Antipsychotic Combinations vs Monotherapy in Schizophrenia: A Meta-analysis of Randomized Controlled Trials

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Context: Despite lacking evidence for its safety and efficacy, antipsychotic cotreatment is common in schizophrenia. *Objective:* To evaluate therapeutic and adverse effects of antipsychotic cotreatment vs monotherapy in schizophrenia. *Data Sources:* Cochrane Schizophrenia Group register and hand searches of relevant journals/conference proceedings. *Study Selection:* Randomized controlled trials comparing antipsychotic monotherapy to cotreatment with a second antipsychotic. *Data Extraction and Analysis:* Two authors independently extracted data. For homogenous dichotomous data, we calculated random effects, relative risk (RR), 95% confidence intervals (CIs), and numbers needed to treat (NNT). For continuous data, weighted mean differences were calculated. *Results:* In 19 studies (1229 patients) with 28 monotherapy and 19 cotreatment arms, antipsychotic cotreatment was superior to monotherapy regarding 2 a priori defined coprimary outcomes: less study-specific defined inefficacy ($N = 22$, $n = 1202$, RR = 0.76, CI = 0.63–0.90, $P = .002$, NNT = 7, CI = 4–17, $P = .0008$, $I^2 = 78.9\%$) and all-cause discontinuation ($N = 20$, $n = 1052$, RR = 0.65, CI = 0.54–0.78, $P < .00001$). Results were consistent using Clinical Global Impressions thresholds of less than much ($P = .006$) and less than minimally ($P = .01$) improved. Specific psychopathology and adverse event data were insufficient to yield meaningful results. In sensitivity analyses, 5 efficacy moderators emerged: concurrent polypharmacy initiation, clozapine combinations, trial duration >10 weeks, Chinese trials, and second-generation + first-generation antipsychotics. In a meta-regression, similar dose combinations, second-generation + first-generation antipsychotics and concurrent polypharmacy initiation remained significant. *Conclusions:* In certain clinical situations, antipsychotic cotreatment may be superior to monotherapy. However, the database is subject to possible publication bias and too heterogeneous to derive firm clinical recommendations, underscoring the need for future research.

Key words: antipsychotics/polypharmacy/combination/monotherapy/schizophrenia/efficacy/all-cause discontinuation/side effects/trial methodology

In schizophrenia, treatment resistance and unsatisfactory functional outcomes continue to be a significant clinical and public health problem.[1–4] To date, clozapine has remained the only treatment that consistently resulted in significantly superior outcomes compared with other antipsychotics in patients unresponsive or partially responsive to antipsychotic monotherapies.[5–7] A multitude of augmentation strategies have been tried in randomized controlled studies, including lithium,[8] carbamazepine,[9] valproate,[10] benzodiazepines,[11] beta-blockers,[12] antidepressants,[13] anti-inflammatory agents,[14] glutamatergic agents,[15] and electroconvulsive therapy.[16] However, none of these strategies has reliably demonstrated efficacy for people whose psychosis did not respond to antipsychotic monotherapy.

In this context, antipsychotic combination treatment, also called antipsychotic polypharmacy, has been utilized frequently in clinical practice. Reports of the prevalence of antipsychotic polypharmacy in the United States vary from 7% to approximately 50%,[3,17–21] with most studies finding prevalence rates of between 10% and 30%. Moreover, some studies have shown a trend toward the increasing use of polypharmacy in the same treatment settings over time,[18,22] despite the fact that evidence-based treatment guidelines recommend antipsychotic cotreatment only after unsuccessful attempts of multiple monotherapies, including clozapine.[23,24]

While the lack of any pharmacologic rationale for combining antipsychotics with the same putative antipsychotic dopamine D2 receptor blockade has been criticized, there

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is also limited mechanistic understanding of antipsychotic efficacy and "polypharmacy" is an intrinsic characteristic of most antipsychotics due to multiple pharmacodynamic neurotransmitter effects. Nevertheless, antipsychotic cotreatment remains a controversial practice because of insufficient evidence supporting its efficacy,[25,26] concerns about long-term safety,[17,27] mortality,[28,29] and increased cost.[26] Moreover, all the few randomized controlled trials (RCTs) of antipsychotic polypharmacy cited in this context involve augmentation of clozapine with a high dopamine D2 affinity antipsychotic.[30–33] This, however, is in contrast to clinical practice in the Western world, where clozapine is used relatively infrequently, both in monotherapy and as antipsychotic cotreatment,[17–21] which is initiated mostly without a prior clozapine trial.

In view of the prevalence of this clinical practice and the paucity of evidence in its support, we conducted a comprehensive review of the available evidence regarding the efficacy, effectiveness, and safety of antipsychotic combinations compared with treatment with antipsychotic monotherapy in patients with schizophrenia.

Methods

Search

We searched the register of the Cochrane Schizophrenia Group (CSG) for published or unpublished RCTs that compared antipsychotic monotherapy with the combination of the same antipsychotic with another one in the treatment of schizophrenia or related disorders (schizoaffective-, schizophreniform-, or delusional disorder, any diagnostic criteria). The CSG register is compiled by regular methodical searches in numerous electronic databases (BIOSIS, CINAHL, Dissertation Abstracts, EMBASE, LILACS, MEDLINE, PSYNDEX, PsycINFO, RUSSMED, Sociofile), supplemented by hand searching of relevant journals and conference proceedings, and searches of several key literature sources (last search June 2006, updated since then by monthly MEDLINE searches until March 2007). For details of the register, see the description of the CSG.[34]

The following search terms were used: [((antipsychot* or neuroleptic* or drug*) and combin*)) or augmentation* or enhancement or add-on* or addition*or supplement*or cotreatment*or co-treatment*or adjunctive* or concurrent* or concomitant* or simultaneous* or parallel* or polypharmacy* in title terms) or (*add-on* or *addition*or *supplement*or *supplementation*or *cotreatment*or *co-treatment*or *adjunctive* or *concurrent* or *concomitant* or *simultaneous* or *parallel* or *polypharmacy* in abstract or index terms of REFERENCE]) or [*Polytherapy* or *Augmentation* or *Parallel* or *Combined* in interventions of STUDY].

Only studies meeting the quality criteria A (adequate randomization) and B (usually studies stated to be

randomized without further details) according to the Cochrane handbook were included.[35] There were no restrictions regarding language, sample size, or time period. In addition, the reference sections of included articles were screened, and the first authors of the included studies were asked whether they were aware of additional trials, as well as about missing data necessary for the meta-analysis. Two authors independently identified and extracted data from the trials.

Outcome Parameters

The primary outcomes of interest were a clinically significant response defined as at least 50% reduction of the Positive and Negative Syndrome Scale (PANSS) or the Brief Psychiatric Rating Scale (BPRS) or at least "much better" on the Clinical Global Impressions (CGI) scale,[36,37] dropout rates, and relapse. If the response criteria mentioned above were not available, we used the authors' definition. Secondary outcomes were general and specific aspects of the mental state (BPRS/PANSS total scores, positive and negative symptoms, depression, mania, aggression), service utilization, functioning, additional drug use, quality of life, general and specific side effects, and cost.

For dichotomous data, we applied a "once randomized—analyzed" end point analysis. Continuous data were reported as presented in the original studies without any assumptions about those lost to follow-up.

