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Editorial
Schizophrenia: improving the treatment through increased understanding

Robin M. Murray

Institute of Psychiatry Division of Psychological Medicine, De Crespigny Park, Denmark Hill, London SE5 8AF (UK)

This supplement examines a number of key issues in the understanding and treatment of schizophrenia. These include the crucial topic of the neurochemical basis of psychotic symptoms but also more specific issues such as the role of second-generation antipsychotics, particularly in the elderly; the possible rationale for polypharmacy; and pharmacoeconomic aspects of treatment with antipsychotics.

In recent years we have learned a lot about the aetiology of schizophrenia and the genetic and environmental risk factors for it [3]. We do not yet understand the exact pathogenic pathways which link the established risk factors to the symptoms of psychosis, but we have known for many years that dopamine plays an important role. This is demonstrated by the evidence that drugs which mimic dopamine (e.g. amphetamine) can cause psychosis in normal individuals and exacerbate schizophrenic symptoms in susceptible individuals, while all known antipsychotics block D_2 receptors.

However, little attention was paid to these facts for much of the 1990s. The dopamine hypothesis was in the doldrums and, beguiled by the evidence that most novel antipsychotics (apart from amisulpride) had serotonergic effects, researchers concentrated on this neurotransmitter. However, recently there has been a dramatic turnaround and a resurgence of interest in the combined ideas that dysregulation of dopamine is crucial to the onset of acute psychosis, and that D_2 blockade is required for antipsychotic action.

In the first paper in this supplement, Tony Grace, one of the world's leading experts on dopamine, examines the normal interaction of various brain areas (ventral hippocampus, basolateral amygdala, and prefrontal cortex). He points out that in health, there is an interplay between the hippocampus and the amygdala which helps to keep the individual in emotional balance. The hippocampus maintains focus on a task, and sets current environmental stimuli in the context of previous experience [2], allowing only response patterns that are appropriate to a given context to impact on mesolimbic dopamine; however, the amygdala can cause an emotional or affective override to this information. Normally the prefrontal cortex provides an overall supervisory input to the hippocampus and amygdala, which tempers their reactions to stimuli and ensures that the responses are appropriate to the particular circumstances.

In schizophrenia there is a malfunction somewhere in this intricate cortical-limbic circuitry. Many patients with schizophrenia show deficits in prefrontal function, while others have decreased volume of the hippocampus and/or amygdala [6]. Dr Grace suggests that either a loss of the normal prefrontal 'brake' on these limbic structures or excessive input from these structures themselves results in increased mesolimbic dopamine, and this in turn causes an overreaction to emotional stimuli, leading to paranoia and psychosis.

SPET and PET receptor imaging techniques have greatly contributed to the revival of interest in the role of dopamine in schizophrenia. In the next paper, Marc Laruelle and Anissa Abi-Dragham discuss the explosive growth in receptor imaging, with the development of new radioligands, as well as improved resolution and analytical techniques. They themselves have made a major contribution to our current ideas concerning dopamine and psychosis, and indeed coined the memorable phrase "dopamine is the wind of psychotic fire". Their crucial demonstration was that people with acute schizophrenia release larger amounts of dopamine from the striatum in response to an amphetamine challenge than controls; furthermore, the extent of this excess release is in proportion to the degree of psychosis, and the greater the release, the better the response to D_2 blockers.

It is now generally accepted that all antipsychotic drugs act by blocking dopamine D_2 receptors, but which drug should the clinician choose to achieve this end? The introduction of second-generation antipsychotics dominated schizophrenia pharmacotherapy in the 1990s, and in his paper, Wolfgang Fleischhacker states that there is an emerging consensus favouring second-generation agents over traditional agents as first-line therapy for most schizophrenic patients. This may be true, but some cautionary voices remain (e.g. Geddes et al. [1]). Dr Fleischhacker goes on to

examine differences between the second-generation agents, and the evidence-base available to help the clinician choose between them in terms of randomised controlled trials of efficacy (general psychopathology, cognition, affective symptoms, etc.), tolerability and safety.

Certainly, there is agreement that clozapine remains the gold standard drug for patients with so-called 'treatment-resistant' illnesses. Otherwise the most striking finding is that there is a strong tendency for the results of comparisons between different novel drugs to favour the drug manufactured by the company supporting the trial. This will surprise no-one! In real life, therefore, the clinician should advise his/her patient of the various side-effect profiles of the different drugs, and the two should try to jointly select that drug whose side-effects will distress the patient least.

As life expectancy increases, the population of elderly people with schizophrenia is also likely to increase. Carlo Altamura and Tony Elliott discuss the particular challenges in the management of such patients. They point out that there is a lack of well-controlled comparisons of typical and atypical antipsychotics in this patient population, and that confounding factors (e.g. chronic physical illness, concomitant disease and polypharmacy) preclude the extrapolation of treatment strategies from younger patients. They conclude that typical antipsychotics should be avoided in the elderly (due to extrapyramidal symptoms and anticholinergic-induced cognitive and visual impairment), and that atypical antipsychotics may offer benefits by avoiding anticholinergic effects, as well as adverse effects on cognition. Certainly, atypical antipsychotics are preferable to the high doses of typical antipsychotics which have often been prescribed to elderly patients in the past; whether they are preferable to the judicious use of low-dose typical antipsychotics remains an article of faith rather than science.

Pharmacotherapy for schizophrenia should aim to provide optimum symptom control with minimal side effects using a simple dosage regimen – ideally monotherapy. However, not infrequently patients require more than one drug. In his paper, Patrice Boyer discusses the rationale for polypharmacy in schizophrenia. This includes adjunctive treatment for specific symptom clusters and augmentation strategies to enhance therapeutic response to antipsychotic medications – mainly in treatment-resistant patients. However, he points out that polypharmacy remains problematic in terms of pharmacokinetic and pharmacodynamic interactions as well as compliance.

Next we come to economics. Psychiatrists should have some sympathy for the practitioners of this, the so-called 'dismal science', because both professions struggle with the complexity of human behaviour and both share an inability to accurately predict the future! Anita Patel provides a comprehensive review of pharmacoeconomic issues, highlighting the cost impact of schizophrenia not only on the sufferer's health but also on relatives, housing, as well as the criminal justice and social security systems. She points out the need for a broader perspective on costs, as drugs represent only a small part of total healthcare costs of schizophrenia, and suggests that higher-priced agents may pay for themselves in savings elsewhere. She also cites a previous review which claims that atypical agents tend to be more cost-effective than traditional agents due to better tolerability and efficacy, improved compliance, fewer relapses and less hospitalisation. It is a pity that so few of the available studies have been independent of industry funding.

It is also worth remembering those aspects of patient care which are not covered in this supplement. There is no discussion of the impact of the use of illicit drugs on the outcome of schizophrenia; if only psychotic patients were as enthusiastic about taking 'our drugs' as they are about taking 'their drugs'! Psychostimulants such as amphetamines and cocaine are well known to play a role in precipitating and perpetuating psychosis, and increasing evidence similarly implicates cannabis [4]. Again, we do not consider which of the various types of community care are most effective [5], or the burgeoning literature demonstrating that cognitive behavioural therapy can benefit positive psychotic symptoms as well as the depression and anxiety which are all too common in people with schizophrenia. Finally, it is worth reminding ourselves that very many people with schizophrenia live in poverty and under adverse social conditions. It is a sad reflection of Western society that we expect psychotic patients, who are very sensitive to the adverse effects of stress, to live in circumstances from which those of us who are more mentally robust, flee. Perhaps psychiatrists, economists, and the pharmaceutical industry could unite to act as more effective advocates for patients with psychosis.

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