Suicide Risk in Placebo vs Active Treatment in Placebo-Controlled Trials for Schizophrenia

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Background: If there is an increased risk of suicide in the placebo arms of placebo-controlled studies in patients with schizophrenia, it would be a strong ethical argument against the conduct of placebo-controlled studies in this patient population. We tested whether the risk of suicide and attempted suicide in the placebo arms of placebo-controlled studies among patients with schizophrenia is higher than in the active treatment arms of such studies.

Methods: All placebo-controlled double-blind studies that were part of a registration dossier for the indication schizophrenia, and that were submitted to the regulatory authority of the Netherlands from January 1, 1992, through December 31, 2002, were reviewed for suicide and attempted suicide.

Results: In 31 studies, 7152 patients were included: 1888 in placebo groups (398.2 person-years) and 5264 in active compound groups (981.3 person-years). One suicide occurred in the placebo groups (0.05%, or an incidence rate of 251 per 100,000 years of exposure) and 1 in the active compound groups (0.02%, or an incidence rate of 102 per 100,000 years of exposure). This difference was not statistically significant. Two attempted suicides occurred in the placebo groups (0.11%, or an incidence rate of 502 per 100,000 years of exposure) and 11 in the active compound groups (0.21%, or an incidence rate of 1121 per 100,000 years of exposure). This difference was also not statistically significant.

Conclusion: Concern about increased risk of suicide or attempted suicide in the placebo group should not be an argument against the conduct of placebo-controlled trials in schizophrenia, provided that appropriate precautions are taken.

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The use of placebo control in clinical trials is associated with ethical problems, especially in cases where effective treatment is available and where progressive disease involves potential deterioration that is likely to be irreversible.1 2 Yet, in Europe, granting a license for the indication of schizophrenia depends on demonstration of efficacy in comparison “in principle” with placebo.3

The lifetime risk of suicide in patients with schizophrenia is 10%4 and that for suicide attempt is 20% to 40%.5 Therefore, there is concern that in placebo-controlled studies, patients in the placebo condition might run an increased risk of committing suicide. In addition to all of the other controversial issues concerning the use of placebo, this might be considered an additional ethical argument against the use of placebo in studies of schizophrenia.

Khan et al6 recently showed that the incidence of suicide and attempted suicide did not differ among the placebo and drug-treated groups. The information used in their study was derived from the public domain data of Food and Drug Administration-reviewed studies for risperidone, olanzapine, and quetiapine fumarate. This database, however, was heterogeneous, including, for example, controlled studies without a placebo arm and open studies. Moreover, the database provided only limited information on suicide attempts. The objectives of our study were to investigate whether the conclusions of the study by Khan et al could be confirmed in a larger data set of placebo-controlled studies only and to provide information on both suicide and attempted suicide.

METHODS

DESIGN

All double-blind placebo-controlled studies (dose-finding studies and 2-armed and 3-armed...
studies) that were part of a registration dossier for the indication schizophrenia and that were submitted to the Medicines Evaluation Board of the Netherlands (MEB) during the years 1992 through 2002 (in 1992 the first “atypical” antipsychotic compound was submitted to the MEB) were reviewed for committed and attempted suicides.

THE MEB

The MEB is the regulatory authority of the Netherlands. To obtain a marketing authorization, pharmaceutical companies are required to submit a dossier to the MEB that includes all clinical trials conducted for a drug under development.

Pharmaceutical companies are required to report in their registration dossiers all efficacy and safety results, including suicides and attempted suicides.7 These dossiers contain studies that may have been published as well as studies that will never be published. The decision of whether to grant a market authorization to a given product is based on the assessment of the complete dossier.

ASSESSMENT

The material from the MEB dossiers was selected from the original studies submitted by the companies. All suicides and suicide attempts that occurred during or shortly after the placebo-controlled phase (as defined in the individual study protocols) of these studies were considered as cases. The a priori definition of suicide and suicide attempt in this investigation was the definition used in the studies submitted to the MEB.

