Looking at the Pathophysiology and Comorbidities Associated with Bipolar Disorder or Schizophrenia
Objectives

• Explore how serious mental illness, including bipolar disorder and schizophrenia, may affect the whole person

• Detail the pathophysiology of both bipolar disorder and schizophrenia and a range of comorbidities that may occur

• Identify opportunities for mental health providers to manage the whole patient
Serious Mental Illness (SMI) Results in Functional Impairment

The NIMH defines SMI as a mental, behavioral, or emotional disorder resulting in serious functional impairment that substantially interferes with or limits 1 or more major life activities

Estimated 1-year prevalence of SMI (2017)\(^1\)

- \(\approx 4.5\%\)
- \(\approx 0.6–1.5\%\) Estimated 1-year prevalence of bipolar I disorder in the US (2011, 2017)\(^2,3\)
- \(\approx 0.25–0.64\%\) Estimated 1-year prevalence of schizophrenia in the US (2018)\(^4\)

NIMH=National Institute of Mental Health.

Higher Mortality Risk Has Been Observed in Patients with Serious Mental Illness

- 1.77x Risk for bipolar disorder
- 2.08x Risk for schizophrenia
- 10-25 Years

In a 2017 observational study, patients diagnosed with bipolar disorder or schizophrenia had an increased risk of mortality compared to the general population (1.77x for bipolar disorder and 2.08x for schizophrenia)†

A 2014 fact sheet from the World Health Organization suggested there is a 10-25 year life expectancy reduction in patients with severe mental disorders‡

*This study was a review of primary care electronic health records in patients in the United Kingdom.
†The severe mental disorders to which this information sheet refers are psychosis, bipolar mood disorder and moderate-severe depression.

Excess Deaths Have Been Observed in Patients with Bipolar Disorder

An analysis of 15,386 patients in Sweden with bipolar disorder suggested respiratory diseases, accidents, suicide and vascular diseases were among the most frequent causes of excess mortality compared with the general population from 1973–1995\textsuperscript{1,2}.

These were the 4 largest determined causes out of 15 causes of excess mortality, calculated by subtracting the expected number of deaths from the observed number of deaths reported in the in-patient register and the national cause-of-death register in Sweden; the study was not powered for direct comparison among causes\textsuperscript{1,2}.

Excess Deaths Have Been Observed in Patients with Schizophrenia

An analysis of 7,784 patients in Sweden with schizophrenia suggested respiratory diseases, accidents, suicide and vascular diseases were among the most frequent causes of excess mortality compared with the general population from 1973–1995.

These were the 4 largest determined causes out of 15 causes of excess mortality, calculated by subtracting the expected number of deaths from the observed number of deaths reported in the in-patient register and the national cause-of-death register in Sweden; the study was not powered for direct comparison among causes.

Patients with SMI May Experience a Range of Common Physical Comorbidities

Studies have reported increased prevalence of several physical comorbidities in patients with SMI, including bipolar disorder and schizophrenia\textsuperscript{1-5}

- **Infectious**
  - HIV
  - Hepatitis B/C

- **Respiratory**
  - COPD
  - Asthma

- **Cardiovascular**
  - Hypertension
  - Stroke

- **Metabolic**
  - Diabetes
  - Obesity
  - Metabolic syndrome

These physical illnesses and disease categories were consistently reported to be more common compared with the general population\textsuperscript{1-5}

COPD=chronic obstructive pulmonary disease.

Schizophrenia: Potential Dysfunction Across Multiple Systems
Schizophrenia May Involve Dysfunction Across Several Systems: Evidence from Antipsychotic-naive Patients

An analysis of patients with first-episode psychosis, including patients with schizophrenia, suggested schizophrenia may involve dysfunction across cardiometabolic, immune, and endocrine systems; the meta-analysis extracted data from antipsychotic-naive patients from 6 studies (2018)

Cardiac Disturbance
- ↑ Triglycerides
- ↓ HDL cholesterol
- ↓ LDL cholesterol

Metabolic Disturbance
- ↑ Insulin resistance
- ↑ Fasting insulin
- ↑ Glucose post-OGTT
- ↑ Oxidative stress

Endocrine Disturbance
- ↑ Prolactin

Immune Disturbance
- ↑ Cytokines
- ↑ Lymphocyte counts

GTT=oral glucose tolerance test.

Figure adapted from: Pillinger T et al. Mol Psychiatry. 2018;24(6):776-794.
Reduced Adiponectin Levels Have Been Observed in Patients with Schizophrenia

• Adiponectin, an adipokine hormone produced primarily by fat cells in adipose tissue, makes tissues more sensitive to insulin, while low levels of adiponectin are associated with insulin resistance, as reported in reviews from 2003, 2012, and 2017\textsuperscript{1-3}

Figure adapted from Menzaghi C et al. *Diabetes*. 2007;56(5):1198-1209.

