TECHNICAL COMMENTARY

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Therapies for negative symptoms

Introduction

Pharmacological therapies alone may provide insufficient respite from the symptoms of schizophrenia. The negative symptoms of schizophrenia refer to an absence of normal functions. This may include (but is not limited to); blunted affect, which is a scarcity of facial expressions of emotion, reduced frequency and range of gestures and voice modulation, and restricted eye contact; alogia (poverty of speech); asociality (reduced social interaction); avolition (reduced motivation and often poor hygiene) and anhedonia, which is reduced experience of pleasure, often manifesting as scarcity of recreation, inability to experience closeness, and reduced interest in sexual activity.

Psychosocial therapies may provide a clinical adjunct to pharmacological therapy, and include cognitive behavioural therapy (CBT), hallucination focused integrative treatment, acceptance and commitment therapy, experience focused counselling, family intervention, metacognitive training, mindfulness, social skills training, and supportive therapy.

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[1]. 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, there is a dose dependent response or if results are reasonably 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 NeuRA (Neuroscience Research Australia).

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Results

We found three systematic reviews that met our inclusion criteria[3-5].

- Moderate to high quality evidence shows a small benefit of CBT for greater improvement in negative symptoms than treatment as usual.
- Moderate to high quality evidence suggests cognitive remediation provided a small to medium-sized benefit for improving negative symptoms compared to various control conditions.
- Moderate quality evidence finds skills or occupational training, music therapy, and exercise all provided small to medium-sized benefits for negative symptoms when compared to treatment as usual but not active controls. The factors providing the most benefit were; skill enhancement, behavioural activation, social engagement and neurocognitive factors.

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Bighelli I, Salanti G, Huhn M, Schneider-Thoma J, Krause M, Reitmeir C, Wallis S, Schwermann F, Pitschel-Walz G, Barbui C, Furukawa TA, Leucht S

Psychological interventions to reduce positive symptoms in schizophrenia: systematic review and network meta-analysis

World Psychiatry 2018; 17: 316-29

View review abstract online

Comparison	**Psychosocial interventions for the negative symptoms of schizophrenia vs. inactive or active comparison conditions.**
Summary of evidence	**Moderate to high quality evidence (unclear sample size, consistent, precise, direct) shows a small benefit of CBT for greater improvement in negative symptoms than treatment as usual. There were no other significant comparisons.**
Negative symptoms	
The only significant difference showed a small benefit of CBT for improving negative symptoms when compared to treatment as usual; Unclear sample size, SMD = -0.16, 95%CI -0.29 to -0.02, $p < 0.05$	
Consistency in results	Authors report results are consistent.
Precision in results	Precise
Directness of results	Direct (pairwise meta-analyses)

Cella M, Preti A, Edwards C, Dow T, Wykes T

Cognitive remediation for negative symptoms of schizophrenia: A network meta-analysis

Clinical Psychology Review 2017; 52: 43-51

View review abstract online

Comparison	**Cognitive rehabilitation (computer or non-computer) vs. a control condition (treatment as usual or any active intervention).**

Summary of evidence	**Moderate to high quality evidence (large sample, consistent, precise, indirect) suggests cognitive remediation provided a small to medium-sized benefit for negative symptoms.**
Negative symptoms	
A small to medium-sized effect showed cognitive remediation improved negative symptoms; 45 studies, N = 2,511, g = -0.35, 95%CI -0.44 to -0.25, $p < 0.01$, I^2 = 28%, p = 0.06 The result was similar with outliers removed, in high quality studies, and at follow-up. There were no differences in drop-out rates.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Indirect comparison (mixed control conditions).

Lutgens D, Gariepy G, Malla A

Psychological and psychosocial interventions for negative symptoms in psychosis: systematic review and meta-analysis

British Journal of Psychiatry 2017; 210: 324-32

View review abstract online

Comparison	**Any psychosocial intervention vs. treatment as usual or an active control.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, precise, indirect) finds cognitive behavioural therapy, skills or occupational training, music therapy, and exercise all provided small to medium-sized benefits for negative symptoms when compared to treatment as usual but not active controls. The factors providing the most benefit were; skill enhancement, behavioural activation, social engagement and neurocognitive factors.**
Negative symptoms	

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There were significant, small to medium-sized improvements in negative symptoms with;

CBT

26 RCTs, N = 2,998, SMD = -0.34, 95%CI -0.55 to -0.12, $p < 0.05$, $I^2 = 74\%$, $p < 0.001$

Subgroup analysis showed this effect was only significant when compared to treatment as usual and not active control. There were no moderating effects of study quality.

Skills-based training

17 RCTs, N = 1,123, SMD = -0.44, 95%CI -0.77 to -0.10, $p < 0.05$, $I^2 = 86\%$, $p < 0.001$

Subgroup analyses showed this effect was apparent when compared to treatment as usual, but not active controls. It was apparent when it involved skills training or occupational therapy, but not cognitive adaptation training or vocational training. It was apparent in high and medium quality studies, but not lower quality studies.

Exercise

10 RCTs, N = 581, SMD = -0.36, 95% CI -0.71 to -0.01, $p < 0.05$, $I^2 = 55\%$, $p = 0.039$

Subgroup analyses showed this effect was apparent when compared to treatment as usual, but not active controls. The effect was greater in low quality studies than in high quality studies.

Music therapy

3 RCTs, N = 300, SMD = -0.58, 95% CI -0.82 to -0.33, $p < 0.05$, I^2 not reported

There were no moderating effects of study quality.

There were no significant effects for;

Neurocognitive therapies

16 RCTs, N = 1,139, SMD -0.15, 95% CI -0.41 to 0.11, $p > 0.05$, $I^2 = 74\%$, $p < 0.001$

This null effect remained in subgroup analyses of treatment and control types and study quality.

Fine arts therapies

2 RCTs, N = 475, SMD = 0.57, 95% CI 0.41 to -0.74, $p > 0.05$, I^2 not reported

There were no moderating effects of study quality.

Family therapies

3 RCTs, N = 177, SMD = -0.19, 95% CI -0.70 to 0.34, $p > 0.05$, $I^2 = 65\%$, $p = 0.056$

There were no moderating effects of study quality.

The factors that were most associated with the similar effects found between experimental interventions and active controls were skill enhancement, behavioural activation, social engagement and neurocognitive factors.

Consistency in results	Inconsistent

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Precision in results	Precise for the significant results.
Directness of results	Indirect comparison (mixed control conditions).

Explanation of acronyms

CBT = cognitive behavioural therapy, CI = confidence interval, *g* = Hedges' *g* = standardised mean difference, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RCT = randomised controlled trial, SMD = standardised mean difference, 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; 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].

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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) that 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. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over 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 are an 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 be 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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