Selegiline in combination with (S)SRIs

Selegiline (deprenyl) is selective for MAO-B at the usual dose of 10 mg daily and may thus be less likely to precipitate ST because 5-HT is metabolised mostly by MAO-A. There have been reports that are probably ST. Gitlin's well-written report demonstrates typical ST features. This reaction occurred 16 days after ceasing selegiline (50 mg daily- more usual dose is 10 mg daily) when the patient took venlafaxine 37.5 mg x 1 dose. It did not recur on re-challenge one week later [1]. Because the margin between a selective and a non-selective dose is narrow it is difficult to be confident in normal clinical practice that ST can be reliably avoided in such situations.

The Zornberg report is the epitome of an incompetent, unrevealing and misleading case report: it is more likely to be explained by the enormous (toxic) dose of imipramine (a total of 700 mg daily- no blood levels documented) and did not show typical ST features [2]. I have to say that I have seen an awful lot of poor case reports in my role as a journal referee and expert on ST, but this one is vying for the top spot of extraordinary treatment and bad case reports. Not only was the patient being given 700 mg daily of imipramine but this was supplemented with 100 mg of desipramine plus heaven knows what else including hydroxyzine. The main clinical picture was that of toxic delirium and there were no signs of ST. How a reputable journal like the Lancet came to publish something like this is almost beyond belief. I would be terrified if I thought doctors of that degree of ignorance and incompetence were looking after one of my nearest and dearest.

There are 3 cases reported from a review of the French pharmacovigilance database; details are unavailable. I lectured for this group in Toulouse in 1997 and they conducted the review following that, thus, they were informed of what symptoms to note [3]. There is a Spanish report of an apparent fatality that I cannot comment on: if anyone can translate it let me know please [4].

There are a couple of retrospective chart reviews: one found 7/28 patients, on selegiline and any class of antidepressant drug, had taken an SSRI type drug; one patient on fluoxetine was diagnosed with ST. The other review found no ST in 23 patients on selegiline and fluoxetine. In my opinion we can be sure that selegiline is less of a risk than tranylcypromine (or other old non-selective MAOIs): I am certain that if you did the same with tranylcypromine deaths would occur, as indeed they did, as reported by Beasley et al in the early fluoxetine trials [5-7].

In 1997 Richard et al published a thorough follow-up of the Parkinson Study Group (PSG) data; they also reviewed the FDA data. This Parkinson Study Group data showed no severe ST, but there was some small suggestion of serotonin-mediated side effects like agitation and restlessness. In a sample of older patients with brain disease, increased susceptibility to serotonin-mediatedside effects is to be expected and does not constitute evidence for an interaction with selegiline. This sample had ~4,500 patients treated with selegiline and an antidepressant; the proportion treated with a serotonergic antidepressant is not known but is likely to have been substantial. There were no deaths from ST. There is little evidence for severe ST and little evidence for a significant increase in serotonin-mediated side effects [8].

I corresponded with the Parkinson Study Group, but they were unable to say what portion of the patients had a tricyclic antidepressant (TCA) or a selective serotonin reuptake inhibitor (SSRI): their estimate of serotonin-mediatedsymptoms in 0.24% of cases may reflect a significant risk of ST in such patients. It would be reasonable to suppose that about half were on non-

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serotonergic antidepressants, and half were on sub-therapeutic doses, the real risk might equate to nearer 1%. Those estimates are reasonable from my experience and the literature on cytochrome P450 enzyme genetic variability. When extrapolated to higher doses in higher risk patients it may be that a 5% risk of significant ST with selegiline and selective serotonin reuptake inhibitors (SSRIs) is more realistic estimate: that would fit better with the reported cases.

The spectrum concept of ST is the key to assessing this risk. Pharmacokinetic and pharmacodynamic interactions are likely to be crucial in tipping the balance; selegiline is selective at lower levels but drugs, especially the SSRIs, that act as cytochrome P450 enzyme inhibitors will probably induce toxicity in some patients in some circumstances. Since we do not yet fully understand some of the intricacies of these drugs' interactions and metabolism even the best-informed specialists can get into difficulty. Providing the dose is not excessive and significant pharmacokinetic interactions can be avoided ST is uncommon with SRIs combined with selegiline: however, one or two deaths may have occurred.

However, there can be a rapid transition from side effects to toxicity, as other sections of this review reveal. Clinicians, who have prescribed such combinations, and observed patients experiencing that transition, tend to go to bed wondering whether they know as much as they thought they did, and contemplating what they might say to the relatives and their medical defence insurer.

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Here are other references concerning ST and selegiline [9-13].

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