Cognitive remediation therapy in schizophrenia: randomised controlled trial
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined cognitive remediation therapy (CRT) for schizophrenia patients with cognitive difficulties. CRT comprised three modules, namely, cognitive flexibility, working memory and planning. It was provided in 40 face-to-face sessions, at a rate of at least 3 per week. CRT was compared with usual care, a description of which was not provided.

Type of intervention
Rehabilitation.

Economic study type
Cost-effectiveness analysis.

Study population
Patients had a diagnosis of schizophrenia based on DSM-IV criteria (American Psychiatric Association, 1994) and evidence of both social functioning (according to the Social Behaviour Scale) and thinking difficulties (according to criteria applied to the Rivermead and/or Wisconsin Card Sorting Test and/or Hayling Sentence Completion Test). Patients were included if they had been in contact with community mental health services for at least 1 year and were at least 17 years of age.

Setting
The setting was the community mental health service in South London and Maudsley National Health Service Trust. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness and resource use data were obtained during the study period, February 1999 to December 2002, and the final follow-up. The final follow-up took place after 40 weeks (6 months after therapy discontinuation). The price year was 2002/03.

Link between effectiveness and cost data
The costing was undertaken prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
A sample size of 29 persons per group was determined in the planning phase of the study. The authors stated that patients were recruited during a structured geographical rotation within the Trust, using what appears to have been convenience sampling. The authors did not seek to justify the sample choice with respect to disease characteristics or generalisability of the findings. A total of 110 patients, representing 43% of the original selection, refused to participate. A further 20% of the original sample failed initial eligibility and 3% failed the cognitive screen. Finally, 85
patients were randomised, 42 to usual care and 43 to CRT.

Study design
The authors conducted a single-blind, multi-centre, randomised controlled trial. An independent statistician randomly allocated the participants using a concealed randomisation method. A psychiatrist unaware of group allocation, and based in a different building to other researchers and the independent site of randomisation, rated the participants’ symptoms. The participants agreed not to reveal their group allocation prior to each symptom assessment and none did so. Independent assessors initially masked to group allocation, although some participants revealed their allocation at the post-treatment assessment, collected cognitive data. Social behaviour data were collected from keyworkers or relative informants who were independent of the trial but not masked to treatment allocation. Follow-up lasted 6 months beyond treatment discontinuation.

In the treatment group, 4 (9%) patients left during the study, while post-treatment, 6 patients left and 1 returned. This equated to a loss to follow-up of 5 patients (12%). In the usual care group, 3 (7%) patients left during the study, while post-treatment 5 (12%) patients were lost to follow-up.

Analysis of effectiveness
Effectiveness was assessed at 14 weeks (post-therapy) and at 40 weeks (6 months post-therapy discontinuation). The three main outcome measures were:

cognitive flexibility (categories achieved from the Wisconsin Card Sorting Test, WCST);
planning (profile score from the Behavioural Assessment of the Dysexecutive Syndrome); and
working memory (total raw score on the Digit Span test of the Wechsler Adult Intelligence Scale III, WAIS-III).

Data on symptoms (Positive and Negative Symptom Scale, PANSS), self-esteem (Rosenberg Self-Esteem Scale) and level of social functioning (Social Behaviour Scale) were also collected. An intention to treat approach was used. Findings were further analysed using linear mixed models. These models included baseline outcome measures and symptoms that may possibly affect cognitive outcome post therapy as explanatory variables, and the experimental factors as fixed variables.

Effectiveness results
Working memory showed an improvement across both post-treatment time points, with an estimated advantage to CRT of 1.33 (95% confidence interval, CI: 0.43 to 2.16), (standardised effect size 0.34, 95% CI: 0.1 to 0.55).

Cognitive flexibility was insignificant at 14 weeks but showed an improvement at the 6-month follow-up, with an estimated advantage to CRT of 1 (95% CI: 0.17 to 8.0), (standardised effect size 0.47, 95% CI: 0.08 to 3.77).

These results correspond to a number-needed-to-treat (NNT) for working memory of 3.1 to produce a clinical change of at least 2 points on the Digit Span test, and an NNT of 6.7 for cognitive flexibility to improve by at least two categories on the WCST.

No other statistically significant changes were found in the primary or secondary end points.

When drug effects were investigated, the results suggested that CRT had an effect on planning for those who received clozapine or typical medications. This effect was absent for patients receiving other atypical medications.

No statistically significant effect was found in terms of the proportion of patients achieving normal range scores in each of the primary end points.

Clinical conclusions
The authors concluded that there was a durable improvement in working memory, a significant improvement in cognitive flexibility, and a non significant advantage in planning. Thus, CRT had demonstrated overall effectiveness in a mixed group of participants.

**Measure of benefits used in the economic analysis**
The measure of benefit used was the percentage of improvers in each group based on WAIS-III Digit Span raw scores, improvers being defined as gaining 2 or more points since baseline.

