Authors' objectives
The authors compared the effect of oral citicoline with placebo on a global measure of stroke recovery in patients with acute ischaemic stroke.

Searching
MEDLINE, the Cochrane Controlled Trials Register, and the bibliographic database of the Ferrer Group were searched. The Citicoline Steering Committee developed guidelines for the meta-analysis.

Study selection
Study designs of evaluations included in the review
The review included individual patient data (IPD) from double-blind randomised controlled trials (RCTs). Only data from RCTs with an adequate randomisation method and more than 10 patients per treatment group were included.

Specific interventions included in the review
Studies that compared oral citicoline with placebo for 6 weeks were eligible for inclusion if they used good clinical practice. The included studies used citicoline at doses of 500, 1,000 and 2,000 mg/day. Concomitant treatments included anticholinergics, calcium-channel blockers and thrombolytics.

Participants included in the review
Studies of patients with acute stroke were eligible for inclusion. Specific criteria for including participants in the analysis were a modified Rankin Scale (mRS) score of 1 or less immediately before the stroke, and a National Institutes of Health Stroke Scale (NIHSS) score of 8 or more. Reasons for exclusion included: brain tumour; cerebral oedema; brain stem or cerebellar infarction; subarachnoid, intracerebral or intraventricular haemorrhage; severe systemic disease; cardiovascular conditions; psychoactive substance-related disorder; dementia; renal or hepatic disease. The participants included in the analysis were men and women with a mean age of 68 years (standard deviation, SD=12), a mean baseline NIHSS score of 14.5 (SD=5), and a mean time between stroke onset and randomisation of 13 hours (SD=6).

Outcomes assessed in the review
Studies that assessed outcomes at 3 months using mRS, functional Barthel Index (BI) and NIHSS were eligible for inclusion. The primary outcome was recovery at 3 months after stroke. This was assessed using a global measure that combined the results for mRS, BI and NIHSS, as recommended for stroke trials (see Other Publications of Related Interest). The secondary outcomes were the individual scales (mRS, BI, NIHSS), mortality and adverse effects (overall, and specific adverse effects with different rates between the treatment groups).

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.

Assessment of study quality
An external clinical research organisation checked the data for accuracy, consistency and completeness of follow-up. Tabulated data were sent to the original trialists for verification. Any differences were verified and the data file amended. The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.
Data extraction
It appears that IPD were obtained variously from trial reports, contact with the source, and case report forms for each trial. Dichotomous data were extracted for three outcome variables: BI 95 or more; mRS less than or equal to 1; and NIHSS less than or equal to 1.

If data were not recorded at week 12 the last observation was carried forward. Information about concomitant treatments, risk factors and reasons for discontinuation was also extracted. Extracted data were sent to representatives of each trial for verification.

Methods of synthesis
How were the studies combined?
Meta-analysis methods were used to combine the data. The main analyses included patients who had moderate or severe stroke and received at least one treatment dose and had at least one outcome assessment; this was called the intention-to-treat (ITT) analysis. If data were not recorded at 3 months the last observation carried forward was used in the analyses. Also analysed were data from all randomised patients, regardless of stroke severity, who were evaluated at 3 months; this was called the per protocol analysis. The global estimation of effect combined the BI, mRS and NIHSS data into a single parameter, which was pooled using linear regression methods adjusted for baseline differences between the groups. Potential confounding factors were explored in the regression analysis: stroke severity, time from onset to treatment, risk factors for stroke, concomitant drugs. The BI, mRS and NIHSS data were also pooled separately using the Cochran-Mantel-Haenszel method in a fixed-effect analysis. The meta-analyses produced pooled odds ratios (OR) with 95% confidence intervals (CI). Survival analysis appears to have been used to assess mortality at 3 months.

How were differences between studies investigated?
Statistical heterogeneity in baseline variables between trials, and between citicoline doses, was tested using the Kruskal-Wallis test. In the meta-analyses, the statistical significance for interaction between study and treatment effect was tested using the chi-squared Wald test. In the meta-analyses, data were pooled by dose subgroup (500, 1,000 or 2,000 mg/day) and overall.

Results of the review
IPD from 4 RCTs (1,652 patients) were included.

Global recovery.

The ITT analysis showed that citicoline significantly increased recovery at 3 months compared with placebo; the OR was 1.33 (95% CI: 1.10, 1.62, P=0.0034). The highest recovery rate was with citicoline 2,000 mg/day; the OR was 1.38 (95% CI: 1.10, 1.72) for 2,000 mg/day (2 RCTs, 485 patients), 0.84 (95% CI: 0.35, 2.15) for 1,000 mg/day (1 RCT, 40 patients) and 1.42 (95% CI: 0.96, 2.09) for 500 mg/day (3 RCTs, 246 patients).

The OR for all 1,652 patients in the RCTs (per protocol) was 1.22 (95% CI: 1.01, 1.45, P=0.045). Similar global recovery rates were found for the 1,246 per protocol patients (OR 1.35, 95% CI: 1.10, 1.65).

Citicoline significantly increased activities of daily living and function in comparison with placebo; the OR for recovery was 1.29 (95% CI: 1.03, 1.62) when measured by BI, and 1.42 (95% CI: 1.08, 1.88) when measured by mRS. Citicoline increased neurological recovery, but the increase was not statistically significant; the OR for recovery measured by NIHSS was 1.28 (95% CI: 0.99, 1.65). The results were similar after adjusting for baseline stroke severity, time from stroke to treatment, primary study, risk factors and concomitant drug treatments. Analysis of per protocol patients gave similar results.

Mortality.

There was no significant difference between citicoline and placebo in mortality at 3 months; 18.8% with citicoline versus 17.8% with placebo. Mortality was significantly higher (P=0.019) with citicoline 1,000 mg/day, but the small number of patients who received this dose had a higher NIHSS score at baseline.
Safety.

There was no difference between citicoline and placebo in the overall adverse effect rate. Compared with placebo, citicoline significantly increased anxiety (13.7 versus 9.9%, P=0.0360) and leg oedema (9.7 versus 6.5%, P=0.032). Depression, falling down and urinary incontinence were significantly more common in the placebo groups.

Authors' conclusions
Oral citicoline given within 24 hours of onset of a moderate to severe stroke increases the chance of complete recovery at 3 months.

CRD commentary
The review question was clear in terms of the study design, intervention, participants and outcomes. Several relevant sources were searched, but no details of the search terms, dates searched, or any language restrictions were given. However, the search for studies was not as extensive as we would expect for a review of IPD, and it seems to have focused on data taken from published trials or trials on the database of the company who developed the drug. Independent unpublished data do not appear to have been sought. There is little reassurance that all relevant data have been included in this review, and it is unclear how the data that were included were obtained or how complete the datasets were. Details of the individual studies were lacking, so we cannot assess the authors' judgments concerning heterogeneity. The methods used to analyse the data are not IPD methods. For example, to assess the effect of dose and stroke severity the authors used subgroups and medians, which should not be necessary when IPD are available. In view of these issues, this does not appear to be a robust review. In addition, the review was partially supported by Grupo Ferrer SA (Grupo Ferrer Internacional developed and launched citicoline) while Interneuron Pharmaceuticals Inc. (who are engaged in the development of citicoline products) provided the original databases of the clinical trials.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that a new trial should be undertaken to verify the results of the review.

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