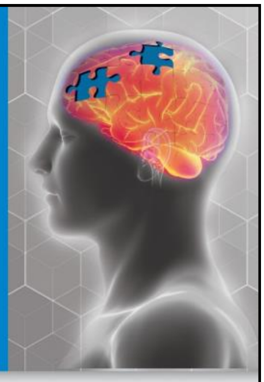
PSYCH FORUM™

Paradigm Shifts in the Biology, Diagnosis and Treatment of **Schizophrenia**

CME MEETING SERIES



Saturday, August 9, 2014

Philadelphia, PA

COURSE CHAIR

Henry A. Nasrallah, MD

This continuing medical education activity is provided by the University of Cincinnati

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We gratefully acknowledge the following companies for their educational grants in support of this educational activity.
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SCHIZOPHRENIA: Clinical and Neurobiological Advances

Henry A. Nasrallah, MD

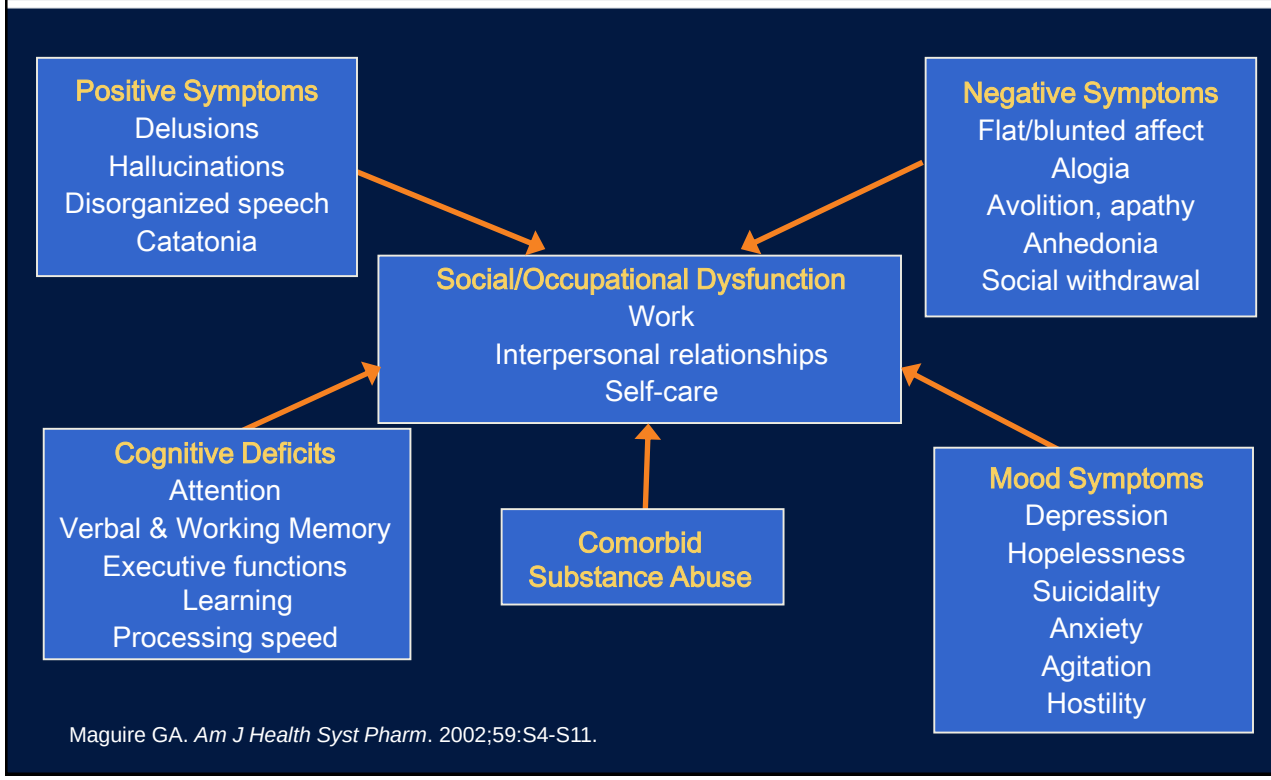
The Sydney W. Souers Endowed Chair
Professor and Chairman
Department of Neurology and Psychiatry
Saint Louis University School of Medicine

Learning Objectives

- Review the genetic and nongenetic factors in schizophrenia
- Recognize the brain structural and functional MRI changes associated with schizophrenia
- Discuss the neuroinflammation and oxidative stress that occur during psychotic episodes
- Review the development of biomarkers in the schizophrenia syndrome that may be used in the future as lab tests for its various biological subtypes

Neuropsychiatric Features of Schizophrenia

Features of Schizophrenia

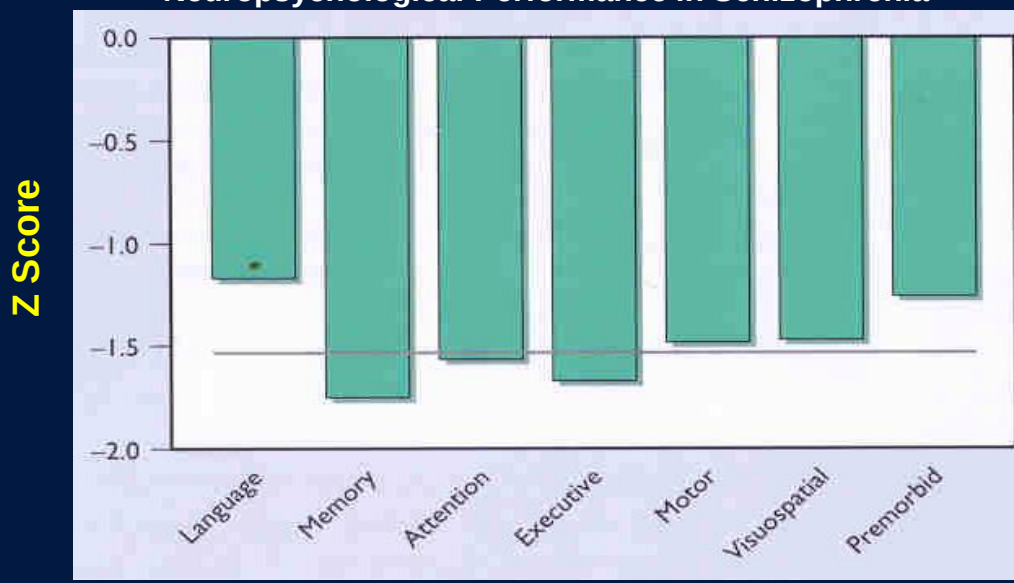


Maguire GA. *Am J Health Syst Pharm*. 2002;59:S4-S11.

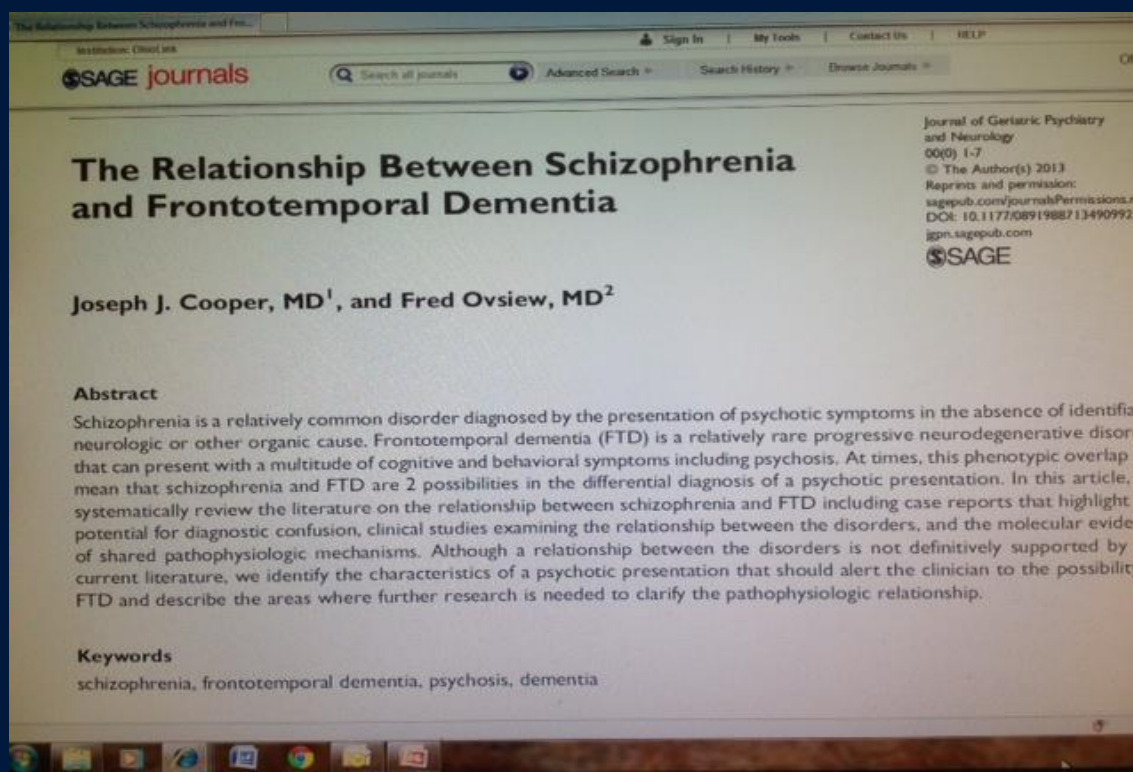
Neurocognitive Impairment in Schizophrenia

Cognitive Deficits in First-Episode Schizophrenia

Neuropsychological Performance in Schizophrenia



Bilder RM et al. Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. *Am J Psychiatry.* 2000;157:549-559.



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Journal of Geriatric Psychiatry and Neurology
00(0) 1-7

DOI: 10.1177/0891988713490992
jgpn.sagepub.com
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The Relationship Between Schizophrenia and Frontotemporal Dementia

Joseph J. Cooper, MD[1], and Fred Ovsiew, MD[2]

Abstract

Schizophrenia is a relatively common disorder diagnosed by the presentation of psychotic symptoms in the absence of identifiab neurologic or other organic cause. Frontotemporal dementia (FTD) is a relatively rare progressive neurodegenerative disord that can present with a multitude of cognitive and behavioral symptoms including psychosis. At times, this phenotypic overlap c mean that schizophrenia and FTD are 2 possibilities in the differential diagnosis of a psychotic presentation. In this article, v systematically review the literature on the relationship between schizophrenia and FTD including case reports that highlight t potential for diagnostic confusion, clinical studies examining the relationship between the disorders, and the molecular eviden of shared pathophysiologic mechanisms. Although a relationship between the disorders is not definitively supported by t current literature, we identify the characteristics of a psychotic presentation that should alert the clinician to the possibility FTD and describe the areas where further research is needed to clarify the pathophysiologic relationship.

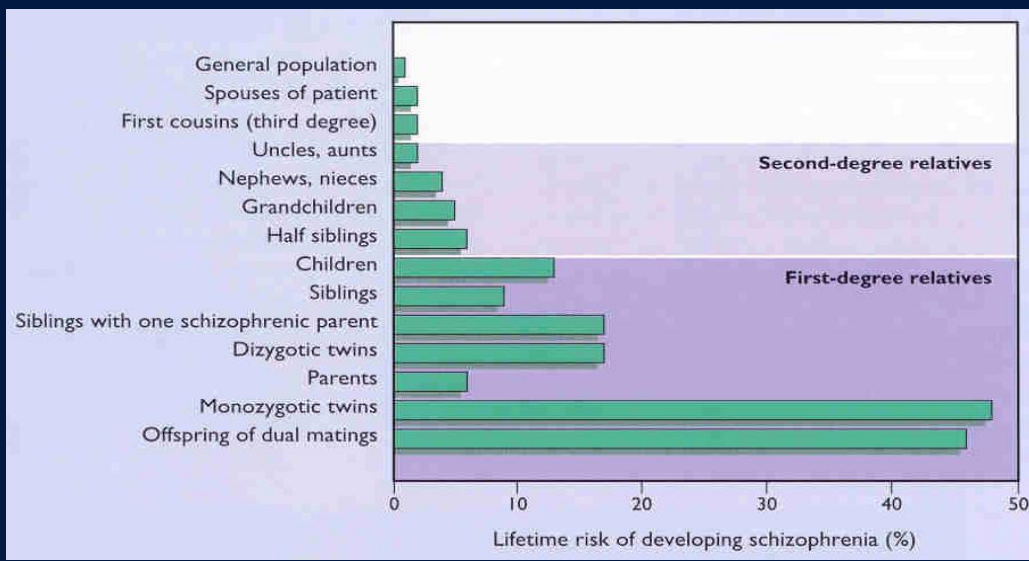
Keywords

schizophrenia, frontotemporal dementia, psychosis, dementia

Recent Advances in the Neurobiology of Schizophrenia

Neurogenetics of Schizophrenia

Lifetime Risk of Developing Schizophrenia



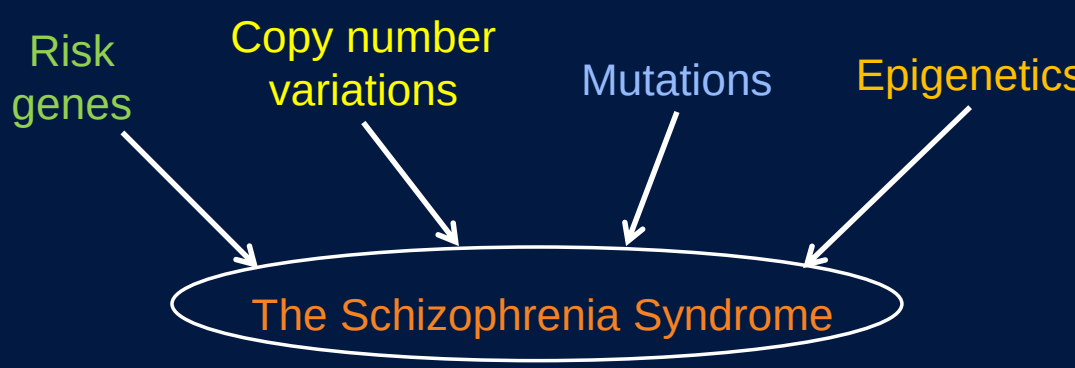
Stefan M, et al. *An Atlas of Schizophrenia*. CRC Press; 2002.
Pennisi E, *Science* 2012; 337: 1159-1160

Genes and Brain Development

- There are about 20,000 genes on the 23 chromosome pairs in humans
- 50% of all the human genes (10,000 genes) are dedicated to brain development or are expressed only in the brain
- The rest of the body (about 200 types of tissue) share the other 10,000 genes

Personal communication

Neurogenetics of Schizophrenia



Corvin A. *Schizophr Bull*. 2013;39(3):490-495.

