Original Investigation

Initial Severity of Schizophrenia and Efficacy of Antipsychotics

Participant-Level Meta-analysis of 6 Placebo-Controlled Studies

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IMPORTANCE Antipsychotic drugs constitute the mainstay in the treatment of schizophrenia, and their efficacy is well established in hundreds of randomized clinical trials. However, it is not known whether they are effective or how effective they are across the wide range of baseline symptom severity.

OBJECTIVE To examine the influence of baseline severity of schizophrenia on the efficacy of antipsychotic drugs.

DESIGN, SETTING, AND PARTICIPANTS Meta-analysis of participant-level data from 3 pivotal randomized trials of acute schizophrenia (n = 611) and 3 pivotal trials in patients with predominantly negative symptoms of schizophrenia (n = 475).

INTERVENTIONS Olanzapine or risperidone vs placebo, and amisulpride vs placebo.

MAIN OUTCOMES AND MEASURES Change scores on the Positive and Negative Syndrome Scale (PANSS; score range, 30-210) and the Scale for the Assessment of Negative Symptoms (SANS; score range, 0-125) up to 6 weeks after baseline. The relationship between baseline and change scores for the drug and placebo groups was examined with 8 competing mixed-effects models for repeated measures.

RESULTS The best-fitting models showed that, for both types of patients, the interactions between baseline symptom severity and treatment were statistically significant ($P < .01$). The greater the baseline severity was, the greater the magnitude of the differences was between active treatment and placebo. In acute treatment, the mean differences in PANSS change scores were 9.5 points for patients who were mildly ill at baseline (baseline PANSS score of 58), 13.7 for moderately ill patients (baseline PANSS score of 75), 18.8 for markedly ill patients (baseline PANSS score of 95), and 24.0 for severely ill patients (baseline PANSS score of 116). In treatment of predominantly negative symptoms, the mean differences in SANS change scores were 1.7 for those who were moderately ill (baseline SANS score of 55), 5.7 for markedly ill patients (baseline SANS score of 70), and 9.7 for severely ill patients (baseline SANS score of 85).

CONCLUSIONS AND RELEVANCE We can expect benefits of antipsychotic drugs for the full spectrum of patients likely to be treated for acute schizophrenia and for highly symptomatic patients with predominantly negative symptoms. Toward the mildest end of the spectrum, clinicians need to be aware that patients benefit less in terms of symptom improvement but may experience full adverse effects of antipsychotics. Clinicians also need to be aware that in addition to the treatment of active symptoms, which was the focus of this study, antipsychotics have another important action, namely to prevent relapses among patients in remission.

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Schizophrenia is one of the most debilitating and chronic mental disorders and ranks among the top 20 causes of disability worldwide.[1] Antipsychotic drugs constitute the mainstay for its treatment, and their efficacy is established beyond question in hundreds of randomized clinical trials (RCTs).[2] Their worldwide annual sale is expected to reach $14.8 billion in 2014.[3]

The efficacy of another major class of psychotropic agents, antidepressants, in the treatment of depressive disorders has recently been called into question. Some studies have suggested that they may have less efficacy for the milder spectrum of the disorder,[4-6] while others did not find such diminishing efficacy with lower baseline severity of depression.[7,8] Earlier studies examining the relationship between average study-level initial severity and treatment response,[5,7,9] however, are limited in statistical power to detect possible effects and are also subject to the ecological fallacy that relationships observed at the group level may not reflect the true relationships at the individual level.[10,11]

Patient-level data are therefore necessary to examine patient-level effect modifiers. The first participant-level meta-analysis examining this question pooled individual-level data from 6 RCTs (718 patients) comparing paroxetine or imipramine vs placebo in the acute treatment of major and minor depressive disorder and concluded that the substantial benefits of medications were seen only for patients with very severe depression.[6] Subsequently, however, a much larger individual-level meta-analysis of 37 trials (8477 patients) examining 2 newer-generation antidepressants, fluoxetine hydrochloride and venlafaxine hydrochloride, found no effect of baseline severity on treatment efficacy.[8]

To our knowledge, the influence of baseline severity of schizophrenia on the efficacy of antipsychotic drugs has yet to be adequately examined. In this study, we carried out 2 separate participant-level meta-analyses of 3 RCTs comparing olanzapine and risperidone with placebo in the treatment of acute schizophrenia and 3 RCTs comparing amisulpride with placebo in the treatment of predominantly negative symptoms to examine the relationship between baseline symptom severity and efficacy of antipsychotics over placebo.

