# Determinants of Antipsychotic Response in Schizophrenia: Implications for Practice and Future Clinical Trials

*Jonathan Rabinowitz, PhD; Nomi Werbeloff, PhD; Ivo Caers, PhD; Francine S. Mandel, PhD; Virginia Stauffer, PharmD; François Ménard, MD; Bruce J. Kinon, MD; and Shitij Kapur, MBBS, PhD*

**ABSTRACT**

***Background:*** Response to antipsychotics in schizophrenia is highly variable, and determinants are not well understood or used to design clinical trials.

***Objective:*** We aimed to understand determinants of response to antipsychotic treatment.

***Method:*** Supported by the Innovative Medicines Initiative, as part of a large public-private collaboration (NEWMEDS), we assembled the largest dataset of individual patient level information from randomized placebo-controlled trials of second-generation antipsychotics conducted in adult schizophrenia patients by 5 large pharmaceutical companies. The dataset included all placebo-controlled trials of risperidone, paliperidone, ziprasidone, sertindole, olanzapine, and quetiapine. We examined patient- and trial-design–related determinants of outcome as measured by change on the Positive and Negative Syndrome Scale in 29 placebo-controlled trials (drug, n = 6,971; placebo, n = 2,200) and initial findings confirmed in additional data from 5 separate trials (drug, n = 1,699; placebo, n = 580).

***Results:*** While it is conventional for trials to be 6 weeks long, drug-placebo differences were observable at week 4 with nearly the same sensitivity, and dropout rates were lower. Having any of these attributes was associated with significantly greater drug versus placebo differences in symptom improvement and rates of study completion: being female ($P \leq .04$), being a young adult patient who is a few years beyond the first episode ($P \leq .03$), having prominent positive and negative symptoms ($P \leq .03$), and living in Eastern Europe versus North America ($P \leq .04$). Contrary to prevalent clinical opinion, age at onset and use of benzodiazepines did not show a differential treatment response, and patients just above PANSS inclusion threshold were not overrepresented.

***Conclusions:*** Proof-of-concept trials can be shorter and efficiency improved by including an even distribution of sexes and of patients with prominent symptomatology, thus reducing patient exposure to placebo and experimental treatments.

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***Corresponding author:*** *Jonathan Rabinowitz, PhD, Bar Ilan University, Ramat Gan, Israel 91000 (jonathan.rabinowitz@biu.ac.il).*

Antipsychotics were first discovered in the 1950s, and, in the 1990s, second-generation antipsychotics (SGAs) were introduced following a large number of double-blind randomized placebo-controlled trials with different compounds. Almost all of these SGA trials were 6 to 8 weeks in duration without any meaningful stratification. They all included adult patients with schizophrenia, regardless of symptom profile—despite evidence that any or all of the following factors may affect clinical response: age at onset,[1,2] sex,[3–5] duration and course of illness,[6] geographic region,[7,8] and use of benzodiazepines.[9] To complicate matters further, nearly half of the patients dropped out of these trials[10] and there are international differences in study results,[11] raising methodological questions. These findings, along with a fair number of negative or failed trials (in which an established drug fails to separate from placebo),[8] the moderate superiority over placebo,[12] and the rising cost and difficulties of completing these trials, have led to questions whether the current approach to trials is most effective—and whether more focused and shorter trials might yield informative results especially in early phases of clinical development. While associations between demographics and outcome have been noted, most datasets are too small to draw conclusions and data have never before been pooled across compounds to allow generalizable conclusions.

To address the above-mentioned impediments to drug development, the National Advisory Mental Health Council[13] has recommended sharing of data to improve efficiency and decrease cost of therapeutic development. This approach could enable identifying moderators and mediators of treatment effects and facilitate establishing a biologically based discovery process. In concert with this, as part of the European Union–funded Innovative Medicines Initiative, an academic and industry collaboration, we merged individual patient data from 29 randomized placebo-controlled trials (RCTs) from 5 pharmaceutical companies. We explored determinants of antipsychotic response in schizophrenia, optimal trial duration, and whether these findings could be used to design more efficient trials in general and proof-of-concept trials specifically.

We examined which key demographic and clinical variables influenced response and dropout and, if so, in what way. Next, as treatment response may be reached earlier than 6 weeks[14,15] and increased trial length increases the probability of dropouts, we tested if study conclusions could have been reached earlier. Finally, we examined whether patients who just meet symptom inclusion criteria and whose scores may have been inflated for inclusion were overrepresented and whether their exclusion might have resulted in different conclusions. We confirmed our findings in a separate similar but smaller dataset. To validate our results, we simulated, using bootstrapping (resampling), optimal trial design scenarios in terms of increasing placebo versus drug response and determined advantages these scenarios might confer on efficiency and validity.

**Clinical Points**

- Proof-of-concept trials can be shorter than they typically have been.
- Earlier onset of illness and greater number of hospitalizations are associated with poorer course of illness but not with drug-placebo differences in response to antipsychotics.
- Use of benzodiazepines is not related to differences in treatment response.
- Efficiency of trials can be improved by including an even distribution of sexes and by including more patients with prominent positive and negative symptoms, so that studies can be smaller—thus reducing patient exposure to placebo and experimental treatments.

## METHOD

The NEWMEDS repository includes anonymized patient data from controlled studies with SGAs in adult schizophrenia patients provided by companies participating in the NEWMEDS initiative: AstraZeneca, Eli Lilly, Janssen, Lundbeck, and Pfizer; data are from 29 placebo-controlled non-failed trials of SGAs (placebo, n = 2,200; drug, n = 6,971) and a later-obtained integrated dataset from 5 trials (placebo, n = 636; drug, n = 1863) used to validate findings. All studies but 2 were studies with orally administered antipsychotics, and the other 2 studied SGAs in a long-acting injectable formulation that in 1 study was supplemented with oral antipsychotic tablets during the first 21 days. Companies contributed all of their placebo-controlled trials of these compounds.

Results of the individual studies (listed in Supplementary eTable 1 with details on study arms, regions, and type of dosing) have been publicized. These data have never, until now, been pooled into a single dataset. All drugs (except for 1 subtherapeutic dose arm that was excluded from analyses) were grouped and compared to placebo. Each study had been approved by the relevant Institutional Review Board when and where it was conducted. All studies included informed written consent of study participants. The individual participant data from all studies were modeled simultaneously while accounting for the clustering of participants within studies as per the 1-step approach to individual participant data meta-analysis, as described by Riley and colleagues.[16] The first and second authors of this article had full access to all of the data in the studies, conducted all of the statistical analyses, and take responsibility for the integrity of the data and the accuracy of the data analysis. There was no commercial funding for this work.

