Trends in Placebo Response and Effect Size in Schizophrenia: A Meta-Analysis

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Introduction: Anecdotal reports and industry perception suggesting apparent diminishing drug-placebo differences and a growing placebo response rate in schizophrenia randomized controlled trials is increasingly supported by a growing but limited body of empirical evidence. Kemp et al. (2008) examined mostly Phase III recent acute schizophrenia trials dating from 1993 to 2006 and found increasing placebo response over time and diminished drug-placebo response. It is noteworthy that both increased placebo response and diminished drug-placebo response was greatest at week 6 of clinical trials, in later compared to earlier trials, but there were no differences in either placebo response or drug-placebo differences at trial endpoint. Potkin (2008) demonstrated further evidence for diminished drug-placebo difference in recent schizophrenia trials not only due to increases in placebo response, but also diminished response to active compounds, including to previously established comparator drugs. Khin (2009) also found increased placebo response in non-US schizophrenia randomized controlled trials. One implication of these findings is the need for larger sample sizes to demonstrate treatment effect.

The purpose of this meta-analysis was to determine whether there was a growing placebo response rate and concurrent diminishing drug-placebo differences in schizophrenia randomized controlled trials over time, casting the broadest net to locate published articles, and both published and unpublished clinical trial reports schizophrenia controlled trials from 1980 to 2008. A limitation to meta-analysis, even with attempts to collect unpublished reports, is that these may be substantially under-represented in the final sample, which may limit validity and generalizability, particularly with regard to questions correlated with the success or failure of studies, such as the present one.

Method: A team of psychologists generated possible literature search terms, reaching consensus that search terms and criteria would include "schiz* and placebo" (with asterisks identifying terms that were truncated to increase hits for potential articles to be included in the analysis) and "schiz* and placebo and [brand/generic name of compound]". A comprehensive literature search was conducted using the consensus search terms, including computer search using PubMed (1980 – present), the U.S. Food and Drug Administration database (by both branded and generic name of compound), and ClinicalStudyResults.org database (by both branded and generic name of compound and schizophrenia as the focus of Studied Indication or Disease), and available databases for pharmaceutical companies manufacturing identified compounds.

The PubMed (1980 – present) computer search resulted in **4,781** potential articles, the abstracts of which were reviewed by the team of psychologists for basic relevancy to the purpose of the meta-analysis, which resulted in **286** articles that were reviewed in their entirety to determine if they met the basic inclusion criteria to the meta-analysis. Inclusion criteria included: diagnosis limited to schizophrenia, use of a clinician administered assessment or outcome measure of positive or negative symptoms, pharmacological compounds approved for use in the United States and Europe, adult sample, double-blind placebo control reported sample size, statistics sufficient to calculate an effect size, publication date after 1980.

Augmentation studies were considered, provided there was placebo-only control. Studies of non-pharmacological compounds, such as hormonal treatments or omega-3, were considered not appropriate for inclusion. Similarly, articles and reports that measured the effect of compounds on cognitive deficits or side effects, such as weight gain, were not considered for inclusion. **Twenty-seven** articles met these pre-established basic criteria for inclusion in the meta-analysis.

Electronic search of the U.S. Food and Drug Administration database, ClinicalStudyResults.org database, and available databases for pharmaceutical companies manufacturing identified compounds resulted in 12 reports that were not published elsewhere. **Two** reports met the pre-established basic criteria for inclusion in the meta-analysis.

Results: A metaregression found that the main effect of decreasing separation of experimental drug from placebo due to increasing placebo effect size over time was not significant, and in fact, separation was increasing slightly (Slope -.012 Q=3.18 p=.074), see Figure 1. A slight increase in placebo effect size over time was not significant (Slope = -.00053, Q= .0068, p = .93396), see Figure 2. Sample sizes showed a significant increase over time for both placebo (F=10.40, p=.003) and treatment (F=6.48, p=.017) groups, see Figures 3 and 4, respectively. Data were reanalyzed pooling active comparators in studies where comparators were utilized; however, no significant or meaningful differences emerged.

