

Presentation 1

Sunday, May 17, 2009

Development of New Agents for the Treatment of Schizophrenia

Welcome and Introduction
Steven G. Potkin, MD (Chair)

30% total recycled fiber



Steven G. Potkin, MD (Chair)

Dr. Potkin (UC Irvine), is the Robert R. Sprague Director of the UCI Brain Imaging Center; Professor of Psychiatry and Human Behavior; and Director of Clinical Psychiatric Research, School of Medicine. Dr. Potkin received his medical degree from Washington University in St. Louis. Trained as a psychiatrist at Duke University, Dr. Potkin spent nine years at the National Institute of Mental Health (NIMH) as a clinical research psychiatrist before coming to UCI in 1985. Dr. Potkin's career has been devoted to understanding the causes of, and development of new treatments for, schizophrenia, bipolar disorder, Alzheimer's disease, and other neuropsychiatric diseases.

Dr. Potkin is the author of more than 200 peer reviewed scientific articles and book chapters. He serves on several editorial boards and is a member of numerous neuropsychiatric organizations, including the Collegium Internationale Neuropsychopharmacologicum (CINP), the largest international neuropsychopharmacology organization, as well as the American College of Neuropsychopharmacology (ACNP), and is a Distinguished Fellow of the American Psychiatric Association. From 1981 to 1983, he was the first US exchange scientist on the bilateral exchange of science and technology between the People's Republic of China and the United States.

Dr. Potkin is the recipient of numerous awards, including the A.E. Bennett Award from the Society of Biological Psychiatry for psychiatric research; the Michtell Balter Award; the Outstanding Psychiatrist Award from the California Alliance for the Mentally Ill; and the Riley Public Service Award from the Mental Health Association of Orange County, a rare distinction for a research psychiatrist. Dr. Potkin has twice been awarded the Exemplary Psychiatrist Award by the National Alliance for the Mentally Ill (NAMI), the most influential family-based organization advocating for the mentally ill, in recognition of the outstanding clinical care he has provided to individuals suffering from mental illness and, most specifically, to those with schizophrenia.

In addition to communicating to the general public, family members, and patients with schizophrenia, he has made many presentations to the California Legislature to educate legislators on mental illness and advocate for the needs of the mentally ill. Dr. Potkin played a key role in passing legislation which allowed treatment-resistant patients to receive new treatments and provided funding for model integrated service programs, such as the Village. He has served on numerous Task Forces, including the Lieutenant Governors' Task Force on Mental Illness (California).

Dr. Potkin has approached decreasing stigma for those suffering from mental illness in a variety of ways. His brain imaging, biological and genetic studies provide evidence that schizophrenia is a brain illness. Dr. Potkin directs two interdisciplinary research consortia. The Biomedical Imaging Research Network (BIRN) is a national consortium of computer scientists, physicist, cognitive scientist and physicians developing tools and the associated infrastructure needed for multi-site neuroimaging studies. He also directs the Transdisciplinary Imaging Genetics that develops new methods for combining imaging and genetic data to leverage the power of these disciplines as a gene discovery tool for neuropsychiatric illness.

Welcome and Introduction

Steven G. Potkin, MD
Professor, Department of Psychiatry
Robert R. Sprague Chair in Brain Imaging
Director, UCI Brain Imaging Center
University of California, Irvine

1

Disclosure of Financial and Off-Label Uses of Drugs and Products

At APA Industry-Supported Symposia

2

AMERICAN PSYCHIATRIC ASSOCIATION
2009 - SAN FRANCISCO, CALIFORNIA

APA Requires Disclosure of Relevant Financial Relationship in Three Ways

- Program book and ISS syllabus disclosure
- Disclosure slide at the beginning of a presentation with
 - Company names
 - Nature of the relationship
- Oral disclosure by presenter of the slide information



3

AMERICAN PSYCHIATRIC ASSOCIATION
2009 - SAN FRANCISCO, CALIFORNIA

Disclosure of a Financial Relationship

- Does not imply that the relationship has an adverse effect on information presented
- It does openly identify existence of potential for and management of a conflict



4

Off-Label Use of Drugs and Products

- Oral disclosure must be made each time before a presenter discusses an off-label use of an FDA-approved drug or product
- Blanket statements before the presentation or in the syllabus are not sufficient



5

Faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational uses (any uses not approved by the FDA) of products or devices

Faculty are also responsible for disclosing any limitations of data discussed during their presentations

Opinions expressed here are those of the presenters and do not necessarily reflect those of the APA or the commercial supporter

As Symposium Chair, I am responsible for ensuring that relevant disclosures are made by all presenters

The APA acknowledges support for this symposium from
Dainippon Sumitomo Pharma Co., Ltd.

Outcomes Measurement Assessment

- Purpose
 - Help us design more effective education
 - Identify changes that you will make in your practice as a result of this symposium
 - Help you evaluate the implementation of your intended changes by following up 6 weeks after the symposium via e-mail
- Postactivity Outcomes Study Form
 - Complete the colored outcomes form, which was located on your chair, at the end of the symposium
 - Hand your form to a staff member as you exit



10

Educational Goal for Our Presentation

To educate psychiatrists and other mental health practitioners regarding the processes and barriers involved in bringing a novel agent to the clinical market, with schizophrenia as an example



11

Agenda

- Unmet Needs in Schizophrenia - **Adrian Preda, MD**
- Drug Development in Psychiatry: Issues and Trends - **Amir H. Kalali, MD**
- New Targets for Drug Development - **Philip D. Harvey, PhD**
- Late Stage and Recently Approved Antipsychotic Agents - **Steven G. Potkin, MD**
- Panel Discussion and Q&A



12

Learning Objective #1

Recognize unmet needs in the treatment of schizophrenia and the development of new agents aimed at these needs



13

Learning Objective #2

Identify barriers to the rapid development and approval of new agents



14

Learning Objective #3

Discuss potential drug development targets to improve cognition in patients with schizophrenia



15

Glossary of Terms

$\alpha 1$	alpha-1 adrenergic receptor	HVLT	Hopkins Verbal Learning Test (MCCB battery)
$\alpha 2c$	alpha-2c adrenergic receptor	LUR	lurasidone
$\alpha 4\beta 3$	alpha-4/beta-3 nicotinic receptor complex	ILO	iloperidone
$\alpha 7$	alpha-7 nicotinic receptor	ITT	intention-to-treat
Δ	delta (change)	Ki	in vitro inhibition constant, a measure of drug-receptor affinity; lower Ki values indicate higher affinity
D1	D1 dopamine receptor	LOCF	last observation carried forward
D2	D2 dopamine receptor	LNS	Letter-Number Span test (MCCB battery)
H1	H1 histamine receptor	LSM	least squared mean
5-HT1A	5-HT1A serotonin receptor	MATRICES	Measurement and Treatment Research to Improve Cognition in Schizophrenia test battery
5-HT2A	5-HT2A serotonin receptor	MOA	mechanism of action
5-HT7	5-HT7 serotonin receptor	MCCB	MATRICES Consensus Cognitive Battery
M1	M1 muscarinic receptor	MITT	modified intention-to-treat
ACh	acetylcholine	Mood Stabil	mood stabilizer
ACHE	acetylcholine esterase	NAB	Neuropsychological Assessment Battery (MCCB battery)
AIMS	Abnormal Involuntary Movement Scale	NE	norepinephrine/noradrenaline
AMPA	glutamate receptor ([alpha]-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)	nM	nanomolar
Antidep	antidepressant	NMDA	glutamate receptor (N-methyl-D-aspartate)
AN	Animal Naming test (MCCB battery)	NS	not statistically significant
Anticholin	anticholinergic	OLZ	olanzapine
Anxioly/Hyp	anxiolytic/hypnotic	PAL	paliperidone
ARI	aripiprazole	PANSS	Positive and Negative Syndrome Scale
ASE	asenapine	PBO	placebo
BACS	Brief Assessment of Cognition (MCCB battery)	PER	perphenazine
BAS	Barnes Akathisia Scale	QLS	Quality of Life scale
BVMT	Brief Visuospatial Memory Test (MCCB battery)	QUE	quetiapine
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness	QOL	quality of life
CGI-S	Clinical Global Impressions-Severity	QTc	cardiac measure of the interval between start of the Q wave and end of the T wave, corrected for heart rate
CLO	clozapine	RIS	risperidone
CNS	central nervous system	SER	sertindole
COMP	composite score - average score across cognitive domains on MCCB battery	SGA	second-generation antipsychotic
DSM-V	Diagnostic and Statistical Manual - version 5	SSRI	selective serotonin reuptake inhibitor
EU	European Union	TMT	Trail Making Test (MCCB battery)
FDA	Food and Drug Administration	USPA	University of California - San Diego (UCSD) Performance-Based Skills Assessment
FGA	first-generation antipsychotic	WMS	Wechsler Memory Scale (MCCB battery)
GEE	generalized estimating equations	Wt	weight
HAL	haloperidol	ZIP	ziprasidone
HAM-D-17	Hamilton Depression Rating Scale - 17 item version		