### Measures

The 30-item clinician-rated Positive and Negative Syndrome Scale (PANSS)[17] was used in 21 studies. The Brief Psychiatric Rating Scale (BPRS)[18] consisting of 18 of the PANSS items was used in 8 studies. By computing weighted means by subscale, PANSS total scores were estimated from BPRS scores. Other measures were similar across studies.

### Analysis Plan

Differential effects of key variables at baseline on drug versus placebo response and dropout were examined primarily based on the literature. These variables included sex, body mass index (BMI), age, age at onset, duration of illness, location of study center (comparing North America vs Eastern Europe, the 2 major locations), symptom prominence (score ≥ 4 [moderate] on at least 3 or ≥ 5 [moderately severe] on at least 2 items on the positive or negative subscale[19]), and concomitant use of benzodiazepines or other hypnotics. Analysis of covariance models examining change from baseline to endpoint in the PANSS total score with last observation carried forward (LOCF) were conducted, as were similar models for dropouts, in which interactions of drug versus placebo were examined. Models were adjusted for study, continent, and patients' weight. For generalizability and consistency, we excluded 9 flexible-dose studies from these analyses. These analyses were followed by an exploratory analysis using Classification and Regression Trees (CART), a type of recursive partitioning, a method that identifies variables, cut points, and interactions that discriminate between groups.[20] CART is a simple nonparametric regression approach. Their main characteristic is that the feature space, ie, the space spanned by all predictor variables, is recursively partitioned into a set of rectangular areas. The partition is created such that observations with similar response values are grouped.[21] We used the CART method in SPSS 18 with the default parameters. Analyses were then conducted by study to determine if findings replicate at study level.

To examine age and age at onset, we divided patients by quartiles separately for males and females as males have an earlier age at onset.[22] Duration of illness quartiles was similarly derived. To examine whether there was an association between benzodiazepine use and clinical outcome, we compared patients who received more than 1 dose of benzodiazepines (n = 3,336) to those who were not given benzodiazepines (n = 2,760). We excluded from the analysis a small group of patients who received only a single dose (n = 148). To see whether shorter trials might be feasible, we examined percent of 6-week LOCF difference between drug and placebo already discernible at each previous week. For example, if week 6 LOCF PANSS total difference between drug and placebo was 5 points and the week 5 difference was 4 points, then 80% (4/5) of this difference was discernible at week 5. Since in most trials a difference is considered to be statistically significant at a $P$ value of $< .05$, we examined if a drug-placebo difference that met this criterion at week 6 would also have met this criterion had the trial been stopped earlier (eg, at 3, 4, or 5 weeks).

Given difficulties in recruiting, patients who are just below eligibility threshold may have had their scores inflated to be included, leading to a more pronounced measured response (with both drug and placebo). To test for this, we identified

patients who were within 6 points of the lower inclusion threshold for symptom severity on PANSS at screening and examined if this determined outcome.

To ensure the reliability and generalizability of our findings, we tested them in a subsequently obtained integrated dataset of studies with a similar design testing a compound not included in our primary analysis. While smaller than the initial data set, it provided sufficient power to test major effects.

To examine implications of selecting patients on the basis of differential predictors of drug and placebo response and implications of trial length on statistical power and sample sizes in studies, bootstrapping was used. Using bootstrapping (resampling), 1,000 simulated trials were created for each scenario representing a different composition of patients on predictor variables of interest drawn from our repository (eg, 70% male, 50% male). Mean effect sizes obtained were then compared to estimate how each predictor incrementally increased power assuming various scenarios. All analyses were conducted using SPSS Version 18 (IBM, Chicago, Illinois).

## RESULTS

### Predictors of Drug Versus Placebo Symptom Response

Based on ANCOVA analysis, mean difference between drug and placebo baseline-to-endpoint LOCF PANSS total score was 9.78 (SE = 0.62; 95% CI, 8.57–11.00). Females receiving placebo improved least (7.96), followed by males receiving placebo (10.55) and males receiving drug (19.58), and the greatest improvement was in females receiving drug (19.83) (Table 1). Females showed 2.84 points (2.84/9.78, ~29%) more drug-placebo differentiation on PANSS total score compared to males. The drug-versus-placebo difference was 3 points lower for the lowest and highest duration of illness group quartiles than the 2 middle quartiles.

Study centers in Eastern Europe had a 3.25-point higher drug-versus-placebo difference in change in PANSS score than those in North America (3.25/9.78, ~33%). There were proportionally more females in the Eastern European group (41.4%) than in the North American group (23.2%). However, overall and within sexes, there was considerably more drug-placebo differentiation in Eastern Europe (females, 15.37; males, 11.07) than in North America (females, 8.41; males, 7.56). There was less of a sex effect in North America (7.56/8.41, ~90%) than in Eastern Europe (11.07/15.37, ~72%); thus, even if both regions had the same proportion of females, the regional effects would remain.

Age and number of years since onset combined produced a 5.6-point difference on PANSS drug-placebo response between those aged 30 years or younger with 4 or more years of illness (young adult non–first episode patients) versus other patients (5.6/9.78, ~57%). Patients with both prominent positive and negative symptoms showed a 2.32-point greater drug-placebo improvement than patients with prominent positive symptoms alone (2.32/9.78, ~24%), and a 6.39-point greater improvement than those with only prominent negative symptoms at baseline (6.39/9.78, ~65%). Age, age at onset, number of previous hospitalizations, and use of benzodiazepines were not significantly associated with treatment response.

### Predictors of Trial Completion

Overall, 60.7% (n = 4,231/6,971) receiving drug and 51.7% (n = 1,137/2,200) receiving placebo completed 6 weeks in a trial. Similar to efficacy, drug-versus-placebo differences in completion rates were greater for women, young adult patients with 4 or more years of illness, those with prominent positive and negative symptoms, patients in Eastern Europe, and patients with BMI within normal limits (Table 2). Patients taking benzodiazepines were less likely to complete studies (drug, 58.6%; placebo, 45.5%), but the drug-placebo completion difference was 5.4% greater among those who received benzodiazepines.

