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Dropout Rates in Randomized Clinical Trials of Antipsychotics: A Meta-analysis Comparing First- and Second-Generation Drugs and an Examination of the Role of Trial Design Features

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Dropout is often used as an outcome measure in clinical trials of antipsychotic medication. Previous research is inconclusive regarding (a) differences in dropout rates between first- and second-generation antipsychotic medications and (b) how trial design features reduce dropout. Meta-analysis of randomized controlled trials (RCTs) of antipsychotic medication was conducted to compare dropout rates for first- and second-generation antipsychotic drugs and to examine how a broad range of design features effect dropout. Ninety-three RCTs that met inclusion criteria were located (n = 26 686). Meta-analytic random effects models showed that dropout was higher for first- than second-generation drugs (odds ratio = 1.49, 95% confidence interval: 1.31–1.66). This advantage persisted after removing study arms with excessively high dosages, in flexible dose studies, studies of patients with symptom exacerbation, nonresponder patients, inpatients, and outpatients. Mixed effects models for meta-analysis were used to identify design features that effected dropout and develop formulae to derive expected dropout rates based on trial design features, and these assigned a pivotal role to duration. Collectively, dropout rates are lower for second- than first-generation antipsychotic drugs and appear to be partly explained by trial design features thus providing direction for future trial design.

Key words: dropout/second-generation antipsychotic/first-generation antipsychotic

Introduction

Dropout occurs frequently in clinical trials of antipsychotic treatment. It is an important outcome because it may reflect drug tolerability, adverse effects, and lack of compliance. For instance, in the recent clinical antipsychotic trials of intervention effectiveness (CATIE) study discontinuation was a primary outcome measure. Seventy four percent of CATIE trial participants discontinued their assigned study medication before study completion at 18 months,[1] and dropout rates were roughly equivalent for first-(ie, typical) and second-generation (ie, atypical) antipsychotics. Indeed, high dropout rates are not uncommon in RCTs of antipsychotic medication. Across studies of different durations, meta-analysis has estimated that dropout rates exceed a third of patients treated with antipsychotic medication in RCTs.[2]

Meta-analyses have reported lower dropout rates for second-generation antipsychotics than placebo.[2–4] Such reviews, however, are inconclusive regarding differences in dropout rates between first- and second-generation medications. One meta-analysis of studies up to the year 2000 has reported that only clozapine shows significantly lower dropout rates than first-generation medications.[2] Another meta-analysis covering studies conducted through 1998[5] has found differences favoring amisulpride, clozapine, risperidone, and olanzapine over first-generation medications. A meta-analysis of 28 published studies covering 4 of the major second-generation antipsychotics in Western populations through 2003 reported lower dropout rates for second-than first-generation treatment but only for flexible dose studies.[6] Thus, research, based on meta-analyses shows lower dropout rates for second-generation antipsychotic drugs than placebo. Research, however, is inconclusive regarding differences in dropout rates between second- and first-generation antipsychotic treatment.

Research has examined how study design features of antipsychotic trials correspond with dropout rates. Wahlbeck et al[2] have reported that dropout increases with trial length and year of publication. Yet, Kemmler et al[3], who examined placebo-controlled trials up to 12 weeks long, did not find a significant association of dropout and duration, publication year, or use of multiple dosages. Yet, they[3] did find that the presence of a placebo arm relates to a higher dropout rate in the active treatment arm. Furthermore, conclusions regarding second-generation antipsychotic medications differ between

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active- and placebo-controlled trials, highlighting the appropriateness of this comparson.[7] Also, flexible rather than fixed dosage[6] and higher dosages of first-generation medications[5] have been reported to increase the difference in dropout rates between first- and second-generation medications. To provide a more comprehensive consideration of design features than has been covered previously, it is appropriate to consider patients levels of symptomatology and whether patients treated were in or outpatients because these may effect dropout rates.

The current meta-analysis compares dropout rates between first- and second-generation antipsychotic drugs and examines the effects of trial design features on dropout rates. Specifically, we examine the effects of trial duration, presence of placebo arm, number of trial arms, fixed vs flexible dosing, dosage, inpatient vs outpatient, symptom severity, and publication year on dropout rates. All published and unpublished studies irrespective of duration and sample size are included.

Methods

Literature Search

Trial reports were retrieved by an extensive literature search of the Cochrane Central Register of Controlled Trials and PubMed. The former includes published and nonpublished clinical trials and is based on extensive database searches, reference lists of published trials, and contacts with drug manufacturers and primary researchers.[8] The search aimed to identify all double-blind randomized clinical trials of second-generation antipsychotic medications (risperidone, olanzapine, clozapine, quetiapine, amisulpride, ziprasidone, sertindole and aripiprazole) fulfilling the following criteria: being published or presented between the years 1990 and 2006, consisting of any adult patient population with a diagnosis of schizophrenia, schizoaffective or schizophreniform disorder.

Cumulatively our searches rendered 202 references using the following search string "(efficacy or effectiveness or relapse or remission or safety) and (schizophrenia or schizoaffective disorder or schizophreniform disorder) and (clozapine or olanzapine or risperidone or amisulpride or aripiprazole or quetiapine or sertindole or ziprasidone) and (adult and double mind)" in either the title, abstract, or keyword for the years 1990–2006. The removal of open-label trials rendered 162 references available. Sixty-two of these references were secondary publications of studies previously presented in a primary publication, and 7 additional references were excluded for missing information on dosing and or on dropout rates. This left 93 trials that met the inclusion criteria (see Appendix). Eight studies compared placebo, first-, and second-generation medications; 44 compared first- and second-generation without placebo; 19 compared second-generation and placebo; and 22 compared second-generation antipsychotic medications. Seven studies (7.5%) were published prior to 1996, 73 (78.5%) from 1997 to 2003, and 13 (14%) from 2004 to 2006.