Meta-analytic Calculations

We applied standard meta-analytic procedures as used by the Cochrane Collaboration throughout. For dichotomous data, we calculated the relative risk (RR), and for continuous data we calculated Hedges's g as effect size measures, both along with their 95% confidence intervals (CIs). To combine studies, the random effects model by Der-Simonian and Laird[38] was used in all cases, which is more conservative than fixed effects models. We explored study heterogeneity using the I^2 statistic, a measure estimating how much of the variance is explained by study heterogeneity.[39] I^2 values of 50% or higher were considered to reflect considerable heterogeneity. In such cases, we sought reasons explaining the heterogeneity, conducting sensitivity analyses. In the case of significant differences between groups, the number of participants needed to treat (NNT) or the number of participants needed to harm was calculated as the inverse of the risk difference (RD). The possibility of publication bias was examined using the "funnel plot" method described by Egger and colleagues.[40]

In the primary analyses, we included all studies that compared monotherapy with one antipsychotic to polytherapy with the same antipsychotic combined with a different one. In the 9 studies that included 3 arms comparing the antipsychotic cotreatment with the

monotherapy of each of the 2 antipsychotics that were part of the combination, we included the cotreatment condition twice in the analyses. This was done to be able to include each of the monotherapy arms separately in the analyses. Thus, the total number of study arms ($N = 19 + 9 = 28$) and patients ($n = 1229 + 238 = 1454$) included in the analyses was higher than the total number of studies ($N = 19$) and patients ($n = 1216$). However, in order to exclude that this methodology could have led to an alteration of the results, we repeated the meta-analysis counting the combination treatment only once, comparing it to the results of both monotherapy arms together in cases of 3 arm studies.

In addition to the primary analyses, we conducted 9 sensitivity analyses. This was done to examine if variations in design, clinical practice, settings, populations, and antipsychotics across studies conducted at different times and in different regions may have been responsible for the heterogeneity of the primary efficacy outcome (ie, inefficacy as defined by each study). These sensitivity analyses included: (1) double-blind vs single-blind/open study design; (2) Chinese vs non-Chinese studies; (3) enrollment of acutely exacerbated or chronically ill patients; (4) combined initiation vs delayed augmentation after nonresponse; (5) comparative vs reduced antipsychotic doses in the cotreatment arm; (6) treatment duration <10 weeks vs ≥10 weeks; (7) clozapine vs nonclozapine combinations; (8) cotreatment with 2 first-generation antipsychotics (FGAs) compared with 1 FGA, cotreatment with 2 second-generation antipsychotics (SGAs) compared with 1 SGA, cotreatment with an FGA plus an SGA compared with either an FGA or SGA, respectively; and (9) counting the cotreatment arm only once, comparing it to both monotherapy arms together in the 9 trials where 2 monotherapy treatment existed. All moderators tested in the sensitivity analyses were also included in an unrestricted maximum likelihood random effects meta-regression. Because these analyses were considered exploratory, we did not correct P values for multiple testing.

Finally, to examine in more detail if dose differences between the antipsychotic combination and monotherapy treatment arms could have influenced the results, we compared (a) the chlorpromazine equivalent doses between the antipsychotic monotherapy and polytherapy arms across all studies with efficacy data and (b) the ratio of the chlorpromazine equivalents between the monotherapy and polytherapy arms in studies finding superior efficacy of combination treatment vs studies that did not find such a difference, defined as either statistical superiority (ie, $P < .05$ indicated by no overlap of the 95% CI with the y-axis), or as the mean value being to the left of the y-axis (ie, favoring antipsychotic combinations), independent of whether or not the 95% CI overlapped with the y-axis (figure 2). Because efficacy as well as dose information for the mono- and polytherapy groups

was available in only 20 of the 47 treatment arms (42.5%), inclusion of the chlorpromazine equivalent ratio into the meta-regression would have lead to the exclusion of the majority of treatment arms, potentially skewing the results of the other moderator variables for which information was available in all studies. Therefore, we repeated the primary end point analysis of efficacy as defined by each study in the subset of studies with both efficacy and dose information. This was done to ensure that the influence of dose was examined in a subset of studies that was representative of the primary efficacy result across all studies. Chlorpromazine equivalents were calculated based on proposed conversion factors for FGAs[41,42] and SGAs.[43]

All meta-analytic calculations were performed with RevMan Analyses, a meta-analytic standard software used by the Cochrane collaboration,[44] and STATA 8.0 for the meta-regression. All analyses were 2 tailed, with alpha set at 0.05.

Results

The Search

The original search yielded 1482 electronic records. A total of 1433 publications were excluded on the abstract level. For 49 hits, full reports were ordered for inspection. Of those, 30 studies were excluded, leaving 19 studies, because they were not randomized ($N = 10$) or only quasi-randomized ($N = 7$), did not analyze comparisons relevant for our review ($N = 10$), or reported no usable data ($N = 3$) (figure 1).

Characteristics of Included Studies and Participants

In total, the 19 studies included 1216 participants. Sample sizes per study varied widely, ranging from 17 to 233 (median 57; table 1). In 10 studies (52.6%), 1 antipsychotic combination treatment was compared with 1 monotherapy arm ($n = 558$, 45.9%). In 9 studies (47.4%), 1 antipsychotic combination treatment was compared with 2 antipsychotic monotherapy arms ($n = 658$, 54.1%). To allow for a comparison of each of the 2 monotherapy arms with the antipsychotic combination group, we entered the 238 patients in the combination arms from these 9 studies a second time in the primary analysis, which increased the total number of patients entered in the meta-analysis from 1216 to 1454.

All included studies used a parallel group design. Fifteen studies (1042 patients) were double blind, 1 was single blind ($n = 46$), 2 were open ($n = 36$), and in one study ($n = 92$), the method of blinding was unclear. The mean trial duration was 12.1 ± 11.3 (range 4–52, median 8) weeks. Seven studies were conducted in China ($n = 511$), 5 in the United States ($n = 217$), 3 in Japan ($n = 354$), 2 in Israel ($n = 45$), 1 in Turkey ($n = 30$), and 1 in Canada, Germany, the United Kingdom, and China ($n = 68$). In
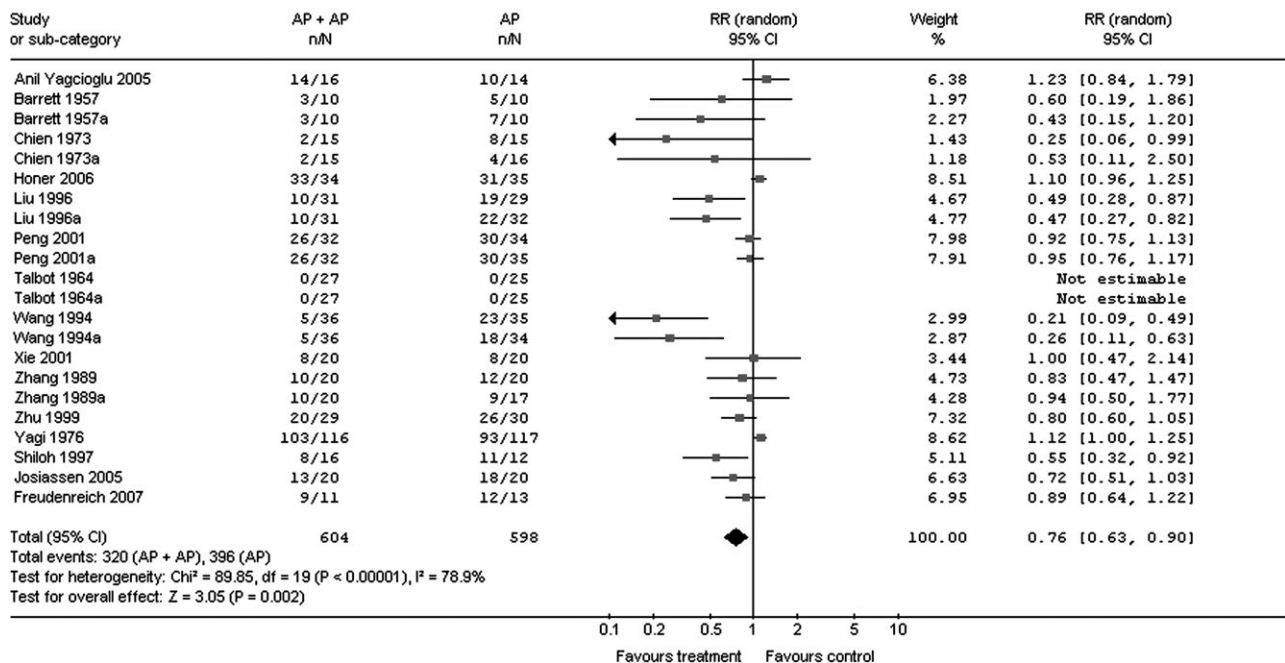
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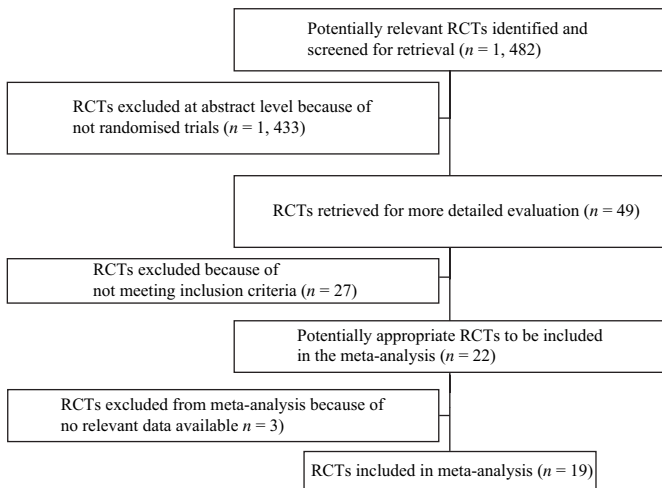
Fig. 1. Included and Excluded Studies With Reasons: The Quality of Reports of Meta-analysis (QUOROM) Flow Diagram.