Development of New Agents for the Treatment of Schizophrenia

Unmet Needs in Schizophrenia Adrian Preda, MD

Over the last 50 years, the field of psychiatry has made enormous strides in identifying effective strategies for managing the core symptoms of schizophrenia. A variety of effective pharmacotherapies exist for both acute and maintenance treatment, and a number of psychosocial strategies and programs have been developed. For instance, remission rates with current treatment are often found to approach 90% in first episode patients and 50% in more chronic populations. Yet there are significant unmet needs in this patient population, as the field shifts away from symptom control to recovery. Effective treatment of cognitive symptoms, for example, has so far remained elusive with current treatments, and the presence of these symptoms can prevent recovery. Patient medication adherence is low and continued strategies and efforts are needed in this area to maximize outcomes. Access to care continues to be a challenge for many patients with schizophrenia and a rethinking of the role of psychiatrists in the overall medical management of their patients has already occurred. This role shift is of particular importance given the long-term cardiometabolic risks associated with the use of some atypical antipsychotic medications. Clearly, challenges exist at the research, clinician, patient, and system levels. In this presentation, faculty will review the major factors undermining successful long-term outcomes for patients with schizophrenia, and will lead an interactive discussion regarding ways to measure and address them with existing as well as emerging resources.

Adrian Preda, MD

Dr. Preda is a Health Sciences Associate Professor of Psychiatry and Human Behavior at UC Irvine and an Attending and Research Psychiatrist at the UC Irvine Psychiatric Center. Dr. Preda received his medical degree from Carol Davila University of Medicine and Pharmacy, in Bucharest, Romania. Trained as a psychiatrist at Yale University, where he was also a program wide Co-Chief Resident and the Yale New Haven Hospital Chief Resident in Psychiatry, Dr. Preda has been on faculty at Yale and UT Southwestern before coming to UC Irvine in 2006. Dr. Preda clinical and research interest is on new interventions for major neuropsychiatric illness with an emphasis on schizophrenia, affective disorders and Alzheimer's disease as well as in the use of novel brain imaging techniques, such as Diffusion Tensor Imaging, to advance our understanding of psychiatric diagnosis and treatment. Dr. Preda has been a recipient of a NARSAD Young Investigator Award and he is a NARSAD Elizabeth Elser Doolittle Investigator.

Unmet Needs in Schizophrenia

Adrian Preda, MD
 Health Sciences Associate Professor
 of Psychiatry and Human Behavior
 University of California, Irvine

1

Adrian Preda, MD Disclosures

- *Research/Grants:* None
- *Speakers Bureau:* None
- *Consultant:* None
- *Stockholder:* None
- *Other Financial Interest:* None
- *Advisory Board:* None



2

Leading Causes of Years of Life Lived with Disability (YLDs), in 15-44-Year-Olds, by Sex, Estimates for 2000

	Both Sexes, 15-44-year-olds	%	Males, 15-44-year-olds	%	Females, 15-44-year-olds	%
1	Unipolar depressive disorders	16.4	Unipolar depressive disorders	13.9	Unipolar depressive disorders	18.6
2	Alcohol use disorders	5.5	Alcohol use disorders	10.1	Iron-deficiency anemia	5.4
3	Schizophrenia	4.9	Schizophrenia	5.0	Schizophrenia	4.8
4	Iron-deficiency anemia	4.9	Bipolar affective disorder	5.0	Bipolar affective disorder	4.4
5	Bipolar affective disorder	4.7	Iron-deficiency anemia	4.2	Obstructed labor	4.0
6	Hearing loss, adult onset	3.8	Hearing loss, adult onset	4.1	Hearing loss, adult onset	3.6
7	HIV/AIDS	2.8	Road traffic accidents	3.8	Chlamydia	3.3
8	Chronic obstructive pulmonary disease	2.4	HIV/AIDS	3.2	Abortion	3.1
9	Osteoarthritis	2.3	Drug use disorders	3.0	Panic disorder	2.8
10	Road traffic accidents	2.3	Chronic obstructive pulmonary disease	2.6	HIV/AIDS	2.5

Neuropsychiatric conditions are highlighted.
 World Health Report 2001. *Mental Health: New Understanding, New Hope.*
 World Health Organization.



3

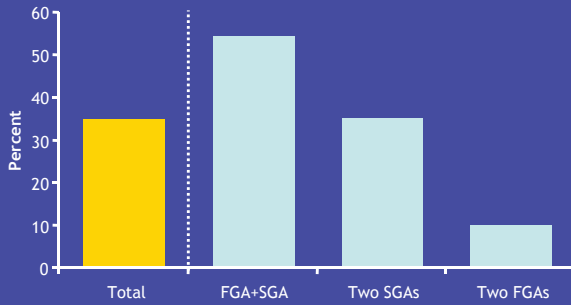
Schizophrenia: Unmet Needs

- Affects 24 million people worldwide
 - < 50% of patients are receiving appropriate care
 - ~70% in US and ~50% in EU treated with > 1 agent
- Unmet Needs
- < 1/3 of treated patients symptom-free and functional
 - Improved maintenance therapy to reduce relapse
 - Side effects and treatment ineffectiveness increase non-compliance
 - Current medications have limited effect on negative and cognitive symptoms



4

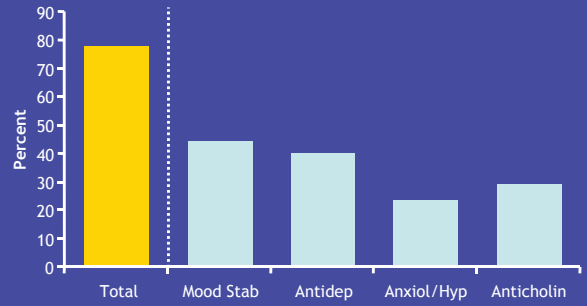
Combination Antipsychotic Treatment in Schizophrenia



Correll CU, et al. *Schizophr Res* 2003;60(Suppl.):37 [abstract].



Polypharmacy with Antipsychotic Plus Other Medication in Schizophrenia



Correll CU, et al. *Schizophr Res* 2003;60(Suppl.):37 [abstract].



Quality of Life

- Multidimensional concept
- Symptoms = poor quality of life
- Lack of symptoms = improved quality of life

[QOL] "measures the extent to which people's 'happiness requirements' are met - i.e., those requirements which are a necessary (although not sufficient) condition of anyone's happiness - those 'without which no member of the human race can be happy.'"

McCall S. 'Quality of Life', Social Indicators Research, 1975



Measurement of Quality of Life Conceptual Categories

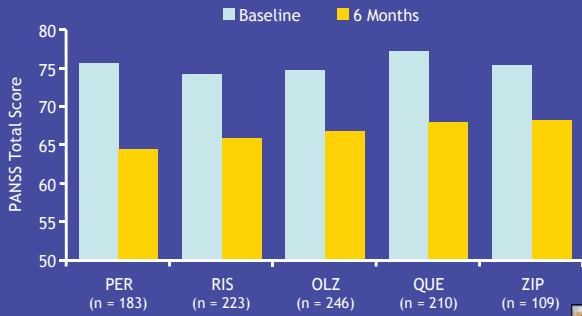
1. Material comforts - home, food, conveniences, financial security
2. Health - being physically fit and vigorous
3. Relationships with parents, siblings and other relatives - communicating, visiting, helping
4. Having and rearing children
5. Close relationships with spouse or significant other
6. Close friends
7. Helping and encouraging others, volunteering, giving advice
8. Participating in organizations and public affairs

Patient self-report ratings from 1-7:
1 = Terrible
2 = Unhappy
3 = Mostly Dissatisfied
4 = Mixed
5 = Mostly Satisfied
6 = Pleased
7 = Delighted

Flanagan JC. *Arch Phys Med Rehabil* 1982;63:56-59.