### Drug-Placebo Differences and Trial Duration

The effect size of the difference in total LOCF change in PANSS total score between placebo and drug at weeks 1 to 6, respectively, was 0.25, 0.32, 0.35, 0.37, 0.38, and 0.39. The percent of the total LOCF difference in change between placebo and drug at 6 weeks that was discernible at weeks 1 to 5, respectively, was 44.5%, 67.3%, 80.15%, 90.2%, and 95.4% in the 24 studies lasting at least 6 weeks. At least 90% of 6-week drug effects could be detected at week 5 in 67% of studies (16/24), at week 4 in 58% of studies (14/24), at week 3 in 25% of studies (6/24), at week 2 in 17% of studies (4/24), and at week 1 in 4% of studies (1/24). In this dataset, 83% of trials (20/24) demonstrated a significant drug-placebo difference at the 6-week mark, while 79% (19/24) had reached significance by both weeks 5 and 4, 75% (18/24) had reached significance by week 3, 71% (17/24) had reached significance by week 2, and 50% (12/24) had reached significance by the end of the first week of the trial. Of the 4 trials in which significance was not reached at 6 weeks, 1 would have shown significance at week 5 and 2 would have shown significance at 4 weeks. Two studies that did not show significant drug-placebo difference at week 4, and 1 that did not reach significance at week 5 did show a significant difference at week 6. Not only were the 4-week trials sufficient for detecting a drug-versus-placebo difference, they had significantly higher completion rates (drug versus placebo, week 1 completion: 85.8% vs 84.4%; week 2 completion: 83.7% vs 80.3%; week 3 completion: 69.1% vs 65.9%; week 4 completion: 68.2% vs 60.1%; week 5 completion: 63.3% vs 54.3%; week 6 completion: 61.8% vs 53.2%).

### Potential Baseline Inflation (margin of eligibility)

Twelve of the 29 studies had minimum symptom eligibility criteria. Patients who just met these criteria (potentially subject to baseline inflation) were not overrepresented in the study population. This group was smaller than the next adjacent 6-point groups in every study and showed slightly less drug-versus-placebo difference in PANSS total score (drug, n = 237; placebo, n = 73; mean = 8.5; 95% CI,

**Table 1. PANSS Baseline to Endpoint (LOCF) Change for Placebo and Drug Difference by Key Variables in the Data Repository and Individual Studies[a]**

| Variable | Placebo, LS Mean (95% CI), n | Drug, LS Mean (95% CI), n | Drug-Placebo Difference, LS Mean (95% CI) | Statistical Comparison | Replicates |
|---|---|---|---|---|---|
| Sex | | | | $P = .04$, ES = 0.06 | 10/14 studies, in 2 almost linear, in 2 not; 5 cells too small |
| Female | 7.96 (4.75–11.16), 372 | 19.83 (17.10–22.55), 1,319 | 11.87 (9.53–14.22) | | |
| Male | 10.55 (7.79–13.71), 1,036 | 19.58 (17.04–22.12), 3,485 | 9.03 (7.61–10.45) | | |
| Age[b] | | | | $P = .74$, ES = NA | 7/11 studies, in 3 almost linear, in 1 not; 8 cells too small |
| Q1 | 9.21 (5.91–12.51), 331 | 19.99 (17.33–23.66), 1,257 | 10.78 (8.31–13.25) | | |
| Q2 | 9.86 (6.64–13.08), 364 | 19.93 (17.21–22.65), 1,128 | 10.07 (7.67–12.49) | | |
| Q3 | 9.78 (6.56–13.01), 362 | 19.18 (16.45–21.91), 1,276 | 9.40 (7.02–11.85) | | |
| Q4 | 9.76 (6.46–13.05), 351 | 18.69 (15.90–21.48), 1,143 | 8.93 (6.50–11.37) | | |
| Age at onset[c] | | | | $P = .94$, ES = NA | 9/9 studies; 6 cells too small |
| Q1 | 9.11 (5.24–12.97), 329 | 18.59 (15.25–21.94), 1,146 | 9.48 (6.95–12.02) | | |
| Q2 | 8.70 (4.68–12.72), 256 | 18.77 (15.40–22.13), 968 | 10.07 (7.22–12.91) | | |
| Q3 | 9.89 (5.94–13.84), 273 | 20.22 (16.85–23.59), 969 | 10.33 (7.56–13.11) | | |
| Q4 | 13.02 (8.99–17.06), 240 | 23.66 (20.28–27.05), 914 | 10.64 (7.70–13.57) | | |
| No. of years since onset[d] | | | | $P = .17$, ES: Q1 and Q4 vs Q2 and Q3 = 0.06 ($P = .03$) | 8/8 studies; 7 cells too small |
| Q1 | 13.75 (9.77–17.74), 256 | 22.07 (18.73–25.40), 1,034 | 8.32 (5.49–11.14) | | |
| Q2 | 9.04 (5.13–12.96), 285 | 20.31 (16.97–23.64), 1,019 | 11.27 (8.55–13.97) | | |
| Q3 | 7.18 (3.29–11.08), 302 | 19.01 (15.62–22.40), 966 | 11.83 (9.16–14.50) | | |
| Q4 | 8.93 (4.84–13.02), 255 | 17.46 (14.03–20.90), 978 | 8.53 (5.68–11.38) | | |
| No. of previous hospitalizations[e] | | | | $P = .57$, ES = NA | 4/5 studies, in 1 almost linear; 10 cells too small |
| Q1 | 12.00 (7.81–16.18), 218 | 22.71 (19.26–26.17), 830 | 10.71 (7.72–13.71) | | |
| Q2 | 11.77 (7.90–15.64), 310 | 21.18 (17.81–24.54), 1,140 | 9.41 (6.89–11.93) | | |
| Q3 | 10.55 (6.27–14.83), 176 | 18.19 (14.66–21.72), 562 | 7.64 (4.23–11.05) | | |
| Q4 | 5.60 (1.71–9.48), 279 | 15.92 (12.54–19.30), 960 | 10.32 (7.63–13.02) | | |
| BMI[f] | | | | $P = .38$, ES = NA | Could not be examined in individual studies due to small cell sizes |
| Underweight | 11.35 (5.34–17.36), 50 | 21.85 (17.96–25.74), 157 | 10.50 (4.11–16.90) | | |
| Normal | 10.43 (7.58–13.28), 639 | 20.68 (18.13–23.23), 2,143 | 10.25 (8.47–12.03) | | |
| Overweight | 10.04 (6.92–13.15), 434 | 19.16 (16.52–21.80), 1,559 | 9.12 (6.99–11.26) | | |
| Obese | 10.57 (7.35–13.80), 371 | 18.27 (15.53–21.02), 1,308 | 7.70 (5.38–10.02) | | |
| Region | | | | $P = .04$, ES = 0.07 | 2/2 conducted in both regions |
| Eastern Europe | 1.67 (−1.76–5.09), 265 | 13.88 (11.14–16.61), 858 | 12.21 (9.40–15.02) | | |
| North America | 3.64 (2.28–5.00), 1,062 | 12.60 (11.68–13.51), 3,608 | 8.96 (7.56–10.36) | | |
| Age and no. of years since onset—combined | | | | $P = .002$, ES = 0.11 | 5/8 studies, in 3 was not linear; 7 cell sizes too small |
| Age ≤ 30 y, 4 or more years of illness | 4.79 (0.44–9.11), 185 | 19.59 (16.16–23.02), 753 | 14.80 (11.48–18.14) | | |
| Others | 11.23 (7.84–14.63), 913 | 20.44 (17.24–23.65), 3,244 | 9.21 (7.68–10.73) | | |
| Baseline PANSS symptomatology | | | | $P = .001$, ES = prominent positive and negative vs other: 0.09 ($P < .001$) | 5/5 studies; 11 cell sizes small |
| Prominent negative | 13.82 (10.23–17.40), 218 | 19.91 (17.12–22.70), 739 | 6.09 (3.03–9.15) | | |
| Prominent positive | 9.00 (5.68–12.32), 292 | 19.16 (16.48–21.85), 957 | 10.16 (7.51–12.82) | | |
| Prominent negative and positive | 7.51 (4.59–10.44), 592 | 19.99 (17.40–22.59), 2,076 | 12.48 (10.63–14.33) | | |
| No prominent symptoms | 12.48 (8.64–16.31), 187 | 19.74 (16.78–22.71), 586 | 7.27 (3.93–10.60) | | |
| Use of benzodiazepine or other hypnotics during trial | | | | $P = .55$, ES = NA | 8/9 studies, in 1 not linear; 10 cell sizes too small |
| No | 12.98 (9.96–15.99), 563 | 21.97 (19.32–24.62), 2,197 | 8.99 (7.12–10.88) | | |
| Yes | 6.95 (3.36–9.13), 829 | 15.99 (13.34–18.64), 2,507 | 9.74 (8.15–11.34) | | |

