CRD summary
This review found that treatment with selective serotonin re-uptake inhibitors was associated with a very low rate of cerebrovascular adverse events. The author's conclusions follow from the evidence presented in the review. However, the limited search and reporting of review methods mean that some relevant information might have been missed, and this weakens the strength of the conclusions.

Authors' objectives
To examine the evidence linking selective serotonin re-uptake inhibitors (SSRI) treatment to cerebrovascular disease.

Searching
MEDLINE was searched from 1966 to 2003; the search terms were reported. Additional data were requested from the drug manufacturers, and PDR was searched for data on adverse events. Data from the World Health Organization's adverse reaction database (ADR) were also searched and included in the review. It was unclear whether any language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Study designs such as randomised controlled trials (RCTs), open trials, case reports involving 5 or more patients, case-control studies and chart reviews were eligible for inclusion.

Specific interventions included in the review
Studies with SSRI treatments were eligible for inclusion. The included studies assessed citalopram, fluoxetine, nortriptyline, sertraline, paroxetine, maprotiline, amitriptylin or mianserin in various doses and schedules.

Participants included in the review
No inclusion criteria were specified with regards to the participants included in the review. The included studies were conducted in adults and children.

Outcomes assessed in the review
Studies assessing or citing SSRI-related cerebrovascular incidents were eligible for inclusion. No primary or secondary outcomes of interest were defined explicitly.

How were decisions on the relevance of primary studies made?
The author did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The author did not state that they assessed validity.

Data extraction
The author did not state how the data were extracted for the review, or how many reviewers performed the data extraction. It appeared that data on treatments and findings were extracted as reported in the original studies.

Methods of synthesis
How were the studies combined?
The studies were grouped according to design (case-control, clinical or case report) and combined in a narrative.

How were differences between studies investigated?
The results were discussed with reference to SSRI treatment and intracranial haemorrhage, vasoconstrictive stroke and ischaemic stroke. Current versus past use of SSRIs, adjustment of confounders, dose of SSRIs, adverse effects, and the limitations and quality of the included studies were also discussed.

Results of the review
Sixteen studies defined by the author as clinical trials, 2 case-control studies (n=86,971) and 3 case reports describing 4 cases were included in the review (total number of participants not reported). The definition of a clinical trial appeared to include RCTs (9), open-label controlled trials (3), cohort studies (1), study with a naturalistic follow-up (1), case-control study (1) and a chart review (1). Data on adverse events from the PDR were also included.

Neither of the 2 case-control studies suggested a significant association between intracranial haemorrhage and SSRI use: the odds ratios (ORs) were 1 (95% confidence interval, CI: 0.6, 1.6) and 0.8 (95% CI: 0.3, 2.3). One of the studies assessed the relationship between ischaemic stroke and SSRI use: this was not significant for current users of SSRIs (OR 1.1, 95% CI: 0.9, 1.4), but was significant for past users (OR 1.3, 95% CI: 1.0, 1.5, P=0.02).

Of the 16 clinical studies, 12 did not report any incidence of stroke; the studies that did report stroke found no evidence for adverse cerebrovascular effects associated with SSRI treatment. The data from PDR and manufacturers found adverse events to be rare or infrequent. No causal relationships between SSRI use and adverse effects were established.

Authors' conclusions
The available evidence suggests that SSRI treatment has a very low rate of cerebrovascular adverse reactions. Vigilance is required in the use of SSRIs in high-risk populations for bleeding and vasoconstrictive stroke.

CRD commentary
The review question was broad in terms of the study design, participants, outcomes and interventions of interest, and the inclusion criteria were not explicitly defined. This means that subjective decisions may have been more likely during the selection of studies for inclusion. The searching of only one database might have resulted in the omission of some relevant studies, although additional data were sought from drug manufacturers and other sources. It was unclear whether any language restrictions were applied, and no attempts were made to minimise or identify possible publication bias. The methods used to select studies, assess validity and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer errors and bias. Given the apparent variety and nature of the studies, a narrative synthesis was appropriate. The author's conclusions follow from the evidence identified and presented in the review. However, given the limited search and lack of reporting of review methods, the reliability of the author's conclusions is weakened.

Implications of the review for practice and research
Practice: Consideration should be given to the evaluation of the risk-benefit relationship when prescribing SSRIs to stroke patients.

Research: Further research examining the variability of pharmacologic and genetic factors, depressive illness and stroke on the adverse effects of SSRIs is warranted.

Bibliographic details

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