Q What is the efficacy and tolerability of pindolol plus selective serotonin reuptake inhibitors (SSRIs) in people with depression?

**METHODS**

**Design:** Systematic review with meta-analysis.


**Study selection and analysis:** Eligible studies were randomised controlled trials (RCTs) comparing pindolol plus SSRIs with placebo plus SSRIs, for the first two weeks of treatment (OR 2.8, 95% CI 1.4 to 5.7; NNT = 6, 95% CI 4 to 20).

**Late response:** seven RCTs met inclusion criteria. There were no significant differences between groups after 3–6 weeks (OR 1.4, 95% CI 0.8 to 2.7). However, the late response studies were heterogeneous.

**Tolerability and safety:** there were no significant differences in tolerability or adverse events between groups (pindolol plus SSRIs v. placebo plus SSRIs; OR for tolerability, 1.3, 95% CI 0.8 to 2.3; OR for adverse events, 1.3, 95% CI 0.7 to 2.1).

**CONCLUSIONS**

During the first two weeks of treatment, the addition of pindolol to an SSRI appears to increase response; however there was no evidence of improved efficacy beyond this period.

**Outcomes:** Depressive symptoms: efficacy assessed by the proportion of total participants experiencing side effects.

**Conclusions:** the addition of pindolol plus SSRIs to placebo plus SSRIs results in improved efficacy over the first 2–3 weeks. This is in line with studies showing that serotonin receptor antagonists may reduce antidepressant latency. However, late response studies are less promising; pindolol did not improve response beyond 3–6 weeks.

**Commentary**

All the current arguments about the mechanism and efficacy of antidepressants, virtually everyone can agree that there is a delay—the antidepressant “latency”—before the specific antidepressant effect is clear. It is common for the antidepressant effect to be delayed. The formulation of a rapidly acting antidepressant would be a major landmark. Manufacturers’ claims of rapid onset for their particular drug should be regarded with caution, as clinical trials are not usually designed with time of onset in mind.

The problem is complicated because we do not know why latency occurs. Selective serotonin reuptake inhibitors (SSRIs) selectively inhibit serotonin reuptake by the synapsic neuron immediately; but there is a common lag of 3–4 weeks before they exert an antidepressant effect. There have been several suggested mechanisms, but as yet no unifying theory.

In the mid-1990s, Artigas et al.1 and Blier et al.2 suggested that continued activity of presynaptic 5HT1A autoreceptors was responsible for antidepressant latency, and that specific blockade of these receptors by the β-antagonist pindolol could reduce this latency—and so it proved in open label studies. The key was of course to test the effect in randomised controlled studies.

Results have been mixed. Roughly speaking, in European hands (including our own3), the addition of pindolol from the outset of antidepressant treatment does indeed seem to accelerate the antidepressant response in many patients, especially if they have not been treated for depression before (the severity of the depression seems to be less important). However, some US studies4 have been less successful, as have studies looking at treatment resistance. So the true place of pindolol augmentation remains debated, with the honours so far in favour of the efficacy of the combination. This meta-analysis is a helpful synthesis of knowledge up to 2002.

The clinical advice would be that pindolol augmentation is worth trying in new patients, as long as β blockers are not otherwise contraindicated, and may lead to dramatic and rapid clinical improvements. There seems to be no point in giving pindolol for more than 2–3 weeks.

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1 Artigas F, Perez V, Alonso E. Pindolol induces a rapid improvement of depressed patients treated with serotonin reuptake inhibitors. Arch Gen Psychiatry 1994;51:248–51.