Methods

Included RCTs

We conducted a comprehensive systematic review of 15 major antipsychotic drugs and identified 97 placebo-controlled trials.[2] Of these, we had access to participant-level data from 6 RCTs without any influence on the design, conduct, or reporting of the data analyses.

Three studies were pivotal RCTs comparing olanzapine or risperidone against placebo in the acute treatment of schizophrenia. The 2 olanzapine RCTs constitute all the placebo-controlled trials for the US Food and Drug Administration registration of the compound.[12,13] The RCT comparing risperidone with placebo is its pivotal registration study.[14,15] Three other studies represent all RCTs that examined amisulpride against placebo in the treatment of schizophrenia with predominantly negative symptoms to obtain market approval for this indication.[16-18] All the data were completely anonymized before we had access to them.

Of all the treatment arms in the RCTs, we only included the arms that used dosages indicated in the US Food and Drug Administration labels or the British National Formulary, ie, 10 to 30 mg/d for olanzapine, 4 to 16 mg/d for risperidone, and 50 to 300 mg/d for amisulpride. All the included arms were fixed-dose arms; in all but 1 trial, the fixed dose was administered immediately after randomization; in the other study,[14,15] the dosage was titrated up to the maintenance dosage within 3 to 7 days. We excluded fixed-dose arms with olanzapine less than 10 mg/d (one 1-mg/d arm[13] and one mean [range] 5 [2.5-7.5]-mg/d arm[12]) and one 2-mg/d risperidone arm[14,15] because in such arms all patients take very low doses that are not effective for many of them,[2] although such very low doses may be effective in individual patients. The optimal dosage of amisulpride for individuals in whom the negative symptoms of schizophrenia are predominant is 50 to 300 mg/d.[19]

Statistical Analyses

Our primary statistical analysis investigated the relationship between baseline symptom severity and subsequent symptom change in the comparisons of antipsychotics vs placebo. We conducted 2 separate analyses in patients with acute schizophrenia and in patients with predominantly negative symptoms to elucidate whether potential effects of baseline severity are restricted to one of these groups or are a more general phenomenon.

Among the acute studies, 1 trial of olanzapine[12] used the Brief Psychiatric Rating Scale (BPRS),[20] while the other trial of olanzapine[13] and the trial of risperidone[15] used the Positive and Negative Syndrome Scale (PANSS)[21] to measure global symptom severity. To have the same outcome measure across all trials and to perform the meta-analysis on the same scale, we converted the BPRS scores into PANSS scores using an established algorithm; the correlation coefficient between BPRS total scores and PANSS total scores has been reported to range between 0.93 and 0.96.[22] All items on the PANSS were recalibrated, where necessary, to be rated between 1 and 7 so that the possible score ranged from 30 to 210. All 3 amisulpride studies of predominantly negative symptoms of schizophrenia used the Scale for the Assessment of Negative Symptoms (SANS)[23] as their primary outcome measure. The SANS has 30 items, each rated between 0 and 5, of which 25 items contribute to the total score. Thus, the possible score ranged from 0 to 125.

We followed the interpretive guides for the raw scores of the PANSS and SANS as established using the anchor-based approach linking these scores with the Clinical Global Impressions ratings: severity ratings of mildly ill, moderately ill, markedly ill, and severely ill corresponded with respective scores of 58, 75, 95, and 116 on the PANSS[24] and 40, 55, 70, and 85 on the SANS.[25]

