See commentary by Laughren

The Trend of Increasing Placebo Response and Decreasing Treatment Effect in Schizophrenia Trials Continues:
An Update From the US Food and Drug Administration

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ABSTRACT

Objective: Concerns of increasing placebo response and declining treatment effect in acute schizophrenia trials have been reported for new drug applications (NDAs) submitted to the US Food and Drug Administration (FDA) during an 18-year period from 1991 through January 2009 (ie, the pre-2009 period). Current exploratory analyses provide an update in the trends observed in placebo response, treatment effect, and dropout rates for NDAs submitted from February 2009 to 2015 (ie, the post-2009 period).

Data Sources: Clinical trial data from all acute schizophrenia trials that were submitted as part of NDAs to the US FDA during a 24-year period from 1991 to 2015.

Study Selection: Aggregate trial-level efficacy data from multicenter, multiregional, randomized, placebo-controlled, 4- to 8-week, fixed- and flexible-dose trials in adult schizophrenia patients were compiled. There were 12 NDAs pre-2009 (32 trials, N = 11,567) and 3 NDAs post-2009 (14 trials, N = 6,434).

Data Extraction: Baseline demographic and disease variables and scores on the Positive and Negative Syndrome Scale (PANSS) were summarized and compared for the two time periods (pre-2009 and post-2009). The primary efficacy measure was mean change from baseline to endpoint in total PANSS score obtained by last-observation-carried-forward analysis. Regional differences in placebo response and treatment effect were explored for the two time periods based on baseline patient characteristics, sample size, and dropout rates.

Results: Trials were predominantly multiregional (10/14; 71%) during the post-2009 period compared to the pre-2009 period (11/32; 34%). The overall trial success rates were 57% (8/14) and 78% (25/32) during the post-2009 and pre-2009 periods, respectively. Comparing the pre-2009 and post-2009 periods, the mean placebo response (change from baseline in PANSS score) increased from −6.4 to −10.5 and the mean treatment effect (drug response − placebo response) declined from −8.6 to −5.8 , with substantial differences observed especially in North American trials. In North American trials, placebo response increased from −4.3 (pre-2009) to −8.5 (post-2009), and treatment effect decreased from −9.0 (pre-2009) to −3.4 (post-2009). The difference in placebo response (pre- and post-2009: −10.0 and −11.3) and treatment effect (pre and post-2009: −8.1 and −6.4) in multiregional trials for the two time periods remained minimal. Baseline disease severity remained similar in the pre- and post-2009 time periods, with PANSS scores ranging between 85 and 100. Trials with higher mean baseline PANSS scores tended to show higher treatment effect irrespective of the time period and region. Post-2009, dropout rates were higher (55%) in North American trials compared with 33% in multiregional trials, similar to the pre-2009 trend.

Conclusions: The continuing trend of increasing placebo responses and decreasing treatment effects in schizophrenia trials over the 24-year period does remain of great concern, especially with respect to North American trials. However, given the current global nature of drug development, close attention to trial conduct and reexamination of design elements for future trials may be warranted.

J Clin Psychiatry 2020;81(2):19r12960

To cite: Gopalakrishnan M, Zhu H, Farchione TR, et al. The trend of increasing placebo response and decreasing treatment effect in schizophrenia trials continues: an update from the US Food and Drug Administration. *J Clin Psychiatry.* 2020;81(2):19r12960.

To share: https://doi.org/10.4088/JCP.19r12960

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Schizophrenia is a chronic, disabling psychiatric disorder affecting approximately 2.4 million adults in the United States, with a prevalence of about 1.5%.[1] Schizophrenia is one of the top 25 leading causes of disability worldwide, producing an economic burden of more than $60 billion per year in the United States alone.[2]

Efficacy trials in patients with schizophrenia have been characterized by an increasing rate of placebo response and a decline in treatment effect over time. In a survey of such trials in New Drug Applications (NDAs) submitted to the US Food and Drug Administration (FDA) between 1991 and January 2009, referred to in this report as the pre-2009 period, the placebo response increased over time and was of great concern in trials conducted in North America.[3] Drug development has now become a global process, and multiregional trials for regulatory submission purposes have become the norm.[4] Global clinical trials may reduce time to drug approval, facilitating earlier patient access to new and innovative treatments. In future decades, therefore, continuing globalization of drug development is inevitable, and efforts to understand global and regional differences in placebo response and treatment effect are essential for efficient drug development. The current exploratory analysis provides updated information about trends in placebo response, treatment effect, and dropout rates for trials included in NDAs submitted to the FDA from

Clinical Points

- Regional differences for increasing placebo response and diminishing treatment effects were previously reported for acute schizophrenia trials during an 18-year time period (ie, 1991–2009).
- The current study encompassing studies from 2009 to 2015 found that the concerning trend for increasing placebo response and diminishing treatment effects continues especially in North American trials leading to higher trial failure rates. Potential reasons for this trend with solutions to improve the trial efficiency are presented.

February 2009 to 2015, referred to in this report as the post-2009 period.

