"State of the Science of Schizophrenia: Just the Facts, Please."

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Disclosures

- Dr. Moller is the recipient of a non-pharmacological grant from Astra Zeneca pharmaceuticals to study the effects of case manager education on outcomes in schizophrenia.
- There may be off-label uses of anticonvulsant medications presented in this session.

Objectives

1. Discuss the 22 known schizophrenia facts based on recent research


2. Discuss implications of the 2009 Schizophrenia Patient Outcomes Research Team (PORT) Updated Treatment Recommendations


The 22 Known Facts-McDonald & Schwartz

- Basic Facts=6
- Etiological Facts=3
- Pharmacological and Treatment Facts=6
- Pathological Facts=5
- Behavioral Facts=2
  - Based on Consensus
    - Minnesota Consensus Group
    - Schizophrenia Research Forum
    - NARSAD
    - Scholarly Community

Diagnostic Criteria: DSM-IV

A. At least two of the following present for a significant portion of time during a 1-month period:

- delusions
- hallucinations
- disorganized speech
- grossly disorganized or catatonic behavior
- negative symptoms

Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.
How do I get away from you--voices?
How do I leave you behind me forever?
You who echo my feelings, haunt my thoughts, and ravage my nights...
How do I get away from you?
I sing at the top of my voice and still I hear you.
I talk loud and listen to people and still I hear you.
I love you and I hate you.
I can’t get away from you.

How do I get away from you?
I sing at the top of my voice and still I hear you.
I talk loud and listen to people and still I hear you.
Is there a me without you?
No, the answer comes loud and clear, there is no me without you.
As long as I have feelings you will be my echo.
As long as I have thoughts you will be the ghost.
As long as there is night you will be in the darkness.
Sharon LeClaire, May 17, 1994

What We Know: The Basic Facts #1

- Schizophrenia has a heterogeneous presentation with:
  - Positive symptoms
  - Negative symptoms
  - Disorganized symptoms
- Each of these symptom clusters have differing levels of prominence across time and across individuals

The Positive and Negative Syndrome Scale (PANSS™)

- Positive symptoms
  - Hostility
  - Excitability
  - Delusions
  - Suspiciousness, persecution
  - Hallucinatory behavior
  - Conceptual disorganization
  - Grandiosity
- Negative symptoms
  - Emotional withdrawal
  - Passive apathetic withdrawal
  - Difficulty in abstract thinking
  - Blunted affect
  - Lack of spontaneity/flow of conversation
  - Stereotyped thinking
  - Poor rapport

Global Burden of Illness (WHO, 2002)

- DALYs—Disability adjusted life years
  - time lived with disability plus
  - time lost to premature mortality
- In 1990, schizophrenia ranked 9th out of ALL DISEASES
- By 2020 will remain at 9th
Diseases with Greatest Global Burden:
% Total Disability Adjusted Life Years

What We Know: The Basic Facts #3
- Prevalence is greater in men throughout most of adulthood, but is equal to women by the end of the risk period
- OR=1.4 males


What We Know: The Basic Facts #4
- Peak onset in young adulthood and is rare before adolescence or after middle age.
- Onset also interacts with sex, such that men are likely to become ill earlier in life than women
  - Males: onset ages 15-25
  - Females: onset ages 25-35

What We Know: The Basic Facts #5
- Liability to schizophrenia is highly heritable (about .81).
- Concordance between identical twins is almost 50% OR=99 (identical twin of patient)
  - Suggests a role for environmental or stochastic (randomly determined) influences as well

The Genain Quadruplets

Brain scans essentially normal at this young age, each developed schizophrenia in their early 20s

Buchsbaum, 1987

What We Know: The Basic Facts #6

- All drugs with established anti-psychotic effects block dopamine D2-like receptors
  - Antipsychotic drugs are not effective for all schizophrenia symptoms
  - Among available agents, the atypical antipsychotic clozapine is the most effective but it carries unique risks for some.

