March 25, 2016

MGH Colloquium on Sequential Parallel Comparison Design (SPCD)
North Bethesda, MD

INNOVATIONS IN CLINICAL TRIAL METHODOLOGY: SEQUENTIAL PARALLEL COMPARISON DESIGN (SPCD)

Conference Summary Report

MASSACHUSETTS GENERAL HOSPITAL

PSYCHIATRY ACADEMY

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Executive Summary

On March 25, 2016 the Massachusetts General Hospital (MGH) Clinical Trials Network and Institute (CTNI) and the MGH Psychiatry Academy hosted a summit meeting in North Bethesda, Maryland, titled *Innovations in Clinical Trial Methodology: Sequential Parallel Comparison Design (SPCD).* This educational program included participation of MGH CTNI faculty, academic clinical researchers, FDA staff and researchers from industry. The purpose of the meeting was to review and discuss a novel, alternative model for conducting clinical trials—the Sequential Parallel Comparison Design (SPCD).

In randomized clinical trials, therapeutic response signals are frequently obscured by high rates and increased variability of placebo response. This is particularly true in psychiatric studies, which frequently have subjectively-defined endpoints. However, high placebo response rates are not confined to studies employing subjective endpoints, as they can also occur in clinical trials with objective endpoints, which can be affected by behavioral changes, expectations, conditioning, observation, and reporting biases in either patients or investigators. In antidepressant studies, where the endpoints are subjective, placebo response rates can be as high as 40 to 45 percent[1].

Excessive placebo response rates are a common cause of false-negative statistical results-- even for FDA-approved therapeutics with demonstrated evidence of effectiveness-- leading to a high clinical trial failure rate, increasing the risk, time and cost of novel therapeutic development, and threatening the economic sustainability of innovation in medicine[2].

Past attempts to minimize placebo response, including open-label, single and double-blind lead-in periods, raising sample size, adaptive trial design and enhancing quality measures have been disappointing, as they did not result in an inflexion of the trend towards higher placebo response rates and rising risk, time and cost of clinical research and development.

To address the problem of high placebo response rates, researchers at Massachusetts General Hospital developed a unique model for conducting clinical trials—the Sequential Parallel Comparison Design

(SPCD). SPCD comprises two stages, with the data being pooled from both stages. In contrast to standard two-arm trials (i.e., placebo vs. active treatment), SPCD study subjects who are placebo non-responders are *re-randomized* into a second stage of analysis, with half receiving the active treatment and half receiving placebo (see Diagram 1). This unique two-stage design enriches the primary analysis population, reducing the impact of high placebo response rates, and allowing trials to be conducted with reduced study sample size without corresponding decreases in statistical power.

Diagram 1: Sequential Parallel Comparison Design (SPCD)

The SPCD model confers substantial advantages. SPCD enables the prospective identification of genuine placebo nonresponders, among whom it is possible to observe the therapeutic response with better accuracy and precision and to contrast such response with that of patients re-randomized to re-exposure to placebo. SPCD has been shown to be able to restore trial assay sensitivity and to reduce false negative rates. In addition, enhanced effect size allows us to obtain equivalent power in trials with smaller sample size, thereby reducing risk, time and cost of therapeutic innovation.
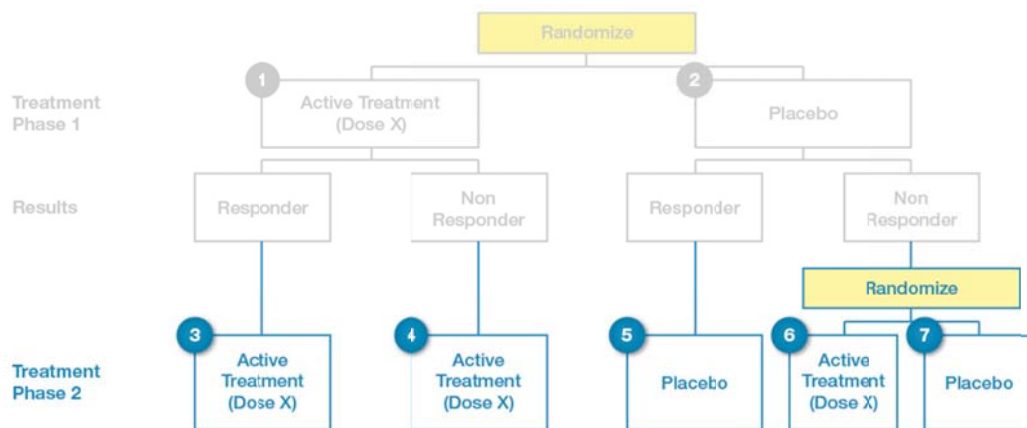
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References

1. Heger, M. Trial designs advance to overcome bitter pill of placebo effect. Nature Medicine. 2013; 19 (11):1353.

2. Fava M, Evins AE, Dorer DJ, Schoenfeld DA. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. Psychother Psychosom 2003; 72:115–127.

