strategies. This happens despite growing evidence substantiating a much reduced life-span risk for suicide in depression than that reported in earlier investigations (Bostwick & Pankratz, 2000). Given the complexity of its pathways, the prevention of suicide, like the prevention of many types of death, requires a combination of approaches, such as public and medical education, promoting community connectedness, controlling access to means, early identification and intervention, etc.

It is certainly true that risk factors for suicide are unstable and may change over time (De Leo, 2002), but probably more important is the (mostly unexplored) interaction between risk and protective factors. This is the really crucial issue in suicide prevention (by the way, protective conditions of course counteract also the risk of ischaemic heart disease: the Mediterranean diet and omega-3-fatty acids have already convincingly underlined the role of local differences in mortality rates). And this recalls another important point raised by Dr Ravi Shankar, which refers to the local (cultural/traditional) specificity of suicidal behaviour. In countries such as China, risk factors for suicide are not dissimilar from those of Western countries – what varies is their ranking in terms of importance and expressivity (Phillips *et al*, 2002). Furthermore, it is well-known that within the same country there may be contiguous areas with largely differing suicide rates and that the same risk factors may operate differently in different social contexts.

To identify the exact components of a multifaceted prevention programme, tailored to local characteristics, greater knowledge of risk and protective factors is needed for both the psychiatric and general populations. Prevention of suicide is currently based on scant evidence. Therefore, I fully agree with Dr Ravi Shankar's view that more sound research is required. Prevention must be grounded in evidence if it is likely to have an effect on suicide mortality.

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I would like to comment on the editorial by De Leo (2002) which came to the conclusion that little is new in suicide prevention. Since nothing was mentioned about pharmacotherapeutic advances in suicide, I would like to take the opportunity to discuss recent information concerning the role of novel antipsychotics in the reduction of suicidality.

Suicide rates in schizophrenia are about 13 times greater than in the general population, and make a substantial contribution to the overall suicide statistics in the UK. Suicide rates in schizophrenia were unaffected by the advent of conventional neuroleptics. This was not because these drugs are ineffective, rather that they also come with adverse events that put patients at risk for suicide – most particularly akathisia and depression. However, there is now evidence that atypical antipsychotics – most particularly clozapine – may have antisuicidal potential. This was first hinted at by a mirror-image study by Meltzer & Okayli (1995), which suggested an 86% reduction in suicidality. Subsequently, a large epidemiological study (Walker *et al*, 1997) including data on completed suicides showed that deaths from suicide in clozapine users occurred at a rate of 39 per 100 000 patient-years compared with 222 per 100 000 patient-years in former users of clozapine. Our own UK clozapine study (Munro *et al*, 1999) confirmed this result. There are also suggestions from pivotal studies of olanzapine that suicidality is also reduced in users of this drug (Tran *et al*, 1997).

All these observations have their limitations, which led Novartis, in collaboration with the US Food and Drug Administration (FDA), to embark on a randomised controlled trial of clozapine *v.* olanzapine in the reduction of suicidality in schizophrenia (the InterSePT study), the results of which have recently been reported (Meltzer *et al*, 2003). Overall there was a 25% reduction in all key measures for suicidality in favour of clozapine. This has recently led the Psychopharmacology Advisory Committee to the FDA to recommend that this body approves suicidality in schizophrenia (not restricted to treatment resistance) as a new indication for clozapine. It is disappointing that the National Suicide Prevention Strategy for England and Wales has little to say about the role of new treatments in suicide prevention. However, in a recent modelling study of ours (Warner *et al*, 2003), which also took into account drop-out rates and treatment failure rates, we calculated that one-quarter of the target for suicide reduction in all patients in contact with mental health services could be achieved by the broader use of clozapine in treatment resistance. If clozapine were to be approved for suicidality, 50% of all patients with schizophrenia would be technically eligible. Again, calculating in drop-outs and failures an even more substantial proportion of the national target could be met. Much is made of the rates of thromboembolism and agranulocytosis with this drug. However, in comparison with overall reduction in all-cause mortality as well as the reduction in suicidality with treatment with clozapine, such caution is not supported by the epidemiological evidence for the overall advantage of this drug (Walker *et al*, 1997).

Declaration of interest

R.K. was the UK Principal Investigator for the InterSePT study funded by Novartis.

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Fluoxetine in relapse prevention of PTSD

Martenyi *et al* (2002) suggest that fluoxetine is effective and well-tolerated in the

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prevention of relapse of post-traumatic stress disorder (PTSD) for up to 6 months. I think that this statement needs careful consideration.

First, the authors start by randomising patients into a placebo group and a fluoxetine group; the latter is later subdivided into a fluoxetine/placebo group and a fluoxetine/fluoxetine group. We see the outcome results of both the groups initially treated with fluoxetine, but those of the placebo/placebo group are not included in the paper.