METHODS

Data Collection

Three antipsychotic drug NDAs have been submitted to the FDA since February 2009 and are referred to herein as post-2009 drugs. As reported previously in this journal by Khin et al,[3] 12 antipsychotic drug NDAs were submitted to the FDA between 1991 and January 2009 and are referred to here as pre-2009 drugs. The data collection methodology for this new study (post-2009 trial data) was similar to that reported previously.[3] All trials were randomized, multicenter, double-blind, placebo-controlled, fixed- and flexible-dose trials with at least 45 subjects in each of the treatment arms. Individuals enrolled in these trials were adults (aged ≥ 18 years) diagnosed with schizophrenia according to *DSM-IV* or *DSM-IV-TR* criteria. The data used in this exploration were derived from trials requiring informed consent. Evaluable subjects were defined as those with a baseline value and at least 1 post-baseline efficacy assessment. The aggregate-level data were collected from FDA reviews and/or clinical study reports submitted by sponsors. These data included summarized demographic information (age, sex, race, weight, body mass index [BMI]), dropout rates, baseline Positive and Negative Syndrome Scale (PANSS) scores, and mean change from baseline in PANSS score for each of the treatment arms.

Data Analysis

No additional analyses were performed on the pre-2009 trials, and the results described in the current report are presented directly from Khin et al.[3] Exploratory analyses of the post-2009 data were conducted on aggregate-trial level data. For all trials, mean changes from baseline in total PANSS score at final visit (week 6 for the post-2009 trials of current primary interest) for placebo and drug treatment arms were calculated by analysis of covariance on last-observation-carried-forward (LOCF) data including baseline PANSS score as a covariate; this was the analysis methodology reported by Khin et al[3] for the pre-2009 data. It should be noted that the majority of post-2009 trials used a (preplanned) mixed-model repeated-measures analysis as the primary analysis to obtain the adjusted mean treatment effects. However, FDA reviews also included treatment effect estimated from LOCF analysis and reported as part of a sensitivity analysis, which was used to compare data pre- and post-2009.

Mean treatment effect was calculated as mean change from baseline in the drug treatment group minus mean change from baseline in the placebo treatment group. As mentioned, for the pre-2009 analysis, the trial was considered a success if at least 1 of the investigational drug groups demonstrated superiority over the placebo group on the primary endpoint after adjustment for multiplicity (as specified in the protocol). All of these analyses compared the regional variations by categorizing the trials as North American (United States and Canada) or multiregional (North America and the rest of the world).

RESULTS

The analysis included both successful and unsuccessful trials to provide a comprehensive overview and reduce selection bias. The search identified 14 acute schizophrenia trials post-2009, which included 6,434 evaluable subjects across 3 NDA programs. Thirteen of the 14 trials included more than one dose group, with 6 trials including an active control treatment arm. The pre-2009 analysis consisted of data from 32 schizophrenia trials comprising 11,567 evaluable subjects.

In the post-2009 period, 3 of the 14 trials used the Brief Psychiatric Rating Scale–derived as the rating scale to evaluate the efficacy of antipsychotics, and 11 trials used the total PANSS score. A majority of the trials used change from baseline in PANSS score as the primary efficacy endpoint. In the current analysis, mean change from baseline in PANSS score was used as the primary outcome of interest whether it was reported as the primary or the secondary efficacy measure in the original study reports.

In the pre-2009 period, 11 (34%) of 32 trials were multiregional and 21 (66%) were North American. In the post-2009 period, the trend was reversed: 10 (71%) of the 14 trials were multiregional and 4 (29%) were North American. Trials primarily used a fixed-dose design during both the pre-2009 (27/32: 84%) and post-2009 (11/14: 79%) periods. In the pre-2009 period, 6 trials were 4-week trials, 23 were 6-week trials, and 3 were 8-week trials. In the post-2009 period, all trials were 6-week trials.

Table 1 summarizes the demographics, baseline disease status, dropout percentages, and number of subjects during the pre-2009 and post-2009 periods by region. A total of 18,001 subjects were included in the exploratory analysis, 11,567 (64%) in pre-2009 trials and 6,434 (36%) in post-2009 trials. Among these subjects, 54% and 16% were from trials conducted in North America pre-2009 and post-2009, respectively. Overall, 26% of pre-2009 and 31% of post-2009 subjects were female, and the mean age at study entry was approximately 39 years in both time periods. Subjects in

Table 1. Demographic and Baseline Characteristics in Schizophrenia Trials[a]

