Dropout Rates in Placebo-Controlled and Active-Control Clinical Trials of Antipsychotic Drugs

A Meta-analysis

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Context: Dropout rates in randomized clinical trials of antipsychotic drugs have consistently been reported to be high, and the use of a placebo-controlled design is hypothesized to be one of the reasons for this.

Objective: To investigate this hypothesis in a meta-analysis of available data from pertinent clinical trials.

Data Sources: Comprehensive search of PubMed- and MEDLINE-listed journals.

Study Selection: Double-blind randomized controlled clinical trials of the second-generation antipsychotics risperidone, olanzapine, quetiapine, amisulpride, ziprasidone, and aripiprazole meeting the following criteria: unselected patient population with a diagnosis of schizophrenia or schizoaffective disorder, change in psychopathologic symptoms as the primary end point, and trial duration of 12 weeks or less.

Data Extraction: Sample size, mean age, baseline disease severity, dropout rate, trial design, trial duration, and publication year.

Data Synthesis: Thirty-one trials meeting the inclusion criteria were found, comprising 10,058 subjects. Weighted mean dropout rates in the active treatment arms were significantly higher in placebo-controlled trials (PCTs) than in active-control trials: 48.1% (PCTs) vs 28.3% (active-control trials) for second-generation antipsychotics (odds ratio, 2.34; 95% confidence interval, 1.58-3.47) and 55.4% (PCTs) vs 37.2% (active-control trials) for classical antipsychotics (odds ratio, 2.10; 95% confidence interval, 1.29-3.40). Within PCTs, attrition rates were significantly higher in the placebo arms than with second-generation antipsychotics (60.2% vs 48.1%; odds ratio, 1.63; 95% confidence interval, 1.37-1.94). Within the subset of trials in which both second-generation and classical antipsychotics were used, dropout rates were significantly higher with classical antipsychotics.

Conclusions: Use of a placebo-controlled design had a major effect on the dropout rates observed. Because high dropout rates affect the generalizability of such studies, it is suggested that, in addition to the PCTs, studies with alternative designs need to be considered when evaluating an antipsychotic’s clinical profile.

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out rate of 33%. Even higher attrition rates have been reported by other authors, namely, 42% in an investigation by Cramer and Rosenheck.12 High dropout rates give rise to considerable problems concerning the generalizability of results obtained from randomized clinical trials (RCTs). Although various statistical methods to adjust for an attrition bias have been developed, such “corrections” build on additional hypothetical assumptions regarding the dropout process.13 Therefore, they at best may be regarded as rough approximations of the unbiased estimate of effect size that one would have obtained in the case of no attrition.

It is interesting to know whether the use of placebo affects the dropout rate in a double-blind RCT. There are 2 ways in which this may happen. First, attrition may be higher in the placebo arm than in the active treatment arm of a PCT because of the lack of efficacy of placebo, causing patients to leave the study prematurely. Second, the attrition rate might be higher not only in the placebo arm but also in the active treatment arm of a PCT, compared with an active-control trial (ACT) using the same treatment. An obvious reason for this could be that because of the blinding the physician responsible for the patient shows increased unease if a placebo arm is included and may be more inclined to withdraw patients from the trial early.

The first of the 2 problems was studied in the meta-analysis by Wahlbeck et al,11 who found that the chance of dropping out was higher for patients treated with placebo than for those treated with new or classical antipsychotics. Similar findings were obtained in large meta-analyses by Geddes et al14 and by Leucht et al.15 However, these authors did not consider the second problem, namely, potential differences in attrition rates between the active treatment arms in PCTs and ACTs. This problem was addressed by Labelle et al16 in a review of 5 PCTs and 3 ACTs of second-generation antipsychotics. Apart from a significantly higher attrition rate in PCTs in general, the authors found that at a trend level the proportion of dropouts was also higher in the active treatment arm of the PCTs compared with the ACTs.

We performed a meta-analysis to address this problem. We pursued the following 2 research questions, with the main emphasis lying on the first: (1) Is the dropout rate in the active treatment arm of an RCT of antipsychotics higher in PCTs than in trials with an active comparator? (2) Do the dropout rates in the placebo and the active treatment arms differ within trials, and are there differences in the dropout rates between second-generation and classical antipsychotics when studied in the same trial?