• The association between adiponectin and antipsychotic-naive schizophrenia is still unclear. Lower serum adiponectin levels have been detected in this subpopulation compared with healthy controls\textsuperscript{1,4}

• Lower adiponectin levels have been observed in antipsychotic-prescribed patients with schizophrenia\textsuperscript{1}

![Diagram showing the effects of adiponectin](image-url)

- ↓ Glucose output
- ↓ Fat accumulation
- ↓ Inflammation
- ↑ Glucose uptake
- ↓ Fat accumulation
- ↑ Energy expenditure
- ↓ Inflammation
- ↓ Endothelial adhesion
- ↓ Foam cell formation

Protection from:
- • Insulin resistance
- • Type 2 diabetes
- • Coronary artery disease
Elevated Blood Cytokines Have Been Observed in Patients with Schizophrenia

- Immune activation may occur both peripherally and centrally in patients with schizophrenia\(^1\)
- Elevated blood cytokine levels, including IL-1\(\beta\), sIL2R, IL-6 and TNF\(\alpha\), have been observed in antipsychotic-naive patients with schizophrenia\(^2,3\)

**BMI**=body mass index; IL-1\(\beta\)=interleukin one beta; IL-6=interleukin six; TNF-\(\alpha\)=tumor necrosis factor alpha; sIL2R=soluble form of interleukin 2 receptor.

Figure adapted from Nakamizo S et al. *Trends in Immunotherapy*. 2017;1(2):67-74.


Elevated pro-inflammatory cytokines have been differentially associated with regional brain volume alterations, although correlations are inconsistent and further studies are required to clarify these alterations in the context of systemic inflammation in first-episode psychosis\(^2\)

Adipose tissue also releases pro-inflammatory cytokines (IL-6 and TNF\(\alpha\)), which may contribute to insulin resistance,\(^1\) and antipsychotic-naive patients with schizophrenia with higher BMI have been observed to have increased levels of c-reactive protein, a biomarker of inflammation directly modulated by IL-6\(^4\).
Elevated Prolactin Levels Have Been Observed in Patients with Schizophrenia

- Prolactin is a polypeptide hormone secreted from the anterior pituitary gland, and it is believed that prolonged elevations in prolactin may be associated with certain health effects, including sexual dysfunction and osteoporosis, as reported in a 2016 study.\(^1\)

- A 2016 meta-analysis of 208 antipsychotic-naive patients, including patients with schizophrenia, reported elevated prolactin levels in male and female patients compared with matched controls.\(^1\)

- Prolactin release may be increased in response to stress and be associated with HPA activity.\(^1,2\)

Hyperprolactinemia is associated with:\(^1\):
- Amenorrhea
- Galactorrhea
- Osteoporosis
- Low libido
- Erectile dysfunction
- Breast cancer

HPA=hypothalamic-pituitary-adrenal

Schizophrenia: Pathophysiology
The Pathophysiology of Schizophrenia May Involve Dysfunction Across Several Neurotransmitter Systems

Dopamine hypothesis of schizophrenia\textsuperscript{1,2}:

Dopamine hyperactivity in the mesolimbic regions of the brain \quad \text{+} \quad \text{Dopamine hypoactivity in the prefrontal cortex} \quad \rightarrow \quad \text{Symptoms of schizophrenia}

N-methyl-d-aspartate (NMDA) hypothesis of schizophrenia\textsuperscript{3,4}:

Dysregulated glutamatergic neurotransmission \quad \rightarrow \quad \text{Negative symptoms & cognitive impairment}

GABA=\gamma\text{-amino-butyric acid.}

Dopaminergic Brain Circuits May Be Associated with Many Functions

- Prefrontal Cortex
  - "Regulation of emotion/affect"
  - "Cognition and executive function"

- Striatum
  - Ventral Striatum
  - Dorsal Striatum

- Mesocortical Pathway
- Mesolimbic Pathway
  - "reward circuitry"

- Brainstem Dopaminergic Neurons
  - Ventral Tegmental Area
  - Substantia Nigra

- Nigrostriatal Pathway
  - "motor control"

References:
Positive Symptoms That Define Schizophrenia May Be Associated with Mesolimbic Dopaminergic Dysregulation

Hyperactivity of dopamine transmission at D2 receptors is hypothesized to contribute to the positive symptoms of schizophrenia\textsuperscript{1,2}

Cognitive Symptoms of Schizophrenia May Be Associated with Mesocortical Dopaminergic Dysregulation

Cognitive symptoms associated with schizophrenia may be due to the hypofunction of dopamine D₁ receptor neurotransmission in the prefrontal cortex.