3. Chen YF, Yang Y, Hung HJ, Wang SJ. Evaluation of performance of some enrichment designs dealing with high placebo response in psychiatric clinical trials. Contemporary Clinical Trials. 2011; 32:592–604.

Innovations in Clinical Trial Methodology: Sequential Parallel Comparison Design (SPCD)

Introduction

Maurizio Fava, MD

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Executive Vice Chair, MGH Department of Psychiatry

Executive Director, MGH Clinical Trials Network and Institute (CTNI)

Associate Dean for Clinical and Translational Research

Slater Family Professor of Psychiatry

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In this presentation, Dr. Fava described the problem of high placebo response rates in clinical trials, and introduced the methodology of SPCD.

Key points from the presentation:

- There are three types of patient response to treatment in studies of neuropsychiatric illness:

  -Those who respond to drug only;
  -Those who respond to neither drug nor placebo;
  -Those who respond to both drug and placebo ("universal donors")

- Patients who respond to drug only (P- D+), which is the informative group, typically comprises only 10 percent of the typical phase III trial participants in psychiatric trials. Patients who respond to neither (P- D-) typically comprise 50 percent, and patients who respond to either, typically comprise approximately 40 percent, reflecting the commonly reported placebo response rate.
- Strategies designed to address the placebo response inflation are aimed at increasing the proportion of the informative group (P- D+), thereby increasing assay sensitivity.
- Effect size is clearly a function of the degree of placebo response.
- Placebo response is greatly affected by expectation, conditioning, observation and reporting biases, as well as behavioral changes which often arise in the context of a clinical trial. It has been shown in meta-analyses of trials that subjects have higher placebo response rates when they believe their likelihood of receiving placebo is low.

- Many biotech companies and therapeutic innovators have limited resources for Phase 2 and 3 clinical development of, for instance, novel antidepressant treatments. If the placebo response rate is too high, a drug may fail a phase III trial; on the other hand, if the placebo response rate had been lower, the drug effect may have reached statistical significance.
- Placebo lead-ins—single-blind or double-blind-- do not appear to significantly affect placebo response rates and to enhance signal detection.
- The Sequential Parallel Comparison Design (SPCD) was developed to address the problem of high placebo response rates. SPCD enables the prospective identification of genuine placebo nonresponders, among whom it is possible to observe the therapeutic response with better accuracy and precision and to contrast such response with that of patients re-randomized to re-exposure to placebo.
- There are now over 30 trials completed or in progress using SPCD.

References

Faries DE et al. The double-blind variable placebo lead-in period: results from two antidepressant clinical trials. J Clin Psychopharmacol 2001; 21:561-568.

Fava M 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: 115-127.

Fava M et al. A double-blind, randomized, placebo-controlled study of cariprazine as adjunctive therapy in MDD. ACNP Annual Meeting, 2014.

Fava M. Implications of a Biosignature Study of the Placebo Response in Major Depressive Disorder. JAMA Psychiatry. 2015 Nov; 72(11):1073-4.

Iovieno N, Papakostas GI. Correlation between different levels of placebo response rate and clinical trial outcome in major depressive disorder. J Clin Psychiatry. 2012; 73(10): 1300-1306.

Papakostas G, Fava M. Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. Eur Neuropsychopharmacol. 2009 Jan; 19(1): 34-40.

Trivedi MH, Rush H. Does a placebo run-in or a placebo treatment cell affect the efficacy of antidepressant medications? Neuropsychopharmacology 1994:11:33-43.

Overview of the Sequential Parallel Comparison Design (SPCD)

Michael J. Pencina, PhD
Director of Biostatistics, Duke University Clinical Research Institute (DCRI)
DCRI Faculty Associate Director
Professor of Biostatistics and Bioinformatics
Duke University

Dr. Pencina provided an overview of the SPCD methodology and addressed several considerations regarding SPCD data analysis, what statistical methods are used for analysis, how to determine the weighting contribution of each stage, how to interpret the combined data from the two SPCD stages, how to address missing data, and how to address non-response in stage 1.