Conclusion: Consistent with recent anecdotal reports and empirical evidence from a small number of studies, the current meta-analysis found an increase in placebo effect size over time, though this increase was slight and not statistically significant. While this meta-analysis cannot answer the question as to whether overall schizophrenia trials are failing at an increasing rate over time due to diminishing drug/placebo separation, the current analysis of primarily positive studies does not empirically support these anecdotes. In fact, when an increased number of studies covering a broader period of time are analyzed, it was found that separation was increasing slightly. The current study did, however, find significant increases in both placebo and treatment sample sizes over time, consistent with the perception by some that increased sample sizes are needed to demonstrate treatment effect. A limitation to the validity and generalizability of the current study is that over 90% of articles and reports included in the analysis were positive trials, and may not be reflective of the true rate of positive versus failed trials in the industry. However, the literature search was exhaustive of all databases that are publicly available and may be reflective of research outcomes industry is willing to report. An additional limitation is the large number of studies that were excluded because of insufficient data reporting by the authors, and it is possible that had those studies reported data from which an effect size could be calculated, their inclusion may have altered the findings of the current meta-analysis. Finally, recently presented data on 10 new drug applications submitted to the FDA for schizophrenia (Khin, N. Presented at the 2009 NCDEU meeting) which would circumvent the selective publication problem, indicate that the effect size decreased from 1996-2006, at least in US studies, for which most data were available over this time period.

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Figure 1 Regression of Date on Std diff in means