In the 17 studies with information, participants were 33.4 ± 5.1 (range 16–65, median 33.9) years old, and 517 (62.3%) of the 1109 patients with available data were male. In the 18 studies ($n = 1176$) with information, most participants (1038, 88.3%) were inpatients. Most participants were in the chronic illness phase ($N = 15$, $n = 1054$); only 4 studies ($n = 162$) were conducted in acutely exacerbated patients. The mean illness duration ($N = 15$, $n = 830$) was 10.2 ± 6.7 (median 6.8) years, and the mean number of psychiatric hospitalizations ($N = 4$, $n = 245$) was 3.9 ± 1.3 (median 3.6). Almost all patients ($N = 19$, $n = 1200$, 98.7%) suffered from schizophrenia. All but 4 studies used some form of standardized diagnostic criteria, but criteria varied across time and country of origin.

Regarding antipsychotic treatments and combinations, the 28 antipsychotic monotherapy arms ($n = 698$) included 14 FGA arms ($N = 10$, $n = 378$) and 14 SGA ($N = 13$, $n = 320$) arms (table 1). The 19 antipsychotic combination arms ($n = 518$) consisted of cotreatment with 2 FGAs ($N = 6$, $n = 224$), an FGA + SGA ($N = 7$, $n = 161$), and 2 SGAs ($N = 6$, $n = 133$). The antipsychotic used the most was clozapine ($N = 11$, $n = 542$). The second most used antipsychotic was chlorpromazine ($N = 6$, $n = 375$), followed by risperidone ($N = 6$, $n = 188$), and sulpiride ($N = 5$, $n = 185$). All other individual antipsychotics were used in only one study, each (pimozide, thioridazine, fluphenazine, trifluoperazine, reserpine, haloperidol, olanzapine, levomepromazine). Mean doses

13 studies ($n = 1009$), the combination treatment was initiated at the start of the trial, while in 6 studies ($n = 207$), the second antipsychotic was added after nonresponse to an adequate dose and duration of antipsychotic monotherapy had been established. In 14 studies ($n = 866$), the monotherapy and polytherapy arms had comparable mean doses and dose ranges, while in 5 studies ($n = 350$), one or both of the antipsychotics in the combination arm were dosed considerably lower than in the monotherapy arm.

Fig. 2. Lack of Efficacy as Defined in Each Study.

Table 1. Study and Patient Characteristics

Study	N	Design:-Blinding-Timing of Cotreatment-Dosing-Setting	Trial Duration (weeks)	Country	Participants:-Diagnosis-Criteria-Illness Phase-Illness Duration	Age[a]: Years (Range)	Sex: Male (%)	Interventions: Antipsychotic Mean Dose (mg/day) Range (mg/day)Number of Patients	Comments
Antipsychotic combinations including clozapine (N = 12, n = 701)									
Clozapine plus a FGA (N = 2, n = 114)									
Potter et al. (1989)[46]	57	-Double blind-Costart -Reduced dose combination-Inpatients	8	China	-Sz-Chronic-DSM-IV and CCMD-2-R-Illness duration: 5.9 years	31.7 (16–58)	n = 35 (61%)	1. CLZ (M = NR; R = 50–600); n = 17. 2. CPZ (M = NR; R = 100–600); n = 20. 3. CLZ (M = NR; R = 50–400) + CPZ (M = NR; R = 100–400); n = 20	Data not shown for 4 BPRS positive and the depressive subscores that were reportedly significantly more improved in each clozapine arm vs the chlorpromazine monotherapy group.
Zhang and Xu (1989)[48]	57	-Double blind-Costart -Reduced dose combination-Inpatients	8	China	-Sz-Acute-DSM-III and CCMD-2-R-Illness duration: 5.8 years	31.7 (NR)	n = 36 (63%)	1. CLZ (M = 363; R = 175–500); n = 17. 2. CPZ (M = 440; R = 350–800); n = 20. 3. CPZ (M = 355; R = 200–500) + CLZ (M = 256; R = 175–500); n = 20	
Clozapine plus a SGA (N = 10, n = 587)									
Freudenreich (2007)[49]	24	-Double blind -Augmentation -Comparative dose combination-Outpatients	6	United States	-Sz-DSM-IV-Chronic (refractory)-Illness duration: 20.6 years	42.3 (27–55)	n = 21 (88%)	1. CLZ (M = 456; R = 200–700); n = 11. 2. CLZ (M = 456; R = 200–700) + RIS (M = 4; R = NR); n = 13	Four (14.3%) of 28 original patients were eliminated during 2-week placebo lead-in due to not reaching the symptom severity criterion anymore.
Anil Yagcioglu et al. (2005)[32]	30	-Double blind -Augmentation-Comparative dose combination -Inpatients (n = 6) and outpatients (n = 24)	6	Turkey	-Sz-DSM-IV -Chronic(refractory) -Illness duration: 12.2 years	33.4 (18–55)	n = 20 (67%)	1. CLZ (M = 414.3; R = 300–900); n = 14. 2. CLZ (M = 515.6; R = 300–900) + RIS (M = 5.1; R = NR); n = 16	Significantly greater number of hospitalizations (P = .01), clozapine dose (P = .05) and number of smokers (P = .03) in cotreatment group.
Honer et al. (2006)[33]	68	-Double blind -Augmentation-Comparative dose combination -Inpatients: n = 26 + outpatients: n = 42	8	Canada, FRG, China, United Kingdom	-Sz (92.6%); SzA (7.4%)- DSM-IV -Chronic (refractory)- Duration: 15.0 years	37.2 (18-65)	n = 50 (74%)	1. CLZ (M = 487; R = NR); n = 34. 2. CLZ (M = 494; R = NR) + RIS (M = 3; R = NR); n = 34	Stability of PANSS score assessed after 1-week single-blind placebo augmentation run-in phase.
Josiassen et al. (2005)[31]	40	-Double blind -Augmentation-Comparative dose combination -Inpatients (n = 32) and outpatients (n = 8)	12	United States	-Sz-DSM-IV-Chronic (refractory)-Illness duration: 22.1 years	40.3 (20–65)	n = 35 (88%)	1. CLZ (M = 403; R = NR); n = 20. 2. CLZ (M = 529; R = NR) + RIS (M = 4.4; R = NR); n = 20	More males (P < .05) and higher clozapine dose (P < .006) in cotreatment than in monotherapy group; CGI data not reported.

