The Treatment of Schizophrenia

Joseph P McEvoy, MD
Medical College of Georgia
Potential COIs

• Advisory Boards/Consultant: Neurocrine, Otsuka, TEVA
• Research Grants: Alkermes, Avanir, Boehringer-Ingelheim, Otsuka, TEVA
• Paid CME Lectures: Global Medical Education, North American Center for Continuing Medical Education
Overview -- 1

• The primary pathophysiology of schizophrenia involves widespread disruption of cortical circuitry, perhaps through excessive pruning, during development.

• This results in deficits in sensorimotor, cognitive, and social function, communication, and motivation, demonstrable in neonates, progressing through development until the transition to psychosis, and then remaining stable.

• 30-50% of the first-degree relatives of patients with schizophrenia demonstrate these deficits, to a less severe degree than in those individuals who transition to psychosis.
Overview -- 2

• These deficits **do not respond to treatment with antipsychotic medications**

• These deficits must be addressed through **accommodations** (we adapt our actions and the therapeutic environment to the deficits) and **protheses** (we bypass the deficits through the actions of unimpaired or less impaired others).
The secondary pathophysiology of schizophrenia involves the loss of control of ventral tegmental area dopamine neurons that ramify through the associative striatum and limbic structures ("dopamine storms").

This results in the abnormal, involuntary assignment of salience to random aspects of sensory experience and intrapsychic life ("limbic chorea").

The manifestations of this secondary pathophysiology include hallucinatory experiences, delusional beliefs, and disorganized behavior.
Overview -- 4

• This “positive” psychopathology does respond to the dopamine - D2 - shielding activity of antipsychotic medication

• This secondary pathophysiology is a chronic biological illness (similar to hypertension or diabetes mellitus); the chronic care model offers an organized action plan for achieving and maintaining remission
Definitions of “Treatment” (Google)

• The manner in which someone behaves toward or deals with someone or something; synonyms: handling of, dealings with, management of

• Medical care given to a patient for illness or injury; synonyms: medical care, therapy, nursing, ministrations; medication, drugs, medicaments
“Treatment” (Medical Care)

• “Treatment” (definition 2, medical care) for schizophrenia is simple; it is limited to the use of DAD2 shields to reduce positive psychopathology, and emanates from four questions:
  • **Start** a first-line antipsychotic medication (APM)?
  • Utilize a **long-acting injected preparation** of the first-line APM?
  • Transition to the second-line APM, **olanzapine** (remission not achieved with a first-line APM)?
  • Transition to the third-line APM, **clozapine** (remission not achieved with olanzapine)?
“Treatment” (Behaves Toward)

• In order to achieve success with treatment (definition 2, medical care), clinicians must be skillful at treatment (definition 1, i.e. how to behave toward or deal with patients with schizophrenia and the important others in their lives)

• Patients with schizophrenia have fixed impairments that interfere with their being informed, activated patients who assist in the self-management of their chronic biological illness; when they are actively psychotic their sensory experience and intrapsychic life is constantly intruded upon, and their conceptual frameworks have little, if any, overlap with the frameworks of treating clinicians
Schizophrenia in DSM -- V

• The DSM – V criterion A for schizophrenia focuses on psychosis (positive psychopathology: delusions, hallucinations, disorganized speech, disorganized or catatonic behavior), with limited mention of negative psychopathology; impaired function is discussed briefly in criterion B.

• However, the primary pathophysiology of schizophrenia is manifest long before the appearance of psychosis as impairments in the grace and efficiency of movement, sensory processing, cognition, motivation, communication, and social interaction. The profundity of the fixed deficits resulting from the primary pathophysiology determines function.
Schizophrenia/Primary Pathophysiology

• The primary pathophysiology and the associated impairments progress until the transition into psychosis, and remain stable thereafter as fixed deficits.

• Treatment (definition 2, medical care) with APMs does not reverse these deficits.

• Treatment (definition 1, behave toward) is comprised of adaptations to these fixed deficits before, during, and after the transition to psychosis in patients with schizophrenia and in the substantial portion of their close relatives who also express these deficits.
The Deficits Resulting from the Primary Pathophysiology

• Clinicians cannot behave toward individuals with these fixed deficits in the same ways they behave toward their unaffected friends, relatives, colleagues, and their patients with other disorders unassociated with these fixed deficits, and expect successful outcomes.