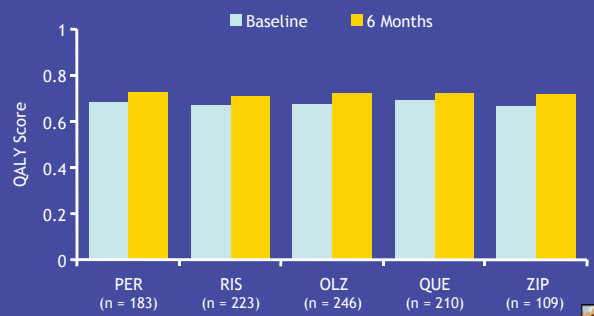
PANSS Total Scores at Baseline and 6 Months After Treatment in CATIE



Rosenheck RA, et al. *Am J Psychiatry* 2006;163:2080-2089.

10

QALY at Baseline and 6 Months After Treatment in CATIE



Rosenheck RA, et al. *Am J Psychiatry* 2006;163:2080-2089.

11

Functional Deficit

- Positive
 - Negative
 - Cognitive
- Schizophrenia
Psychotic Disorder

Quality of Life

12

Functional Deficit

- Positive
 - Negative
 - Cognitive
- Schizophrenia
Psychotic Disorder

Unmet Need

Quality of Life

13

~~The Ideal Antipsychotic~~

14

The Ideal Drug for Schizophrenia

RESTORING FUNCTION

15

AMERICAN PSYCHIATRIC ASSOCIATION
2009 - SAN FRANCISCO, CALIFORNIA

Summary

- Schizophrenia is among the top causes of disability worldwide, affecting 24 million people
- There are significant unmet needs in the treatment of schizophrenia, including improvement in functional outcomes and cognitive function, and reduced disability
- Polypharmacy is common, and new receptor targets are urgently needed to improve outcomes



16

Bibliography

The World Health Report 2001. Mental Health: New Understanding, New Hope. Available at: <http://www.who.int/whr/2001/en/>. Accessed May 1, 2009.

Correll CU, Kane JM, O'Shea D, Razi K, Malhotra AK. Antipsychotic polypharmacy in the treatment of schizophrenia. *Schizophr Res* 2003;60(Suppl.):37 [abstract].

Flanagan JC. Measurement of quality of life: current state of the art. *Arch Phys Med Rehabil* 1982;63:56-59.

Harvey P, et al. *Am J Psychiatry* 2009 (in press).

McCall S. Quality of Life. *Soc Indic Res* 1975;2:229-248.

Rosenheck RA, Leslie DL, Sindelar J, et al. Cost-effectiveness of second-generation antipsychotics and perphenazine in a randomized trial of treatment for chronic schizophrenia. *Am J Psychiatry* 2006;163:2080-2089.

Development of New Agents for the Treatment of Schizophrenia

Drug Development in Psychiatry: Issues and Trends

Amir H. Kalali, MD

Drug development efforts are proceeding at a rapid pace as scientists and industry try to address unmet needs in the treatment of schizophrenia. Getting a newly developed compound to the marketplace is a long and arduous task with many steps, challenges and pitfalls along the way. In part, the complexity of the process arises from the number of stakeholders involved in generating the compound, testing its effects in animal models, and conducting Phase I, 2, and 3 clinical trials to assess toxicity, safety, dosing, and efficacy in humans. At each juncture there is the potential for the compound to be abandoned, and even those that reach a formal application to the FDA may not receive approval. As previous attempts to address unmet needs have been unsuccessful, new laboratory models have been developed for evaluating agents, and new pharmacological targets are being identified. Physicians attempting to navigate this process to stay abreast of new developments will inevitably encounter many questions. What is the role, if any, of NIH in this process? What is the role of the pharmaceutical sponsor and what are their limitations? What does the FDA look for, and why do applications get denied? Faculty in this symposium will discuss the steps involved in getting a novel drug to the marketplace, and will use approved, non-approved and pending treatments as case studies along the way.

Amir H. Kalali, MD

Dr. Kalali is currently Vice President, Medical and Scientific Services, and Global Therapeutic Team Leader CNS, at Quintiles Inc., focusing on developing novel compounds for the treatment of disorders of the central nervous system. He is globally responsible for the medical and scientific aspects of development programs in psychiatry and neurology. He is also Professor of Psychiatry at University of California San Diego.

He was the Founding Chairman of the Executive Committee of the International Society for CNS Drug Development (ISCDD), and currently the Executive Secretary. Dr. Kalali is also Chair of the Membership Committee of the International Society for CNS Clinical Trials and Methodology (ISCTM), as well as a member of the Scientific Committee. In these roles he is active in facilitating scientific collaboration between academia, government, and pharmaceutical industry scientists.

Dr. Kalali received his MD from the University of London, United Kingdom. He completed his psychiatry training at University College and Middlesex School of Medicine, London University. He was then appointed to a clinical research faculty position at the University of California Irvine, where he also held several positions including Director of the Mood and Anxiety Disorders Clinical Research Program, and the Director of the Consultation Liaison Psychiatry Program at the Clinical Cancer Research Center. He was also involved as an investigator on several NIH Center research programs, including the Center for Neuropathological and Genetic Abnormalities in Depression, and the Center for Neuroscience and Schizophrenia, investigating Neurobiological Brain Abnormalities in Schizophrenia. Dr. Kalali has been an academic investigator in over 70 psychopharmacological clinical trials and at Quintiles has had medical and scientific responsibility for over 300 clinical trials. He is an expert in CNS clinical trial methodology, including clinical rating scales, and has trained investigators from over 40 countries.

Dr. Kalali is the Editor of the journal *Psychiatry*, and is on the editorial board of several other journals. He has published widely in journals such as the *Archives of General Psychiatry*, *The American Journal of Psychiatry*, and the *British Journal of Psychiatry*. Dr. Kalali regularly presents at national and international scientific meetings, and lectures frequently on psychopharmacological and drug development topics. He is particularly interested in educating clinicians worldwide, and is facilitating this currently by being the Chairman of the Educational Committee of the Collegium Internationale Neuro-Psychopharmacologicum (CINP).

In 2005, 2006 and 2008 PharmaVOICE magazine named Dr. Kalali as one its 100 most inspiring leaders in the life sciences. Dr. Kalali is an active member of many professional societies including the American Association for the Advancement of Science, the American Association of Pharmaceutical Physicians, the American Society for Clinical Psychopharmacology, the American Psychiatric Association, the Canadian College of NeuroPsychopharmacology, the Collegium Internationale Neuro Psychopharmacologicum, the Drug Information Association, the International Society for CNS Drug Development, the International Society for CNS Clinical Trials and Methodology, the Royal College of Psychiatrists, United Kingdom, and the Society for Neuroscience.

Drug Development in Psychiatry: Issues and Trends

Amir H. Kalali, MD

Vice President, Global Therapeutic Group Leader CNS
Quintiles Inc.

Clinical Professor of Psychiatry
University of California, San Diego

1

AMERICAN PSYCHIATRIC ASSOCIATION
2009 - SAN FRANCISCO, CALIFORNIA

Amir H. Kalali, MD Disclosures

- *Research/Grants:* None
- *Speakers Bureau:* None
- *Consultant:* None
- *Stockholder:* None
- *Other Financial Interest:* Board of Directors, Cypress Bioscience, Inc.
- *Advisory Board:* AstraZeneca Pharmaceuticals LP
- Dr. Kalali is an employee of Quintiles, Inc.



2

AMERICAN PSYCHIATRIC ASSOCIATION
2009 - SAN FRANCISCO, CALIFORNIA

Where Are CNS Programs Now?

