



Thursday, May 29, 2008

PANEL 13

**Could There Be a Role for Beta-Amyloid (Abeta) Lowering
Drugs in the Treatment of Late-Life Depression?**

11:35 a.m.–12:00 p.m.

Cancelled Discussant:

Substitute Discussant:

George S. Alexopoulos, M.D., Weill Medical College of Cornell University
Nunzio Pomara, M.D., Nathan S. Kline Institute for Psychiatric Research and New York
University School of Medicine

PANEL 18

**Ethics Applications in Child and Adolescent
Psychopharmacology Clinical Research and Practice
4:00 p.m. – 5:30 p.m.**

4:05 p.m.–4:25 p.m.

**Consensus Building to Generate Conflict-of-Interest Guidelines For
Practitioners**

Cancelled Presenter:

Substitute Presenter:

Laurence L. Greenhill, M.D.
Christopher J. Kratochvil, M.D.

Tuesday, May 27, 2008

Workshop 3

Geriatric Psychopharmacology: Predicting Response, Side Effects, and Safety 9:00 a.m.–12:00 p.m.

Continuity of Efficacy and Adverse Effects of Atypical Antipsychotics for Alzheimer's Disease: Further Outcomes From the CATIE-AD Trial and Other Trials

Lon S. Schneider, M.D.
USC Keck School of Medicine

A range of neuropsychiatric symptoms (e.g., delusions, aggression, agitation) affect nearly all people with Alzheimer's disease (AD) over their illness and cause significant additional disability and illness burden. These behaviors have been a major focus of treatment. Efforts to manage these non-pharmacologically have not been successful. Antipsychotics had been the mainstay of treatment for these behaviors as other pharmacologic approaches have not been successful, and were actively promoted for this use. Some pharmaceutical companies unsuccessfully pursued specific indications for the treatment of "Psychosis of AD" with atypical antipsychotics, mainly because the drugs did not show efficacy. From 2003 significant safety concerns arose with use of antipsychotics with respect to diabetes, cerebrovascular adverse events and deaths. This presentation reviews additional CATIE-Alzheimer's disease outcomes including adverse events in phases 1 and 2, predictors of adverse events in phase 2, cognitive and potential metabolic effects across the length of the study, the relationship between symptom improvement and quality of life, effects of the drugs on health utilities, and effects of discontinuation. In addition it will review several recent randomized withdrawal trials as examples of unbiased estimates of continuing efficacy of antipsychotics and ultimate effectiveness.

Learning Objectives:

- Understand methodological issues in clinical trials of neuropsychiatric symptoms in dementia.
- Review findings examining adverse effects and effectiveness of atypical antipsychotics from the CATIE-AD trial
- Understand the evidence for withdrawal trials.

References:

Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail SI, Lebowitz BD, Lyketsos CG, Ryan JM, Stroup SS, Sultzer DL, Weintraub D, Lieberman JL. Effectiveness of atypical antipsychotic drugs for patients with Alzheimer's disease. *New England Journal of Medicine*, 355(15):1525-1538, 2006.

Rosenheck RA, Leslie DL, Sindelar J, Miller EA, Tariot PN, Dagerman KS, Davis S, Lebowitz BD, Rabins P, Hsiao JK, Lieberman JA, Schneider LS. Cost-benefit analysis of second-generation antipsychotics and placebo in a randomized trial of the treatment of psychosis and aggression in Alzheimer disease. *Archives of General Psychiatry* 2007; 64: 1259-1268.

Sultzer DL, Davis SM, Tariot PN, Dagerman KS, Lebowitz BD, Lyketsos CG, Rosenheck RA, Hsiao JK, Liberman JA, Schneider LS for the CATIE-AD Study Group. Clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease: Phase 1 outcomes from the CATIE-AD effectiveness trial. *American Journal of Psychiatry*, 2008 (in press).

Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized placebo-controlled trials. *American Journal of Geriatric Psychiatry*, 14 (3): 191-210, 2006.