We conducted a participant-level meta-analysis to examine the relationship between baseline symptom severity and the differences in change scores between the drugs and placebo using a 3-level mixed-effects model repeated-measures analysis (MMRM) with maximum likelihood estimation.[8,26] The

levels accounted for the data structure such that level 1 represented time, level 2 the participant, and level 3 the trial. The following competing models with increasing complexity were tested: model 1, time, treatment, and the 2-way time × treatment interaction; model 2, model 1 plus baseline symptom score and all 2-way interactions among time, treatment, and baseline score; model 3, model 2 plus the 3-way interaction of linear time × treatment × baseline score; and model 4, model 3 plus the 2-way and 3-way interactions among quadratic time, treatment, and baseline score. These models were tested unadjusted and adjusted for confounders (age, sex, and duration of illness for patients with acute schizophrenia; age and sex for patients with predominantly negative symptoms). The model with the smallest Bayesian information criterion was chosen as the most parsimonious.[27] We reported 6-week results based on the best-fitting models because it was the maximum duration for some of the included trials and therefore we were able to perform an analysis that accounted for follow-up time differences across studies. All statistical analyses were done in R statistical software version 3.1.0[28] using the nlme package version 3.1-117 (R Foundation for Statistical Computing).[29]

Sensitivity Analyses

Three sensitivity analyses of change from baseline using MMRM were conducted in our analysis of acutely ill patients, each comparing the 8 models as specified earlier. To check the consistency of our primary analysis using the PANSS, we carried out a sensitivity analysis using the BPRS instead of the PANSS. To examine whether the overall results observed with the total score also held for the positive and/or negative symptoms separately, we ran the same analyses for the positive and negative symptoms in the acute treatment of schizophrenia (eAppendix in the Supplement).

Results

Characteristics of the Included RCTs

Table 1 shows the main characteristics of the included studies. The analysis of acute schizophrenia included a total of 611 inpatients diagnosed with the *DSM-III-R*, and the analysis of schizophrenia with predominantly negative symptoms included 475 such outpatients and inpatients diagnosed with the *DSM-III* or *DSM-III-R*.

Baseline Severity and Symptom Change in the Acute Treatment of Schizophrenia

The best-fitting MMRM model to predict PANSS score change in the acute treatment of schizophrenia was model 2 (eTable 1 in the Supplement). In this model, the baseline PANSS score by treatment interaction was statistically significant ($P = .004$). **Figure 1** shows a scatterplot of all observed scores, superimposed with regression lines for the antipsychotic and placebo arms at 6 weeks. The magnitude of the difference in PANSS change scores between the treatments increased with baseline PANSS score. The mean score difference between antipsychotics and placebo at 6 weeks was estimated to be 9.5 points for patients who were mildly ill at baseline (baseline PANSS score of 58), 13.7 points for patients who were moderately ill (baseline PANSS score of 75), 18.8 for markedly ill patients (baseline PANSS score of 95), and 24.0 for severely ill patients (baseline PANSS score of 116).

Baseline Severity and Symptom Change in the Treatment of Schizophrenia With Predominantly Negative Symptoms

The best-fitting model to predict SANS score change in the treatment of schizophrenia with predominantly negative symptoms was model 4, which contained linear and quadratic times and baseline SANS score without adjustment for sex or age (eTable 2 in the Supplement). We found that 3-way interactions of treatment × baseline SANS score × time, for both the quadratic and linear terms of time, were statistically significant ($P = .02$ and $P = .004$, respectively). This signifies that how the difference between treatments depended on the baseline SANS score over time was not simply linear but that a quadratic (ie, curvature) model improved the model fit to the data.

At 6 weeks, the 2 regression lines converged toward baseline SANS score around 50 and the difference between treatment and placebo increased with increasing baseline SANS score. The mean score difference between antipsychotics and placebo at 6 weeks was estimated to be 1.7 for patients who were moderately ill (baseline SANS score of 55), 5.7 for markedly ill patients (baseline SANS score of 70), and 9.7 for severely ill patients (baseline SANS score of 85).

Sensitivity Analyses

The sensitivity analyses using the BPRS total score instead of the PANSS, BPRS positive subscale, and BPRS negative subscale scores in the 2 olanzapine and risperidone studies revealed similar trends. The same model as in the primary analysis was replicated to best fit the data based on the Bayesian information criterion, and the interaction between baseline severity and treatment was statistically significant in all instances (BPRS total score, $P = .008$; BPRS positive subscale, $P = .003$; and BPRS negative subscale, $P = .03$), with the greater between-treatment differences for the patients with more severe illness (eTables 3-5 in the Supplement).