Key points from the presentation:

- High placebo response rates pose a major problem for CNS trials, particularly when outcomes are based on psychometric scales.
- The SPCD was developed to address this problem.
- In the first stage of SPCD, subjects are randomized to active treatment or placebo, with a larger proportion of subjects randomized to placebo in comparison to all subjects assigned to active arm(s).
- In the second stage of SPCD, placebo non-responders are re-randomized to either active treatment or placebo, typically in equal proportions.
- The data used for analysis are from all subjects involved in the drug vs. placebo comparison in stage 1 and from the placebo non-responders during stage 1 re-randomized to drug vs. placebo in stage 2.
- Analyzing binary outcomes is feasible in SPCD trials, but is often associated with loss of information and statistical power; greater trial efficiency and power are gained by using continuous outcomes.
- Overall treatment in SPCD trials is defined as the weighted average of effects in stage 1 and stage 2:

$$\delta_w = w \bullet \delta_1 + (1 - w) \bullet \delta_3$$

  - δ_1 and δ_3 are estimated stage 1 and 2 treatment effects (e.g., differences in response to active

treatment versus placebo).

- W = weight of information from each stage.

- In typical usage, W choices between 0.5 and 0.8 are common.
- Chi et al. (2016) proposed for SPCD a model for response to placebo and data-driven weighting such that, under the proposed model, δ_w is the estimated treatment effect that accounts for placebo response.
- Regarding missing data:
  For data missing at random:
  -Multiple imputation works well with OLS, GEE and SUR.
  -Mixed model (ML or REML) is appropriate for ignorable missing data.

  For data missing not at random:
  -Simulations suggest that alpha inflation remains below 0.10 except in extreme cases.
  -Tipping point evaluation is a useful sensitivity analysis option for continuous outcomes (response shift, effect change, variance scaling)

- The definition of a responder in a trial is arbitrary, and results might be sensitive to changes in response definition.
- Study power might be increased if response is not dichotomized (e.g., considered as binary), e.g., represented by an individual patient weight reflecting the estimated propensity for placebo response or treating response as a latent characteristic (currently in development).

References

Tamura RN, Huang X, Boos DD. Estimation of treatment effect for the sequential parallel design. Stat Med. 2011 Dec 30; 30(30): 3496-506.

Ivanova A, Qaqish B, Schoenfeld DA. Optimality, sample size, and power calculations for the sequential parallel comparison design. Stat Med. 2011 Oct 15; 30(23): 2793-803.

Doros G, Pencina M, Rybin D, Meisner A, Fava M. A repeated measures model for analysis of continuous outcomes in sequential parallel comparison design studies. Stat Med. 2013 Jul 20; 32(16): 2767-89.

Chi G, Li Y, Liu Y, Lewan D, Lim P. On clinical trials with a high placebo response rate. Contemporary Clinical Trials Communications. 2016 April 15; 2: 34-53.

Different Approaches for Analyses of SPCD and Comparisons with other Enrichment Designs

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Mathematical Statistician, Division of Biometrics III
Office of Biostatistics, Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Dr. Chen reviewed specific considerations in the analysis of SPCD data, and common methodologies to manage high placebo response. Several study designs were discussed, including the Placebo Lead-in Design, the Sequential Parallel Comparison Design (SPCD), the Two-Way Enriched Design (TED), and the Sequential Enriched Design (SED).

Key points from the presentation:

- High placebo response has been observed in numerous areas, including psychiatric diseases and pain-associated diseases.
- Over the past 30 years, placebo response rates appear to have increased in antidepressant studies, and treatment effect sizes have decreased.
- Placebo lead-in design is a traditional parallel design with a placebo lead-in phase. It is commonly used to exclude patients with a high placebo response from randomization.
- A drawback of placebo lead-in design is that, since clinicians know the patients' assignment to placebo, it is difficult to eliminate clinician bias. Consequently, patients are more likely to experience regression to the mean with or without treatment.
- The most popular type of analysis of SPCD data is the linear combination test.
- The covariance between treatment effect estimates from both SPCD stages is zero under the null hypothesis.
- When missing data are a concern, the weighted test statistics based on mixed-effect model repeated measures (MMRM) estimates offer robust type I error control, accuracy and precision for SPCD with re-randomization.
- In Sequential Enriched Design (SED), the target patient population consists of placebo non-responders who are active responders. A placebo lead-in phase is implemented before randomization to screen out placebo responders. In stage 2, only drug responders are further re-randomized (to drug or placebo) and evaluated.
- Study designs ranked by power, from highest to lowest, are: two-way enriched design, sequential enriched design, sequential parallel comparison design (SPCD), placebo lead-in design, traditional parallel design.