**Direct costs**
Health, social care and criminal justice system resource use were assessed using the Client Service Receipt Inventory retrospectively from health care staff or records, and/or by participant self-report for the relevant assessment intervals. Details of the included costs were not reported, and the costs and the quantities were not addressed separately. The unit costs at 2000/01 levels were based on national statistics. Discounting was not relevant.

**Statistical analysis of costs**
Mean costs (with standard deviations, SDs) by treatment group, both during the treatment period and at the final follow-up, were reported for health/social care costs and societal costs. Differences in mean costs and 95% CIs were calculated using bootstrap techniques.

**Indirect Costs**
Societal costs were reported as the total per patient costs only. No details of the methods or sources were provided.

**Currency**
UK pounds sterling (¥).

**Sensitivity analysis**
For the cost-effectiveness results, the percentages of improvers were compared using non-parametric bootstrapping, adjusted for baseline WAIS-III Digit Span raw score and total PANSS score.

**Estimated benefits used in the economic analysis**
It was stated that at the post-treatment evaluation, a mean difference of 21% of patients showed cognitive improvement in the CRT group (95% CI: 0 to 41), while at the 6-month follow-up, a mean difference of 21% of patients showed improvement (95% CI: 2 to 41).

**Cost results**
For the intervention group, the mean health/social care costs were 7,756 (SD=5,936) post-treatment and 15,639 (SD=12,453) at follow-up. The mean societal costs were 8,868 (SD=5,849) post-treatment and 17,586 (SD=12,197) at follow-up.

For the usual care group, the mean health/social care costs were 8,271 (SD=7,494) post-treatment and 13,426 (SD=12,852) at follow-up. The mean societal costs were 9,497 (SD=7,413) post-treatment and 15,735 (SD=12,654) at follow-up.

At post-treatment evaluation, the CRT group differed in health/social care costs by -1,086 (95% CI: -3,146 to 1,152) and in societal costs by -1,284 (95% CI: -3,348 to 942). At 6-month follow-up, the figures were 975 (95% CI: -3,330 to 5,255) and 494 (95% CI: -3,564 to 4,577), respectively.
The costs were not statistically significant.

**Synthesis of costs and benefits**

The intervention dominated at the post-treatment evaluation.

At the 6-month follow-up, the incremental cost-effectiveness ratio was 46 additional health/social care costs per additional 1% of improvers in the Digit Span test, and 24 additional societal costs per additional 1% of improvers in the Digit Span test.

**Authors’ conclusions**

In addition to effectiveness in cognitive outcomes, there was an advantage in terms of both health care and societal costs for cognitive remediation therapy (CRT) at the post-treatment assessment (though this was non significant). The cost-effectiveness analysis demonstrated that the cost of treatment is a small price to pay for memory improvements which are likely to translate into further benefits in social behaviour.

**CRD COMMENTARY - Selection of comparators**

The authors chose usual care in their setting in order to evaluate the effect of CRT. Usual care was not fully defined. CRT was selected as the comparator as it had already been shown to be effective in a previous study. You should decide whether this represents a valid and useful comparison in your own setting.

**Validity of estimate of measure of effectiveness**

The analysis was based on a randomised controlled trial, which was appropriate for the study question. Details of the study sample were provided. The method of randomisation, single (assessor) blinding, length of study and loss to follow-up were reported clearly and suggest that the internal validity of the study is good. Blinding was not fully maintained, but the authors suggested that the impact on the study findings was minimal. It seems likely that this loss of blinding is unavoidable in studies where assessment relied on interacting with patients with severe mental illness. Appropriate statistical analyses were performed to take potential biases and confounding into consideration. The results of these analyses were presented in full.

**Validity of estimate of measure of benefit**

The proportion of patients improving their WAIS-III raw score was used as the summary benefit measure. This was obtained directly from the effectiveness study. This measure could be considered a natural unit of measurement and may be difficult to compare with the benefits of other health interventions.

**Validity of estimate of costs**

As no details of the costs or quantities were reported, the validity of the cost estimates was unclear. The categories of costs included appear to have been appropriate to the economic perspective adopted (societal), but it was not clear from the presentation or discussion of the results whether societal costs included health/social care costs or whether the total costs equated to the sum of the two categories. The unit costs were taken from national data. The mean costs were appropriately examined using non-parametric bootstrap methods and skewness was acknowledged. Cost-differences were universally non significant, although the discussion appeared to (inappropriately) rely on the point estimates to confer benefits on the intervention.

**Other issues**

The authors compared their findings with the results of other studies. Rater bias was adequately discussed, given the loss of blinding in the study. The authors acknowledged that the sample size was low and thus had low power to examine subtle effects. The issue of generalisability was not addressed, nor was it explained how the summary benefit measure used in the economic analysis was chosen from the three primary outcomes of the effectiveness study.
Interpretation of the cost and effectiveness results tended to favour the intervention, although the only significant effects were in two of the primary outcomes. Given the large CIs and non significance of many of the results, the strength of the authors’ conclusions regarding the benefits of CRT does not appear to be supported by the evidence.

Implications of the study
Further study is needed to establish the relationship between working memory change and functional behaviour, differentiating between changes in routine behaviour efficiency and novel behaviour flexibility.

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