Characteristic	North American Trials (US and Canada)		Multiregional Trials (US and Canada + Rest of World)		All Trials	
	Pre-2009 (21 Trials)	Post-2009 (4 Trials)	Pre-2009 (11 Trials)	Post-2009 (10 Trials)	Pre-2009 (32 Trials)	Post-2009 (14 Trials)
ITT patients, n (%)	6,268 (54.2)	1,055 (16.4)	5,299 (45.8)	5,379 (83.6)	11,567 (100)	6,434 (100)
Age, y[b]	39.3 (1.6)	40.8 (1.2)	38.4 (2.0)	38.9 (2.6)	39.0 (1.8)	39.3 (2.5)
Sex, % female[c]	22.2 (6.0)	23.7 (4.5)	31.7 (8.7)	33.1 (6.6)	25.7 (8.4)	30.9 (7.3)
Race, %						
White[c]	50.5 (10.1)	39.0 (7.0)	54.5 (15.3)	48.0 (20.6)	52.0 (12.1)	46.0 (18.6)
African[b]	40.3 (10.9)	52.7 (8.2)	28.7 (16.2)	22.8 (10.0)	35.9 (14.1)	29.9 (16.0)
Asian[d]	1.3 (0.8)	1.6 (1.0)	12.7 (11.5)	25.1 (26.5)	5.9 (9.1)	19.6 (25.2)
Weight, kg[b,e]	84.5 (4.5)	89.1 (3.2)	77.6 (6.0)	75.4 (5.6)	81.8 (6.1)	76.8 (6.9)
BMI (kg/m^2)[e,f,g]	28.9 (1.4)	29.5 (1.4)	26.5 (1.4)	26.4 (1.3)	27.8 (1.8)	26.8 (1.7)
Dropout rate, %						
Overall	49.1 (10.1)	54.5 (9.0)	37.5 (7.3)	33.3 (6.5)	45.1 (10.7)	38.3 (11.5)
4-wk trials[h]	37.6 (7.6)	…	33.5 (NA)	…	36.9 (7.0)	…
6- or 8-wk trials[i]	52.6 (8.0)	54.5 (9.0)	37.9 (7.6)	33.3 (6.5)	47.0 (10.6)	38.3 (11.5)
Baseline PANSS total score[c]						
Overall	88.7 (11.9)	94.0 (1.8)	93.3 (3.2)	96.0 (1.9)	90.4 (9.8)	95 (2.0)
4-wk trials[h]	93.5 (4.0)	…	91.6 (NA)	…	93.2 (3.6)	…
6- or 8-wk trials[i]	87.0 (13.4)	94.0 (1.8)	93.4 (3.3)	96.0 (1.9)	89.7 (10.8)	95 (2.0)

[a]All values except number and percentage of ITT patients (first row of data) are expressed as mean (SD).
[b]Data missing from 3 pre-2009 North American trials.
[c]Data missing from 2 pre-2009 North American trials.
[d]Data missing from 5 pre-2009 North American trials.
[e]Data missing from 2 post-2009 North American trials.
[f]Data missing from 8 pre-2009 North American trials.
[g]Data missing from 1 post-2009 multiregional trial.
[h]Five North American trials and 1 multiregional trial pre-2009 were 4-week trials.
[i]Thirteen North American and 10 multiregional trials pre-2009 were 6-week trials. Four North American and 10 multiregional trials post-2009 were 6-week trials.
Abbreviations: BMI = body mass index, ITT = intent to treat, NA = not available, PANSS = Positive and Negative Syndrome Scale.
Symbol: … = not applicable as there were no 4-week post-2009 trials.

multiregional trials had a lower mean body mass (78 kg [pre-2009] and 75 kg [post-2009]) and BMI (27 kg/m^2 [pre-2009] and 26 kg/m^2 post 2009]) compared with North American counterparts (body mass: 85 kg [pre-2009] and 89 kg [post-2009]; BMI: 29 kg/m^2 [pre-2009] and 30 kg/m^2 [post-2009]). The overall subject populations consisted predominantly of subjects of white origin (52% and 46%) followed by African origin (36% and 30%) and Asian origin (6% and 20%) during the pre-2009 and post-2009 time periods, respectively, with a noticeable increase in the Asian study population in the post-2009 multiregional trials (13% pre-2009 vs 25% post-2009).

Table 2 summarizes placebo response, drug response, and treatment effect during the pre- and post-2009 periods, with the pre-2009 results further segregated as 1991 to 1998 and 1999 to 2008. The mean placebo response (ie, mean change from baseline in PANSS total scores in the placebo group) was −6.4 and −10.5 in the pre-2009 and post-2009 periods, respectively. North American trials showed a lower placebo response (−4.3 and −8.5) in the pre-2009 and post-2009 periods compared with multiregional trials (−10.0 and −11.3) during the same periods. Placebo responses have been gradually increasing in North American trials, with responses of −2.3, −7.0, and −8.5 in 1991 to 1998, 1999 to 2008, and 2009 to 2015, respectively. The trend of increasing mean placebo response over time is depicted in Figure 1A. The mean drug responses (ie, mean change from baseline in PANSS total scores in the drug-treated groups) over time (Figure 1B) have been relatively stable at changes of −15.0 (mean; range, −31.3 to −5.4) and −16.9 (mean; range, −26.7 to −4.3) in PANSS total score during the pre-2009 and post-2009 time periods, respectively (Table 2). A larger mean drug response (−18.0) was observed consistently in the multiregional trials during both pre-2009 and post-2009 periods as compared to approximately −13.0 in North American trials during the same time period (Table 2). The mean treatment effects for all trials (North American and multiregional) were −8.6 and −5.8 during the pre-2009 and post-2009 time periods, respectively (Table 2). In the North American trials, the mean treatment effect has declined substantially from a change of −10.8 in the period 1991 to 1998 to a change of −6.0 in the period 1999 to 2008 and a change of −3.4 in the period 2009 to 2015. For the multiregional trials, the decline in treatment effect has been much smaller, from −8.1 pre-2009 to −6.4 post-2009. The diminishing treatment effect over time is evident from the yearly mean values shown in Figure 1C.

