

# Relapse Prevention in Schizophrenia With New-Generation Antipsychotics: A Systematic Review and Exploratory Meta-Analysis of Randomized, Controlled Trials

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**Objective:** The authors performed a systematic review and meta-analysis of studies of the potential of new-generation antipsychotic drugs to improve adherence and decrease relapse rates in patients with schizophrenia.

**Method:** Randomized, controlled trials comparing new-generation antipsychotic drugs with placebo and/or conventional antipsychotics were identified. Data on relapse, general treatment failure, and dropout due to adverse events were extracted and combined in a meta-analysis.

**Results:** Because few trials were available for each individual drug, the effects of new-generation antipsychotic drugs as a group were analyzed. The analysis of six placebo comparisons, involving a total of 983 patients, clearly demonstrated that new-generation antipsychotic drugs are effective for relapse prevention. Eleven studies with a total of 2,032 patients provided

comparative data on relapse/treatment failure for new-generation and conventional antipsychotics. The analysis revealed that rates of relapse and overall treatment failure were modestly but significantly lower with the newer drugs. Whether this advantage was partly mediated by improved adherence to treatment remains unclear. No significant superiority in terms of fewer dropouts due to adverse events was found for the newer drugs. Furthermore, a number of methodological problems were identified.

**Conclusions:** Overall, the currently available data suggest that new-generation antipsychotics have the potential to reduce relapse rates. Methodological issues to be addressed in future trials include the choice of comparator, use of appropriate doses, application of clinically relevant relapse criteria, monitoring of adherence, and minimization of dropouts.

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It has been well established that maintenance treatment with antipsychotic medication decreases relapse rates (1). Despite this effect, a substantial proportion of patients either relapse despite taking medication or become nonadherent with antipsychotic treatment. Adverse events might contribute to the latter outcome (2). Given that the new, so-called “atypical” antipsychotic drugs are associated with a lower frequency of extrapyramidal side effects and have a different spectrum of receptor effects, compared with conventional antipsychotics, it was hoped that the newer medications would substantially improve treatment adherence and reduce the risk of relapse (3). Studies evaluating outcomes before and after a switch to the newer medication have shown promising results (4, 5), but interpretation of data from studies with this design must take into account the inherent bias in favor of the second drug regimen. We reviewed prospective, randomized, controlled trials of relapse prevention with new antipsychotics. Given the small number of studies of each individual atypical antipsychotic, the effects of the new antipsychotics as a group were examined. Our objec-

tives were 1) to examine the potential of the newer antipsychotic drugs to reduce relapse rates by conducting an explorative meta-analysis across different drugs and trial designs and 2) to identify and discuss methodological problems that might be of potential interest for future trials.

## Method

### Identification of Studies

Randomized, controlled trials comparing atypical with conventional antipsychotics and/or placebo in the maintenance treatment of schizophrenia and schizophrenia-like psychoses were identified. The search strategy included three steps. First, MEDLINE (1966–April 2001), Current Contents (January 2001–May 2001), and the Cochrane Schizophrenia Group's Register (last search July 2002) were searched by using the following search terms: amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone, and zotepine, as well as relapse and maintenance. Second, the reference lists of the relevant Cochrane reviews, review articles, and study reports were examined. Third, pharmaceutical companies were requested to provide the results of any relevant unpublished trials.

**TABLE 1. Randomized, Controlled Studies Comparing New-Generation Antipsychotic Medications With Placebo for the Prevention of Relapse in Schizophrenia**

Study	Number of Subjects <sup>a</sup>	Mean Age of Subjects (years)	Study Duration (weeks)	Antipsychotic and Dose (mg/day)	Selected Inclusion Criteria
Loo et al. (23)	141	34	26	Amisulpride, 100 (fixed)	Outpatient; residual or disorganized schizophrenia; predominant negative symptoms
Beasley et al. (24)	326	36	42 <sup>c</sup>	Olanzapine, 10–20	Outpatient; minimally symptomatic; negative symptoms; at least 6 weeks of stability; continued stability while taking olanzapine during an 8-week observation period
Dellva et al. study 1 (25)	58	~35	46	Olanzapine, ~12 (semifixed)	Responder from 6-week acute treatment phase (responders had at least 40% reduction in BPRS score or BPRS score ≤18); outpatient at the last visit
Dellva et al. study 2 (25)	62	~37	46	Olanzapine, ~12 (semifixed); ineffective olanzapine, 1	Responder from 6-week acute treatment phase (responders had at least 40% reduction in BPRS score or BPRS score ≤18); outpatient at the last visit
Arato et al. (26) <sup>d</sup>	277	~50	52	Ziprasidone, 40, 80, or 160 (fixed)	Lack of acute relapse, lack of treatment resistance, and living under medical supervision for at least 2 months
Cooper et al. (27)	119	~42	26	Zotepine, 150 or 300 (fixed)	Inpatient or outpatient; rating of at least mildly ill according to Clinical Global Impression; relapse in the 18 months before inclusion

<sup>a</sup> The number of patients included in the study's maintenance phase is presented.

<sup>b</sup> Not indicated.

<sup>c</sup> The study was terminated early because of the clear superiority of olanzapine.

<sup>d</sup> Sixteen patients with protocol violations from one center were excluded and were not included in results shown here or in any other result.

### Inclusion Criteria

We restricted our analysis to trials with a minimum duration of 6 months, as shorter trials were not considered adequate for a reasonable assessment of relapse prevention. Although all long-term studies were examined, only studies that reported on the main focus of this review—relapse—were included in the meta-analysis. (Other long-term trials are mentioned in the section on excluded studies.) Trials were included irrespective of whether randomization was performed during the acute phase and the relapse rates of responders were determined in a long-term extension or whether stable outpatients were randomly assigned to study groups.

### Outcome Parameters

Three outcome parameters—relapse, overall treatment failure, and dropout due to adverse events—were analyzed. Relapse was defined according to the definitions used in the individual studies. Raw relapse rates were used in the primary analysis, because it is unclear which is the best way to handle relapse rates estimated from survival curves in a meta-analysis. However, a secondary analysis was carried out by using relapse rates derived from the survival curves that were available. Overall treatment failure was defined as the total number of patients who had either relapsed or dropped out for any reason, including inefficacy of treatment that did not fulfill all criteria for relapse, adverse events, and loss to follow-up. Dropouts due to adverse events were analyzed as a measure of tolerability. A meta-analytic assessment of adherence rates was not possible because of inadequate reporting in the individual studies (see the Results section).

### Statistical Method

The outcome data from all the eligible studies were combined in a meta-analysis that used the risk difference as a measure of effect size. The risk difference (RD) and its standard error (SE) were calculated by using the following equations:  $RD = (a/n_1) - (c/n_2)$  and

$$SE = \sqrt{ab/n_1^3 + cd/n_2^3},$$

where  $a$  is the number of patients with an event in the intervention group,  $b$  is the number of patients without an event in the

intervention group,  $n_1$  is the total number of patients in the intervention group,  $c$  is the number of patients with an event in the comparison group,  $d$  is the number of patients without an event in the comparison group, and  $n_2$  is the total number of patients in the comparison group. The risk difference was used because it leads to more comparable results when outcomes with relatively low event rates (in this case, relapse) and outcomes with relatively high event rates (in this case, overall treatment failure) are analyzed. Furthermore, compared with other effect-size measures, risk difference can be more readily understood intuitively by clinicians (6). Odds ratios and relative risks are also presented. In the case of homogeneous outcomes, pooled risk differences were calculated by using the following fixed-effects model:

$$RD_{\text{pooled}} = \sum (W_i RD_i) / \sum W_i,$$

where  $W_i$  is the weight of the effect sizes of the single studies, which is calculated with the formula  $n_1 n_2 / N$ , where  $N = (n_1 + n_2)$ , and  $RD_i$  is the risk difference of the individual studies. The SE of  $RD_{\text{pooled}}$  was calculated with the formula

$$\sqrt{(P/O^2)},$$

where

$$P = \sum (abn_2^3 + cdn_1^3) / n_1 n_2 N^2 \text{ and}$$

$$O = \sum n_1 n_2 / N.$$

In the case of statistically significant heterogeneity of single trials, the random-effects model described by Der-Simonian and Laird (7) was used. In this model the assumption of a common treatment effect is relaxed, and it is assumed that the risk differences have the following distribution:  $RD_i \sim N(RD, \tau^2)$ . The estimate of  $\tau$  is given by

$$\tau^2 = \max \{ [Q - (k - 1)] / [\sum W_i - (\sum (W_i^2)) / \sum W_i], 0 \},$$

where  $Q$  is a heterogeneity statistic described later in this section,  $W_i$  is the inverse of the variance weight of the single risk differences calculated as  $1/SE(RD_i)^2$ . Then the weight for each study is calculated with the formula  $W_i^* = 1/(SE(RD_i)^2 + \tau^2)$ . The pooled