Risk Genes for Schizophrenia: The Majority Are Related to Glutamate Pathways

Genes for:

Dysbindin (dystrobrevin binding protein 1 or DTNBP1)	ERBB4
Neuregulin (NRG1)	FEZ1
DISC1 (disrupted in schizophrenia 1)	MUTED
DAOA (d-amino acid oxidase activator; G72/G30)	MRDS1 (OFCC1)
DAO (d-amino acid oxidase)	BDNF (brain-derived neurotrophic factor)
RGS4 (regulator of G protein signaling 4)	Nur77
COMT (Catechol-O-methyl transferase)	MAO-A (monoamine oxidase A)
CHRNA7 (alpha-7-nicotinic cholinergic receptor)	Spinophilin
GAD1 (glutamic acid decarboxylase 1)	Calcyon
GRM3 (mGluR3)	Tyrosine hydroxylase
PPP3CC	Dopamine-D2 receptor (D2R)
PRODH2	Dopamine-D3 receptor (D3R)
AKT1	

Nasrallah HA; The Neurology of Schizophrenia, edited by HA Nasrallah and DR Weinberger, Elsevier, 1986

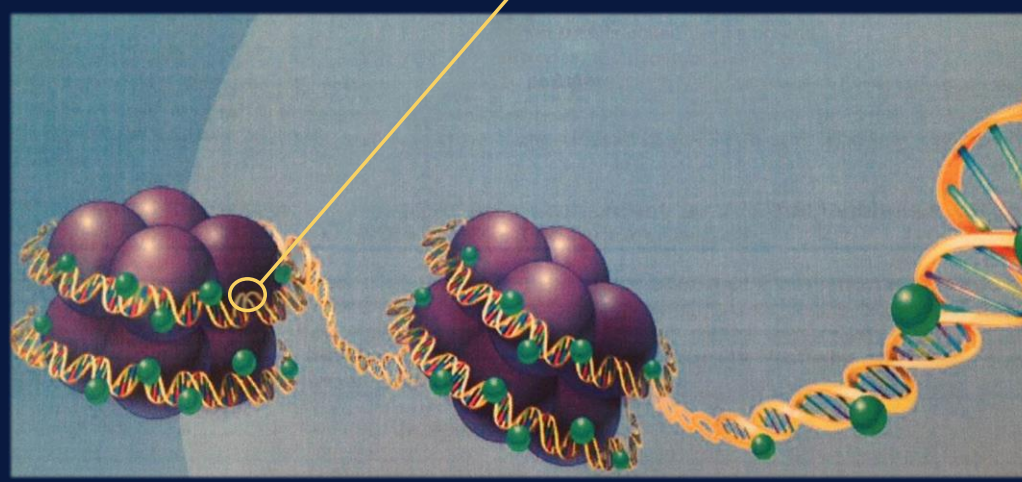
Can EPIGENETICS Help Prevent Schizophrenia?

SILENCING culprit genes

or

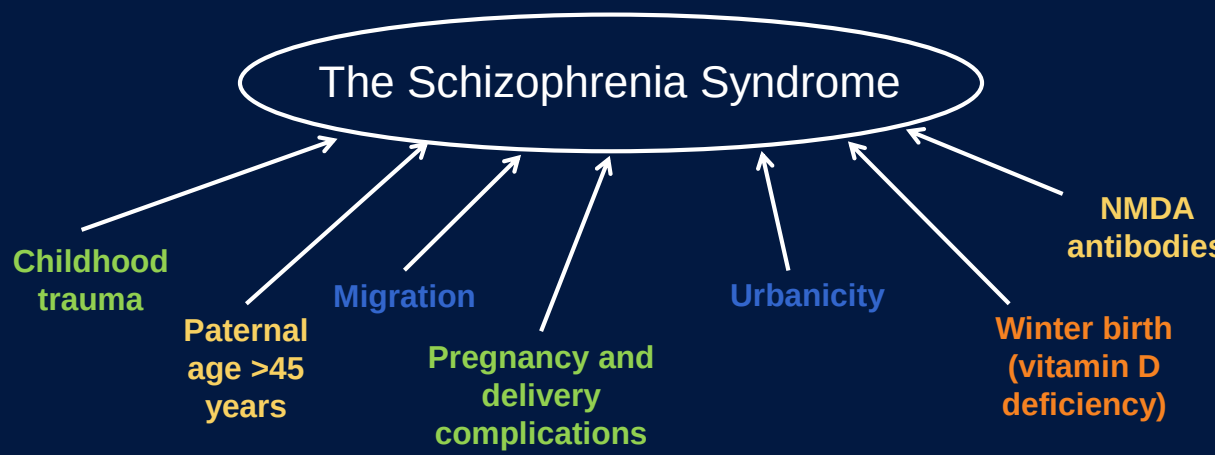
EXPRESSING protective genes

When DNA is coiled tightly around the histones, the genes within it tend to be inaccessible and silent



NIMH online communication. 2011

Nongenetic (Environmental) Factors Associated With the Schizophrenia Syndrome



van Os J, et al. *Nature*. 2010;468(7321):203-212.

SCHIZOPHRENIA IS ASSOCIATED WITH MANY GENETIC AND ENVIRONMENTAL FACTORS.

THUS, SCHIZOPHRENIA IS A VERY HETEROGENEOUS SYNDROME!

Tandon R, et al. *Schizophr Res*. 2009;110:1-1123.

Neuroimaging Findings in the Schizophrenia Syndrome

- Structural changes MRI
  - Numerous hypoplastic regions, especially frontal, temporal, and limbic cortices
- Neurochemical changes on MRS
  - Abnormalities in NAA using proton spectroscopy and in high-energy phosphates (ADP, ATP) using 31p spectroscopy
- Aberrations in brain activity on ʃ MRI
  - Especially low frontal blood flow
- White matter changes on DTI
  - Abnormalities in myelin integrity in white matter tracts, leading to widespread disconnectivity both intra- and interhemispheric. The initial pathology is brain edema (swelling) due to excessive extra-cellular water in both white and gray matter, detected with free-water imaging. This triggers a neuroinflammatory response.

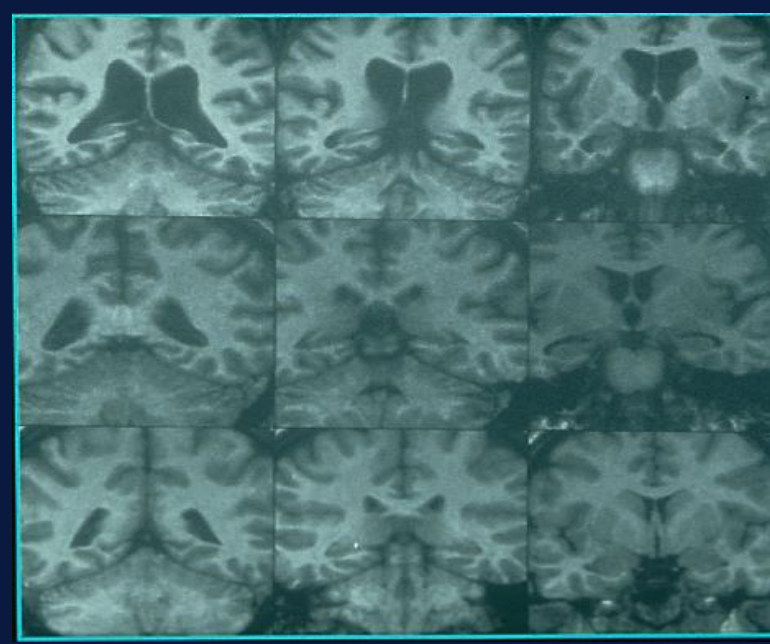
Fitzsimmons J, et al. *Curr Opin Psychiatry*. 2013;26(2):172-187. Zierhut KC, et al. *Brain*. 2013;136(Pt 3):804-814. Szulc A, et al. *Curr Med Chem*. 2013;20(3):414-427. Pasternak O, et al. *J Neurosci*. 2012;32(48):17365-17372.

Impaired Neuroplasticity in the Schizophrenia Syndrome

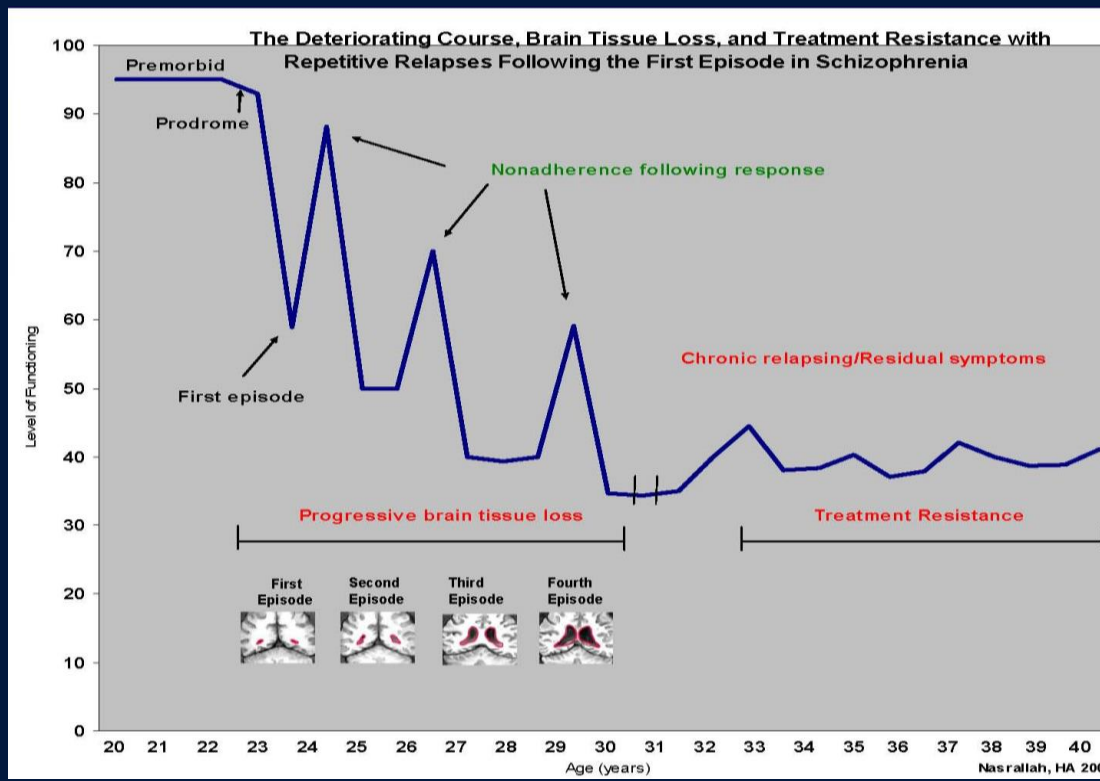
- Several perturbations of neuroplasticity in schizophrenia
  - Increased apoptosis (cell death)
  - Decreased neurogenesis (in the hippocampus and SVZ)
  - Low neurotropic factors (NGF, BDNF, etc)
- The risk genes of schizophrenia are involved in regulating neuroplasticity.
  - DISC-1
  - Neuregulin/ErbB4
  - Dysbindin
  - AKt
- Impaired neuroplasticity disrupts neuronal development, neurotransmission, and signaling pathways, especially of the key neurotransmitters glutamate and GABA.

Balu DT, et al. *Neurosci Biobehav Rev*. 2011;35(3):848-870.

Progressive MRI Changes After Multiple Psychotic Relapses in a Man With Schizophrenia Over Several Years

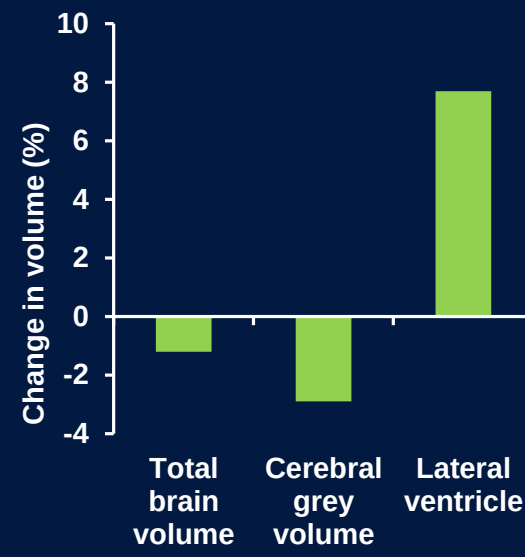


Nasrallah HA and Smeltzer DJ: Contemporary Diagnosis and management of Schizophrenia. Second Edition, Handbooks in Health Care Co., Newtown, PA 2011


The Deteriorating Course, Brain Tissue Loss, and Treatment Resistance with Repetitive Relapses Following the First Episode in Schizophrenia
Premorbid
Prodrome
First episode
Nonadherence following response
Chronic relapsing/Residual symptoms
Progressive brain tissue loss
Treatment Resistance
First Episode
Second Episode
Third Episode
Fourth Episode
Level of Functioning
Age (years)
Nasrallah, HA 2009

Brain Volume Changes in First-episode Schizophrenia: A 1-year Follow-up Study

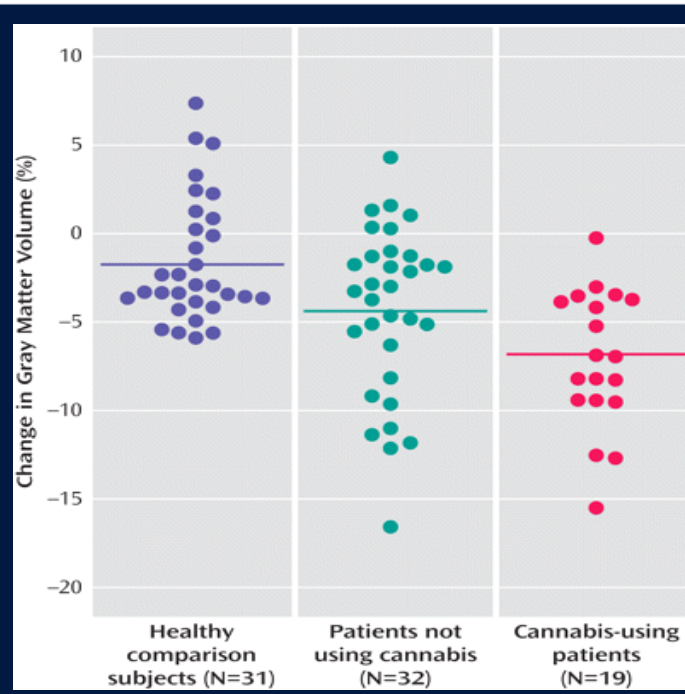
- First-episode schizophrenia (n=34) and matched healthy controls (n=36)
- MRI obtained at inclusion and after 1 year
- Outcome measured at 2 years
- Total brain volume and cerebral gray volume significantly decreased and lateral ventricle volume significantly increased in patients compared with controls
- Decrease in global gray matter volume significantly correlated with outcome and, independent of that, with higher cumulative dosage of antipsychotic medication



MRI, magnetic resonance imaging

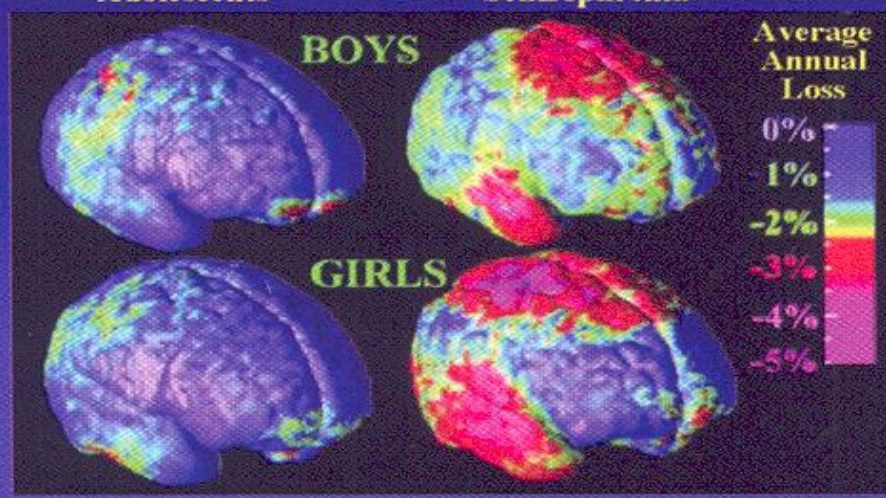
Adapted from Cahn W, et al. *Arch Gen Psychiatry*. 2002;59:1002-1010.