- In considering missing data, simply imputing dropouts as failures can easily bias against placebo, especially when the dropout rate in the placebo arm is much larger than that in the drug arm. Even when the dropout rates are the same in both arms, the results can be always against the drug arm unless there are no dropouts. We need more sophisticated methods for handling missing data.
- Different study designs require different placebo allocation ratio and weights to achieve optimal (minimal) sample size.
- The optimal SPCD stage 1 weight is typically between 0.6 and 0.9.
- The optimal placebo allocation ratio is typically 0.6, 0.5, and 0.4 for SPCD, TED, and SED respectively.
- For SPCD in particular, more patients need to be randomized to placebo to achieve optimal power.

References

Borges S, Chen YF, Laughren T, et al. Review of maintenance trials for major depressive disorder: a 25-year perspective from the U.S. Food and Drug Administration. J Clin Psychiatry. 2014; 75(3):205-214.

Chen YF, Yang Y, Hung HM, Wang SJ. Evaluation of performance of some enrichment designs dealing with high placebo response in psychiatric clinical trials. Contemp Clin Trials. 2011 Jul; 32(4):592-604.

Chen YF, Zhang X, Tamura RN, Chen CM. A sequential enriched design for target patient population in psychiatric clinical trials. Stat Med. 2014 Jul 30; 33(17):2953-67.

Chi G et al. On clinical trials with a high placebo response rate. Contemp Clin Trials Communications 2016; 34-53.

Fava M, Evins A, Dorer D, Schoenfeld D. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. Psychotherapy and Psychosomatics. 2003; 72:115-127.

Ivanova A, Tamura RN. A two-way enriched clinical trial design: combining advantages of placebo lead-in and randomized withdrawal. Stat Methods Med Res. 2015 Dec; 24(6):871-90.

Khin NA, Chen YF, Yang Y, Yang P, Laughren TP. 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 Apr; 72(4):464-72.

Khin NA, Chen YF, Yang Y, Yang P, Laughren TP. Exploratory analyses of efficacy data from schizophrenia trials in support of new drug application submitted to the US Food and Drug Administration. J Clin Psychiatry. 2012; 73(6):856-864.

Liu Q, Lim P, Singh J, Lewin B, Schwab B. Doubly randomized delayed start design for enrichment studies with responders or non-responders. J Biopharm Stat. 2012; 22:737-757.

Tamura RN, Huang X, Boos DD. Estimation of treatment effect for the sequential parallel design. Stat Med. 2011 Dec 30; 30(30):3496-506.

Testing for Treatment Effect and the Type I Error Rate Control in SPCD

Anastasia Ivanova, PhD
Associate Professor, Department of Biostatistics
University of North Carolina at Chapel Hill

Dr. Ivanova discussed challenges in SPCD data analysis, specifically how to take into account the correlation between observations obtained from the same subject.

Key points from the presentation:

- A major challenge in SPCD data analysis is that some patients contribute two data points to SPCD analysis.

- Let D_1 and D_2 be the plug-in estimates of treatment effects in SPCD (Chen et al., 2011), then, under the null hypothesis that active treatment is indistinguishable from placebo, $\mathrm{cov}(D_1, D_1) = 0$.

- Therefore the following two test statistics

$$Z_{NoCov} = \frac{wD_1 + (1-w)D_2}{\sqrt{w^2 Var(D_1) + (1-w)^2 Var(D_2)}}$$

$$Z_{Cov} = \frac{wD_1 + (1-w)D_2}{\sqrt{w^2 Var(D_1) + w(1-2)\mathrm{cov}(D_1, D_1) + (1-w)^2 Var(D_2)}}$$

preserve the type I error rate in SPCD under the null hypothesis.

- The test statistic Z_{NoCov} has higher power compared to Z_{SUR} in set-ups where SPCD is used.
- The test statistic Z_{NoCov} does not yield a confidence interval with correct coverage when inverted. Z_{SCov} yields a confidence interval with correct coverage when inverted, thus ensuring consistency between combined inference (test statistic, p-value) and estimation (confidence interval) for an SPCD trial.
- The primary assumption in the Mixed Model Repeated Measure (MMRM) is multivariate normality across visits within a patient. One can estimate the parameters in a multivariate normal distribution of patients receiving placebo in both SPCD stages, and in patients receiving placebo in stage 1 and active treatment in stage 2. Treatment effect then can be computed from stage 1 distribution directly and from stage 2 distribution after conditioning on placebo non-

responder status. The weighted combination of treatment effects can be tested using χ squared test with 1 degree of freedom.