Definition of Relapse	Definition of Noncompliance	Noncompliance Rate	Dropout Rate for Reasons Other Than Relapse (%)
Withdrawal because of inefficacy of treatment and score >50 on Scale for the Assessment of Positive Symptoms	— <sup>b</sup>		50
Hospitalization for positive symptoms or ≥4 increase on BPRS positive score or increase of single BPRS item to 4 and increase from baseline ≥2	— <sup>b</sup>		26
Hospitalization for psychopathology	Noncompliance (criteria not specified) or not meeting study criteria	Olanzapine: 11%; placebo: 0%	38
Hospitalization for psychopathology	Noncompliance (criteria not specified) or not meeting study criteria	Olanzapine: 10%; placebo: 14%	53
“Impending relapse”	— <sup>b</sup>		23
1) ≥2 increase in CGI rating and ≥2 increase in two Brief Psychiatric Rating Scale (BPRS) positive items for 3 days; 2) same level of deterioration as under 1 for 24 hours and requiring hospitalization; 3) CGI rating of severely ill for 24 hours	Pill count	Zotepine: 15%; placebo: 4%	55

risk difference and its SE are calculated by using the following equations:

$$RD_{pooled} = (\sum W_i' RD_i) / (\sum W_i')$$

and

$$SE = 1 / \sqrt{\sum W_i'}.$$

The random-effects model is usually considered to be more conservative than the fixed-effects model because it takes into account the variability between studies. Therefore, homogeneous outcomes were also checked with this method to corroborate the findings, but no relevant differences were found.

Heterogeneity—i.e., whether the differences between the results of trials were greater than would be expected by chance alone—was examined by the following statistic:

$$Q = \sum W_i' (RD_i - RD_{pooled})^2,$$

where  $W_i'$  are the weights calculated as  $1/SE(RD_i)^2$ . Under the null hypothesis that there are no differences in treatment effect between trials, examination of heterogeneity uses a chi-square distribution with  $k-1$  degrees of freedom, where  $k$  is the number of studies contributing to the meta-analysis. In addition to using a random-effects model instead of a fixed model in such occasions, we conducted a sensitivity analysis and excluded the outlier studies that accounted for the significant heterogeneity. The overall test statistic is given by  $Z = RD / SE(RD)$  in all cases. Furthermore, a number-needed-to-treat (NNT) statistic was calculated in the case of significant results. NNT indicates the number of patients who need to be treated to prevent one bad outcome and was calculated as the inverse of the risk difference.

Studies with negative or nonsignificant results are less likely to be published than those with significant results. The possibility of such a publication bias, which can affect the results of a meta-analysis, was examined using the “funnel-plot” method described by Mulrow and Oxman (8). Here, the effect sizes of the individual studies are plotted against their sample sizes. When all studies that have been conducted have been published, a symmetrical figure resembling a funnel should result.

In the figures, the results are presented as (mean) effect sizes along with their 95% confidence intervals (CIs), calculated as fol-

lows:  $CI = RD - SE(RD) \Phi(0.975)$  to  $RD + SE(RD) \Phi(0.975)$ , where  $\Phi$  is the standard normal deviate. Values below 0 indicate effects favoring the new antipsychotic, and whenever the 95% CI does not cross the y axis the result is statistically significant ( $p < 0.05$ , two-tailed). All calculations were done with Review Manager 4.1 (9), a standard software for meta-analyses that is used by the Cochrane Collaboration. Other meta-analysis software programs are available. Some of them use slightly different formulas, but this does not commonly give rise to important differences in results (10).

## Results

### Excluded Studies

Several long-term, randomized, controlled trials were excluded because they did not report on relapse. More specifically, Lee et al. (11), Velligan et al. (12), and Purdon et al. (13, 14) compared the long-term effects on cognitive functions of clozapine, quetiapine, and olanzapine with those of conventional antipsychotics. The study by Hirsch et al. (15) comparing ziprasidone and haloperidol could have been included as a typical relapse prevention study with stable outpatients, but only symptom ratings were reported, with no mention of a relapse measure. Bouchard et al. (16) compared risperidone with standard treatment in a 12-month, randomized, naturalistic study and used change in Positive and Negative Syndrome Scale score as the primary outcome parameter. The 6-month trial by Kane et al. (17) compared clozapine with haloperidol in patients with treatment-resistant schizophrenia. While other long-term, randomized trials were underway at the time of the analysis, the published abstracts did not provide data on relapse (18–21). One study compared two new antipsychotics—olanzapine and risperidone (22).

**TABLE 2. Randomized, Controlled Studies Comparing New-Generation Antipsychotic Medications With Conventional Antipsychotics for the Prevention of Relapse in Schizophrenia**

Study	Number of Subjects	Mean Age of Subjects (years)	Study Duration (weeks)	Antipsychotic and Dose (mg/day)	Selected Inclusion Criteria
Colonna et al. (28)	322	~38	52	Amisulpride, 200–800; haloperidol, 5–20 (flexible)	Responder from the first 4 weeks of an acute treatment phase ( $\geq 20\%$ reduction in BPRS score)
Speller et al. (29)	60	~63	52	Amisulpride, 100–800; haloperidol, 3–20 <sup>b</sup>	Chronic, long-term hospitalized inpatient; moderate to severe negative symptoms
Essock et al. (30)	124	~40	104	Clozapine, mean=496; usual care, mean=1386 chlorpromazine equivalents	Initially hospitalized state hospital patient who could be discharged
Rosenheck et al. (31, 32)	49	— <sup>a</sup>	52	Clozapine, 100–900; haloperidol, 5–30	Initially hospitalized patient; treatment-refractory schizophrenia; 20% reduction in BPRS score after 6 weeks <sup>c</sup>
Tamminga et al. (33)	39	~36	52	Clozapine, mean=294; haloperidol, mean=29	Outpatient with tardive dyskinesia; stabilized during 1–6 months before random assignment to study group
Tran et al. study 1 (34)	55	~37	52	Olanzapine, ~12; haloperidol, ~14 (semifixed)	Responder from a 6-week acute treatment (at least 40% reduction of BPRS score or BPRS score $\leq 18$ ); outpatient at the last visit
Tran et al. study 2 (34)	62	~37	52	Olanzapine, ~12; haloperidol, ~16 (semifixed)	Responder from a 6-week acute treatment (at least 40% reduction of BPRS score or BPRS score $\leq 18$ ); outpatient at the last visit
Tran et al. study 3 (34)	690	~37	22–84	Olanzapine, 5–20 (mean=14); haloperidol, 5–20 (mean=13) (flexible)	Responder from a 6-week acute treatment (at least 40% reduction of BPRS score or BPRS score $\leq 18$ ); outpatient at the last visit
Csernansky et al. (35)	365	~40	130	Risperidone, 2–8 (mean=5); haloperidol, 5–20 (mean=12)	Outpatient; stability according to clinical judgment; receipt of the same medication for 30 days; same residence for 30 days
Marder et al. (36)	63	~43	104	Risperidone, 2–16 (mean=6); haloperidol, 2–16 (mean=5)	At least two acute episodes in last 2 years or 2 years of continuing symptoms; receipt of treatment as an outpatient for at least 1 month
Daniel et al. (37)	203	~39	52	Sertindole, 24; haloperidol, 10 (fixed)	Outpatient with medication-responsive schizophrenia; clinical stability for at least 3 months while taking an antipsychotic; Clinical Global Impression (CGI) rating $\leq 4$

<sup>a</sup> Not indicated.<sup>b</sup> A minimum effective dose strategy was followed.<sup>c</sup> An analysis of data for responders after 3 and 6 months yielded similar results.<sup>d</sup> The pooled analysis of all three olanzapine trials showed no significant superiority of olanzapine in terms of dropouts due to noncompliance/protocol violation (7% in both groups).<sup>e</sup> The primary outcome of this study was a combined measure of treatment failure; rehospitalization was used as a relapse measure in the current analysis.