### METHODS

#### SELECTION OF TRIALS

Trial reports were retrieved by an extensive literature search (PubMed and MEDLINE). Included in the analysis were all double-blind randomized controlled clinical trials of the second-generation antipsychotics risperidone, olanzapine, quetiapine, amisulpride, ziprasidone, and aripiprazole published before October 2004 fulfilling the following criteria (clozapine trials were excluded because they have exclusively studied treatment-resistant patients and therefore reflect a different population):

1. The primary outcome criterion was treatment efficacy in terms of reduction of psychopathologic symptoms, assessed by the Brief Psychiatric Rating Scale (BPRS)17 or the Positive and Negative Syndrome Scale.18 Trials focusing mainly on 1 or several subcriteria, such as negative symptoms or cognitive functioning, were excluded.

2. The patient population consisted of patients with schizophrenia (acute or chronic). Trials with a mixed population of patients with schizophrenia and schizoaffective disorder were also included. Trials focusing only on a subgroup of schizophrenia patients, for example, only patients with schizoaffective disorder, were excluded.

3. Trials had to be short or medium term, with a duration of 4 to 12 weeks.

4. Regarding sample size, only weak restrictions were made, because the statistical analysis method that was used down-weights small trials. However, trials with a total sample size of fewer than 40 participants were excluded. Such studies with obvious power deficiencies are more likely to get published if they show significant group differences. To reduce the potential effect of such a publication bias, exclusion of these trials seemed advisable.

5. Trials had to be published in a PubMed- or MEDLINE-listed journal.

In total, 31 trials10-44 met the inclusion criteria. An overview of these is given in Table 1. All were double-blind randomized multicenter trials using placebo (11 trials) or an active-control antipsychotic (20 trials). Haloperidol was used as the active-control treatment in 12 ACTs; perphenazine, zuclopenthixol, chlorpromazine, and flupentixol were used in 1 ACT each; and second-generation antipsychotics were used as active comparators in 4 ACTs. Five of the PCTs included an arm with a classical antipsychotic (always haloperidol) in addition to the novel antipsychotic arm, and 1 PCT used a second-generation antipsychotic (risperidone) as an additional comparator treatment. In 14 of the trials (10 PCTs and 4 ACTs), multiple dosages of the novel antipsychotic were used.

#### DATA ACQUISITION

The following was obtained for each trial, using the information given in the published study reports: the number of patients randomized to the different treatment arms, the total number of dropouts in the individual treatment arms, and the number of patients dropping out because of lack of efficacy. In 2 of the studies,20,31 the dropout rates were only reported as percentages rounded to the nearest integer number. In these 2 instances, the numbers of dropouts in the individual treatment arms were estimated from the given percentages, and these numbers may differ from the correct ones by ±1. In addition, the patients’ mean age, disease severity (measured by the mean BPRS or Positive and Negative Syndrome Scale score at baseline), trial duration, year of publication (as an approximation of the year in which the study was conducted, which was unavailable for about half of the studies), and geographic area in which the trial was conducted (United States or Canada vs Europe or other countries) were recorded. Because disease severity had been assessed by the BPRS in most studies and Positive and Negative Syndrome Scale–derived BPRS scores were available from several other studies, the BPRS was used as the measure of disease severity in the meta-analysis. In trials that used 0 to 6 scoring, the reported BPRS total score was adapted to 1 to 7 scoring. Regarding trial duration, the actual duration for an individual
patient may differ from the targeted trial duration. Although the former measure would be of significant interest, we could not make use of it because few studies provide relevant data. Concerning the geographic area, the problem arose that, because of different attitudes toward PCTs held by clinical researchers in Europe and the United States, many clinical trials of antipsychotics performed in the United States use a placebo arm. The strong confounding of the trial design (PCT vs ACT) with the geographic area constrains the separability of the 2 factors in a statistical analysis.

**STATISTICAL ANALYSIS**

All statistical analyses were carried out using a random-effects linear model approach for meta-analysis (meta-regression) as suggested by Berkey et al and by Brockwell and Gordon. The individual trials were considered as the units in this analysis. The following analyses were carried out twice, once for all dropouts (irrespective of the cause of study withdrawal) and once for dropouts because of lack of efficacy.