References

Chi G et al. On clinical trials with a high placebo response rate. Contemp Clin Trials Communications 2 2016; 34-53.

Chen YF, Yang Y, Hung HM, Wang SJ. Evaluation of performance of some enrichment designs dealing with high placebo response in psychiatric clinical trials. Contemp Clin Trials. 2011 Jul; 32(4):592-604.

Doros G, Pencina M, Rybin D, Meisner A, Fava M. A repeated measures model for analysis of continuous outcomes in sequential parallel comparison design studies. Stat Med. 2013 Jul 20; 32(16): 2767-89.

Fava M, Evins A, Dorer D, Schoenfeld D. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. Psychotherapy and Psychosomatics. 2003; 72:115-127.

Huang X, Tamura RN. Comparison of test statistics for the sequential parallel design. Statistics in Biopharmaceutical Research. 2010; 2:42-50.

Ivanova A, Qaqish BF, Schoenfeld DA. Optimality, sample size, and power calculations for the sequential parallel comparison design. Stat Med. 2011 Oct 15; 30(23): 2793-803.

Ivanova A, Qaqish BF. Basic models and parameter estimation in the sequential parallel comparison design with continuous outcomes (in preparation, 2017).

Tamura RN, Huang X. An examination of the efficiency of the sequential parallel design in psychiatric clinical trials. Clinicial Trials: Journal of the Society of Clinical Trials. 2007; 4:309-317.

Review of Completed SPCD Studies in CNS

George I. Papakostas, MD

Scientific Director, Clinical Trials Network and Institute (CTNI)

Massachusetts General Hospital

Associate Professor of Psychiatry, Harvard Medical School

Dr. Papakostas reviewed several completed SPCD studies for treatment augmentation in major depressive disorder, one study for monotherapy in major depressive disorder, and one study for agitation in Alzheimer's dementia. A common theme throughout the studies was a significant reduction in placebo response in SPCD stage 2, reflecting a key benefit of the SPCD study design.

Key points from the presentation:

ADAPT-A Study

Funding: BMS

Double-blind, dummy placebo-controlled SPCD trial of low-dose aripiprazole for augmentation in major depressive disorder among patients with inadequate response to antidepressant therapy.

The trial consisted of two 30-day stages with pre-randomization to the sequence placebo-placebo, placebo-drug, and drug-drug; aripiprazole 2mg in stage 1 for the drug-drug group, aripiprazole 2mg in stage 2 for those in the placebo-drug arm, and 5mg in stage 2 for those assigned to drug-drug.

N= 221 (54 drug-drug, 84 placebo-drug, 84 placebo-placebo).

Primary outcome measure: MADRS

Separation between active and placebo was not statistically significant, pooling the data from both phases. However, there was a statistically significant advantage of drug over placebo in stage 2 for placebo non-responders, as placebo response rate declined from stage 1 (17.3%) to stage 2 (7.9%), as well as a reduction in change in MADRS score on placebo as well between the two stages (-8.1 in stage 1 and -3.3 in stage 2).

TRD-1 and TRD-2 Studies

Funding: PAMLAB LLC

Studies identical except for the L-Methylfolate dose.

TRD-1 study:

Double-blind, dummy pill controlled SPCD trial of l-methylfolate for augmentation in major depressive disorder among patients with inadequate response to antidepressant therapy, with pre-randomization to the sequence placebo-placebo, placebo-drug, and drug-drug.

Two 30-day stages; l-methylfolate 7.5mg in stage 1 for the drug-drug group, and in stage 2 for the placebo-drug group, and 15mg in stage 2 for the drug-drug group.

N= 148 (36 drug-drug, 58 placebo-drug, 54 placebo-placebo).

Primary outcome measure: HAMD-17.

This study was an informative, negative trial as it did not show a statistically significant difference between drug and placebo, despite the fact that the placebo response rate decreased dramatically from stage 1 (28.5%) to stage 2 (9%).