Because the dossiers submitted to the MEB are confidential and are the property of the pharmaceutical companies, the dossiers were made anonymous.

DATA ANALYSIS

Analyses were based on the intention-to-treat population, including all patients who were randomized. The incidence of suicide and suicide attempts was estimated on the basis of person-years at risk (ie, the cumulative time that patients were enrolled in the different studies in either placebo or active compound group and hence at risk to attempt or commit suicide during the study). The significance of the difference in incidence of suicide and attempted suicide between placebo and active control groups was calculated with a Poisson regression using the likelihood ratio statistic.

RESULTS

SAMPLE CHARACTERISTICS

A total of 7 dossiers were submitted to the MEB for the indication schizophrenia during the period under investigation. Although not all compounds are (yet) on the market, they all demonstrated efficacy in the population in which they were tested.

The 7 files contained 31 double-blind, placebo-controlled studies conducted in 7152 patients: 1888 in placebo groups contributing 398.2 person-years and 5264 in active compound groups contributing 981.3 person-years. The size of the active compound group was almost 3 times the size of the placebo group because most studies contained several active compound arms.

In 12 studies at least 1 haloperidol arm was included in the study, and in 1 study an atypical compound was used as comparator.

In all 31 studies DSM criteria were used: in 3 studies DSM-III criteria,8 in 21 studies DSM-III-R criteria,9 in 2 studies DSM-III-R/DSM-IV criteria,10 and in 5 studies DSM-IV criteria. In 20 studies a pure schizophrenic population was included (n = 4792); in 10 studies a mixed population of schizophrenic and schizoaffective patients (n = 2333), and in 1 study also patients with a schizotypal personality disorder (n = 27) were included. Four studies were conducted in patients with predominantly negative symptoms (n = 514).

In 23 studies only patients who were hospitalized at the start of the study were included (n = 6326). Three studies were conducted in outpatients (n = 94) and 2 studies in a mixed population (n = 269). In 3 studies the setting was not mentioned explicitly (n = 463).

In 18 studies suicidal patients were excluded at baseline (n = 3759). In the other 7 studies suicidal patients were not explicitly excluded (n = 1457). In 6 studies it could not be determined (n = 1936).

In the 18 studies that excluded suicidal patients, “suicide risk” was determined by the clinician at entry of the study. The different protocols used different words for suicide risk. Expressions like “patients at suicidal risk,” “any suicidal attempt within the previous year,” “judged by the investigator to have imminent risk of suicide,” “serious suicidal threats or behavior within 1 year of trial enrollment,” and “violent, suicidal, or serious suicidal ideation in the opinion of the investigator” were used as exclusion criteria for suicide risk.

COMPLETED SUICIDES

All suicides occurred in studies with a duration of less than 9 weeks conducted in hospitalized, schizophrenic patients where suicidal patients were excluded explicitly in the protocol. The Table shows that 1 patient committed suicide in the combined placebo group (0.05% of the total number of patients, or an incidence rate of 251 per 100000 years of exposure) and 1 in the combined active compound groups (0.02% of the total number of patients or an incidence rate of 102 per 100000 years of exposure). The difference between the 2 incidence rates was not significant (likelihood ratio test, 0.394; df = 1; P = .53). The patient in the active treatment group committed suicide less than a week after starting the study drug. The investigator judged this death to be unrelated to the study drug and attributed it to preexisting depression. No detailed information was provided about the suicide in the placebo group.

One patient randomized to an active compound committed suicide more than 30 days after the end of the study. Another patient in the placebo group committed suicide 7 days after completing the study. This patient was doing well clinically and was prescribed active treatment and discharged from the hospital. The patient, however, did not fill the prescription. When these patients were included in the analysis, the difference in the incidence rate of suicide between the active compound and placebo remained nonsignificant (likelihood ratio test, 0.787; df = 1; P = .38).

Not included in the analyses was 1 patient with an attempted suicide after 3 days in the placebo single-
blind period, ie, before randomization. This patient de-compensated during this period with concurrent medication including chloral hydrate and lorazepam.