Discussion

Analyzing the individual-level data from 3 pivotal trials of olanzapine and risperidone in the acute treatment of schizophrenia and 3 pivotal trials of amisulpride in the treatment of schizophrenia with predominantly negative symptoms, we found that the difference in symptom reduction between antipsychotics and placebo increased as the baseline severity increased. This effect was replicated for global as well as positive and negative symptoms in acute schizophrenia and for negative symptoms in predominantly negative schizophrenia.

Clinical Interpretations of the Findings

Many studies have examined possible predictors of change on antipsychotic drugs among patients with schizophrenia, including their initial symptom severity. Some studies have reported

Table 1. Characteristics of the Included Studies

Source	Antipsychotic Drug (Dosage, mg/d)	Sample Size for Drug/Placebo, No.	Trial Duration, wk	Mean (Range)		Men, %	Illness Duration, Mean (Range), y	Selected Inclusion Criteria
				Baseline Symptom Severity Score	Age, y			
Beasley et al,[12] 1996	Olanzapine (10, 15), placebo	121/57	6	106.1 (75-158) on PANSS	36.2 (18-63)	84	14.1 (0-40)	Inpatients with acute exacerbations of schizophrenia (*DSM-III-R*), BPRS total score ≥42, CGI-S score ≥4 both before and after placebo run-in
Beasley et al,[13] 1996	Olanzapine (10), placebo	49/47	6	96.8 (69-128) on PANSS	37.8 (19-63)	70	16.4 (1-40)	Inpatients with schizophrenia (residual type excluded; *DSM-III-R*), BPRS total score ≥42, CGI-S score ≥4 both before and after placebo run-in
Marder and Meibach,[15] 1994 and Chouinard et al,[14] 1993	Risperidone (6, 10, 16), placebo	251/86	8	93.3 (49-145) on PANSS	36.8 (18-67)	84	15.5 (0-46)	Inpatients with schizophrenia (*DSM-III-R*), PANSS total score ≥60 before placebo run-in
Boyer et al,[18] 1995	Amisulpride (100, 300), placebo	65/31	6	84.3 (60-125) on SANS	32.3 (18-48)	64	10.6	Inpatients with schizophrenia (*DSM-III*) and Andreasen and Olsen's criteria for negative schizophrenia,[30] SANS score ≥75 and SAPS score ≤50 before placebo run-in
Loo et al,[16] 1997	Amisulpride (100), placebo	69/71	24	81.6 (60-113) on SANS	34.4 (17-58)	71	NA	Schizophrenia, disorganized or residual type (*DSM-III-R*), 2 of Andreasen's negative components present to a marked degree,[23] SANS score ≥60 and SAPS score ≤50
Danion et al,[17] 1999	Amisulpride (50, 100), placebo	158/81	12	76.6 (60-116) on SANS	34.5 (18-66)	64	9.6	Inpatients or outpatients with schizophrenia, residual type (*DSM-III-R*), SANS score ≥60 and SAPS score ≤50 before placebo run-in

Abbreviations: BPRS, Brief Psychiatric Rating Scale; CGI-S, Clinical Global Impressions severity subscale; *DSM-III*, *Diagnostic and Statistical Manual of Mental Disorders*, third edition; *DSM-III-R*, *Diagnostic and Statistical Manual of Mental Disorders*, third edition revised; NA, not available; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

