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News Story 27 June 2007

Serotonin reuptake inhibitors (SSRI) and bone density - cause for concern?

Two studies reported in the Archives of Internal Medicine this week raise concerns that the SSRI antidepressive drugs may have significant adverse effects on bone. Recent research has found that there are serotonin transporters in bone cells, and animal studies suggest that disruption of this system has adverse effects on bone density. There is, therefore, the possibility that use of drugs affecting serotonin transport may affect bone mineral density (BMD) in humans. The two reported studies investigate this using data from two related existing prospective cohort studies. These studies, funded through the US National Institutes of Health, are the Study of Osteoporotic Fractures (SOF, women) and the Osteoporotic Fractures in Men Study (MrOS): the first has been running for nearly two decades, and the second for over five years.

SOF initially recruited women aged 65 and over between 1986 and January 1989 from four areas of the US. Participants were followed up regularly, and this analysis uses data collected at the sixth (1997-9) and eighth (2002-4) clinic visits. Women were eligible for this analysis if at the two visits they completed a medication inventory, and had technically adequate hip BMD measurement, and had also completed the geriatric depression scale (GDS) at visit six. For the purpose of analysis, they were classified according to SSRI or tricyclic (TCA) antidepressive drug use: non-users (no recorded use of any antidepressive), SSRI users, and TCA users; users were classed as continuous (use reported at both visits) or partial (use reported at one visit). Those who used other antidepressive drugs or both SSRI and TCA were excluded from analysis.

There were 2,722 in the study cohort with a mean age of 78.5 years; 198 (7.3%) reported SSRI use, and 118 (4.3%) TCA use. The remaining 2,406 (88.4%) reported no use of any antidepressive. Over the mean 4.9 years between the two visits, mean total hip BMD decreased by 0.47% after adjustment for confounding factors in non-users, by 0.82% in SSRI users, and by 0.47% in TCA users. The difference between non-users and SSRI users was statistically significant ($p<0.001$). The authors conclude that in their cohort, use of SSRI was associated with faster bone loss compared to non-use, whereas use of TCA was not. They suggest that this may be due to a direct adverse effect of SSRI on bone. They note that depression itself is associated with reduction in BMD and is therefore a confounding factor: when those with the highest depression scores were excluded from analysis the association was reduced but not eliminated, suggesting at least some confounding by indication. Nevertheless, they consider that their results indicate the need for further research in this area.

The second study reported aimed to determine whether SSRI use was associated with effects on BMD in older men. Previous analysis of data from MrOS suggested an association, and this cross-sectional analysis aimed to clarify that. MrOS included men aged 65 years or older at recruitment, and all had BMD measurement at baseline. Medication histories were obtained, and based on this data participants were classified as non-users, trazodone users, SSRI users, TCA users, and combination users. Outcome measures were medication use and BMD.

There were 5,995 men in the study cohort with a mean age of 73.7 at baseline. Proportions reporting antidepressive use were SSRI 2.7% (n=160), TCA 1.7% (n=99), trazodone 0.9% (n=52). Total hip BMD was 3.9% lower in SSRI users compared to non-users and lumber

spine BMD was 5.9% lower (p=0.002 for hip and p<0.001 for spine). TCA and trazodone users did not differ significantly from non-users. Analysis including a wide range of potentially relevant variables in the model did not make any significant difference to the association. The authors conclude that SSRI use in this cohort was associated with significant reductions in hip and spine BMD compared to non-users. They note that this was not affected by potential confounding variables, and consider that it represents a real and clinically significant effect. They comment that it is similar in magnitude to the effect of corticosteroids reported in this population, and consider that further studies are needed to confirm their results.

An accompanying editorial comments on the studies. The author notes that both have been carefully carried out, but warns that unmeasured confounders may still be significant. The lack of any association with TCA use is suggestive, however TCA are used for other indications, the number of users was smaller, and they may have different risk factors. Nevertheless, the evidence now available satisfies at least some of the standards for establishing causal relationships from observational studies. Further well designed studies are needed to investigate the effect, and characterise it further.

Arch Intern Med 2007; 167: 1240-45 (women, link to abstract); *Arch Intern Med 2007; 167: 1246-51* (men, link to abstract); *Arch Intern Med 2007; 167: 1231-2* (editorial, link to extract)