Data Acquisition

The following information was extracted from each trial study report: the number of patients randomized to the different treatment arms, the total number of dropouts in the individual treatment arms, trial duration, patient type (stable responder, symptom exacerbation, nonresponder), hospitalization status (inpatients, outpatients, or both), study year, fixed vs flexible dosing, dose for fixed dose studies, and mean dose for flexible dose studies. In some studies, mean dose was not provided and so was estimated from the dosage range. To provide an overview, table 1 includes all studies with at least 100 patients per treatment (see Appendix for data from all studies), and Table 2 presents all placebo-controlled trials.

Data Analysis

To compare the dropout rates within study arms between first- and second-generation antipsychotic medications, meta-regression (random effects meta-analysis) was conducted in R[52] with the rmeta package.[53] For comprehensiveness, this analysis was conduced first for all studies and then for those with at least 30, 50, and 100 patients per treatment. To test whether dropout differences might relate to the use of excessive dosages, analysis was rerun after removing study arms using excessive dosages and then for each second-generation drug. To see whether differences persisted, additional subanalyses were conducted of studies using flexible nonexcessive dosing, studies of nonresponder patients, studies of inpatients, and studies of outpatients.

Excessive dosing was operationalized as doses over the maximal effective dose based on the Davis et al[54] meta-analysis of dose responses. That meta-analysis aimed to identify the near-maximal effective dose, namely, the threshold dose required to cumulate in all or almost all clinical responses for each drug. For example, the near-maximal efficacy dose for chlorpromazine is 450 mg/day and for risperidone is 4 mg/day.

In the second part of the analysis to predict dropout, mixed effects models for meta-analysis were conduced with the Mima function in the R statistical software environment.[55] Covariates included were duration in weeks, number of study arms, presence of placebo, fixed vs flexible dosing, patient type (stable responder, symptom exacerbation, nonresponder), whether study was conducted on inpatients only, whether or not a study arm used excessively high dosages, and study year. Separate models were conducted for first-generation, second-generation, and placebo arms. This permitted us to derive

Table 1. Summary of Studies Comparing Dropout in First- and Second-Generation Antipsychotic Medications With a Sample Size of At Least 100 Patients Per Treatment Arm

Reference	Duration in wk	*n*	Treatment and Dosage	Dropout *n*	% Dropout	*n*	Dropout	% Dropout	Treatment and Dosage	Arms Overdose Nonsignificant and Dropout Notes Supplemented Where Applicable
Colonna et al[9]	52	370	Am 605	167	45.1	119	62	52.1	H 14.6	Both arms overdosed
Copolov et al[10]	6	221	Qu 455	69	31.2	227	80	35.2	H 8	
Csernansky et al[11]	52	179	Ri 3	104	58.1	188	142	75.5	H 7.5	
Daniel et al[12]	52	141	SE 24	27	19.1	141	43	30.5	H 10	
Emsley et al[13]	12	143	Qu 600	32	22.4	145	28	19.3	H 20	Qu overdosed only
Hirsch et al[14]	28	148	Zi 116.5	82	55.4	153	89	58.2	H 8.6	
Kane et al[15,16]	6	154	Pe 39.10	44	28.6	146	31	21.2	Ar 28.8	Ar overdosed
Kane et al[17]	4	384	Ar 15, 30	149	38.8	104	42	40.4	H 10	Ar is overdosed
Kasper et al[18]	52	861	Ar 30	494	57.4	433	305	70.4	H 10	Ar is overdosed
Lieberman et al[19,20]	12	131	Ol 9.1	42	32.1	132	61	68.1	H 4.4	
Lieberman et al[1]	78	1175	Ol 11.25, Qu 300, Ri 2.25, Zi 60	869	74.0	257	192	74.7	Pe 12	
Peuskens[21]	8	1136	Ri 1, 4, 8, and 16	284	25.0	226	63	27.9	H 10	Ri > 4 overdosed, (r = 8, n = 230, dropout = 24.35%, r = 12, n = 226, dropout = 27.43%, r = 16, n = 224, dropout = 28.3%)
Rosenheck et al[22]	52	205	Cl 552	88	42.9	218	157	72.0	H 28	Both arms overdosed
Rosenheck et al[23]	52	159	Ol 15.8	91	57.2	150	96	64.0	H 14.3	H overdosed
Schooler et al[24]	104	278	Ri 3.3	117	42.1	277	101	36.5	H 2.9	
Tollefson et al[25,26]	6	1336	Ol 13.2	448	33.5	660	351	53.2	H 11.8	H overdosed

Note: H = Haloperidol, Qu = Quetiapine, Ri = Risperidone, SE = Sertindole, Zi = Ziprasidone, Ol = Olanzapine, Rinj = Risperidone Injectable, Cl = Clozapine, Pe = Perphenzine, Ar = Aripiprazole, Ch = Chlorpromazine. Trials with more than 2 treatments are ordered by drug and corresponding *n*, dropout number, and % dropout. Placebo arm details omitted.

equations for the prediction of dropout that operate much in the manner of typical regression models.