- CNS drug development programs are high risk compared to other therapeutic areas
- High clinical trial failure rate
- Increasingly large and expensive phase 3 programs



3

AMERICAN PSYCHIATRIC ASSOCIATION
2009 - SAN FRANCISCO, CALIFORNIA

The Drive Towards Globalization of Clinical Research

- Drive to bring new treatments to patients expeditiously
- Slow patient recruitment in the US and Western Europe delays program completion
- Need more ethnically diverse and representative patient populations



4

Advantages of Global Clinical Trials

- Data can address ethnic diversity
- Better access to drug-naïve patients
- Improved patient retention rates
- Higher medication adherence rates
- More stability of patients facilitates better long-term follow-up



5

The Crisis in CNS Drug Development *Macro Factors*

- Politics
 - Black boxes
 - New suicidality assessment requirements
- Impact of media coverage
- Declining trust in science and research
 - Cases of scientific misconduct
 - Some lack of transparency in disseminating data
 - Question of relationship between academia and industry
- Anti-science groups



6

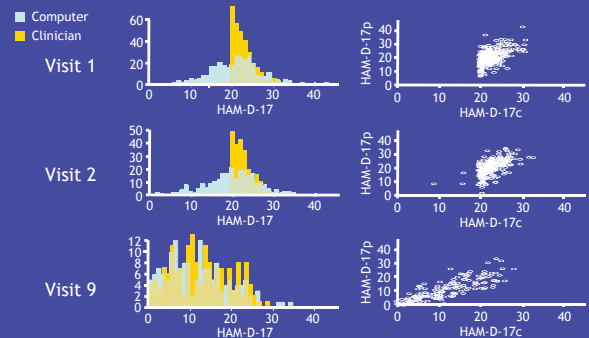
The Crisis in CNS Drug Development *Methodological Factors*

- Statistically, some should fail by definition
- Study design
- Instruments
- Study conduct
- Clinic sites
- Patients



7

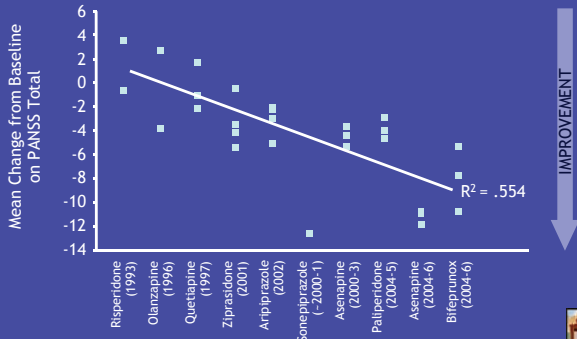
Objective vs. Subjective HAM-D Ratings



DeBrota D, et al. Poster presented at NCDEU, 1999.

8

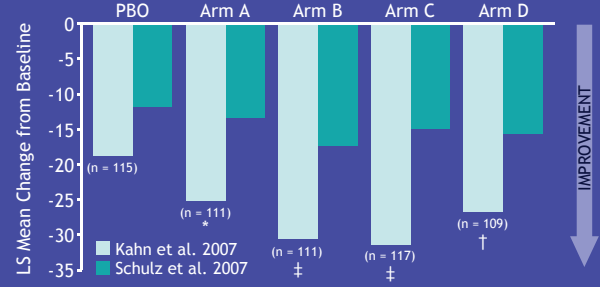
Increasing Placebo Response Over Time in Acute Schizophrenia Trials



Kemp AS, Schooler NR, Kalali AH, et al. *Schizophr Bull* 2008 [epub ahead of print].

9

PANSS Total Score at Day 42 Comparison of Two Studies



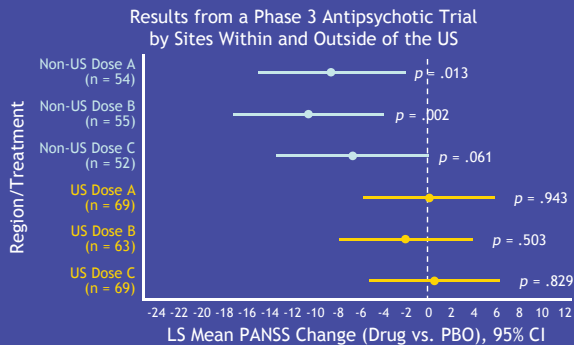
MITT, LOCF; * p < .05; † p < .01; ‡ p < .001

1. Kahn RS et al. *J Clin Psychiatry* 2007;66:832-842.

2. Schulz C, et al. Poster presented at the 2007 annual meeting of the American Psychiatric Association, San Diego, CA.

10

Recent Acute Schizophrenia Trial Experience Treatment Effect by Geographic Region (LOCF)



11

The Crisis in CNS Drug Development

- In the era of:
 - Generic SSRIs
 - Generic SGAs
 - More demanding, educated, and skeptical regulators, payors, and patients
- High hurdle to demonstrate value
- Urgent need for new molecules with novel mechanisms of action

12

So What Might We Expect for the Future?

- To be sustainable, drug development has to be done more efficiently and demonstrate value
- Reimbursement trends will encourage personalized medicine
- Disease management and personalized healthcare more prominent
- Continued drive to globalization
 - Have not scratched the surface (e.g., India and China)



13

So What Might We Expect for the Future?

- Patient Issues
 - Available pool of patients
 - Patient selection
 - Diagnosis (impact of DSM-V and beyond)



14

So What Might We Expect for the Future?

- Methodological Issues
 - Novel designs
 - Outcome measures
 - Administration of assessments
 - Self-assessment
 - Adapting methodology to new mechanisms of action



15

Summary

- Drug development efforts face a number of challenges including efficiency, methodological limitations, and political/social barriers
- Globalization of clinical trials may help to address barriers related to efficiency and diversity
- Future studies with more targeted patient samples and better methodology are needed to overcome some of the current barriers to drug development



16

Bibliography

DeBrotá DJ, Demitrack MA, Landin R, et al. A comparison between interactive voice response system-administered HAM-D and clinician-administered HAM-D in patients with major depressive episode. Presented at the 39th Annual Meeting of the NIMH New Clinical Drug Evaluation Unit; 1999 June 1-4; Boca Raton, FL.

Kahn RS, Schulz C, Palazov VD, et al. Efficacy and tolerability of once-daily extended release quetiapine fumarate in acute schizophrenia: A randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2007;68:832-842.

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* 2008; epub ahead of print.

Schulz C, Kahn R, Palazov V, et al. Efficacy of Once-Daily Extended Release Quetiapine Fumarate in Patients with Acute Schizophrenia. Presented at the Annual Meeting of the American Psychiatric Association; 2007 May 19-24; San Diego, CA. Research poster board NR04.

Development of New Agents for the Treatment of Schizophrenia

New Targets for Drug Development Philip D. Harvey, PhD

The pharmacology of cognitive impairment in schizophrenia is still evolving and new drug targets are identified often. These targets include both well-known transmitter systems, such as the dopamine, glutamate, serotonin, norepinephrine, GABA, and acetylcholine, as well as nontransmitter brain processes such as white matter integrity and inflammatory processes. The success rate in transmitter based approaches has been limited to date, with clear failures recorded in most of the transmitter systems just mentioned. There are several possible reasons for these failures, including the need to continue concomitant antipsychotic medications in the patients and lack of clear guidance on doses and penetrance into the CNS. An additional substantial issue is whether medications should be developed that target positive and negative schizophrenia symptoms as well as cognitive abnormalities (i.e., broad spectrum agents). Such agents might reduce the potential problem of interference from concurrent antipsychotic medications. While this idea appears reasonable, regulatory concerns have been expressed regarding demonstrating that the cognitive effects with such agents would be direct or due to reductions in other symptoms. We will critically evaluate the evidence that “pseudo-specificity” is an issue in cognitive enhancement trials in schizophrenia. We will also evaluate the possibility that non-transmitter based approaches have promise, including anti-inflammatory treatments, promotion of neurogenesis, and modulation of white matter integrity. Further, we will examine previous efforts and evaluate them in terms of whether possible modification in research designs, subject populations, or dosing or delivery strategies could have a more beneficial finally. Finally, we will consider data regarding alternate outcomes targets, including direct measures of disability, have more potential to detect change than the standard cognitive tests used in previous efforts.