### Included Studies

Table 1 and Table 2 present the main characteristics of the studies included in the meta-analysis. Altogether, 17 studies involving 3,015 participants were found: three studies of amisulpride, three of clozapine, six of olanzapine, two of risperidone, and one each of sertindole, ziprasidone, and zotepine. The participants' mean ages ranged from 34 to 63 years. Most had DSM-III-R schizophrenia, although some trials included patients with schizoaffective disorder or schizophreniform disorder. About half of the trials included relatively stable patients in order to assess relapse risk, whereas the other half followed responders from acute-phase trials. Only three studies lasted longer than 1 year (30, 35, 36). The 1-year relapse rates reported for these studies were used to allow comparability with the other trials. With the exception of trials organized by the same pharmaceutical company, each study had its own definition of relapse, although hospitalization due to an exacerbation of psychotic symp-

toms was included in most definitions of relapse. Funnel plots were drawn for all outcome parameters analyzed, but they did not suggest any obvious publication bias. However, the ability to detect a publication bias with this method, which is based on geometrical symmetry, was limited by the small number of trials identified. The existence of unpublished trials cannot be excluded.

### New Antipsychotics Versus Placebo

Six studies compared new-generation antipsychotics with placebo. All were double-blind studies, and four included outpatients (Table 1). The number of patients dropping out for reasons other than relapse was high, ranging from 23% to 55%, with a median of 44%.

**Relapse rates.** Figure 1 shows that for the individual new antipsychotic drugs a statistically significant superiority in raw relapse rates was found for olanzapine (NNT=4, 95% CI=3–6), ziprasidone (NNT=4, 95% CI=3–8), and zotepine (NNT=3, 95% CI=2–6). The use of relapse rates estimated

Definition of Relapse	Definition of Noncompliance	Noncompliance Rate	Dropout Rate for Reasons Other Than Relapse (%)
Failure to maintain $\geq 20\%$ reduction in BPRS score; withdrawal from study (treatment failure)	— <sup>a</sup>		— <sup>a</sup>
Increase of three or more BPRS positive symptom items that did not respond to a dose increase	— <sup>a</sup>	Amisulpride: <1%; haloperidol: <1%	20
Rehospitalization	— <sup>a</sup>		<10
Failure to maintain 20% reduction in BPRS score after 1 year	Pill count	n.s.	— <sup>a</sup>
Discontinuation because of decompensation	— <sup>a</sup>	Clozapine: 4%; haloperidol: 0%	18
Hospitalization for psychopathology	— <sup>a</sup>	— <sup>d</sup>	44
Hospitalization for psychopathology	— <sup>a</sup>	— <sup>d</sup>	53
Hospitalization for psychopathology	— <sup>a</sup>	— <sup>d</sup>	34
1) Hospitalization; 2) increase of level of care and 20% increase in Positive and Negative Syndrome Scale score; 3) self-injury, suicidal or homicidal ideation, violent behavior; 4) CGI rating $>6$	Pill count	Risperidone: 3%; haloperidol: 4% (n.s.)	48 (2 years)
Increase $>3$ in the sum of Brief Psychiatric Rating Scale (BPRS) scores for the thought disorder and hostile-suspiciousness clusters, or an increase $>2$ in the score for either of these clusters and a score $>3$ on at least one item of these clusters	— <sup>a</sup>		29 (1 year)
Hospitalization for schizophrenia <sup>e</sup>	— <sup>a</sup>	Sertindole: 2%; haloperidol: 12% ( $p<0.05$ )	— <sup>a</sup>

from survival curves yielded more pronounced superiorities of these new drugs (olanzapine: NNT=2, 95% CI=1.8–2.8; ziprasidone: NNT=3, 95% CI=2–4; zotepine: NNT=2, 95% CI=1.7–3.2). The only study of amisulpride that was available found no significant difference in relapse rates between amisulpride and placebo. No placebo-controlled trials of the other new antipsychotic drugs were identified.

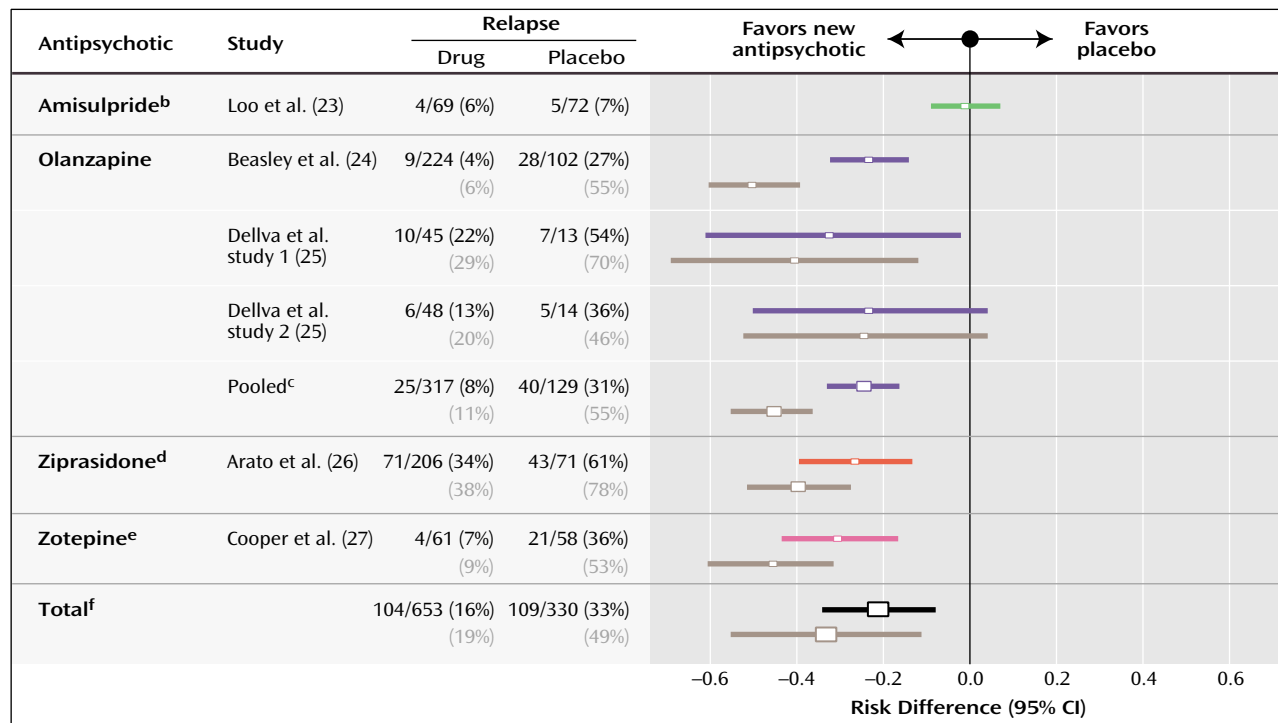
Considered as a group, the new antipsychotics were clearly and statistically significantly superior to placebo in both raw relapse rates (NNT=5, 95% CI=3–13) and relapse rates estimated from survival curves (NNT=3, 95% CI=2–9). The inclusion of the study that did not find any significant difference in relapse risks between amisulpride and placebo (23) led to statistically significant heterogeneity. In this study the relapse rate was very low in both treatment groups, perhaps because the majority of the patients in the study had residual schizophrenia and predominantly negative symptoms. When this study was excluded, the risk difference in raw relapse rates was  $-0.26$

(95% CI= $-0.32$  to  $-0.19$ ,  $z=-7.93$ ,  $p<0.00001$ , NNT=4, 95% CI=3–5; heterogeneity:  $\chi^2=0.75$ ,  $df=4$ ,  $p=0.95$ ).

**Overall treatment failure.** Figure 2 shows that all of the new antipsychotics examined were significantly superior to placebo in terms of overall treatment failure (amisulpride: NNT=4, 95% CI=3–14; olanzapine: NNT=3, 95% CI=2–4; ziprasidone: NNT=3, 95% CI=2.6–5.6; zotepine: NNT=6, 95% CI=3–50). Overall, 279 (43%) of 653 patients treated with new antipsychotics, compared to 237 (72%) of 330 patients treated with placebo, left the studies early because of relapse, inefficacy of treatment that failed to fulfill the criteria for relapse, adverse events, or loss to follow-up (NNT=3, 95% CI=2.9–4.2).