The overall schizophrenia trial success rate (at least 1 dose significantly better than placebo) over the 3 decades of current interest was 72% (33/46), with a higher success rate of 78% for trials in the pre-2009 period compared with a 57% success rate for trials in the post-2009 period (Table 2). During the post-2009 period, the success rates in North American and multiregional trials were 25% and 70%, respectively. The success rate for the North American trials decreased markedly from 81% during the pre-2009 time period to 25% during the post-2009 time period. As noted

Table 2. Summary of Placebo Response, Drug Response, Treatment Effect, and Trial Success Rates

Characteristic	North American Trials	Multiregional Trials	All Trials
Placebo response[a,b]			
Pre-2009 timespan (1991–2008)	−4.3 (−12.6 to 3.6)	−10.0 (−18.8 to −2.5)	−6.4 (−18.8 to 3.6)
1991–1998	−2.3 (−12.6 to 3.6)	NA	−2.3 (−12.6 to 3.6)
1999–2008	−7.0 (−12.3 to 2.3)	−10.0 (−18.8 to −2.5)	−8.7 (−18.8 to 2.3)
Post-2009 timespan (2009–2015)	−8.5 (−12.3 to −5.5)	−11.3 (−17.3 to −2.5)	−10.5 (−17.3 to −2.5)
Drug response[a,b]			
Pre-2009 timespan (1991–2008)	−13.1 (−21.3 to −5.4)	−18.0 (−31.3 to −9.4)	−15.0 (−31.3 to −5.4)
1991–1998	−12.8 (−21.3 to −5.4)	NA	−12.8 (−21.3 to −5.4)
1999–2008	−13.4 (−17.0 to −7.0)	−18.0 (−31.3 to −9.4)	−16.2 (−31.3 to −7.0)
Post-2009 timespan (2009–2015)	−13.0 (−17.0 to −7.1)	−18.0 (−26.7 to −4.3)	−16.9 (−26.7 to −4.3)
Treatment effect[c]			
Pre-2009 timespan (1991–2008)	−9.0 (−22.2 to 5.1)	−8.1 (−18.9 to 0.5)	−8.6 (−22.2 to 5.1)
1991–1998	−10.8 (−22.2 to −3.6)	NA	−10.8 (−22.2 to −3.6)
1999–2008	−6.0 (−12.8 to 5.1)	−8.1 (−18.9 to 0.5)	−7.2 (−18.9 to 5.1)
Post-2009 timespan (2009–2015)	−3.4 (−10.8 to 5.2)	−6.4 (−16.6 to 4.9)	−5.8 (−16.6 to 5.2)
Trial success rate[d]			
Pre-2009 timespan (1991–2008)	17/21 (81.0%)	8/11 (72.7%)	25/32 (78.1%)
1991–1998	11/13 (84.6%)	NA	11/13 (84.6%)
1999–2008	6/8 (75.0%)	8/11 (72.7%)	14/19 (73.7%)
Post-2009 timespan (2009–2015)	1/4 (25.0%)	7/10 (70.0%)	8/14 (57.1%)

[a]Data not available from 2 North American trials.
[b]Change from baseline in total PANSS score, expressed as mean (range).
[c]Calculated as drug effect – placebo effect for each drug treated group in each trial and expressed as mean (range).
[d]Numerators indicate the number of successful trials, denominators indicate the total number of trials. Success rates expressed as percentages in parentheses.
Abbreviations: NA = not available, PANSS = Positive and Negative Syndrome Scale.

by Khin et al,[3] the success rate (85%) of North American trials was higher for trials conducted before 1998 compared with the 1999 to 2008 time period, in which the success rate of North American trials (75%) was similar to that for the multiregional trials (73%).

Figures 2 and 3 provide exploratory graphic analyses of the impact of potential predictive factors on treatment effect over time in the pre-2009 and post-2009 periods. The sample size per treatment arm has been consistently increasing since 1993, with a mean of 90 subjects per arm during the pre-2009 period compared with 117 subjects per arm in the post-2009 period (Figure 2A). Thus, treatment effects have been generally decreasing despite generally increasing sample sizes, ie, sample size does not seem to have had an impact on the treatment effect over time (Figure 2B).