Philip Harvey, PhD

Dr. Harvey is Professor of Psychiatry at Emory University School of Medicine. He was formerly professor of Psychiatry at Mt. Sinai School of Medicine and Chief Psychologist at Mt. Sinai Hospital. He received his PhD in Clinical Psychology from SUNY at Stony Brook in 1982. He is a widely cited author whose work has been cited more than 400 times per year for the past decade, with over 1,200 citations of his work in 2008 alone. He is the author of over 700 scientific papers and abstracts and he has written over 30 book chapters. He has given more than 1,300 presentations at scientific conferences and medical education events. He has edited five books and written four books on topics of psychological assessment, schizophrenia, and aging. He is a member of the American Psychological Association, the American College of Neuropsychopharmacology, the Collegium Internationale Neuropharmacologium (Fellow), the Society for Research in Psychopathology (Founding Member), International College of Geriatric Psychoneuropharmacology (Founding Member), the Society for Biological Psychiatry, International Neuropsychological Society, the Schizophrenia International Research Society (Founding Director), and the International Society for Clinical Trials and Methodology (Founding Member).

His research has focused for years on cognition and he has written extensively on aging in schizophrenia, functional impairments in the illness, the cognitive effects of typical and atypical antipsychotics, as well as studying the effects of cognitive enhancing agents in various conditions, including schizophrenia, dementia, and traumatic brain injury. He directs a biennial conference on cognition that is an official satellite of the International Congress on Schizophrenia Research.

New Targets for Drug Development

Philip D. Harvey, PhD
 Professor of Psychiatry and
 Behavioral Sciences
 Emory University School of Medicine

1

Philip D. Harvey, PhD Disclosures

- **Research/Grants:** AstraZeneca Pharmaceuticals LP
- **Speakers Bureau:** None
- **Consultant:** Dainippon Sumitomo Pharma America, Inc.; Shire Pharmaceuticals; Wyeth Pharmaceuticals
- **Stockholder:** None
- **Other Financial Interest:** Royalties for the Brief Assessment of Cognition in Schizophrenia
- **Advisory Board:** Eli Lilly and Company; Janssen, L.P.; Merck & Co., Inc.



2

Severity of Cognitive Deficits in Schizophrenia

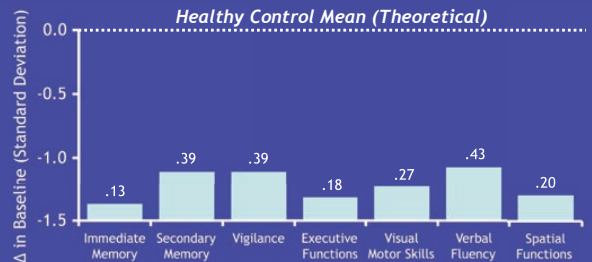
Mild	Moderate	Severe
Perceptual skills	Distractibility	Serial learning
Delayed recognition memory	Delayed recall	Executive functioning
Confrontation naming	Visuo-motor skills Immediate memory skills Working memory	Vigilance Motor speed Verbal fluency

Severity is measured as number of standard deviations (SD) below the mean for normal subjects (mild = 0.5 -1 SD; moderate = 1-2 SD; severe = 2-5 SD)



3

Effect Sizes* for Average Improvement in Cognition with Atypical Antipsychotics



* Values represent average improvement as measured by changes from baseline in standard deviations; figures are weighted for the study group size in each study and collapsed across all newer medications.

Harvey PD, Keefe RS. *Am J Psychiatry* 2001;158:176-184.



4

Cognitive Impairment, Functional Disability, and Negative Symptoms

- The US FDA has agreed to a regulatory pathway to approve pharmacological treatments for cognitive impairment
- This pathway includes assessment of disability as well
- Similar research designs would be used to treat persistent negative symptoms



5

Clinical Relevance of Cognitive Impairments

- Best single predictor of disability
- Relates to several different functional domains
 - Social
 - Independent living
 - Vocational
- Predicts medication adherence
- Correlates with subjective quality of life



6

Features of the Research Design

- Use of a consensus-derived cognitive battery
 - The MCCB
- Use of a co-primary outcomes measure
 - Either a performance-based assessment of functional skills or a structured interview
- Enrollment of clinically stable patients
 - To rule out “pseudospecificity”
- Long trial duration



7

The MATRICS Consensus Cognitive Battery (MCCB)

- MATRICS battery¹
 - Speed of processing
 - Attention/vigilance
 - Working memory
 - Verbal learning
 - Visual learning
 - Reasoning and problem solving
 - Used mean of Z-scores for an estimate of global neuropsychological performance
- UPSA-Brief²
 - Finances
 - Communication
- Advanced Finances³

1. Neuchterlein KH, Green MF. *MCCB-MATRICS Consensus Cognitive Battery Manual*. California, USA. MATRICS Assessment, Inc. 2006.
2. Mausbach BT, et al. *J Psychiatr Res* 2008;42:320-327.
3. Heaton RK, et al. *J Int Neuropsychol Soc* 2004;10:317-331.



8

Verbal Memory List Learning

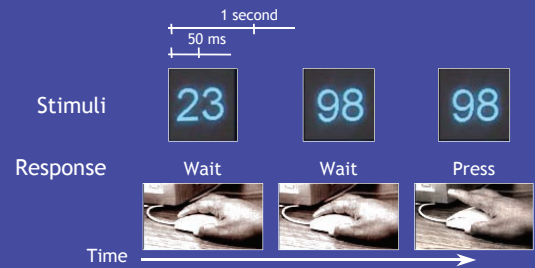
- Tester reads list of words aloud to the subject
 - List includes 16 words such as “wrench,” “trousers,” “oregano,” “cherries”
- Subject is asked to recall as many words as possible
- Normal controls recall an average 10/16 words vs. 6/10 for patients with schizophrenia
- When subjects are given the list 4 more times, normal controls will recall almost all of the words
- Patients with schizophrenia will not have the same rate of learning



9

Continuous Performance Test Identical Pairs (CPT-IP)

“Push down with your finger on the mouse button when you see the same number twice in a row”



10

Verbal Fluency

- Semantic fluency (category fluency)
 - Example: Name as many animals as possible in 60 seconds
- Patients with schizophrenia generate fewer words within the specified category, and they often produce words outside of the category



11

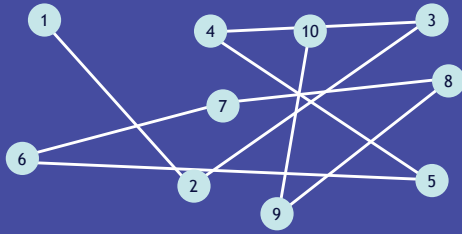
Processing Speed

- Can be measured with a variety of methods
 - Coding
 - Tracing



12

Example Tracing Test Trail Making Part A

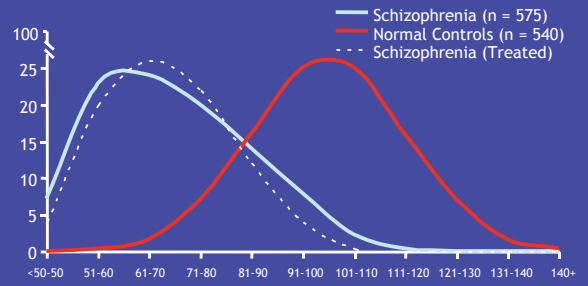


Note: This is simulation of the test, not an exact replica.

13



Normative Data Compared to a Schizophrenia Sample RBANS Total Scale Score Distribution



RBANS = Repeatable Battery for Assessment of Neuropsychological Status
Randolph C. *RBANS Manual-Repeatable Battery for the Assessment of Neuropsychological Status*; 1998.
Wilk CM, et al. *Schizophr Res* 2004;70:175-186.

14



Functional Co-Primary Measures Examples

- UCSD performance-based skills assessment
 - 5 functional domains, normed to 100-point scale
 - Communication
 - Emergency calls, rescheduling
 - Finance
 - Paying bills, making change
 - Planning/comprehension
 - Planning for an outing
 - Transportation
 - Reading transit maps
 - Home maintenance
 - Preparing meals

Mausbach BT, et al. *J Psychiatr Res* 2008;42:320-327.