### Comparison of Dropout Rates During Active Treatment in ACTs and PCTs

In a first step, the active treatment arms of the same drug within a trial were pooled if several such arms with different dosing regimens existed. The dropout rates were then transformed into log odds, as this is the more natural scale for ratios, as follows: \( \log\left(\frac{\text{dropout rate}}{1 - \text{dropout rate}}\right) \). Log odds were used as the dependent variable in the meta-regression analyses, which were performed separately for second-generation and classical antipsychotics. The type of study (PCT vs ACT) was the independent variable of primary interest and was therefore entered into the model first. To assess the effect of covariates and to adjust for them if necessary, these were added to the model and tested for significance. To keep the number of independent variables at a minimum, only 1 covariate was entered at a time and only significant covariates were kept. Covariates considered were year of publication, duration of the study, multiple dosages (yes or no), mean patient age, and mean BPRS score at baseline.

#### Table 1. Overview of the Trials

<table>
<thead>
<tr>
<th>Trial No./Location/Duration, wk</th>
<th>Treatments</th>
<th>Sample Size</th>
<th>Second-Generation</th>
<th>Classical</th>
<th>Placebo</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antipsychotics</td>
<td>Antipsychotics</td>
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<tr>
<td>Placebo-Controlled Trials</td>
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</tr>
<tr>
<td>1/US/8</td>
<td>Risperidone, haloperidol, placebo</td>
<td>135 (92, 21, 22)</td>
<td>39.1</td>
<td>61.9</td>
<td>72.7</td>
<td>Chouinard et al, 1993</td>
</tr>
<tr>
<td>2/US/8</td>
<td>Risperidone, haloperidol, placebo</td>
<td>388 (256, 66, 66)</td>
<td>47.7</td>
<td>58</td>
<td>68</td>
<td>Marder and McIlhamb, 1994</td>
</tr>
<tr>
<td>3/US/6</td>
<td>Olanzapine, haloperidol, placebo</td>
<td>335 (198, 69, 68)</td>
<td>56.1</td>
<td>56.5</td>
<td>67.6</td>
<td>Beasley et al, 1996</td>
</tr>
<tr>
<td>4/US/6</td>
<td>Olanzapine, placebo</td>
<td>152 (102, 50)</td>
<td>69.1</td>
<td>...</td>
<td>80.0</td>
<td>Beasley et al, 1996</td>
</tr>
<tr>
<td>5/US/6</td>
<td>Quetiapine, placebo</td>
<td>109 (54, 55)</td>
<td>48.1</td>
<td>...</td>
<td>60.0</td>
<td>Borison et al, 1996</td>
</tr>
<tr>
<td>6/US and EU/6</td>
<td>Quetiapine, placebo</td>
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<td>59.4</td>
<td>Small et al, 1997</td>
</tr>
<tr>
<td>7/US/6</td>
<td>Quetiapine, haloperidol, placebo</td>
<td>361 (258, 52, 51)</td>
<td>55.4</td>
<td>65.4</td>
<td>68.6</td>
<td>Arvanitis et al, 1997</td>
</tr>
<tr>
<td>8/US/4</td>
<td>Ziprasidone, placebo</td>
<td>139 (91, 48)</td>
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<td>50.0</td>
<td>Kee et al, 1998</td>
</tr>
<tr>
<td>9/US/6</td>
<td>Ziprasidone, placebo</td>
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<td>51.1</td>
<td>Daniel et al, 1999</td>
</tr>
<tr>
<td>10/US/4</td>
<td>Aripiprazole, haloperidol, placebo</td>
<td>414 (204, 104, 106)</td>
<td>37.3</td>
<td>40.4</td>
<td>45.3</td>
<td>Kane et al, 2002</td>
</tr>
<tr>
<td>11/US/4</td>
<td>Aripiprazole, risperidone, placebo</td>
<td>404 (202, 99, 103)</td>
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<td>49.5</td>
<td>Potkin et al, 2003</td>
