comparators and outcome measures. Seperate meta-analyses will be carried out for separate classes of pharmacological interventions and separate meta-analyses will also be carried where there are different comapartors e.g. placebo, standard care or psychological interventions. In carrying out meta-analysis, the weight given to each study will be the inverse of the variance so that the more precise estimates (from larger studies with more events) are given more weight.

Subgroup analysis and investigation of heterogeneity—If sufficient studies are found, we will undertake subgroup analysis by type of offending, severity of offending, conviction vs self report.

Sensitivity analysis—We will use sensitivity analysis to assess the impact of study quality if there sufficient data are identified, particularly to consider the potential impact of outcome assessors being blinded, or other factors identified in the risk of bias analysis.

We will also undertake a sensitivity analysis to investigate the robustness of the overall findings where there has been uncertainty or disagreement regarding, for example, the

inclusion of studies, data extraction or missing data, or in the event of one or more large studies dominating the results.

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HISTORY

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* *Indicates the major publication for the study*