Treating Schizophrenia in the Real World to Improve Outcomes

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Disclosure Statement

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The Treatment of Psychosis is Really Simple

- Detect psychosis early
- Pick a DAD2 shield and use it correctly
- Support compliance
- Treat prominent affective psychopathology
- If therapeutic response is inadequate, try olanzapine, then clozapine
- Maintain general physical health

What Would We Like to Be Able to Treat?

- Positive psychopathology
- Affective psychopathology
- Negative psychopathology
- Cognitive psychopathology

Positive Psychopathology

- This is what defines “psychosis”
- This appears far along in the process of psychotic disorders such as schizophrenia. We do not know the patho-physiology of the primary processes
- Positive psychopathology results from storms of dopamine into limbic structures
- All of our “antipsychotic” medications shield DAD2 receptors from the dopamine storms

Affective Psychopathology

- The “boundaries” between “psychotic” and “affective” disorders are insubstantial
- We treat affective psychopathology with the same medications whether it arises in a “psychotic” or “affective” disorder
- Affective psychopathology can “worsen” positive or negative psychopathology

Negative Psychopathology

- This may appear well before psychosis and likely reflects loss of tissue and function in regions that support motivation and engagement
- Longer duration of untreated psychosis is associated with more negative psycho-pathology
- We have no treatments that reverse negative psychopathology

Cognitive Psychopathology

- Cognitive impairment is present years before psychosis appears, likely reflecting loss of tissue and function in areas that support cognition.
- There appears to be accelerated loss of cognitive function during the prodrome.
- We have no treatments that reverse cognitive psychopathology, though some agents with potential are in clinical trials
- Maintaining patients' general health limits further progressive decline

When Do We First Treat?
First-episode Psychosis

- This is when patients with schizophrenia come to our attention.
- This is actually well along in the course of schizophrenia. Much has already been lost, and we cannot bring it back.

What Do We Treat?
Positive Psychopathology

- Dysregulation of mesolimbic dopamine systems leads to storms/squalls of dopamine release in limbic structures
- Limbic structures assign salience to features of sensory experience and internal life
- Aberrant attribution of salience occurs

Heinz A, et al. *Schizophr Bull.* 2010;36(3):472-485.

Positive Psychopathology

- “True-ness,” “connectedness” is incorrectly assigned to events and experiences (delusions)
- Internal speech becomes vivid and externalized (hallucinations)
- Experience and purpose are intruded upon (disorganization)

Heinz A, et al. *Schizophr Bull*. 2010;36(3):472-485.

Positive Psychopathology
"Limbic Chorea"

- Abnormal involuntary salience is applied, much as abnormal involuntary movements occur when storms/ squalls of excessive dopamine activity pass through nigro-striatal dopamine systems
- Instead of a uninitiated, random movements, the individual first experiencing psychosis has uninitiated, random "trueness," "connectedness," and emotional power assigned to sensory experience and internal life

Ben-Pazi H, et al. *PLoS One*. 2013;8(9):e73516

Disturbances in Speech Production

- “The words wouldn’t come out right. I know how to explain myself but the way it comes out of my mouth isn’t right.
- “My thoughts run too fast and I can’t stop the train at the right point to make them go the right way.
- “Big magnified thoughts come into my head when I am speaking and put away the words I wanted to say, and make me stray away from what was in my mind.”

Chapman J. *Brit J Psychiatry*. 1966;112(484):225-251.

How Do We Treat Positive Psychopathology? DAD2 Shields

- DAD2 antagonists or partial agonists
- The sooner we start treatment with DAD2 shields, the better.
- The more consistently we maintain treatment with DAD2 shields, the better.

Fraguas D, et al. *Schizophr Res*. 2014. pii: S0920-9964(14)00330-2.

Duration of Untreated Psychosis

- The longer positive psychopathology endures prior to the application of effective treatment (DAD2 shields in limbic structures), the longer it endures after treatment begins and the more likely some positive psychopathology will persist.
- Repeated treatment noncompliance and relapse is also associated with declining treatment responsiveness

Cechnicki A, et al. *Psychiatry Res*. 2014;219(3): 420-425.
Emsley R, et al. *Schizophr Res*. 2013; 148(1-3):117-121.

First-Generation (Conventional) Antipsychotic Medications

- DAD2 antagonism is all these agents offer toward therapeutic benefit
- Their other varying pharmacologic actions only contribute to the differences in their side effect profiles

McEvoy JP, Zigman D, Margolese HC. *Can J Psychiatry*. 2010 Mar;55(3):144.

The Neuroleptic Threshold

- Blockade of 60-70% of DAD2 receptors is adequate to initiate therapeutic response
- Blockade of 70-80% of DAD2 receptors results in coarse bradykinesia-rigidity
- Tailoring individualized doses to the appearance of slight bradykinesia-rigidity (the neuroleptic threshold) allows therapeutic benefit to unfold with minimal EPSE

McEvoy JP, Hogarty GE, Steingard S. *Arch Gen Psychiatry*. 1991 Aug;48(8):739-45.