TRD-2 study:

Double-blind, dummy pill controlled SPCD trial of l-methylfolate for augmentation in major depressive disorder among patients with inadequate response to antidepressant therapy, with pre-randomization to the sequence placebo-placebo, placebo-drug, and drug-drug.

Duration: Two 30-day stages; l-methylfolate 15mg in stages 1 and 2.

N= 75 (19 drug-drug, 28 placebo-drug, 24 placebo-placebo).

Primary outcome measure: HAMD-17.

A statistically significant difference in efficacy between drug and placebo was shown, with the placebo response rate decreasing from stage 1 (19.6%) to stage 2 (9.5%).

Ziprasidone Monotherapy Study

Funding: Pfizer Inc.

Double-blind, placebo controlled SPCD study of ziprasidone 20 – 80mg BID for monotherapy in major depressive disorder, with pre-randomization to the sequence placebo-placebo, placebo-drug, and drug-drug.

Duration: Two 6-week stages.

N=120 (29 drug-drug, 48 placebo-drug, 43 placebo-placebo).

Primary outcome measure: HAMD-17.

The study did not show a statistically significant difference in efficacy between drug and placebo, with the placebo response rate decreasing from stage 1 (31.8%) to stage 2 (28%).

Buprenorphine/Samidorphan (ALKS 5461) Study

Funding: Alkermes, Inc.

Phase IIb double-blind, dummy pill controlled SPCD trial of ALKS 5461 for augmentation in major depressive disorder among patients with inadequate response to antidepressant therapy.

Duration and design: Two 4-week stages, with placebo non-responders *re-randomized* in stage 2 to drug or placebo.

Three treatment arms in both stages 1 and 2: Antidepressant + Placebo, Antidepressant + ALKS 5461 2mg/2mg, Antidepressant + ALKS 5461 8mg/8mg.

Primary outcome measure: HAMD-17.

Separation between 2/2mg dose and placebo was clinically and statistically significant in SPCD stage 2 as well as in combined inference, with the placebo response rate decreasing from stage 1 (26%) to stage 2 (15%). Similarly, the placebo HAMD-17 reduction in stage 1 (-7.3) markedly decreased in stage 2 (-1.4).

Intranasal Esketamine Study

Funding: Janssen R&D

Phase IIb double-blind, dummy pill controlled SPCD trial of intranasal esketamine for augmentation in major depressive disorder among patients with inadequate response to antidepressant therapy.

Duration and design: Two 1-week stages; placebo non-responders re-randomized in stage 2 to drug or placebo.

Intranasal esketamine or placebo on days 1 and 4.

Primary outcome measure: MADRS.

Three drug arms: 28mg, 56mg, 84mg.

In pooled data from stages 1 and 2, all three drug arms showed statistically significant MADRS reductions vs. placebo (-4.2 for 28mg; -6.3 for 56mg; -9 for 84mg), with the placebo MADRS reduction in stage 1 (-10) decreasing in stage 2 (-7).

Riluzole Study

Funding: NIMH

Double-blind, dummy pill controlled SPCD trial of riluzole for augmentation in major depressive disorder among patients with inadequate response to antidepressant therapy, with pre-randomization to the sequence placebo-placebo, placebo-drug, and drug-drug.

Duration and drug: Two 4-week stages; Riluzole 50mg bid.

N= 104 (25 drug-drug, 39 placebo-drug, 40 placebo-placebo).

Primary outcome measure: MADRS.

Results showed riluzole to be no different in efficacy from placebo in both stages 1 and 2, despite the placebo MADRS reduction from stage 1 (-5) to stage 2 (-3).

Dextromethorphan/Quinidine Study for Agitation in Alzheimer's Dementia

Funding: Avanir Pharmaceuticals Inc.

Double-blind, dummy pill controlled SPCD trial of dextromethorphan/quinidine for agitation in Alzheimer's dementia.

Duration and design: Two 5-week stages; placebo non-responders re-randomized in stage 2 to drug or placebo.

Primary outcome measure: NPI Agitation/Aggression (Ag/Ag) Domain.

Separation between dextromethorphan/quinidine and placebo was clinically and statistically significant in SPCD in the combined inference from both stages, and dextromethorphan/quinidine NPI Ag/Ag score reduction was statistically significant in both stages 1 and 2 (-3.3, -2.0), with the placebo NPI Ag/Ag score reduction being -1.7 in stage 1 and -0.8 in stage 2.