Results

Descriptive Statistics

The 94 studies constituted a total sample size of 26 686 subjects. They received first- (n = 5465) or second-generation antipsychotic medications (n = 19 400) or placebo (n = 1821). Participants allocated to first-generation medication ranged from 21 to 660 in each trial. The number treated with second-generation drugs ranged from 21 to 1336, and the number treated with placebo ranged from 22 to 155. The distribution of number of study arms was 2 arms (k = 66; 70.2%), 3 arms (k = 10; 10.6%), 4 arms (k = 6; 6.4%), and 5–8 arms (k = 12; 12.8%). The sample size for each dose arm ranged from 21 to 1336.

Comparing Dropout in First- and Second-Generation Antipsychotic Drugs

First- and second-generation treatments were compared utilizing random effects meta-analysis. To enable comparison of first- and second-generation medications, if the number of treatment conditions was not 2 (ie, one first- and one second-generation arm) then the arms were aggregated. The inclusion of all 52 studies comparing first- and second-generation medications, in figure 1, showed significantly lower dropout rates for second-generation drugs (OR = 1.49, 95% CI = 1.31, 1.66; test for heterogeneity: χ^2_{51} = 116.39, P = 0, estimated random effects variance = 0.1). As shown in table 3, this finding replicated in the 43 trials with over 30 participants in each treatment condition, the 33 trials with over 50 participants in each treatment condition, and the 16 trials with over 100 participants in each condition. It is noted that although the odds ratios dropped slightly in

Table 2. Description of Placebo-Controlled Studies

Publication	Publication Year	Duration in wk	*n*	% Dropout	Study Arms
Arvanitis and Miller[27]	1997	6	51	68.6	7
Beasley and Sanger[28]	1996	6	50	80.0	3
Beasley and Tollefson[29]	1996	6	68	67.6	5
Beasley et al[30]	2003	52	102	53.9	2
Borison et al[31]	1996	6	55	60.0	2
Boyer et al[32]	1995	6	34	26.5	3
Chouinard et al[33]	1993	8	22	72.7	6
Cooper et al[34]	1999	8	53	47.2	3
Cooper et al[35]	2000	26	58	84.5	2
Corrigan et al[36]	2004	6	86	25.6	8
Daniel et al[37]	1999	6	92	46.7	3
Danion et al[38]	1999	12	83	39.8	3
Kane et al[17]	2002	4	106	45.3	4
Kane et al[15,16]	2003	12	98	67.3	6
Keck et al[39]	1998	4	48	50.0	3
Lecrubier et al[40]	2006	26	34	64.7	4
Loo et al[41]	1997	26	72	68.1	2
Marder et al[42]	1994	8	66	68.2	6
Meltzer et al[43]	2004	6	98	79.6	6
Pigott et al[44,45]	2003	26	155	71.0	2
Potkin et al[46]	2003	4	103	49.5	4
Small et al[47]	1997	6	96	59.4	3
Tollefson et al[48]	1999	.70	53	15.1	2
Van-Kammen et al[49]	1996	5.70	38	39.5	4
Arato et al[50]	2002	52	71	85.9	4
Woods et al[51]	2003	8	29	27.6	2

Note: $k = 26$ studies.

magnitude with arm sample size, the results suggested that second-generation treatment persistently had lower dropout rates than first-generation treatments. Dropout rates of specific second-generation drugs were compared with first-generation drugs in figure 2. These results showed a significant difference for amisulpride, olanzapine, risperidone, and an almost significant difference for clozapine and quetiapine.

Dropout rates of first- and second-generation drugs were further compared in table 3 by examining subgroups of studies. First, differences were retested after removing study arms with excessive doses (see Methods section) from both first- and second-generation drug arms. After removing 52 study arms in 53 studies due to excessive dosing, 21 studies remained available for analysis that compared first- and second-generation medication. While based on only a small number of studies, these results showed a significant advantage for olanzapine and a nearly significant difference for risperidone but not for ziprasidone, clozapine, and quetiapine. No data were available to examine amisulpride and aripiprazole after removing excessive dosing. This analysis was repeated after removing fixed dose studies with excessive dosages. Collectively, 122 fixed and 84 overdosed study arms were removed leaving 17 studies available for analysis. Advantages for second-generation drugs were observed (see table 3). Next studies of patients with symptom exacerbation, nonresponder patients, inpatient, and outpatient were examined. These too all showed an advantage for second-generation drugs. Collectively, therefore, the current results consistently demonstrate at the aggregate level, for specific drugs even if not overdosed, and accounting for relevant moderators a unitary trend of higher dropout for first- than second-generation antipsychotic treatment.

Predictors of Dropout

Mixed effects regression models presented in table 4 were conducted separately for first generation, second generation, and placebo to examine the association of trial design features and dropout. Trial duration was consistently significant ($<.01$) in the 3 models. Specifically, the longer the trial the higher the dropout rate. Duration had a large effect size ($Zs > 2.56$), indicating its influence. In second-generation trials, flexible vs fixed dose also significantly reduced dropout, and for first-generation drugs, there was a nearly significant effect ($P = .06$) for excessive dosing which increased dropout. Numbers of study arms, presence of a placebo arm, and study year were not significantly associated with dropout.