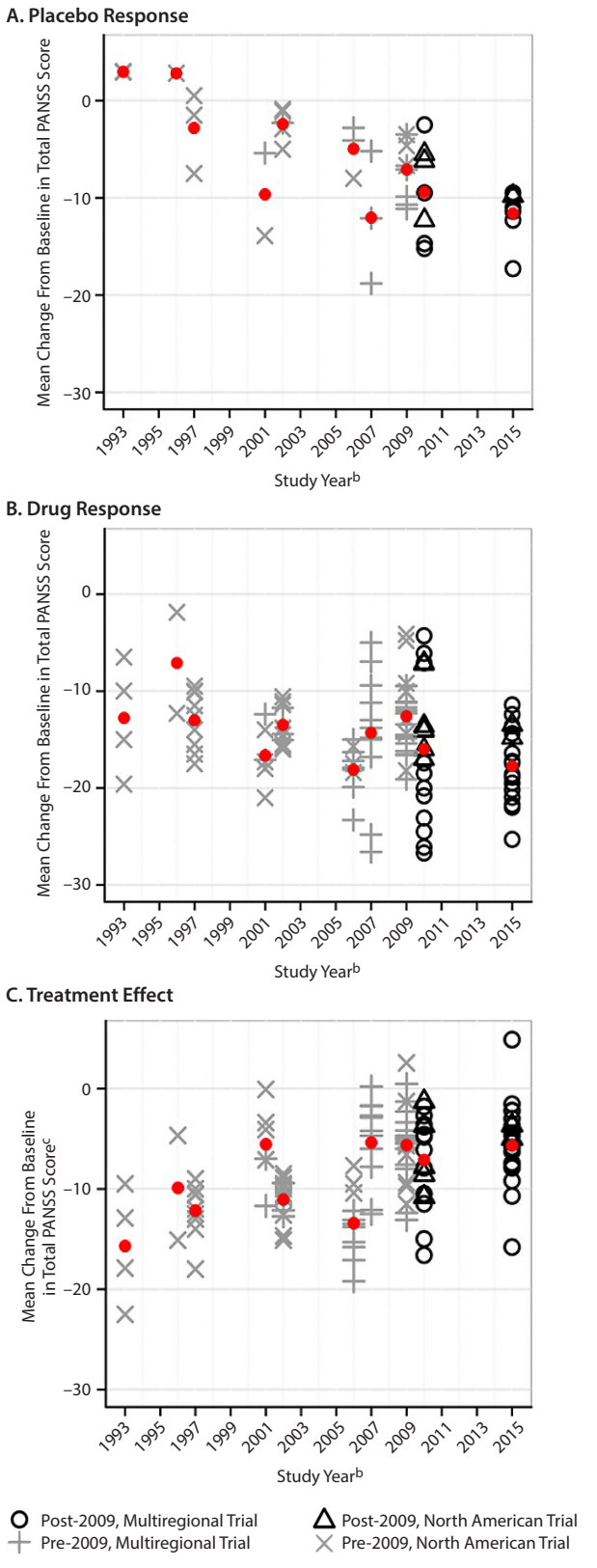
Baseline total PANSS scores (with the typical trial inclusion criteria for baseline total PANSS score between 60 and 120) have been consistent over time, ranging from 85 to just over 100 during both the pre- and post-2009 time periods, irrespective of geographic location (Figure 3A), indicating similar severities of illness. As indicated in Figure 3B, treatment arms with mean baseline total PANSS score less than 90 tended to have lower treatment effects, irrespective of the time period and geographical location, although most of the higher baseline trials were in the post-2009 period.

The overall mean dropout rate in North American trials (49.1%) was larger than for multiregional trials (37.5%) in the pre-2009 period, with the dropout rate difference between North American (54.5%) and multiregional trials (33.3%) further increasing during the post-2009 period (Table 1). The dropout rates observed post-2009 were solely from 6-week trials, whereas the dropout rates in the pre-2009 time period were from a mixture of 4-, 6-, and 8-week trials. When separated by placebo- and drug-treated groups, in both time periods (pre-2009 and post-2009), North American trials had a higher dropout rate in both the placebo (60% vs 54%) and drug-treated groups (50% vs 55%), respectively, compared with multiregional trials (placebo: 51% vs 39%; drug: 41% vs 32%). The mean dropout rate has decreased over time with a mean of 45% and 38% in the pre-2009 and post-2009 periods, respectively (Figure 3C), for combined placebo- and drug-treated groups. However, the dropout rates in the placebo groups pre-2009 ranged from 34% to 80% with a mean of 56% compared with a mean of 43% (range, 28%–70%) post-2009. A similarly higher dropout rate was found in the drug-treated groups: these values were 46% pre-2009 and 37% post-2009. However, no clear relationship between dropout rates and treatment effect over time was observed, with a similar trend with respect to geographic location (Figure 3D).