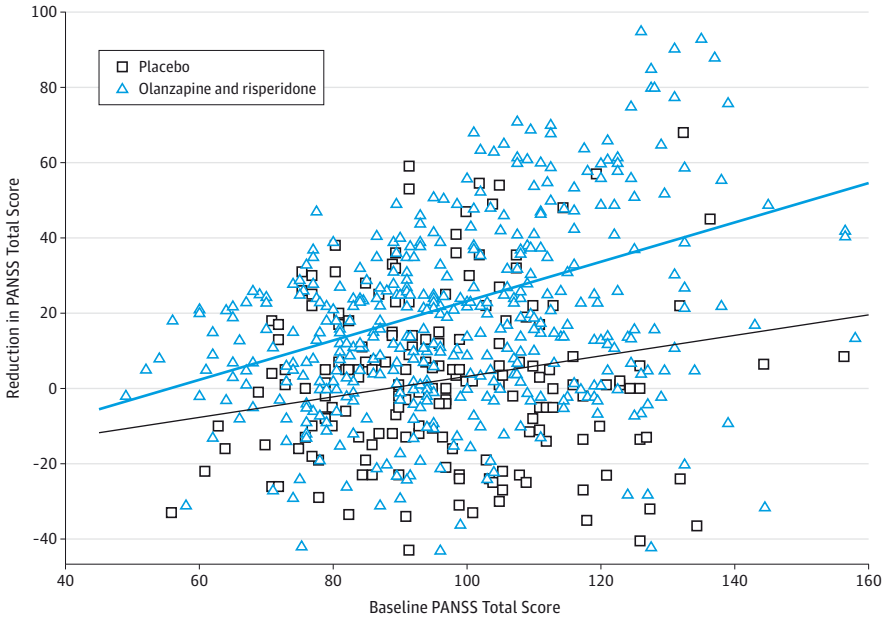
the association,[31,32] but overall the results have been inconsistent, possibly owing to small sample sizes and/or methodological limitations.[33] Moreover, these studies were interested in baseline severity merely as a predictor and none of them addressed its clinical implication for patient subgroups with different baseline severity (eg, mildly ill, moderately ill, and severely ill).

This problem was addressed in our study with the statistically appropriate and powerful method using individual-level data from multiple clinical trials and MMRM. We found that the 2 regression lines depicting the relationships between baseline severity and changes in severity grew apart as the baseline severity increased in both patients with acute schizophrenia and patients with predominantly negative symptoms. The baseline severity that is needed to have measurable treatment effects on antipsychotic drugs in comparison with placebo can be discussed from several points of view.

One approach is to calculate the between-group effect size. The standard deviations of change scores at 6 weeks for 3 severity groups with baseline PANSS scores up to 75, between 76 and 95, and greater than 95 were 20.0, 20.5, and 29.3, respectively. Dividing the expected mean differences by the corresponding standard deviation gives the expected effect sizes for the PANSS (**Table 2**). Because it has been commonly suggested that between-group effect sizes of 0.2, 0.5, and 0.8 would roughly correspond with small, medium, and large effects, respectively,[34] one may say that the baseline PANSS scores must be around 40, 70, and 95 to have small, medium, and large between-group effect sizes, respectively, in the treatment of acute schizophrenia. In the treatment of patients with predominantly negative symptoms, the baseline SANS scores must be around 65 or 95 to have a small or medium effect, respectively (**Table 3**).

Another approach is to calculate the number needed to treat (NNT) of achieving the minimally important change. The minimally important change is defined as the smallest change in score that the patient would perceive as beneficial and that would mandate, in the absence of adverse effects and excessive cost, a change in the patient's health care.[35,36] In the case of PANSS, the minimally important change has been established as approximately 15 points of absolute change using the anchor-based approach based on the Clinical Global Impressions improvement scores.[24,37,38] By calculating the percentage of patients showing changes of 15 or

Figure 1. Observed and Estimated Changes in the Positive and Negative Syndrome Scale (PANSS) Score Following 6-Week Acute Treatment of Schizophrenia



Lines indicate the expected reduction in PANSS score with placebo (black line) or drug (olanzapine or risperidone; blue line) at 6 weeks corresponding to the baseline score.

Table 2. Baseline PANSS Scores and Expected Effect Sizes and NNT at 6 Weeks

Baseline PANSS Score[a]	Expected Reduction in PANSS Score		Effect Size	Expected % of Patients Showing MIC or Greater Reduction		NNT
	Antipsychotic	Placebo		Antipsychotic	Placebo	
50	−3.4	−10.4	0.31	19	10	12
60	2.3	−7.7	0.42	26	13	8
70	7.5	−4.9	0.51	35	16	6
80	12.8	−2.2	0.62	46	20	4
90	18.0	0.5	0.73	56	24	4
100	23.2	3.2	0.83	61	34	4
120	33.7	8.7	1.04	74	41	4
140	44.1	14.1	1.25	84	49	3

Abbreviations: MIC, minimally important change; NNT, number needed to treat; PANSS, Positive and Negative Syndrome Scale.