References

Fava M, Memisoglu A, Thase ME, Bodkin JA, Trivedi MH, de Somer M, Du Y, Leigh-Pemberton R, DiPetrillo L, Silverman B, Ehrich E. Opioid modulation with buprenorphine/samidorphan as adjunctive treatment for inadequate response to antidepressants: a randomized double-blind placebo-controlled trial. Am J Psychiatry. 2016 Feb 12. [Epub ahead of print]

Fava M, Mischoulon D, Iosifescu D, Witte J, Pencina M, Flynn M, Harper L, Levy M, Rickels K, Pollack M. A double-blind, placebo-controlled study of aripiprazole adjunctive to antidepressant therapy among depressed outpatients with inadequate response to prior antidepressant therapy (ADAPT-A Study). Psychother Psychosom. 2012;81(2):87-97.

Iovieno N, Papakostas GI. Correlation between different levels of placebo response rate and clinical trial outcome in major depressive disorder. J Clin Psychiatry. 2012; 73(10): 1300-1306.

Mathew S, Fava M et al. A randomized placebo-controlled adjunctive trial of riluzole in treatment-resistant major depressive disorder. ACNP 2015.

Papakostas GI, Shelton RC, Zajecka JM, Etemad B, Rickels K, Clain A, Baer L, Dalton ED, Sacco GR, Schoenfeld D, Pencina M, Meisner A, Bottiglieri T, Nelson E, Mischoulon D, Alpert JE, Barbee JG, Zisook S, Fava M. L-methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials. Am J Psychiatry. 2012 Dec;169(12):1267-74.

Papakostas GI, Vitolo OV, Ishak WW, Rapaport MH, Zajecka JM, Kinrys G, Mischoulon D, Lipkin SH, Hails KA, Abrams J, Ward SG, Meisner A, Schoenfeld DA, Shelton RC, Winokur A, Okasha MS, Bari MA, Fava M. A 12-week, randomized, double-blind, placebo-controlled, sequential parallel comparison trial of ziprasidone as monotherapy for major depressive disorder. J Clin Psychiatry. 2012 Dec;73(12):1541-7.

Singh J et al. A double-blind, doubly-randomized, placebo-controlled study of intranasal esketamine in an adaptive treatment protocol to assess safety and efficacy in treatment-resistant depression. ACNP 2015.

Cummings JL et al. Effect of dextromethorphan-quinidine on agitation in patients with Alzheimer disease dementia: a randomized clinical trial. JAMA. 2015 Sep 22-29;314(12):1242-54.

Clinical and Regulatory Perspective on Utilization of SPCD in Registration Trials

Thomas Laughren, MD
Director of Regulatory Affairs, Clinical Trials Network and Institute (CTNI)
Massachusetts General Hospital

Dr. Laughren discussed the problem of high placebo response in psychiatric drug trials, and highlighted practical issues and questions regarding the use of SPCD. He identified a need for a more definitive regulatory process to accept novel design approaches in drug development.

Key points from the presentation:

- According to FDA data on trials for major depression, the placebo response rate has increased over the past 25 years. Over the same period, the treatment effect has gradually decreased.
- Data for trials in schizophrenia show a similar pattern over the past 25 years (increasing placebo response, decreasing treatment effect), although data outside of the U.S. are less clear.
- Antidepressant trials become much less efficient as placebo response rate increases. As placebo response rate increases, the antidepressant/placebo response ratio decreases and the number needed to treat increases.
- In double-blind, randomized, placebo-controlled trials in major depression, greater probability of receiving placebo, greater baseline severity, and earlier year of publication all independently predict greater antidepressant-placebo efficacy separation.
- Topics to consider when considering unsuccessful psychiatry trials include: study design, inclusion/exclusion criteria, patient selection, fraudulent patients, assessment instruments, severity ratings, patient adherence, and statistical analysis plan.
- Regarding generalizability of SPCD, SPCD may better represent the study population than traditional study designs because it pools data from two stages: the first stage includes all comers, and the stage 2 population is enriched in placebo non-responders. Therefore, SPCD leads to only a partial enrichment, in contrast to studies with placebo-lead-ins.
- IRBs have generally not had ethical objections to SPCD methodology.
- Regarding the cost of using SPCD: although SPCD is patented and there is a fee associated with using this design, many innovative approaches and rating scales are also patented and associated with a use fee. Regulatory agencies do not appear to consider this a barrier to gaining regulatory acceptance.
- SPCD might be particularly useful in phase 2 proof of concept studies and in phase 3 trials. SPCD might be less appropriate in illnesses for which a long period of placebo treatment would not be acceptable.