Gray Matter Loss and Marijuana Use



Rais M, et al. *Am J Psychiatry*. 2008;165(4):490-496.

Rate of Gray Matter Loss in Schizophrenia and Control Subjects



Thompson PM, et al. *Proc Natl Acad Sci USA*. 2001;98(20):11650-11655.

Slide courtesy of Martha Shenton, PhD

Bipolar Disorders 2009: 11: 11–18

BIPOLAR DISORDERS

Original Article

White matter abnormalities in bipolar disorder and schizophrenia detected using diffusion tensor magnetic resonance imaging

Sussmann JE, Lymer GKS, McKirdy J, Moorhead TWJ, Muñoz Maniega S, Job D, Hall J, Bastin ME, Johnstone EC, Lawrie SM, McIntosh AM. White matter abnormalities in bipolar disorder and schizophrenia detected using diffusion tensor magnetic resonance imaging.
Bipolar Disord 2009: 11: 11–18. © 2009 The Authors Journal compilation © 2009 Blackwell Munksgaard

Objectives: Strong qualitative and quantitative evidence exists of white matter abnormalities in both schizophrenia and bipolar disorder (BD). Diffusion tensor imaging (DTI) studies suggest altered connectivity in both disorders. We aim to address the diagnostic specificity of white matter abnormalities in these disorders.

Methods: DTI was used to assess white matter integrity in clinically stable patients with familial BD (n = 42) and familial schizophrenia (n = 28), and in controls (n = 38). Differences in fractional anisotropy (FA) were measured using voxel-based morphometry and automated region of interest analysis.

Results: Reduced FA was found in the anterior limb of the internal capsule (ALIC), anterior thalamic radiation (ATR), and in the region of the uncinate fasciculus in patients with BD and those with schizophrenia compared with controls. A direct comparison between patient groups found no significant differences in these regions. None of the findings were associated with psychotropic medication.

Conclusions: Reduced integrity of the ALIC, uncinate fasciculus, and ATR regions is common to both schizophrenia and BD. These results imply an overlap in white matter pathology, possibly relating to risk factors common to both disorders.

Jessika E Sussmann[a], G Katherine S Lymer[a,b], James McKirdy[a], T William J Moorhead[a], Susana Muñoz Maniega[b], Dominic Job[a], Jeremy Hall[a], Mark E Bastin[c], Eve C Johnstone[a], Stephen M Lawrie[a] and Andrew M McIntosh[a]

[a]Division of Psychiatry, University of Edinburgh, Royal Edinburgh Hospital, [b]SFC Brain Imaging Research Centre, [c]Medical and Radiological Sciences, University of Edinburgh, Western General Hospital, Edinburgh, UK

Key words: bipolar disorder – diffusion tensor imaging – schizophrenia – white matter

Received 7 January 2008, revised and accepted for publication 24 April 2008

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Sussman JE, et al. ***Bipolar** Disord*. 2009;11(1):11-18.

Mechanisms of disease

Oligodendrocyte dysfunction in schizophrenia and bipolar disorder

Dmitri Tkachev, Michael L Mimmack, Margaret M Ryan, Matt Wayland, Tom Freeman, Peter B Jones, Michael Starkey, Maree J Webster, Robert H Yolken, Sabine Bahn

Summary

Background Results of array studies have suggested abnormalities in expression of lipid and myelin-related genes in schizophrenia. Here, we investigated oligodendrocyte-specific and myelination-associated gene expression in schizophrenia and bipolar affective disorder.

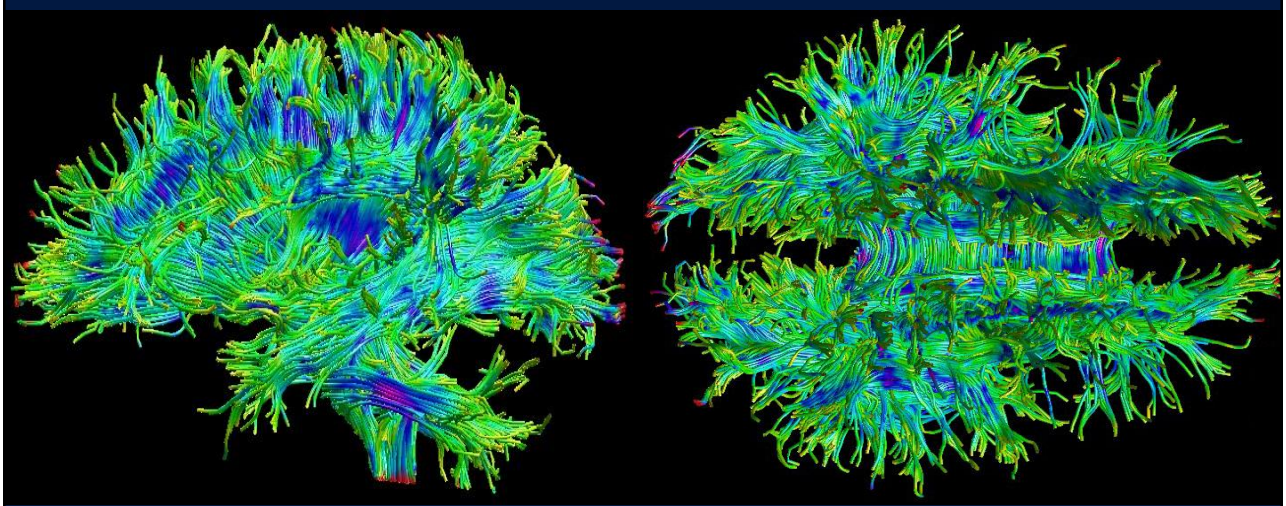
Methods We used samples from the Stanley brain collection, consisting of 15 schizophrenia, 15 bipolar affective disorder, and 15 control brains. Indexing-based differential display PCR was done to screen for differences in gene expression in schizophrenia patients versus controls. Results were cross-validated with quantitative PCR, which was also used to investigate expression profiles of 16 other oligodendrocyte and myelin genes in schizophrenia and bipolar disorder. These genes were further investigated with an ongoing microarray analysis.

Findings Results of differential display and quantitative PCR analysis showed a reduction of key oligodendrocyte-related and myelin-related genes in schizophrenia and bipolar patients; expression changes for both disorders showed a high degree of overlap. Microarray results of the same genes investigated by quantitative PCR correlated well overall.

Interpretation Schizophrenia and bipolar brains showed downregulation of key oligodendrocyte and myelination genes, including transcription factors that regulate these genes, compared with control brains. These results lend support to and extend observations from other microarray investigations. Our study also showed similar expression changes to the schizophrenia group in bipolar brains, which thus lends support to the notion that the disorders share common causative and pathophysiological pathways.

Lancet 2003; 362: 798–805

White Matter Tractography From 3T Magnet



Park HJ, et al. *Neuroimage*. 2004;23(1):213-23.

Oxidative Stress

- Oxidative stress is defined as an imbalance between toxic reactive species or ROS (free radicals) and antioxidant systems
- It is relevant to the pathophysiology of schizophrenia
- Free radicals are counteracted by several cytoprotective antioxidant enzymes that limit their damage, such as:
  - Superoxide dismutase
  - Glutathione peroxide

Ciobica A, et al. *Psychiatr Danub*. 2011;23(3):237-245. Pedrini M, et al. *J Psychiatr Res*. 2012;46(6):819-24. Nasrallah H, Rush S. *Biol Psychiatry*. 2013. Poster presented at the annual meeting of the Society of Biological Psychiatry, April 2013.

Oxidative Stress (cont'd)

- Oxidative stress markers in schizophrenia studies include: SOD, GPX, MDA, TBARS, CAT, TAOP, TpERoX, 4-HNE, TRY.
- Mitochondria dysfunction has been reported in schizophrenia and may account for the low levels of the powerful antioxidant glutathione
- Atypical antipsychotics have been reported to normalize the abnormal free-radical metabolism, but the first-generation antipsychotics like haloperidol increase oxidative stress.

Ciobica A, et al. *Psychiatr Danub*. 2011;23(3):237-245. Pedrini M, et al. *J Psychiatr Res*. 2012;46(6):819-24. Nasrallah H, Rush S. *Biol Psychiatry*. 2013. Poster presented at the annual meeting of the Society of Biological Psychiatry, April 2013.

Neuroinflammation

- There are many lines of evidence for immune dysregulation and neuroinflammation in schizophrenia.
- Microglia activation by various mechanisms directly contribute to neuronal degeneration by producing proinflammatory cytokines and free radicals, inhibition of neurogenesis, and toxicity to white matter.
- Elevated inflammatory cytokines in schizophrenia (TNF-α, 1FN-γ, IL-6). Microglia are the primary reservoirs of proinflammatory cytokines, which act as antigens in the CNS and play a major role in innate immunity.

Ciobica A, et al. *Psychiatr Danub*. 2011;23(3):237-245. Pedrini M, et al. *J Psychiatr Res*. 2012;46(6):819-824. Nasrallah H, *Rush S. Biol Psychiatry*. 2013. Poster presented at the annual meeting of the Society of Biological Psychiatry, April 2013.

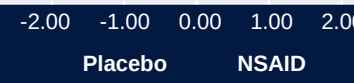
Neuroinflammation (cont'd)

- Some antipsychotic drugs (second generation) reduce inflammation and oxidative stress while others (first generation) increase inflammation and oxidative stress.
- Adding anti-inflammatory agents to antipsychotic drugs potentiates response, eg, minocycline, Cox-2 inhibitors, omega-3 fatty acids. ESPECIALLY in first episode!

Ciobica A, et al. *Psychiatr Danub*. 2011;23(3):237-245. Pedrini M, et al. *J Psychiatr Res*. 2012;46(6):819-824. Nasrallah H, *Rush S. Biol Psychiatry*. 2013. Poster presented at the annual meeting of the Society of Biological Psychiatry, April 2013.

Meta-analysis Suggests NSAID Augmentation May Improve Symptom Severity in Schizophrenia

Study	Hedges g	Lower Limit	Upper Limit	*P* Value	Hedges g & 95% CI	NSAID, mg/d
Müller et al, 2002	0.54	-0.01	1.10	0.06		Celecoxib, 400
Rapaport et al, 2005	-0.34	-0.99	0.31	0.31		Celecoxib, 400
Akhondzadeh et al, 2007	0.93	0.41	1.46	0.00		Celecoxib, 400
Müller et al, 2010	0.52	-0.03	1.08	0.06		Celecoxib, 400
Laan et al, 2010	0.37	-0.10	0.83	0.13		Asprin, 1,000
Overall	0.43	0.06	0.80	0.02		

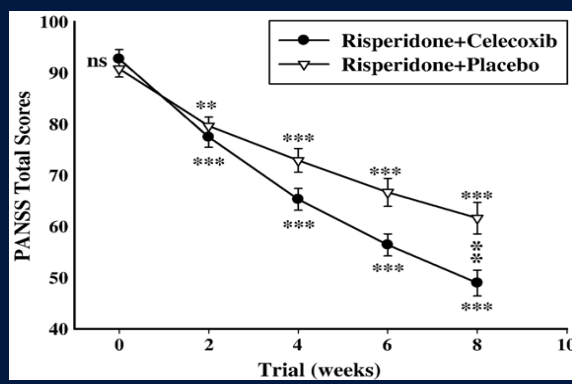


NSAID, nonsteroidal anti-inflammatory drug; PANSS, Positive and Negative Syndrome Scale.
Sommer IE, et al. *J Clin Psychiatry*. 2012;73(4):414-419.

Adjunctive Nonsteroidal Anti-inflammatory Drugs (NSAIDs) in Schizophrenia

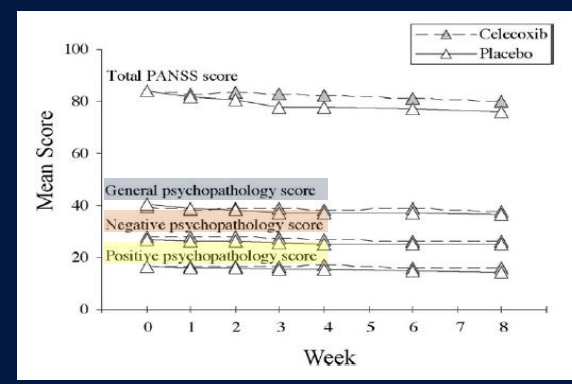
Inpatients with acute psychosis

Akhondzadeh et al. (2007)



Chronically ill, but stable

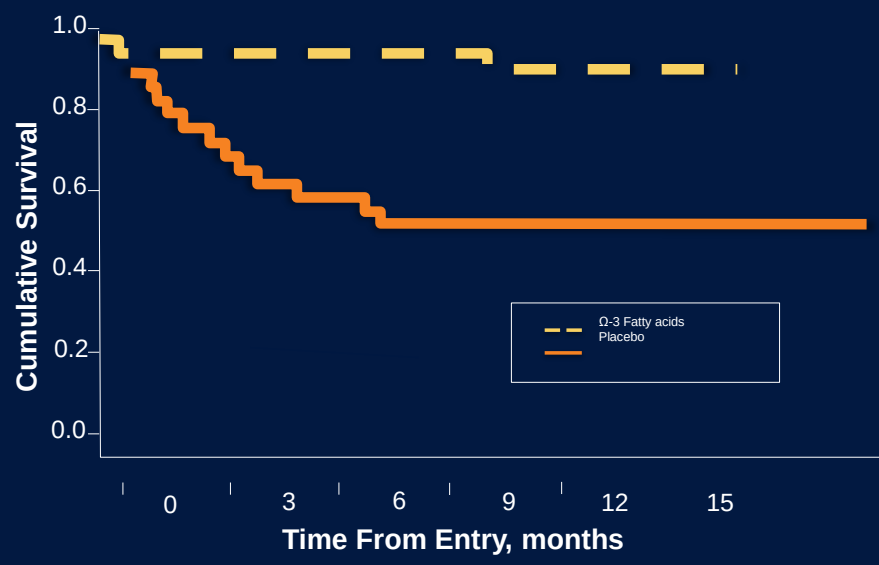
Rapaport et al. (2005)



Also, subjects with higher levels of inflammatory parameters may be more likely to respond to adjunctive NSAIDs.