[a]Results are based on fixed-dose studies. Analyses were not possible in some cases in which cell sizes were small (less than 10) in individual studies. ES not presented when *P* values are > .05.
[b]For females: Q1: ≤ 33, Q2: 34–41, Q3: 42–49, Q4: > 49; for males: Q1: ≤ 30, Q2: 31–37, Q3: 38–45, Q4: > 45 (values shown in years).
[c]For females: Q1: ≤ 18, Q2: 19–23, Q3: 24–30, Q4: > 31; for males: Q1: ≤ 18, Q2: 19–21, Q3: 22–26, Q4: > 27 (values shown in years).
[d]For females: Q1: ≤ 8, Q2: 9–14, Q3: 15–24, Q4: > 24; for males: Q1: ≤ 7, Q2: 8–14, Q3: 15–21, Q4: > 21 (values shown in years).
[e]Q1: 0–2, Q2: 3–4, Q3: 5–8, Q4: > 8.
[f]Based on World Health Organization criteria: underweight: < 18.5, normal: 18.5–24.9, overweight: 25–29.9, obese: ≥ 30 (values shown in $kg/m^2$).
Abbreviations: BMI = body mass index, ES = effect size, LOCF = last observation carried forward, LS = least squares, PANSS = Positive and Negative Syndrome Scale, Q = quartile.

**Table 2. Week 6 Completion Rates for Placebo and Drug Difference by Key Variables (%, 95% CI) in the Data Repository and Individual Studies[a]**