The regression models in table 4 may be applied to derive expected dropout rates. Caution is warranted because they have not been validated in trials not included in the analysis. To illustrate the use of the equations, the following are examples based on a placebo, first-, and second-generation study arms. Based on the placebo study arm of Pigott et al[44] in 2003 the placebo equation is applied as follows: (intercept 2226.70) + (year 2003 × −1.10) + (symptom level 0 × 4.67) + (in patient study 1 × 5.96) + (arms 2 × 1.86) + (duration in weeks 26 × 0.94) + (fixed dosing 1 × 10.02). This produces an estimated dropout rate of 67.5% where the actual rate was 71.0%. The first-generation drug equation is illustrated using the haloperidol arm from Lieberman et al (2003)[19] as follows: (intercept − 1760.18) + (year 2003 × 0.89) + (symptom level 1 × −3.75) + (in patient study 0 × −0.75) + (with placebo arm 1 × 11.75) + (number of arms 6 × 3.13) + (duration in weeks 12 × 0.31) + (fixed dosing 0 × 4.18) + (excessive dosing 0 × 11.05). This produces an estimated dropout rate of 53.0% where the rate was 46.2%. The second-generation drug equation is illustrated

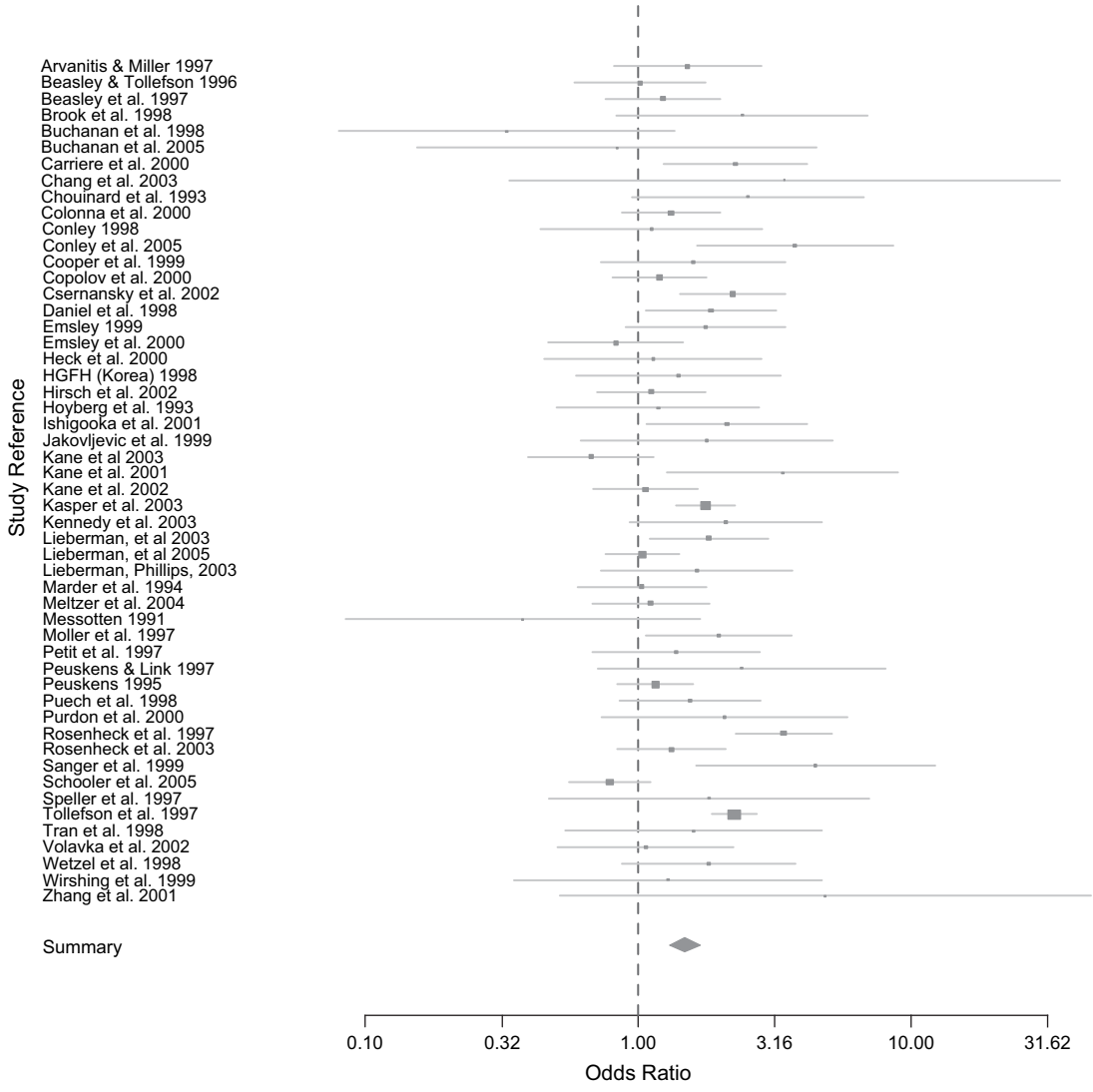

Fig. 1. Forest Plots Comparing All First- and Second-Generation Studies.

using the olanzapine arm from CATIE[1] as follows: (intercept − 1063.80) + (year 2005 × 0.54) + (symptom level 1 × 1.85) + (in patient study 0 × −1.49) + (with placebo arm 0 × 4.23) + (arms 5 × 0.52) + (duration in weeks 78 × 0.38) + (fixed dosing 0 × 8.23) + (excessive dosing 0 × −3.50). This produces an estimated dropout rate of 52.99% where actual dropout rate was 63.64%.