Dopamine Hypothesis of Schizophrenia

- Mesocortical pathway
  - Hypoactivity: negative symptoms
  - The VTA is the origin of the dopaminergic cell bodies of the mesocorticolimbic dopamine system

- Nigrostriatal pathway
  - Hyperactivity: positive symptoms
  - Substantia nigra projects to EP

- Mesolimbic pathway

Comparative Receptor Binding Profiles

- Haloperidol
- Clozapine
- Risperidone
- Olanzapine
- Quetiapine
- Ziprasidone

What We Know: Etiological Fact #1

- Linkage studies (which identify regions of the genome where schizophrenia genes might be found) suggest a number of regions that show genome-wide significance-8p and 22q
- Several other regions also receiving strong support
  - 1q, 21, 3p, 5q, 6p, 11q, 13q, 14p, 20q
Genes associated with increased risk for schizophrenia

- Chromosome 1q (disrupted-in-schizophrenia)
- Chromosome 2q (glutamate decarboxylase 1)
- Chromosome 6p (dysbindin-1) (cognitive function)
- Chromosome 7 (metabotropic glutamate receptor) (hippocampus)
- Chromosome 8p (neuregulin 1) expressed at central nervous system synapses and has a clear role in the expression and activation of neurotransmitter receptors, including glutamate receptors
- Chromosome 22q (catechol-O-methyltransferase (COMT)) (prefrontal cortex)

What We Know: Etiological Fact #2

- The unexpressed genetic liability to schizophrenia affects cognitive and brain functioning and brain structure
- The most prominent impairments in individuals with heightened genetic liability, such as patients’ nonpsychotic relatives, have been measured on executive functioning
- Overall gray matter and hippocampal volume are also slightly smaller in the relatives of patients with schizophrenia

What We Know: Etiological Fact #3

- Several early neurological insults, later life stressors, and nonhereditary genetic risk factors confer additional risk.
  - Migrant status OR 4.6
  - Older fathers OR 3.8
  - Toxoplasmosis gondii antibodies OR 2.73
  - Prenatal famine OR 2.3
  - Lifetime cannabis use OR 2.1
  - Obstetrical complications OR 1.79
  - Urban rearing OR 1.72
  - Winter or spring birth OR 1.07

What We Know: Pharmacological and Treatment Fact #1

- While antipsychotics can lead to immediate improvement for some individuals, the time course of medication effects varies widely with some patients showing responses to medication more than a month after beginning treatment
  - Is receptor occupancy only one of several ways in which antipsychotics produce therapeutic effects?

Evoked Potential On and Off Haldol

- Average of 64 normal controls
- Patient with schizophrenia off meds

http://www.genomenewsnetwork.org/resources/whats_a_genome/Chp1_2_1.shtml
Evoked Potential On and Off Haldol

Patient with schizophrenia one hour after a dose of haldol
Buchsbaum, 1987

Evoked Potential On and Off Haloperidol

Patient with schizophrenia 24 hours after resuming haloperidol
Buchsbaum, 1987

Evoked Potential On and Off Haloperidol

Patient with schizophrenia 96 hours after resuming haloperidol
Buchsbaum, 1987

Evoked Potential On and Off Haloperidol

Patient with schizophrenia one week after resuming haloperidol
Buchsbaum, 1987

What We Know:
Pharmacological and Treatment Fact #2

• Exposure to amphetamine, a dopamine agonist, can result in schizophrenia-like symptoms in some individuals
• This effect may interact with liability, such that a single dose can trigger relapse in patients, but more chronic use is usually needed to induce psychosis in low risk populations.

2011: Mary D Moller DNP, APRN, PMHCNS-BC, CPRP, FAAN

What We Know:
Pharmacological and Treatment Fact #3

• A single exposure to phencyclidine and other NMDA receptor antagonists (such as ketamine) can result in schizophrenia-like symptoms in some individuals

http://www.defense.gov/specials/drugawareness/pcp.html
What We Know: Pharmacological and Treatment Fact #4

- Effective psychosocial treatments in reducing psychotic symptoms
  - social skills training $d=0.23-0.77$
  - family interventions $d=0.22-0.71$
  - cognitive behavioral therapy $d=0.39-0.47$
  - cognitive training $d=0.20-0.49$

What We Know: Pharmacological and Treatment Fact #5

- Longer duration of untreated psychosis is associated with a poorer treatment response
  - $d=0.50$ (increased symptoms in untreated patients)
- Progressive brain tissue atrophy in the neuropil occurs with each psychotic episode
  - Region between neuronal cell bodies in the gray matter of the brain and blood-brain barrier, consists of a dense tangle of axon terminals, dendrites and glial cell processes. Where synaptic connections formed between branches of axons and dendrites.