Second, the authors dismiss the issue of discontinuation-emergent adverse effects, referring to a study by Rosenbaum *et al* (1998). That study, also sponsored by Eli Lilly, concluded that fluoxetine had fewer adverse events than other selective serotonin reuptake inhibitors. However, fluoxetine was used up to a maximum dose of 60 mg/day with a mean dose close to 25 mg/day, whereas in the Martenyi *et al* study, the maximum dose was 80 mg/day and the mean close to 50 mg/day – double that in the Rosenbaum *et al* study. This is more significant as the results are not analysed on an intention-to-treat basis. Martenyi *et al* state that there were no significant differences when comparing drop-outs due to adverse events, but if we compare the total number of patients discontinuing the study, the percentages are almost double for those switched to placebo compared with those continued on fluoxetine (33.4% *v.* 17.3%).

Third, the authors mention that the reason behind the failure to show significant differences in the improvement of symptoms between the two treatment groups is the result of inconsistent patient self-rating. Could it not simply be that there are no differences?

The study addresses an important area, but the interpretation of the results should have been more rigorous.

Martenyi, F., Brown, E. B., Zhang, H., *et al* (2002) Fluoxetine *v.* placebo in prevention of relapse in post-traumatic stress disorder. *British Journal of Psychiatry*, **181**, 315–320.

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Authors' reply: Dr Agell raises concerns regarding the conclusions proposed in our original article (Martenyi *et al*, 2002*a*) that the results of our study suggest that fluoxetine is effective and well-tolerated in the prevention of PTSD relapse for up to 6 months. Dr Agell's concerns that (a) we do not discuss the results of the placebo/placebo group; (b) we do not adequately address the study results regarding SSRI discontinuation-emergent adverse events; and (c) 'the authors mention that the reason behind the failure to show significant differences in the improvement of symptoms between the two treatment groups is the result of inconsistent patient self-rating'. We will attempt to address each of these concerns.

First, the results presented in our original article pertain to the relapse-prevention phase of a larger study. Results of the acute treatment phase (including the acute results of the placebo/placebo group) may be found in Martenyi *et al* (2002*b*). The primary objective of the relapse-prevention phase of our study and the focus of our original article was to assess the efficacy and tolerability of fluoxetine in the prevention of PTSD relapse. It then follows that the relevant results should come from acute phase fluoxetine responders who were continued on fluoxetine in the relapse-prevention phase or switched to placebo. The efficacy results from the placebo/placebo group would not address our question regarding the efficacy of fluoxetine in the prevention of PTSD relapse and, therefore, the full relapse-prevention efficacy results from the placebo/placebo group were not provided. We did, however, provide a breakdown of the reasons for discontinuation in the study for all treatment groups (Marteyni *et al*, 2002*a*, Fig. 1). Of the 31 patients in the placebo/placebo group (note that the sample size is small because the original randomisation was 3:1 fluoxetine : placebo), the discontinuation profile was quite similar to that of the fluoxetine/placebo group. Discontinuation profiles for the fluoxetine/placebo group *v.* the placebo/placebo group, respectively, were: 66.1% *v.* 61.3% completed the protocol; 0% *v.* 0% discontinued because of adverse events; 16.1% *v.* 16.1% discontinued because of clinical relapse; 4.8% *v.* 12.9% were lost to follow-up; 3.2% *v.* 0% discontinued because of patient decision; 9.7% *v.* 6.5% discontinued because of non-compliance; and 0% *v.* 3.2% discontinued because of lack of efficacy. These discontinuation data suggest that patients with an initial placebo response face a similar risk of recurrence of symptoms to those who had achieved an adequate pharmacological response and were then switched to placebo.

Second, it is true that approximately twice as many patients discontinued from the fluoxetine/placebo group compared with the fluoxetine/fluoxetine group. It is important, however, to note the reasons for discontinuations (Martenyi *et al*, 2002*a*, Table 2). The protocol specified that patients meeting pre-defined criteria for clinical relapse should be discontinued, which allowed the investigators to provide follow-up care at their discretion. Only one patient in the fluoxetine/fluoxetine group discontinued because of an adverse event compared with none in the fluoxetine/placebo group, and the primary difference between the two treatment groups with regard to reason for patient discontinuation was clinical relapse (5.8% *v.* 16.1% for the fluoxetine/fluoxetine and fluoxetine/placebo groups, respectively). Accounting for all reasons for discontinuation with the exception of clinical relapse, 8 patients (12%) *v.* 11 patients (18%) discontinued early for the fluoxetine/fluoxetine and fluoxetine/placebo groups, respectively (Martenyi *et al*, 2002*a*, Table 2). It should also be noted that there were no statistically significant differences in the numbers of patients reporting any single adverse event. The adverse events most commonly reported by patients in the fluoxetine/fluoxetine group were insomnia (15%), anxiety (6%) and headache (6%); those most commonly reported by patients in the fluoxetine/placebo group were insomnia (10%), headache (5%) and pain (5%). These data provide further support that the long half-life of fluoxetine and its active metabolite, norfluoxetine, provide benefit with regard to the minimisation of the risk of discontinuation-emergent signs and symptoms.

Third, statistically significant differences were detected between treatment groups for the *a priori* defined primary analysis (time to relapse, $P=0.027$; Martenyi *et al*, 2002*a*, Fig. 2). In addition, using repeated-measures analysis of variance (Martenyi *et al*, 2002*a*, Fig. 3), we can see that those patients in the fluoxetine/fluoxetine group continued to improve over time, with a statistically significant difference between groups occurring from week 28 to the study end-point (week 36), based on our primary efficacy measure, and

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