The average difference between the estimated and actual percentage dropout across study arms was 6.44 (SD = 16.26). Differences were observed by drug and are presented in ascending order as follows: chlorpromazine, M = −6.64 (SD = 12.69, k = 5), placebo, M = −5.85 (SD = 15.48, k = 26), amisulpride, M = −0.95 (SD = 11.38, k = 19), ziprasidone, M = 1.87 (SD = 17.76, k = 15), haloperidol, M = 7.78 (SD = 16.45, k = 41), olanzapine, M = 8.52 (SD = 14.94, k = 43), risperidone, M = 8.69 (SD = 2.46, k = 40), clozapine, M = 8.87 (SD = 15.65, k = 9), aripiprazole, M = 10.80 (SD = 13.55, k = 10), quetiapine, M = 14.87 (SD = 3.65, k = 15). This highlighted that the formula was generally accurate but estimated dropout for some drugs with greater accuracy than others.

Discussion

The current meta-analysis indicates that the use of second-generation antipsychotic medication has lower dropout rates than first-generation treatments. Several design features of randomized clinical trials of antipsychotic medications are identified that are significantly associated with dropout rates. Among these, a longer duration was most consistently and strongly associated with dropout, although effects are observable also for dosing (fixed vs flexible) and excessive dosing. Significant effects are not found for publication year, number of study arms, the presence of a placebo study arm, inpatient study, or symptom level. The trial design features that we examined were used to develop an equation to estimate expected dropout

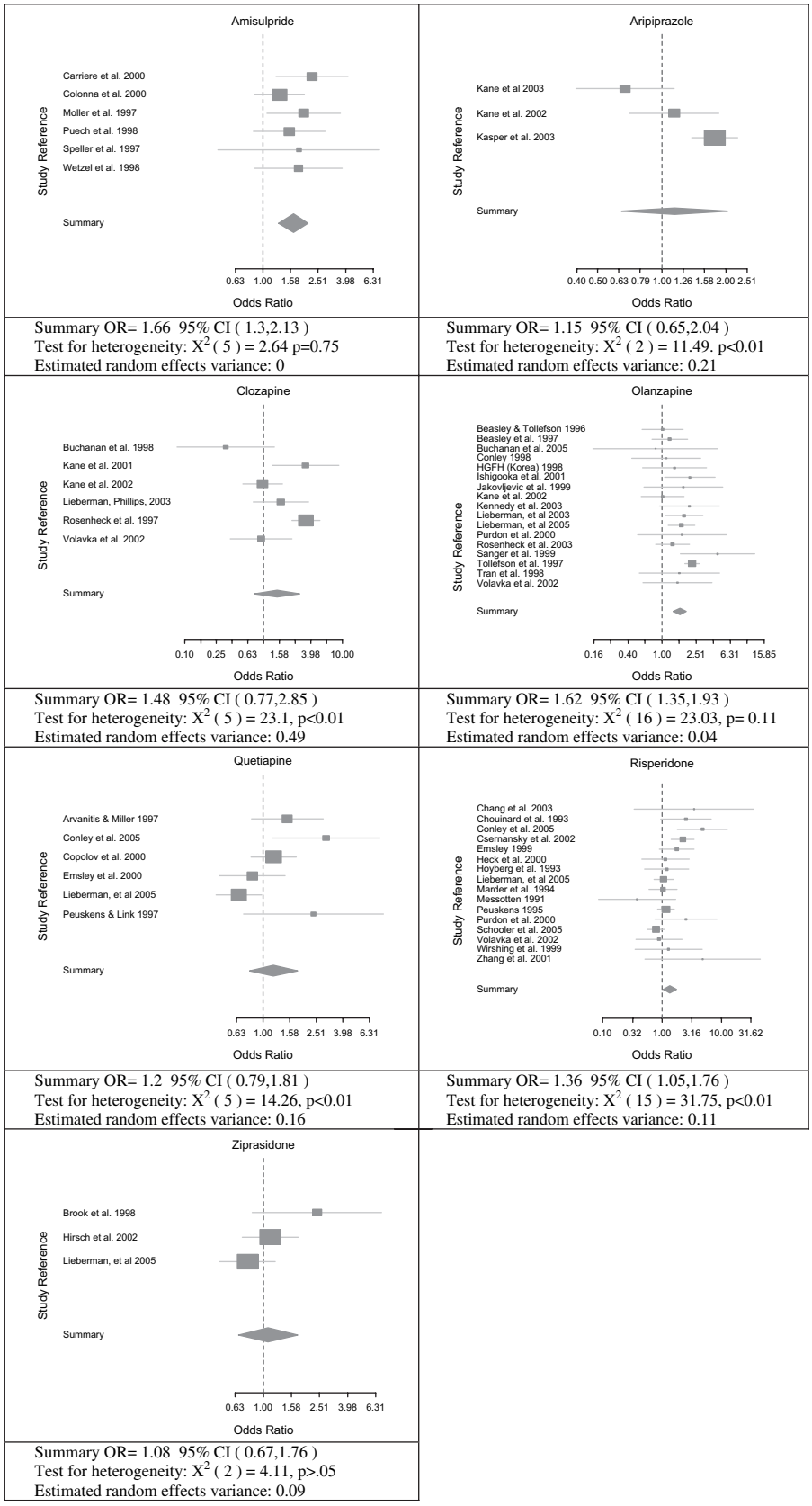

Fig. 2. Forest Plots Comparing First- and Second-Generation Antipsychotic Drugs.