The Neuroleptic Threshold

- In patients with prior extended exposure to conventional antipsychotic medications, the mean NT haloperidol dose is ~ 6 mg daily. In patients experiencing first-episode psychosis, the mean NT dose is ~ 2 mg daily

McEvoy JP, Hogarty GE, Steingard S. *Arch Gen Psychiatry*. 1991 Aug;48(8):739-45.

Extrapyramidal Side Effects

- Conventional antipsychotic medications should only be used at doses below those that produce coarse extra-pyramidal side effects
- Anticholinergic drugs are not an acceptable solution and should be used sparingly, if at all
- Some patients are exquisitely sensitive to EPSE and should be treated with atypical antipsychotic medications

Extrapyramidal Side Effects

- Dystonia
- Bradykinesia-rigidity
- Akathisia
- Tremor

Tardive Dyskinesia

- Risk is limited by using appropriate low doses of conventional antipsychotic medications
- The strongest predictor of TD is the prior presence of acute EPSE (bradykinesia-rigidity, restlessness, dystonia, tremor)

Neuroleptic Malignant Syndrome

- Muscle rigidity
- Muscle damage (creatine phosphokinase and myoglobin release)
- Fever (heat produce by muscle rigidity and infections resulting from immobility). Immobility leads to mortality.
- “Autonomic instability” (resulting from muscle rigidity and dehydration)

Catatonia

- Immobility leads to mortality
- Benzodiazepines relieve catatonic immobility in the great majority of cases; electro-convulsive therapy relieves the rest
- Patients who manifest catatonic features are at increased risk for NMS

Not Everyone Gets Better; What Should We Do?

- If treatment resistance is present at first-episode (e.g. with early onset psychosis) or develops over the course of several relapses, move to clozapine
- Prominent aggression/violence or self-injurious/suicidal behavior should accelerate the move to clozapine

Warnez S, et al. *BMC Psychiatry*. 2014;14:102.

Clozapine

- ~30% of patients with schizophrenia should be receiving clozapine
- < 5% of patients with schizophrenia are receiving clozapine
- Clozapine clinics, like warfarin clinics, are needed, staffed by clinicians willing to develop the knowledge and skill to safely prescribe and manage clozapine

The Logistics of Clozapine

- A knowledgeable, skilled clozapine prescriber
- A laboratory where required tests can be performed and that will reliably fax results to the prescriber and to the dispensing pharmacy
- A pharmacy that will stay in contact with the laboratory and the prescriber

Preparations for Starting Clozapine

- Review the potential benefits and risks with the patient and involved others.
- Inform them that the patient may need to take several additional medications
- Taper and discontinue agents that are not needed, especially those with the potential to lower WBC and ANC (e.g. valproate)
- Consider starting lithium

Clozapine Side Effects

- Early and dangerous: agranulocytosis, myocarditis, venous thromboembolism, seizures
- Enduring and dangerous: atherosclerotic cardiovascular disease (via weight gain, insulin resistance, and dyslipidemia), constipation
- Annoying: excess saliva, enuresis/nocturia, sleepiness

Agranulocytosis

- CBC weekly for 6 months, then Q2weeks for 6 months, then Q4weeks thereafter
- Benign ethnic neutropenia
- Lithium, afternoon blood draws

Myocarditis

- Risk is front-loaded with peak at 2 weeks
- Baseline and weeks 1, 2, 3, and 4: eosinophil counts, CPK or troponins, sedimentation rate or C-reactive protein

Venous Thrombo-embolism

- Seven-fold increased risk with clozapine and olanzapine
- Preempt with aspirin and a statin

Seizures

- Ask about prior seizure history, including febrile convulsions
- Preempt or manage with anticonvulsants (preferably not valproate or carbamazepine)

Atherosclerotic Cardiovascular Disease (Heart Attacks and Strokes)

- Weight gain and insulin resistance can be mitigated with metformin
- If non-HDL cholesterol > 130, consider a statin
- Consider aspirin

Mizuno Y, Suzuki T, Nakagawa A, et al. *Schizophr Bull*. 2014 Nov;40(6):1385-403.

Constipation

- Fluid, fiber, and exercise
- Stool softener
- Non-stimulating laxatives
- Nausea/vomiting may indicate constipation

Second-Generation (Atypical) Antipsychotic Medications

- Serotonin 5HT2 antagonism added to DAD2 shields
- Clozapine was noted to manifest strong 5HT2 antagonism
- DAD2/5HT2 hypothesis originally tested by adding ritanserin (a 5HT2 antagonist) to low-dose haloperidol, leading to the synthesis of risperidone

Second-Generation (Atypical) Antipsychotic Medications

- Mitigation of EPSE
- Mitigation of “misery”
- Improved sleep architecture
- No improvement in therapeutic efficacy*

Second-Generation (Atypical) Antipsychotic Medications

- The first SGAs traded off less EPSE for substantial weight gain, insulin resistance, and dyslipidemia
- *Olanzapine offers additional therapeutic efficacy, but not as much as clozapine

Lieberman JA, Stroup TS, McEvoy JP. *N Engl J Med*. 2005 Sep 22;353(12):1209-23.