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<td>Active-Control Trials</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/EU and other/12</td>
<td>Risperidone, haloperidol</td>
<td>42 (21, 21)</td>
<td>4.8</td>
<td>23.8</td>
<td>...</td>
<td>Claus et al, 1992</td>
</tr>
<tr>
<td>13/EU and other/8</td>
<td>Risperidone, perphenazine</td>
<td>107 (55, 52)</td>
<td>25.5</td>
<td>28.8</td>
<td>...</td>
<td>Hoyberg et al, 1993</td>
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<tr>
<td>14/EU and other/8</td>
<td>Risperidone, haloperidol</td>
<td>62 (31, 31)</td>
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<td>...</td>
<td>Ceskova and Svestka, 1993</td>
</tr>
<tr>
<td>15/EU and other/8</td>
<td>Risperidone, haloperidol</td>
<td>1362 (1136, 226)</td>
<td>24.6</td>
<td>28.0</td>
<td>...</td>
<td>Peuskens, 1995</td>
</tr>
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<td>16/EU and other/6</td>
<td>Risperidone, zuclopenthixol</td>
<td>98 (48, 50)</td>
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<td>...</td>
<td>Huttunen et al, 1995</td>
</tr>
<tr>
<td>17/US and EU/6</td>
<td>Olanzapine, haloperidol</td>
<td>1996 (1336, 660)</td>
<td>33.5</td>
<td>53.2</td>
<td>...</td>
<td>Tollefson et al, 1997</td>
</tr>
<tr>
<td>18/EU and other/6</td>
<td>Olanzapine, haloperidol</td>
<td>431 (350, 81)</td>
<td>41.7</td>
<td>46.9</td>
<td>...</td>
<td>Beasley et al, 1997</td>
</tr>
<tr>
<td>19/EU and other/6</td>
<td>Amisulpride, haloperidol</td>
<td>191 (95, 96)</td>
<td>26.3</td>
<td>40.6</td>
<td>...</td>
<td>Möller et al, 1997</td>
</tr>
<tr>
<td>20/EU and other/6</td>
<td>Quetiapine, chlorpromazine</td>
<td>201 (101, 100)</td>
<td>30.7</td>
<td>36.0</td>
<td>...</td>
<td>Peuskens and Link, 1997</td>
</tr>
<tr>
<td>21/US/4</td>
<td>Ziprasidone, placebo</td>
<td>90 (73, 17)</td>
<td>52.1</td>
<td>...</td>
<td>47.1</td>
<td>Goff et al, 1998</td>
</tr>
<tr>
<td>22/EU and other/4</td>
<td>Amisulpride, haloperidol</td>
<td>319 (255, 64)</td>
<td>23.9</td>
<td>32.8</td>
<td>...</td>
<td>Puech et al, 1998</td>
</tr>
<tr>
<td>23/EU and other/6</td>
<td>Amisulpride, flupentixol</td>
<td>132 (70, 62)</td>
<td>27.1</td>
<td>40.3</td>
<td>...</td>
<td>Wetzel et al, 1998</td>
</tr>
<tr>
<td>24/EU and other/8</td>
<td>Amisulpride, risperidone</td>
<td>228 (115, 113)</td>
<td>30.3</td>
<td>...</td>
<td>40.0</td>
<td>Peuskens et al, 1999</td>
</tr>
<tr>
<td>25/EU and other/6</td>
<td>Risperidone, haloperidol</td>
<td>183 (99, 84)</td>
<td>20.2</td>
<td>31.0</td>
<td>...</td>
<td>Emsley et al, 1999</td>
</tr>
<tr>
<td>26/US/6</td>
<td>Quetiapine, haloperidol</td>
<td>448 (221, 227)</td>
<td>31.2</td>
<td>35.2</td>
<td>...</td>
<td>Copolov et al, 2000</td>
</tr>
<tr>
<td>27/EU and other/8</td>
<td>Risperidone, olanzapine</td>
<td>377 (188, 189)</td>
<td>25.5</td>
<td>...</td>
<td>33.7</td>
<td>Conley and Mahmoud, 2001</td>
</tr>
<tr>
<td>28/US/4</td>
<td>Olanzapine, haloperidol</td>
<td>182 (93, 89)</td>
<td>19.3</td>
<td>34.7</td>
<td>...</td>
<td>Ishigooka et al, 2001</td>
</tr>
<tr>
<td>29/US and EU/6</td>
<td>Amisulpride, risperidone</td>
<td>48 (23, 25)</td>
<td>6.3</td>
<td>...</td>
<td>66.0</td>
<td>Hwang et al, 2003</td>
</tr>
<tr>
<td>30/US and EU/12</td>
<td>Olanzapine, haloperidol</td>
<td>263 (131, 132)</td>
<td>32.8</td>
<td>46.2</td>
<td>...</td>
<td>Lieberman et al, 2003</td>
</tr>
<tr>
<td>31/US/6</td>
<td>Ziprasidone, olanzapine</td>
<td>273 (136, 137)</td>
<td>42.1</td>
<td>...</td>
<td>49.5</td>
<td>Simpson et al, 2004</td>
</tr>
</tbody>
</table>