Table 3. Results of Meta-analysis for All Studies and Subgroups of Studies

Grouping	OR (95% CI)	Test for Heterogeneity (χ^2); Estimated Random Effects Variance (REV)
All studies (n = 52)	1.49 (1.31, 1.69)	116.39, df = 51, P = 0; REV = 0.1
Studies with at least 30 patients per arm	1.46 (1.27, 1.66)	106.02, df = 42, P = 0, REV = 0.1
Studies with at least 50 patients per arm	1.43 (1.24, 1.64)	90.14, df = 32, P = 0, REV = 0.1
Studies with at least 100 patients per arm	1.38 (1.11, 1.71)	90.14, df = 15, P = 0, REV = 0.15
Studies not using excessive doses for first- and second-generation drugs (n = 21)	1.34 (1.14, 1.57)	30.72, df = 20, P = .059; REV = 0.04
Clozapine (n = 3)	0.97 (0.49, 1.92)	3.81, df = 2, P = .149; REV = 0.17
Olanzapine (n = 8)	1.74 (1.38, 2.2)	1.57, df = 7, P = .98; REV = 0
Quetiapine (n = 3)	1.04 (0.58, 1.87)	6.84, df = 2, P = .03; REV = 0.17
Risperidone (n = 5)	1.30 (0.88, 1.93)	15.3, df = 4, P = .004; REV = 0.13
Ziprasidone (n = 2)	0.93 (0.65, 1.34)	1.26, df = 1, P = .26; REV = 0.01
Flexible dose studies not using excessive dosing (n = 17)	1.37 (1.12, 1.68)	27.77, df = 16, P = .03; REV = 0.07
Studies of patients with symptom exacerbation (n = 40)	1.40 (1.26, 1.57)	48.64, df = 39, P = .14; REV = 0.02
Studies of nonresponder patients (n = 10)	1.53 (1.01, 2.32)	47.77, df = 9, P = 0; REV = 0.31
Inpatient studies (n = 23)	1.54 (1.3, 1.84)	38.4, df = 22, P = .02; REV = 0.06
Outpatient studies (n = 29)	1.45 (1.2, 1.74)	77.69, df = 28, P = 0; REV = 0.13

rates. The equation shows a reasonable correspondence between predicted and actual dropout rates.

Clinical Implications

A previous meta-analysis[2] covering studies up to the year 2000 reported an effect only for clozapine. Unlike that review, but like a review of 36 selected studies through 2003,[6] our results show significant effects spanning second-generation drugs. Beyond those reviews, the results identify drug-specific effects. Our results also differ from another meta-analysis covering studies through 1998[5] that reports differences favoring amisulpride, clozapine, risperidone, and olanzapine. In that meta-analysis for all but amisulpride, these differences are found only in the

Table 4. Mixed Effects Regression for Meta-analysis (Mima in R) Predicting Dropout

	Second Generation (Arms = 171)[a]				First Generation (Arms = 52)[b]				Placebo (Arms = 26)[c]			
	Estimate	SE	z	P	Estimate	SE	z	P	Estimate	SE	z	P
Intercept	−1063.80	774.72	−1.37	0.17	−1760.18	1726.94	−1.02	0.31	2226.70	2296.50	0.97	0.33
Publication year	0.54	0.39	1.41	0.16	0.89	0.86	1.03	0.30	−1.10	1.15	−0.96	0.34
Symptom level[d]	1.85	3.20	0.58	0.56	−3.75	5.91	−0.63	0.52	4.67	11.13	0.42	0.67
Inpatient	−1.49	2.98	−0.50	0.62	−0.75	5.99	−0.12	0.90	5.96	8.23	0.72	0.47
With placebo	4.23	3.57	1.19	0.24	11.75	10.42	1.13	0.26	—	—	—	—
Number of arms	0.52	0.92	0.56	0.57	3.13	2.69	1.16	0.24	1.86	2.47	0.75	0.45
Duration in weeks	0.38	0.08	4.99	0.0001	0.31	0.12	2.57	0.01	0.94	0.33	2.88	0.004
Fixed dose	8.23	3.39	2.43	0.01	−4.18	7.03	−0.59	0.55	10.02	10.57	0.95	0.34
High dosage	−3.50	2.68	−1.30	0.19	11.05	5.92	1.87	0.06	—	—	—	—

[a]Estimate of (residual) heterogeneity: 257.92; test for (residual) heterogeneity: QE = 83076.29; df = 162; $P < .0001$; omnibus test of all moderators: QME = 50.32; df = 8; $P < .0001$.
[b]Estimate of (residual) heterogeneity: 307.14; test for (residual) heterogeneity: QE = 23856.1; df = 43; $P < .0001$; omnibus Test of all Moderators: QME = 20.00; df = 8; P = .01.
[c]Estimate of (residual) heterogeneity: 314.62; test for (residual) heterogeneity: QE = 9494.47; df = 19; $P < .0001$; omnibus Test of all Moderators: QME = 10.62; df = 6; P = .10.
[d]Based on study inclusion criteria: 0 nonresponder patients, 1 patient with symptom exacerbation, 2 stable responder patients.

