Choosing a Selective Serotonin Reuptake Inhibitor for Depression

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Each of the selective serotonin reuptake inhibitors (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) is alleged to have advantages and disadvantages in relation to its competitors. These were evaluated in a meta-analysis of 21 trials involving about 3000 patients and a review of data on safety monitoring, overdoses, interactions, and costs[1]. How should the results influence choice?

Each of the antidepressants was compared with the others as a group and with the other individual drugs when the numbers of patients included in trials were sufficient. The results showed no significant differences in *efficacy*, which is not surprising given the pharmacology of the compounds. However, fluoxetine had a slower onset of action than the other drugs at weeks 2 and 3 of treatment. This is plausibsy due to its lower potency at inhibiting serotonin reuptake and slower attainment of steady state therapeutic concentration due to the long elimination half-life of fluoxetine and its active metabolite, norfluoxetine[2]. The results indicate that there is nothing to choose between the individual antidepressants on the grounds of efficacy, but fluoxetine may not be the drug of choice in severely depressed patients in whom a rapid response is desirable. If fluoxetine is given to such patients a higher than usual starting does should be considered.

The overall discontinuation rate from treatment (an indication of *tolerability*) was almost 26%. More patients dropped out of treatment with fluvoxamine than its comparators, a finding consistent with the results of prescription event monitoring[3,4]. The observations support the view that fluvoxamine is less well tolerated than other serotonin reuptake inhibitors and thus cannot be recommended as first choice.

The meta-analysis revealed a significantly higher incidence of *agitation* in patients treated with fluoxetine, but not of other CNS stimulatory effects. Although the validity of this finding is questionable because figures were only reported in a minority of studies, it is in keeping with the

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higher ranking for agitation in reports to the Committee on Safety of Medicines (CSM) for fluoxetine compared with other serotonin reuptake inhibitors[1]. Caution should therefore be exercised when prescribing fluoxetine for agitated patients.

CSM reports suggested that *discontinuation reactions* occur more often after stopping paroxetine than other selective serotonin reuptake inhibitors,[1,5] which is consistent with prescription event monitoring findings.[3,4]. These also gain support from controlled studies in which patients on serotonin reuptake inhibitors had treatment interrupted by double-blind placebo substitution[6,7]. Discontinuation reactions were greatest on paroxetine and least on fluoxetine, suggesting that paroxetine is best avoided in patients who have previouly had troublesome discontinuation reactions and that fluoxetine should be considered for such patients.

Much concern has been expressed concerning *sexual dysfunction* occurring during treatment with selective serotonin reuptake inhibitors. A prescription event monitoring study[4] and a prospective descriptive study[8] found that paroxetine was associated with more impotence and delayed orgasm than other inhibitors. In a controlled trial in men with lifetime rapid ejaculation, paroxetine delayed ejaculation more strongly than other serotonin reuptake inhibitors while fluvoxamine was the only one that did not differ from placebo[9]. Thus, if sexual dysfunction is troublesome, paroxetine should be avoided and fluvoxamine considered.

More potentially hazardous *drug interactions* have been reported during treatment with fluoxetine and fluvoxamine than the other selective serotonin reuptake inhibitors. However, the relevance of this is uncertain because of biases in reporting and the avoidance of concomitant medication shown to be dangerous when taken with these older selective reuptake inhibitors. Perhaps of more relevance are differences in in vitro inhibition of cytochrome P-450 enzymes. These suggest that citalopram and sertraline should be the least likely to cause to interactions at this site[2]. When there is a risk of an interaction, such as with a monoamine oxidase inhibitor, a longer drug-free interval should be allowed after stopping fluoxetine because of its prolonged action.

Six deaths have been associated with *overdoses* of citalopram[10]. However, in five of these CNS depressants were also taken and the death due to citalopram alone involved a similar large quantity to the only other documented death due to an overdose of a selective inhibitor taken alone-fluoxetine". The quantity taken was also considered to be important in a subsequent fatality from citalopram alone[12]. No deaths occurred among 44 patients who took overdoses of citalopram alone in quantities ranging from 70 to 3000 mg, but widened QRS complexes in the ECG and/or convulsions occurred in over a third of patients who took more than 600 mg (30 x 20mg tablets)[13]. Such findings have not been associated with overdoses of the other serotonin reuptake inhibitors. While the deaths associated with citalopram may have been chance occurrences, clinicians might not wish to choose this drug as first-line treatment in seriously suicidal patients and those prone to repeated self-poisoning[14].

The use of antidepressants in *pregnancy*[15] and *breast feeding* mothers is controversial[16]. We subscribe to the view that these drugs should only be prescribed when absolutely essential, even though harm has not been demonstrated. The antidepressants chosen should be those on which most data are available. Of the serotonin reuptake inhibitors, this means fluoxetine in pregnancy (but not during breast feeding because of the long half-life) and sertraline in lactating mothers.

The acquisition *cost* of individual selective inhibitors has until recently been similar with differences in the cost of treatment being attributable to doses increases. Pharmacoeconomic measures are insufficiently well established to allow for valid recommendations based on individual drug costs, but the expiry of the patent on fluoxetine has give this drug an economic advantage over its competitors.

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