Table 1. Continued

Study	N	Design:-Blinding-Timing of Cotreatment-Dosing-Setting	Trial Duration (weeks)	Country	Participants:-Diagnosis-Criteria-Illness Phase-Illness Duration	Age[a]: Years (Range)	Sex: Male (%)	Interventions: Antipsychotic Mean Dose (mg/day) Range (mg/day)Number of Patients	Comments
Liu et al. (1996)[50]	92	-Blindness "unclear" -Costart-Comparative dose combination -Inpatients	12	China	-Sz (negative symptom type)-Chronic-DSM-III-R-Illness duration: 6.9 years	25.2 (16–54)	$n = 60$ (65%)	1. CLZ (M = 466.8; R = 450–600); $n = 32$. 2. SUL (M = 1296.6; R = 900–1500); $n = 29$. 3. CLZ (M = 436.6; R = 450–600) + SUL (M = 1127.2; R = 900–1500); $n = 31$	No information about the group assignment in the 5 patients who dropped out.
Peng et al. (2001)[51]	101	-Double blind-Costart -Reduced dose combination-Inpatients	8	China	-Sz-Chronic (refractory)-CCMD-2-R-Illness duration: 7.1 years	25.2 (16–60)	$n = 67$ (66%)	1. CLZ (M = NR; R = 75–600 TID); $n = 34$. 2. RIS (M = NR; R = 1–8 QD); $n = 35$. 3. CLZ (M = NR; R = 25–200 QD) + RIS (M = NR; R = 1–6 QD); $n = 32$	Flexible dosing.
Shiloh (1997)[30]	28	-Double blind -Augmentation-Comparative dose combination-Inpatients	10	Israel	-Sz-Chronic (refractory)-DSM-IV-Illness duration: 20.0 years	38.9 (NR)	$n = 19$ (68%)	1. CLZ (M = 446; R = NR); $n = 12$. 2. CLZ (M = 403; R = NR) + SUL (M = NR; R = 100–600); $n = 16$	All mental state data skewed. Significantly longer past hospitalization in PBO group ($P < .05$); CGI data not reported; CLZ serum levels not reported.
Wang et al. (1994)[52]	105	-Double blind-Costart -Reduced dose combination-Inpatients (for acute 8-week trial)	8 (plus follow-up at 12, 52, and 156 weeks)	China	-Sz (negative symptom type)-Acute-CCMD-2-Illness duration: 3.4 years	30.3 (18–64)	$n = 0$ (0%)	1. CLZ (M = 186.9; R = 50–300); $n = 34$. 2. SUL (M = 821.5; R = 600–1000); $n = 35$. 3. CLZ (M = 52.7; R = 25–100) + SUL (M = 738.5; R = 400–1000); $n = 36$	No information about the group assignment in the 5 patients who dropped out during the 8-week inpatient trial, apparently only scores of completers included in the analyses at 3, 12, and 36 months.
Xie and Ni (2001)[53]	40	-Double blind-Costart -Comparative dose combination-Setting: NR	8	China	-Sz-Acute-CCMD-2-R-Illness duration: 3.2 years	32.3 (15–53)	$n = 27$ (68%)	1. RIS (M = NR; R = 4–6); $n = 20$. 2. RIS (M = NR; R = 4–6) + CLZ (M = 141; R = 50–300); $n = 20$	
Zhu et al. (1999)[54]	59	-Double blind-Costart -Comparative dose combination-Setting: NR	12	China	-Sz (negative symptom type)-Chronic-CCMD-2-R-Illness duration: NR	34.6 (NR)	$n = 32$ (54%)	1. CLZ (M = NR; R = 50–500 BID); $n = 30$ 2. CLZ (M = NR; R = 50–500 BID) + SUL (M = NR; R = 0.2–1); $n = 29$	Third treatment group, consisting of CLZ + chlorimipramine (tricyclic antidepressant, $n = 29$), was excluded.

Nonclozapine antipsychotic combinations ($N = 7$, $n = 528$)
FGA + FGA ($N = 6$, $n = 511$)

Table 1. Continued

Study	N	Design:-Blinding-Timing of Cotreatment-Dosing-Setting	Trial Duration (weeks)	Country	Participants:-Diagnosis-Criteria-Illness Phase-Illness Duration	Age[a]: Years (Range)	Sex: Male (%)	Interventions: Antipsychotic Mean Dose (mg/day) Range (mg/day)Number of Patients	Comments
Barrett et al. (1957)[45]	30	-Triple blind(raters blind to active control) -Reduced dose combination-Costart -Inpatients	12	United States	-Sz (regressed) -Chronic- Illness duration: NR	35.3 (27–47)	NR	1. CPZ (M = 520; R = 200–1200); n = 10. 2. RES (M = 5.9; R = 4–8); n = 10. 3. CPZ (M = 230; R = 100–400) + RES (M = 2.3; R = 1–4); n = 10	2 months placebo run-in; raters told that study had placebo arm to reduce rater expectation bias. IP duration: 7–8 years. No diagnostic instrument.
Chien and Cole (1973)[55]	46	-Single blind: (raters blind) -Costart-Comparative dose combination -Inpatients	4	United States	-Sz (76%), psychotic depression (19.6%), substance induced psychosis (4.4%)-Acute-Illness duration: NR	36.8 (17–62)	NR	1. CPZ (M = 388; R = NR); n = 15. 2. FLU ENAN (M = 28.5; R = 12.5–75); n = 16. 3. CPZ (M = 350; R = NR) + FLU (M = 26; R = 12.5–75); n = 15	Data analyzed only for 10-day time point, due to "sequential" design patients who were much or very much improved or much or very much worse were removed from the study after day 10. No diagnostic instrument.
Higashima et al. (2004)[56]	19	-Open label-Costart -Comparative dose combination-Inpatients	8	Japan	-Sz-DSM-IV-Acute -Illness duration: 3.8 years	28.1 (NR)	n = 12 (63%)	1. HAL (M = 5.4; R = NR); n = 10. 2. HAL (M = 5.4; R = NR) + LEV (M = 54; R = NR); n = 9	Patients untreated at time of enrollment. Efficacy data only presented for week 1 and 2. Patients with subscores ≤3 excluded from the analyses to "reduce possibility of underestimation of therapeutic benefits."
Nishikawa (1985)[57]	106	-Double blind-Costart -Comparative dose combination-Outpatients	52	Japan	-Sz (residual)-Chronic -DSM-III-Illness duration: 12.3 years	39.3 (NR)	n = 69 (75%)	1. PIM (fixed dose at 2 or 6 mg; M = 3.8; R = 2–6); n = 24. 2. THI (fixed dose at 25 or 75 mg; M = 47.7; R = 25–75); n = 22. 3. PIM (fixed dose at 2 or 6 mg, M = 4.1; R = 2–6) + THI (fixed dose at 25 or 75 mg; M = 50.5; R = 25–75); n = 47	Six patients who dropped out not included in final analyses, which were performed on 92 patients on active drug only. Outcome criteria of symptomatic relapse and adverse effect leading to study discontinuation were not defined.
Talbot (1964)[58]	77	-Double blind-Costart -Comparative dose combination-Inpatients	32	United States	-Sz-Chronic-Illness duration: NR	NR	NR	1. CPZ (150 × 2 months, 300 × 4 months); n = 25. 2. TRI (10 × 2 months, −20 × 4 months); n = 25. 3. CPZ (150 × 2 months, −300 × 4 months) + TRI (10 × 2 months, 20 × 4 months); n = 27	Baseline characteristics of treatment groups not compared. No diagnostic instrument.

