

## Reduction of suicidal thoughts with paroxetine in comparison with reference antidepressants and placebo

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### Abstract

In order to determine whether paroxetine was associated with any increase in suicidal thoughts or acts all controlled studies of paroxetine were examined in a series of meta-analyses. Paroxetine showed an advantage in reducing suicidal thoughts in all analyses compared with placebo. On the MADRS there was a significant advantage compared with active controls at weeks 1, 3, 4 and 6 ( $P < 0.01$ ).

There were significantly fewer emergent suicidal thoughts on paroxetine compared with placebo in all analyses, and a significant advantage for paroxetine compared with active controls on the MADRS. A significant advantage for active controls compared with placebo was seen only on the HAMD.

In the analysis of the data from controlled studies and open extension studies of paroxetine calculated by patient year of exposure there were 2.8 times fewer suicides in the paroxetine-treated group compared with active control and 5.6 times fewer compared with placebo.

**Keywords:** Paroxetine; Suicidal thoughts; Suicidality; Placebo

### 1. Introduction

A number of studies of the neurobiological correlates of suicide have suggested a link between suicidal behaviour and central serotonergic dysfunction. Some post-mortem studies found lower levels of 5-hydroxy-indoleacetic acid (5-HIAA), the primary metabolite of serotonin, in the brains of suicide victims compared with controls (Mann et al., 1989), and a decrease in the number of tritiated imipramine binding sites has also been reported (Stanley et al., 1982). Platelet MAO activity is also reported to be low in depressed patients with a serious suicide attempt (Traskman et al., 1981) though this measure does not reliably identify suicide attempters. An association between a history of suicide attempts, particularly violent attempts, and low levels of 5-HIAA in the cerebrospinal

fluid (CSF), taken as an indirect measure of central serotonergic function, is one of the most consistent findings in biological psychiatry, both in depressed patients and in other diagnostic categories (Åsberg et al., 1976; Roy et al., 1989; van Praag, 1988; Traskman et al., 1981; Banki and Arato, 1983; Brown et al., 1982; Linnoila et al., 1983) though not all studies have found a significant association.

A somewhat simplistic view might be to postulate that drugs having a marked effect in inhibiting the reuptake of serotonin could be of benefit in depressed patients where there is a suicidal component. The mechanism of action of antidepressants is of course unclear and their net effect on different receptor subtypes undoubtedly complicated. Nevertheless some encouragement for the concept that selective serotonin reuptake inhibitors (SSRIs) might have a beneficial effect on suicidality in depressed patients is provided by the differential reduction in suicidal thoughts early in treatment compared with comparator antidepress-

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sants that has been reported with some SSRIs, for example zimeldine and fluvoxamine (Montgomery et al., 1981; Wakelin, 1988). For the most part the advantage is overwhelmed by the general antidepressant effect later in treatment.

If there are differences between antidepressants in their effect on suicidality it is important that this aspect of the spectrum of activity should be tested. A valid assessment of relative risk of suicide or attempts is unlikely to be possible from the individual clinical trials since the chance of a sufficient number occurring within the trial period is low. Moreover efforts will usually have been made in the early stages of clinical testing of an antidepressant to exclude suicidal patients, though these have only limited success because of the difficulty in identifying suicidal patients. Assessment may be more readily based on analyses of large pooled data bases which have methodological problems, for example the variability between centres, but their increased size increases the ability to test for differences between treatments.

A second approach is to examine differences in the response of suicidal thoughts measured during clinical trials as an indirect but possibly related measure of potential suicidality. Suicidal thoughts are common in depression (Montgomery and Åsberg, 1979) and are recognised as being a core diagnostic symptom for major depression in classifications such as DSM-III-R (APA, 1980) or ICD10 (WHO, 1992). The time course of amelioration or indeed of deterioration of the thoughts can be measured on the depression rating scales.

Antidepressants are prescribed on the assumption that they will improve the depression; suicidal thoughts, which are part of depression, should improve as the depression improves. Concerns are however expressed that antidepressants may paradoxically worsen certain symptoms, for example open anecdotal reports have described a development or worsening of suicidality or suicidal thoughts associated with fluoxetine therapy (Teicher et al., 1990). The inherent bias of open reports requires that the reported phenomena be tested in controlled conditions. Inspection of the pooled data in large data bases from controlled studies is one useful means of checking whether relatively rare events reported from open observations occur more frequently during treatment with a drug than with placebo. A meta-analysis of this type carried out with fluoxetine (Beasley et al., 1991a,b) found no evidence of an increase in suicidality compared with placebo.

Paroxetine is a potent SSRI and one of the most selective currently available (Johnson, 1989). Its antidepressant efficacy has been established in extensive clinical trials (Dunbar et al., 1991) and it has a benign side-effect profile with a relative lack of cardiotoxicity

(Dunbar, 1989; Warrington et al., 1989). The SSRIs as a class are reported to be less toxic in overdose than the older tricyclic antidepressants (TCA).

## 2. Methodology

### 2.1. Patients

The clinical trial programme for the assessment of efficacy and safety of paroxetine prior to its registration as an antidepressant provided the data bases for the meta-analysis. The methodology and results of these studies are published elsewhere (Dunner and Dunbar 1992; Dunbar et al., 1991). Flexible dose regimes in the range 10–50 mg were used in most studies and fixed doses of 10 mg, 20 mg, 30 mg and 40 mg were used in one study.

Analyses of suicidal thoughts were made on the pooled data from all controlled short-term (up to 6 weeks) efficacy studies of paroxetine carried out worldwide. These were all double-blind parallel-group comparison studies in moderate to severe major depression. Data were available for 2852 patients treated with paroxetine, 554 with placebo and 1101 with reference antidepressants. Analysis of suicidal thoughts on the Hamilton rating scale of depression (HAMD) (Hamilton, 1967) was carried out on this total data base of 4507 patients.

In a separate analysis the data were pooled from all studies conducted that used the Montgomery and Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) and the symptom check list (SCL-56) (Derogatis et al., 1974). 1510 patients were treated with paroxetine, 459 with an active control and 454 with placebo. Analysis of suicidal thoughts was made on the MADRS in this data base of 2423 patients and on the SCL-56 in 2371 patients for whom the SCL-56 was available.

Additionally the data from the pooled six-centre paroxetine, imipramine, placebo comparison carried out in the US (Dunbar et al., 1991), which used an identical protocol and which provides the most direct comparison, were reviewed separately. There were 234 patients treated with paroxetine, 233 with imipramine and 235 with placebo. Suicidal thoughts on the HAMD and MADRS were analysed in this data base of 702 patients.

Suicides and attempts were analysed in the worldwide data base from controlled studies, extensions of controlled studies and open studies. Paroxetine ( $n = 2963$ ) was compared with placebo ( $n = 554$ ) and active control ( $n = 1151$ ). This latter group included the standard antidepressants, amitriptyline ( $n = 331$ ), imi-

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