TECHNICAL COMMENTARY

Oestrogen

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Introduction

Overall, women tend to have a later age of onset of schizophrenia than men and have a second peak of onset after menopause. To explain these sex differences, the hormone oestrogen has been proposed to confer a protective effect for women prior to menopause, as oestrogen levels drop over time and particularly with the onset of menopause. This protection may also mean that pre-menopausal women who develop schizophrenia may experience a less severe illness than males. This theory is still being investigated, as a causal link has not been proven[1].

Oestrogens are not used routinely for people with schizophrenia; however some studies have trialed the use of oestrogen as an additional, adjunctive treatment to standard antipsychotic treatment. This table presents the current evidencefor the effectiveness of oestrogen as an adjunctive treatment for people with schizophrenia.

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, which describes a preferred way to present a meta-analysis[2]. 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)[3]. 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).

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Results

We found four systematic reviews that met inclusion criteria[1, 4-6].

- High quality evidence indicates a medium-sized effect of adjunctive oestrogen for improving positive and negative symptoms in females with schizophrenia.
- Low quality evidence is unclear as to the benefit of oestrogen (alone or combined with progesterone) as an adjunctive therapy for improving cognitive function or tardive dyskinesia in females with schizophrenia.
- Moderate quality evidence suggests no benefit of oestrogen therapy as an adjunctive treatment for study retention.

Begemann MJH, Dekker CF, van Lunenburg M, Sommer IE

Estrogen augmentation in schizophrenia: A quantitative review of current evidence

Schizophrenia Research 141; 2012: 179-184

View review abstract online

Comparison	**Oestrogen therapy (2 to 4 weeks, varying doses) plus standard care vs. placebo plus standard care in female patients.**
Summary of evidence	**High quality evidence (consistent, precise, direct) indicates a medium effect of adjunctive oestrogen (particularly oestradiol) for improving positive and negative symptoms in female patients.**

Mental state

Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale (BPRS)

There is a significant, medium size benefit of adjunctive oestrogen for improving symptom severity (PANSS or BPRS) in females;

Total symptoms (females): 4 RCTs, N = 214, g = 0.66, 95%CI 0.21 to 1.11, p = 0.004, I^2 = 58%

Positive symptoms (females): 4 RCTs, N = 214, g = 0.54, 95%CI 0.27 to 0.82, p = 0.002, I^2 = 0%

Negative symptoms (females): 4 RCTs, N = 214, g = 0.34, 95%CI 0.01 to 0.67, p = 0.04, I^2 = 25%

Oestradiol only:

Total symptoms (females): 3 RCTs, N = 170, g = 0.79, 95%CI 0.28 to 1.31, p = 0.003, I^2 = 56%

Positive symptoms (females): 3 RCTs, N = 170, g = 0.57, 95%CI 0.26 to 0.87, p < 0.001, I^2 = 0%

Negative symptoms (females): 3 RCTs, N = 170, g = 0.45, 95%CI 0.14 to 0.75, p = 0.004, I^2 = 0%

Authors report possible publication bias.

Risks	Not reported
Consistency in results‡	Consistent, particularly for positive and negative symptoms.
Precision in results§	Precise
Directness of results‖	Direct

Chua WL, Izquierdo de Santiago A, Kulkarni J, Mortimer A

Estrogen for schizophrenia

Cochrane Database of Systematic Reviews 2005; Issue 4. Art. No.: CD004719. DOI: 10.1002/14651858.CD004719.pub2

View review abstract online

Comparison 1	**Oestrogen therapy plus standard care vs. placebo plus standard care.**
Summary of evidence	**Low quality evidence (1 very small RCT, unable to assess precision, direct) is unclear as to the benefit of oestrogen as an adjunctive therapy for improving mental state in females with schizophrenia.** **Moderate quality evidence (consistent, imprecise, direct) suggests no benefit of oestrogen therapy as an adjunctive treatment for study retention.**

Mental state

Positive and Negative Syndrome Scale (PANSS)

4 weeks of oestrogen patches (50 or 100 mcg/day dose) or placebo in pre-menopausal women in the acute phase of their illness.

No significant differences between groups immediately post-treatment in PANSS total scores;

50 mcg per day: 1 RCT, N = 24, MD = -4.62, 95%CI = -14.60 to 5.36, *p* = 0.36

100 mcg per day: 1 RCT, N = 24, MD = -2.26, 95%CI = -15.44 to 10.92, *p* = 0.74

No significant differences between groups immediately post-treatment in PANSS positive scores;

50 mcg per day: 1 RCT, N = 24, MD = -0.37, 95%CI = -5.36 to 4.62, *p* = 0.88

No significant differences between groups immediately post-treatment in PANSS negative scores;

50 mcg per day: 1 RCT, N = 24, MD = -2.21, 95%CI= -4.73 to 0.31, *p* = 0.08

100 mcg per day: 1 RCT, N = 24, MD = -0.51, 95%CI = -3.65 to 2.63, *p* = 0.75

No significant differences between groups immediately post-treatment in PANSS general scores;

50 mcg per day: 1 RCT, N = 24, MD = -2.04, 95%CI= -7.01 to 2.93, *p* = 0.42

100 mcg per day: 1 RCT, N = 24, MD = -0.83, 95%CI = -7.88 to 6.22, *p* = 0.82

Leaving the study early (indication of treatment tolerance)