Akhondzadeh S, et al. *Schizophr Res*. 2007b;90(1-3):179-85; Rapaport MH, et al. *Biol Psychiatry*. 2005;57(12):1594-6.

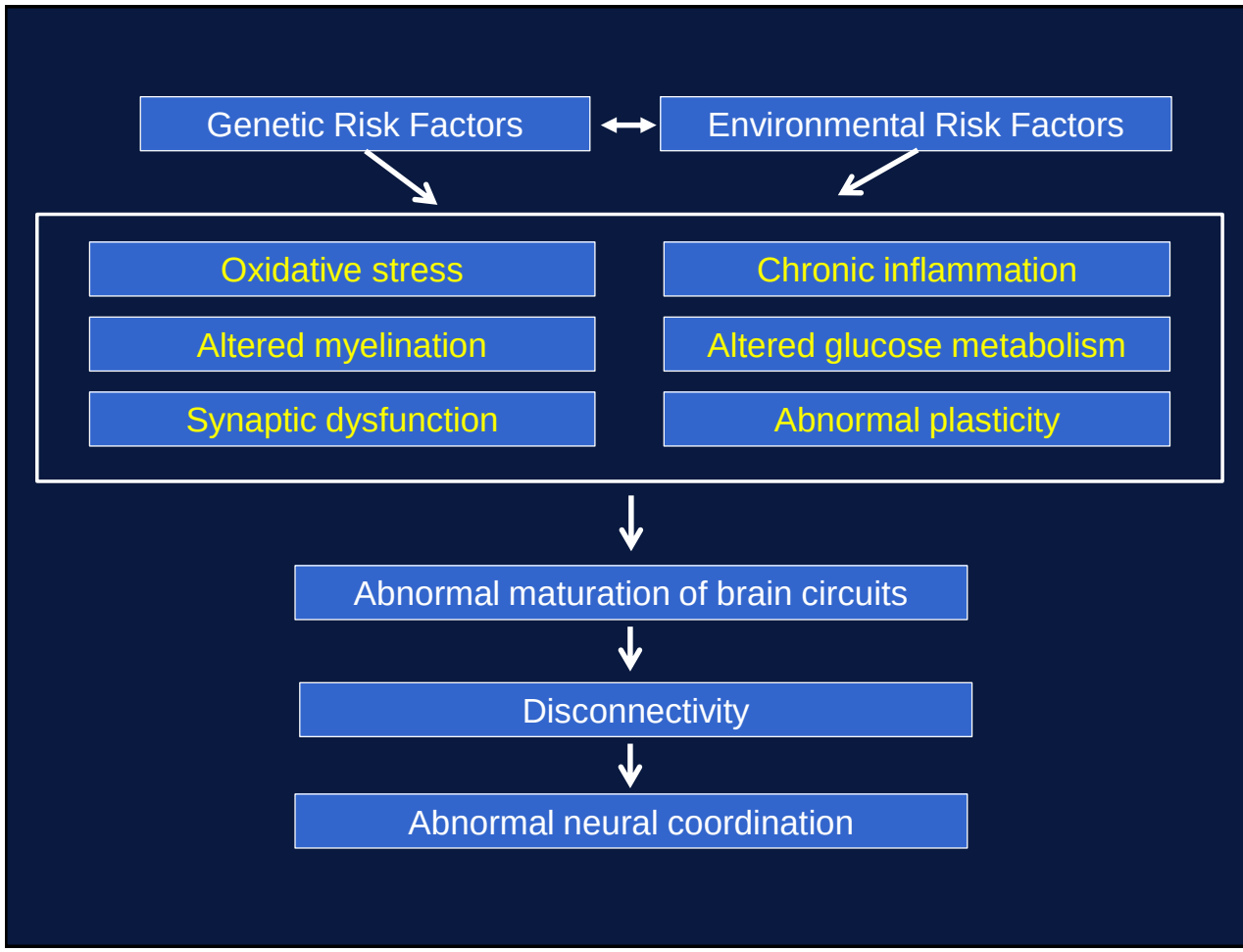
Long-chain Omega-3 Fatty Acids May Prevent Progression to Psychosis



p=0.007 by log-rank test

GAF, Global Assessment of Functioning.

Amminger GP, et al. *Arch Gen Psychiatry*. 2010;67(2):146-154.


Genetic Risk Factors
Environmental Risk Factors
Oxidative stress
Chronic inflammation
Altered myelination
Altered glucose metabolism
Synaptic dysfunction
Abnormal plasticity
Abnormal maturation of brain circuits
Disconnectivity
Abnormal neural coordination

WHAT COMPONENTS OF BRAIN TISSUE ARE LOST IN SCHIZOPHRENIA DURING PSYCHOTIC RELAPSES??

THE NEUROPIL !

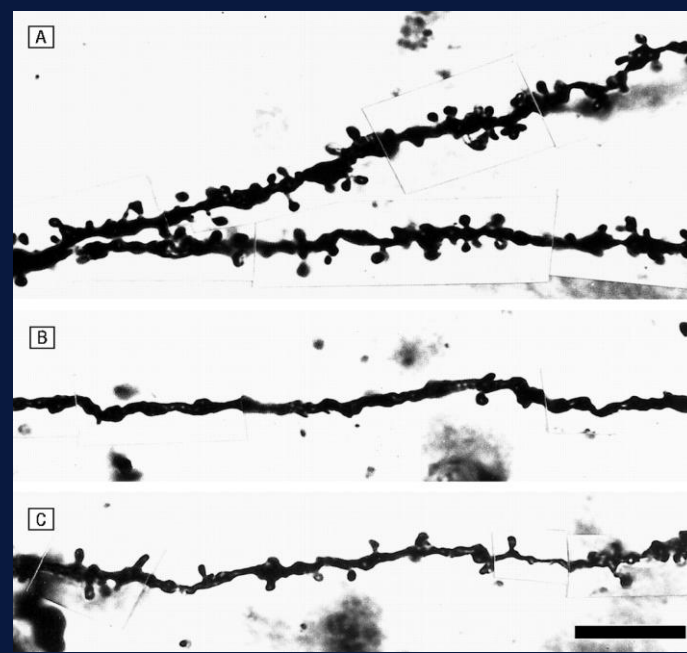
Selemon LD, et al. *Biol Psych.* 1999;45:17-25.

Brain Tissue Atrophy in Schizophrenia: Mostly in the Neuropil

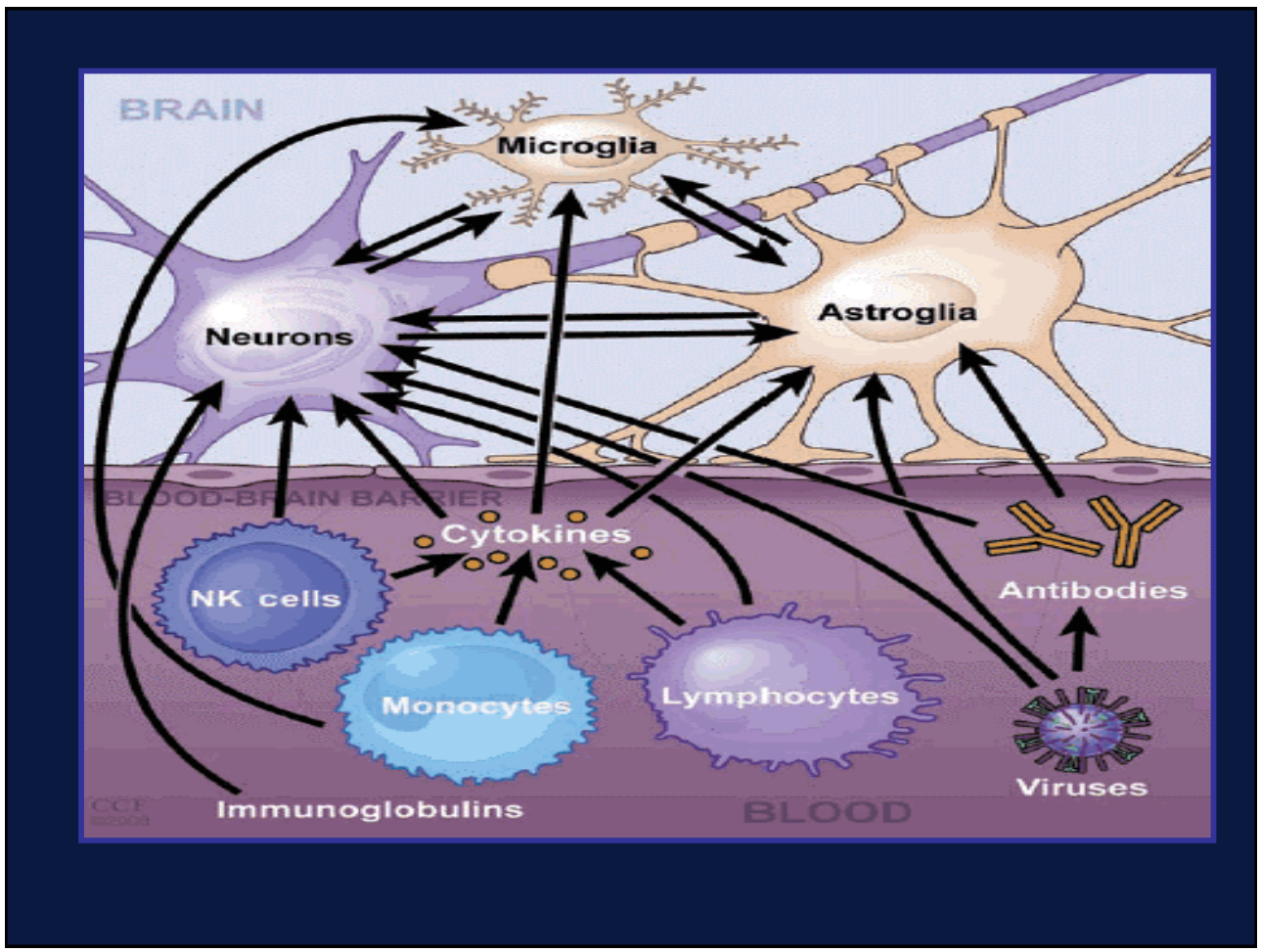
- ↓ Dendrite length by 50%
- ↓ In the number and size of dendritic spines
- ↓ In the size (contraction) of neurite extension
- ↓ In # of glial cells

Black JE , et al. *Am J Psychiatry*. 2004;161(4):742-4; Glantz LA, et al. *Arch Gen Psychiatry*. 2000;57(1):65-73.

Brightfield Photomicrographs Illustrating Golgi-impregnated Basilar Dendrites and Spines on Dorsolateral Prefrontal Cortex Layer 3 Pyramidal Neurons from Normal Control Subject 390 (A) and 2 Subjects with Schizophrenia (Subjects 410 [B] and 466 [C])



Black JE , et al. *Am J Psychiatry*. 2004;161(4):742-4; Glantz LA, et al. *Arch Gen Psychiatry*. 2000;57(1):65-73.


BRAIN
Microglia
Neurons
Astroglia
BLOOD-BRAIN BARRIER
Cytokines
NK cells
Antibodies
Monocytes
Lymphocytes
Viruses
Immunoglobulins
BLOOD

Decline in Neurotropic Factors in Schizophrenia

- ↓ in neurotrophin 3 (NT-3)
- ↓ nerve growth factor (NGF)
- ↓ brain-derived growth factor (BDNF)

Buckley P, et al. *Schizophr Res*. 2007;94:1-11.

Biomarkers of Schizophrenia

- Contrary to the belief that there are no lab tests or biomarkers for schizophrenia, there are more than 365 biomarkers for this syndrome, 273 of which are identifiable in plasma.
- 81 are diagnostic, 77 are markers of drug response, and 115 are for both.
- These biomarkers are associated with the “various biological subtypes” of schizophrenia and thus cannot be used to diagnose the syndrome.
- The Stanley Foundation postmortem studies of the brain in schizophrenia have identified more than 2,000 tissue biomarkers.

Nasrallah HA. Curr Psychiatry. 2013;11:5-6.
Tomasik J, et al. *Eur Arch Psychiatry Clin Neurosci*. 2012;262(suppl 2):S79-S83.

Examples of Serum Biomarkers of the Schizophrenia Syndrome

- BDNF: brain derived neurotropic factor
- CD5L: CD5-like molecule
- CTGF: connective tissue growth factor
- EGFR: epidermal growth factor receptor
- FSH: follicle-stimulating hormone
- ICAM1: intercellular adhesion molecule1
- IL-6: interleukin 6
- IL-7: interleukin 7 (same for 10, 11, 17)
- KIM-1: kidney injury molecule-1
- MCP-2: monocyte chemotactic protein
- MDC: mature dendritic cell
- MIF: macrophage migration inhibiting factor
- MI-1α: macrophage inflammatory protein 1α
- MMP-2: matrix metalloproteinase 2
- PYY: peptide YY
- TNFR2: tumor necrosis factor receptor 2

Schwarz E, et al. *Biomark Insights*. 2010;5:39-47.
Chan MK, et al. *Int Rev Neurobiol*. 2011;101:95-144.