Second-Generation (Atypical) Antipsychotic Medications

- Later atypical antipsychotic medications produce less weight gain/metabolic burden, e.g. aripiprazole, lurasidone
- Appropriately-dosed antipsychotic treatment should now result in no subjective burden and minimal or no objective side effects

Future Treatments: Phase III

- Raloxifene Hcl
- Paliperidone LAI
- Aripiprazole Lauroxil
- Cariprazine
- Lamotrigine
- Encenicline hydrochloride
- Zicronapine
- AVN-211

Cariprazine in Schizophrenia

- D3 preferring D3/D2 partial agonist
- Four double blind placebo controlled six week trials reported
- Three of four studies positive at doses of 1.5-9 mg/day including one 48 week open label extension
- Insomnia, EPS, sedation, nausea, akathisia, constipation, and dizziness side effects
- Minimal weight gain and metabolic effects

Citrome L. *Adv Therapeutics* 2012:29: 815-825.

Not Everyone Gets Better; What Should We Do?

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Warnez S, et al. *BMC Psychiatry*. 2014;14:102.

Cognitive Psychopathology

- Children who will eventually develop schizophrenia begin school at a level of functioning that is a full grade behind their peers, with the gap increasing by the time they finish high school

Cognitive Psychopathology

- The cognitive deficits in patients with schizophrenia are robust, with a 1.5 to 2.5 standard deviation gap between patients and healthy controls on composite scores
- Even at first episode, these large deficits are already established

Keefe RS. *J Clin Psychiatry*. 2014;75 Suppl 2:8-13.

Cognitive Psychopathology

- First-episode and chronic schizophrenia patient groups have nearly identical profiles showing generalized impairment, particularly in verbal memory and learning, attention-vigilance, and speeded visual-motor processing and attention
- Verbal memory and learning accounted for most of the variance between patients and controls

Saykin AJ, et al. *Arch Gen Psychiatry*. 1994 ;51(2): 124-131.

How Do We Treat Cognitive Psychopathology?

- So far, multiple pharmacological strategies including enhancing glutamatergic activity, cholinesterase inhibitors, and stimulants have failed to improve cognitive functioning
- Enhancing nicotinic activity still remains viable as a strategy to enhance cognition

Negative Psychopathology

- Factor analyses of negative symptom scales routinely identify only 2 domains:
- Diminished expression, which includes affective, linguistic and paralinguistic expression deficits
- Avolition/apathy for daily life and social activities

Messinger JW, et al. *Clin Psychol Rev*. 2011;31(1):161-168.

Negative Psychopathology and Duration of Untreated Psychosis

- Long DUP correlated statistically significantly with poor general symptomatic outcome, more severe positive and negative symptoms, lesser likelihood of remission and poor social functioning and global outcome (correlations 0.13-0.18)
- Long DUP was not associated with employment, quality of life or hospital treatment

Lutgens D1, Lepage M, Iyer S, Malla A. *Schizophr Res*. 2014 Jan;152(1):164-9.

Functional Outcomes

- Both amotivation/apathy and cognitive psychopathology independently contribute to longitudinal functional outcomes among patients with schizophrenia

Fervaha G, et al. *Acta Psychiatr Scand*. 2014. doi: 10.1111/acps.12289.

How Do We Treat Negative Psychopathology?

- So far, multiple pharmacological strategies have failed to reduce negative psychopathology

Poor Outcomes

- The poor outcomes so commonly observed are likely best explained by poor access to treatment, poor engagement in ongoing care, and poor adherence, together with the cumulative negative impact of substance abuse, comorbid medical and psychiatric disorders, and multiple social determinants of health

Zipursky RB. *J Clin Psychiatry*. 2014; 75 Suppl 2:20-24.

Metabolic Syndrome

- Repeatable Battery for the Assessment of Neurocognitive Symptoms (RBANS) total scale score as well as attention, immediate memory, and delayed memory scores in the Metabolic Syndrome group were significantly lower than those in the non-MS group ($p < 0.05$)

Li C, Zhan G, Rao S, Zhang H. *J Nerv Ment Dis*. 2014 Apr;202(4):313-8.

How Do We Limit Negative and Cognitive Psychopathology?

- Identify psychosis early and intervene immediately
- Avoid medication non-compliance and relapse
- Maintain physical health with both lifestyle change and pharmacological interventions

Long-Acting Injectable Antipsychotic Medications

- Real-time accurate intelligence about compliance
- Shared decision-making should be based on facts
- Only works if clinicians and important others in the patient's life will utilize the information about compliance

Long-Acting Injectable Antipsychotic Medications

- Greatest differential effects if started in hospital on patients who have relapsed because of non-compliance
- A reasonable strategy for patients experiencing a first psychotic episode

Affective Psychopathology

- Lithium carbonate
- Antidepressants

If Psychosis Treatment Was Run Like an Airline…

- We would have fewer antipsychotic medications. More, different airplanes mean that mechanics, pilots, and ground crews have to learn to do the same things lots of different ways
- We would have routines and checklists. Instead we have artists crafting non-evidence-based poly-pharmacies. There is copious evidence as to exactly how to use haloperidol, or olanzapine, or clozapine, evidence that is largely ignored

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