PANEL 4

Quality Indicators in the Practice of Psychopharmacology 2:00 p.m. – 3:30 p.m.

Use of Quality Indicators in a Behavioral Health Delivery System: An Industry Perspective

Rhonda Robinson-Beale, M.D.

United Behavioral Health

Bernice R. Friesen, Pharm. D.

United Behavioral Health

Managed Behavioral Health Organizations have the opportunity to identify behavioral health indicators that promote the quality of care in the population and contribute to improved treatment for individual patients. Use of quality indicators to improve care can take on three roles: improve population health, improve individual health, and improve clinician treatment practice alignment with evidence based practice. The first process requires identification and monitoring of population health metrics, the second process requires identification of individuals, and the third leverages performance indicators for evaluating clinicians use of evidence based clinical practices.

The health behavior of individual patients and the practices of their clinicians often vary widely from those recommended by evidence-based and consensus-based guidelines for the treatment of various behavioral health disorders.

Although most MBHO plans adopt and measure population outcomes using HEDIS® mental health measures there is growing interest in development and use of indicators to identify individual patient behavior and measure clinician's practice. OptumHealth Behavioral Solutions has developed claims based indicators to identify improvement opportunities and drive intervention at the population, individual member, and clinician level.

Descriptions and examples of such population based, individual, and clinician metrics and the use of medical, pharmacy and behavioral claims data to drive the indicators will be discussed.

Learning Objectives:

- Identify the three areas one Managed Behavioral Health Organization leverages quality indicators to improve care.
- Provide examples of the use of quality indicators to improve care.

References:

Hermann, R.C., Palmer, H., Leff, S., Schwartz, M., Provost, S., Chan, J., Chui, W.T., Lagodmos, G. (2004). Achieving consensus across diverse stakeholders on quality measures for mental healthcare. *Medical Care*, 42, 1246-1253.

Javitt, J.C., Steinberg, G., Locke, T., Couch, J., Jacques, J., Juster, I., Reisman, L. (2005). Using a claims data-based sentinel system to improve compliance with clinical guidelines: results of a randomized prospective study. *The American Journal of Managed Care*. Vol 11, No 2, 93 – 102.

National Committee for Quality Assurance. (2006a) *HEDIS 2007: Narrative*. NCQA: Washington D.C..

Wednesday, May 28, 2008

PANEL 7

**Patient Reported Outcomes in CNS Clinical Trials:
The Importance of Validation From Scientific and Regulatory Perspectives
4:00 p.m.–5:30 p.m.**

Sponsor Strategies for Incorporating Electronic Patient Reported Outcomes (ePRO) to Support a Product Labeling Claim

Gahan J. Pandina, Ph.D.

Johnson & Johnson Pharmaceutical Research and Development

Patient rated outcomes are being used to better understand complex and hard-to-treat clinical populations including mood and anxiety disorders and schizophrenia. Understanding the relationship between patient-rated symptoms and clinician-based reports, and how these two perspectives relate to functional outcome, can help us better identify clinically meaningful treatment outcomes. It may also facilitate use of clinical I provide some case examples of two ePRO measures, and contrast with a more standard, paper-based measure, discussing the strengths, and the challenges, of each approach.

Learning Objectives:

Describing the relationship between patient-rated symptoms and clinician-based reports.

Describing examples of an ePRO measures that were adapted from a standard paper based instrument.

References:

Schonfeld WH, Verboncoeur CJ, Fifer SK, Lipschutz RC, Lubeck DP, Buesching DP. The functioning and well-being of patients with unrecognized anxiety disorders and major depressive disorder. *J Affect Disord.* 1997 Apr;43(2):105-19.

Morosini PL, Magliano L, Brambilla L, et al. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand* 2000; 101(4): 323-329.

PANEL 7

**Patient Reported Outcomes in CNS Clinical Trials:
The Importance of Validation From Scientific and Regulatory Perspectives
4:00 p.m.–5:30 p.m.**

Practical and Data-driven Approaches to Assessing Decision-making

Laurie B. Burke, R.Ph., M.P.H.