**Dropouts due to adverse events.** Only in the zotepine study by Cooper et al. (27) did significantly more patients receiving a new antipsychotic drop out due to adverse events, compared with those receiving placebo (NNT=5, 95% CI=3–14). No significant differences between any other new antipsychotic and placebo were found (Figure



FIGURE 1. Differences in Risk of Relapse in Patients With Schizophrenia in Studies Comparing New-Generation Antipsychotic Medications With Placebo<sup>a</sup>

<sup>a</sup> Colored lines represent analyses of risk difference based on raw relapse rates; gray lines represent analyses of risk difference based on relapse rate estimates derived from survival curves.

<sup>b</sup> Risk difference=-0.01, 95% CI=-0.09 to 0.07,  $z=-0.28$ ,  $p=0.80$ .

<sup>c</sup> For raw relapse rates, heterogeneity:  $\chi^2=0.28$ ,  $df=2$ ,  $p=0.87$ ; risk difference=-0.24, 95% CI=-0.33 to -0.16,  $z=-5.72$ ,  $p<0.00001$ . For survival curve estimates, heterogeneity:  $\chi^2=2.96$ ,  $df=2$ ,  $p=0.23$ ; risk difference=-0.45, 95% CI=-0.55 to -0.36,  $z=-9.87$ ,  $p<0.00001$ .

<sup>d</sup> For raw relapse rates, risk difference=-0.26, CI=-0.39 to -0.13,  $z=-3.91$ ,  $p=0.00009$ . For survival curve estimates, risk difference=-0.39, 95% CI=-0.51 to -0.27,  $z=-6.51$ ,  $p<0.00001$ .

<sup>e</sup> For raw relapse rates, risk difference=-0.30, 95% CI=-0.43 to -0.16,  $z=-4.20$ ,  $p=0.00003$ . For survival curve estimates, risk difference=-0.45, 95% CI=-0.60 to -0.31,  $z=-6.09$ ,  $p<0.00001$ .

<sup>f</sup> For raw relapse rates, heterogeneity:  $\chi^2=27.15$ ,  $df=5$ ,  $p=0.0001$ ; risk difference=-0.21, 95% CI=-0.34 to -0.08,  $z=-3.21$ ,  $p=0.001$ . For survival curve estimates, heterogeneity:  $\chi^2=82.42$ ,  $df=5$ ,  $p<0.00001$ ; risk difference=-0.33, 95% CI=-0.55 to -0.11,  $z=-2.92$ ,  $p=0.003$ .

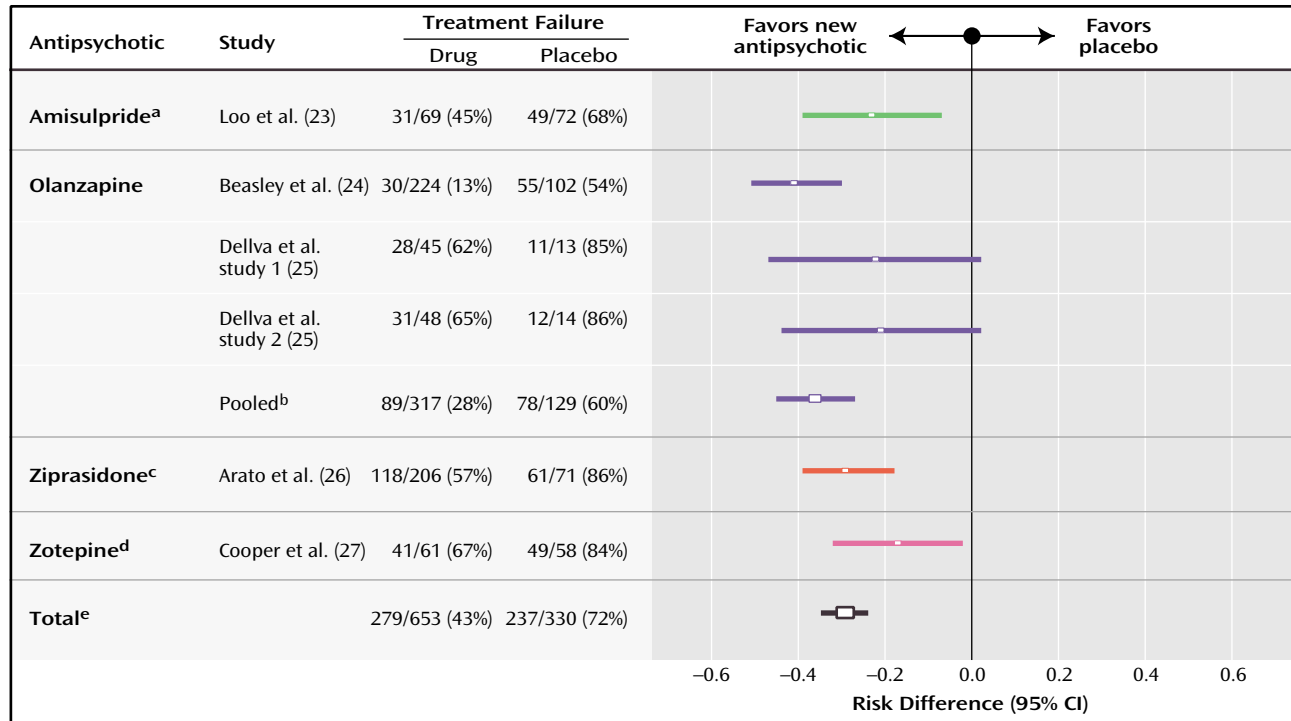
3). The results of the individual olanzapine studies were heterogeneous, with Beasley et al. (24) reporting a result that was heavily in favor of olanzapine. The reasons for this outlying result were not clear. When this study was excluded, the overall effect was not reversed (heterogeneity:  $\chi^2=0.04$ ,  $df=1$ ,  $p=0.84$ ; risk difference=0.06, 95% CI=-0.07 to 0.18,  $z=0.85$ ,  $p=0.40$ ).

Considering the new antipsychotic drugs as a group, no significant difference compared to placebo was found. As mentioned earlier, Beasley et al. (24) found an effect that was opposite that found by Cooper et al. (27), and thus the results had statistically significant heterogeneity. Aside from the difference in the particular new antipsychotics used in the two studies, no other explanations for this heterogeneity were identified, and excluding both studies in a sensitivity analysis did not change the overall effect (heterogeneity:  $\chi^2=3.31$ ,  $df=3$ ,  $p=0.35$ ; risk difference=-0.04, 95% CI=-0.09 to 0.02,  $z=-1.33$ ,  $p=0.18$ ). Therefore, the overall tolerability of the new antipsychotics appears to be equivalent to that of placebo, at least within the confines of the 6–12-month randomized, double-blind trials included in the analysis.

### New Antipsychotics Versus Conventional Compounds

Ten of the 11 studies comparing new antipsychotics with conventional antipsychotics used haloperidol as the comparator. All but one of these studies (30) had a double-blind design, and seven had outpatient rather than inpatient participants. The proportion of dropouts for reasons other than relapse varied more than in the placebo-controlled trials, from <10% to 53%, with a median value of 32%.

**Relapse rates.** Considering the new antipsychotic drugs individually, the few studies available found significantly lower raw relapse rates compared to haloperidol only for risperidone (NNT=10, 95% CI=6–50) and sertindole (NNT=11, 95% CI=7–50) (Figure 4). When relapse rates calculated from survival curves were used instead of raw relapse rates, olanzapine also emerged as superior compared to haloperidol (risperidone: NNT=7, 95% CI=4–17; sertindole: NNT=10, 95% CI=6–33; olanzapine: NNT=11, 95% CI=6–50). No statistically significant differences were found for amisulpride and clozapine, although the findings were in favor of these new drugs.

**FIGURE 2. Differences in Risk for Treatment Failure in Patients With Schizophrenia in Studies Comparing New-Generation Antipsychotic Medications With Placebo**

<sup>a</sup> Risk difference=-0.23, 95% CI=-0.39 to -0.07,  $z=-2.85$ ,  $p=0.004$ .

<sup>b</sup> Heterogeneity:  $\chi^2=3.57$ ,  $df=2$ ,  $p=0.17$ ; risk difference=-0.36, 95% CI=-0.45 to -0.27,  $z=-7.84$ ,  $p<0.00001$ .