Summary

- Schizophrenia is a heterogeneous brain syndrome, not 1 disease
- There are several genetic pathways to schizophrenia such as risk genes, copy number variations and de novo mutations
- Many environmental factors are associated with the risk for schizophrenia, most of them during fetal life, disrupting neurodevelopment
- Several neuroimaging techniques reveal multiple structural and functional abnormalities in schizophrenia
- Neuroinflammation, oxidative and nitrosative stress appear to play a role in brain tissue loss during psychotic episodes
- The apoptosis in schizophrenia is mainly in the neuropil, involving dendritic length and spines, neurite extension and glial cells

Treatment of Schizophrenia: Current Strategies and Future Paradigm Shifts

Peter J. Weiden, MD
Professor of Psychiatry
University of Illinois Medical Center
Chicago, Illinois

Advances in Psychopharmacology of Schizophrenia

- New information on “old” therapies
- Most recently approved oral antipsychotics
- Recently approved long-acting formulations
- Treatment selection
- In the pipeline

Achieving Stability: PORT 2009 Evidence-based Interventions

- Select antipsychotic based on individual factors related to tolerability and past history
- Olanzapine and clozapine not recommended for "first-episode" patients
- Stay within recommended therapeutic dose range

Achieving Stability

Sources: Schizophrenia Patient Outcomes Research Team (PORT) Recommendations and Summary Statement Schizophrenia Bulletin 36:71-93 (2009)

Port Schizophrenia 2009 Antipsychotic Doses

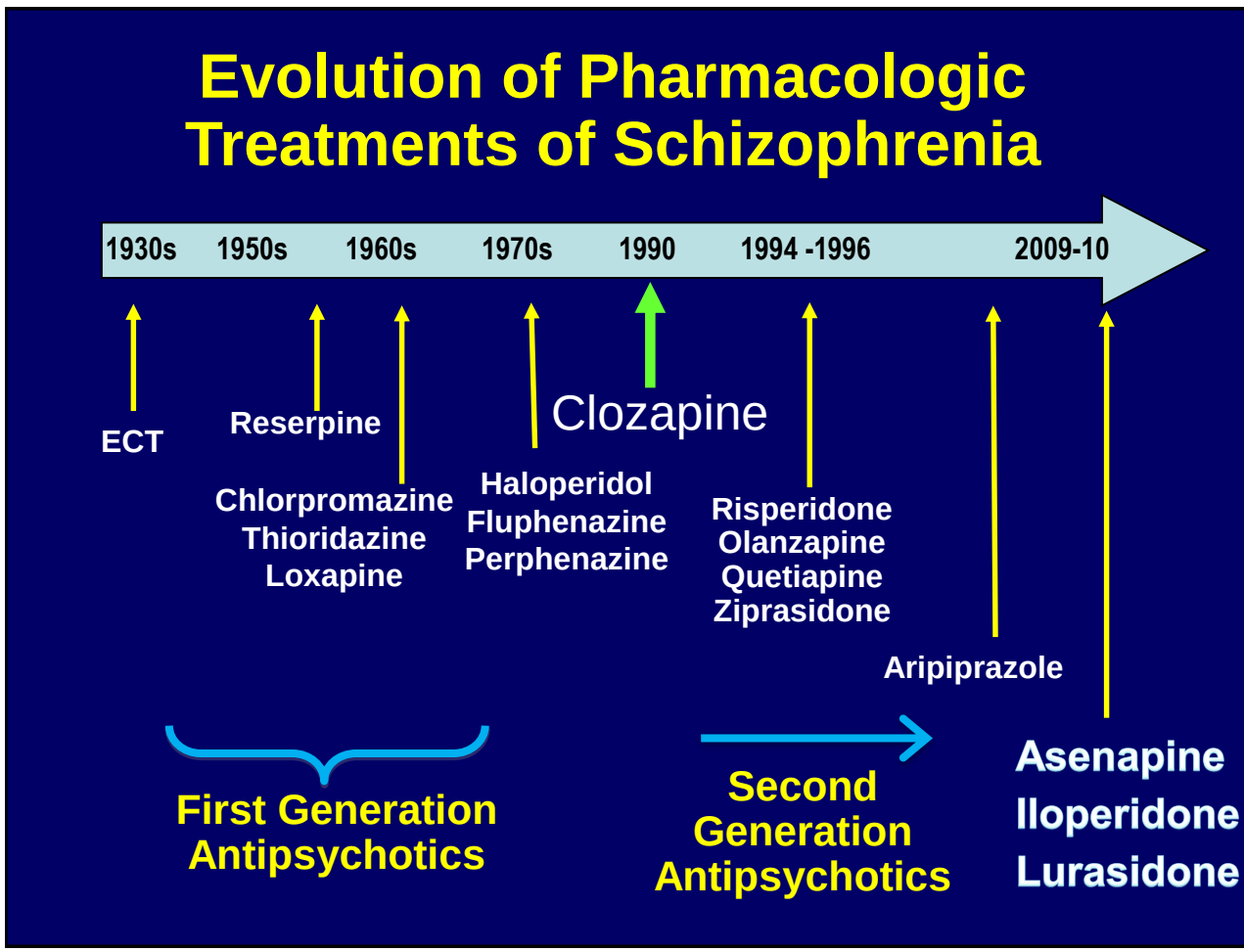
- Older medications still accepted as first-line therapy
- Maintenance doses lower than acute doses
- Newer medications cannot be classified in dose equivalent
- Cannot use same dose-response across newer medications

Relapse Prevention: PORT 2009 Pharmacologic Interventions

- Avoiding medication gaps
  - "those who experience acute and sustained symptom relief should be offered continued antipsychotic treatment [to] maintain symptom relief and to reduce risk of relapse or worsening of positive symptoms"
  - Targeted, intermittent antipsychotic maintenance strategies should not be used routinely…due to increased risk of symptom worsening and relapse

Relapse Prevention

Sources: Schizophrenia Patient Outcomes Research Team (PORT) Recommendations and Summary Statement Schizophrenia Bulletin 36:71-93 (2009)


Evolution of Pharmacologic Treatments of Schizophrenia
1930s
1950s
1960s
1970s
1990
1994 -1996
2009-10
ECT
Reserpine
Chlorpromazine
Thioridazine
Loxapine
Haloperidol
Fluphenazine
Perphenazine
Clozapine
Risperidone
Olanzapine
Quetiapine
Ziprasidone
Aripiprazole
Asenapine
Iloperidone
Lurasidone
First Generation Antipsychotics
Second Generation Antipsychotics

Atypical Antipsychotics for Schizophrenia

Drug	Formulation (Approval)	Dose Range
Aripiprazole (Abilify)	Oral (2002)	10-30 mg/day
Aripiprazole Monohydrate (Abilify Maintena)	Long-acting IM (2013)	300 to 400 mg per month
Olanzapine (Zyprexa)	Oral (1996)	10-20 mg/day; higher doses are often used if treatment refractory
Olanzapine (Zyprexa Relprevv)	Long-acting IM (2009)	150-300 mg IM every 2 weeks
Quetiapine (Seroquel, Seroquel XR)	Oral (1997, 2007)	150-800 mg/day; higher doses are often used if treatment refractory
Risperidone (Risperdal)	Oral (1993)	4-16 mg/day
Risperidone (Risperdal Consta)	Long-acting IM (2003)	25, 37.5, or 50 mg IM every 2 weeks
Ziprasidone (Geodon)	Oral (2001)	80-160 mg/day
Clozapine (Clozaril)	Oral (1989)	300-900 mg/day
Paliperidone (Invega)	Oral (2006)	6-12 mg/day
Paliperidone (Invega Sustenna)	Long-acting IM (2009)	117 to 234 mg per month
Asenapine (Saphris)	Oral – sublingual (2009)	5-10 mg twice daily
Iloperidone (iloperidone)	Oral (2009)	6-12 mg twice daily
Lurasidone (Latuda)	Oral (2010)	40-160 mg once daily

TMAP Schizophrenia Clinician's Manual. http://www.dshs.state.tx.us/mhprograms/pdf/SchizophreniaManual_060608.pdf. Accessed October 2010.
FDA. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name. Accessed Dec 2010.

Advances in Psychopharmacology of Schizophrenia

- New information on “old” therapies
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- In the pipeline

Recent Approvals of Oral Antipsychotics

- Asenapine (Saphris)
  - Approved and available in late 2009
- Iloperidone (Fanapt)
  - Approved in 2009 and available 2010
- Lurasidone (Latuda)
  - Approved late 2010 and available in early 2012

	Asenapine (Saphris)	Iloperidone (Fanapt)	Lurasidone (Latuda)
Indications	Adults with schizophrenia + bipolar	Adults with schizophrenia	Adults with schizophrenia + bipolar disorder
Comparable in efficacy trials	~ risperidone, haloperidol	~ risperidone, haloperidol, ziprasidone	~ olanzapine
Tablet strengths	5mg and 10mg in a clamshell package for sublingual	1mg, 2mg, 4mg, 6mg, 8mg, 10mg and 12 mg strengths	20, 40, 60mg (round) and 80 and 120mg (oval) strengths
Starting dose	Label is 5mg twice a day but most clinicians start just at bedtime	1mg twice a day with up-titration to 12mg within 4 days but many clinicians will do a slower up-titration and just at bedtime	40mg with food; starting dose is therapeutic dose for many patients
Target dose	5-10mg twice a day (10-20 total daily dose)	12-24mg/day (total daily dose). Lower target dose if patient on a CYP2D6 or CYP3A4 inhibitor	40-80mg/day (once a day) usual dose but high end of dose = 160mg/d
Dose-response characteristics	Unknown; suggestion that lower dose range (e.g. 5mg twice a day) is preferable for acute treatment of schizophrenia	Robust dosage efficacy within the lower doses (e.g. between 8 and 16mg/day total daily dose). Dose-response at higher end of dose range not well characterized	Doses < 20mg likely to be subtherapeutic for schizophrenia. No apparent dose-response between doses of 40, 80, and 120mg/day
Problems	Sublingual Bad taste Rapidly sedation Some akathisia and weight gain	Significant orthostatic hypotension Needs up-titration tp get therapeutic QTc labeling	Needs to be taken with food Akathisia Early nausea or vomiting
Possible advantage(s)	Bypass GI absorption Need to get to therapeutic dose right away Need for rapid sedation When there is a strong CYP3A4 inducer like carbamazepine (Tegretol)	Best in class for EPS and akathisia without the sedation or dyslipidemia associated with quetiapine	Ease of use; start at therapeutic, once a day, Excellent weight and metabolic profile without other serious problems (except akathisia)

Advances in Psychopharmacology of Schizophrenia

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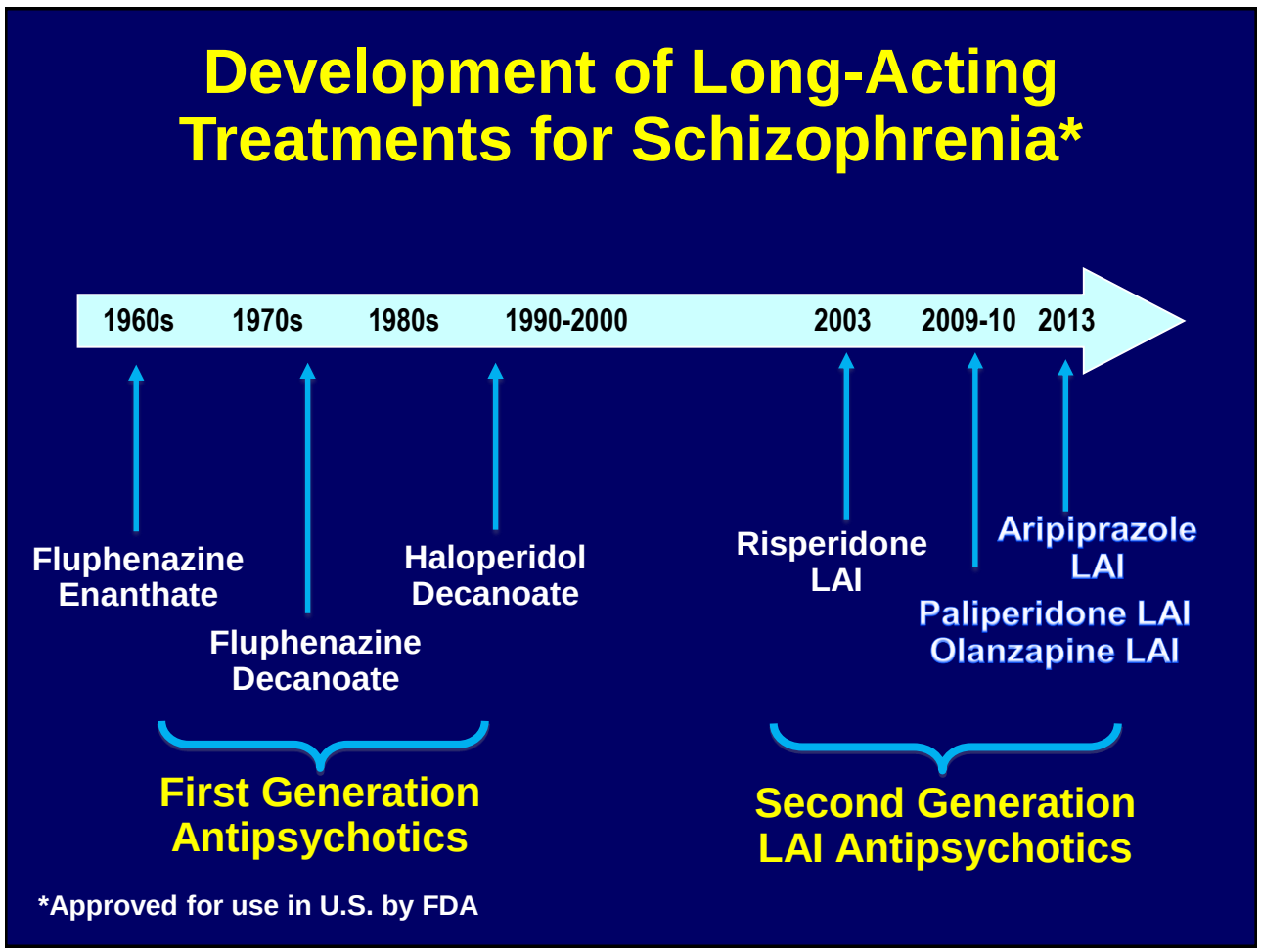
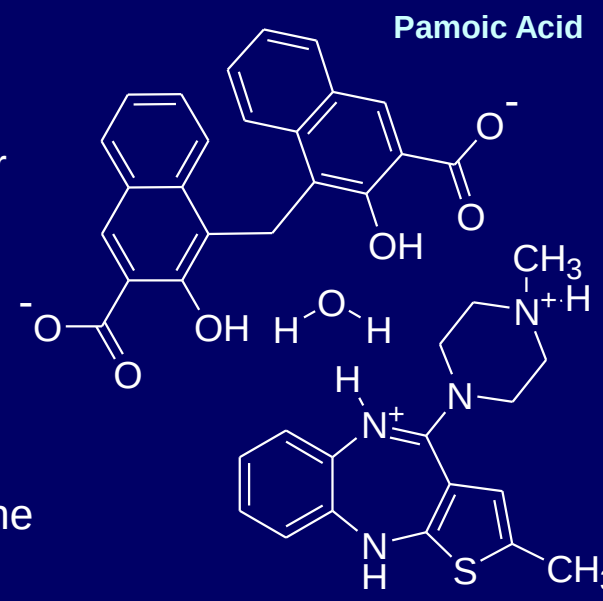
Development of Long-Acting Treatments for Schizophrenia*