• Informed, useful ways we can behave toward patients with schizophrenia and the subset of their close relatives with these fixed deficits (treatment, definition 1) include accommodations (we adapt our actions and the therapeutic environment to the deficits) and prostheses (we bypass the deficits through devices or the actions of unimpaired or less impaired others).
The Fixed Deficits Have Been Demonstrated Through...

• Studies of the **offspring of parents with schizophrenia**
• **Cohort studies** prospectively characterizing large populations for decades and then retrospectively comparing the early attributes of those who transition to psychosis versus those who do not
• Studies comparing patients with **first episode psychoses or established psychosis** to matched general population controls
• Studies comparing the **first-degree relatives of patients with schizophrenia** to matched general population controls
The Offspring of Parents with Schizophrenia

**Psychiatric Outcomes in Adulthood**

- From 15% (one parent) to 40% (both parents) of the offspring of parents with schizophrenia develop psychotic disorders in adulthood.
- Many also receive other psychiatric diagnoses such as mood or anxiety disorders.
- The offspring of patients with schizophrenia are at high risk for schizophrenia but, more broadly, for poor developmental and general mental health outcomes.
The Offspring of Parents with Schizophrenia

*Perceptual and Motor Development*

- “’Pan-dysmaturation’… a global pattern of **delayed motor and visual-motor ability**...in early infancy” (Barbara Fish)
- “…rated low on motor development …significantly more clumsy, spontaneous movements, choreatic involuntary movements…and poor motor balance with eyes closed” (Swedish High-Risk Study)
- “…more likely to have **lower scores on motor coordination, sensory perceptual signs, and motor balance**” (Israeli High-Risk Study)
The Offspring of Parents with Schizophrenia

Cognitive Development

• “IQ in infancy, verbal ability in early childhood, and visual-spatial skills in late childhood had the largest between group differences” (Hameed and Lewis, 2016)

• FHR children produced less speech and had a number of distinct discursive features, such as less cohesion between ideas and unclear or ambiguous references to previous ideas (Stony Brook High-Risk Study)

• “…a significant main effect of parental diagnosis on child IQ at age 7, which was robust to control for socioeconomic status, ethnicity, site, and mother’s age at birth (Boston and Providence NCPP High-Risk Study)
The Offspring of Parents with Schizophrenia

Social Behavior

• “In late childhood, FHR children exhibited lower social competence at school, were prone to higher emotional distress and aggressive distractible behavior, and were more likely to be identified as socially abrasive and withdrawn” (Hameed and Lewis)

• FHR children (during infancy) were characterized as passive, quiet, and socially isolated, and as having poor affective control, on teacher, peer, and parent reports” (New York Infant Study)
The Offspring of Parents with Schizophrenia

Social Behavior, continued

• “...the FHR group showed more **confusion, contradiction, and conflict in their self-perception**; lower self-esteem; higher levels of defensiveness about their self-concept; higher levels of maladjustment; and less personality integration” (Israeli High-Risk Study)

• “FHR children had significantly lower profiles pertaining to expression of affection and hostility; **poorer communicative competence**; and higher levels of expressed negative affect” (Emory University Project)
A Prospective Cohort Study

• The 9,236 members of the Philadelphia cohort of the National Collaborative Perinatal Project were screened for mental health service utilization in adulthood, and chart reviews were performed to establish diagnoses according to DSM-IV criteria.

• Pre-schizophrenic cases (and their unaffected siblings who were also cohort members) manifested cognitive impairment, abnormal involuntary movements and coordination deficits, and poor social adjustment during childhood.

• Preschizophrenic cases did show deviance on an increasing number of functional indicators with age.

