The National Academies of
SCIENCES · ENGINEERING · MEDICINE

FORUM ON NEUROSCIENCE AND NERVOUS SYSTEM DISORDERS

Multimodal Therapies for Brain Disorders: A Workshop

June 14-15, 2016

Keck Center
500 5th St., NW | Room 100
Washington, DC 20001

Background: Multimodal therapy approaches (i.e., combinations of interventions aimed at different aspects of a disease) are emerging as potential ways to enhance clinical outcomes for patients with psychiatric and neurological disorders. This could include, for example, concomitant prescription of a drug along with a device, biologic, or behavioral/psychosocial intervention (including, for example, cognitive remediation, lifestyle adjustment, dietary intervention, or animate therapy). Another example would be the simultaneous use of a neuromodulation device during performance of a specific neurocognitive task. While such a multimodal approach is consistent with the common clinical practice of combining interventions, there are important questions regarding how these interventions interact (in terms of additive, subtractive, or synergistic therapeutic as well as adverse effects), how they should be used, in what subsets of patients, and in what amounts or for what period of time. Further discussion is needed about methodologies for determining efficacy and safety in multimodal therapies compared with monotherapies and for comparing across multiple types of multimodal therapy. Multimodal therapy approaches also raise a number of important regulatory issues, both regarding combinations of regulated products (e.g., drug plus device) and approaches in which only one product is regulated (e.g., drug/device plus psychosocial intervention). Related questions arise for reimbursement, for example, would payers only pay for care if it includes both drugs and psychotherapy if that is what the data show is effective?

This workshop, hosted by the Forum on Neuroscience and Nervous System Disorders, will bring together key stakeholders to examine scientific, clinical, regulatory, and reimbursement issues related to multimodal approaches and identify potential opportunities to enhance clinical outcomes for individuals with psychiatric and neurological disorders. Rather than delving deeply into specific interventions, the workshop will aim to examine general principles, barriers, and potential solutions and opportunities that may apply across multimodal therapy development for brain disorders.

Meeting objectives:

- Explore recent advances in the development of multimodal therapeutic approaches for psychiatric and neurological disorders and approaches to using these therapies (e.g., earlier versus later in disease progression), and discuss future research needs to further advance understanding of these approaches.
- Highlight disease areas in which a multimodal approach could be particularly useful (e.g., areas in which the pathophysiology is well understood, or areas in which mono-modal approaches have been insufficiently effective).
- Discuss methodologies for establishing efficacy and safety for multimodal therapies compared to monotherapies, including clinical trials and statistical considerations.

- Consider regulatory issues for multimodal therapies, including for approaches in which only one component is regulated (e.g., drug plus psychosocial intervention), and discuss potential opportunities for addressing challenges.
- Consider reimbursement issues for multimodal therapies for nervous system disorders, and discuss potential opportunities for addressing challenges.
- Incorporate lessons learned from other therapeutic areas in which multimodal approaches are more frequently used (e.g., cardiology, diabetes, cancer).

DAY ONE: June 14, 2016

1:30 p.m. *Opening Remarks and Discussion of Definitions*

KARL KIEBURTZ, *Workshop Co-Chair*
Robert J. Joynt Professor in Neurology
Senior Associate Dean for Clinical Research
Director of the Clinical & Translational Science Institute
University of Rochester Medical Center

SARAH H. LISANBY, *Workshop Co-Chair*
Director, Division of Translational Research
National Institute of Mental Health
National Institutes of Health

SESSION I: STATE-OF-THE-SCIENCE IN MULTIMODAL THERAPIES FOR BRAIN DISORDERS

Session Objectives:
- Explore examples of recent advances in the development of multimodal therapeutic approaches for brain disorders and approaches to using these therapies.
- Discuss future research needs to further advance understanding of these approaches.
- Highlight disease areas in which a multimodal approach could be particularly useful.

1:50 p.m. *Overview and Session Objectives*

TIMOTHY STRAUMAN, *Session Co-Moderator*
Professor of Psychology and Neuroscience
Duke University

KEITH HILDEBRAND, *Session Co-Moderator*
Senior Principal Scientist, Technical Fellow
Neuromodulation
Medtronic, Inc.