*Approved for use in U.S. by FDA

Olanzapine Pamoate

- Olanzapine pamoate monohydrate
- Practically insoluble in water
- Pamoic acid not pharmacologically active
- Crystalline pamoate salt formulation that slowly dissolves into olanzapine (base) and pamoic acid at the injection site



Olanzapine

Meyer, JM. *CNS Spectrums*. 2013;18:55-68

Olanzapine Pamoate: Post-injection Delirium/Sedation Syndrome

- Dizziness, confusion, disorientation, extreme sedation/reduced consciousness
  - Incidence rate per injection = 0.07%
  - Incidence rate per patient = 1.4%
  - Approximately 1 event per 1,400 injections
- Clinicians reluctant to use
- ? Preceding clozapine

http://pi.lilly.com/us/zyprexa_relprevv.pdf; McDonnell DP, et al. *BMC Psychiatry*. 2010.
Meyer, JM. *CNS Spectrums*. 2013;18:55-68

Paliperidone Palmitate Formulation and Mechanism of Action

- Paliperidone palmitate is a palmitate ester of paliperidone

Paliperidone

Ester bond

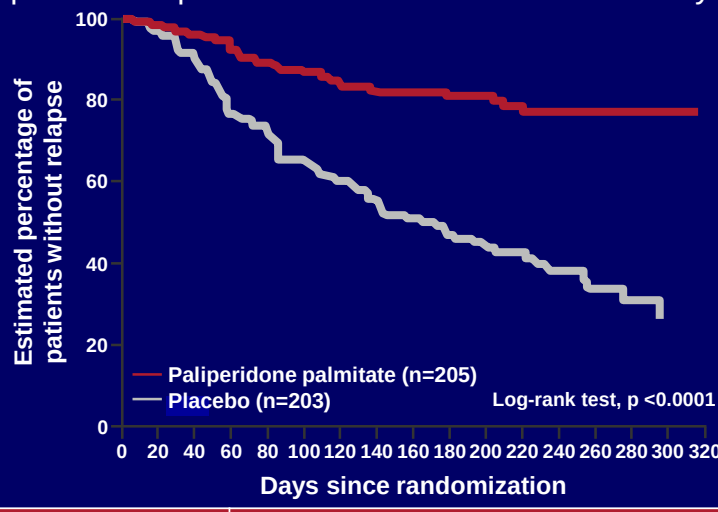
palmitate

- The palmitate ester of paliperidone is nearly insoluble
- Uses technology to create an aqueous suspension for IM administration
- After IM injection, paliperidone palmitate slowly dissolves at the injection site

1. paliperidone palmitate® EU SmPC; 2. http://www.elandrugtechnologies.com/nanocrystal technology; accessed 18 June 2010; 3. Citrome L. *Int J Clin Pract.* 2010;64:216–239; 4. Gopal et al. *Curr Med Res Opin.* 2010;26:377–387

Long-acting Paliperidone Palmitate in Maintenance Phase

Kaplan–Meier plot of time to recurrence – final analysis



The hazard ratio (placebo/long-acting paliperidone palmitate was 3.60 (95% CI: 2.45, 5.28)

Number of patients at risk																	
Time	0	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300	320
Placebo	203	192	163	136	121	101	84	71	58	47	37	34	22	13	9	6	6
long-acting paliperidone palmitate	205	194	180	168	158	146	130	120	106	89	72	61	40	22	15	14	11

CI, confidence interval; BMI, body mass index

Hough, et al. *Schizophr Res* 2010;116:107–117

Paliperidone Palmitate Injectable 3 Month Formulation FDA Trial

- Phase III randomized, double-blinded trial, 509 patients with schizophrenia
- Paliperidone palmitate vs. Placebo injection
- Patients initially stabilized on once monthly palpiperidone injectable and then switched to the 3-month formulation
- Trial halted early by IDMC due to significant efficacy in delaying time to relapse

Clinical Pearls: Paliperidone Palmitate

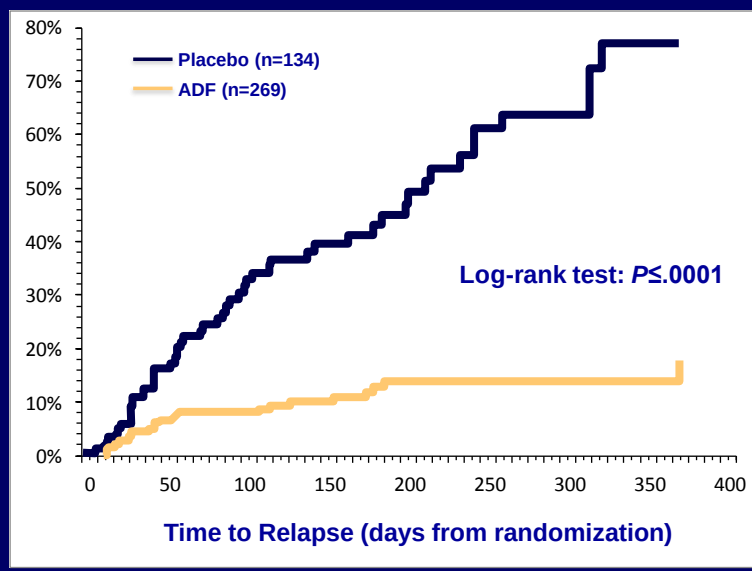
- Efficacy established for acute phase of illness without oral supplementation
- Relative ease of use
  - Monthly injection
  - No refrigeration requirement
  - Small injection volumes (all doses 1 mL or less, except for 234 mg {1.5 mL})
- Lower potential for drug-drug interactions due to renal excretion

Aripiprazole Long-Acting Injectable

- Lyophilized powder for intramuscular gluteal injection
- Pros
  - Q 4 wk dosing
- Cons
  - Not indicated for acute psychotic episode
  - Relatively complex preparation prior to injection
  - Gluteal only
  - Oral overlap for first 2 weeks

ADF [package insert]. Tokyo, Japan: Otsuka Pharmaceutical Co., Ltd.; 2012.
Kane, et al. *J Clin Psych*. 2012.

Time to Impending Relapse for Aripiprazole LAI vs Placebo



Relapse was defined as clinical worsening, psychiatric hospitalization, increased risk of suicide, or violent behavior

Kane JM, Sanchez R, Perry PP, et al. *J Clin Psychiatry*. 2012;73(5):617-624

Clinical Pearls: Aripiprazole

- Starting dose of 400 mg but still need oral overlap
- At steady state 400 mg every 4 weeks is effective
  - Provides plasma levels comparable to ~ 15 to 20 mg/d oral
  - Dose reduction to 300 mg if 400 mg not tolerated
  - Dose reduction options also defined for those on CYP 2D6 and 3A4 inhibitors
- Relatively favorable side effect profile of oral aripiprazole is helpful for patients who cannot tolerate other LAIs due to prolactin, EPS, weight gain or sedation

Kane JM, Sanchez R, Perry PP, et al. *J Clin Psychiatry*. 2012;73(5):617-624

Advances in Psychopharmacology of Schizophrenia

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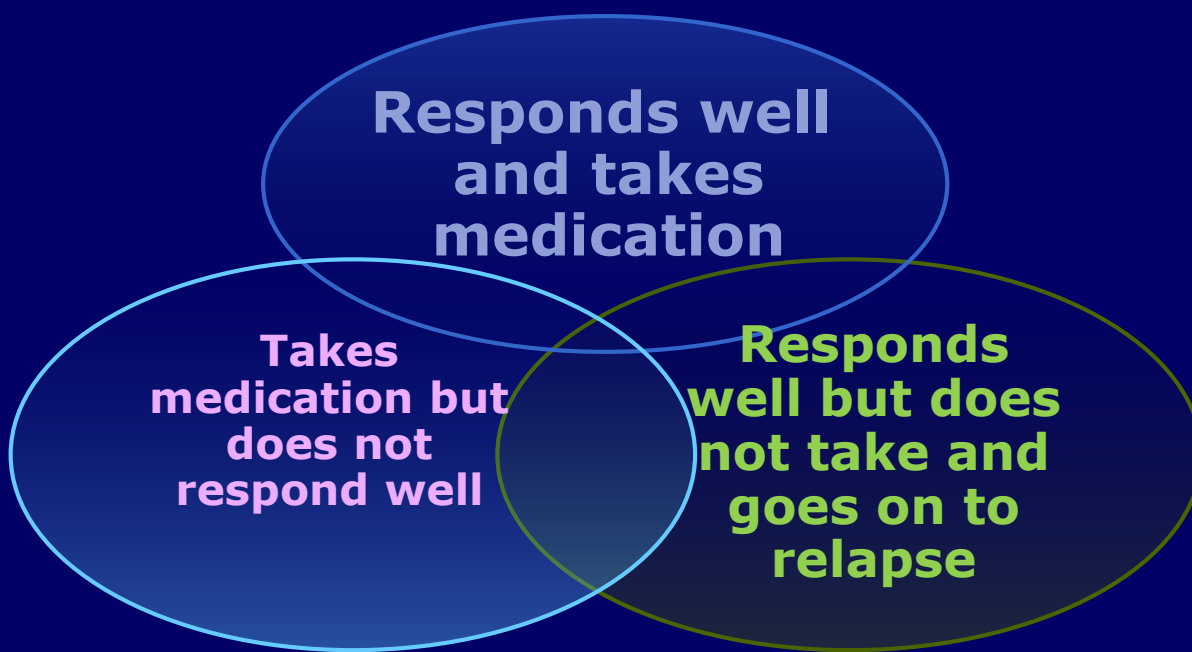
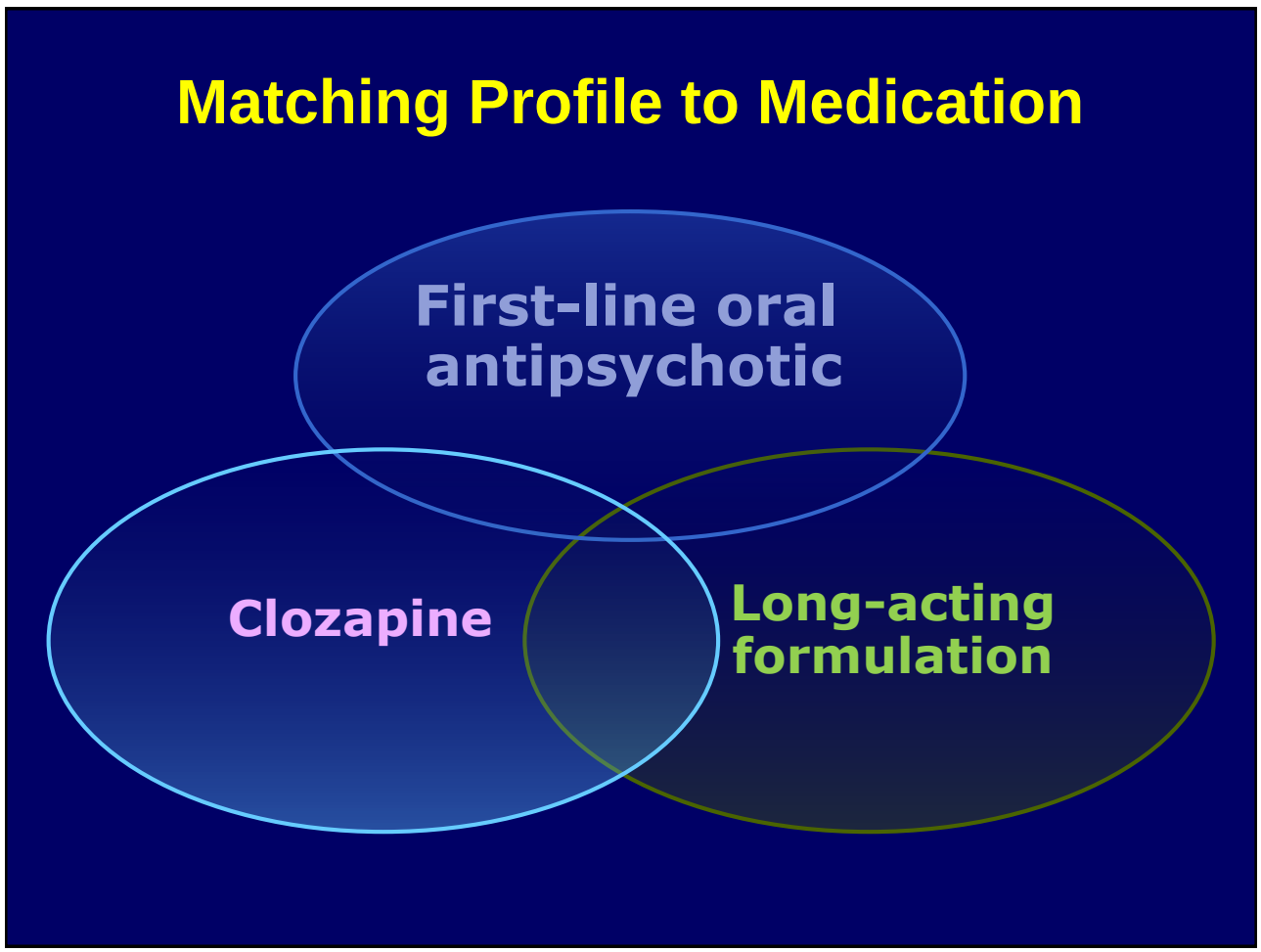
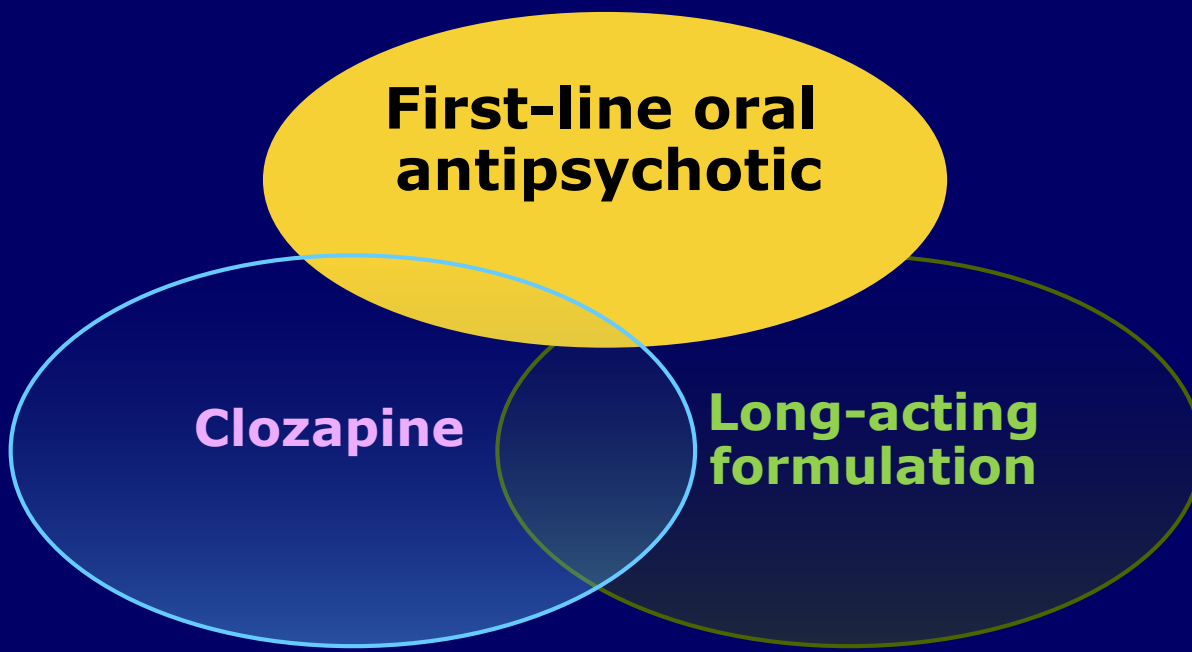
Idealized Patient Profiles