Cannon TD et al. Dev Psychopathol. 1999 Summer;11(3):467-85
First-Degree Relatives of Patients with Schizophrenia: Cognitive Deficits

• This review reports mean effect sizes for 43 cognitive test scores from 58 studies of cognitive performance in the unaffected adult relatives of schizophrenia patients. Results indicate **reliable relative-control differences**

• Four of the 6 largest effect sizes reflect **tasks with high executive control demands in common**, such as working memory demands, set shifting, and inhibition of prepotent responses

Neurological Soft Signs in Schizophrenia

Relationship with Negative Psychopathology

• Neurological soft signs are **present in 50-65% of patients** with schizophrenia

• The **negative subtype of schizophrenia** showed significantly higher **neurological soft signs** in comparison to the positive subtype

• In first episode psychosis patients, a **relationship between severity of neurological soft signs and negative psychopathology** was found

Overview

Evenly Hovering Attention

- The fixed deficits in the grace and efficiency of movement, sensory processing, cognition, motivation, communication, and social interaction are **demonstrable in neonates and youth who will later transition to psychosis**, and, **to a less severe degree in a substantial (30-40%) percentage of the first-degree relatives** of those who transition to psychosis.

- The **deficits are overlapping**; those who have any are likely to have others.

- **Composite scores** are more robust as measures of the deficits than any individual item or subscale.
Overview

Evenly Hovering Attention

• The primary pathophysiology appears to be widespread, unfocussed, suggesting it affects a common mechanism in multiple (perhaps all) brain areas rather than a mechanism unique to a particular brain region.

• 2016 offered a candidate for the fundamental process. (Sekar et al. Schizophrenia risk from complex variation of complement component 4. Nature 2016; 530: 177-183)
Complement Component C4

Excessive Pruning

• Schizophrenia’s strongest genetic association at a population level involves variation in the major histocompatibility complex (MHC) locus... this association arises in part from many structurally diverse alleles of the complement component 4 (C4) genes.

• In mice, C4 mediates synapse elimination during postnatal development. These result implicate excessive complement activity in the development of schizophrenia and may help explain the reduced numbers of synapses in the brains of individuals with schizophrenia.” (Sekar et al, 2016)
Complement Component C4

Excessive Pruning

• “The complement pathway has been implicated in synaptic pruning, a developmental process in which the synaptic connections between neurons are continuously eliminated in the brain until early adulthood.

• Using a mouse model, Sekar et al found that C4 expression is upregulated during periods of synaptic pruning. By contrast, mice deficient in C4 showed signs of decreased pruning. Thus, the authors postulate that increased C4A expression in individuals with schizophrenia results in increased synaptic pruning.

• Interestingly, studies of the brains of humans with schizophrenia have shown that affected individuals exhibit thinning and reduced synaptic structures in the cortical region of the brain compared with people without the disorder. Hyperactive synaptic pruning might explain these findings.”

The Fundamental Process

Evenly Hovering Attention

- Widespread, unfocussed, excessive pruning could explain the widespread fixed deficits in multiple brain functions, through degradation (but not elimination) of the circuits (wiring diagrams) that underlie these functions.
Pathways

Environmental risk + genetic risk factors → Basic symptoms → UHR → Early prodrome → Late prodrome → Schizophrenia, Other psychotic disorder, Other psychiatric disorder, No symptoms

Multiple pathways to schizophrenia + multiple pathways from UHR

UHR = ultra high risk.
The Epiphenomenon

*Unmanaged Dopamine-Releasing Tracts*

• In a subgroup of those afflicted, the primary pathophysiology accelerates in late adolescence and early adulthood and results in degradation of prefrontal-thalamic-hippocampal circuits that manage the activity of ventral tegmental area dopamine-releasing tracts ramifying through the associative striatum and limbic structures. **Storms of dopamine** buffet those **brain areas that assign salience** (“true-ness”, emotional valence, connectedness) **to items of sensory experience and intrapsychic life**. Random events in sensory experience are imbued with significance and/or interconnection; aspects of intrapsychic life (e.g. internal speech) are made vivid and externalized.
Dopamine Storms

• Consider the dopamine tracts that rise from the substantia nigra and ramify through the motor networks of the basal ganglia
• When these die (Parkinson Disease) there is a decreased readiness to move
• When there is excessive disorganized neuro-transmission through these pathways (chorea) there is an increased readiness to move
Dopamine Storms

- Consider a **limbic chorea**
- When there is excessive disorganized neuro-transmission through the dopamine pathways that ramify through the limbic system (limbic chorea; psychosis) there is an **increased readiness to assign salience to random incoming sensory experience, internal life, associations, etc**
Exacerbated Psychosis

• All investigations of patients experiencing an active psychotic episode at the time of scanning [18F-DOPA] report increased striatal DOPA uptake.

