Schizophrenia 3

Course and prognosis of Schizophrenia

Kraepelin initially believed that dementia praecox had an invariably poor outcome, although later reported that 17% of his patients eventually were socially well-adjusted. Manfred Bleuler (1974), son of Eugen Bleuler, personally followed up 208 patients who had been admitted to his hospital in Switzerland between 1942 and 1943. He concluded that the outcome was not so gloomy: 20 years after admission, 20% exhibited complete remission, 35% had good social adjustment, and 24% remained severely disturbed

It was found that the risk of death from all causes was increased 1.6-fold. About 60% of the excess early mortality in schizophrenia is accounted for by unnatural causes (suicide and accidents), and the rest from natural causes. The latter are especially cardiovascular disease, partly reflecting the high rates of smoking, as well as poor diet, sedentary lifestyle, and higher rates of obesity, type 2 diabetes, and other .physical illnesses

The lifetime risk of suicide in schizophrenia is often quoted as 10% or more, but recent meta-analyses suggest a figure of about 5%. The risk is greatest early in the illness, and in those with affective symptoms, a history of suicide attempts, recent discharge from hospital, and number of psychiatric admissions

Factors predicting a poor outcome in schizophrenia

Demographic factors

Male. Single. Younger age at onset. Family history of schizophrenia. Comorbid substance abuse

Clinical features

Poor premorbid adjustment. Insidious onset. Long duration of untreated psychosis. Hebephrenic (disorganized) subtype. Negative symptoms. Cognitive impairment. Absence of affective symptoms. Poor insight

Other factors

High expressed emotion in family. Poor adherence with treatment

International studies suggest that the course and outcome of schizophrenia may differ between countries. The International Pilot Study of Schizophrenia (World Health Organization, 1973) found the 2-year outcome was better in India, Colombia, and Nigeria than in western countries, particularly for the proportion achieving complete remission. A 15- and 25-year follow-up study confirmed the stability of geographical differences in course, and suggested that a difference in the severity and type of illness at first presentation is an important contributory factor

Treatment

There is a strong evidence base supporting the use of antipsychotic drugs in the treatment of schizophrenia for prevention of relapse. However, there are important limits to their effectiveness, .and significant side effects and other potential harms

The effectiveness of antipsychotic medication in the treatment of acute schizophrenia is well established by multiple placebo-controlled and active comparator studies. The median effect size compared to placebo is 0.44. About two-thirds of patients show a significant therapeutic response, but at present there are no clinically useful ways of predicting whether an individual patient will respond. Importantly, antipsychotic drugs only treat the positive symptoms of schizophrenia. They .have little or no clinically significant effect on negative or cognitive symptoms

There are no substantial differences in efficacy between one antipsychotic and another (with the exception of clozapine), nor between typical and atypical antipsychotics. However, this does not mean that all antipsychotics are the same. There are considerable differences in their side effect .profile

Antipsychotic drugs

This term is applied to drugs that reduce psychomotor excitement and control symptoms of psychosis. Alternative terms for these agents are neuroleptics and major .tranquillizers. None of these names is wholly satisfactory

The main therapeutic uses of antipsychotic drugs are to reduce hallucinations, delusions, agitation, and psychomotor excitement in schizophrenia, mania, or psychosis secondary to a medical condition. The drugs are also used prophylactically .to prevent relapses of schizophrenia and other psychoses

Dopamine receptors are of several subtypes. It is the D2 receptor that is critical for antipsychotic action, and all licensed drugs in the category are antagonists at this .receptor, with varying affinities for the D2 subtype

Distinction between typical and atypical antipsychotic drugs

The term atypical antipsychotic agent was introduced to distinguish the newer antipsychotic drugs from conventional typical agents, such as chlorpromazine and haloperidol. An alternative term is second generation. Although the definition of the term ‘atypical’ varies in the literature, a fundamental property of an atypical antipsychotic is its ability to produce an antipsychotic effect without causing extrapyramidal side effects. This definition is problematic, not least because antipsychotics do not fall clearly into two classes in this respect, but lie along a spectrum. For example, low potency conventional antipsychotic drugs such as chlorpromazine have a relatively low risk of producing extrapyramidal symptoms when prescribed at modest dosages; conversely, extrapyramidal side effects can also occur with the atypical antipsychotic risperidone. However, it is true to say that atypical antipsychotic agents have a lower likelihood of causing extrapyramidal side effects within their usual therapeutic range. In addition, the risk of tardive dyskinesia appears to be lower with the newer antipsychotic drugs