Matching Profile to Medication



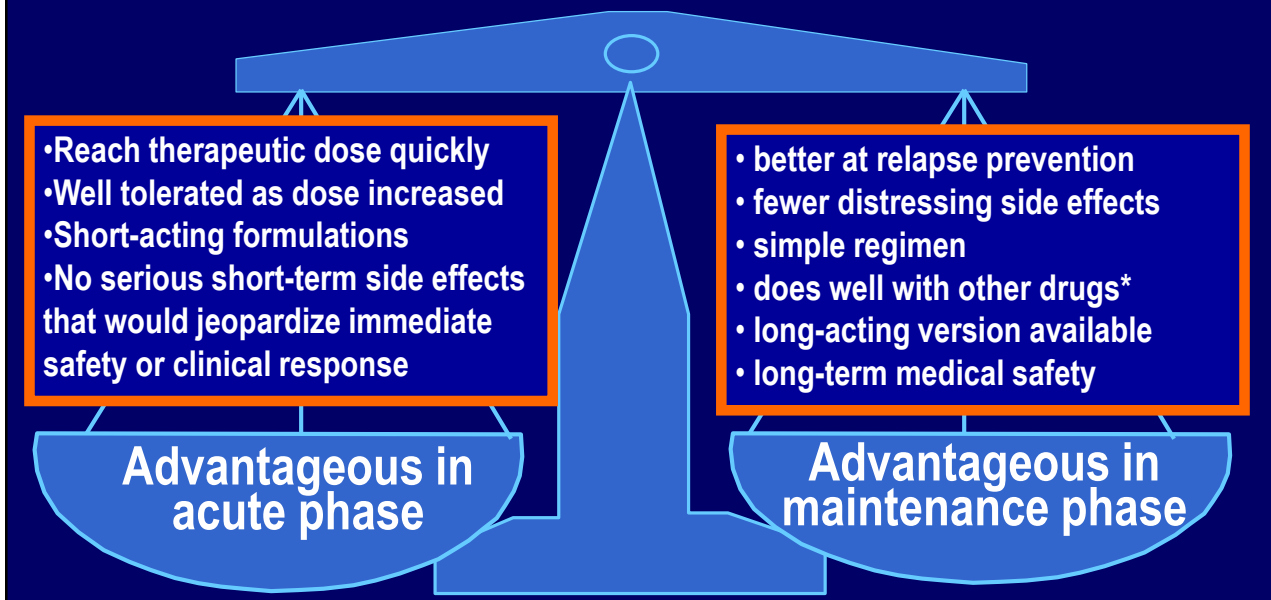
Matching Profile to Medication



Implications of Phase of Illness Model in Medication Selection

- All antipsychotics can be used for all phases of schizophrenia
- Relative advantages and disadvantages of specific antipsychotics may change across different phases
- Antipsychotics are not interchangeable for individual patients

How Phase of Illness Influences Medication Priorities



* "our" drugs = adjunctive pharmacologic agents
"their" drugs = marijuana, alcohol

First-line Antipsychotics
Selection Based on Side Effect Burden

- Patients with schizophrenia do not get a “day off” from side-effect burden
- All antipsychotics have significant side effects but relative burden differs across medications
- Side effect differences predictable and can be used to predict what will happen after switching
- Major improvements in reducing side effect burden
- No longer “catch 22” of high EPS vs. high metabolic problems

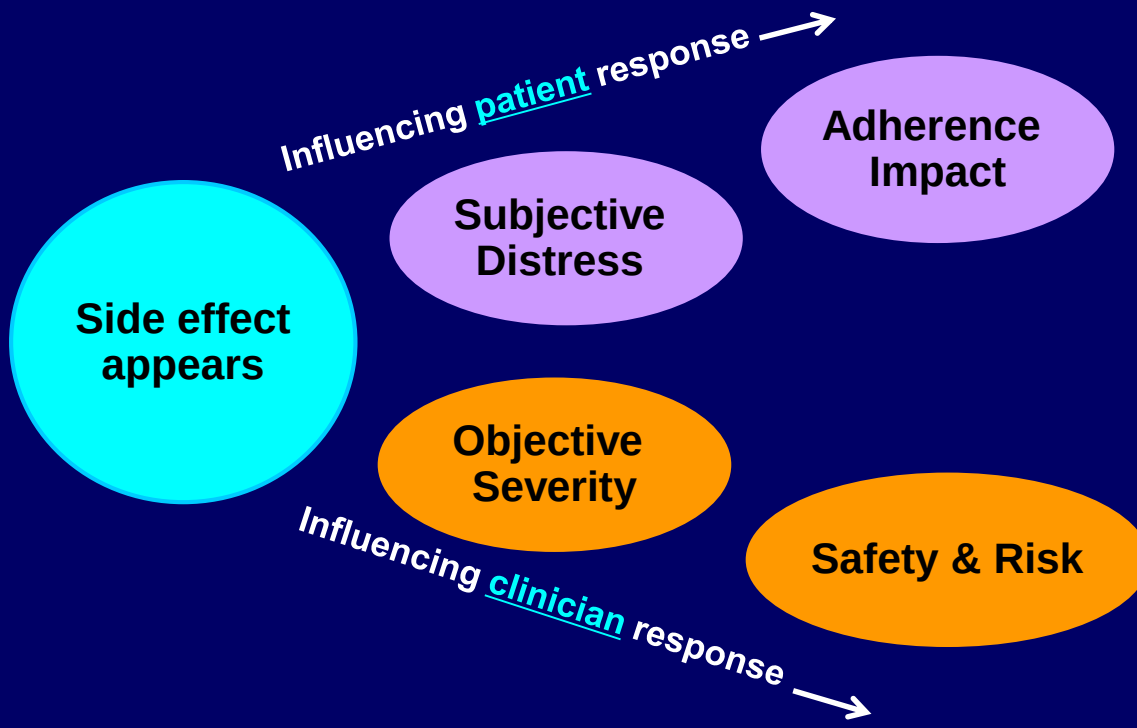
Weiden and Buckley 2007

Evidence to Reject Theories Associating Antipsychotic Side Effects and Efficacy

Theory	Era	Evidence for Rejection
EPS and efficacy	1960-1980 1990s	Clozapine most effective Other atypicals = haloperidol
Weight gain and efficacy	1960s 2000-	Haloperidol = chlorpromazine Ziprasidone & aripiprazole = olanzapine
Sedation and efficacy	1970s 1980s 2000-	Haloperidol = chlorpromazine No benefit from massive doses of haloperidol IM aripiprazole = IM olanzapine

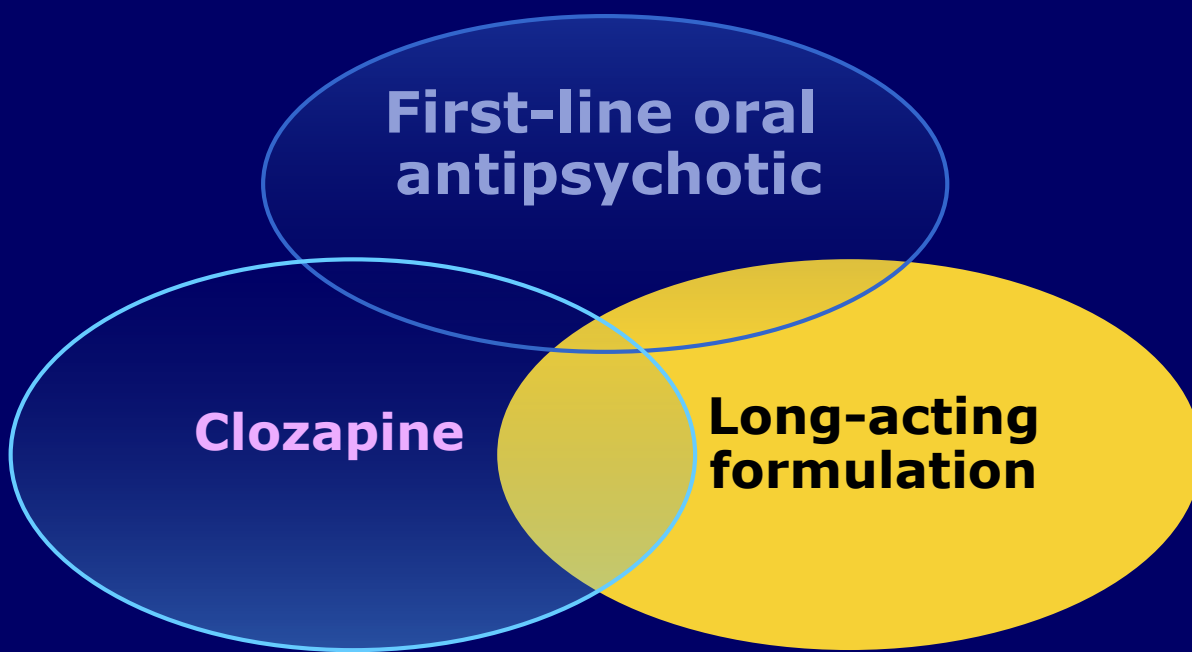
Reverberations From Side Effects

How Patient and Clinician Responses May Differ



Weiden PJ, Buckley PF. *J Clin Psychiatry*. 2007;68(S6):14-23.

Matching Profile to Medication



Potential Advantages of Long-acting Injectable Antipsychotics

- Reduces dosage deviations[1]
- Eliminates guessing about adherence status[2]
- Shows start date of nonadherence[2]
- Helps disentangle reasons for poor response to medication
- Eliminates need for the patient to remember to take a pill daily[1]
- Enables prescribers to avoid first-pass metabolism by using lowest effective dose[1]
- Results in predictable and stable plasma levels[1]
- Eliminates abrupt loss of efficacy if dose is missed[1]
- Many patients prefer them, especially if already receiving them[3,4]

1. McEvoy JP. *J Clin Psychiatry*. 206;67(suppl):1518.
2. Olfson M, et al. *Schizophr Bull*. 2007;33:1379-1387.
3. Patel MX, et al. *J Pscyhopharmacology*.2008;1-8.
4. Kane JM, et al. *J Clin Psychiatry*. 2003;64(suppl 12):1-100.

Potential Obstacles to Long-acting Injectable Antipsychotics

- Systems barriers
  - Logistic barriers (appointments, staffing)
  - Administrative barriers
- Pharmacologic barriers
  - Oral/LAI conversion
  - Fewer choices among antipsychotics
- Attitudinal barriers
  - Perceived stigma
  - Anti-injection attitudes among clinicians

McEvoy JP. *J Clin Psychiatry*. 206;67(suppl 5):1518.
Kane JM, et al. *J Clin Psychiatry*. 2003;64(suppl 12):1-100.

What Does the Research Tell Us?

- Two generations of research
  - 1970-1985
  - 1990s – present
- Inconsistencies in findings
  - RCTs are less likely to show favourable results
  - Cohort studies tend to favour long-acting route
- Relative effectiveness of long-acting formulations depends on more than the direct benefits of the long-acting medication
  - More variation in services context for long acting than for pills

Adams et al. Br J Psychiatry 2001;179:290–299

Relapse and Atypical Antipsychotics:
RCTs show Relapse Still Happens with Depot Formulations

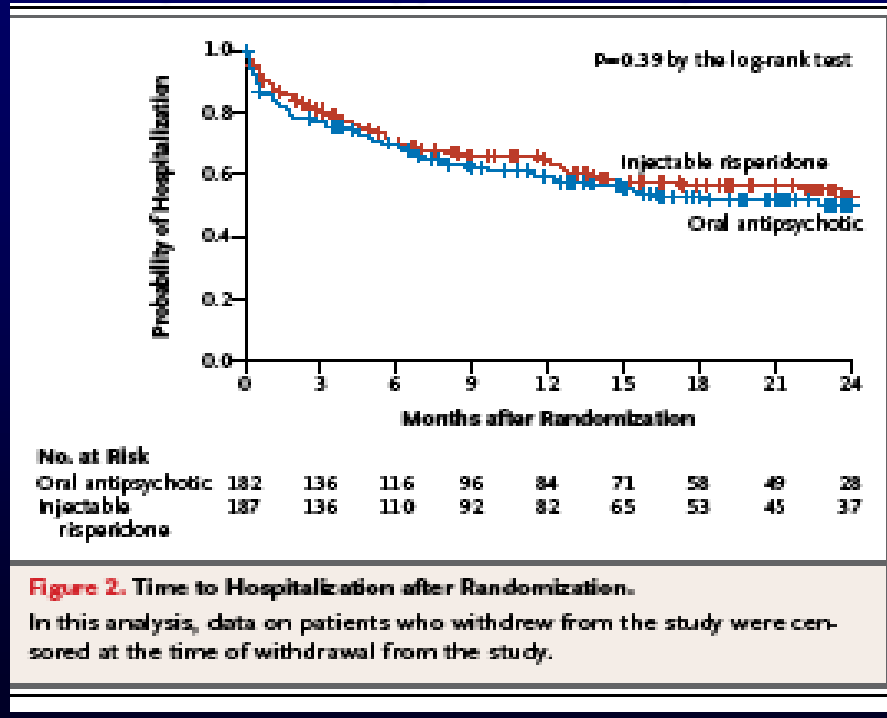


Figure 2. Time to Hospitalization after Randomization.