• As a group, individuals with schizophrenia are characterized by elevated presynaptic DA synthesis and storage, and this abnormality is most evident in individuals with active psychosis.
Howes et al, 2009

• Striatal [18F-DOPA] uptake significantly increased among individuals experiencing prodromal features of schizophrenia

• **DOPA uptake correlated significantly with the severity of prodromal features**

• Observed in the associative, but not the limbic or sensorimotor striatum
DA Release

• Patients experiencing an acute phase of illness, including those experiencing a first psychotic episode, have significantly increased striatal DA release compared to those in remission

• Hyper-responsive, dys-regulated subcortical DA system that fluctuates in its degree of dys-regulation during different phases of illness
Related to Positive Psycho-Pathology

• Increased striatal DA activity seems most relevant to positive psychopathology

• Severity

• Response

• Response of negative psychopathology is unrelated to striatal occupancy
The Early Experience of Schizophrenia

Accommodations in Interview Style

• “...observations of the attentive behaviour of schizophrenic patients suggested that communication might be improved if extraneous stimulation, in and outwith the room, were reduced. The interview was therefore conducted in a quiet setting, the patient and the observer sitting squarely face to face. The observer remained relatively immobile, avoiding irrelevant movements which had been noted previously to have a distracting effect on the patient.”
The Early Experience of Schizophrenia

Accommodations in Interview Style

• “The observer's verbal output was kept at a minimum, and the patient was allowed as much time as he wished to express himself. The patient was not discouraged or distracted from staring while speaking, since it was considered that this naturally reduced his visual perceptual intake, which might otherwise interfere with his performance.”

• “With this method of interviewing, patients who in ordinary circumstances might have had difficulty in providing information, could speak more spontaneously and coherently of their experiences, and the method proved fruitful in collecting clinical data which might not otherwise have been obtained.”
The Early Experience of Schizophrenia

Visual Perception

- Visual adaptation to the environment is normally achieved by the individual developing **the capacity to select, from the diffuse mass of visual stimuli impinging upon him, that information which is relevant and necessary for him to function efficiently.** In this process, sensory information is automatically organized during the act of perception itself, prior to short-term storage and subsequent integration with previous learning and experience.
The Early Experience of Schizophrenia

Visual Perception

• The following reports illustrate how visual perception may be disturbed in schizophrenia

• “Things go too quick for my mind. Everything is too fast and too big for me, too quick to study. Things get blurred and it's like being blind. I can't make them out clearly. It's as if you were seeing one picture one minute and another picture the next. I just stop and watch my feet. If I move, everything alters every minute and I have no control over my legs. My legs are too quick for the top half of my body. It's my head that's weak.
The Early Experience of Schizophrenia

Visual Perception

• Case 29: “Everything I see is split up. It's like a photograph that's torn in bits and put together again. If somebody moves or speaks, everything I see disappears quickly and I have to put it together again.”

• Case 22: “I’ve to put things together in my head. If I look at my watch I see the watch, watchstrap, face, hands and so on, then I have got to put them together to get it into one piece.”
First-Line Antipsychotic Medication

Goal of Treatment

• **Remission**: all positive psychopathology is rated “mild” or less, implying it is not constantly present, not distressing, and does not drive behavior

• **The sooner treatment is initiated** after the onset of first psychosis, or after a relapse resulting from discontinuation of medication

• **The longer treatment is assured**, the more patients achieve remission

• Younger patients, early in the course of illness, who have been psychotic for briefer periods are more likely to achieve remission and to achieve remission sooner
Treatment (Definition 2, Medical Care) for the Secondary Pathophysiology of Schizophrenia

• **Question 1: Start a first-line antipsychotic medication (APM)?**

• What will determine this?
  • Intrusiveness and **distress** caused by the experiences
  • Degree with which the experiences **affect behavior**
  • Presence of **self-injury** or thoughts of suicide
  • Presence of **aggression/violence** or thoughts of harming others

• **Duration of untreated psychosis** is a powerful predictor or remission
First-Line Antipsychotic Medication

Desirable Characteristics

• If oral administration, **once daily dosing**
• Availability of a **long-acting injected (LAI) preparation**
• **Benign side-effect profile** at appropriate dosing (EPSE, weight gain, metabolic abnormalities, prolactin-related side effects, sedation)
• **Affordable**
First-Line Antipsychotic Medication

Long-Acting Injected Preparation

• Question 2: Utilize a long-acting injected preparation of the first-line APM?

