Editorial

CITATION: Andrade C, Radhakrishnan R, Fernandes PP. Psychopharmacology of Schizophrenia: The Future Looks Bleak. Mens Sana Monogr 2012; 10: 4-12.

Psychopharmacology of Schizophrenia: The Future Looks Bleak

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ABSTRACT

Introduction: *More than half a century after the introduction of effective pharmacotherapy for the illness, in most patients schizophrenia remains a chronic, relapsing condition with poor long-term outcomes.*

Methods: *We examine the pharmacological treatment of schizophrenia from different perspectives to understand why there have not been significant advances, and to consider what the future might hold in store.*

Results: *We argue that the treatment of schizophrenia addresses the phenotype and not the cause; that the causes may not be treatable even if identifiable; that secondary prevention approaches involving treating the phenotype before full-fledged illness develops have, so far, not yielded promising results; and that shifting the focus of treatment from dopamine to other neurotransmitter systems is merely a tertiary prevention approach which will not reverse the extensive structural and functional pathology of schizophrenia.*

Conclusions: *We believe that, given the current state of our knowledge of the illness, the future of the pharmacotherapy of schizophrenia looks bleak.*

Key Words: *Pharmacotherapy; Primary prevention; Schizophrenia; Secondary prevention; Tertiary prevention*

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Received 6 Dec 2011. Revised 8, 9, 10, 14, 21 Dec 2011.Final Acceptance 23 Dec 2011.

DOI: 10.4103/0973-1229.91293

Introduction

Although medications have been available for schizophrenia for over half a century, the diagnosis remains a heavy cross to bear. What might the future have in store? In the rest of this article, we paint a pessimistic picture.

Diagnosis

The problem begins with the diagnosis itself. An important tenet of good medical practice is that efficient treatment is based on a knowledge of diagnosis and the underlying pathophysiology. Schizophrenia, however, is not a diagnosis; it is a description; that is, a phenotype. What schizophrenia is cannot be discerned from its phenomenology any more than what a person's gender is can be determined from the clothing. Furthermore, schizophrenia is almost certainly not a single disorder; it is a group of conditions (van Os *et al*., 2009[36]). Additionally, it is a group of conditions with extensive pathophysiological features (Keshavan *et al*., 2008[13]). Finally, it is a group of conditions with widely varying phenotypes, biological characteristics, and outcomes (Tandon *et al*., 2009[34]).

Treatment: Cause *vs* Phenotype

Current treatments of schizophrenia are based on the phenotype and treat the phenotype (Andrade, 2012[2]). Consider fever or pain as a parallel. We can effectively treat fever with antipyretics or pain with analgesics; but, if the underlying condition is not self-limiting, our treatment will remain incomplete until we treat the cause of the fever or of the pain. Most forms of schizophrenia do not appear to be self-limiting (Rabinowitz *et al*., 2007[27]). Therefore, we may treat the phenomenology of the illness with dopamine receptor antagonists, but unless we are able to effectively treat the cause of the illness, the diagnosis will remain with the patient. Treatment of the cause is also important because if causes are different, treatments can be different and even individualized.

Cause: Predispositions and Triggers

Can we treat the cause and the pathophysiological mechanisms that are intermediate between cause and phenotype? To do this, we must be able to identify both cause and mechanisms. So far, our knowledge of cause and pathophysiology, though extensive, is incomplete. The most popular model posits that, for schizophrenia to develop, there must be a predisposition and, afterwards, a trigger (Maynard *et al*., 2001[19]). Other models are possible; the predisposition may be so strong that no trigger is necessary and the individual will inevitably develop the illness. Or, no predisposition may be present, but the exposure to stress is so severe that psychosis manifests.

What are the predispositions? A wide range of genetic influences have been suggested, with important candidates including the DISC, dysbindin, neuregulin, and COMT genes (Stahl, 2008[31]). Other predisposing influences include viral infection during the second trimester of pregnancy (Penner *et al.*, 2007[24]), perhaps with season of birth moderating this variable (Davies *et al*., 2003[9]); maternal exposure to famine (St Clair *et al*., 2005[30]); obstetric complications around childbirth (antenatally, intranatally, and/or postnatally) (Cannon *et al*., 2002[5]); neurological insults such as head injury during early childhood (AbdelMalik *et al*., 2003[1]), and others (Tandon *et al*., 2008[33]).