| Variable | Placebo, % (95% CI) | Drug, % (95% CI) | Drug-Placebo Difference, % (95% CI) | Statistical Comparison | Replicates |
|---|---|---|---|---|---|
| Sex | | | | $P = .03$, ES = 0.06 | 6/13 studies, in 1 almost linear, in 6 not; 5 cells too small |
| Female (n = 1,640) | 50.7 (43.1–58.4) | 67.1 (60.6–73.7) | 16.4 (10.9–22.0) | | |
| Male (n = 4,418) | 54.2 (47.6–60.7) | 63.6 (57.5–69.7) | 9.4 (6.2–12.7) | | |
| Age[b] | | | | $P = .10$, ES = NA | 6/11 studies, in 5 it was not linear; 7 cell sizes too small |
| Q1 (n = 1,564) | 47.1 (39.4–54.9) | 63.3 (57.0–69.7) | 16.2 (10.5–21.9) | | |
| Q2 (n = 1,471) | 52.9 (45.3–60.5) | 65.6 (59.1–72.0) | 12.7 (7.1–18.2) | | |
| Q3 (n = 1,599) | 56.8 (49.2–64.4) | 63.5 (57.0–70.0) | 6.7 (1.2–12.3) | | |
| Q4 (n = 1,424) | 56.4 (48.5–64.3) | 66.2 (59.5–72.9) | 9.8 (4.1–15.6) | | |
| Age at onset[c] | | | | $P = .67$, ES = NA | 6/9 studies, in 3 it was not linear; 5 cell sizes too small |
| Q1 (n = 1,475) | 50.9 (42.0–59.7) | 62.6 (54.9–70.3) | 11.7 (6.0–17.5) | | |
| Q2 (n = 1,224) | 48.9 (39.7–58.1) | 64.3 (56.6–72.1) | 15.4 (9.0–21.9) | | |
| Q3 (n = 1,242) | 54.9 (45.8–63.9) | 65.2 (57.5–73.0) | 10.3 (4.1–16.6) | | |
| Q4 (n = 1,154) | 57.5 (48.2–66.7) | 68.0 (60.2–75.8) | 10.5 (3.8–17.2) | | |
| No. of years since onset[d] | | | | $P = .97$, ES = NA | 3/9 studies, in 6 it was not linear; 5 cell sizes too small |
| Q1 (n = 1,290) | 51.8 (42.7–61.0) | 65.0 (57.2–72.7) | 13.2 (6.7–19.5) | | |
| Q2 (n = 1,304) | 54.4 (45.4–63.4) | 66.2 (58.5–74.0) | 11.8 (5.7–18.0) | | |
| Q3 (n = 1,268) | 51.8 (42.8–60.7) | 63.9 (56.1–71.8) | 12.1 (6.1–18.2) | | |
| Q4 (n = 1,233) | 54.2 (44.8–63.6) | 65.3 (57.3–73.2) | 11.1 (4.5–17.5) | | |
| No. of previous hospitalizations[e] | | | | $P = .46$, ES = NA | 0/5 studies, in 2 almost linear, in 3 not; 9 cells too small |
| Q1 (n = 1,048) | 54.8 (44.9–64.7) | 71.4 (63.2–79.6) | 16.6 (9.6–23.7) | | |
| Q2 (n = 1,450) | 55.8 (46.7–65.0) | 68.4 (60.4–76.4) | 12.6 (6.6–20.5) | | |
| Q3 (n = 738) | 53.3 (43.2–63.3) | 63.9 (55.5–72.2) | 10.6 (2.9–18.4) | | |
| Q4 (n = 1,239) | 52.6 (43.4–61.8) | 60.8 (52.8–68.8) | 8.2 (2.0–14.5) | | |
| BMI[f] | | | | $P = .03$, ES = very obese vs others: 0.07 ($P = .005$) | Could not be examined in individual studies due to small cell sizes |
| Underweight (n = 194) | 57.4 (42.6–72.3) | 64.8 (55.4–74.2) | 7.4 (−8.3–23.1) | | |
| Normal (n = 2,702) | 50.0 (43.1–56.9) | 64.0 (57.8–70.2) | 14.0 (9.8–18.2) | | |
| Obese (n = 1,947) | 52.6 (45.1–60.2) | 63.4 (57.0–69.8) | 10.8 (5.7–15.8) | | |
| Very obese (n = 1,666) | 61.0 (53.2–68.8) | 64.5 (57.8–71.1) | 3.5 (−2.0–8.9) | | |
| Region | | | | $P \leq .001$, ES = 0.15 | 2/2 conducted in both regions |
| North America (n = 4,670) | 45.7 (41.1–58.2) | 53.7 (51.8–55.6) | 8.0 (4.8–11.2) | | |
| Eastern Europe (n = 969) | 49.6 (42.8–48.7) | 73.9 (67.2–80.6) | 24.2 (17.1–31.3) | | |
| Age and no. of years since onset—combined | | | | $P = .03$, ES = 0.08 | 5/8 studies, in 3 not; 6 cells too small |
| Age ≤ 30 y, 4 or more years of illness (n = 938) | 44.0 (34.2–53.9) | 63.4 (55.5–71.3) | 19.4 (11.9–26.9) | | |
| Others (n = 4,157) | 54.9 (47.1–62.7) | 65.5 (58.1–72.9) | 10.6 (7.1–14.0) | | |
| Baseline PANSS symptomatology | | | | $P = .03$, ES = prominent positive and negative vs other: 0.05 ($P = .07$) | 3/5 studies, in 2 not; 10 cells too small |
| Prominent negative (n = 879) | 67.2 (58.5–75.8) | 69.1 (62.4–75.7) | 1.9 (−5.4–9.3) | | |
| Prominent positive (n = 1,241) | 49.4 (41.6–57.3) | 61.8 (55.5–68.2) | 12.4 (6.3–18.5) | | |
| Prominent negative and positive (n = 2,640) | 50.7 (43.7–57.6) | 65.5 (59.3–71.7) | 14.8 (10.5–19.0) | | |
| No prominent symptoms (n = 723) | 51.6 (42.4–60.7) | 64.9 (57.9–72.0) | 13.3 (5.5–21.3) | | |
| Use of benzodiazepine or other hypnotics during trial | | | | $P = .03$, ES = 0.06 | 6/8 studies, in 2 not; 10 cells too small |
| No (n = 2,699) | 62.1 (54.9–69.2) | 69.8 (63.4–76.1) | 7.7 (3.4–10.88) | | |
| Yes (n = 3,244) | 45.5 (38.6–52.4) | 58.6 (52.2–64.9) | 13.1 (9.4–16.9) | | |

[a]Results are based on fixed-dose studies. Analyses were not possible in some cases in which cell sizes were small (less than 10) in individual studies. ES not presented when *P* values are > .05.
[b]For females: Q1: ≤ 33, Q2: 34–41, Q3: 42–49, Q4: > 49; for males: Q1: ≤ 30, Q2: 31–37, Q3: 38–45, Q4: > 45 (values shown in years).
[c]For females: Q1: ≤ 18, Q2: 19–23, Q3: 24–30, Q4: > 31; for males: Q1: ≤ 18, Q2: 19–21, Q3: 22–26, Q4: > 27 (values shown in years).
[d]For females: Q1: ≤ 8, Q2: 9–14, Q3: 15–24, Q4: > 24; for males: Q1: ≤ 7, Q2: 8–14, Q3: 15–21, Q4: > 21 (values shown in years).
[e]Q1: 0–2, Q2: 3–4, Q3: 5–8, Q4: > 8.
[f]Based on World Health Organization criteria: underweight: < 18.5, normal: 18.5–24.9, overweight: 25–29.9, obese: ≥ 30 (values shown in $kg/m^2$).
Abbreviations: BMI = body mass index, ES = effect size, PANSS = Positive and Negative Syndrome Scale, Q = quartile.

**Table 3. Drug-Placebo Difference From Bootstrap Simulations in Each Scenario Based on 1,000 Simulated Studies of 120 Patients per Arm[a]**