<sup>c</sup> Risk difference=-0.29, 95% CI=-0.39 to -0.18,  $z=-5.32$ ,  $p<0.00001$ .

<sup>d</sup> Risk difference=-0.17, 95% CI=-0.32 to -0.02,  $z=-2.25$ ,  $p=0.02$ .

<sup>e</sup> Heterogeneity:  $\chi^2=8.14$ ,  $df=5$ ,  $p=0.15$ ; risk difference=-0.29, 95% CI=-0.35 to -0.24,  $z=-9.81$ ,  $p<0.00001$ .

Exploring the effects of the new antipsychotic drugs as a group, a statistically significant superiority compared to conventional antipsychotics was evident (NNT=13, 95% CI=8–25) (Figure 4). Again, this effect was more pronounced when relapse rates estimated from survival curves were analyzed (NNT=9, 95% CI=7–14).

**Overall treatment failure.** A statistically significant superiority was found only for risperidone (NNT=5, 95% CI=4–8) and olanzapine (NNT=13, 95% CI=6–250). However, with one exception (33), the findings for all other studies were in favor of the new drugs (Figure 5).

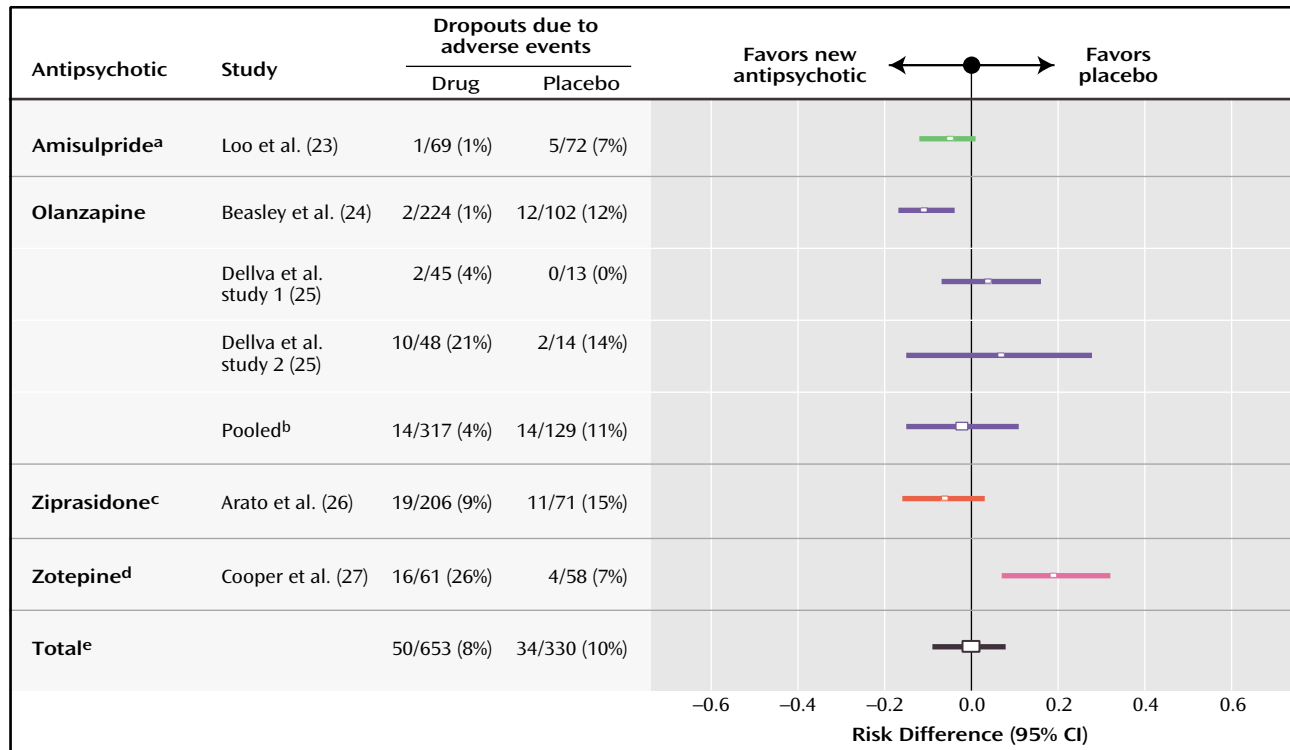
When the results across drugs were pooled, a significant superiority of the new antipsychotics was found. A total of 646 (49%) of 1,314 patients treated with new antipsychotics, compared to 440 (66%) of 669 patients treated with conventional antipsychotics, left the studies early because of an undesirable outcome, as defined earlier (NNT=10, 95% CI=6–33). There was a statistically significant heterogeneity among the studies due to the study that favored the conventional antipsychotic (33). This trial included long-term patients and had the treatment of tardive dyskinesia as its main focus. Because of this study's small sample size, removal of the study in a sensitivity analysis did not greatly change the overall effect (heterogeneity  $\chi^2=$

11.59,  $df=8$ ,  $p=0.17$ ; risk difference=-0.12, 95% CI=-0.16 to -0.07,  $z=-5.13$ ,  $p<0.00001$ , NNT=8, 95% CI=6–14).

**Dropouts due to adverse events.** Eight of the 11 studies reported on dropouts due to adverse effects (Figure 6). No significant superiority for any of the new antipsychotic drugs compared to conventional antipsychotics was found (only pooled data from the three olanzapine studies were available, so that these studies could not be considered separately in the analysis shown in Figure 6). When the results were pooled across drugs, no overall significant superiority of the new antipsychotics was found. Therefore, no clear advantage in terms of tolerability of the new antipsychotics was found by utilizing this measure.

**Adherence.** Although poor adherence with antipsychotic treatment is a major factor in schizophrenic relapse, only Rosenheck et al. (31, 32) and Csernansky et al. (35) explained how adherence was assessed. Both studies used a pill-count measure, but they found no significant difference between the two treatment groups. The trial by Daniel et al. (37) was the only one to report significantly more dropouts due to nonadherence with haloperidol than with the atypical antipsychotic (sertindole). Tran et al. (34) presented a pooled analysis of three 1-year extensions of pivotal trials comparing olanzapine and haloperidol and analyzed a combined measure of dropout due to

FIGURE 3. Differences in Risk for Dropout Due to an Adverse Event of Patients With Schizophrenia in Studies Comparing New-Generation Antipsychotic Medications With Placebo



<sup>a</sup> Risk difference = -0.05, 95% CI = -0.12 to 0.01,  $z = -1.65$ ,  $p = 0.10$ .

<sup>b</sup> Heterogeneity:  $\chi^2 = 6.64$ ,  $df = 2$ ,  $p = 0.04$ ; risk difference = -0.02, 95% CI = -0.15 to 0.11,  $z = -0.30$ ,  $p = 0.80$ .

<sup>c</sup> Risk difference = -0.06, 95% CI = -0.16 to 0.03,  $z = -1.32$ ,  $p = 0.19$ .

<sup>d</sup> Risk difference = 0.19, 95% CI = 0.07 to 0.32,  $z = 2.96$ ,  $p = 0.003$ .

<sup>e</sup> Heterogeneity:  $\chi^2 = 20.88$ ,  $df = 5$ ,  $p = 0.0009$ ; risk difference = 0.00, 95% CI = -0.09 to 0.08,  $z = -0.08$ ,  $p = 0.90$ .

nonadherence and failure to meet the study's protocol criteria. No significant difference was found. Csernansky et al. (35), Speller et al. (29), and Tamminga et al. (33) all reported on dropouts due to nonadherence but did not indicate specifically how nonadherence was ascertained. No significant differences in adherence between treatment groups were found. Marder et al. (36), Colonna et al. (28), and Essock et al. (30) did not present adherence data.

