TECHNICAL COMMENTARY

Adjunctive treatments - Oxytocin

Introduction

A supplementary, or adjunctive, treatment is administered in conjunction with a patient’s ongoing antipsychotic therapy.

Oxytocin is a neuromodulatory neuropeptide which is important for the correct processing of emotional stimuli in a social context. It has been proposed that difficulties in social cognition in schizophrenia and other disorders such as autism, are underpinned by disruption in the dopaminergic/oxytonergic circuitry linked to socio-emotional processing.

Oxytocin therapy has been linked to prosocial behaviours in some studies, but the opposite in others. So, the impact of oxytocin may be moderated by features of the social environment or individual differences.

This summary table assesses the effects of adjunctive oxytocin therapy in 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. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. 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.

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(1). Reviews were assigned a low, medium or high possibility of reporting bias* depending on how many items were checked. For instance, a low possibility of bias would be assigned to reviews checking over 66% of items, a medium possibility between 33 and 66% and a high possibility would be given to reviews checking less than 33%. Due to the increased number of reviews published since 2014, reviews reporting less than 50% of items have been excluded from the library, prior to this date we excluded reviews reporting less than 33% of items. 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 (RCT) may be downgraded to moderate, low or very 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
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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)(2). The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of the Schizophrenia Research Institute.

Results

We found one review that met our inclusion criteria (3). Click on review ID for a link to the review’s abstract.

See PRISMA checklist for review quality assessments.

Conclusions

- Moderate to low quality evidence suggests adjunctive oxytocin may have a small to medium size effect for improvement of symptoms. Low quality evidence is unable to determine any benefit of oxytocin for social cognition.
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**Gumley A, Braehler C, Macbeth A**

A meta-analysis and theoretical critique of oxytocin and psychosis: Prospects for attachment and compassion in promoting recovery

*British Journal of Clinical Psychology 2014; 53: 42 - 61*

View review abstract online

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<thead>
<tr>
<th>Comparison</th>
<th>Adjunctive oxytocin therapy vs. placebo for people with psychosis</th>
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<td><strong>Note:</strong> most people had a diagnosis of schizophrenia</td>
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| Summary of evidence | Moderate to low quality evidence (small samples, inconsistent, precise, direct) suggests adjunctive oxytocin may have a small to medium size effect for improvement of symptoms. Low quality evidence (very small samples) is unable to determine any benefit of oxytocin for social cognition |

### Symptoms

*A significant, medium size effect of improvement in total and negative symptoms, and small size effects for improvement in positive and general symptoms compared to placebo*

- 4 RCT, N = 105, PANSS total: $d = 0.52$, 95%CI 0.34 to 0.70, $p < 0.01$, $I^2$ 96.5%, $p < 0.001$
- 3 RCT, N = 87, PANSS negative: $d = 0.47$, 95%CI 0.17 to 0.76, $p < 0.01$, $I^2$ 85.6%, $p < 0.001$
- 3 RCT, N = 87, PANSS positive: $d = 0.35$, 95%CI 0.04 to 0.66, $p < 0.01$, $I^2$ 80.5%, $p < 0.001$
- 3 RCT, N = 87, PANSS general: $d = 0.25$, 95%CI -0.07 to 0.57, $p < 0.01$, $I^2$ 41.8%, $p < 0.01$

### Social cognition

No meta-analysis

- 1 placebo-controlled crossover trial, N = 10, reported improved emotion recognition with no effects for specific emotions
- 1 within-subject crossover trial, N = 35, reported improved accuracy of social judgments about interpersonal situations viewed on videotape. Particular improvements were noted in participants with psychosis recognizing familial relationships but not intimate relationships
- 1 RCT N = 23, reported no improvements in affect recognition, but improvements on detection of sarcasm
- 1 RCT N = 20, reported more accurate identification of second-order false belief in the Breune Task but not in other theory-of-mind or trustworthiness tasks
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1 RCT, N = 28 also reported improved identification of smells, particularly pleasant odours

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<tr>
<th><strong>Risks</strong></th>
<th>Not reported</th>
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<tr>
<td><strong>Consistency in results</strong></td>
<td>Highly inconsistent</td>
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<tr>
<td><strong>Precision in results</strong></td>
<td>Precise</td>
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<tr>
<td><strong>Directness of results</strong></td>
<td>Direct</td>
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**Explanation of acronyms**

CI = Confidence Interval, $d = \text{Cohen’s } d = \text{standardised mean differences (see below for interpretation of effect size)}$, $I^2 = \text{the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance)}$, $N = \text{number of participants}$, $p = \text{statistical probability of obtaining that result (}\ p < 0.05 \ \text{generally regarded as significant})$, RCT = randomized controlled trial, 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 which 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(4).

† 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 which are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives which are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

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(4).

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 of 1.00 means there is no difference between groups. A medium to large effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2(5). Odds ratios (ORs) are similar to RRs, but they are based on the probability of an
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Event occurring divided by the probability of that event not occurring. ORs and RRs are similar in size when the event is rare, such as with schizophrenia. In OR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios (HRs) 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 unforeseen 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.

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

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) which 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(4);

§ 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(5).

|| 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.

This topic is yet to be reviewed by a content expert.
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References