| Variable | Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4 |
|---|---|---|---|---|
| Male vs female | 70% vs 30%[b] | 50% vs 50% | 70% vs 30%[b] | 50% vs 50% |
| Young non–first episode group (age ≤ 30 y, 4 or more years of illness) vs otherwise | 20% vs 80%[b] | 20% vs 80%[b] | 50% vs 50% | 50% vs 50% |
| **Week 6** | | | | |
| All | | | | |
| Completion rate difference (completion rate for drug) | 11.5% (61.5%) | 13% (61.5%) | 15.7% (59.5%) | 17.0% (60.1%) |
| Effect size | 0.522 | 0.55 | 0.618 | 0.647 |
| Sample needed, n[c] | 79 | 71 | 57 | 52 |
| Reduction from scenario 1, n | … | 8 | 22 | 27 |
| Enriched selection criteria[d] | | | | |
| Completion rate difference (completion rate for drug) | 16.4% (56.9%) | 17.2% (58.0%) | 17.7% (56.1%) | 18.0% (57.0%) |
| Effect size | 0.582 | 0.604 | 0.637 | 0.684 |
| Sample needed, n[c] | 64 | 60 | 53 | 46 |
| Reduction from scenario 1, n | … | 4 | 11 | 18 |
| **Week 5** | | | | |
| All | | | | |
| Completion rate difference (completion rate for drug) | 11% (64.9%) | 12.9% (63.5%) | 13.8% (63.3%) | 14.3% (64.1%) |
| Effect size | 0.498 | 0.527 | 0.60 | 0.627 |
| Sample needed, n[c] | 86 | 77 | 60 | 55 |
| Reduction from scenario 1, n | … | 9 | 26 | 31 |
| Enriched selection criteria[d] | | | | |
| Completion rate difference (completion rate for drug) | 15.3% (61.7%) | 15.6% (63.0%) | 15.0% (60.8%) | 14.6% (61.9%) |
| Effect size | 0.581 | 0.606 | 0.657 | 0.695 |
| Sample needed, n[c] | 64 | 59 | 50 | 45 |
| Reduction from scenario 1, n | … | 5 | 14 | 19 |
| **Week 4** | | | | |
| All | | | | |
| Completion rate difference (completion rate for drug) | 9.4% (68.5%) | 11.4% (71.1%) | 11.1% (71.7%) | 12.6% (72.5%) |
| Effect size | 0.473 | 0.50 | 0.572 | 0.594 |
| Sample needed, n[c] | 95 | 86 | 66 | 61 |
| Reduction from scenario 1, n | … | 9 | 19 | 34 |
| Enriched selection criteria[d] | | | | |
| Completion rate difference (completion rate for drug) | 12.0% (69.7%) | 13.0% (71.2%) | 10.3% (69.0%) | 11.3% (70.0%) |
| Effect size | 0.551 | 0.573 | 0.626 | 0.662 |
| Sample needed, n[c] | 71 | 65 | 55 | 49 |
| Reduction from scenario 1 | … | 6 | 16 | 22 |

[a]Bootstrap sample drawn from fixed-dose studies with at least 20 females.
[b]Observed distribution of pooled data.
[c]Sample size per arm for 90% power, $P = .05$, 2-sided test, assuming 1:1 placebo:drug ratio.
[d]Enriched selection criteria: prominent positive and negative symptoms, a score ≥ 4 "moderate" on at least 3, or ≥ 5 "moderately severe" on at least 2 subscale items in both PANSS subscales.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.
Symbol: … = not applicable.

3.65–13.29) than the other patients (drug, n = 3,034; placebo, n = 835; mean = 10.01; 95% CI, 8.28–11.74).

### Validation of Findings in Another Dataset

We analyzed 4 later-obtained studies (placebo, n = 580; drug, n = 1,699); 1 additional failed study was excluded. Baseline to endpoint LOCF mean difference in PANSS total score between drug and placebo was 7.03 (SE = 0.92; 95% CI, 5.22–8.84). Sex, region, and young adult non–first episode effects replicated. Females had a 3.1-point greater drug versus placebo improvement than males (females = 2.6 vs 11.8; males = 4.6 vs 10.6, linear trend, $P < .0001$; 3.1/7.0, ~ 44%). In Eastern Europe, drug-placebo difference was 7.84 and in North America, 4.40, resulting in a difference of approximately 49% (3.4/7.0). No study had patients from both regions, disallowing within-study comparisons. Age and number of years since onset combined produced a 3.2-point difference on the PANSS between those 30 or younger with 4 or more years of illness (9.96; 95% CI, 4.64–15.3; drug, n = 174; placebo, n = 80) versus other patients (6.74; 95% CI, 4.76–8.71; drug, n = 1,450; placebo, n = 483) (3.2/7.0, ~ 46%). Baseline inflation and benzodiazepine use data were not available in this database, and there was an insufficient number of patients in each category to test symptom prominence. Seventy-four percent of the week 6 drug effects (5.91) were already apparent at week 5 (4.37) (by study, 88%, 69%, 63%, and 58%). This was less than in the repository, possibly due to fewer effects in these studies and because 1 study was a 26-week study. Unlike in the repository, males and females showed approximately the same drug and placebo dropout rates.

### Implications for Future Trials

Table 3 presents the bootstrap simulations putting together the results on differential predictors of drug and placebo response and duration of study. Differences in completion rates and effect size differences on PANSS and sample sizes needed for 90% power ($\alpha = .05$, 2 sided) are illustrated.

Scenario 1 represents the current distribution (70% male, 20% young non–first episode, effect size of drug-placebo = 0.52) and requires 79 patients in each arm treated for 6 weeks to find a statistically significant difference; thereby requiring a total patient-trial exposure of 948 weeks (ie, 79 × 2 arms × 6 weeks) and patient-placebo exposure of 479 weeks. Given the evidence of potential success of a 4-week trial, we found that a slight increase in patient numbers per arm (79 to 95) can achieve similar statistical certainty, with fewer dropouts (68.5% receiving drug completed 4 weeks vs 61.5% at 6 weeks), and considerably fewer patient trial-weeks (760 vs 948) and placebo-weeks (380 vs 479) of exposure. For 6-week trials, Scenario 2 shows that when patients are evenly divided by sex, 71 patients are needed per arm. Scenario 3 shows that when patients are evenly divided between young non–first episode and the rest, 57 patients would be needed per arm; and Scenario 4 combines Scenarios 2 (evenly divided by sex) and 3 (half young adult non–first episode patients) and shows a further reduction in sample size to 52 patients per arm. These can be further reduced to 46 by using enriched selection criteria of taking only patients with prominent positive and negative symptoms, thus a total reduction of 33 patients. The lowest section of this table shows the results for a 4-week study in which sample sizes would move from 95 to 49.

## DISCUSSION

Based on this unprecedented private-public collaboration that enabled merging data from the majority of placebo-controlled studies of SGAs conducted by 5 pharmaceutical companies over the last 2 decades, we were able to identify response determinants that could inform clinical practice and help improve efficiency of future drug discovery trials in this area. While the differences found have an impact on effect size and thereby power and sample size, the differences are not large. We found that such trials can be shorter and that, by increasing the proportion of women, young adult non–first episode patients, and patients with prominent symptoms and (when relevant) excluding patients with baseline inflation, trials can be more powerful and sample sizes smaller.

A central finding is the differential response between men and women. Women show a lesser response to placebo and a greater response to medication leading to a significantly greater drug-placebo difference (29% greater than men). The reasons for this are not clear, but the finding is robust, as it was convincingly replicated in our second data set. One hypothesis might be that increased male placebo response is due to males' better response to psychosocial and material aspects of participation in a clinical trial (such as being admitted to a hospital where shelter and nutrition conditions might be superior to the alternative).