Abbreviations: EU and other, Europe and/or other countries; US, United States or Canada; US and EU, United States and Europe.

*The numbers in parentheses refer to the treatment arms (listed in the same order as in column 2).*
psychotic” as a categorical variable (antipsychotics for which only ACTs or only PCTs existed were grouped into a single category of “others”).

Comparison of Dropout Rates With Placebo, Second-Generation Antipsychotics, and Classical Antipsychotics Within Trials

As in the previous paragraph, the dropout rates were pooled if several arms of the same drug with different dosages existed; these rates were then transformed into log odd ratios. To compare the types of treatment (eg, second-generation antipsychotic vs placebo) with respect to the dropout rates, log odds ratios (ORs) of the 2 dropout rates involved were calculated for each individual trial, and random-effects meta-analyses based on these were conducted using the same meta-regression approach as in the previous paragraph. Statistical inference regarding the type of treatment can then be obtained from the constant in the model, as the null hypothesis of no effect of treatment type is equivalent to constant = 0. The effect of covariates was studied in the same way as in the previous paragraph.

RESULTS

DESCRIPTIVE STATISTICS

The 31 trials constituted a total sample size of 10,058 subjects. The trial duration ranged from 4 to 12 weeks (median, 6 weeks), and sample sizes varied from 42 to 1996 patients. Ten of the 11 PCTs were conducted in North America (United States or Canada), and 1 was a joint European and US study. Conversely, 13 of the 20 ACTs were carried out outside the United States (12 in Europe, sometimes including centers in other parts of the world, and 3 in other countries); only 3 ACTs were conducted in the United States, and another 2 ACTs were joint studies by US and European centers. The dropout rates showed a wide spread between trials and study arms, ranging from 0.0% to 69.1% (weighted mean, 35.5%) for second-generation antipsychotics, from 9.7% to 65.4% (weighted mean, 41.2%) for classical antipsychotics, and from 43.3% to 80.0% (weighted mean, 60.2%) for the placebo arms.

DROPOUT RATES DURING ACTIVE TREATMENT IN ACTS AND PCTS

Results concerning the comparison of dropout rates during active treatment in ACTs and PCTs are summarized in Table 2. With novel and classical antipsychotics, the attrition rates found in PCTs were substantially higher than those observed in ACTs, attaining high levels of statistical significance (P < .005 for all). The difference between the mean attrition rates in PCTs and ACTs reached approximately 20 percentage points (eg, 48.1% for second-generation antipsychotics in PCTs and 28.3% for second-generation antipsychotics in ACTs), or, equivalently, ORs of about 2.1 to 2.3. Omission of the 3 smallest trials, which were also those trials with the lowest dropout rates, changed the results only slightly, with a 1% to 2% increase in weighted mean attrition rates in ACTs.

DROPOUT RATES IN ACTIVE TREATMENT ARMS AND PLACEBO ARMS

A comparison of the dropout rates in the active treatment arms and placebo arms within PCTs is given in Table 3. In the 11 trials in which second-generation antipsychotics were compared with placebo, dropouts were more common in the placebo arms, resulting in an OR of 1.63 (P < .001). Similar findings were obtained for classical antipsychotics compared with placebo (significantly higher attrition rates in the placebo arms, P = .03).

<table>
<thead>
<tr>
<th>Table 2. Comparison of Dropout Rates in Active Treatment Arms of Placebo-Controlled Trials (PCTs) and Active-Control Trials (ACTs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Active Treatment</td>
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<tr>
<td>---</td>
</tr>
<tr>
<td>Second-generation antipsychotic</td>
</tr>
<tr>
<td>Classical antipsychotic</td>
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<tr>
<td>All antipsychotics</td>
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</tbody>
</table>

*Weighted mean using the weights of the random-effects meta-regression.