Food and Drug Administration

This presentation addresses the use of patient-reported outcomes (PROs) in clinical trials to evaluate medical products. A PRO is any report coming directly from patients, without interpretation by physicians or others, about how they function or feel in relation to a health condition and its therapy. PRO instruments are used to measure these patient reports. PROs provide a unique perspective on medical therapy, because some effects of a health condition and its therapy are known only to patients. Properly developed and evaluated PRO instruments can provide more sensitive and specific measurements of the effects of medical therapies, thereby increasing the efficiency of clinical trials that measure treatment benefit of those therapies. This presentation reviews the process by which FDA evaluates PRO instruments to support labeling claims including a review of the endpoint model for the clinical study, the conceptual framework of the instrument, the content validity of the instrument and other measurement properties of the instrument. A PRO dossier template for submission of instrument documentation to the FDA is also described.

Learning Objectives:

- To provide participants with an overview of FDA's Guidance for Industry: Patient-Reported Outcome (PRO) Measures: Use in Medical Product Development to Support Labeling Claims.
- To provide participants with an understanding of the importance of documenting the endpoint model, conceptual framework, content validity, and other measurement properties of a PRO instrument used to show treatment benefit of a medical product in a clinical trial.

References:

Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Draft Guidance for Industry: Patient-Reported Outcome (PRO) Measures: Use in Medical Product Development to Support Labeling Claims, <http://www.fda.gov/cder/guidance/5460dft.pdf>. Federal Register: February 3, 2006 (Volume 71, Number 23) Docket No. 2006D-0044

PANEL 19

The Latest Developments in the Assessment of Cognitive Impairments and Functional Disability in Clinical Treatment Studies 4:00 p.m. – 5:30 p.m.

Implementation of Clinical Trials Using the MATRICS-FDA-NIMH Guidance to the Pharmaceutical Industry

Werner Rein, M.D.,
Sanofi - Aventis Group

As a major pharmaceutical company (sanofi-aventis) currently conducting a large (~ 700 patients), multi-site (~ 55) study in patients with cognitive impairment associated with schizophrenia, we have experienced both opportunities and challenges implementing the study methodology for this novel therapeutic approach¹.

The study is a 24-week, multicenter, double blind, randomized, parallel-group, dose ranging study of the efficacy and safety of three oral doses of AVE1625, and placebo on top of an established treatment regimen of either risperidone, paliperidone, quetiapine or aripiperazole monotherapy. The primary endpoint of this study is the MATRICS Consensus Cognitive Battery (MCCB)^{2,3} and the co primary endpoint for functional capacity is the UCSD Performance-Based Skills Assessment (UPSA2)⁴ (see *Clinicaltrials.gov*).

Sanofi-aventis acknowledges the many positive opportunities this experience has provided our company, both scientifically and professionally. These opportunities include clear guidance from the FDA regarding protocol requirements for potential compound registration, expertise in the use of the MCCB and UPSA2 and the establishment of relationships with many experts in this therapeutic area. The involvement in the MATRICS-CT Scientific Board as a pharmaceutical partner helping to facilitate the development of Intermediate Measures and Translations of the MCCB has also been a unique experience for s-a.

While challenges have been encountered as a result of performing such a study, these too have led to positive outcomes that will be a great asset as s-a moves forward with other similar studies.

Challenges experienced occurred in 3 basic areas include:

- 1) Limited number of English- speaking countries in which to perform the study greatly impacting site selection, patient, recruitment and enrollment
- 2) Need for increased financial resources due to intensive training on MCCB (eg, one-on-one), large number of assessments required at certain study visits (can be time consuming for both staff and patients), long treatment period (6 months), extra tasks required of blinded raters involved in processing and checking of certain assessments, purchase of additional site equipment (laptops, printers, faxes) and the need to amend protocol well into the conduct of the study to include the Columbia-Suicide Severity Rating Scale.
- 3) Because of the length of the study, patient retention has become a very large concern and has required additional resources for both the sites and s-a.

