PSYCHOPHARMACOLOGY OF SCHIZOPHRENIA

- Past, present, but no future
-

Chittaranjan Andrade, MD
Professor in Psychopharmacology
National Institute of Mental Health and Neurosciences
Bangalore, India

INTRODUCTION

- Almost 70 years after the introduction of CPZ, scores of newer drugs have been introduced or studied in clinical trials.
  - Most of the marketed drugs are me-too: variations on a theme of D2 (and/or 5-HT2) blockade with differences in adverse effect profile but not efficacy.
  - Drugs with novel targets have failed (AMPA, NMDA, mGlu etc.).
  - Clozapine is slightly special, but mostly in refractory patients, and we still do not know why.

INTRODUCTION

- Almost 70 years after the introduction of CPZ:
  - Tardive dyskinesia has become rare.
  - But has the course and outcome of schizophrenia changed?
- The diagnosis of schizophrenia remains a heavy cross to bear.
- I suggest in this lecture that there may not be much room for hope with regard to new drug discovery.

THE PROBLEM OF DIAGNOSIS

Schizophrenia: What are we talking about?

- Effective treatment is usually based on good diagnosis and understanding of pathology.
- Schizophrenia is not a diagnosis; it is a description.
  - Like mental retardation
- Schizophrenia represents a large group of disorders
  - Heterogeneous in phenotype, etiology, biological characteristics, and outcomes.
- This inbuilt heterogeneity influences outcomes.
  - Medications only treat the **epiphenomena.**

TREATMENT: CAUSE vs PHENOTYPE: 1

- Treating the epiphenomena of schizophrenia without addressing the underlying pathology is like
  - Treating the fever in malaria without killing the parasite.
  - Or like treating the pain due to a fracture without resetting and immobilizing the broken bone.
- Symptomatic treatment will work only in conditions that are self-limiting
  - Viral fever
  - Many kinds of headache
  - The "inbuilt" good prognosis schizophrenias

Chittaranjan
Andrade

TREATMENT: CAUSE vs PHENOTYPE: 2

- Implication 1: Unless we treat the cause, the underlying pathology will remain with the patient.
  - Except in the "inbuilt" good prognosis schizophrenias.
- Implication 2: If we can understand and treat the cause, different and even individualized treatments will be necessary
  - With interventions beyond antipsychotics
  - Parallel with reversible dementias.

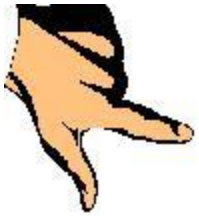
Chittaranjan
Andrade

CAUSES OF SCHIZOPHRENIA: Predispositions vs triggers: 1

- Do we know what the causes of schizophrenia are?
- Do we know what the pathogenesis of schizophrenia is?

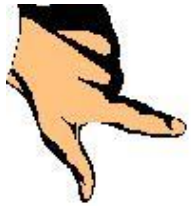
Chittaranjan
Andrade

CAUSES OF SCHIZOPHRENIA: Predispositions vs triggers: 2



- Possible models, based on genetic vulnerability:
  - Strong predisposition, no need for large trigger (e.g. stress)
  - Moderate predisposition, presence of trigger
  - Weak or no predisposition, presence of strong trigger (high levels of stress)

CAUSES OF SCHIZOPHRENIA: Predispositions vs triggers: 3

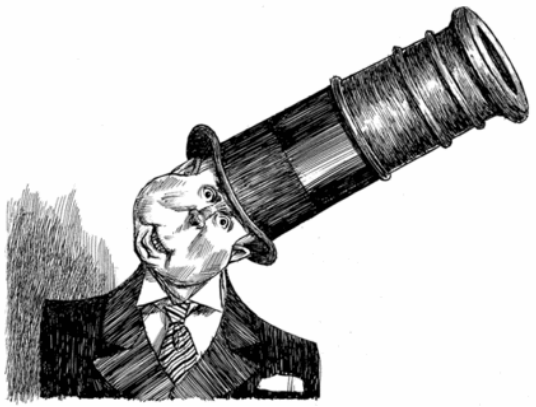


- Examples of neurodevelopmental predispositions:
  - Genes (DISC, dysbindin, neuregulin, COMT etc.)
  - Viral infection during pregnancy
  - Maternal exposure to famine during pregnancy
  - Perinatal complications
  - Head injury during early childhood

Chittaranjan
Andrade

CAUSES OF SCHIZOPHRENIA: Predispositions vs triggers: 4

- Examples of triggers with epigenetic effects:
  - Hormonal changes during adolescence
  - Toxins in air
  - Stress



CAUSES OF SCHIZOPHRENIA: Predispositions vs triggers: 4

- Interrelationships:
  - Genetic influences may increase the risk of obstetric complications.
  - Genetic influences and obstetric complications may each influence the risk of head injury
  - All of the above may increase the risk of exposure to stress, poor coping.