DISCUSSION

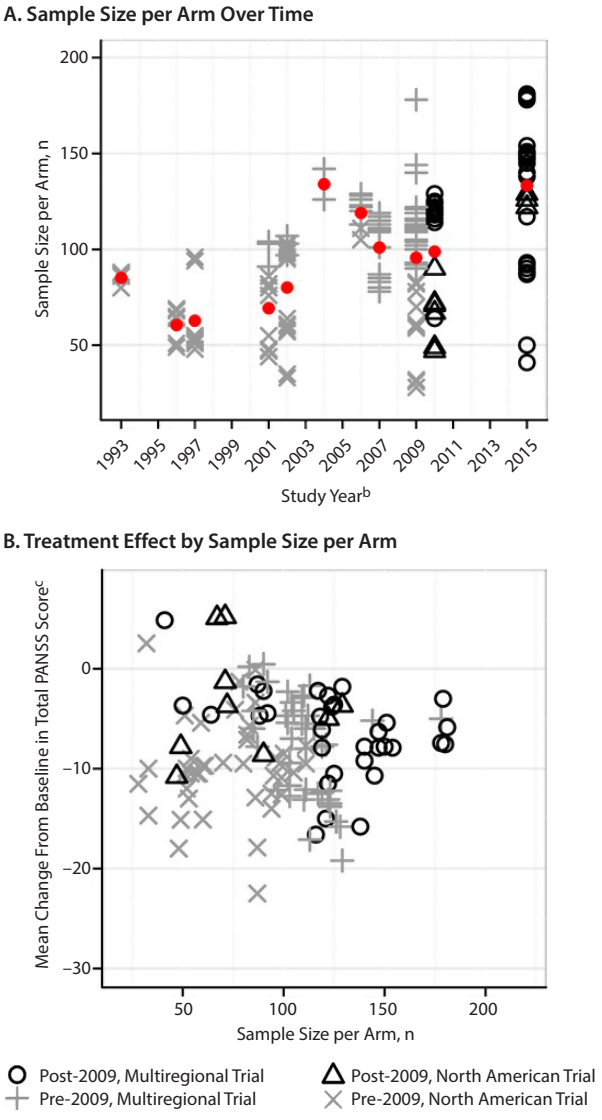
Our analyses revealed a consistent and continuing trend of increasing placebo response and diminishing treatment effect over time post-2009, particularly in North American trials (Table 2 and Figure 1A and 1C). These findings suggest continuation of the trends of increasing placebo response, decreasing treatment effect, and increased trial failure rate seen in the pre-2009 acute schizophrenia trials. Given that drug responses are stable in both geographic locations, increasing placebo response has led to a substantial decrease in the apparent treatment effect in North American trials

Figure 1. (A) Placebo Response, (B) Drug Response, and (C) Treatment Effect Pre- and Post-2009[a]



[a]Solid red circles represent the mean value of the response variable for each year.
[b]Year of study start, submission, or approval.
[c]Placebo-corrected.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Figure 2. Impact of Sample Size on Treatment Effect Pre- and Post-2009[a]