15



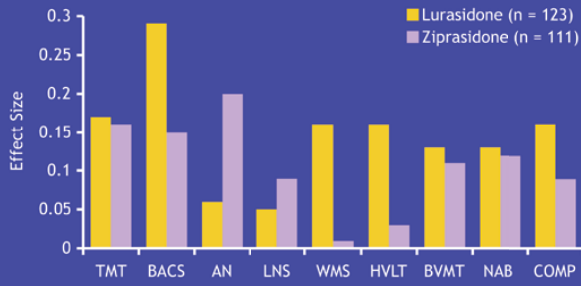
Functional Co-Primaries Interview-Based Measures

- Interviews and patients and/or informants
- Ask cognitively relevant questions
- The Schizophrenia Cognition Rating Scale (SCoRS)
 - 20 items, rated by the interviewer, the informant, and the patient, on a four-point (1-4) absent to severe scale, e.g.,
 - Do you have difficulty with remembering names of people you know?
 - Do you have difficulty following a TV show?
 - The interviewer also generates a global rating based on the results of both interviews and all 20 ratings

16



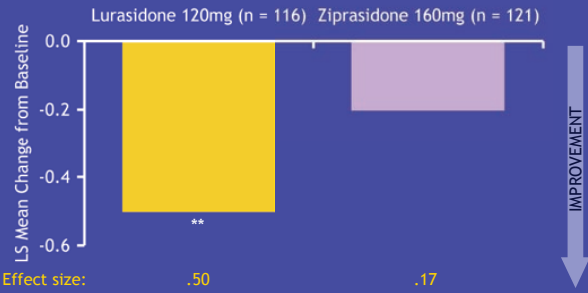
Effect Sizes for Improvements on MCCB *Lurasidone vs. Ziprasidone*



Note: 3-week, outpatient study in stable patients with schizophrenia
Harvey PD, et al. Poster presented at ICOSR, 2009.



Schizophrenia Cognition Rating Scale (SCoRS) Mean Change



** p < .01 from baseline
NS (p = .161) between groups (ITT, LOCF)
Harvey PD, et al. Poster presented at ICOSR, 2009.



Persistent Negative Symptoms

- Defined as symptoms still moderate or severe after improvement of positive symptoms
- Would be treated with add-on pharmacotherapy or psychosocial interventions (e.g., clozapine for suicidality)
- Same general research design as for cognitive symptoms



Clinical Importance of Persistent Negative Symptoms

- Associated with several aspects of impairment in functional outcomes
- Social activities most affected
 - Persistent social avoidance
 - Social anhedonia
- May be present in 30-60% of people with schizophrenia, depending on the definition



The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST)

- Randomized, double-blind study of glycine, d-cycloserine, vs. placebo
- Clinically stable patients with moderate or more severe negative symptoms
- SANS as the outcomes measure
- Cognitive outcomes measured with a battery similar to MCCB
- Results were negative

Buchanan RW, et al. *Am J Psychiatry* 2007;164:1593-1602.



What Are the Pharmacological Mechanisms of Interest to Add to Atypical Antipsychotic Medications?

- Dopamine D₁ agonists
- Nicotinic
 - $\alpha 7$; $\alpha 4\beta 3$
- Muscarinic
 - M₁; AChE inhibitors
- Glutamatergic
 - NMDA; AMPA; precursors, uptake
- 5HT_{1A}, 5HT₆, and 5HT₇
- NE
 - Agonists, transport modulation

22



Summary

- Cognitive symptoms are associated with significant disability in patients with schizophrenia
- Available medications do not provide sufficient improvement in cognition
- Several cognitive measures have recently been incorporated into clinical testing
- Novel drugs and targets are promising

23



Bibliography

Buchanan RW, Javitt DC, Marder SR, et al. The Cognitive and Negative Symptoms in Schizophrenia Trial (CONSIST): the efficacy of glutamatergic agents for negative symptoms and cognitive impairments. *Am J Psychiatry* 2007;164:1593-1602.

Harvey PD, Keefe RS. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. *Am J Psychiatry* 2001; 158:176-84.

Harvey PD, Loebel A, Ogasa M, Cucciario J, Keefe R. A double-blind comparison of the effects of lurasidone and ziprasidone on cognitive function: differential sensitivity of performance-based and interview measures. Presented at the Annual meeting of the International Congress of Schizophrenia Research; 2009 Mar 28-Apr 1; San Diego, CA.

Heaton RK, Marcotte TD, Mindt MR, et al. The impact of HIV-associated neuropsychological impairment on everyday functioning. *J Int Neuropsychol Soc* 2004;10:317-331.

Mausbach BT, Bowie CR, Harvey PD, et al. Usefulness of the UCSD performance-based skills assessment (UPSA) for predicting residential independence in patients with chronic schizophrenia. *J Psychiatric Res* 2008;42:320-327.

Neuchterlein KH, Green MF. MCCB-MATRICES Consensus Cognitive Battery Manual. Los Angeles, California; MATRICES Assessment, Inc., 2006.

Randolph C. Repeatable Battery for the Assessment of Neuropsychological Status (RBANSTM). Oxford, UK; Pearson Education, LTD, 1998.

Wilk CM, Gold JM, Humber K, Dickerson F, Fenton WS, Buchanan RW. Brief cognitive assessment in schizophrenia: normative data for the Repeatable Battery for the Assessment of Neuropsychological Status. *Schizophr Res* 2004; 70:175-186.

Development of New Agents for the Treatment of Schizophrenia

Late Stage and Recently Approved Antipsychotic Agents Steven G. Potkin, MD

In keeping with the urgent need for advances in the pharmacotherapy of schizophrenia, a number of medications are in various stages of the pipeline on their way to seeking FDA approval. Some of these agents are simply new formulations of existing medications, others have been proposed as adjunctive or combination therapies, while still others represent novel pharmacologic approaches to management. Faculty in this symposium will review agents in Phase III testing as well as those that have recently been through FDA review, with an emphasis on the way in which specific agents are expected to advance care and improve outcome. Data from clinical trials on these agents will be reviewed, and, in the case of those with novel mechanisms of action, the pharmacology of the agents will be described. Faculty will lead an interactive discussion about recently approved and emerging agents and their integration into practice. Patient cases will be used to illustrate the ways in which newly available medications may address existing treatment gaps.

Late Stage and Recently Approved Antipsychotic Agents

Steven G. Potkin, MD
Professor, Department of Psychiatry
Robert R. Sprague Chair in Brain Imaging
Director, UCI Brain Imaging Center
University of California, Irvine

1

AMERICAN PSYCHIATRIC ASSOCIATION
2009 - SAN FRANCISCO, CALIFORNIA

Steven G. Potkin, MD Disclosures

- **Research/Grants:** AstraZeneca Pharmaceuticals LP; Bioline; Brigham and Women's Hospital; Bristol-Myers Squibb Company; Dainippon Sumitomo Pharma; Elan Pharmaceuticals, Inc.; Forest Laboratories, Inc.; Fujisawa; Janssen, L.P.; Eli Lilly and Company; Merck & Co., Inc.; National Institutes of Health; Novartis Pharmaceuticals Corporation; Ono Pharmaceutical USA, Inc.; Organon/Schering Plough Corporation; Otsuka America Pharmaceutical, Inc.; Pfizer Inc.; Solvay Pharmaceuticals, Inc.; Roche; Vanda Pharmaceuticals; Wyeth Pharmaceuticals
- **Speakers Bureau:** AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; The International Society for CNS Clinical Trials and Methodology; Novartis Pharmaceuticals Corporation; Pfizer Inc.



2

AMERICAN PSYCHIATRIC ASSOCIATION
2009 - SAN FRANCISCO, CALIFORNIA

Steven G. Potkin, MD Disclosures

- **Consultant/Advisory Board:** American Psychiatric Association; AstraZeneca Pharmaceuticals LP; Bioline; Ceregene, Inc.; Cortex Pharmaceuticals, Inc.; Dainippon Sumitomo Pharma; Eli Lilly and Company; Janssen, L.P.; Novartis Pharmaceuticals Corporation; Organon/Schering Plough Corporation; Otsuka America Pharmaceutical, Inc.; Pfizer Inc.; Roche; Vanda Pharmaceuticals
- **Stockholder:** None
- **Other Financial Interest:** None



3

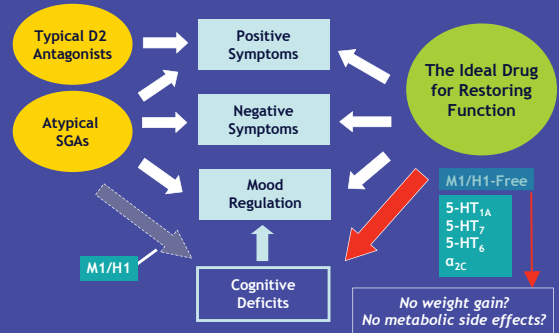
Is Remission a Realistic Goal for Our Patients with Schizophrenia?

