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Editorial

Psychosis and Antipsychotics: A Short Résumé

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Introduction

Definitions

Psychosis is a morbid condition of the mind where the patient loses contact with reality. It is coined to include severe forms of disorders during which stupor, impaired insight and cognition, hallucinations and delusions may occur. Delusion is a significant landmark in the spectrum of psychosis, because it has a key diagnostic importance in mental disorders such as schizophrenia, manic episodes of bipolar affective disorder and deep psychotic depression (melancholia).

Schizophrenia, the major category in the spectrum of psychotic disorders, is a severe devastating mental disorder in which behavioral, emotional and cognitive disturbances follow a chronic course often with relapses and remissions.

Epidemiology and clinical presentation

Schizophrenia is more prevalent in males, the onset is at late adolescence and the life-time prevalence is *circa* 1%. The disease is characterized by cognitive, emotional, and behavioral abnormalities [1-3]. The psychological and behavioral abnormalities as well as cognitive impairments fragment the personality and isolate these individuals from their family and occupation, subsequently making them a burden on society and in the long-term affecting the national economy of the country of residence. The characteristic symptoms/signs of the disease fall into two (or three) broad categories: the positive and negative (deficit) symptoms; sometimes "disorganized" is added to include the 3rd group of symptoms. The positive symptoms include delusions and hallucinations. Negative symptoms include restricted range and intensity of emotional expression (flattened effectiveness), reduced thought and poverty of speech (alogia), anhedonia (dissociation from what is going on in the near environment) and a volition (decreased initiation of goal-directed behavior) [4]. Disorganized symptoms include disorganized speech and behavior, and poor attention [5,6].

Etiology

The corner stone in etiology of this ailment is the genetic factor, because schizophrenia runs in families [7-11]. The greatest risk is having a first-degree relative who is affected by the disease. It is believed that environmental factors can contribute to the etiology. For example, drugs (amphetamine, cocaine) and alcohol use are considered as risk factors. Cannabis, although not alone, can be a contributory factor in schizophrenia [12-14]. The invisible barriers that isolate schizophrenic individuals from their family, friends and society in general, encourage the abuse of psychedelic agents. These individuals then hoping to cope and deal with anxiety, loneliness (depression) and boredom (misery) [15,16].

Prevention

The problem with psychoses generally, and schizophrenia in particular, is that there exist no proven applicable preventive measures to protect against the development of this ailment, because as stated above, a hereditary factor is the cornerstone of the etiology. In fact, some believe that it is a sort of myth to talk about this issue.

Outcome of treatment

Depends mainly on many factors such as diagnostic accuracy, management plans, treatment evaluation and the prognosis generally is dependent on subjective assessments. This is because despite extensive research and improvement in imaging technology, as well as advanced genetic and molecular methodologies, the biological basis of this disease remains obscure [17].

Lines of treatment

Generally include biological and supportive measures. Supportive measures include psychotherapy and rehabilitation in certain stages of the disease.

Biological treatment or medicinal treatment with antipsychotics is the mainstay of this issue.

Antipsychotics and Nomenclature

Tranquilizers

Tranquilizers are, and as the name indicates, drugs that cause tranquility (relaxation). The term though is actually imprecise when talking about psychosis, because these agents traditionally are distinguished into two groups; minor tranquilizers (such as benzodiazepines) and major tranquilizers, which actually include antipsychotic agents. To avoid this ambiguity, the term tranquilizer has been abandoned; instead "antipsychotic and/or neuroleptic" have now been introduced into the pharmacological and psychiatric literature, with the former being mostly used.

A psychotropic

A psychotropic is more comprehensive than antipsychotic (neuroleptic), actually it includes antipsychotics and other drugs acting on the central nervous system (CNS). It is a chemical substance that crosses the blood–brain barrier and acts primarily upon the CNS where it affects brain function, resulting in alterations in perception, mood, consciousness, cognition, and behavior.

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The discovery of chlorpromazine in the 1950s [18], which is the prototype phenothiazine, made a real change in treatment of schizophrenia. Although this drug is not potent when compared to new drugs it has a broad spectrum of side-effects. It has become a milestone in management of the embarrassing symptoms of schizophrenia, especially the positive ones. Some phenothiazines are still in clinical use, especially in depot forms to treat schizophrenics in outpatient clinics. These oily preparations indeed encouraged psychiatrists and health authorities to deinstitutionalize many psychotic patients, because these preparations have longer half-lives. Psychopharmacologists traditionally categorize phenothiazines in a group called 1st generation antipsychotics, or sometimes conventional or typical antipsychotics. 1st generation antipsychotics include other agents such as haloperidol and pimozide and others, these two last mentioned drugs are potent drugs but unfortunately have serious side-effects, namely extrapyramidal side-effects (EPS) such as tardive dyskinesia, neuroleptic malignant syndrome, hyperprolactinemia, sedation and many others [19]. Chemical pharmacists and drug designers have been working laboriously to design and prepare better agents that are selective dopamine (D2) receptor blockers, in other words more potent agents that can be administered in lower daily doses in order to cause negligible side-effects. Clozapine is one of these agents [20]. These agents are called 2nd generation (atypical or nonconventional) antipsychotics. These remedies are better tolerated by psychotic individuals and are effective drugs especially against the negative symptoms of schizophrenia. Unfortunately these new preparations were found to cause other kinds of side-effects in addition to those caused by the conventional ones. These are blood dyscrasias and the diseases of metabolic syndrome: hyperlipidemia, obesity, diabetes type II and consequences of these. One plausable explanation for this is that these agents might impair the normal mitochondrial function [21], and the abnormality of these organelles may actually be a contributing factor to the etiology of psychosis [22]. All these problems are attributed to the fact that we do not understand the exact pathophysiology behind psychosis.