Pharmacology of typical (conventional) antipsychotics

Chlorpromazine is the prototypic phenothiazine. It antagonizes α1 - adrenoceptors, histamine H1 -receptors, and muscarinic cholinergic receptors. Blockade of α1 -adrenoceptors and histamine H1 -receptors gives chlorpromazine a sedating profile, while α1 -adrenoceptor blockade also causes hypotension. The anticholinergic activity may cause dry mouth, urinary difficulties, and constipation, while on the other hand offsetting the liability to cause extrapyramidal side effects. In contrast to chlorpromazine, other typical antipsychotics such as haloperidol, trifluoperazine and fluphenazine are more selective dopamine-receptor antagonists, and are therefore less .sedating but more likely to cause extrapyramidal effects

Extrapyramidal effects

These are related to the antidopaminergic action of the drugs on the basal ganglia. As already noted, the therapeutic effects may also derive from the antidopaminergic action, although at mesolimbic and mesocortical sites. The effects on the .extrapyramidal system fall into four groups, which are summarized below

Acute dystonia

This occurs soon after treatment begins, especially in young men. The main features are torticollis, tongue protrusion, grimacing, and opisthotonos, an odd clinical picture that can easily be mistaken for histrionic behaviour. It can be controlled by an .anticholinergic agent given carefully by intramuscular injection

Akathisia

This is an unpleasant feeling of physical restlessness and a need to move, leading to an inability to keep still. Agitation with suicidal ideation can also occur. Akathisia may wrongly be mistaken for a worsening of psychosis, and more antipsychotic medication may then be inappropriately prescribed. It usually occurs during the first 2 weeks of treatment with antipsychotic drugs, but may begin only after several months. Akathisia is not reliably controlled by antiparkinsonian drugs. Beta-adrenoceptor antagonists and short-term treatment with .benzodiazepines may be helpful. The best strategy is to reduce the dose of antipsychotic drug, if possible

Parkinsonian syndrome

Antipsychotic-induced parkinsonism is characterized by akinesia, an expressionless face, and lack of associated movements when walking, together with rigidity, coarse tremor, stooped posture, and, in severe cases, a festinant gait. This syndrome often does not appear until a few months after the drug has been taken, and then sometimes diminishes even though the dose has not been reduced. The symptoms can be controlled with antiparkinsonian drugs. However, it is not good practice to prescribe antiparkinsonian drugs .prophylactically as a routine, because not all patients will need them

Tardive dyskinesia

This is particularly serious because, unlike the other extrapyramidal effects, it does not always recover when the drugs are stopped. It is characterized by chewing and sucking movements, grimacing, choreoathetoid movements, and possibly akathisia. The movements usually affect the face, but the limbs and the muscles of respiration may also be involved. Although the syndrome is seen occasionally among patients who have not taken antipsychotic drugs, it is more common among those who have taken antipsychotic drugs for a number of years. Many treatments for tardive dyskinesia have been tried, but none of them is universally effective. Therefore it is important to reduce its incidence as far as possible by limiting long-term .antipsychotic drug treatment to patients who really need it

The neuroleptic malignant syndrome

This rare but serious disorder occurs in a small minority of patients who are taking antipsychotic drugs, especially high-potency compounds. The overall incidence is probably about 0.2% of patients who are treated with antipsychotic drugs. The onset .is often, but not invariably, during the first 10 days of treatment

The clinical picture includes the rapid onset (usually over 24–72 hours) of severe .motor, mental, and autonomic disorders, together with hyperpyrexia

- The prominent motor symptom is generalized muscular hypertonicity. Stiffness of the muscles in the throat and chest may cause dysphagia and dyspnoea.
- The mental symptoms include akinetic mutism, stupor, or impaired consciousness.
- Hyperpyrexia develops, with evidence of autonomic disturbances in the form of unstable blood pressure, tachycardia, excessive sweating, salivation, and urinary incontinence.
- In the blood, creatinine phosphokinase (CPK) levels may be greatly elevated, and the white cell count may be increased.
- Secondary complications may include pneumonia, thromboembolism, cardiovascular collapse, and renal failure.
- The mortality rate of neuroleptic syndrome appears to have been declining over recent years, but can still be of the order of 10%. The syndrome lasts for 1–2 weeks after stopping an oral neuroleptic, but may last two to three times longer after stopping long-acting preparations. Patients who survive are usually, but not invariably, without residual disability.

Atypical drugs

Clozapine is a weak dopamine D2 -receptor antagonist but has a high affinity for 5-HT2receptors. it is clear that the use of clozapine is associated with a significant risk of leucopenia, which restricts its use to patients who do not respond to or who are .intolerant of other antipsychotic drugs

Olanzapine, Risperidone, Quetiapine, Aripiprazole

The main problem with these drugs is the ‘metabolic syndrome’ (a combination of central obesity with two out of four of: hypertension, raised fasting glucose, low HDL cholesterol, and raised triglycerides). The presence of this syndrome significantly .increases the risk of cardiovascular disease such as myocardial infarction and stroke