<table>
<thead>
<tr>
<th>Table 3. Comparison of Dropout Rates in Placebo-Controlled Trials (PCTs) With Placebo Arms and With Active Treatment Arms</th>
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<tbody>
<tr>
<td>Type of Antipsychotic</td>
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<td>Second-generation antipsychotic</td>
</tr>
<tr>
<td>Classical antipsychotic</td>
</tr>
<tr>
<td>All antipsychotics</td>
</tr>
</tbody>
</table>

*Weighted mean using the same weights as in Table 2.
†Weighted mean dropout rate for the placebo arms of the 5 PCTs that included an arm with a classical antipsychotic.
A comparison of the ORs in Tables 2 and 3 indicates that the differences in the dropout rates between PCTs and ACTs (considering only active treatment arms) were considerably larger than those between placebo and active treatment within PCTs. This is also shown in the Figure.

### DROP OUT RATES WITH SECOND-GENERATION AND CLASSICAL ANTIPSYCHOTICS

A comparison of second-generation and classical antipsychotics in those trials (PCTs and ACTs) in which both types of antipsychotics were used showed that attrition was significantly higher with classical antipsychotics (42.7% vs 32.4%; OR, 1.51; 95% confidence interval, 1.32-1.73; t\_19=6.43, P<.001). There was no indication that this pattern was different for ACTs and PCTs. The difference in attrition rates between the 2 types of antipsychotics was mainly due to higher numbers of dropouts because of adverse events in patients treated with classical antipsychotics (11.6% vs 5.8%; OR, 2.14; 95% confidence interval, 1.63-2.80; t\_19=5.91, P<.001). The dropout rates because of lack of efficacy were not significantly different between the 2 types of antipsychotics.

### INVESTIGATION OF COVARIATES

None of the sample characteristics (patients’ mean age or mean baseline BPRS score) or study characteristics (targeted trial duration, use of multiple-dosage regimens or publication year) considered had a statistically significant effect on attrition rates in active treatment arms. The only factor found to affect patient dropout significantly was the type of second-generation antipsychotic. The overall F test indicated heterogeneity of the dropout rates among the individual second-generation antipsychotics (F\_4,25=2.79, P=.048), and post hoc pairwise comparisons revealed a higher chance of dropout with olanzapine compared with risperidone (OR, 1.85; 95% confidence interval, 1.11-3.08; t\_19=2.55, P=.02). Adjustment for the publication year did not essentially change this finding. However, because this meta-analysis included few trials of the newer second-generation antipsychotics quetiapine, amisulpride, ziprasidone, and aripiprazole and because the type of medication was the only significant predictor variable of 7, these findings should be interpreted with caution. Regarding the ORs between the dropout rates in the placebo arm and the active treatment arms within PCTs, none of the covariates was found to be a significant predictor in the meta-regression analysis.

### DROP OUT RATES BECAUSE OF LACK OF EFFICACY

Similar results were obtained when considering only dropouts because of lack of efficacy. Again, the dropout rates in active treatment arms were significantly higher in PCTs than in ACTs, for second-generation antipsychotics (weighted mean dropout rate of 25.8% in PCTs vs 10.2% in ACTs; OR, 3.09; 95% confidence interval, 1.76-5.41; P<.001) and for classical antipsychotics (weighted mean dropout rate of 28.0% in PCTs vs 12.1% in ACTs; OR, 2.84; 95% confidence interval, 1.73-4.61; P<.001). There was no indication that this pattern was different for ACTs and PCTs. The overall F test indicated heterogeneity of the dropout rates among the type of second-generation antipsychotic. The overall F test indicated heterogeneity of the dropout rates among the type of second-generation antipsychotic. The overall F test indicated heterogeneity of the dropout rates among the type of second-generation antipsychotic. The overall F test indicated heterogeneity of the dropout rates among the type of second-generation antipsychotic. The overall F test indicated heterogeneity of the dropout rates among the type of second-generation antipsychotic.