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Up to 8 weeks of oestrogen oral or patches in pre-menopausal women in the acute phase of their illness or post-menopausal women in the chronic stable phase of their illness. *No significant differences between groups;* 4 RCTs, N = 96, RR = 0.95, 95%CI = 0.15 to 6.07, *p* = 0.96, I^2 = 0.0%	
Risks	Not reported
Consistency in results	Consistent for leaving the study early, not applicable for mental health outcomes (1 RCT).
Precision in results	Imprecise for leaving the study early, unable to assess mental state as standardised measure not reported.
Directness of results	Direct
Comparison 2	**Oestrogen plus progesterone plus standard care vs. placebo plus standard care.**
Summary of evidence	**Low quality evidence (1 very small RCT, unable to assess precision and consistency, direct) is unclear as to the benefit of oestrogen plus progesterone as an adjunctive therapy for improving mental state, study retention or cognitive functioning in females with schizophrenia.**
Mental state **Positive and Negative Syndrome Scale (PANSS)**	
6 months of estradiol 1mg and medroxyprogesterone acetate 2.5mg, given orally to post-menopausal women in the chronic stable phase of their illness. *Trend effect for better PANSS total scores for oestrogen + progesterone compared to placebo;* 1 RCT, N = 9, MD = -25.30, 95%CI = -50.74 to 0.14, *p* = 0.051 *No significant differences between groups in PANSS positive scores;* 1 RCT, N = 9, MD = -2.00, 95%CI = -10.52 to 6.52, *p* = 0.65 *Significantly better PANSS negative scores for oestrogen + progesterone compared to placebo;* 1 RCT, N = 9, MD = -9.00, 95%CI = -17.11 to -0.89, *p* = 0.03 *Trend relationship for better PANSS psychopathology scores in oestrogen + progesterone compared to placebo;* 1 RCT, N = 9, MD = -14.30, 95%CI = -29.31 to 0.71, *p* = 0.062	

Cognitive functioning Benton Visual Retention Test-Revised (BVRT-R) Motor speed – finger tapping speed	
6 months of estradiol 1mg and medroxyprogesterone acetate 2.5mg, given orally to post-menopausal women in the chronic stable phase of their illness. *Significantly better total scores for oestrogen + progesterone group compared to placebo group;* 1 RCT, N = 8, MD = -3.50, 95%CI = -5.73 to -1.27, *p* = 0.0021 *No difference in finger tapping speed between groups or between tasks;* Dominant hand: 1 RCT, N = 9, MD = -5.10, 95%CI = -19.22 to 9.02, *p* = 0.48 Non-dominant hand: 1 RCT, N = 9, MD = -7.70, 95%CI = -23.72 to 8.32, *p* = 0.35 Q_B = 7.73, *p* = 0.05, I^2 = 61%	
Leaving the study early (indication of treatment tolerance)	
6 months of estradiol 1mg and medroxyprogesterone acetate 2.5mg, given orally to post-menopausal women in the chronic stable phase of their illness. *No significant differences between groups;* 1 RCT, N = 10, RR = 0.33, 95%CI = 0.02 to 6.65, *p* = 0.47	
Risks	Not reported
Consistency in results	Not applicable (1 RCT).
Precision in results	Imprecise for leaving the study early, unable to assess mental state and cognitive measures as standardised measure not reported.
Directness of results	Direct

Soares-Weiser KV, Joy C

Miscellaneous treatments for neuroleptic-induced tardive dyskinesia

Cochrane Database of Systematic Reviews 2003; (2): CD000208

View review abstract online

Comparison	**Oestrogen (1.25 mg/day) plus standard care vs. placebo plus standard care for 3 weeks.**

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Summary of evidence	**Low quality evidence (1 very small RCT, unable to assess precision and consistency, direct) is unclear as to the benefit of oestrogen as an adjunctive therapy for improving tardive dyskinesia or study retention in females with schizophrenia.**
Tardive dyskinesia	
One RCT (N = 12) compared 3 weeks of oestrogen therapy to placebo in females with schizophrenia, and reported no difference in tardive dyskinesia severity between groups; Clinical improvement: N = 12, RR = 1.18, 95%CI 0.76 to 1.83, *p* = 0.45 Deterioration of tardive dyskinesia: N = 12, RR = 0.33, 95%CI 0.02 to 6.86, *p* = 0.48 *There was also no difference reported in study attrition;* N = 12, RR = 1.00, 95%CI 0.08 to 12.56, *p* = 1.0	
Risks	There was no difference in risk of any adverse effect (N = 12, RR = 0.33, 95%CI 0.02, 6.86, *p* = 0.48).
Consistency in results	Not applicable
Precision in results	Imprecise
Directness of results	Direct

Sommer IE, van Westrhenen R, Begemann M, de Witte L, Leucht S, Kahn RS

Efficacy of Anti-inflammatory Agents to Improve Symptoms in Patients With Schizophrenia: An Update

Schizophrenia Bulletin 2013: 40(1): 181-191

View review abstract online

Comparison	**Adjunctive oestrogen (0.05 to 2mg daily for 3 to 4 months) vs. placebo.**
Summary of evidence	**Moderate quality evidence (inconsistent) suggests a medium size effect of reduced symptom severity in females with schizophrenia taking adjunctive estrogen.**
Symptom severity – measured by PANSS, BPRS	

Oestrogen

A medium size effect of reduced symptom severity in patients receiving oestrogen; 6 RCTs, N = 260, *g* = 0.51, 95%CI 0.04 to 0.97, *p* = 0.03, I^2 = 62% Note: heterogeneity dropped to moderate and the effect size increased when the only study including males was excluded.	
Risks	Not reported
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, CI = Confidence Interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), mcg = micrograms, MD = mean difference, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = positive and negative syndrome scale, RR = relative risk, vs = versus

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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[7].

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† 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[7].

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[8]. 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.

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‡ 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[7];

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

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§ 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[9].

‖ 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, which 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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