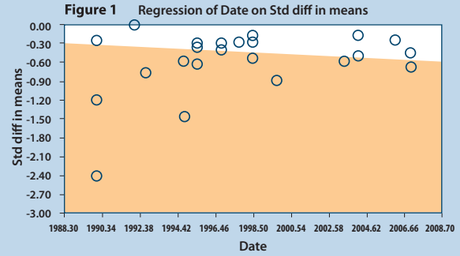

Figure 2 Regression of PL Date on Std diff in means

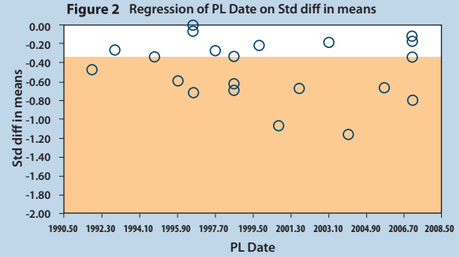

Figure 3 Placebo N Over Time

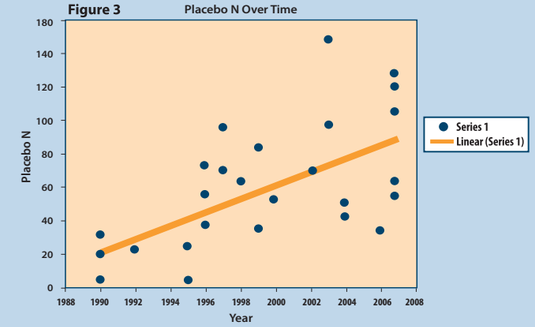

Figure 4 Treatment N Over Time

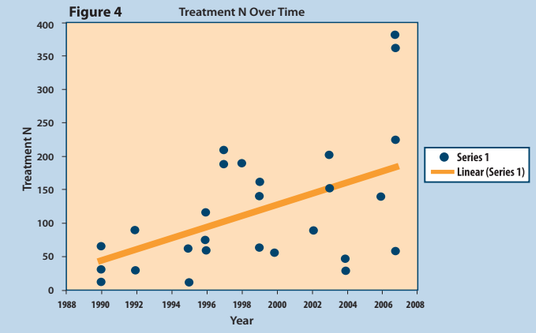

Table 1. Articles Included in the Meta-Analysis, By Date of Publication

Date of Publication	Authors	Journal/Report	Compound	Number Tx Arms	Tx *N*	Pl *N*
1990	Chouinard, G.	Acta Psychiatr Scand	Remoxipride Chlorpromazine	1 1	20 21	21
1990	Edmond, P. I., et al.	Neuro-Psychopharm & Biol Psychiatry	Thioridazine	1	7	5
1992	Montgomery, S. A. et al.	Acta Psychiatr Scand	DE-gamma-E Thioridazine	1 1	30 31	33
1995	Boyer, P., Lecrubier, A., Puech, A. J., Dewailly, J., & Aubin, F.	British Journal of Psychiatry	Amisulpride	2	36 34	34
1995	Fabre, L.F., et al.	Clinical Therapeutics	Quetiapine	1	8	4
1996	Borison, R. L., Arvanitis, L. A., Milier, B.G.	Journal of Clinical Psychopharmacology	Quetiapine	1	54	55
1996	Loo, H., Poirier-Littre, M. F., Theron, M., Rein, W., & Fleurot, O.	British Journal of Psychiatry	Amisulpride	1	69	72
1997	Small, J. G., et al.	Arch Gen Psychiatry	Quetiapine	2	96 94	96
1997	Zimbroff, D. I, et al.	American Journ of Psychiatry	Sertindole Haloperidol	3 3	72 65 70 68 63 68	71
1998	Chouinard, G. et al.	Journ Clin Psychopharm	Risperidone Haloperidol	4 1	24 22 22 24 21	22
1998	Hamilton, S. H., Revicki, D. A., Genduso, L. A., & Beasley, C. M.	Neuropsychopharmacology	Olanzapine Haloperidol	3 1	16 19 27 18	15
1998	Tollefson, G. D., Sanger, T. M., Beasley, C.M., & Tran, P. V.	Biological Psychiatry	Olanzapine Haloperidol	3 1	65 62 65 68	63
1999	Danion, J.-M., Rein, W., & Fleurot, O.	American Journ of Psychiatry	Amisulpride	2	84 75	83
1999	Truffinet, P., et al.	American Journ of Psychiatry	Fananserin	1	63	34
2000	Cooper, S. J., Tweed, J., Raniwalla, J., Butler, A., & Welch, C.	Acta Psychiatr Scand	Zotepine Chlorpromazine	1 1	53 52	53
2001	Potkin, S. G., Fleming, K., Jin, Y., & Gulasekaram, B.,	Journ Clin Psychopharm	Clozapine Haloperidol	1 1	27 27	27
2002	Arato, M., O'Connor, R., & Meltzer, H. Y.	Intnl Clin Psychopharm	Ziprasidone	3	71 68 67	71
2003	Kane, J. M., et al.	American Journ of Psychiatry	Risperidone	3	93 98 87	92
2003	Pigott, T. A., et al.	Journal of Clinical Psychiatry	Aripiprazole	1	148	149
2004	Lilly CT Trial Registry ID #982	Lilly Clinical Study Summary	Clozapine	2	51 49	50
2004	Moller, H. J., Riedel, M., Muller, N., Fischer, W., & Kohnen, R.	Pharmacopsychiatry	Zotepine	1	38	41
2006	Lecrubier, Y., Quintin, P., Bouhassira, M., Perrin, E., & Lancrenon, S.	Acta Psychiatr Scand	Olanzapine Amisulpride	2 1	70 70 70	34
2007	Davidson, M., et al.	Schizophrenia Research	Paliperidone Olanzapine	3 1	123 123 113 126	120
2007	Kane, J., et al.	Schizophrenia Research	Paliperidone	3	123 122 129	126
2007	Kramer, M., et al.	Journ Clin Psychopharm	Paliperidone	1	104	101
2007	Marder, S. R. et al.	Biological Psychiatry	Paliperidone Olanzapine	2 1	111 111 105	105
2007	Potkin, S. G., Cohen, M., & Panagides, J.	Journal of Clinical Psychiatry	Asenapine Risperidone	1 1	58 56	60

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