What are the triggers? Hormonal changes during adolescence (van Rijn *et al*., 2011[37]) and toxins in air and diet (Do *et al*., 2009[10]) have both been suggested, but stress is the most significant candidate (Corcoran *et al*., 2003[7]). Muddying the picture, genetic influences may affect the risk of obstetric complications; both may separately affect the risk of cerebral insult during childhood; and all may separately affect the risk of poor coping and susceptibility to stress (Mittal *et al*., 2008[22]). So, treating the phenotype of schizophrenia after the clinical phenotype appears is akin to starting treatment for hypertension after the patient has suffered a myocardial infarction or an intracranial bleed.

Models of Treatment

Models of treatment in medicine are classified as primary, secondary, and tertiary prevention interventions. Primary prevention refers to the prevention of occurrence of the disorder. Secondary prevention describes early diagnosis and treatment. Tertiary prevention addresses prevention of complications and rehabilitation (Caplan, 1964[6]).

Primary Prevention

The primary prevention of schizophrenia is a pipe dream. With regard to genes, we cannot change the genes with which a person is born. At best, we can provide genetic counselling. However, this is a drop in the ocean because > 80% of patients with schizophrenia have no family history of illness (Tsuang, 2000[35]).

Can improved antenatal care, improved obstetric care, and improved neonatal and paediatric care reduce risks? In theory, yes; in practice, there are no data to indicate that countries with higher health care standards have a lower risk of schizophrenia (Saha *et al*., 2006[28]). One possible reason is that perinatal complications contribute little to the variance in the risk of the illness (Verdoux, 2004[38]).

Can we screen for and identify vulnerable individuals at birth and institute corrective or compensatory interventions? At present, we do not even know for

certain the extent to which various candidate genes contribute to the risk (Prasad *et al*., 2010[26]). Furthermore, it is now widely believed that no single gene causes schizophrenia; rather, a group of genetic influences are probably responsible (Girard *et al*., 2011[11]), and that's where our current understanding stops. With regard to perinatal complications, as already mentioned, such effects contribute little to the variance in the risk of the illness and so a very large number of persons with obstetric contributions will not develop schizophrenia in later life (Dalman *et al*., 1999[8]). When we cannot identify persons at risk, there is no possibility of even considering corrective or compensatory measures in order that the effect of the casual factors do not progress.

In theory, cellular or gene-based approaches should be considered at a primary prevention level, but have we made progress with simpler, monogenic disorders, such as Huntington's dementia, for which the genetic causes are known? If not, where is there scope to hope that we will succeed with schizophrenia?

Secondary Prevention

Where does psychopharmacology come in for the secondary prevention of schizophrenia? We cannot reliably identify persons who will go ahead to develop schizophrenia in later life. Even if we can identify such persons, there is nothing that we can do to treat the effects that genetic factors, obstetric complications, and other insults have on the developing brain. In the highest risk individuals, the use of antipsychotic drugs and behavioural interventions have yielded mixed results, are considered controversial and, at best, postpone the onset of the schizophrenia phenotype by a short period (McGorry, 2008[20]; Pelosi, 2008[23]; Marshall and Lockwood, 2004[17]).

With specific regard to prophylactic psychopharmacological intervention in high-risk individuals: The advantages theoretically include all the benefits associated with early recruitment into treatment in the true positives. These benefits could be better social outcomes, less risk of substance abuse and suicide, and other benefits that have been described with minimization of the duration of untreated psychosis (Marshall *et al*., 2005[16]; Perkins *et al*., 2005[25]; Melle *et al*., 2008[21]). The disadvantages are all the disadvantages associated with institution of treatment in the false positives, including medication adverse effects, stigma, and load on the healthcare system.

Tertiary Prevention

Tertiary prevention targets in psychopharmacology include positive symptoms, negative symptoms, mood symptoms, cognitive deficits, quality of life, and occupational functionality; the benefits are modest. Current psychopharmacological strategies primarily address the dopaminergic

neurotransmitter system (Andrade, 2012[2]). Fifty years of drug development towards dopamine postsynaptic receptor blockade with or without serotonergic modulation have merely resulted in variations on a theme of tolerability, with broad efficacy no different across the entire spectrum of drugs (clozapine excepted) (Kane and Correll, 2010[12]). Efforts in drug development now address various targets in glutamatergic, cholinergic, adenosine, serotonergic, and other neurotransmitter systems. There is no reason to believe that these strategies will be any more successful than those so far in use. Tinkering with proteins outside the cell can do little to change fundamental abnormalities that lie within.

