TECHNICAL COMMENTARY

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Treatments for sexual dysfunction

Introduction

A supplementary, or adjunctive, treatment is administered in conjunction with a patient's ongoing antipsychotic therapy. Adjunct medications prescribed to treat side effects of antipsychotic medication may contribute to increasing adherence to antipsychotic medications, which can reduce the risk of psychotic relapse. One side effect of some antipsychotic medications is sexual dysfunction. Sexual dysfunction can take many forms, but affects both men and women, and can have far-reaching implications on self-esteem, quality of life, and relationships, as well as considerably reducing medication compliance[1, 2].

Various pharmacological approaches have been developed to alleviate this problem, and this table presents the current findings relating to adjunctive treatments for sexual dysfunction.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[3]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[4]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found two systematic reviews that met our inclusion criteria[1, 5].

- Low quality evidence is unclear of the benefits of adjunct treatments for sexual dysfunction in people with schizophrenia.

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Treatments for sexual dysfunction

Costa AMN, de Lima MS, Mari JD

A systematic review on clinical management of antipsychotic-induced sexual dysfunction in schizophrenia

Sao Paulo Medical Journal 2006; 124(5): 291-7

View review abstract online

Comparison	**Adjunctive therapies for sexual or gonadal dysfunction in males with schizophrenia.**
Summary of evidence	**Low quality evidence (small samples, unable to assess consistency or precision) is unclear of the benefits of adjunct treatments for sexual dysfunction.**

Sexual functioning

2 open-label studies (N = 22) and 2 case studies found ~70% of males with erectile dysfunction showed improvement following sildenafil.

2 open-label studies (N = 65) found ~70% had improvement in erectile dysfunction in males and return of menstrual cycle in women receiving bromocriptine.

A case series (N = 5) found 3 patients showed some improvement in sexual dysfunction following cabergoline.

1 open label study (N = 8) found 50% showed improvement in ejaculatory function following imipramine.

1 RCT (N = 10) found no benefit of selegiline for improving sexual dysfunction.

Some benefits of antiviral amantadine were reported in two open label studies (N = 22) for several domains of sexual function and the neuroendocrine side effects of antipsychotics.

1 open label study (N = 20) found 5 patients reported reductions in prolactin levels following herbal medicine (Shakuyaku-kanzo-to) and three men experienced improvements in subjective desire.

Consistency in results‡	Unable to assess, no measure of consistency is reported.
Precision in results§	Unable to assess, no measure of precision is reported.
Directness of results‖	Direct

Schmidt HM, Hagen M, Kriston L, Soares-Weiser K, Maayan N, Berner MM

Management of sexual dysfunction due to antipsychotic drug therapy

Cochrane Database of Systematic Reviews 2012; Issue 11. Art. No.: CD003546. DOI: 10.1002/14651858.CD003546.pub3

View review abstract online

Comparison	**Sildenafil (trade name Viagra, dose 25-50mg/day) or selegiline (a monoamine oxidase [MAO] inhibitor antidepressant, dose 15mg/day) in addition to standard antipsychotic treatment in males with schizophrenia, vs. placebo plus standard antipsychotic treatment. Treatment duration 2 weeks**
Summary of evidence	**Low quality evidence (very small samples, imprecise, unable to assess consistency) is unclear of the benefit of adjunct sildenafil or selegiline for improving sexual function.**

Sexual functioning

1 RCT, N = 32, assessed sildenafil compared to placebo, adjunct to antipsychotics (risperidone, olanzapine, clozapine or fluphenazine decanoate) for improving sexual function in males with schizophrenia and antipsychotic-induced erectile dysfunction. Overall improvement (OR = 11.76, 95%CI 6.54 to 21.13, $p < 0.00001$), increase in the number of erections WMD = 3.20, 95%CI 1.83 to 4.57, $p < 0.00001$ and longer duration of erections (WMD = 1.18, 95%CI 0.52 to 1.84, $p = 0.00042$) were reported and patients reported a greater frequency of satisfactory intercourse (WMD = 2.84, 95%CI 1.61 to 4.07, $p < 0.00001$). A significant proportion of participants reported willingness for future use of sildenafil in the treatment group vs. placebo group (OR = 2.50, 95%CI 1.48 to 4.22, $p = 0.00059$).

1 RCT, N = 10, assessed selegiline compared to placebo, adjunct to antipsychotics (perphenazine or haloperidol), for improving sexual function in males with schizophrenia. There was no significant difference in the average 'change' score on Aizenberg's sexual functioning scale over 2 weeks (WMD = -0.40, 95%CI -3.95 to 3.15, $p = 0.83$).

1 RCT reported significant improvement in sexual functioning when participants switched from risperidone or a typical antipsychotic to olanzapine (N = 54, WMD -0.80, 95%CI -1.55 to -0.05, $p < 0.05$). No evidence was found for switching from risperidone to quetiapine.

Risks	Treatment with selegiline was associated with no significant increase in risk of extrapyramidal symptoms (WMD -0.90, 95%CI -3.88 to 2.08, $p = 0.55$) when compared to placebo. There was also no difference in risk of worsening psychotic symptoms, measured by PANSS (WMD = 0.50, 95%CI -0.61 to 1.61, $p = 0.38$).
Consistency in results	Not applicable, 1 RCT for all outcomes.

Precision in results	Imprecise for ORs, unable to assess WMD.
Directness of results	Direct

Explanation of acronyms

CI = confidence intervals, N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Syndrome Scale, Q = Q statistic for the test of heterogeneity, RCT = randomised controlled trial, WMD = weighted mean difference

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[6].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous), which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[6].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[7]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[6];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[8].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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