### COMMENT

The present meta-analysis of dropout rates in PCTs and ACTs of antipsychotics yielded the following main result: For the trials investigated, the dropout rates not only depended on the type of medication (second-generation antipsychotics vs classical antipsychotics vs placebo) but also on the trial design, ACT vs PCT. Regarding the type of medication, we found, in line with other investigators, that the dropout rates in RCTs of antipsychotics tend to be higher in the placebo
arms than in the active treatment arms, particularly if second-generation antipsychotics are used. Moreover, we found lower dropout rates with second-generation antipsychotics than with classical antipsychotics, which has been shown previously by Wahlbeck et al.11

With regard to our primary finding of the effect of the trial design on attrition, our meta-analysis showed that attrition rates were substantially higher in the active treatment arms of PCTs compared with ACTs. This effect of the trial design on patient dropout was considerably larger than the effect of the type of medication described in the previous paragraph. While there was an approximately 10% mean difference between the dropout rates in the placebo and active treatment arms, the difference in the dropout rates between the 2 trial designs studied, ACT and PCT, reached almost twice this amount (Tables 2 and 3).

Before discussing the implications of this finding, we want to address an important methodological point. In contrast to several other meta-analyses that are based on all RCTs suitable for the research problem investigated (eg, Wahlbeck et al11 and Davis et al12), we imposed more restrictions on trial selection. By considering only short- and medium-term trials of second-generation antipsychotics and excluding trials that concentrate on special aspects of outcome (cognition and negative symptoms) or certain subpopulations of schizophrenia patients (eg, patients partially refractory to classical antipsychotics), we attempted to increase the homogeneity of the set of trials.

A comparison of our study with that by Labelle et al,10 the only other meta-analysis known to us dealing with the effect of the trial design (PCT vs ACT) on patient dropout in RCTs of antipsychotics, reveals similar findings despite the somewhat different conclusions proposed. In their analysis of 5 PCTs and 3 ACTs of second-generation antipsychotics and excluding trials that concentrate on special aspects of outcome (cognition and negative symptoms) or certain subpopulations of schizophrenia patients (eg, patients partially refractory to classical antipsychotics), we attempted to increase the homogeneity of the set of trials. A comparison of our study with that by Labelle et al,10 the only other meta-analysis known to us dealing with the effect of the trial design (PCT vs ACT) on patient dropout in RCTs of antipsychotics, reveals similar findings despite the somewhat different conclusions proposed. In their analysis of 5 PCTs and 3 ACTs of second-generation antipsychotics, Labelle et al10 found that, after excluding patients assigned to placebo, attrition rates in PCTs were considerably higher (47%) than in ACTs (29%). However, because this difference missed statistical significance by a narrow margin (P = .052), the authors were careful to avoid overinterpretation, thereby leaving the misleading impression that the difference in question was negligibly small. Therefore, our meta-analysis results can be regarded as an extension, rather than a contradiction, of the report by Labelle et al.

Of the covariates considered in the meta-analysis, the geographic area, type of second-generation medication, and year of publication were potentially related to the dropout rate. The geographic area (United States or Canada vs Europe or other countries) was closely linked with the trial design, because PCTs were performed almost exclusively in North America and ACTs were performed preponderantly in Europe and other countries outside the United States and Canada. This is not a particularity of the selection of trials in our study but a general phenomenon, as pointed out before. As a consequence, it is impossible to separate the effects of the trial design and the geographic area in a statistical analysis. Therefore, in principle we cannot rule out the possibility that the dropout rates may be generally higher in the United States than in other countries, which in turn may account for part of the observed large differences in attrition rates between ACTs and PCTs.

Our meta-regression analysis suggests a certain heterogeneity among the 6 second-generation antipsychotics regarding the dropout rates. Based on 19 trials involving risperidone, olanzapine, or both, significantly lower dropout rates were found with risperidone compared with olanzapine. However, because this meta-analysis was not designed to compare individual drugs and lacked power for this type of comparison, this finding should be interpreted with caution. Further research is required to explore the differences between individual drugs in greater detail. Notably, Wahlbeck et al11 also found differences between the dropout rates of individual second-generation antipsychotics. However, in their case, higher retention rates with clozapine, a drug not considered in our meta-analysis, compared with other second-generation antipsychotics were responsible for the differences.