Table 1. Continued

Study	N	Design:-Blinding-Timing of Cotreatment-Dosing-Setting	Trial Duration (weeks)	Country	Participants:-Diagnosis-Criteria-Illness Phase-Illness Duration	Age[a]: Years (Range)	Sex: Male (%)	Interventions: Antipsychotic Mean Dose (mg/day) Range (mg/day)Number of Patients	Comments
Yagi (1976)[47]	233	-Double blind-Costart -Comparative dose combination-Inpatients	8	Japan	-Sz-Chronic-Illness duration: 3 years in 92% of patients	NR (18–50)	$n = 126$ (54%)	1. CPZ (M = NR; R = 0–225); $n = 117$. 2. CPZ (M = NR; R = 0–225) + PER (M = NR; R = 100–599); $n = 116$	Third treatment group, consisting of CPZ + carpipramine (tricyclic antidepressant, $n = 118$), was excluded. Diagnostic separation from depressive disorders unclear, primary outcome insensitive. Inpatient: 66% > 1 year. No diagnostic instrument.
SGA + SGA ($N = 1$, $n = 17$)									
Kotler et al. (2004)[59]	17	-Open label-Augmentation -Comparative dose combination-Inpatients	8	Israel	-Sz-Chronic (refractory) -DSM-IV-Illness duration: 11.3 years	31.2 (18–60)	$n = 9$ (53%)	1. OLZ (M = 22.5; R = 20–30); $n = 8$. 2. OLZ (M = 22.2; R = 20–30) + SUL (M = 600; fixed dose); $n = 9$	All outcome data skewed. Surprisingly low BMI (25.8 and 24.3) after a mean of 33.0 and 32.3 months on olanzapine in the 2 treatment groups and BMI increase of only 1.1 and 0.8 during 8-week trial.

[a]Weighted mean; M = mean; R = range; CLZ, clozapine; CPZ, chlorpromazine; FGA, first-generation antipsychotic; FLU, fluphenazine; ENAN, Enanthate given every 11 days; HAL: haloperidol, LEV, levomepromazine; OLZ, olanzapine; PIM, pimozide; RES, reserpine: RIS, risperidone; SGA, second-generation antipsychotic; SUL, sulpiride; THI, thioridazine; TRI, trifluoperazine.
The 19 individual antipsychotic combination arms ($n = 518$) consisted of cotreatment with 2 FGA ($N = 6$, $n = 224$), a first- plus a SGA ($N = 7$, $n = 161$), and 2 SGA ($N = 6$, $n = 133$). Mean number of inpatients and outpatients based on 1176 patients (96.7%) with available information. Age based on 906 patients (74.5%) with available information. Percent male based on 1109 patients (91.2%) with available information. Mean illness duration based on 830 patients (68.3%) with available information.

Review: Antipsychotic combinations for schizophrenia (Final_Reduced_Clean 1)
Comparison: 01 Comparison 1: 2 AP vs 1 AP (incl different dose and different AP)
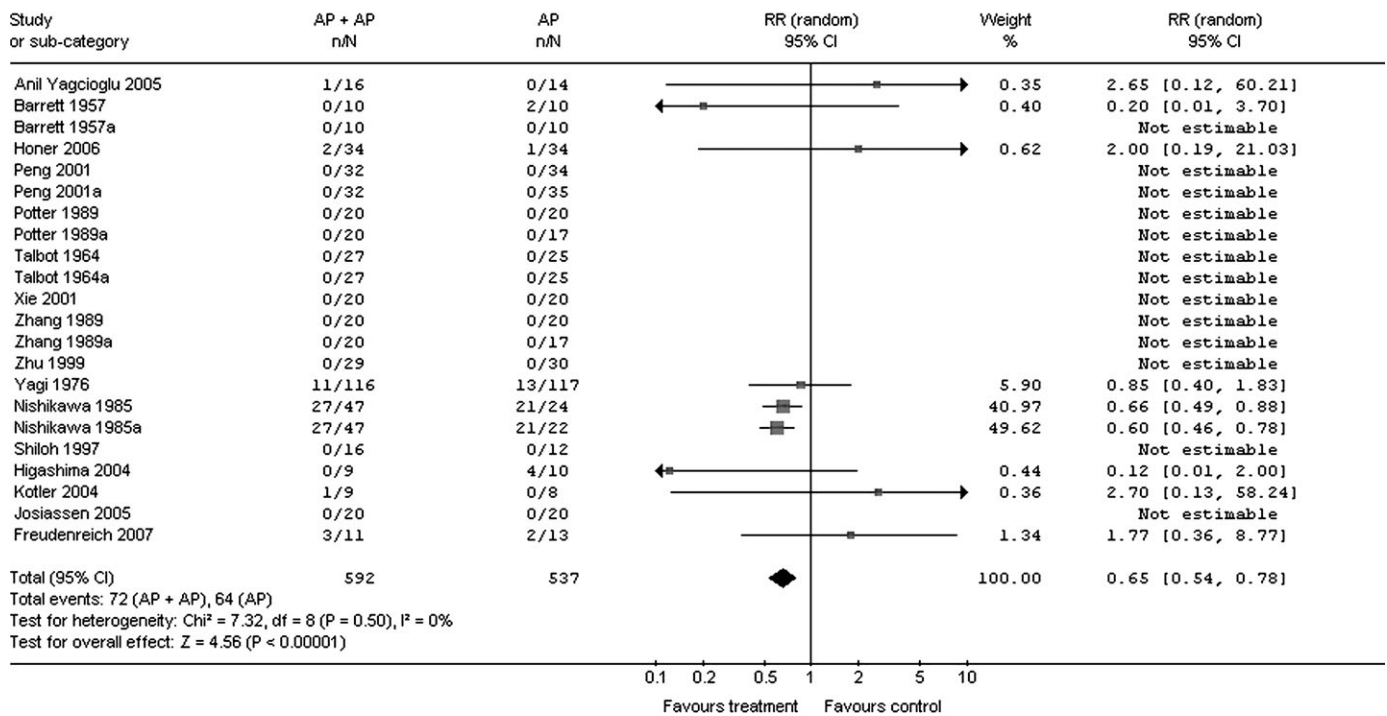Outcome: 01 Leaving the study early: 1. Any reason