What We Know: Pharmacological and Treatment Fact #6

- Patients have a 4.9% rate of suicide
  - This is far greater than the average risk in the US
- 2-fold increase in age-standardized mortality beyond the increased risk for suicide
What We Know: Pathological Fact #1

- In postmortem studies, pyramidal neurons in input layers of prefrontal cortex have a reduced dendritic spine density
  - Prefrontal cell abnormalities $d=0.98-1.121$
- Hippocampal neurons appear abnormally oriented with signs of arrested migration
  - Hippocampal cell abnormalities $d=0.36-0.90$

Pyramidal cell dendrites in DLPFC, spine formation

A Look Inside the Brain

Thalamus
Hippocampus
Amygdala

Hippocampus in bipolar, schizophrenia, PTSD

NIMH
Cortex Changes in Serious Mental Illness

Gray Matter Deficits in Schizophrenia

Normal Hippocampus

Peches, Schizophrenia Bulletin, 1987
What We Know: Pathological Fact #2

- GAD67 that converts glutamate to GABA is reduced (glutamic acid decarboxylase)
- Reelin, important factor involved in synaptic plasticity which co-localizes to GABAergic interneurons, is reduced

Reelin

Directs neuronal migration during brain development and plays a fundamental role in layer formation.

Nogi, et al, 2006

HMMMMM......There's a story here

- Too much dopamine can cause psychotic symptoms
- Not enough glutamate can cause psychotic symptoms
- A reduction of NMDA receptors can cause negative symptoms
- Blockade of NMDA neurons of corticolimbic circuits disrupts cortical inhibition causing disinhibition of glutamatergic (pyramidal) neurons associated with excessive neuronal activity

What We Know: Pathological Fact #3

- The lateral and third ventricles are somewhat larger, even in 1st episode patients
  - Lateral ventricle increase $d=0.32$
  - 3rd ventricle increase $d=0.59$
- Total brain volume is slightly smaller
  - $D=0.24$ (about 2.7% total brain volume decrease)

Ventricular System

http://radiopaedia.org/images/23628

WELL TWIN AFFECTED TWIN
What We Know: Pathological Fact #4

- Medial temporal lobe structures smaller
  - Hippocampus \(d=0.55\)
  - Superior temporal gyri \(d=0.40\)
  - Prefrontal cortices \(d=0.39-0.41\)
- Thalamus smaller \(d=0.30\)

What We Know: Pathological Fact #5

- Functional abnormalities in brain systems
  - Prefrontal cortices
  - Temporal cortices
  - Sub-cortical structures
    - \(d=0.99\) reduction in MMN (mismatch negativity)
    - \(d=0.87\) reduction in P300
    - \(d=0.20\) decrease in dorsolateral prefrontal cortex activity with performance as a significant moderator
What We Know: Behavioral Fact #1

- Cognitive tests are challenging for many, but not all, patients even during remission
  - Overall cognitive performance $d=0.90$
- The greater deficits appear on tasks such as
  - Verbal memory $d=1.4$
  - Performance IQ $d=1.4$
  - Coding tasks $d=1.57$
Cognitive dysfunction

- Cognitive functioning impaired in all patients with schizophrenia and 50% of their families
- Involves:
  - Attention
  - Memory
  - Executive functions (abstraction)

What We Know: Behavioral Fact #2

- The extent of patients’ cognitive deficits generally predicts functioning in work, social interactions, and independent living perhaps even more than symptom expression
  - $d=0.50$ (performance predicting outcome)

Summary: What is Schizophrenia?

- A serious and persistent neurobiological disorder of key mental functions involving:
  - Cognition
  - Perception
  - Emotion
  - Behavior
  - Relationships

Cognitive impairment

- Mild
  - Difficulty with perception
  - Delayed recognition memory
  - Difficulty with confrontation
  - Difficulty with naming (nomia)

- Moderate
  - Delayed recall
  - Highly distractible
  - Impaired immediate memory span
  - Visual-motor skill impairment
  - Impaired working memory
  - Anosognosia (lack of awareness of illness)

- Severe
  - Impaired serial learning
  - Impaired executive function
  - Hypervigilance
  - Impaired motor speed
  - Impaired verbal fluency

Summary: What is Schizophrenia?

- Not a single disorder/heterogenous
- Series of consequences resulting from a fundamental brain dysfunction, perhaps beginning in utero
- Genetic predisposition likely establishes a psychosis “threshold” subject to environmental factors
- Incidence of 1% worldwide
Summary:
What is Schizophrenia?

- Etiology unknown
  - Genetic predisposition, viruses, developmental
- Abnormal neurocircuitry e.g. cortico-limbic-thalamic dysfunction
  - Implicates multiple central nervous system neurotransmitters
  - Early age of onset (15-25 years of age)
- Chronic, relapsing course is common

Before...
I was an artist...before
I went to college...before
...things I could do before
Now my hands shake
My mind wanders
The world pushes me aside
I can still love
Come and sit with me
I will talk about before
Because lonely are the nows

THANK YOU FOR ATTENDING!

Questions

References


References
References