In this analysis, data on patients who withdrew from the study were censored at the time of withdrawal from the study.

Long-Acting Risperidone and Oral Antipsychotics in Unstable Schizophrenia
Robert A. Rosenheck, M.D., John H. Krystal, M.D., Robert Lew, Ph.D. et al *N Engl J Med* 2011;364:842-51.

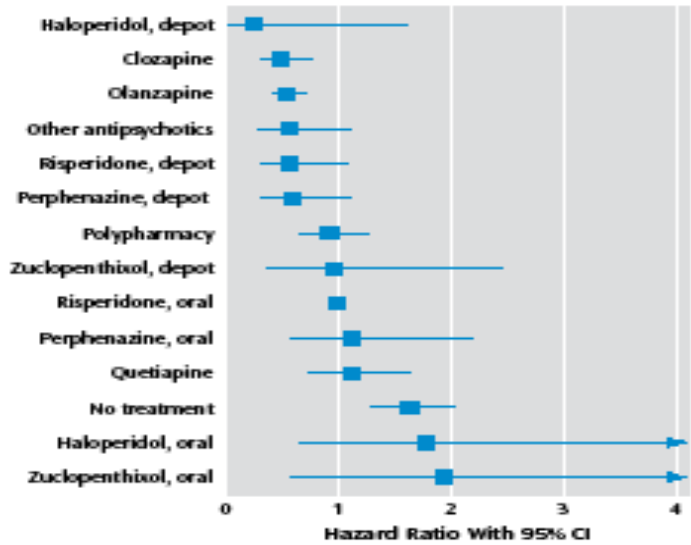
Finish study following first admission for schizophrenia

- Prospective cohort study using national registers in Finland
- 2588 consecutive patients admitted for first time with schizophrenia (2000–2007)
- Followed up according to first drug dispensed post-discharge
- Mean follow-up 2 years
- Rates of discontinuation and rehospitalisation calculated for patients treated with the four most widely used depots in Finland
  - Risperidone depot
  - Zuclopenthixol decanoate
  - Haloperidol decanoate
  - Perphenazine decanoate
- And patients treated with the same four antipsychotics in oral form

Tiihonen et al. Am J Psychiatry 2011;168:603–609

Early Intervention with LAI may Prevent or Delay Rehospitalization

FIGURE 1. Risk of Rehospitalization After a First Hospitalization for Schizophrenia, by Antipsychotic Treatment Pattern (N=2,588)[a]



[a] This is an illustration of the fully adjusted hazard ratios reported in Table 2.

Tilhonen et al: A Nationwide Cohort Study of Oral and Depot Antipsychotics After First Hospitalization for Schizophrenia AJP AJP in Advance. Published March 1, 2011 (doi: 10.1176/appi.ajp.2011.10081224)

The PRIDE Trial

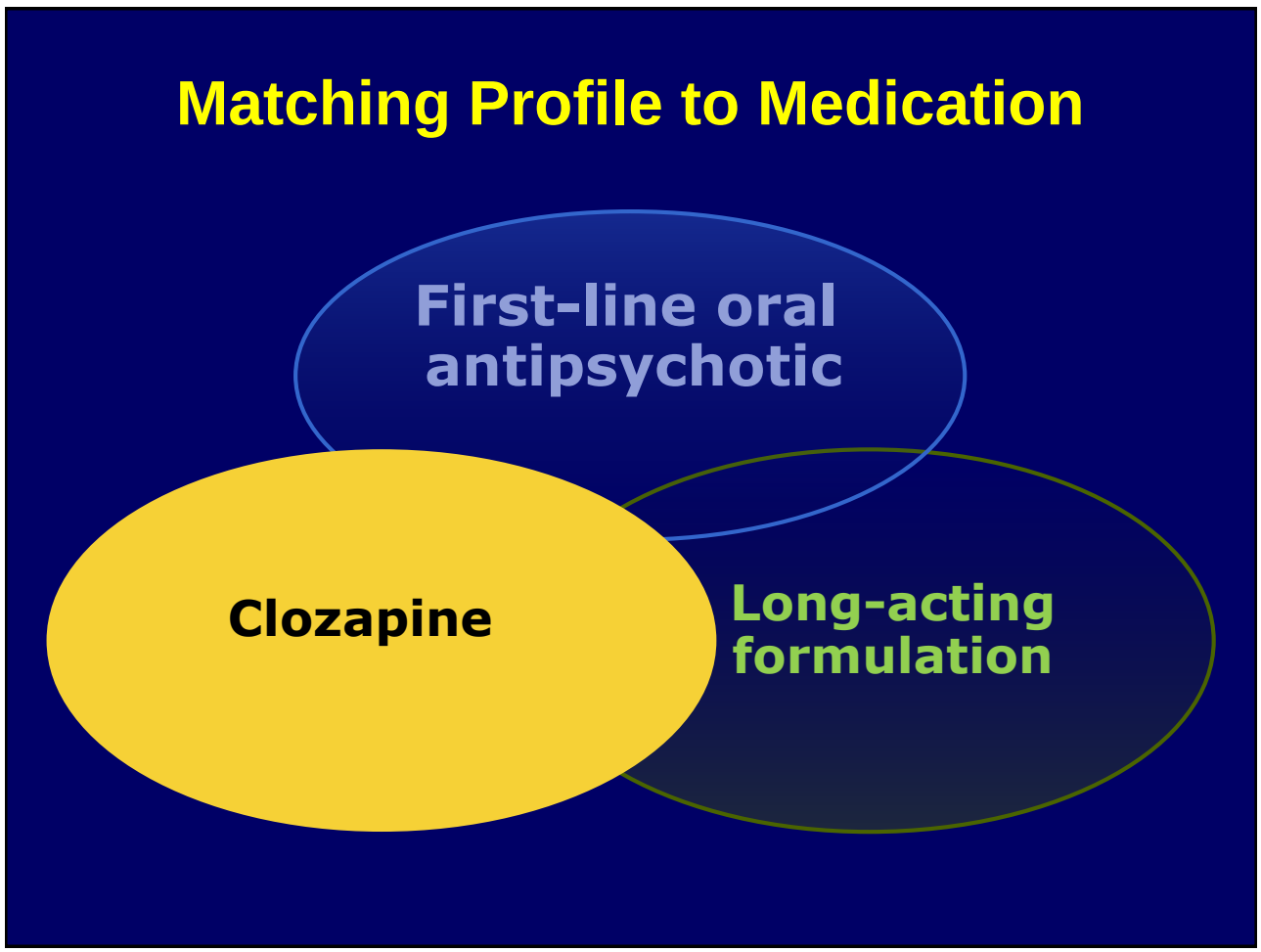
(Paliperidone Palmitate Research in Demonstrating Effectiveness)

- First prospective randomized clinical trial looking at real world consequences of relapse
- Fifteen month trial of 444 adults with one incarceration in the previous two years
- Once monthly injection vs. daily oral antipsychotics
  (aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine and risperidone)
- Results:
  - Significantly delayed time to relapse vs. oral
  - Reduced overall relapse (relapse rates 1.4 times higher in oral group)

Summary on Use of LAI

- We often miss nonadherence in our patients; this can sabotage assessment of pharmacologic response
- LAI is an excellent adherence tracking method
- LAI can be an adherence tracking intervention, especially for patients who WILL NOT take medication down the road
- LAI can be a direct adherence intervention, especially for patients who CANNOT take their oral antipsychotic consistently

Matching Profile to Medication



Clozapine
Clinical Uses

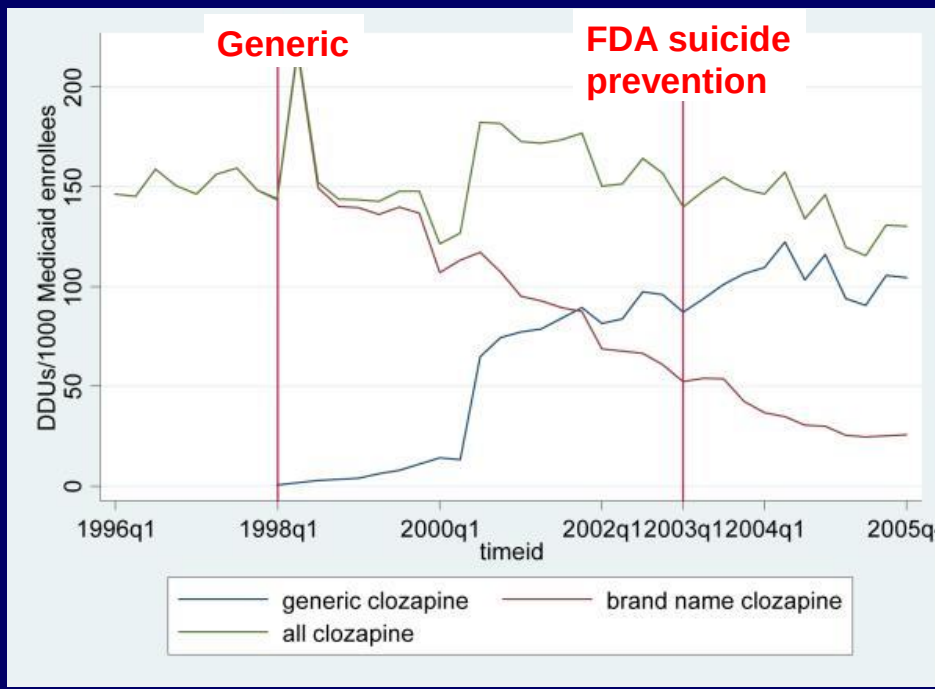
- Persistent symptoms after failing several first-line antipsychotics (~ 30%)
- High suicide risk (~ 10%)
- Aggression and violence (~ 5%)
- EPS and tardive dyskinesia (~ 2%)
- Other serious complications (e.g. polydispsia) (~2%)

Meyer JM. Pharmacotherapy of Psychosis and Mania, in Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th edition. Edited by Brunton LL, Chabner B, Knollman B. Chicago, Illinois, McGraw-Hill; 2010:417-456

Clozapine
The Real World

- What does “treatment-resistant” mean?
- How to disentangle from poor adherence or substance abuse
- Patient keeps changing treatment settings
- Patient too disorganized to follow up with monitoring
- Clinician not trained or too overwhelmed

Clozapine Rates have Not Budged in US Despite Availability of Generics (1998) and Suicide Prevention Indication (2003)



Horvitz-Lennon M, et al. *Health Affairs.* 2009;28:701-712

Clozapine Underutilization and Discontinuation in African Americans Due to Leucopenia

Deanna L. Kelly[1], Julie Kreyenbuhl, Lisa Dixon, Raymond C. Love, Deborah Medoff, and Robert R. Conley

The Maryland Psychiatric Research Center, Box 21247, Baltimore, MD 21228 and the Center for Mental Health Services Research

Table 1. Reasons for Discontinuation by Racial Group

	African American (%), $N = 588$	Caucasian (%), $N = 1287$	Test Statistic
Total	48.6, $N = 286$	44.9, $N = 578$	Chi square = 2.26, $df = 1$, $P = 0.13$
Lack of efficacy	9.18, $N = 54$	11.27, $N = 145$	Chi square = 1.85, $df = 1$, $P = 0.17$
Agranulocytosis	0	0.62, $N = 8$	Chi square = 3.67, $df = 1$, $P = 0.06$
Leucopenia	5.27, $N = 31$	2.41, $N = 31$	Chi square = 10.35, $df = 1$, $P = 0.001$
Other hematologic adverse effect[a]	0.34, $N = 2$	0.31, $N = 4$	Chi square = 0.01, $df = 1$, $P = 0.92$
Other nonhematologic adverse effect	5.27, $N = 31$	6.22, $N = 80$	Chi square = 0.65, $df = 1$, $P = 0.42$
Nonadherence	14.6, $N = 86$	12.5, $N = 161$	Chi square = 1.58, $df = 1$, $P = 0.21$
Death	1.36, $N = 8$	1.63, $N = 21$	Chi square = 0.19, $df = 1$, $P = 0.66$
Other	3.23, $N = 19$	3.41, $N = 44$	Chi square = 0.04, $df = 1$, $P = 0.83$
Unknown	9.35, $N = 55$	6.52, $N = 84$	Chi square = 4.70, $df = 1$, $P = 0.03$

Kelly DL. *Schiz Bull*. 2007;33(5):1221-1224

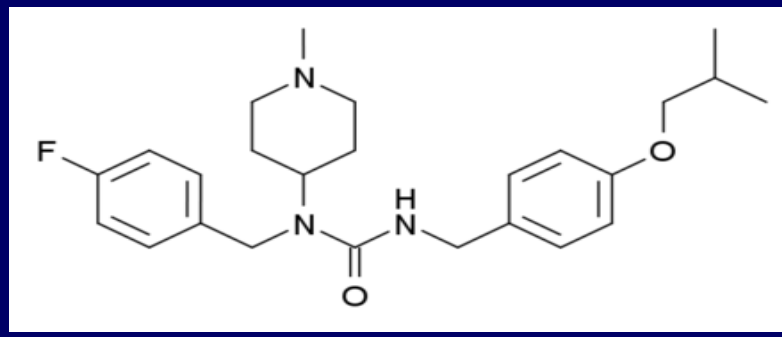
Current Challenges with Reducing Treatment Burden with Antipsychotic Medications

- Persistent psychosis
- Persistent anxiety
- Depressive symptoms
- Suicide risk
- Negative symptoms
- Cognitive and attentional problems

Serotonin Systems

Example of Serotonin Modulation

Pimavanserin (ACP-103) is a drug developed by Acadia Pharmaceuticals which acts as an inverse agonist on the serotonin receptor subtype 5-HT2A, with 10x selectivity over 5-HT2C, and no significant affinity or activity at 5-HT2B or dopamine receptors… and is in Phase II trials for adjunctive treatment of schizophrenia alongside an antipsychotic medication. It is expected to improve the effectiveness and side effect profile of antipsychotics.



Wikipedia accessed October 19, 2013

Nicotinic Systems
Example of Nicotinic Receptor Modulation

EVP-6124: Is an Alpha-7 Nicotinic Partial Agonist and Co-agonist with Acetylcholine. It is currently in Phase III trials for treatment of cognitive dysfunction in persons with schizophrenia (and also Alzheimer's disease)

Summary

- Use our current medications wisely
  - Clozapine underused
  - Long-acting injections underused
- Newer medications and formulations
  - Can use differential efficacy to help more patients
  - Reduce side-effect burden overall
- Future developments
  - Refining dopamine model while also…
  - Moving away from dopamine
  - Improving formulations