Other issues that limited the conduct of this study to some degree were the need for monotherapy, exclusion of some concomitant medications typically given to this patient population and strict enforcement of rules for substance use/abuse.

In conclusion, s-a sees this as a positive endeavor that has provided the company with many 'Lessons Learned' which will be very beneficial in future clinical trials. Additionally, the translations of the MCCB and development of the co primary functional outcome measures⁵ will be of great benefit for the future. S-a also recognizes the many 'experts' who have helped us along the way.

Learning Objectives:

- Summarize the experiences of a major pharmaceutical company conducting a large study in the therapeutic area of cognitive impairment associated with schizophrenia
- Identify some of the challenges encountered due to the limit of English-speaking countries only describe some of the unique situations that occurred with first time use of new methodology – the MCCB and co primary UPSA2

References:

- ¹ Buchanan, et al. (2005): A summary of the FDA-NIMH-MATRICES Workshop on clinical trial design for neurocognitive drugs for schizophrenia. *Schiz Bull*; 31:5-19.
- ² Nuechterlein, et al. (2008): The MATRICS Consensus Cognitive Battery, Part 1: Test Selection, Reliability and Validity. *Am J Psychiatry*; 165:203-213.
- ³ Kern, et al. (2008): MATRICS Consensus Cognitive Battery, Part 2: C0-Norming and Standardization. *Am J Psychiatry*; 165:214-220.
- ⁴ Patterson, et al. (2001): UCSD Performance-Based skills Assessment: development of a new measure of everyday functioning for 4 severely mentally ill adults. *Schiz Bull*; 27(2) 235-245.
- ⁵ Green, et al. (2008): Functional Co-Primary Measures for Clinical Trials in Schizophrenia: Results From the MATRICS Psychometric and Standardization Study. *Am J Psychiatry*; 165:221-228.

Wednesday, May 29, 2008

12:00 p.m. – 2:00 p.m.

Presentation Date Change, originally scheduled for Thursday, May 28.

Session II - 51 **A Novel Patient-Rated Scale for Side Effects: Proof-of-Concept Study**
Nancy Diazgranados, National Institute of Mental Health
Rajnish Mago, Constantine Daskalakis, Scott Waldman, David Oslin, Barry Rovner, Michael Thase

Thursday, May 30, 2008

12:00 p.m. – 2:00 p.m.

Substitutions:

Session I - 70 **Predicting Patient Adherence With Antipsychotic Therapy: Results Using a Medication Adherence Assessment Tool**
R. Bruce Simonson, Ortho-McNeil Janssen Scientific Affairs, L.L.C.
Larry Alphs, Wayne Macfadden, J. Thomas Haskins, Cynthia A. Bossie, Mary Kujawa, Jeff Veach, Carol Clayton, Jean-Pierre Lindenmayer

Cancelled Presenter: R. Bruce Simonson, Ortho-McNeil Janssen Scientific Affairs, L.L.C.
Substitute Presenter: Wayne MacFadden, Ortho-McNeil Janssen Scientific Affairs, L.L.C.

Withdrawn:

Session II – 21 **The Effect of Bipolar Disorder and Its Comorbidities on Cognition in Older Adults**
Arie G. Gildengers, University of Pittsburgh School of Medicine
Meryl A. Butters, Adriana V. Hyams, Amy Begley, Charles F. Reynolds,
David J. Kupfer, Benoit H. Mulsant

Session II - 66 **Lack of Benefi cial Galantamine Effect for Smoking Behavior: A Double-Blind Randomized Trial in People With Schizophrenia**
Deanna L. Kelly, University of Maryland School of Medicine
Robert P. McMahon, Elaine Weiner, Douglas Boggs, Dwight Dickinson, Robert R. Conley, Robert W. Buchanan