The increased treatment effect for the young adult non–first episode patients is possibly because they participate after the tumultuous first episode but are young enough to have not had extensive exposure to multiple antipsychotic medications. Better outcomes in study centers in Eastern Europe, as compared to North America, are consistent with the findings of Khin et al[8] and Chen et al.[7] The European Medicines Agency (EMA) has suggested that geographic differences in outcomes may be related to intrinsic (genetic, physiologic, and pathological conditions) and extrinsic (environmental, eg, climate, culture, medical practice) factors.[11] Relating to antipsychotic trials, the differences may be related to the fact that patients in the United States may have participated in more trials and, thus, had exposure to more medications, thus lowering response. Future studies should include an inventory of patients' experience in previous clinical trials and detailed medication history. Since the proportion of dropouts receiving placebo, but not active treatment, was similar in North America and Eastern Europe, these differences do not appear to relate to better compliance in Eastern Europe.

The lack of overrepresentation of patients just meeting symptom eligibility criteria counters concerns that investigators may inflate scores to allow including additional patients. The results do, however, suggest that in cases in which there is evidence of baseline inflation, it would be prudent to include in the statistical analysis plan a sensitivity analysis after removing persons just meeting eligibility criteria.

Our results show that trials can both be shorter and have fewer patients. A conventional 6-week trial currently requires approximately 79 patients per arm (a total of 474 weeks of patient exposure to both placebo and drug). If the information identified herein is used, trial duration could be reduced to 4 weeks for 49 patients per arm for 196 weeks of patient exposure. In addition to having fewer weeks of exposure, shorter trials have the advantage of higher completion rates, as shown by our data. In addition, recruitment for shorter trials will probably be easier and retention rates should be even higher than shown here, as patients may be willing to stay in a shorter study with the end in sight. Shorter trials also cost less money, and lower dropout rates result in less imputation of missing data.

The results have implications for clinical practice, though trial results are often different from routine clinical practice. Nonetheless, the findings confirm the general clinical impression that earlier onset of illness and greater number of hospitalizations were associated with poorer course of illness, but not to response to antipsychotics. Two major findings, however, would come as a surprise to most clinicians. First, patients with both positive and negative symptoms show greater drug-placebo difference than those with only positive or negative symptoms. Thus, the current antipsychotics seem more effective in pan-symptomatic patients than in those with predominantly psychotic presentation. Secondly, the use of benzodiazepines was not related to differences in treatment response. This finding would surprise many given the generally widespread use of benzodiazepines as adjunctive medications. However, our data are rather consistent with several other controlled trials which show that the addition of a benzodiazepine to ongoing treatment in schizophrenia has only marginal, if

any, effects on overall symptomatic improvement.[9] Though benzodiazepines did not affect treatment response, patients who received benzodiazepines more than once during the trial were overall less likely to complete 6 weeks of trial and showed a greater drug-placebo difference in completion rates. This may be because benzodiazepines were used as some type of rescue medication with relatively more use in patients with poorly responding prominent symptoms, who tend to stop studies prematurely. We were not able to examine the effects of concurrent use of antidepressants or mood stabilizers, which are sometimes used in these populations. Antidepressants were not allowed in 15 of the 29 studies, in 2 they were not allowed during the first 2 weeks of the study, in 6 they were allowed only if the patient entered the study with a prior stable dose, and in 6 they were not mentioned as being allowed or disallowed. Other psychotropics were not permitted at all in 27 of the studies, and in 2 they were not allowed for the first 2 weeks.

The study has several important limitations. Data are representative of clinical trials of medications that have proven superior to placebo on antipsychotic effect; however, data on compounds that failed in the last 2 decades were not available to us. Our analysis was conducted on data from placebo-controlled trials of risperidone, paliperidone, sertindole, olanzapine, ziprasidone, and quetiapine. Outside of one ziprasidone study, which showed superiority to placebo on some arms but failed to meet study criteria as a positive study, these compounds did not have studies in which study drug was not significantly better than placebo on efficacy in schizophrenia. We further tested our findings using data from bifeprunox trials that came to us later. Although bifeprunox was not approved, 4 of the 6 studies were positive, there was 1 failed study (in which neither bifeprunox nor haloperidol separated from placebo), 1 negative study, and 1 that was negative on the primary efficacy measure but positive on a secondary efficacy measure. Age at onset was a salient variable in our analysis as it was used to determine number of years of illness. This was referred to in some studies as "age of first diagnosis of schizophrenia," in others as "age of first hospitalization," and in yet others as "age of onset." Studies were not explicit as to how they operationalized these.

The compounds on which our conclusions are based, like all compounds currently available for clinical use, share dopamine $D_2$ receptor blockade as their common mechanism. While these drugs provide the only data-driven estimate for future drugs, it is conceivable that newer drugs working on different mechanisms may show a different profile or timeframe of response. The results of this work may not be generalizable to compounds not included in this work, and we were not able to test the results by compound; however, the results were replicated in most studies. All SGAs were given orally so that data cannot be generalized to long-acting injectable formulations. Future work should attempt to replicate these findings using data from compounds with a different mechanism of action.

The focus of our work is on efficacy as measured by the PANSS and trial completion, and our objective was to test the possibility of conducting shorter proof-of-principle trials. Time to discontinuation is an important pragmatic outcome measure which reflects both safety and tolerability but is more relevant in longer trials and thus was not a measure of interest for this article. Our data suggest that including more women may be good, not only for better generalizability, but also for statistical power. While our analysis suggests enrollment criteria that maximize drug-placebo differences, using selective criteria (eg, certain phase of illness, age groups, or symptom severity) may decrease generalizability of results to routine clinical practice and make recruitment more difficult. However, in the early stages of drug development, in which finding evidence of efficacy is more critical than generalizability, our data suggest a way forward.

In summary, sex, age, duration of illness, symptomatology, and geographic location all significantly influence outcome of schizophrenia trials with effect sizes that are clinically relevant. Implementing this information in patient selection for early stage proof-of-principle trials may make trials shorter and more efficient. Implementing this information in the pivotal trials could allow for more generalizable pivotal studies.

***Drug names:*** haloperidol (Haldol and others), olanzapine (Zyprexa), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

***Author affiliations:*** Bar Ilan University, Ramat Gan, Israel (Drs Rabinowitz and Werbeloff); Janssen Research & Development, Beerse, Belgium (Dr Caers); Pfizer, New York, New York (Dr Mandel); Eli Lilly, Indianapolis, Indiana (Drs Stauffer and Kinon); Lundbeck SAS, Paris, France (Dr Ménard); and Institute of Psychiatry, Kings College, London, United Kingdom (Dr Kapur).