Neuroleptic Malignant Syndrome (NMS)

This is a life threatening adverse reaction to antipsychotic (neuroleptic) drugs. It is manifested as a complicated syndrome of neurologic and metabolic disorders. Typically appears as muscle rigidity, unexplained hyperpyrexia, autonomic instability (hypertension), cognitive impairment (delirium may develop to coma) and elevation of serum creatine phosphokinase [23]. The muscular symptoms are most likely attributed to the fact that these agents block the dopamine receptor subgroup D2 leading to imbalance in the function of the basal ganglia in a mechanism similar to that occurring in Parkinson's disease [24].

Due to changes in prescribing patterns, the incidence has decreased considerably since it was first documented. Psychiatrists should realize that the potential danger of NMS is still there to patients being treated with antipsychotic medication. The worst aspect of this grave side-effect is its unpredictability (because of its rarity) and it can occur even with the most newly available antipsychotics, the so-called atypical (2nd generation) antipsychotics. NMS is often overlooked and immediate intensive treatment for the syndrome is therefore delayed. Other reasons for overlooking the situation is intoxication with certain drugs that a psychotic patient is liable to use, such as cocaine or amphetamine, since these agents may also produce similar symptoms [23,25]. Some of the most commonly mistaken disorders are pontine hemorrhage, encephalitis, toxic encephalopathy, status epilepticus, heat stroke, malignant hyperthermia and serotonin syndrome.

The symptoms of NMS can last up to a month or so [23,25], during which time leukocytosis, metabolic acidosis, and dark (yellow-brown) urine discoloration can occur. The latter is attributed to rhabdomyolysis (destruction of skeletal myocytes) and release of myoglobin into the blood stream, a phenomenon that can cause renal shutdown [26].

Treatment of this unpredictable side-effect varies substantially from one center to another, although it is generally based on removal of the offending antipsychotic drug and supportive care in an intensive care unit.

Classification of Antipsychotics

The point with the design of 2nd generation antipsychotic drugs was actually to make available mono-therapeutic potent drug(s) against positive and negative symptoms of schizophrenia, with side-effects being as scarce as possible. We know that there is huge variation in therapeutic outcome and side-effects among the agents belonging to these two groups. This variation is even true for the agents within the same group. One can ask the following question: is there any point in categorizing antipsychotics to 1st and 2nd generation drugs? Or it is best to classify them according to their chemical structure (composition)? For example: phenothiazines (e.g. chlorpromazine), butyrophenones (e.g. haloperidol), and diphenylbutylpiperidines (e.g. pimozide) and so on. The idea behind this concept is that the majority of antipsychotics are dopamine receptor antagonists (as is obvious from the side-effects that these agents are liable to cause).

The Impact of Oxidative Stress

Reactive Oxygen Species (ROS) (free radicals) have also been blamed for their contribution to the etiology of many neuropsychiatric diseases, as well as having adverse effects on certain antipsychotics such as clozapine [27]. Dietary micronutrients such as antioxidants including selenium, vitamins (C, A and E) and poly unsaturated fatty acids (PUFAs, obtainable cheaply from e.g. fish and olives) may protect psychotic patients against both malnutrition because of the psychosis *per se* (impaired insight and cognition) and against side-effects of some antipsychotics that cause release of ROS [28-31]. PUFAs are situated at *sn-2* positions in the lipid-tail of the neuromembranal glycerophospholipids. These fatty acids might potentiate the therapeutic action of psychotropics and contribute to membrane fluidity and neuronal integrity, which is required for sound mental function in humans [32-34].

Conclusion

It is clear that the dopamine theory of psychosis is inapplicable to all cases of psychosis. As a basic principle in contemporary medicine, one should understand the pathophysiology of a disease in order to be able to prepare therapeutic agents. This fact is also true for psychiatric disease. Without an understanding of the actual molecular mechanisms involved, and the nature of the biochemical changes occurring in psychosis at the neuronal level, we will not be in

a position to combat schizophrenia.

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