Regarding the year of publication, we found a decreased dropout rate because of lack of efficacy over time (1992–2004), for second-generation and classical antipsychotics. One might speculate that this could be due to a cohort effect, in which patients participating in the more recent trials of antipsychotics are often chronically ill and may be partially treatment refractory. Patients who had a meaningful response to any of the newer antipsychotics may be hesitant to participate. This might lead to better retention in the more recent trials, because these patients, being fairly stable (despite an exiguous response), also have a lower tendency to drop out of a study. For the total dropout rate, such a time effect was not observed, but there was at least no indication of an increase in attrition over time. This may appear contradictory to the findings reported in the large meta-analysis by Wahlbeck et al11 describing a significant increase in attrition rates over time. However, because the latter meta-analysis encompassed a much longer time span than ours (45 vs 12 years), our finding may simply indicate that the upward trend in dropout rates observed during the past decades has plateaued.

Regarding our main finding, several reasons for the higher dropout rates in PCTs compared with ACTs appear likely. First, for physicians participating in a PCT, a higher level of alertness and worry due to the fact that 1 of the treatments used is biologically ineffective may result in an increased readiness to discontinue a patient prematurely because of the lacking efficacy. Second, considering the patients’ view, it has been shown in independent investigations that their willingness to participate in a study is negatively affected when being informed that the study is placebo controlled.13 Although patient refusal to participate in a study and patient-induced dropout are 2 distinct matters, they may well be related. Therefore, a patient with a reserved attitude toward PCTs may possibly be convinced by the treating physician to participate in such a trial but may not be prepared to endure longer periods with few or no signs of improvement. Third, the influence of nurses or significant others in such decisions must not be underestimated. These considerations may help in understanding why the dropout rates are higher in the active treatment arms of PCTs compared with ACTs.

High dropout rates entail the important problem of biased estimation of treatment effects. In particular, if attrition rates are as high as in the PCTs studied herein and...
elsewhere, with values approaching or exceeding 50%, the amount of bias may be considerable and may lead to erroneous conclusions. Lavoi²⁹ demonstrated that, by use of standard imputation methods (eg, the last observation carried forward method), estimates of treatment effects may be biased. Even if more sophisticated methods of missing value replacement (eg, multiple imputation strategies) are used, biased estimation of treatment differences remains a problem because all of these methods rely on hypothetical assumptions regarding the nature of the dropout process.

The deliberation outlined herein underscores that, although the most rigorous way to establish the efficacy of a new drug is to demonstrate its superiority over placebo (ideally in a trial using an established treatment as a reference), one has to acknowledge problems with the validity of this approach because of high attrition rates. Because other difficulties in performing PCTs have been reported, particularly regarding the willingness to participate in such a trial,⁵,¹⁰ second-best alternatives need to be contemplated. The ACT, that is, a clinical trial with 1 or several active comparators, would seem to be the most obvious alternative, once an efficacious active treatment has been established as a standard. Although the problem of biased estimation of treatment effects due to the high dropout rates is not completely solved by using ACTs, it is diminished. There are supporters⁷,⁸ and critics¹¹ of this view. From a statistical point of view, a more liberal use of ACTs would be allowed, particularly regarding inclusion criteria and are reflecting real-life treatment practice more closely.

This discussion does not imply that PCTs can be replaced by ACTs. Rather, we argue that increased use should be made of the ACT to complement the PCT. To prove the efficacy of a new drug, the following 2 results should be shown: (1) superiority over placebo, most reliably verified by a well-designed PCT (using a method of statistical analysis that takes into account a potential attrition bias)¹³,⁵⁵ and (2) noninferiority to an established standard treatment, preferably demonstrated by an ACT. Because of the risk of higher dropout rates, the use of a 3-armed PCT (new active drug, active comparator, and placebo) should not be considered equivalent to such a procedure. The trial design to be chosen in a particular situation (PCT vs ACT) depends on the research question to be answered. It also depends on balancing the methodological limitations of ACTs (noninferiority to a standard drug does not necessarily imply superiority over placebo) with the problem of compromised generalizability of study findings caused by high attrition rates as seen in PCTs.

The objective of this meta-analysis was to shed some additional light on the relationship between the use of a placebo control and the high dropout rates encountered in clinical trials of antipsychotics. It was our aim to illustrate the considerable effect the former has on the latter and to draw attention to the consequences arising for the design and interpretation of clinical trials evaluating antipsychotic drugs.

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