Study or sub-category	AP + AP n/N	AP n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Anil Yagcioglu 2005	1/16	0/14		0.35	2.65 [0.12, 60.21]
Barrett 1957	0/10	2/10		0.40	0.20 [0.01, 3.70]
Barrett 1957a	0/10	0/10			Not estimable
Honer 2006	2/34	1/34		0.62	2.00 [0.19, 21.03]
Peng 2001	0/32	0/34			Not estimable
Peng 2001a	0/32	0/35			Not estimable
Potter 1989	0/20	0/20			Not estimable
Potter 1989a	0/20	0/17			Not estimable
Talbot 1964	0/27	0/25			Not estimable
Talbot 1964a	0/27	0/25			Not estimable
Xie 2001	0/20	0/20			Not estimable
Zhang 1989	0/20	0/20			Not estimable
Zhang 1989a	0/20	0/17			Not estimable
Zhu 1999	0/29	0/30			Not estimable
Yagi 1976	11/116	13/117		5.90	0.85 [0.40, 1.83]
Nishikawa 1985	27/47	21/24		40.97	0.66 [0.49, 0.88]
Nishikawa 1985a	27/47	21/22		49.62	0.60 [0.46, 0.78]
Shiloh 1997	0/16	0/12			Not estimable
Higashima 2004	0/9	4/10		0.44	0.12 [0.01, 2.00]
Kotler 2004	1/9	0/8		0.36	2.70 [0.13, 58.24]
Josiassen 2005	0/20	0/20			Not estimable
Freudenreich 2007	3/11	2/13		1.34	1.77 [0.36, 8.77]
Total (95% CI)	**592**	**537**		**100.00**	**0.65 [0.54, 0.78]**

Total events: 72 (AP + AP), 64 (AP)
Test for heterogeneity: Chi² = 7.32, df = 8 (P = 0.50), I² = 0%
Test for overall effect: Z = 4.56 (P < 0.00001)

```
          0.1   0.2   0.5   1    2    5   10
              Favours treatment   Favours control
```

Fig. 3. Leaving the Study Early for any Reason.

in the antipsychotic monotherapy and polytherapy groups were similar for clozapine (374.2 ± 167.9 vs 404.5 ± 96.9 mg/day, P = .65), sulpiride (1059 ± 335.9 vs 821.9 ± 273.3, P = .44), and chlorpromazine (412.0 ± 92.3 vs 282 ± 52.6 mg/day, P = .053). Doses of the other antipsychotics were reported too infrequently to enable a meaningful comparison.

Data Reporting and Study Quality

Most usable data existed regarding study discontinuation and lack of clinically relevant response. Very limited data were available regarding specific aspects of psychopathology. Data were mostly insufficient for adverse events.

Outcome Results

Antipsychotic Monotherapy vs Augmentation With a Second Antipsychotic Drug. Concerning primary outcomes, antipsychotic polypharmacy was significantly superior regarding study-specific defined inefficacy (N = 22, n = 1202, RR = 0.76, CI = 0.63–0.90, P = .002, NNT = 7, CI = 4–17, P = .0008) (figure 2). However, the overall results were highly heterogeneous (I² = 78.9%). When only those studies were considered that used the CGI to define response, the superiority was consistent when a cutoff of less than much improved (N = 13, n = 867, RR = 0.65, CI = 0.47–0.88, P = .006, NNT = 5, CI = 5–17, P = .004) or less than minimally improved was

used (N = 13, n = 950, RR = 0.80, CI = 0.67–0.95, P = .01, NNT = 25, CI = 11 to unable to estimate, P = .07).

Overall, more participants dropped out due to any reason in the monotherapy groups than in the combination groups (N = 22, n = 1129, RR = 0.65, CI = 0.54–0.78, P = .00001) (figure 3). However, the RD/NNT result was not significant (P = .26), probably because 13 study arms had no dropouts in either group, excluding them from the RR analyses due to having a zero in the denominator. Analyzing specific dropout reasons, the superiority of the combination treatment was driven by less dropouts due to inefficacy of treatment (N = 18, n = 960, RR = 0.93, CI = 0.12–0.73, P = .003; NNT: again not estimable), rather than adverse events (N = 18, n = 960, RR = 1.69, CI = 0.73–3.92, P = .22).

Usable data on relapse, on secondary, scale-derived outcomes on overall efficacy (PANSS or BPRS total score) and on specific aspects of psychopathology (positive symptoms, negative symptoms, depression, agitation, functioning) were very sparse, involving no more than 4 studies. Because this low number of available study drastically limits the interpretability of the findings, these results are not shown here, but can be obtained from the authors upon request.

Limited results based on 1–11 studies found no group differences for the following adverse events: at least one adverse event, movement disorders, use of anticholinergic comedications, anticholinergic side effects, arousal,
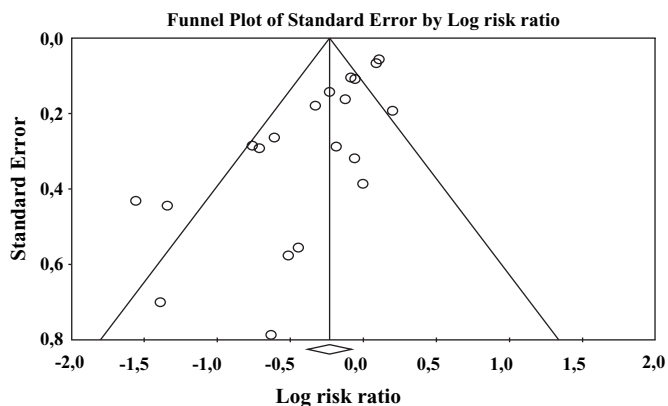
Funnel Plot of Standard Error by Log risk ratio

Fig. 4. Funnel Plot of Symmetry of Published Results.

cardiovascular problems, central nervous system effects, endocrine disorders, gastrointestinal side effects, weight gain, hematology, and laboratory values including metabolic measures and drooling. The exception was prolactin levels that were significantly higher in the combination groups where sulpiride or risperidone was added to continued clozapine treatment ($N = 2$, $n = 86$, weighted mean difference: 65.1, CI = 51.1–79.1, $P < 0.00001$).

The funnel plot showed a statistically significant asymmetry (figure 4), suggesting the possibility that studies with negative results were not published (Egger's regression intercept: −2.11, df = 18, $P < 0.0001$).

Sensitivity Analyses. Most of the sensitivity analyses confirmed the significant superiority for antipsychotic cotreatment vs monotherapy regarding the primary efficacy outcome, ie, lack of study-specific defined clinically significant response (table 2). Antipsychotic cotreatment was superior to monotherapy in studies that were double blind or open label (only 2 studies), conducted in China, lasted ≥10 weeks, included acutely exacerbated or chronically ill patients, started antipsychotic combinations at the beginning of treatment, used reduced or similar antipsychotic doses in the cotreatment compared with the monotherapy arms, included clozapine in the cotreatment arm, or used SGA + FGA combination, either compared with SGA or FGA monotherapy. Results were also confirmed when in the overall analyses the cotreatment arm was counted only once in the 9 trials where 2 monotherapy treatments existed. By contrast, 5 variables emerged as potential moderators of the superior efficacy of antipsychotic combinations (table 2). These included trials that were conducted outside of China, lasted <10 weeks, started antipsychotic combination treatment after nonresponse to monotherapy (mostly by prior history), or used combinations of 2 FGAs compared with 1 FGA, 2 SGAs compared with 1 SGA, or antipsychotics other than clozapine in the cotreatment arm.

When grouping combinations by antipsychotic class, only SGA + FGA combinations, either compared with SGA or FGA monotherapy ($N = 8$, $n = 428$), were statistically superior to antipsychotic monotherapy (table 2). In the studies comparing SGA + FGA vs antipsychotic monotherapy, 351 patients (82.0%) received sulpiride, and 305 patients (71.3%) received clozapine either in monotherapy or combination treatment. In these trials, again, the majority of patients (400, 93.5%) came both from Chinese studies and had cotreatment initiated at the start of the trial. In addition, 218 patients (50.9%) had both an acute illness exacerbation and received reduced doses in the cotreatment arm.