### Sensitivity analysis

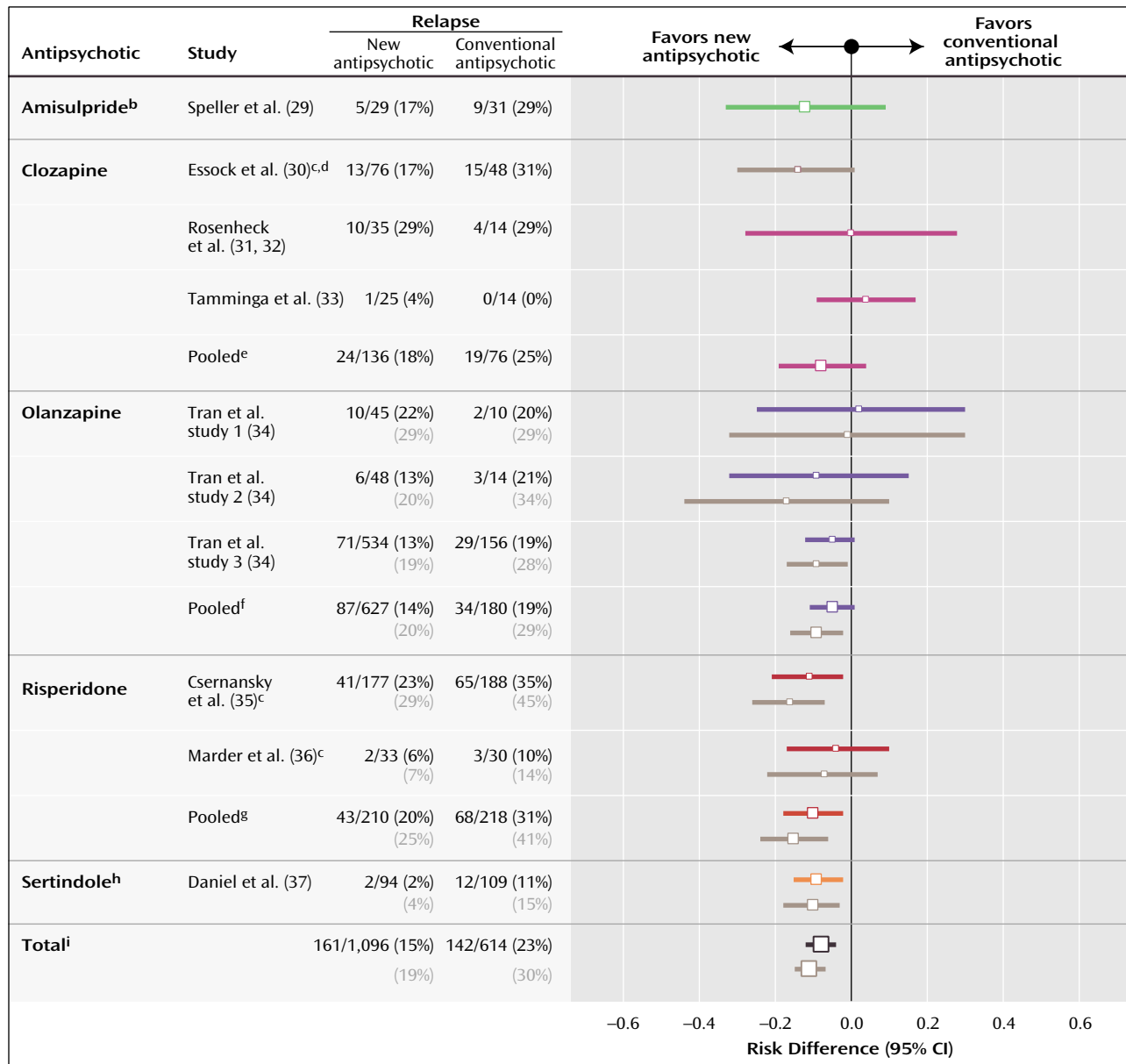
Table 3 shows the pooled results of the main analysis—new antipsychotics as a group versus placebo or conventional antipsychotics—using relative risks or odds ratios as measures of effect size. Differences in outcome that were statistically significant when risk differences were calculated were also significant when relative risks or odds ratios were calculated, and differences in outcome that were not statistically significant when risk reductions were used were also not significant when relative risks or odds ratios were used.

### Discussion

Since schizophrenia is typically a chronic disorder, one of the main hopes for the new generation of antipsychotic

drugs is more effective prevention of relapse, accompanied or mediated by better overall tolerability of and improved adherence to the medication regimen. The main strength of a meta-analysis is its objectivity, which is provided by the quantitative measurement of overall treatment effects. A weakness is that meta-analysis cannot do justice to the design particularities of individual studies. Indeed, the studies included in this meta-analysis varied substantially in design, the relapse and adherence criteria used, and the clinical characteristics of the subjects—particularly whether the patients randomly assigned to treatment groups were in stable remission or were acute-phase treatment responders whose treatment was continued. Furthermore, given the small number of relevant trials, the results for the individual new drugs were pooled in an exploratory way. The new antipsychotics are frequently considered as one class of “atypicals” that share a lower liability for causing extrapyramidal side effects compared to high-potency conventional antipsychotics. It is often assumed that this characteristic will lead to better adherence and thus lower relapse rates. However, each of the newer antipsychotics has a unique receptor-binding profile, and future direct comparisons may reveal differences in efficacy. The direct comparisons of new antipsychotics that have been done have failed to show any such differ-



**FIGURE 4. Differences in Risk of Relapse in Patients With Schizophrenia in Studies Comparing New-Generation Antipsychotic Medications With Conventional Antipsychotics<sup>a</sup>**

<sup>a</sup> Colored lines represent analyses of risk difference based on raw relapse rates; gray lines represent analyses of risk difference based on relapse rate estimates derived from survival curves.

<sup>b</sup> Risk difference=-0.12, 95% CI=-0.33 to 0.09, z=-1.10, p=0.30.

<sup>c</sup> The 1-year relapse rate was used to enhance comparability with the other studies. The reported 2-year relapse rates were 23% for clozapine and 41% for usual care in the study by Essock et al. (30), 25% for risperidone and 40% for haloperidol in the study by Csernansky et al. (35), and 12% for risperidone and 27% for haloperidol in the study by Marder et al. (36).

<sup>d</sup> Only relapse rate estimates derived from survival curves were available.

<sup>e</sup> Heterogeneity:  $\chi^2=4.24$ , df=2, p=0.12; risk difference=-0.08, 95% CI=-0.19 to 0.04, z=-1.35, p=0.18.

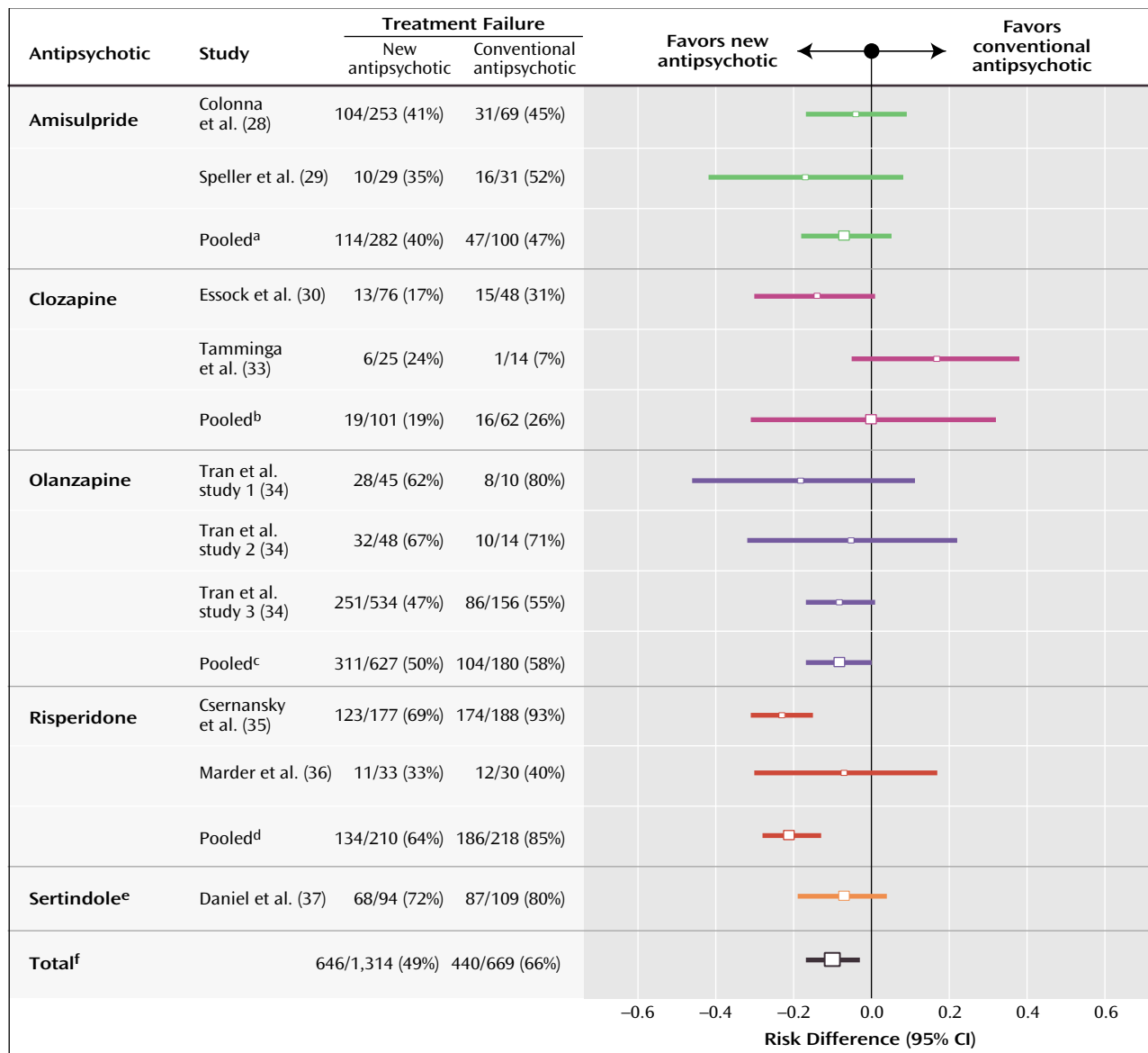
<sup>f</sup> For raw relapse rates, heterogeneity:  $\chi^2=0.38$ , df=2, p=0.83; risk difference=-0.05, 95% CI=-0.11 to 0.01, z=-1.59, p=0.11. For survival curve estimates, heterogeneity:  $\chi^2=0.57$ , df=2, p=0.75; risk difference=-0.09, 95% CI=-0.16 to -0.02, z=-2.43, p=0.01.