• Correlates of non-compliance with antipsychotic medication:
  • Male
  • Young
  • Co-morbid substance use
  • Lack of insight

Risk of symptom recurrence with medication discontinuation in first-episode psychosis

• Six studies were identified that met our criteria and these reported a weighted mean one-year recurrence rate of 77% following discontinuation of antipsychotic medication.

• By two years, the risk of recurrence had increased to over 90%.

• By comparison, we estimated the one-year recurrence rate for patients who continued antipsychotic medication to be 3%.

• In the absence of uncertainty about the diagnosis or concerns about the contribution of medication side effects to problems with health or functioning, a trial off of antipsychotic medications is associated with a very high risk of symptom recurrence and should thus not be recommended.

Zipursky RB et al. Schizophr Res. 2014 Feb;152(2-3):408-14
Medication Compliance

Following First-Episode Psychosis

• Treatment adherence and clinical course were assessed during the 18 months following presentation in 136 consecutive patients with a first episode of psychosis in 2003-2005 by a systematic retrospective case-note review.

• There were breaks in antipsychotic treatment of ≥1month in more than half of the patients (n=73; 58%). When these occurred before they had recovered (n=22; 17%), the time to remission was almost twice as long as in patients in whom treatment was continuous (t=2.9, P=0.01).

• Patients in whom treatment was interrupted were 5 times more likely to have relapsed than those in whom it was continuous (p=0.0001, 95%CI 2.1-11). The mean time to relapse following an interruption in treatment was 3 months.

Winton-Brown TT et al. Schizophr Res. 2017 Jan;179:50-56
Identifying the Patient’s Viewpoint


titl{Insight Deficits}

• Was it your idea to come to hospital/clinic?
• (If YES) What was your concern? What were you worried about?
• (If NO) Whose idea was it? What was that person’s concern? What was that person worried about?

• As you see it, do you have any nervous/mental problems?
• As you see it, do you need any treatment for nervous/mental problems?

“Trust but Verify”
Insight

First Episode Psychosis

• Older age, female gender and white ethnicity were associated with more insight.

• Higher total, positive, negative and general psychopathology scores on the Positive and Negative Syndromes Scale (PANSS) were associated with less insight.

• Higher depression scores were associated with more insight.

• Better neurocognitive function and large brain volumes were associated with more insight.

• More insight throughout the study was associated with longer time to medication non-adherence.

Medication Compliance
The Viewpoints of Patients

• This article is based on interviews with 19 persons diagnosed with psychosis. It challenges the notion of patients being either adherent or non-adherent to the doctor's orders. The findings show that persons with psychosis are active agents when it comes to adjusting medication. The interviewees created their own strategies to gain power over treatment with psychotropic drugs. The most common strategies were to adjust the doses or take breaks of varying lengths from the medication. These deviations from prescriptions were important to conceal, not only from their own psychiatrists, but from all psychiatric staff.

Medication Compliance
Financial Incentives – A Prosthesis

- Patients with a diagnosis of schizophrenia, schizoaffective psychosis or bipolar illness, receiving ≤ 75% of their prescribed LAI medication. In total, 73 teams with 141 patients (intervention n = 78 and control n = 63) were included.
- Participants in the intervention group received £15 for each LAI medication. Patients in the control group received treatment as usual.
- During the intervention period, adherence was significantly higher in the intervention group than in the control group (85% vs. 71%) Patients in the intervention group showed statistically significant improvement in subjective quality of life.
- Follow-ups: after incentives stopped, adherence did not differ significantly between groups, neither during the first 6 months nor during the period from month 7 to month 24.

Medication Compliance

Financial Incentives

• Financial incentives are effective in improving adherence to LAI medication.

• Once the incentives stop, the advantage is not maintained.

• The experiences of both patients and clinicians are largely, but not exclusively, positive.

With Great Power Comes Great Responsibility

• “I would not take a medication that made me feel like garbage. I do not expect you to.”