[a] On the PANSS, a score of 58 indicates mild; 75, moderate; 95, marked; and 116, severe.

more points in the drug and placebo arms using a validated formula,[39,40] an NNT of 20 can be expected for patients with a baseline PANSS score around 40, an NNT of 10 for those with a baseline PANSS score around 55, and an NNT of 5 for those with a baseline PANSS score around 75 (Table 2). In the case of amisulpride studies, the corresponding NNTs would be 20 and 10 for patients with baseline SANS scores around 58 and 65, respectively (Table 3).

The treatment threshold would naturally differ from patient to patient and from treatment setting to treatment setting; indeed, Figure 1 and **Figure 2** depict great variability in patient responses. However, on average, for patients scoring higher than 55 on the PANSS in the acute episode or 65 on the SANS when negative symptoms predominate, we may expect reasonable beneficial balance between benefits and risks of antipsychotic treatment. Below these thresholds, there may be more of a trade-off between benefits and risks: mildly ill patients benefit less in terms of effectiveness but still experience full adverse effects of antipsychotics.

Baseline Severity as Effect Modifier

Several explanations have been advanced for the observed interaction between baseline severity and change. The so-called law of initial value[41] is sometimes cited to explain the influence of baseline severity. It states that the higher the initial value is, the greater the organism's response is; it would therefore explain the greater symptom reductions among the more severely ill patients but cannot explain the difference in them between treatment and placebo.

Regression to the mean may have influenced the results. Generally, regression to the mean may be an analytic obstacle. This is especially true when allocation to treatment

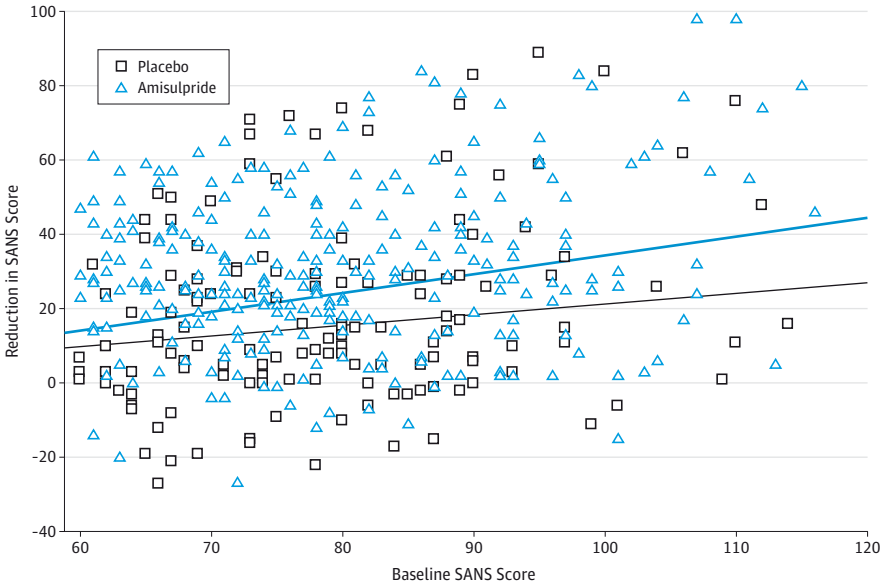
Table 3. Baseline SANS Scores and Expected Effect Sizes and NNT at 6 Weeks

	Expected Reduction in SANS Score			Expected % of Patients Showing MIC or Greater Reduction		
Baseline SANS Score[a]	Antipsychotic	Placebo	Effect Size	Antipsychotic	Placebo	NNT
50	8.7	8.4	0.01	25	25	150
60	13.9	10.9	0.13	36	30	16
70	19.1	13.4	0.24	48	35	8
80	24.3	15.9	0.35	59	41	6
90	29.4	18.4	0.46	69	47	5
100	34.6	20.9	0.57	73	51	5
110	39.8	23.4	0.68	80	56	5
120	45.0	25.8	0.80	85	60	4

Abbreviations: MIC, minimally important change; NNT, number needed to treat; SANS, Scale for the Assessment of Negative Symptoms.

[a] On the SANS, a score of 55 indicates moderate; 70, marked; and 85, severe.