4

What Functional Domains and Receptor Targets Do We Need to Affect to Support Remission?

7

Functional Domains and Receptor Targets in Schizophrenia



8

Receptor Binding Profiles

Binding Affinities (K _i : nM)	HAL	CLO ³	RIS ³	PAL ¹¹	OLZ ³	QUE ³	ZIP ⁴	ARI ⁴	ILO ⁶⁻⁸	ASE ⁵	LUR ⁹	SER ^{7,10}
D ₂ Antipsychotic	4.4 ¹	110	2.9	6.6	14	200	3	3.3	21.4	8.9	1.7	7.4
5-HT _{2A} Antipsychotic/Attenuate EPS	158 ²	9.2	0.2	0.83	5.8	340	0.3	34	5.6	10.1	2.0	0.85
5-HT _{2B} Mood/Cognition	>1000 ²	120	260	1030	2700	320	8.5	2.1	93.1	8.6	6.8	2200
5-HT _{1A} Mood/Cognition	400 ⁺²	18	6.6	6.8	110	310	6.0	10	112	9.9	0.50	na
α _{2c} Cognition	360 ¹	16	11	2.7	210	350	400	38	16.2	8.9	11	na

References available in supplemental bibliography section of course guide.

Receptor Binding Profiles

Binding Affinities (K _i : nM)	HAL ¹	CLO ²	RIS ²	PAL ⁹	OLZ ²	QUE ²	ZIP ³	ARI ³	ILO ^{3,7}	ASE ⁴	LUR ⁸	SER ¹
Histamine H ₁ impair cognition, sedation, weight gain	1400	2.0	3.5	34	3.8	9.0	510	67	6.3	9.0	>1000	5700
ACh M1 impair cognition	13000	4.9	>1000		7.6	210	>1000	>1000	4898	5.1	>1000	11000
α ₁ Orthostatic hypotension, sedation	530	7	2	11	19	7	2	26	8.4	8.9	48	1.4

References available in supplemental bibliography section of course guide.

Asenapine

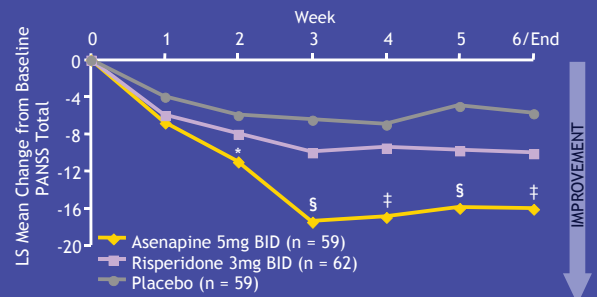
- Discovered by Organon
- Clinical profile
 - Efficacy shown in schizophrenia
 - Minimal EPS risk
 - Weight and lipid neutral
 - ? Potential role in treatment of negative symptoms
 - Sublingual formulation requires BID dosing; minimal dose titration required
- Current status—phase 3 program in schizophrenia completed, under review at FDA

Agent not approved by the US Food and Drug Administration.

11



Asenapine in Acute Schizophrenia PANSS Total Score



Agent not approved by the US Food and Drug Administration.
* $p < .05$, asenapine vs. placebo; † $p \leq .005$, asenapine vs. placebo;
§ $p = .001$, asenapine vs. placebo
Potkin SG, et al. *J Clin Psychiatry* 2007;68:1492-1500.

12



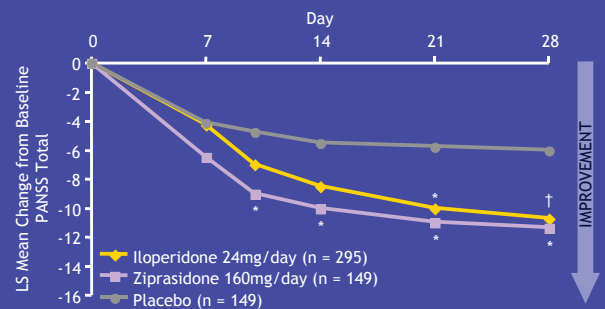
Iloperidone

- Discovered by Hoechst Marion Roussel
- Clinical profile
 - Efficacy shown in schizophrenia
 - Minimal EPS risk
 - Weight and lipid neutral
 - QTc interval prolongation
 - Genetic markers may be associated with efficacy and safety parameters
 - BID dosing; dose titration required
- Current status—recently approved by the FDA

13



Iloperidone in Acute Schizophrenia PANSS Total Score

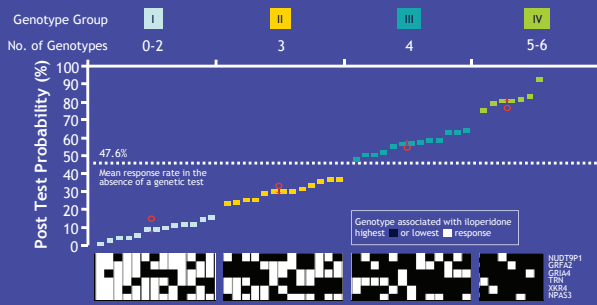


* $p < .05$ (2-tailed) vs. placebo; † $p < .01$ (2-tailed) vs. placebo
Cutler AJ, et al. *J Clin Psychopharmacology* 2008;28:S20-S28.

14



Genotypes Associated with Enhanced Clinical Response to Iloperidone



Volpi S, et al. *J Clin Psychiatry* 2009;doi:JCPJ08-M04391R.

15

Lurasidone

- Discovered by Dainippon Sumitomo Pharma (DSP)
- Clinical profile
 - Efficacy shown in schizophrenia
 - Minimal EPS risk
 - Weight and lipid neutral
 - ? Potential role in treatment of cognitive impairment and depressive conditions
 - QD dosing; no dose titration required
- Current status—late phase 3 trials ongoing in schizophrenia

Agent not approved by the US Food and Drug Administration.

16

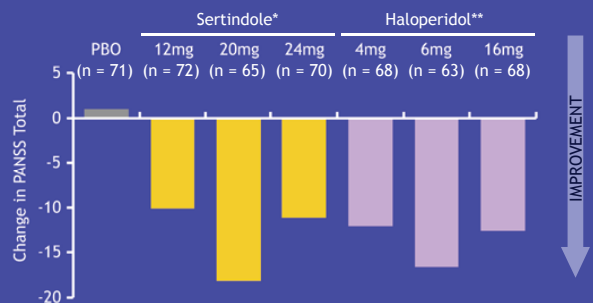
Sertindole

- Discovered by Lundbeck
- Clinical profile
 - Efficacy shown in schizophrenia
 - Minimal EPS
 - May have role in the treatment of suicidality
 - QTc interval prolongation therefore not first-line treatment
 - Dose titration required
- Current status—application voluntarily withdrawn in 1998 due to QTc-related concerns, currently under re-review at FDA

Agent not approved by the US Food and Drug Administration.

18

Sertindole in Acute Schizophrenia



Agent not approved by the US Food and Drug Administration.
Zimbroff DL, et al. *Am J Psychiatry* 1997;154:782-791.

19

Summary

- Staying on medication can have accruing benefit, including remission
- There is variability in individual patients' responses to medications - one size does not fit all
- Patients and prescribers need access to all medications



20

Summary (cont.)