2:00 p.m. **Part A: Two Pharmacological Interventions Approved as a Co-Delivery**

Drug/Drug and Drug/Biologic Combinations for Alzheimer's Disease

JAMES HENDRIX
Director, Global Science Initiatives, Medical and Scientific Relations
Alzheimer's Association

2:10 p.m. **Part B: Concomitant Prescription of Two Interventions with Different Modalities**

Drug-Device Combinations for Epilepsy

MARTHA MORRELL
Chief Medical Officer, NeuroPace
Clinical Professor of Neurology and, by courtesy, Neurosurgery
Stanford University

Combining Drugs and Psychosocial Interventions in Adolescents with Bipolar Disorder

KIKI CHANG *(via WebEx)*
Professor of Psychiatry and Behavioral Sciences
Stanford University Medical Center

2:30 p.m. **Part C: Simultaneous Use of Two Modalities in a Single Procedure**

Combining Devices with Cognitive Enhancement

BRUCE LUBER
Staff Scientist
Experimental Therapeutics & Pathophysiology Branch
National Institute of Mental Health

Individually-Targeted Combination of Transcranial Magnetic Stimulation and a Psychosocial Intervention

TIMOTHY STRAUMAN
Professor of Psychology and Neuroscience
Duke University

2:50 p.m. Discussion among Speakers and Workshop Participants

3:30 p.m. Break

SESSION II: REGULATORY AND REIMBURSEMENT CONSIDERATIONS

Session Objectives:

- Consider regulatory and reimbursement issues for multimodal therapies, including for approaches in which two components are regulated (e.g., drug plus device) and approaches in which only one component is regulated (e.g., drug plus psychosocial intervention).
- Explore evidentiary standards needed for regulation and reimbursement, and consider how different approval pathways and evidentiary standards across FDA centers impact multimodal approaches.
- Discuss potential opportunities for addressing challenges.

3:45 p.m. *Session Overview and Objectives*

SARAH H. LISANBY, *Session Moderator*
Director, Division of Translational Research
National Institute of Mental Health, National Institutes of Health

3:55 p.m. **Part A: Regulatory Considerations**

Combination Products at the Food and Drug Administration

PATRICIA LOVE
Deputy Director, Office of Combination Products
Food and Drug Administration

Evaluating Multimodal Products at the Center for Drug Evaluation and Research

BILLY DUNN
Director, Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration

Evaluating Multimodal Products at the Center for Devices and Radiological Health

CARLOS PEÑA
Director, Division of Neurological and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

Evaluating Multimodal Products at the Center for Biologics Evaluation and Research

WILSON BRYAN
Director, Division of Clinical Evaluation & Pharmacology / Toxicology
Office of Cellular, Tissue, and Gene Therapies
Center for Biologics Evaluation and Research
Food and Drug Administration

4:35 p.m. **Part B: Payer Considerations**

Private Payer Considerations

RHONDA ROBINSON BEALE
SVP and Chief Medical Officer
Blue Cross of Idaho

Perspectives from a Government Payer

STEVEN PIZER
Associate Professor of Health Economics
Department of Pharmacy and Health Systems Sciences
Northeastern University
and Chief Economist, Health Care Financing & Economics
U.S. Department of Veterans Affairs

4:55 p.m. Discussion among Speakers and Workshop Participants

5:30 p.m. Adjourn Day One

DAY TWO: June 15, 2016

8:30 a.m. *Day Two Opening Remarks*

KARL KIEBURTZ, *Workshop Co-Chair*

SARAH H. LISANBY, *Workshop Co-Chair*

KEYNOTE TALK: FUTURE DIRECTIONS IN CLINICAL TRIALS AND REGULATORY APPROACHES FOR MULTIMODAL THERAPIES

8:40 a.m. ROBERT CALIFF
Commissioner of Food and Drugs
Food and Drug Administration

9:00 a.m. Questions and Answers with Workshop Participants

9:30 a.m. BREAK

SESSION III: ESTABLISHING EFFICACY AND SAFETY IN MULTIMODAL THERAPIES FOR BRAIN DISORDERS

Session Objectives: Discuss methodologies for establishing efficacy and safety for multimodal therapies compared to monotherapies, including clinical and statistical considerations. Potential topics may include:

- Addressing challenges of intervention fidelity (e.g., site-to-site and time-to-time consistency) with behavioral interventions (psychotherapy, exercise).
- Interpretation when the two modalities have different time courses (e.g., drug goes for longer than behavioral intervention).
- Interpretation when one modality encounters more intolerability.
- Different approaches to assessing dose, especially in psychosocial interventions.
- Innovative approaches to trial design that are specifically relevant to multimodal approaches and may help address the levels of evidence required for regulation and reimbursement.