- Pre-randomization (all patients randomized to a sequence at start of trial) vs. re-randomization (placebo non-responders re-randomized at beginning of stage 2): either approach is acceptable, but re-randomization may be preferred as there may be slightly less chance of treatment allocation imbalance among placebo nonresponders in stage 2.
- Regarding weighting of data in SPCD stages 1 and 2: the FDA initially argued for greater weighing of stage 1 data. Others believe that stage 2 data provides a better opportunity to detect drug effect and should be weighted higher. A compromise would be the 50:50 weighting.
- The Division of Psychiatry Products at the FDA has had a generally positive view of SPCD, often characterizing it as a "review issue".
- There is a need for a more definitive process for gaining regulatory acceptance of novel approaches in drug development. The current regulatory process appears quite variable across review divisions.
- Regulatory agencies can determine that an approach is "acceptable" without giving a formal "endorsement". A less daunting process for evaluating "acceptability" of novel approaches could encourage innovation.

References

Iovieno N, Papakostas GI. Correlation between different levels of placebo response rate and clinical trial outcome in major depressive disorder. J Clin Psychiatry. 2012; 73(10): 1300-1306.

Papakostas G, Fava M. Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. Eur Neuropsychopharmacol. 2009 Jan; 19(1): 34-40.

Panel Discussion with Q & A

Moderator: Madhukar H. Trivedi, MD

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In this interactive panel session, program faculty and FDA staff reviewed the potential benefits and limitations of SPCD study design, and discussed their key considerations when evaluating new drug applications (NDAs).

Key points from the Q & A session:

- Regarding use of SPCD, it is worth considering whether inclusion of stage 1 data undermines the effects seen in stage 2. An alternative strategy could be to use stage 1 as a lead-in and include only stage 2 data in the analysis. This, however, does not take advantage of the information derived from stage 1.
- If effect sizes are similar in stage 1 and stage 2, you may gain power by including the results of both stages. If there is no effect or a negative effect in stage 1 and a strong effect in stage 2, you may lose power by including both stages in analysis. Simulations may help determine the "sweet spots" that maximize study power.
- For the FDA, discarding stage 1 data and evaluating only stage 2 may be "too big of a leap". If the two SPCD stages of the trial are long enough, stage 1 may provide the same information the FDA would have typically received from traditional studies.
- Some regulatory agencies do not like lead-ins; they view them as a full enrichment. It may be a "lesser evil" to have the SPCD partial enrichment because subjects are not excluded in the first stage.
- Consider a study design that uses the second two parts of the two-way enriched design (TED): take patients who responded to the drug and do a randomized withdrawal, and take patients who were placebo non-responders and re-randomize them.
- Two of the FDA's biggest concerns are ensuring safety and maintaining the type I error rate, which appears to be addressed by simulations.
- The FDA encourages the submission of innovative study designs.
- The FDA does not enforce any particular design for studies. A study would only be rejected if it violated certain principles (e.g. not accounting for type I error), but would not be rejected simply because of study design. There is support for exploring novel designs like the SPCD as long as the rationale and statistics are well explained.

- It may be possible to pre-specify a decision algorithm that would allow a shifting of the weighting of SPCD analysis depending on the degree of placebo response. If this strategy were to be pursued, simulations would need to be performed to show that type I error is controlled.
- In order for a drug to be approved, the FDA must be shown what the drug is doing in a meaningful population, i.e. the population must be able to be described or characterized. An advantage of the two-stage model of SPCD is that all subjects entering the study are included.
- It's theoretically possible that the subject population in stage 2 would have different baseline characteristics than the population in stage 1. If so, this would pose problems for drug-labeling. However, there has been no evidence to date suggesting that the characteristics of subjects in the two stages have consistent differences.
- Based on analysis of clinical trial data, approximately eighty percent of placebo response occurs in the first half of a clinical trial, regardless of trial length. Subjects' expectations appear to shift depending on trial length. This provides a strong rationale in support of SPCD.
- Treatment effects in depression and schizophrenia studies tend to appear by week three or week four, so stages of 4 weeks would be adequate in these conditions.
- SPCD allows for shorter trials, which may be beneficial in schizophrenia, depression and other severe illnesses.
- The best results in SPCD have been seen in studies of antidepressants with stage 1 and stage 2 durations of 4 weeks each. This trial length may best capture treatment effect while minimizing dropout rates.
- The FDA encourages anyone who has conducted studies using SPCD to submit the study data to the Agency.