- Declarative memory
- Verbal & working memory
- Executive functions
- Deficits in attention

Negative Symptoms of Schizophrenia May Be Associated with Mesocortical Dopaminergic Dysregulation

The negative symptoms of schizophrenia include anhedonia and lack of motivation, and may be associated with reduced dopaminergic signaling in the prefrontal cortex. 

- Alogia
- Avolition, apathy
- Anhedonia
- Flat affect

Mesolimbic Reward System Dysconnectivity May Relate to Reward Deficits in Patients with Schizophrenia

In a connectome-wide analysis involving 225 patients, including 51 patients with schizophrenia, reward deficits were associated with dysconnectivity between the ventral striatum and major functional areas.


BAS=behavioral activation scale; DMN=default mode network; NAc=nucleus accumbens.

*This is a graphic figure adapted from Sharma A et al. Am J Psychiatry. 2017;174(7):657-666.

Schizophrenia: Behavioral Risk Factors and Common Physical Comorbidities in Patients
Dopamine Reward Circuit Dysregulation is Hypothesized to Be Associated with Comorbid Substance Use in Patients with Schizophrenia

Mesocorticolimbic dopamine reward circuit dysregulation is hypothesized to contribute to vulnerability to both the initiation and continued use of substances in patients with schizophrenia; this content is theoretical and more research is needed before the co-occurrence of schizophrenia and substance use disorder can be understood.

Genetic risk or an early environmental insult may lead to a dysfunctional mesocorticolimbic brain reward circuit.

Greater risk of substance use in pre-psychotic individuals

Onset of schizophrenia

Initiation/continued substance use

Studies Have Reported Greater Odds or Risk of Infectious Diseases in Patients with Schizophrenia with Co-Occurring Substance Use

In a 2006 review of records from the Veterans Integrated Service Network, patients with schizophrenia and co-occurring substance use disorder had ≈8x greater odds of hepatitis C infection compared with controls

In a 2015 review of nationwide records in Denmark, patients with schizophrenia and co-occurring substance use disorder had ≈1.8x greater risk of HIV infection compared with the general population

Tobacco Use Is More Common in Patients with Schizophrenia

The estimated odds for tobacco use among patients with first-episode schizophrenia compared to age- and gender-matched controls

There are many hypotheses for the higher prevalence of smoking in patients with schizophrenia, including theories of increased negative symptomatology, deficits in reward processing, and alterations in reward-related brain circuitry

Cigarette cravings were assessed using the 10-item Questionnaire on Smoking Urges-brief form (QSU); this is an illustrative graphic adapted from the QSU F2.

Higher Odds of Respiratory Diseases Have Been Observed in Patients With Schizophrenia

A 2004 survey study reported greater odds of respiratory diseases in patients with schizophrenia compared with the general population.

The odds for asthma, chronic bronchitis, and emphysema were approximately 2.2, 3.1, and 7.2 times greater, respectively, when controlling for tobacco smoking.

Dopamine Signaling is Hypothesized to Be Related to Altered Reward Anticipation and Dysregulated Energy Allocation in Patients with Schizophrenia

- Striatal dopaminergic dysregulation may be related to weight gain and obesity in schizophrenia, but our understanding is limited.

- Decreased striatal dopamine signaling may be associated with reduced sensitivity to natural rewards and lead to compensatory, compulsive eating in both obesity and schizophrenia.

- Low dopamine levels associated with schizophrenia may also result in dysregulated energy allocation.

This content is theoretical and more research is needed to confirm this hypothesis.

There May Be Several Factors Related to Increased Cardiovascular Disease in Patients with Schizophrenia

**Metabolic Risk Factors**
- Increased likelihood of risk factors, including:
  - Diabetes
  - Hypertension
  - Dyslipidemia
  - Obesity

**Lifestyle and Environment**
- Unhealthy lifestyle
  - Poor diet
  - Sedentary behavior
  - Smoking
- Less access to healthcare and cardiovascular risk screening

Bipolar Disorder: Potential Dysfunction Across Multiple Systems
Bipolar Disorder May Involve Dysfunction Across Several Systems

Immune Disturbance

- ↑ Pro-inflammatory cytokines
- ↑ CRP

Endocrine Disturbance

- ↑ Cortisol

Metabolic Disturbance

- Insulin dysregulation

CRP=C-reactive protein
Figure adapted from: Pillinger T et al. Mol Psychiatry. 2018;24(6):776-794.