Appendix Randomized Controlled Trials of Second Generation Antipsychotic Medications Summary

Publication	Total *n*	Total Dropout	Duration in wk	Arms	Placebo *n*	Placebo Dropout	First Generation *n*	First Generation Dropout	Second Generation *n*	Second Generation Dropout	Placebo	Symptoms	Fixed	Dosage	In Hospital
Addington et al[56]	296	98	8	2					296	98		SE			In
Arato et al[50]	278	179	52	4	71	61			207	118	P	SE	fix		
Arvanitis and Miller[27]	361	212	6	7	51	35	52	34	258	143	P	SE	fix	NME	In
Azorin et al[57]	273	72	12	2					273	72		SE		NME	
Beasley Sanger et al[28]	152	107	6	3	50	40			102	67	P	NR	fix		In
Beasley et al[29]	335	196	6	5	68	46	69	39	198	111	P	SE	fix	NME	
Beasley et al[58]	431	184	6	5			81	38	350	146		SE	fix	NME	In
Beasley et al[30]	326	85	52	2	102	55			224	30	P	SR			
Bitter et al[59]	150	63	18	2					150	63		SE		NME	In
Borison et al[31]	109	59	6	2	55	33			54	26	P	SE			In
Boyer et al[32]	104	19	6	3	34	9			70	10	P	SE	fix	NME	In
Brook et al[60]	132	16	1	2			42	8	90	8		SE			
Buchanan et al[62]	75	11	10	2			37	3	38	8		NR			
Buchanan et al[61]	63	6	16	2			34	3	29	3		SE			
Carriere et al[63]	199	70	16	2			105	46	94	24		SE		NME	
Casey et al[64]	207	55	8	3					207	55		SR	fix	NME	In
Chan et al[65]	60	8	8	2					60	8		SE			In
Chang et al[66]	62	4	8	2			30	3	32	1		SE		NME	
Chouinard et al[33]	135	65	8	6	22	16	21	13	92	36	P	SE	fix		In
Chue et al[67]	640	527	12	2					640	527		SE	fix		
Colonna et al[9]	489	229	52	2			119	62	370	167		SE		NME	
Conley and Mahmoud[69]	377	96	8	2					377	96		SE		NME	
Conley 1998[70]	84	25	8	2			42	13	42	12		NR	fix	NME	In
Conley et al[68]	114	54	12	3			38	26	76	28		NR	fix		In
Cooper et al[34]	159	69	8	3	53	25	53	25	53	19	P	SE			
Cooper et al[35]	119	90	26	2	58	49			61	41	P	SR	fix		
Copolov et al[10]	448	149	6	2			227	80	221	69		SE			In
Corrigan et al[36]	735	154	6	8	86	22			649	132	P	SE			In
Csernansky et al[11]	367	246	52	2			188	142	179	104		SR			
Daniel et al[12]	282	70	52	2			141	43	141	27		SE	fix		
Daniel et al[37]	302	86	6	3	92	43			210	43	P	SE	fix		
Danion et al[38]	242	62	12	3	83	33			159	29	P	SE	fix		
Emsley[71]	183	46	6	2			84	26	99	20		SE		NME	
Emsley et al[13]	288	60	12	2			145	28	143	32		NR	fix		
Gureje et al[72]	65	36	30	2					65	36		SE		NME	
Heck et al[73]	77	30	7	2			37	15	40	15		SE		NME	
HGFH Korea[74]	104	29	6	2			51	16	53	13		SE			
Hirsch et al[14]	301	171	28	2			153	89	148	82		SR			

Appendix Continued

Publication	Total *n*	Total Dropout	Duration in wk	Arms	Placebo *n*	Placebo Dropout	First Generation *n*	First Generation Dropout	Second Generation *n*	Second Generation Dropout	Placebo	Symptoms	Fixed	Dosage	In Hospital
Hoyberg et al[75]	107	29	8	2			52	15	55	14		SE			In
Huttunen et al[76]	98	40	6	2					98	40		SE			In
Ishigooka et al[77]	182	48	8	2			89	30	93	18		SE			
Jakovljevic et al[78]	60	22	6	2			30	13	30	9		SE			In
Jeste et al[79]	175	41	8	2					175	41		SE			
Kane et al[15,16]	300	75	6	2			146	31	154	44		NR		NME	
Kane et al[80]	71	35	26	2			34	22	37	13		NR		NME	
Kane et al[17]	594	239	4	4	106	48	104	42	384	149	P	SE	fix	NME	
Kane et al[15,16]	400	222	12	6	98	66			302	156	P	SE	fix		
Kasper et al[18]	1294	799	52	2			433	305	861	494		SE	fix		In
Keck et al[39]	139	64	4	3	48	24			91	40	P	SE	fix		
Kennedy et al[81]	117	47	6	2			34	18	83	29		SE			
Kudo et al[82]	180	59	8	2					180	59		SE			
Lecrubier et al[40]	244	143	26	4	34	22			210	121	P	SE	fix		
Lee et al[83]	54	9	6	2					54	9		SE			
Lieberman et al[19,20,84]	263	103	12	6			132	61	131	42	P	SE			
Lieberman et al[1]	1432	1061	78	5			257	192	1175	869		SE			
Lieberman et al[20]	160	30	52	2			80	18	80	12		SE			In
Loo et al[41]	141	80	26	2	72	49			69	31	P	SE	fix		
Marder et al[42]	388	199	8	6	66	45	66	32	256	122	P	SE	fix		In
Martin et al[85]	377	81	26	2					377	81		SE		NME	
McQuade et al[86]	317	230	26	2					317	230		SE			
Meltzer et al[43]	481	337	6	6	98	78	98	68	285	191	P	SE	fix		In
Messotten[87]	60	9	8	2			32	3	28	6		SE		NME	In
Moller et al[88]	191	64	6	2			96	39	95	25		SE	fix	NME	In
Mortimer et al[89]	377	135	26	2					377	135		SE		NME	In
Mullen et al[90]	728	235	16	2					728	235		SE			
Naber et al[91]	114	71	26	2					114	71		SE			
Petit et al (1997)	126	55	8	2			63	30	63	25		SE			In
Peuskens and Link[93]	201	13	6	2			100	9	101	4		SE			In
Peuskens[21]	1362	347	8	6			226	63	1136	284		SE	fix		In
Peuskens et al[92]	228	69	8	2					228	69		SE	fix	NME	
Pigott et al[44,45]	310	194	26	2	155	110			155	84	P	SR	fix	NME	In
Potkin et al[46]	404	162	4	4	103	51			301	111	P	SE	fix	NME	In
Puech et al[94]	319	82	4	5			64	21	255	61		SE	fix	NME	In
Purdon et al[95]	65	32	54	3			23	14	42	18		SE			
Ritchie et al[96]	66	14	4	2					66	14		SR			
Rosenheck et al[22]	423	245	52	2			218	157	205	88		NR		NME	In
Rosenheck et al[23]	309	187	52	2			150	96	159	91		NR			