In 13 studies and 23 treatment arms with available dose and efficacy information, the chlorpromazine equivalent dose was higher in the antipsychotic combination vs monotherapy treatment groups ($N = 9$, 1092.6 ± 366.7 mg/day vs $N = 14$, 670.0 ± 330.5 mg/day, $F = 8.23$, $P = 0.0092$). The mean chlorpromazine equivalent dose ratio in the monotherapy arms compared with the polytherapy arms was 0.64 ± 0.22 (range 0.19–0.91, 95% CI = 0.53–0.75). Like in the total sample, in the studies with available dose information, antipsychotic polytherapy was also associated with less inefficacy compared with monotherapy ($N = 13$, $n = 669$, RR = 0.63, CI = 0.43–0.92, $P = 0.02$, NNT = 6, CI = 3–33, $P = 0.01$). However, the monotherapy to polytherapy chlorpromazine equivalent dose ratio did not differ significantly in the studies with significant superiority for polytherapy (defined as $P < 0.05$, $N = 5$, see figure 2) compared with studies without significant superiority ($N = 9$) (0.67 ± 0.17 vs 0.61 ± 0.27, $F = 0.28$, $P = 0.61$). The same was true when superiority of combination treatment ($N = 9$) compared with monotherapy ($N = 5$) was defined as a favorable separation of the mean values independent of the 95% CI (see figure 2) (0.68 ± 0.23 vs 0.59 ± 0.17, $F = 0.63$, $P = 0.44$).

Meta-regression Analyses. After subjecting all variables from the sensitivity analyses to a meta-regression that takes the interaction between variables into account, 3 moderators of superior efficacy of antipsychotic cotreatment emerged: similar doses in the mono- and polytherapy arm ($P = 0.006$, coeff = 0.48), SGA + FGA combinations ($P = 0.027$, coeff = 0.39) and concurrent polypharmacy initiation ($P = 0.050$, coeff = 0.35). Study duration ($P = 0.057$, coeff = 0.28), blinding ($P = 0.067$, coeff = 0.45), and clozapine combinations ($P = 0.10$, coeff = 0.39) trended toward significance.

Discussion

This first comprehensive meta-analysis of RCTs investigating antipsychotic cotreatment vs monotherapy in schizophrenia suggests superiority of antipsychotic cotreatment regarding the 2 a priori defined coprimary outcomes of all-cause discontinuation and inefficacy as

Table 2. Sensitivity Analyses of the Effect of Mediator Variables on the Outcome "Lack of Efficacy as Defined by Each Study"

Variable	Study Arms	Patients	Risk Ratio	95% CI	P Value	NNT	95% CI	P Value
1. Double-blind design	20	1041	0.78	0.65–0.93	0.005	7	4–20	0.002
Open design	2	61	0.35	0.13–0.98	0.04	—	—	0.08
2. Chinese studies[a]	10	573	0.67	0.51–0.89	0.006	5	3–11	0.004
Non-Chinese studies[a]	12	629	0.88	0.72–1.08	0.22	—	—	0.14
3. Acutely exacerbated patients	7	319	0.52	0.30–0.90	0.02	4	2—12	0.003
Chronically ill patients	15	883	0.85	0.73–0.99	0.04	11	6—100	0.002
4. Costarting second antipsychotic	17	1011	0.68	0.53–0.87	0.002	6	4–17	0.001
Augmenting with second antipsychotic	5	191	0.90	0.69–1.17	0.42	—	—	0.38
5. Comparative cotreatment doses	12	707	0.81	0.67–1.00	0.05	7	4–100	0.03
Reduced cotreatment doses	10	495	0.64	0.43–0.93	0.02	6	3–50	0.03
6. Trial duration <10 weeks	13	808	0.87	0.72–1.06	0.16	-	-	0.09
Trial duration ≥10 weeks	9	394	0.65	0.54–0.78	<0.00001	5	3–20	0.01
7. Cotreatment including clozapine	15	764	0.75	0.61–0.93	0.008	6	3–17	0.003
Cotreatment not including clozapine	7	438	0.59	0.28–1.25	0.17	—	—	0.37
8. FGA + FGA vs FGA	7	438	0.59	0.28–1.25	0.17	—	—	0.37
SGA + SGA vs SGA	7	336	0.98	0.87–1.10	0.70	ns	—	0.65
SGA + FGA vs FGA	3	171	0.47	0.22–0.98	0.04	3	2–9	0.004
SGA + FGA vs SGA	5	257	0.59	0.40–0.88	0.009	3	2–6	<0.0001
9. Counting cotreatment group once	15	1031	0.81	0.67–0.98	0.03	8	4–33	0.01

[a]Twelve patients with self-reported Asian ethnicity in the study by Honer et al. (2006)[33] originated from the Chinese site.
CI, confidence interval; FGA, first-generation antipsychotic; NNT, number needed to treat; SGA, second-generation antipsychotic.

defined by each study. The relevance of this finding is underscored by the fact that antipsychotic combinations were superior to monotherapy even when using a cutoff score of "much improved" on the CGI and by the relatively low NNT in the efficacy analyses that ranged mostly between 5 and 7. The interpretation of the results for specific psychopathology ratings and adverse effects was limited, however, by the low number of studies and participants with available data.

In 12 of 18 subgroup analyses, antipsychotic combinations were associated with significantly greater efficacy compared with monotherapy. Exceptions were studies with trial durations of <10 weeks and conducted outside of China, as well as those that used combinations after nonresponse to monotherapy rather than right from the start, nonclozapine antipsychotics, and combinations of 2 FGAs or 2 SGAs. However, Chinese studies used mostly designs that were also associated with increased efficacy of antipsychotic combinations. The reverse was true for non-Chinese studies, such as augmentation with a second antipsychotic after nonresponse to monotherapy and use of combinations not including clozapine.

The finding of superior efficacy of antipsychotic cotreatment compared with antipsychotic monotherapy is in contrast to the generally upheld notion that there is no support for combining 2 antipsychotics.[17,25,26]

However, all the studies discussed widely to date involved antipsychotic augmentation strategies of chronically ill patients refractory to clozapine.[30–33] By contrast, positive effects for the antipsychotic polypharmacy were apparent the most in patients with acutely exacerbated schizophrenia and those who had 2 antipsychotics started at the same time, scenarios that have not been investigated except in studies conducted in China. Although, mean chlorpromazine equivalent doses were approximately one-third higher in the antipsychotic combination groups and although the use of therapeutic doses in both the mono- and polytherapy groups was a significant moderator variable, the mono- vs polytherapy chlorpromazine equivalent ratio did not differ between the studies finding superiority for the combination groups compared with those not finding such superiority.