**SUICIDE ATTEMPTS**

All 13 attempted suicides occurred in patients who were hospitalized at the start of the study. Nine of them occurred in studies with a pure schizophrenic population, and 5 occurred in studies where suicidal patients were excluded at baseline. There were 2 attempted suicides in the placebo groups (0.11%, or an incidence rate of 502 per 100,000 years of exposure) and 11 in the active compound groups (0.21%, or an incidence rate of 1,121 per 100,000 years of exposure). The difference between the 2 incidence rates was not statistically significant (likelihood ratio test, 1.30; $df = 1; P = .25$).

**EXCLUSION OF SUICIDAL PATIENTS**

The 2 completed suicides occurred in studies with explicit exclusion criteria for patients with suicide risk. The suicide attempts were divided almost equally between studies that excluded suicide risk (4 cases in 586.7 person-years in the active compound groups and 1 case in 218.9 person-years in the placebo groups) and studies that did not (4 cases in 201.1 person-years in the active compound groups and 0 cases in 61.7 person-years in the placebo groups), indicating that the application of explicit exclusion rules for suicidal patients may not be related to the risk of suicide attempts in the placebo condition.

### COMMENT

The results presented in this article indicate that the incidence of suicide and attempted suicide in placebo-treated patients with schizophrenia does not differ significantly from the incidence in patients who were treated with active compounds under the conditions of the trials. Although these findings are counterintuitive, they are compatible with similar findings from antidepressant clinical trials.11,12

The period after giving consent and before randomization, when patients are treated with placebo single-blind, is presumed to be a high-risk period for suicide and/or suicide attempt, as medication is withheld. However, in the studies presented herein, this period was not characterized by suicides or a high incidence of attempted suicide. We excluded a priori this period and the period after the trial, as these periods are not part of the placebo-controlled phase. Moreover, the inclusion in the analysis of the 2 suicides that occurred after the completion of the study did not affect our findings.

The studies included in our investigation are part of registration files. As some studies are not submitted to the MEB (eg, because a company decided to stop further development of the drug), our investigation did not cover all studies conducted in the period of 1992 to 2002. However, “negative” studies and new studies that have not yet been published were available in the current database. Therefore, this information is not likely to be affected by publication bias and is hence adequate to address the current research question.

Studies with a longer duration might have a higher probability of suicides and/or suicide attempts in the placebo group, as the patients randomized to the placebo group have active treatment withheld longer. However, all suicides and attempted suicides occurred in short-term studies with a duration of less than 9 weeks. It should be noted, however, that only a limited number of placebo-controlled studies with a duration longer than 8 weeks have been conducted.

All suicides and most of the suicide attempts took place in a pure schizophrenic patient population. This result, however, does not mean that the schizophrenic patient population is more at risk than the schizoaffective population in placebo-controlled studies, since only a very limited number of patients with schizoaffective disorder were included in the studies. No suicides and no attempted suicides occurred in studies with patients with predominantly negative symptoms. This is consistent with the literature.13

In the outpatient studies, no suicides or attempted suicides occurred. However, most studies were conducted in patients who were hospitalized at the start of the study. Because there were only 3 studies conducted in outpatients, with few patients included, a comparison between inpatient studies and outpatient studies on suicides and attempted suicides is not possible.

The incidence rate for suicide in the general population is about 11 per 100,000 per year in the United States.14 In our study, the incidence of suicides was much higher but was considerably lower in both treatment groups compared with the incidence found by an earlier study.6 This relatively low rate of suicides might be ex-

### Placebo-Controlled Studies (Schizophrenia) in the MEB Database (1992-2002)

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<th>Active Compound</th>
<th>Placebo</th>
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<td>5264</td>
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<td>2 (0.11)</td>
<td>11 (0.21)</td>
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</table>

Abbreviation: MEB, Medicines Evaluation Board.
plained by the clinical observation that clinicians try to exclude patients with suicidal risk from randomized placebo-controlled trials whether or not this exclusion is explicitly mentioned in the protocol.

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