• **EPSE**: Look for akinesia, restlessness, tremor; ask about slowness, restlessness, tremor; examine for cog-wheeling, tremor

• **Anticholinergic**: ask about blurred vision, dry mouth, constipation; look at the pupils, look in the mouth

• **Weight**: Weigh the patient before starting the medication, and at least monthly; preempt weight gain (especially if using olanzapine or clozapine) with metformin, or topiramate
With Great Power Comes Great Responsibility

• **Limited physical activity**: this requires a prosthesis (an energetic, delightful activity therapist); avoid sedation and akinesia

• **Insulin resistance and dyslipidemia**: check lipid panel and HbA1c prior to starting an antipsychotic (especially olanzapine or clozapine); triglycerides are a leading metabolic indicator for insulin resistance; following glucose is a bad idea; preempt with metformin

• **Sexual function**: Ask about interest/desire, performance, orgasm
Team-Based Intervention for FEP

- Education/Employment Specialist: Patients recovering from a FEP are interested in returning to school or work, a social life, living independently
- Educator/Family Educator: Identification of key points, and making sure everyone is using the same playbook
- Prescriber
- These are prostheses
- They accommodate their interventions
Treatment (Definition 2, Medical Care) for the Secondary Pathophysiology of Schizophrenia

- Transition to the second-line APM, olanzapine (remission not achieved with a first-line APM)?
- Olanzapine offers **greater therapeutic efficacy for positive psychopathology** (including violence) than the first-line antipsychotic medications
- Olanzapine has a **substantially greater side effect burden** than the preferred first-line antipsychotic medications

- Should you preempt these side effects?

Zhao YJ et al. BJPsych Open. 2016 Feb 5;2(1):59-66
Treatment (Definition 2, Medical Care) for the Secondary Pathophysiology of Schizophrenia

• Transition to the third-line APM, clozapine (remission not achieved with olanzapine)?

• Clozapine offers clinically meaningful additional efficacy in reducing positive psychopathology in the majority of patients who do not achieve remission with first-line APMs or olanzapine

• Self-injury/suicide and/or aggression/violence should expedite the transition to clozapine
Krakowski
Intercept
Chronic Care Model

• A prepared, proactive practice team interacting with an informed, activated patient

• Self-management support
• Clinical information systems
• Delivery system re-design
• Decision support
• Health care organization
• Community resources

Bodenheimer T et al. JAMA 2002: 288: 1775-1779
Chronic Care Model

• Under a system designed for acute rather than chronic care, patients are not adequately taught to care for their chronic illnesses. Visits are brief and little planning takes place to ensure that acute and chronic needs are addressed. Lacking is a division of labor that would allow non-physician personnel to take greater responsibility in chronic care management. Too often, caring for chronic illness features an uninformed, passive patient interacting with an unprepared practice team, resulting in frustrating, inadequate encounters.

Bodenheimer T et al. JAMA 2002: 288: 1775-1779
Accommodations in Information Transfer

**Slow-Drip**

- Reduce the information to the key material
- Break this key material into multiple brief sessions in which small amounts of material are presented in each session
- The material in each session should be overlapping, briefly reprising the prior material and adding new material
- Test at the end of each session for comprehension, and remediate

- Use multiple media (not at the same time)
Accommodations in Information Transfer

The Environment for Transfer

• Limited distractions (quiet, the smallest number of people possible)
• Limited stress
• Availability of trusted others (e.g. family)
Prosthetics

• Long-acting injected medications (replacing insight and a commitment to compliance)

• Activity therapists (enthusiastically encouraging patient through enjoyable activities that optimally include socialization and physical activity)

• Transportation (shuttle buses, bus passes, taxis)

• Incentives (payment per LAI injection)
Disease/Course Alteration or Prosthesis
Disease/Course Alteration or Prosthesis
When the FEP Program is Stopped...
The myth of schizophrenia as a progressive brain disease

• The majority of people with schizophrenia have the potential to achieve long-term remission and functional recovery.

• The fact that some experience deterioration in functioning over time may reflect poor access, or adherence, to treatment, the effects of concurrent conditions, and social and financial impoverishment.

Thank you for your attention
Pathways

Multiple pathways to schizophrenia + multiple pathways from UHR

UHR = ultra high risk.
“Trust but Verify”
Disease/Course Alteration or Prosthesis
Disease/Course Alteration or Prosthesis
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