In secondary sensitivity analyses, we confirmed and extended the finding of a relevant effect of study duration from a recent meta-analysis of the 4 well-known clozapine augmentation trials.[60] Like in that meta-analysis where superiority of cotreatments was apparent only in the 2 studies lasting ≥10 weeks (n = 68), we also found antipsychotic cotreatments to be superior in the 6 studies (N = 9, n = 394) lasting 10 weeks or longer (NNT = 5, CI = 3–20), but not in the studies lasting <10 weeks. Obviously, this has relevant implications for the design of

future studies. However, 4 of 6 studies lasting ≥10 weeks included a combination of clozapine plus either sulpiride ($N = 3$) or risperidone ($N = 1$). Therefore, it remains to be tested whether combinations that involve antipsychotics other than clozapine are significantly more effective than monotherapy and whether the time course of separation between antipsychotic cotreatment from monotherapy is similar or different if clozapine is not part of the cotreatment. Moreover, in the non-Chinese countries where clozapine is reserved for refractory patients, the 2 moderators of superior efficacy for antipsychotic cotreatment, ie, use of clozapine and simultaneous initiation of antipsychotics in acutely ill patients, present us with a dilemma. Thus, the latter finding needs to be replicated in trials of simultaneous initiation of 2 nonclozapine antipsychotics in acutely ill patients. Nevertheless, in acutely exacerbated patients with confirmed refractory schizophrenia, clozapine could be coinitiated with a second antipsychotic in patients who stopped their prior antipsychotic due to nonadherence or experienced a significant exacerbation despite treatment with a non-clozapine antipsychotic.

Unfortunately, insufficient data were available to evaluate the acute and even less data were available to evaluate the long-term safety of antipsychotic cotreatments. This is an important shortcoming as several cross-sectional and naturalistic studies reported an increased risk for diabetes[27] and cardiovascular mortality[28,29] associated with antipsychotic polypharmacy. However, it is unclear if these naturalistic findings are related to a direct toxic effect of specific or all antipsychotic combinations or whether it may be related to a cohort effect, in that patients who are selected for antipsychotic combination treatments are both psychiatrically and physically sicker than patients receiving monotherapy. The latter is suggested by a recent study in which the significant association between antipsychotic cotreatment and metabolic syndrome was solely explained by a significant greater prevalence of traditional risk factors compared with patients receiving antipsychotic monotherapy.[17] On the other hand, controlled adverse event data in patients cotreated with a second antipsychotic are also required to assess the possibility that certain combinations may be associated with a decreased, rather than increased adverse effect burden because reduced weight gain and metabolic abnormalities have been reported after the addition of aripiprazole to clozapine.[61,62]

Several limitations need to be considered when interpreting these results. These include the fact that meta-analyses combine results from trials that differ in their methodology, study size and year, use of diagnostic instruments, patient and treatment selection, primary outcome variables, and study conduct. This fact was reflected by the significant heterogeneity of the results, suggesting the effect of relevant moderator and mediator variables. However, we sought to include all available data and were able to confirm the superiority of anti-

psychotic cotreatments in most of the secondary and sensitivity analyses that sought to disentangle relevant moderator variables, strengthening the primary finding. Importantly, although antipsychotic combination treatments did not separate statistically from monotherapy in all the sensitivity analyses, monotherapy was not superior in any of the analyses, and trends were almost all in the direction of antipsychotic cotreatment. Furthermore, despite extensive clinical utilization of antipsychotic cotreatment, data were restricted to 19 studies worldwide and limited regarding specific combinations, long-term outcomes, and psychopathology and adverse event domains. Moreover, there was a regional effect in that patients from Chinese studies predominated in many of the trials with characteristics that were also associated with superiority of the antipsychotic cotreatment. However, we only included randomized studies and the vast majority of them were double blind. Furthermore, explicit dose information was not available for all studies/ treatment arms with data on similar vs reduced dose combination strategies. Besides the fact that the level of accuracy is higher regarding explicit dose information and that meta-regression results of heterogeneous studies have to be interpreted with caution, this partial lack of data could be an additional reason for the seeming disconnect between the fact that "similar dose" combination emerged as a significant moderator of the superior antipsychotic polytherapy efficacy, whereas the chlorpromazine ratio in the mono- vs polytherapy groups did not differ between studies favoring antipsychotic polypharmacy compared with those not finding an advantage of antipsychotic cotreatment. In addition, we cannot exclude a file drawer phenomenon because the funnel plot was significantly skewed toward positive studies. However, a significantly skewed funnel plot does not prove a publication bias because other reasons can lead to marked asymmetry, such as true heterogeneity or differences in the quality of assessments in smaller vs larger studies. In addition, data were insufficient to determine to what degree these results generalize to females, patients treated in the Western world, nonclozapine combinations, and whether antipsychotic cotreatment should be initiated concurrently in acutely exacerbated patients or whether it should be limited to sequential combinations in patients with insufficient response to antipsychotic monotherapy. Moreover, data were insufficient to determine the effect of specific combinations, long-term effects, and cost, further pointing to the need for more studies. Finally, the lack of conclusive adverse effect data make it difficult to weigh potential benefits against risks of antipsychotic polypharmacy because it is possible that certain relevant adverse effects may be additive some or most combinations.

Despite these limitations, this is the largest analysis of RCTs that have investigated the effect of antipsychotic cotreatment vs monotherapy in schizophrenia.

Moreover, it is the first study to include all trials available without applying any language restrictions. This allowed the inclusion of previously unrecognized trials that utilized antipsychotic polypharmacy in acutely exacerbated patients and that initiated cotreatment from the beginning of the trial, rather than waiting for nonresponse to antipsychotic monotherapy, especially clozapine. In this sense, the analyzed data extend to some aspects of the general clinical practice where antipsychotic cotreatment strategies seem to be predominantly utilized in patients who have not failed clozapine. On the other hand, most combinations utilized in clinical practice also do not include clozapine, indicating the need to conduct studies with nonclozapine antipsychotic combinations that employ some of the design features that may have mediated the superior efficacy of antipsychotic combinations vs monotherapy in the examined trials. Such studies are necessary to determine whether the superiority of antipsychotic combinations generalizes to a variety of clinical settings and populations.

In summary, these data suggest that, at least, under certain circumstances, antipsychotic cotreatment may be superior to antipsychotic monotherapy regarding all-cause discontinuation and general measures of efficacy. Benefits may be apparent in acutely exacerbated patients in whom cotreatment is initiated at the beginning of treatment and when the cotreatment is administered for 10 weeks or more. Moreover, benefits of antipsychotic cotreatment did not seem to be simply a function of an increase in antipsychotic dose and resultant dopamine blockade in the polytherapy group. However, results were heterogeneous, suggesting the influence of relevant mediator and moderator variables, and there is the possibility of publication bias. Furthermore, the database was too limited to determine the effects of specific combinations, with the exception of the suggested benefits of including clozapine. It is also unclear whether potential benefits in acutely ill patients are restricted to combinations that include clozapine or that include clozapine augmented with an FGA and what the potential short-term and, particularly, long-term risks of antipsychotic combinations are. Thus, the results from this meta-analysis are insufficient to derive conclusive clinical recommendations. Rather, it provides relevant information regarding the need for specific studies and highlights methodological considerations that should guide the design of future controlled trials. Further, large-scale studies are needed, which compare antipsychotic monotherapy to antipsychotic combinations that do not necessarily involve clozapine. Further, studies combining nonclozapine SGAs with each other and with FGAs, utilized most in clinical practice, are required. Such studies should also explore the merits of combining antipsychotics in the acute phase, instead of waiting until nonresponse has occurred, last at least 10 week, and should be conducted in non-Asian countries too. To exclude the possibility of a dose effect in the cotreatment arm, one may need to consider including a "high dose" lead-in phase, high dose monotherapy arm, or both a similar dose plus a reduced dose cotreatment arm. Furthermore, recent data, suggesting that nonresponse at 1–4 weeks is highly predictive of future nonresponse,[63,64] should also be taken into account when deciding at what time patients with unsatisfactory response should be randomized to antipsychotic combinations vs continued monotherapy. Until results from such studies are available, the use of antipsychotic cotreatment should most likely be reserved to severely ill patients with a documented lack of response to antipsychotic monotherapy during the acute or chronic illness phase.

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