***Potential conflicts of interest:*** **Dr Rabinowitz** has served as a consultant to Janssen (Johnson & Johnson), Eli Lilly, Pfizer, BiolineRx, Roche and Amgen, and is on scientific advisory board at MedAvante. **Dr Caers** is an employee and stock shareholder of Johnson & Johnson. **Dr Mandel** is an employee and stock shareholder of Pfizer. **Dr Kinon** is an employee and stock shareholder of Eli Lilly. **Dr Stauffer** is an employee of Eli Lilly. **Dr Ménard** is an employee of H. Lundbeck A/S. **Dr Kapur** has received grant support from GlaxoSmithKline, GW Pharmaceuticals, and Roche; has served as a one-off consultant and/or speaker for AstraZeneca, Bristol Meyers Squibb, Eli Lilly, Envivo, Janssen (Johnson & Johnson), Otsuka, Pfizer, and Takeda; and serves on the Scientific Advisory Boards for Lundbeck and Roche. **Dr Werbeloff** has no conflict of interests to report.

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***Additional information:*** The NEWMEDS database can be accessed at http://www.newmeds-europe.com/en/project-structure.php.

***Supplementary material:*** See accompanying pages.

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Supplementary material follows this article.

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# Supplementary Material

**Article Title:** **Determinants of Antipsychotic Response in Schizophrenia: Implications for Practice and Future Clinical Trials**

**Author(s):** **Jonathan Rabinowitz, PhD; Nomi Werbeloff, PhD; Ivo Caers, PhD; Francine S. Mandel, PhD; Virginia Stauffer, PharmD; François Ménard, MD; Bruce J. Kinon, MD; and Shitij Kapur, MBBS, PhD**

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## List of Supplementary Material for the article



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This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1.

Placebo controlled trials included in NEWMEDS

| Name/Publication /Registration number | Treatment (active treatment, placebo sample sizes) | Regions | Fixed dose study |
|---|---|---|---|
| Repository | | | |
| Janssen | | | |
| RIS-INT-3 [1]; [2] NCT00249132 | Risperidone + Haloperidol: n=435 Placebo: n=88 | North America | yes |
| RIS-USA-72 [3] | Risperidone: n=162 Placebo: n=83 | North America | yes |
| RIS-USA-121 [4] NCT00253136 | Risperidone: n=332 Placebo: n=107 | North America | yes |
| RIS-USA-9001 [5] | Risperidone + Haloperidol: n=106 Placebo: n=54 | North America | no |
| Ris-SCP-402 [6] NCT00061802 | Risperidone + Quetiapine: n=309 Placebo: n=73 | North America, Eastern Europe & Asia | no |
| R076477-SCH-301 [7] NCT00086320 | Paliperidone: n=104 Placebo: n=102 | North America, Eastern Europe, Middle East & Asia | no |
| R076477-SCH-302 [8] EUCTR2004-000326-70-CZ | Paliperidone: n=76 Placebo: n=38 | Europe & South Africa | no |
| R076477-SCH-303 [9] NCT00078039 | Paliperidone + Olanzapine: n=503 Placebo: n=126 | Europe & Asia | yes |
| R076477-SCH-304 NCT00077714 [10] | Paliperidone + Olanzapine: n=503 Placebo: n=126 | North America | yes |
| R076477-SCH-305 [11] NCT00668837 | Paliperidone + Olanzapine: n=491 Placebo: n=123 | North America, South America, Europe, Middle East & Asia | yes |
| R076477-SCH-3015 [12] NCT00334126 | Paliperidone + Quetiapine: n=319 Placebo: n=80 | North America, Eastern Europe, & Asia | no |
| Pfizer | | | |
| 128-104 | Ziprasidone: n=150 Placebo: n=50 | North America | yes |
| 128-106 [13] | Ziprasidone: n=91 Placebo: n=48 | North America | yes |
| 128-114 [14] | Ziprasidone: n=207 Placebo: n=91 | North America | yes |
| 128-115 | Ziprasidone + Haloperidol: n=336 Placebo: n=83 | North America | yes |
| 128-303 [15] | Ziprasidone: n=219 Placebo: n=75 | Eastern Europe | Yes |
| 128-307 | Ziprasidone: n=126 Placebo: n=64 | Eastern Europe | Yes |
| Lundbeck | | | |
| M91-645 | Sertindole: n=27 Placebo: n=11 | North America | No |
| M92-762 | Sertindole, n=157 | North America | Yes |

| Name/Publication /Registration number | Treatment (active treatment, placebo sample sizes) | Regions | Fixed dose study |
|---|---|---|---|
| | Placebo: n=48 | | |
| M93-098 | Sertindole + Haloperidol: n=346<br>Placebo: n=116 | North America | Yes |
| M93-113 [16] | Sertindole + Haloperidol: n=424<br>Placebo: n=73 | North America | Yes |
| M92-817 | Sertindole + Haloperidol: n=114<br>Placebo: n=42 | North America | Yes |
| Astra Zeneca | | | |
| 5077IL/0006 | Seroquel: n=53<br>Placebo: n=53 | North America | No |
| 5077IL/0013 [17] | Seroquel + Haloperidol: n=240<br>Placebo: n=39 | North America | Yes |
| 5077US/0001;<br>204,636/0008 [18] | Seroquel: n=186<br>Placebo: n=94 | North America & Europe | No |
| D1444C00133 [19]<br>NCT00085891 | Seroquel: n=447<br>Placebo: n=117 | North America | Yes |
| Lilly | | | |
| F1D-MC-HGAD [20] | Olanzapine + Haloperidol: n=267<br>Placebo: n=68 | North America | No |
| F1D-MC-HGAP [21] | Olanzapine: n=101<br>Placebo: n=50 | North America | Yes |
| Yes | North America & Eastern Europe | Olanzapine: n=305<br>Placebo: n=98 | F1D-MC-HGJZ [22]<br>NCT00088478 |
| Integrated data base for validation | | | |
| Yes | Eastern Europe & Other | Bifeprunox: n=331<br>Placebo: n=166 | LU10214 |
| Yes | Eastern Europe & North America | Bifeprunox+Haloperidol: n=161<br>Placebo; n=53 | S154.2.002 |
| Yes | North America | Bifeprunox & Risperidone: n=408<br>Placebo, n=105 | S154.2.010 [23] |
| Yes | North America & Other | Bifeprunox+Olanzapine: n=408<br>Placebo: n=129 | S154.3.003 |
| Yes | North America | Bifeprunox+ Risperidone: n=391<br>Placebo: n=127 | S154.3.001 |

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