Appendix Continued

Publication	Total *n*	Total Dropout	Duration in wk	Arms	Placebo *n*	Placebo Dropout	First Generation *n*	First Generation Dropout	Second Generation *n*	Second Generation Dropout	Placebo	Symptoms	Fixed	Dosage	In Hospital
Sanger et al[97]	83	31	6	2			24	15	59	16		SE			
Schooler et al[24]	555	218	104	2			277	101	278	117		SE			
Sechter et al[98]	310	123	26	2					310	123		SR		NME	
Simpson et al[99]	269	115	6	2					269	115		SE			In
Small et al[47]	286	159	6	3	96	57			190	102	P	SE	fix		In
Speller et al[100]	60	11	52	2			31	7	29	4		SE		NME	In
Tollefson et al[25,26]	1996	799	6	2			660	351	1336	448		NR			
Tollefson et al[48]	106	11	1	2	53	8			53	3	P	SE	fix		
Tran et al[102]	339	161	28	2					339	161		SE		NME	
Tran et al[101]	54	24	14	2			28	14	26	10		SE			
Van-Kammen et al[49]	153	53	6	4	38	15			115	38	P	SE	fix		In
Volavka et al[103]	157	66	14	4			37	16	120	50		SE		NME	In
Wetzel et al[104]	132	44	6	2			62	25	70	19		SE		NME	In
Wirshing et al (1999)[105]	67	11	8	2			33	6	34	5		NR		NME	
Woods et al[51]	60	19	8	2	29	8			31	11	P	SE			
Zhang et al[106]	78	5	12	2			37	4	41	1		SE	fix	NME	In

fixed and not random effects analysis, and no evidence supporting differences for quetiapine are identified. Like Wahlbeck et al[2] we found that dropout increases with trial length, however, we did not find a significant effect of publication year. While Kemmler et al[3] reports an effect for placebo arms in studies up to 12 weeks long, we did not find a significant placebo arm effect, which may be related to our inclusion of studies regardless of length. We also did not find an effect of multiple dosage regimes. Corresponding to others,[6] flexible rather than fixed dosage was found to effect dropout in second-generation and not first-generation arms. Like Geddes et al[5], we found a nearly significant effect of high dosages on dropout for first-generation medications. Collectively, therefore, our findings support the use of second-generation treatment over first-generation treatment where dropout is the outcome.

Limitations

Several limitations are notable. It is not possible to estimate the possible bias introduced by studies not published, although our review was used by the Cochrane database that includes unpublished studies. Also, our meta-analysis does not eliminate studies due to a priori criteria that may have biased the results (eg, including only large clinical trials or only trials of a certain duration). Another limitation is that the current data contain limited clinical information. Such information is likely to influence the study outcomes, although the clinical information our study contained did not (ie, hospitalization status and symptom severity). It is noted that there is a payoff in meta-analysis between number of variables and the number of studies. The approach taken here was to opt for more studies in an unbiased manner, thus maximizing statistical power. Statistical power was, however, small when examining the specific effects of some of the second-generation medications. The number of studies included in the current meta-analysis, however, is much larger than previous reviews. The available data do not yet permit the analysis of long-acting injectable second-generation antipsychotics (eg, risperidone injectable) and thus highlight a direction for future research once enough studies become available. The formula to derive expected dropout rates may be useful to plan trials and compare study results. The formula should, however, be used with caution until it is validated by predicting dropout rates in future studies.

Conclusions

The current results demonstrate that dropout rates are moderately yet consistently reduced by second- rather than first-generation antipsychotic medication. This trend replicates across medications and irrespective of

a series of moderators investigated (eg, hospitalization status, dosage). The current meta-analysis represents, to our knowledge, the largest study of how methodological factors effect dropout in clinical trials of antipsychotic medication. The results indicate that dropout rates are significantly influenced by the trial duration, fixed vs flexible dosing, and excessive dosing. These findings provide a significant increment in understanding dropout rates in clinical trials and may contribute to the design of future clinical trials. Collectively, these results show moderate and consistent benefits, indicated by dropout reduction, that favor second- over first-generation medications and provide formulae to assist future trial designs.

Supplementary Material

Supplementary material for this article is available online at http://schizophreniabulletin.oxfordjournals.org/.

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