<sup>g</sup> For raw relapse rates, heterogeneity:  $\chi^2=0.91$ , df=1, p=0.34; risk difference=-0.10, 95% CI=-0.18 to -0.02, z=-2.49, p=0.01. For survival curve estimates, heterogeneity:  $\chi^2=1.16$ , df=1, p=0.28; risk difference=-0.15, 95% CI=-0.24 to -0.06, z=-3.43, p=0.0006.

<sup>h</sup> For raw relapse rates, risk difference=-0.09, 95% CI=-0.15 to -0.02, z=-2.65, p=0.008. For survival curve estimates, risk difference=-0.10, 95% CI=-0.18 to -0.03, z=-2.62, p=0.009.

<sup>i</sup> For raw relapse rates, heterogeneity:  $\chi^2=6.43$ , df=9, p=0.70; risk difference=-0.08, 95% CI=-0.12 to -0.04, z=-3.87, p=0.0001. For survival curve estimates, heterogeneity:  $\chi^2=8.35$ , df=9, p=0.50; risk difference=-0.11, 95% CI=-0.15 to -0.07, z=-4.96, p<0.00001.

FIGURE 5. Differences in Risk for Treatment Failure in Patients With Schizophrenia in Studies Comparing New-Generation Antipsychotic Medications With Conventional Antipsychotics



<sup>a</sup> Heterogeneity:  $\chi^2=0.87$ ,  $df=1$ ,  $p=0.35$ ; risk difference=-0.07, 95% CI=-0.18 to 0.05,  $z=-1.13$ ,  $p=0.30$ .

<sup>b</sup> Heterogeneity:  $\chi^2=5.52$ ,  $df=1$ ,  $p=0.02$ ; risk difference=0.00, 95% CI=-0.31 to 0.32,  $z=0.03$ ,  $p=1.00$ .

<sup>c</sup> Heterogeneity:  $\chi^2=0.49$ ,  $df=2$ ,  $p=0.78$ ; risk difference=-0.08, 95% CI=-0.17 to 0.00,  $z=-2.03$ ,  $p=0.04$ .

<sup>d</sup> Heterogeneity:  $\chi^2=1.70$ ,  $df=1$ ,  $p=0.19$ ; risk difference=-0.21, 95% CI=-0.28 to -0.13;  $z=-5.41$ ,  $p<0.00001$ .

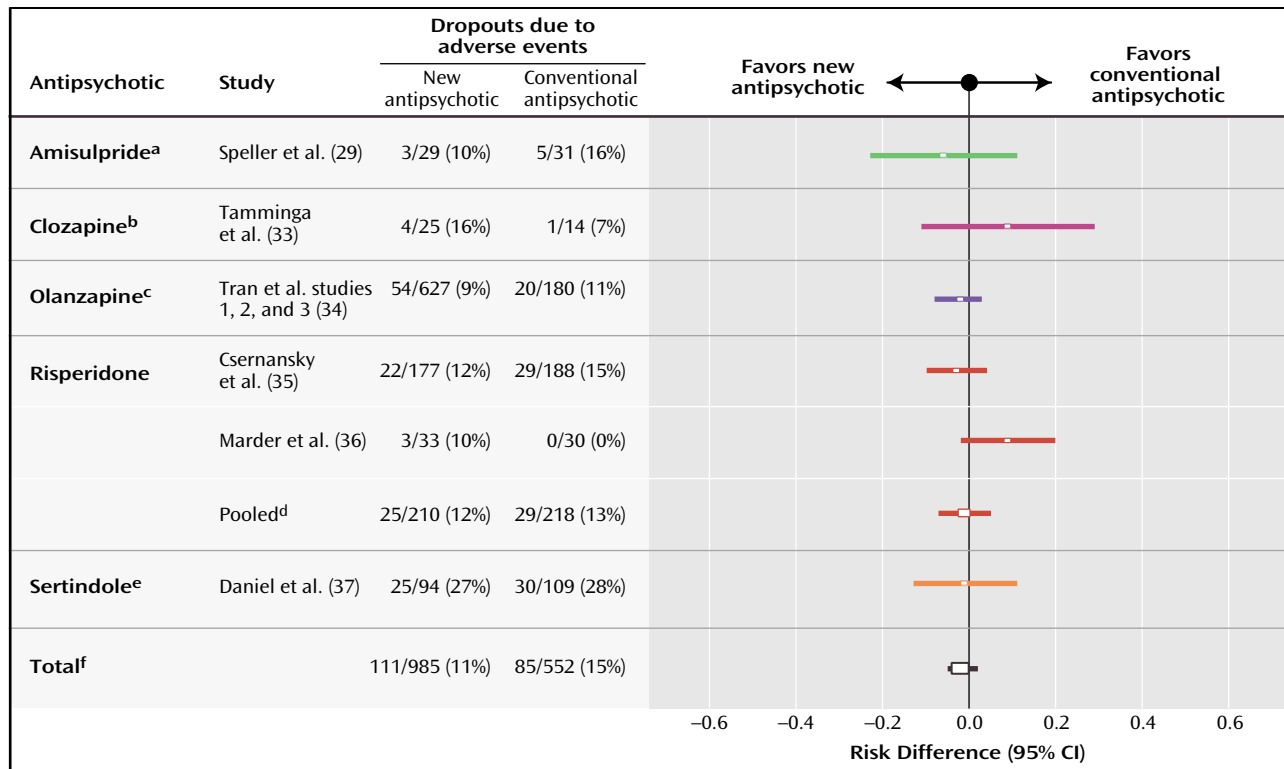
<sup>e</sup> Risk difference=-0.07, 95% CI=-0.19 to 0.04,  $z=-1.24$ ,  $p=0.20$

<sup>f</sup> Heterogeneity:  $\chi^2=18.53$ ,  $df=9$ ,  $p=0.03$ ; risk difference=-0.10, 95% CI=-0.17 to -0.03,  $z=-2.73$ ,  $p=0.006$ . The total number of patients is different than in the relapse analysis because Colonna et al. (28) did not present data on relapse and Rosenheck et al. (31, 32) did not present data on treatment failure.

ences (38, 39), but design problems in the individual studies, especially the doses used, may have biased the results (22, 40). For these reasons, this meta-analysis should be considered as an exploration of the potential of the new drugs to reduce relapse rates rather than as a definitive statement. The findings will change when further studies are published and more differentiated meta-analyses become feasible.