9:45 a.m. *Session Overview and Objectives*

KARL KIEBURTZ, *Session Moderator*
Robert J. Joynt Professor in Neurology
Senior Associate Dean for Clinical Research
Director of the Clinical & Translational Science Institute
University of Rochester Medical Center

9:55 a.m. *Platform Trials for Multimodal Therapies*

ROGER LEWIS
Senior Medical Scientist, Berry Consultants
Professor and Chair, Department of Emergency Medicine, Harbor-UCLA Medical Center

Quantification of Dose with Devices

MAROM BIKSON
Professor of Biomedical Engineering
The City College of The City University of New York

Quantification of Dose in Psychosocial Interventions

WOLFGANG LUTZ *(via WebEx)*
Professor and Head of Clinical Psychology and Psychotherapy
University of Trier, Germany

10:45 a.m. *Discussants:*

BILLY DUNN
Director, Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration

RHONDA ROBINSON BEALE
SVP and Chief Medical Officer
Blue Cross of Idaho

STEVEN PIZER
Associate Professor of Health Economics
Department of Pharmacy and Health Systems Sciences
Northeastern University
and Chief Economist, Health Care Financing & Economics
U.S. Department of Veterans Affairs

11:15 a.m. Discussion among Speakers, Discussants, and Workshop Participants

11:45 p.m. LUNCH

SESSION IV: INDUSTRY PERSPECTIVES

Session Objectives:

- Discuss industry perspectives on particular technical, scientific, and commercial challenges to bringing these systems to market, and examine lessons learned from successful examples of collaborations on multimodal approaches.
- Explore potential mechanisms for addressing challenges and enabling multimodal therapy development programs.

12:30 p.m. *Session Overview and Objectives*

STEVIN ZORN, *Session Moderator*
Executive Scientist in Residence
Lundbeck

12:40 p.m. *Challenges and Opportunities for Integration of Therapeutic Devices into Psychiatry*

JEFFREY NYE
Vice President, Neuroscience Innovation and Scientific Partnership Strategy
Janssen Research and Development, LLC
Johnson and Johnson Innovation

Intrathecal Infusion Therapy for Chronic Pain: Challenges, Lessons and Opportunities

KEITH HILDEBRAND
Senior Principal Scientist, Technical Fellow
Neuromodulation
Medtronic, Inc.

Pfizer–MedGenesis Therapeutix Collaboration on Glial Cell Line-Derived Neurotrophic Factor (GDNF) Protein and Convection Enhanced Delivery (CED) Technology for Parkinson's Disease

ERICH MOHR
Chairman & Chief Executive Officer
MedGenesis Therapeutix Inc.

CHRISTOPHER SHAFFER
Associate Research Fellow
Pfizer Inc.

1:20 p.m. Discussion among Speakers and Workshop Participants

2:00 p.m. BREAK

SESSION V: MOVING FORWARD

Session Objectives:

- Discuss the roles of NIH, other research agencies, and disease-specific organizations in supporting the development of multimodal therapies.
- Synthesize and discuss key highlights from the workshop presentations and discussions and, most importantly, identify next steps and promising areas for future action and research.

2:15 p.m. *Session Overview and Objectives*

KARL KIEBURTZ, *Workshop Co-Chair and Session Moderator*

SARAH H. LISANBY, *Workshop Co-Chair and Session Moderator*

2:20 p.m. *Role of Research Agencies in De-Risking Multimodal Therapy Development*

AMIR TAMIZ
Program Director, NIH Blueprint NeuroTherapeutics Network
National Institutes of Health

STUART HOFFMAN
Senior Scientific Advisor for Brain Injury
Office of Research and Development
Department of Veterans Affairs

2:40 p.m. *Role of Disease-Specific Research Funding in Multimodal Therapy Development*

JAMES HENDRIX
Director, Global Science Initiatives, Medical and Scientific Relations
Alzheimer's Association

BRIAN FISKE
Senior Vice President, Research Programs
The Michael J. Fox Foundation for Parkinson's Research

3:00 p.m. Discussion with Workshop Participants

3:15 p.m. *Panel Discussion: Identifying Gaps, Opportunities, and Next Steps Highlighted in Workshop Presentations and Discussions*

KARL KIEBURTZ, *Workshop Co-Chair and Session III Moderator*

SARAH H. LISANBY, *Workshop Co-Chair and Session II Moderator*

KEITH HILDEBRAND, *Session I Co-Moderator*

TIMOTHY STRAUMAN, *Session I Co-Moderator*

STEVIN ZORN, *Session IV Moderator*

EMMELINE EDWARDS
Director, Division of Extramural Research
National Center for Complementary and Integrative Health

4:00 p.m. Discussion with Workshop Participants

4:20 p.m. Closing Remarks

KARL KIEBURTZ, *Workshop Co-Chair*

SARAH H. LISANBY, *Workshop Co-Chair*

4:30 p.m. Adjourn Workshop