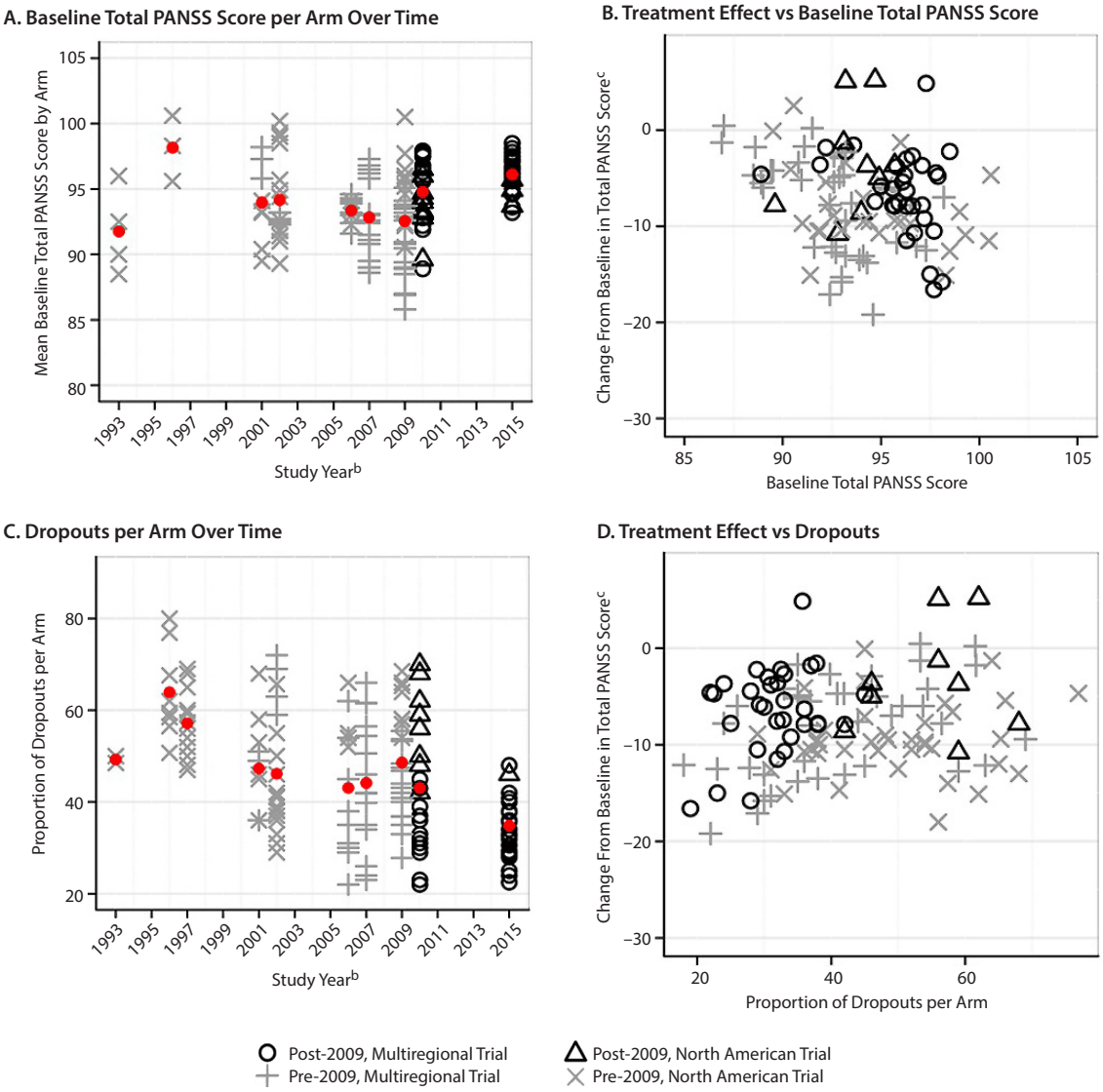


[a]Solid red circles represent the mean value of the response variable for each year.
[b]Year of study start, submission, or approval.
[c]Placebo-corrected.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

from the pre-2009 to the post-2009 period compared with a far smaller decrease in multiregional trials during the same time. If only the 1999 to 2008 period is considered in the pre-2009 period, there was still a decrease of treatment effect from −6.0 to −3.4 in North American trials. The trend in higher placebo response has also led to higher trial failure rates post-2009: 75% in North American trials and 30% in multiregional trials. Of note, a similar trend of decreasing treatment effect and higher failure rate has been reported for other psychiatric disorders (eg, major depressive disorder) when comparing North American and non–North American regions.[5]

The overall dropout rates were higher in pre-2009 trials (45.1%) compared with post-2009 trials (38.3%), which can

Figure 3. Impact of Baseline PANSS Total Score and Percentage of Dropouts on Treatment Effect Pre- and Post-2009[a]



[a]Solid red circles represent the mean value of the response variable for each year.
[b]Year of study start, submission, or approval.
[c]Placebo-corrected.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

be attributed to the presence of more multiregional trials in the post-2009 period, as dropout rates in multiregional trials have always been lower (23%–38% lower) than in North American trials. The current analysis shows that subjects' baseline characteristics in the pre- and post-2009 time periods were similar in terms of disease severity, age, body weight, and BMI, with the slightly lower body weight in the post-2009 trials very likely being due to the trials' being multiregional. Trial participation of Asians increased from pre- to post-2009, with a similar trend for women.

The observations of high and increasing placebo response in schizophrenia clinical trials have been identified as major concerns in the literature.[6–10] Study design, study conduct, regional variations, and certain subject characteristics have been suggested as factors contributing to this trend in placebo response. Kemp et al[6] concluded that diminishing treatment effect can be attributed to study factors such as including subjects with longer exacerbation of symptoms (>1 month), use of benzodiazepines, and variability in outcome assessments. Moreover, variations in health care standards (eg, duration of hospitalization during the double-blind period) and ethnic and demographic differences across multiregional or national centers could result in differences in symptom presentation, description and rating of severity, and willingness to participate in research, leading to considerable heterogeneity in drug and placebo responses and dropout patterns.

Given the increase in multiregional trials, recognition of regional differences in trial conduct is critically important when designing schizophrenia efficacy trials. With the

globalization of drug development, sponsors may be opting for only multiregional trials for drug approval applications across global regulatory bodies. Therefore, it is important to identify and address trial design, subject, and regional factors that will contribute to valid interpretation of results in such trials. Additional efforts to ensure trial integrity and adherence to principles of good trial design may help decrease the impact of placebo response and enhance the signal-to-noise ratio in clinical trial data.[11]

A 2017 article by Leucht et al[10] discusses the various trial characteristics that are moderators of acute schizophrenia trial efficacy differences based on a meta-regression of antipsychotic trials over a span of 60 years. The authors conclude that decreased effect sizes (standardized treatment effects) are a result of industry's sponsoring larger studies that lead to additional heterogeneity (due to multiple sites and recruitment pressure) and increased placebo response and not due to decreased drug response; these reduced effect sizes then feed into the increase in sample size in subsequent studies. The authors suggest smaller trials in better selected subjects, although details on subject selection were not provided. Alternative trial designs, such as the addition of a placebo run-in phase[12] or sequential parallel comparison designs,[13,14] have been proposed to minimize placebo response and improve signal detection by identifying subjects with anomalous placebo response. However, such designs are less commonly used in registration trials submitted to the FDA, though the FDA is actively engaged with sponsors in exploring sequential parallel comparison designs despite its challenges.