- CNS drug development is ongoing but has met with some challenges
- Cognition and negative symptoms are important indicators in the quality of life of patients
 - "...Treatment providers should consider evaluating patients' cognitive status using objective neuropsychological measures whenever possible. With respect to treatment effects...treatments with greater positive effects on cognition are urgently needed."¹
- Emerging treatments, some with unique binding characteristics or novel mechanism of action, may improve outcome for patients



1. EUFEST Study Group. 2009.

21

Panel Discussion/Q&A



22

Closing Comments

- There is variability across patients in their responses to medications
- CNS drug development is ongoing but has met with some challenges
- Cognition and negative symptoms are important indicators in the quality of life of patients
- Staying on medication has benefit
- Physicians need access to all medications
- Emerging treatments may improve outcome for patients



23

Supplemental Bibliography

Slide Title: Receptor Binding Profiles

1. Ma J, Ye N, Cohen BM. Expression of noradrenergic α_1 , serotonergic 5HT_{2a} and dopaminergic D₂ receptors neurons activated by typical and atypical antipsychotic drugs. *Prog Neuropsychopharmacol Biol Psychiatry* 2006;30:647-657.
2. Thiesen FM, Haberhausen M, Firnges MA, et al. No evidence for binding of clozapine, olanzapine and/or haloperidol to selected receptors involved in body weight regulation. *Pharmacogenomics J* 2007;275-281.
3. Bymaster FP, Calligaro DO, Falcone JF, et al. Radioreceptor binding profile of the atypical antipsychotic olanzapine. *Neuropsychopharmacology* 1996;14:87-96.
4. Wood MD, Scott C, Clarke K, et al. Pharmacological profile of antipsychotics at monoamine receptors: atypicality beyond 5-HT_{2a} receptor blockade. *CNS Neurol Disord* 2006;5:445-452.
5. Shahid M, Walker GB, Zorh SH, Wong EHF. Asenapine: a novel psychopharmacologic agent with a unique human receptor signature. *J Psychopharmacol* 2009;23:65-73.
6. Kongsamut S, Roehr JE, Cai J, et al. Iloperidone binding to human and rat dopamine and 5-HT receptors. *Eur J Pharmacol* 1996; 317:417-423.
7. Sanchez C, Arnt J. In vivo assessment of 5-HT₂ and 5-HT_{2c} antagonist properties of newer antipsychotics. *Behav Pharmacol* 2000;11:291-298.
8. Kalkman HO, Subramanian N, Hoyer D. Extended radioligand binding profile of iloperidone: a broad spectrum dopamine/serotonin/norepinephrine receptor antagonist for the management of psychotic disorders. *Neuropsychopharmacology* 2001;35:904-914.
9. Data on file.
10. Spina E, Zoccali R. Sertindole: pharmacological and clinical profile and role in the treatment of schizophrenia. *Exp Opin Drug Metab Toxicol* 2008;4:629-638.
11. Heylen L, Gys L, Meulders G, et al. Comparative in vitro receptor and transporter binding profile and neurotransmitter uptake of paliperidone and risperidone, J&J Pharmaceutical Research & Development, June 8, 2006.

Slide Title: Receptor Binding Profiles

1. Sanchez C, Arnt J, Dragsted N, et al. Neurochemical and in vivo pharmacological profile of sertindole, a limbic-sensitive neuroleptic compounds. *Drug Dev Res* 1991;22:239-242.
2. Bymaster FP, Calligaro DO, Falcone JF, et al. Radioreceptor binding profile of the atypical antipsychotic olanzapine. *Neuropsychopharmacology* 1996;14:87-96.
3. Wood MD, Scott C, Clarke K, et al. Pharmacological profile of antipsychotics at monoamine receptors: atypicality beyond 5-HT_{2a} receptor blockade. *CNS Neurol Disord* 2006;5:445-452.
4. Shahid M, Walker GB, Zorh SH, Wong EHF. Asenapine: a novel psychopharmacologic agent with a unique human receptor signature. *J Psychopharmacol* 2009;23:65-73.
5. Kongsamut S, Roehr JE, Cai J, et al. Iloperidone binding to human and rat dopamine and 5-HT receptors. *Eur J Pharmacol* 1996; 317:417-423.
6. Sanchez C, Arnt J. In vivo assessment of 5-HT₂ and 5-HT_{2c} antagonist properties of newer antipsychotics. *Behav Pharmacol* 2000;11:291-298.
7. Kalkman HO, Subramanian N, Hoyer D. Extended radioligand binding profile of iloperidone: a broad spectrum dopamine/serotonin/norepinephrine receptor antagonist for the management of psychotic disorders. *Neuropsychopharmacology* 2001;35:904-914.
8. Data on file.
9. Heylen L, Gys L, Meulders G, et al. Comparative in vitro receptor and transporter binding profile and neurotransmitter uptake of paliperidone and risperidone, J&J Pharmaceutical Research & Development, June 8, 2006.

Bibliography

- Bymaster FP, Calligaro DO, Falcone JF, et al. Radioreceptor binding profile of the atypical antipsychotic olanzapine. *Neuropsychopharmacology* 1996;14:87-96.
- Cutler AJ, Kalali AH, Weiden PJ, Hamilton J, Wolfgang CD. Four-week, double-blind, placebo- and ziprasidone-controlled trial of iloperidone in patients with acute exacerbations of schizophrenia. *J Clin Psychopharmacol* 2008;28:S20-S28.
- EUFEST: Atypical antipsychotics offer no advantage in improving cognitive function in schizophrenia. Available at: <http://www.medscape.com/viewarticle/701876>. Accessed May 1, 2009.
- Heylen L, Gys L, Meulders G, et al. Comparative in vitro receptor and transporter binding profile and neurotransmitter uptake of paliperidone and risperidone, J&J Pharmaceutical Research & Development, June 8, 2006.
- Kalkman HO, Subramanian N, Hoyer D. Extended radioligand binding profile of iloperidone: a broad spectrum dopamine/serotonin/norepinephrine receptor antagonist for the management of psychotic disorders. *Neuropsychopharmacology* 2001;35:904-914.
- Kongsamut S, Roehr JE, Cai J, et al. Iloperidone binding to human and rat dopamine and 5-HT receptors. *Eur J Pharmacol* 1996; 317:417-423.
- Ma J, Ye N, Cohen BM. Expression of noradrenergic α_1 , serotonergic 5HT_{2a} and dopaminergic D₂ receptors neurons activated by typical and atypical antipsychotic drugs. *Prog Neuropsychopharmacol Biol Psychiatry* 2006;30:647-657.
- Nakamura M, Ogasa M, Guarino J, et al. Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009; in press.
- Potkin SG, Cohen, M, Panagides. Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. *J Clin Psychiatry* 2007;68:1492-1500.
- Potkin SG, Litman RE, Torres R, Wolfgang CD. Efficacy of iloperidone in the treatment of schizophrenia. Initial Phase 3 studies. *J Clin Psychopharmacol* 2008;28(Suppl 1):S4-S10.
- Potkin SG, Weiden PJ, Loebel AD, Warrington LE, Watsky EJ, Sui CO. Remission in schizophrenia: 196-week, double-blind treatment with ziprasidone vs. haloperidol. *Int J Neuropsychopharmacology* 2009; in press.
- Perquin L, Steinert T. A review of the efficacy, tolerability, and safety of sertindole in clinical trials. *CNS Drugs* 2004;18(Suppl 2):19-30.
- Sanchez C, Arnt J. In vivo assessment of 5-HT₂ and 5-HT_{2c} antagonist properties of newer antipsychotics. *Behav Pharmacol* 2000;11:291-298.
- Sanchez C, Arnt J, Dragsted N, et al. Neurochemical and in vivo pharmacological profile of sertindole, a limbic-sensitive neuroleptic compounds. *Drug Dev Res* 1991;22:239-242.
- Shahid M, Walker GB, Zorh SH, Wong EHF. Asenapine: a novel psychopharmacologic agent with a unique human receptor signature. *J Psychopharmacol* 2009;23:65-73.
- Spina E, Zoccali R. Sertindole: pharmacological and clinical profile and role in the treatment of schizophrenia. *Exp Opin Drug Metab Toxicol* 2008;4:629-638.
- Thiesen FM, Haberhausen M, Firnges MA, et al. No evidence for binding of clozapine, olanzapine and/or haloperidol to selected receptors involved in body weight regulation. *Pharmacogenomics J* 2007;275-281.
- Wood MD, Scott C, Clarke K, et al. Pharmacological profile of antipsychotics at monoamine receptors: atypicality beyond 5-HT_{2a} receptor blockade. *CNS Neurol Disord* 2006;5:445-452.
- Zimbroff DL, Kane JM, Tamminga CA, Daniel DG, Mack RJ, Wozniak PJ, Sebree TB, Wallin BA, Kashkin KB, and the Sertindole Study Group. Controlled, dose-response study of sertindole and haloperidol in the treatment of schizophrenia. *Am J Psychiatry* 1997;154:782-791.