This analysis also identified methodological problems that could be important for the design of future trials. The

studies comparing the new antipsychotics with placebo showed that the former were consistently more effective in preventing schizophrenic exacerbations and overall treatment failure, but only a few of the newer antipsychotics were tested. Furthermore, five of the six relevant studies had design features that could limit the generalizability of the findings to routine clinical practice. More specifically, four studies were continuation-phase studies rather than maintenance-phase studies of fully remitted or stable patients. The study by Cooper et al. (27) included only pa-

**FIGURE 6. Differences in Risk for Dropout Due to an Adverse Event of Patients With Schizophrenia in Studies Comparing New-Generation Antipsychotic Medications With Conventional Antipsychotics<sup>a</sup>**

<sup>a</sup> Risk difference=-0.06, 95% CI=-0.23 to 0.11,  $z=-0.67$ ,  $p=0.50$ .

<sup>b</sup> Risk difference=0.09, 95% CI=-0.11 to 0.29,  $z=0.88$ ,  $p=0.40$ .

<sup>c</sup> Risk difference=-0.02, 95% CI=-0.08 to 0.03,  $z=-0.96$ ,  $p=0.30$ . Only pooled data on dropouts were available from the three studies by Tran et al.

<sup>d</sup> Heterogeneity:  $\chi^2=3.53$ ,  $df=1$ ,  $p=0.06$ ; risk difference=-0.01, 95% CI=-0.07 to 0.05,  $z=-0.38$ ,  $p=0.70$ .

<sup>e</sup> Risk difference=-0.01, 95% CI=-0.13 to 0.11,  $z=-0.15$ ,  $p=0.90$ .

<sup>f</sup> Heterogeneity:  $\chi^2=5.16$ ,  $df=5$ ,  $p=0.40$ ; risk difference=-0.02, 95% CI=-0.05 to 0.02,  $z=-0.87$ ,  $p=0.40$ .

tients who were at least mildly ill according to Clinical Global Impression (CGI) ratings, so that many participants were symptomatic when they entered the trial. A similar problem is apparent in the study by Arato et al. (26), which included only subjects who had been inpatients for at least 2 months. The only symptom criterion for inclusion was that patients had to be less than severely ill according to the CGI rating. The studies by Dellva et al. (25) comparing olanzapine with placebo are problematic because they were extension studies that included responders in trials involving acutely ill patients. There was no stabilization period for these patients, and random assignment to treatment groups occurred before the maintenance phase of treatment. Loo et al. (23) studied a highly selected group of patients with mainly residual schizophrenia, which may explain the low relapse rates both in the amisulpride group (6%) and the placebo group (7%). Only the study by Beasley et al. (24) can be considered a traditional maintenance study. Here, patients who were retrospectively judged to be stable while taking an antipsychotic had their medication switched to olanzapine. Stability was then confirmed during 8 weeks of olanzapine monotherapy be-

fore the patients were randomly assigned to treatment groups for a 6-month trial.

Studies that compared atypical drugs with conventional drugs found that the former were, as a group, significantly more effective in the prevention of relapse. The magnitude of this advantage for atypical drugs was modest, and for the individual new antipsychotics a statistically significant superiority was demonstrated only for risperidone, sertindole, and olanzapine. However, due to differences in study design, no conclusions about the relative efficacy of the new drugs can be drawn.

A similar advantage was found when overall treatment failure was analyzed. This is an important measure because it reflects not only how many relapses can be avoided but also how many patients remain free of other problems that can lead to treatment discontinuation. Despite the significant superiority of the new antipsychotics, it should be noted that the number of treatment failures was high in both the atypical and conventional drug groups.

The available data do not allow for any conclusions about whether this modest superiority for the new antipsychotics in relapse prevention is related to enhanced efficacy, better adherence, or a combination of these factors.

**TABLE 3. Relative Risk and Odds Ratios Measuring Pooled Effect Sizes in Randomized, Controlled Studies Comparing New-Generation Antipsychotic Medications With Placebo and Conventional Antipsychotics**

Outcome Comparison and Type of Analysis	Relative Risk				Odds Ratio			
	Ratio	95% CI	z	p	Ratio	95% CI	z	p
New-generation antipsychotic drugs versus placebo								
Raw relapse rate	0.35	0.19–0.62	–3.56	0.0004	0.24	0.13–0.42	–4.91	<0.00001
Relapse rate estimated from survival curves	0.31	0.15–0.63	–3.25	0.001	0.16	0.07–0.35	–4.56	0.00001
Treatment failure	0.62	0.46–0.83	–3.23	0.001	0.28	0.20–0.37	–8.29	<0.00001
Dropout due to adverse events	0.68	0.21–2.15	–0.67	0.50	0.67	0.18–2.44	–0.61	0.50
New-generation antipsychotic drugs versus conventional antipsychotic drugs								
Raw relapse rate	0.65	0.53–0.81	–3.49	0.00008	0.58	0.44–0.76	–3.97	0.00007
Relapse rate estimated from survival curves	0.63	0.53–0.75	–5.05	<0.00001	0.53	0.41–0.68	–5.06	<0.00001
Treatment failure	0.82	0.76–0.89	–4.93	<0.00001	0.58	0.39–0.85	–2.78	0.005
Dropout due to adverse events	0.89	0.68–1.16	–0.89	0.40	0.86	0.63–1.19	–0.89	0.40

Although adherence is a critical issue in the maintenance treatment of schizophrenia, it was poorly monitored in the trials. Even in the trials reporting adherence data, the methods used to measure adherence were usually not described. One relatively simple measure, pill count, was applied only in the studies by Csernansky et al. (35) and Rosenheck et al. (31, 32). No study measured drug plasma levels.

Although it is difficult to define relapse, many of the symptom-scale criteria are perhaps of limited clinical relevance, particularly in some maintenance-phase extension studies involving acute-phase responders. A reduction of at least 40% in Positive and Negative Syndrome Scale or Brief Psychiatric Rating Scale (BPRS) scores and a change in status from inpatient to outpatient by the last visit in an acute study might reflect a reasonable degree of remission, and subsequent rehospitalization for psychosis a reasonable criterion for relapse (25, 34). However, after an initial 20% reduction in BPRS or Positive and Negative Syndrome Scale score, the inability to maintain the lower score over time is more questionable as a measure of relapse (28, 32). Several trials in the 1970s and 1980s showed that low doses of high-potency, conventional antipsychotics were effective for relapse prevention and could substantially reduce the risk of side effects (41). With the exception of the studies by Speller et al. (29) and Marder et al. (36), no trial included in the meta-analysis followed a low-dose strategy. Specifically, no study used haloperidol doses below 5 mg/day, and many of the patients received doses between 10 mg/day and 20 mg/day. For acute studies, Geddes et al. (42) suggested by means of meta-regression that the efficacy advantages of the new antipsychotics disappear when doses below 12 mg of haloperidol equivalents are used as comparators. The same finding may apply to relapse prevention, but the studies published thus far do not allow for such an analysis with regard to the dose of the comparator drug. Given the superiority of depot compared to oral formulations of the conventional compounds (43), there is also a need for studies that compare the new antipsychotics with depot doses of conventional drugs.

A further methodological issue is the use of fixed doses in long-term trials. A flexible-dose regimen would better

reflect clinical practice, where the prescribing clinician commonly titrates the dose in response to changes in the patient's mental state or emergent side effects. With the exception of the study by Essock et al. (30), all trials used haloperidol as a comparator, although it is generally recognized that this medication may be particularly liable to induce extrapyramidal side effects. Some clinicians therefore prefer low-potency antipsychotics for long-term treatment. These factors might also help to explain the high rates of dropout for reasons other than relapse. More randomized pragmatic trials, in which clinicians can choose an atypical or a conventional antipsychotic (including depot preparations) with flexible doses and where switching of antipsychotics within both classes would be allowed, might help to minimize dropouts for reasons other than relapse and to generate findings that more closely reflect the real-life clinical situation. Such a design might also allow trials to be successfully conducted for longer than 1 year. Indeed, the only three trials that lasted longer than 1 year found an increasing superiority of the new drugs over time (30, 35, 36).

Although this meta-analysis was subject to the limitations resulting from these methodological problems, we conclude that modest reductions of relapse rates and treatment failures with the new antipsychotics have been shown. Any enhancement of adherence that might be associated with the new antipsychotics remains to be established. However, the absolute reduction of the relapse risk by 8%, i.e., 80 relapses prevented per 1,000 patients treated for 1 year, is as strong as the evidence supporting the use of aspirin to prevent vascular events (44), which is now a widespread clinical practice.

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