CAUSES OF SCHIZOPHRENIA: Predispositions vs triggers: 5

- Implication:
- Starting treatment for schizophrenia after the phenotype emerges is like starting treatment for complications of hypertension after the patient has suffered a myocardial infarction or intracranial bleed.

MODELS OF TREATMENT

- Primary prevention
  - Prevention of occurrence of the disorder
- Secondary prevention
  - Early diagnosis and treatment
- Tertiary prevention
  - Prevention of complications, and rehabilitation
- What are we doing in schizophrenia?

PRIMARY PREVENTION: A pipe dream: 1

- About a hundred genes have been implicated.
- We cannot change even a single gene and in specific anatomic loci
  - Consider Huntington's disease, as a parallel.
- The schizophrenia genes probably work in sets.
- At best, we can provide genetic counselling
  - But, how useful is this, given that 80% of schizophrenia occurs without family history; and penetrance of the genes is poor and variable.

PRIMARY PREVENTION: A pipe dream: 2

- Can improved antenatal, perinatal, and pediatric care reduce the risks?
  - No evidence of decreased risk of schizophrenia in developed countries.
  - Famine, viral infection in pregnancy, obstetric complications etc. may contribute very little to the variance in risk.
  - Or, the epigenetic effects of stress may drown out the benefits of improved healthcare.

PRIMARY PREVENTION: A pipe dream: 3

- Can early screening and institution of corrective or compensatory measures prevent the illness in predisposed persons?
  - Screening for what??
  - What compensatory measures??
  - The issue of lack of specificity of early diagnosis

SECONDARY PREVENTION: Disappointments

- Studies in high risk patients:
  - Difficulty in identifying patients with specificity
  - Inconsistent results with antipsychotic treatment (may delay but not necessarily prevent illness)
  - Success with omega-3 fatty acids not replicated
- Advantages: associated with reducing duration of untreated psychosis
- Disadvantages: associated with medication adverse effects, stigma, healthcare burden in false +ves

Chittaranjan
Andrade

TERTIARY PREVENTION: Where psychopharmacology is

- Targets:
  - +ve symptoms, mood symptoms (some efficacy)
  - -ve symptoms, cognitive deficits, impaired QoL, impaired functionality (little efficacy)
- Strategies:
  - Only D2 blockade, with or without 5HT2 blockade
  - Other strategies have not reaped dividends (other DA, NE, 5HT, ACh, NMDA, AMPA, mGlu, adenosine etc. approaches)
- Why the failures?

KEY POINTS: 1

- Schizophrenia is characterized by gross neuroanatomical changes:
  - Cortical atrophy, ventriclular dilatation
  - Changes from PFC to hippocampus to cerebellum, involving both hemispheres and including the corpus callosum
  - Histological changes (cortical cytoarchitecture)

KEY POINTS: 2

- These neuroanatomical changes do not develop overnight
- They are often present at birth, and progress through childhood into adult life; most are already present when psychosis is diagnosed, and there is little change thereafter.
- **These changes are almost certainly irreversible.**
- **By the time schizophrenia is diagnosed, it is already too late.**

TAKE-HOME MESSAGE: 1

- Primary prevention is almost impossible.
- Secondary prevention is impractical, and so far largely unsuccessful
- **The focus of psychopharmacological intervention and research is on tertiary prevention, by which time irreversible gross and histological changes have already developed.**
- If nothing has changed since 1952, nothing will change. This is the future.

TAKE-HOME MESSAGE: 1

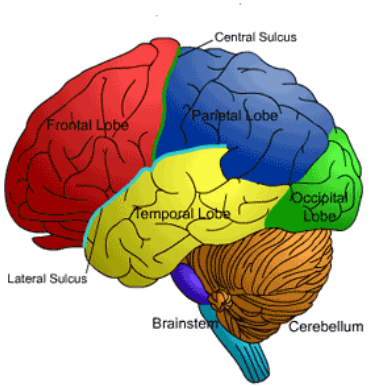
- The psychopharmacology of schizophrenia has reached its plateau, a glass ceiling that cannot be pierced.
- At best, we can hope for minor lateral improvements (compare with MR).
- Outcomes will continue to be determined by whether the patient has "inbuilt" good or poor prognosis schizophrenia.
- If nothing has changed since 1952, nothing will change. This is the future.

Chittaranjan
Andrade

AFTERNOTE, LEST I BE MISUNDERSTOOD

- Tertiary prevention is important.
- Tertiary prevention interrupts the potentially pathoplastic effect that failure to intervene exerts on course and outcome.
- Tertiary prevention is maximally helpful in "inbuilt" good prognosis syndromes.

REFERENCES



- Andrade et al (MSM 2012)
- Reply: Carpenter (MSM 2012)

FOR E-MAIL UPDATES ON RESEARCH IN PSYCHIATRY

- Synergytimes
- Write to andradec@gmail.com

ENFIN…

- That’s it, folks; thanks for listening!