Figure 2. Observed and Estimated Changes in Scale for the Assessment of Negative Symptoms (SANS) Score Following 6-Week Treatment of Schizophrenia With Predominantly Negative Symptoms



Lines indicate the expected reduction in SANS score with placebo (black line) or drug (amisulpride; blue line) at 6 weeks corresponding to the baseline score.

groups is nonrandom. However, its effect is minimized by randomization allocation, and it has an equal effect on both treatment and placebo groups.[42,43] In the current RCT data, it cannot explain the differences in change between drug and placebo groups.

The greater reduction among the patients with initially severer illness who receive antipsychotics may be due to greater leeway for improvement among such people when antipsychotics are effective, while the same did not seem to apply to those taking placebo. If there are few symptoms at baseline, there is also little room for improvement compared with placebo. As an analogy from internal medicine, fewer patients with hypercholesterolemia die of cardiovascular events within a year when the baseline risk is low than when it is high, and therefore the absolute benefit derived from lowering the cholesterol level is accordingly lower among the former than among the latter.[44]

Symptom Treatment and Episode Prophylaxis

All the studies included in our analyses aimed to reduce symptoms of schizophrenia, either positive or negative. Antipsychotics are used for another very important action, ie, to prevent relapses.[45] Our findings regarding baseline severity on symptom reduction therefore do not inform the influence of baseline severity on the prophylactic effectiveness of antipsychotics. We would need participant-level data from long-term maintenance trials of antipsychotics to address this question.

Limitations and Implications

Our study is not without weaknesses. First, we did not have many mildly ill patients or any borderline ill patients. The baseline severity of the included patients ranged from scores between 49 and 158 on the PANSS and between 60 and 125 on the SANS; the obtained relationships should be valid for baseline scores in and around that range, but our

regression lines may be unstable toward the lowest end of baseline severity. We therefore should not place too much confidence in the crossing values but rather should focus on the implications of the strong interaction that we observed. Second, although we included trials of olanzapine, risperidone, and amisulpride, the findings need be replicated with other placebo-controlled trials involving other antipsychotics as well. However, the availability of individual-level data in this study was apparently not dependent on the observed relationship between baseline severity and decline in symptoms, and we remain unsure whether the possible availability bias worked toward overestimating or underestimating our primary outcome. It is also notable that we observed a significant influence of baseline symptom severity in the 2 separate but parallel analyses with different populations (acute schizophrenia and schizophrenia with predominantly negative symptoms) using different medications (risperidone/olanzapine and amisulpride) and different outcome measures (PANSS and SANS).

The clinical implications of our findings may be as follows: we can expect benefits of antipsychotics for patients with the full spectrum of severity who we are likely to treat for acute schizophrenia and for highly symptomatic patients with predominantly negative symptoms, and the severer the illness is at baseline, the bigger the benefits will be. Only toward the mildest end of the spectrum, there may be trade-offs between benefits and risks of the short-term acute treatment, and the clinician needs to confirm the patient's diagnosis and start treatment judiciously, probably with low doses of antipsychotics with fewer adverse effects.

There are 3 main research implications. First, our study has provided another example of fruitful data sharing especially with regard to examination of possible effect modifiers. Such participant-level analyses should be further encouraged, and efforts need be expended to remove ethical and logistical barriers to such collaboration. Second, in conducting placebo-controlled trials of antipsychotics, our results suggest that trials would be more likely to detect signals if they were to concentrate on patients with severer illness. The current practice of setting this threshold to a score of 75 on the PANSS may be justifiable to strike a balance between patient recruitment and signal detection; if there is less difficulty in patient recruitment, the threshold could be higher. Third, the questions remain as to why we often but not always observe an influence of baseline severity on symptom reduction in depression and schizophrenia and whether we observe similar relationships in anxiety, insomnia, and other psychiatric disorders and in treatment of general medical diseases. Further empirical studies are needed to shed light on the mechanisms involved and to inform the clinical practice and research methods.

Conclusions

We can expect benefits of antipsychotic drugs for the full spectrum of patients we are likely to treat for acute schizophrenia and for highly symptomatic patients with predominantly negative symptoms. Toward the mildest end of the spectrum, judicious clinical consideration of trade-offs between benefits and risks of the antipsychotic treatment is required.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Furukawa, Levine, Leucht.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Furukawa, Levine, Tanaka, Goldberg, Leucht.
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