The era of "big data" presents some promising approaches to dealing with the problem of increasing placebo response in clinical trials. For example, use of advanced quantitative analysis methodologies such as unsupervised/supervised learning algorithms (machine learning techniques) on pooled trial databases may provide greater insights regarding identification of individuals who will respond to placebo based on subject-specific risk factors. These prognostic factors may further dictate the inclusion and exclusion criteria for trials, enabling protocol-driven trial enrichment. Nevertheless, identifying risk factors using quantitative methods would need to be adequately validated before protocol implementation. Using the recursive partitioning technique, Chen et al[15] identified age (younger patients) and baseline total PANSS score (≥ 93) as key discriminators for patients showing improvement with placebo based on data from randomized controlled trials submitted to the FDA between 1993 and 2005 comprising 12,585 subjects. An updated analysis could provide additional insights regarding identification of subject-specific factors influencing placebo response.

Some of the limitations of the study include (1) fewer trials contributing to the regional differences analysis in the post-2009 time period (N = 6,434) as compared to 12 NDAs (N = 11,567) in the pre-2009 time period and (2) inability to ascertain regional differences in placebo and treatment effect for trial completers, as LOCF estimates are known to be influenced by dropouts due to the aggregate nature of the data considered.

Overall, our updated analyses using post-2009 trials have demonstrated similar findings—increasing placebo response and diminishing treatment effect—to those for the pre-2009 trials. With more pharmaceutical sponsors embracing multiregional clinical trials for regulatory submissions, trial design and conduct that incorporates mechanisms to minimize placebo response need to be carefully considered to increase the efficiency of drug development in schizophrenia.

Submitted: June 16, 2019; accepted September 30, 2019.

Published online: March 3, 2020.

Potential conflicts of interest: The authors report no conflicts of interest.

Funding/support: Dr Gopalakrishnan was supported in part by an appointment to the Research Fellowship Program at the Office of Clinical Pharmacology/Center for Drug Evaluation and Research, US Food and Drug Administration (FDA), administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and the FDA.

Role of the sponsor: The funding agency had no role in the conduct and publication of the study.

Previous presentation: Poster presented at the annual meeting of the American Society for Clinical Pharmacology and Therapeutics; March 8–12, 2016; San Diego, California.

REFERENCES

1. Jablensky A. The 100-year epidemiology of schizophrenia. *Schizophr Res*. 1997;28(2–3):111–125.
2. Chong HY, Teoh SL, Wu DB, et al. Global economic burden of schizophrenia: a systematic review. *Neuropsychiatr Dis Treat*. 2016;12:357–373.
3. Khin NA, Chen YF, Yang Y, et al. Exploratory analyses of efficacy data from schizophrenia trials in support of new drug applications submitted to the US Food and Drug Administration. *J Clin Psychiatry*. 2012;73(6):856–864.
4. Shenoy P. Multi-regional clinical trials and global drug development. *Perspect Clin Res*. 2016;7(2):62–67.
5. Khin NA, Chen YF, Yang Y, et al. Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications. *J Clin Psychiatry*. 2011;72(4):464–472.
6. Kemp AS, Schooler NR, Kalali AH, et al. What is causing the reduced drug-placebo difference in recent schizophrenia clinical trials and what can be done about it? *Schizophr Bull*. 2010;36(3):504–509.
7. Alphs L, Benedetti F, Fleischhacker WW, et al. Placebo-related effects in clinical trials in schizophrenia: what is driving this phenomenon and what can be done to minimize it? *Int J Neuropsychopharmacol*. 2012;15(7):1003–1014.
8. Agid O, Siu CO, Potkin SG, et al. Meta-regression analysis of placebo response in antipsychotic trials, 1970–2010. *Am J Psychiatry*. 2013;170(11):1335–1344.
9. Rutherford BR, Pott E, Tandler JM, et al. Placebo response in antipsychotic clinical trials: a meta-analysis. *JAMA Psychiatry*. 2014;71(12):1409–1421.
10. Leucht S, Leucht C, Huhn M, et al. Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: systematic review, Bayesian meta-analysis, and meta-regression of efficacy predictors. *Am J Psychiatry*. 2017;174(10):927–942.
11. Kinon BJ, Potts AJ, Watson SB. Placebo response in clinical trials with schizophrenia patients. *Curr Opin Psychiatry*. 2011;24(2):107–113.
12. Downing AM, Kinon BJ, Millen BA, et al. A double-blind, placebo-controlled comparator study of LY2140023 monohydrate in patients with schizophrenia. *BMC Psychiatry*. 2014;14(1):351.
13. Fava M, Evins AE, Dorer DJ, et al. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. *Psychother Psychosom*. 2003;72(3):115–127.
14. Tamura RN, Huang X. An examination of the efficiency of the sequential parallel design in psychiatric clinical trials. *Clin Trials*. 2007;4(4):309–317.
15. Chen YF, Wang SJ, Khin NA, et al. Trial design issues and treatment effect modeling in multi-regional schizophrenia trials. *Pharm Stat*. 2010;9(3):217–229.