Increased Prevalence of Type 2 Diabetes and Greater BMI Have Been Observed in Patients with Bipolar Disorder

In a 2002 study, increased prevalence of type 2 diabetes was observed in patients with bipolar I disorder compared with national norms, independent of psychotropic medication\(^1\)

In a 2008 study, greater weight and BMI were observed in drug-naive patients with bipolar disorder compared with controls\(^2\)

There is a need for prospective observational studies to further evaluate these observations

Elevated Pro-Inflammatory Cytokines Have Been Observed in Patients with Bipolar Disorder

In a 2015 study of 30 patients with bipolar disorder before and after treatment with an antipsychotic and mood stabilizer, inflammatory cytokine ratios were elevated compared with healthy controls.

IL-6=interleukin 6; IL-4=interleukin 4; IFN-γ=interferon gamma; IL-10=interleukin 10.

Elevated Activity in the HPA Axis Has Been Observed in Patients with Bipolar Disorder

- Cortisol, a glucocorticoid product of the HPA axis, may be elevated following increased adrenocorticotropic hormone (ACTH) secretion in patients with bipolar disorder, as reported in a 2014 review.\(^1\)

- Although the role of abnormal HPA axis activity in bipolar disorder pathophysiology is unclear, associations between HPA axis activity and neural-structural alterations have been observed in drug-free patients.\(^2\)

- Elevated cortisol was reported in meta-analyses of drug-free and medicated patients with bipolar disorder.\(^2,3\)

Bipolar Disorder: Pathophysiology, Behavioral Risk Factors, and Common Physical Comorbidities
Dopamine and Glutamate May Be Disrupted in Bipolar Disorder

Abnormalities in dopamine and glutamate signaling have been found across states of bipolar disorder\textsuperscript{1,2}

The dopamine hypothesis of bipolar disorder suggests hyperdopaminergia/hypodopaminergia during mania versus depression, respectively\textsuperscript{2}

The effects of dopamine may be mediated by glutamatergic signals in the prefrontal cortex\textsuperscript{1,3}

This content is theoretical and more research is needed to confirm this hypothesis for bipolar disorder

Dopamine Dysregulation May Be Associated with the Manic Features of Bipolar Disorder

Evidence from pharmacologic and imaging studies suggest a hyperactive dopaminergic network underlies mania in bipolar disorder\(^1,2\)


This content is theoretical and more research is needed to confirm this hypothesis.
Increased Odds of Hepatitis C Were Observed in Patients With Both Bipolar Disorder and Substance Use Disorder

A 2008 study suggested patients with bipolar disorder, substance use disorder, or co-occurring disorders had greater rates of hepatitis C infection compared with controls.

Higher Odds of Respiratory Diseases Have Been Observed in Patients With Bipolar Disorder

A 2004 survey study reported greater odds of respiratory diseases in patients with bipolar disorder compared to the general population.

The odds for asthma, chronic bronchitis, and emphysema were approximately 2.5, 4.2, and 3.6 times greater, respectively, when controlling for tobacco smoking.

Patients with Bipolar Disorder Experienced Increased Odds for Cardiovascular Comorbidities

A 2017 electronic health records data analysis identified patients with bipolar disorder had >1.5 times the odds for cardiovascular comorbidities compared with controls.

Greater odds of hypertension compared with controls

Greater odds of stroke compared with controls

Opportunities for Mental Health Providers to Manage the Whole Patient
There Are Several Strategies for Improving Care for Patients with SMI


- Sharing electronic health records between physical and mental health care systems
- Regular monitoring
- Referral to specialized services
- Enhancing tobacco smoking cessation efforts
- Promoting integration of care
The APA practice guideline for schizophrenia suggests patients with SMI, and schizophrenia in particular, may more frequently experience a variety of health conditions and should discuss relevant physical and laboratory assessments that may be needed with their physician as part of initial evaluation and follow up assessment.

These health conditions include, but are not limited to:

- Cancer
- Cardiovascular Disease
- Obesity
- Metabolic Syndrome
- Diabetes Mellitus
- Hepatitis C
- HIV infection
- Sleep Apnea
- Poor Oral Health

The APA published these guidelines with a statement that they are undergoing copyediting and that the final version is expected to be released summer 2020.
Summary

• The pathophysiology of bipolar disorder or schizophrenia may include dysfunction across several neurotransmitter systems¹-⁵

• Dysfunction and comorbidities across several non-CNS systems have also been observed⁶-¹⁰

• There is an opportunity to improve whole patient care through comprehensive management of comorbidities and behavioral risk factors that may be present in patients living with bipolar disorder or schizophrenia¹¹,¹²

For more information and to download this presentation, please visit:

ExamineComorbidities.com