Use of selective serotonin reuptake inhibitors and risk of fracture: a systematic review and meta-analysis
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CRD summary
The review concluded that selective serotonin reuptake inhibitor use was associated with a relatively high fracture risk and clinicians should consider bone mineral density screening before prescribing. The review was generally well conducted, but due to the potential for publication bias and substantial heterogeneity in the analyses, the authors’ conclusions should be considered tentative.

Authors’ objectives
To assess the effects of selective serotonin reuptake inhibitors (SSRIs) usage on the risk of fracture.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to October 2010 without restriction; limited search terms were reported. The reference lists of relevant articles were also searched.

Study selection
Randomised controlled trials (RCTs), cohort studies and case-control studies that assessed the use of SSRIs and incidence of bone fracture were eligible for the review. Studies were required to quantify risk of fracture with adjusted odds ratios (ORs) or relative risks (RRs).

Two studies required participants to be over the age of 17 years but most studies required participants to be at least 50 or 65 years old. Site of fractures was either hip, spine, arm or wrist. Some studies controlled for a range of comorbidities and use of other types of drugs; others controlled only for demographic characteristics such as age, sex and bone mineral density. Studies were undertaken in the Netherlands, Denmark, Canada, USA and the UK.

Two reviewers independently selected studies for the review, with disagreements resolved by discussion or consultation with other reviewers.

Assessment of study quality
Studies were assessed for quality using the 9-point Newcastle-Ottawa Scale; criteria included items evaluating selection, comparability and exposure. Studies were considered low quality if they achieved scores less than seven points.

Two reviewers independently performed data extraction.

Data extraction
Data were extracted on the incidence of bone fracture. Odds ratios (ORs) and relative risks (RRs) of the likelihood of fracture associated with the use of SSRIs were extracted or calculated, with corresponding 95% confidence intervals (CIs).

Two reviewers independently extracted data for the review.

Methods of synthesis
The results of the studies were pooled in meta-analyses and summary effect odds ratios, with 95% confidence intervals, were calculated using the DerSimonian-Laird random-effects model. Where individual studies reported relative risks, these were considered to approximate odds ratios. Where stratified estimates were reported, these were combined using the inverse variance method. Heterogeneity was assessed with I². Subgroup analyses were undertaken according to study design (case-control versus cohort study), geographic location (latitude), the number of clinical risk factors used for statistical adjustment (four or more versus less than four), anatomical site of fracture (hip/femur, spine or wrist/forearm), methodological quality of the study (high versus low), medication dose (high versus usual), exposure
duration, age and sex. Meta-regression was used to assess the relationship between fracture risk and potential effect modifiers. Publication bias was assessed by inspection of the funnel plot and Begg's test.

**Results of the review**

Twelve studies, seven case-control and five cohort studies, were included in the review. The number of participants was at least 855,377 (ranging from 4,871 to 456,866); one cohort study did not report on numbers of participants in the study. The mean quality score was 6.91 out of a maximum score of 9; four studies were considered of low quality.

**Overall analysis**

There was a significant positive association between the use of SSRIs and risk of fracture (adjusted OR 1.69, 95% CI 1.51 to 1.90; 12 studies; I²=89.9%).

**Subgroup analyses**

Significant positive associations between risk of fracture and use of SSRIs were identified for all subgroup analyses, except exposure to SSRIs more than six weeks before the test date. All subgroup analyses had heterogeneity values greater than 40% except for two subgroup factors: geographic location in the USA and men. The authors reported that higher risks were found for the following subgroups: case control studies; studies undertaken in countries with high latitude; studies adjusting for fewer than four variables; studies of fracture of the hip or femur; and studies of SSRIs administered within six weeks of the test date. However, they did not report statistical tests of the difference in treatment effect.

No statistically significant effect on fracture risk was identified in meta-regression analyses for latitude, quality assessment, study design and the number of key adjusted variables for osteoporotic fracture risk factors.

There was no evidence of publication bias from inspection of funnel plots or the results of the Egger test (P=0.051).

**Authors’ conclusions**

A relatively high fracture risk associated with SSRI use may have a significant clinical impact; clinicians should consider bone mineral density screening prior to prescribing SSRIs.

**CRD commentary**

The review addressed a clear research question, supported by appropriate inclusion criteria. Relevant sources were searched to identify studies without language restriction, but no attempts were made to find unpublished studies so some studies may have been missed. Appropriate methods were used to select studies, extract data and assess studies for quality, which minimised the chance of reviewer error or bias. A valid tool was used for quality assessment and most observational studies identified for the review were considered of high quality, but authors acknowledged that the potential for bias could not be ruled out.

Synthesis of the studies in meta-analyses and assessment of heterogeneity and publication bias were appropriate. Although the results of a formal assessment of publication bias were not significant, the p value was very close to the p<0.05 limit. Substantial heterogeneity was identified for the overall analysis. The authors explored the identified heterogeneity through a range of pre-specified subgroup analyses and meta-regression of potential variables that could influence the findings. Substantial heterogeneity was also identified for most of the subgroup analyses which limited the interpretation of the results. The included studies were all undertaken in Western countries which limited the generalisability of the results.

The review was generally well conducted, but due to the potential for publication bias and substantial heterogeneity in the analyses, the authors’ conclusions should be considered tentative.

**Implications of the review for practice and research**

**Practice:** The authors stated that clinicians should carefully consider bone mineral density screening before prescribing SSRIs, especially for patients who were already at high risk for fracture and proper management of the high risk population of patients.
Research: The authors did not state any implications for research.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.