Concluding Remarks [See Figure 1: Flowchart of Paper]

In summary, as already discussed, there is no way in which psychopharmacology can be called into play for primary prevention, and there is controversy about the benefits of current psychopharmacology for secondary prevention. Where psychopharmacology presently focuses is on tertiary prevention, after the disease has taken root. In affected patients, there are extensive changes in multiple territories in the brain, ranging from the prefrontal cortex to the cerebellum; from the hippocampus to the corpus callosum (Arnsten, 2011[4]; Andreasen and Pierson, 2008[3]; Tamminga *et al*., 2010[32]; Whitford *et al*.,

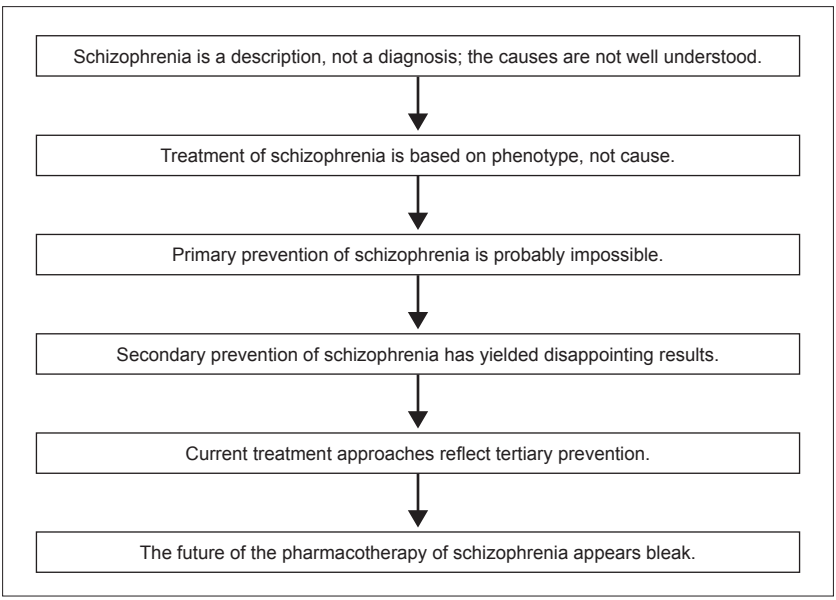

Figure 1: Flowchart of the paper

2010[39]). The changes are both gross, detectable on magnetic resonance imaging (Levitt *et al*., 2010[15]), and microscopic, identified by histopathological studies post mortem (Schnieder and Dwork, 2011[29]). These changes do not develop overnight; rather, they progress during childhood into adult life (Mattai et al., 2011[18]). And, these changes are almost certainly irreversible; it is unlikely, for example, that abnormal cytoarchitecture of the cerebral cortex can be changed by drug therapy. So, by the time the clinical phenotype is imminent or actually appears and drugs are pressed into play, it is already too late. In most forms of schizophrenia, therefore, all that psychopharmacology can do is to reduce complications and reduce symptoms so that rehabilitatory measures can be implemented.

As bleak as the future may seem, it is however, worth remembering that most of the significant discoveries in science have been unpredictable, serendipitous, and contradictory to scientific paradigms that were current (Kuhn, 1962[14]). The past and present state of research may hence not necessarily reflect the future.

Take home message

Primary prevention in schizophrenia is probably impossible. Secondary prevention approaches have so far met with disappointing results. The focus of drug discovery in schizophrenia lies in the realms of tertiary prevention, when the phenotype manifests, by which time extensive and probably irreversible structural and functional brain changes have developed. The future of the pharmacotherapy of schizophrenia appears bleak.

Support/funding/conflict of interest

Nil relevant to the contents of this article

Declaration

This is an original manuscript. The contents have not been published elsewhere in part or whole, nor have they been submitted elsewhere for consideration for publication.

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Questions that this Paper Raises

1. Will the causes of schizophrenia eventually be pinned down into discrete sets so that the illness can be partitioned into discrete disorders?

2. Can drug development address intracellular targets that correct or compensate for intracellular disturbances without disturbing normal cellular functioning in the targeted cells and in cells elsewhere in the brain and body?

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