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Introduction

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The introduction of antipsychotic drugs was indisputably a great advance in the pharmacotherapy of mental disorders. Since the discovery of the prototype antipsychotic chlorpromazine (Delay *et al*, 1952) in 1950, more than 30 analogue antipsychotics have been developed. This class of compounds has been termed 'typical antipsychotic drugs'. Although these compounds may differ in their biochemical structure, potency, and side-effect profiles, they have a common pharmacological action, that is, D_2 receptor antagonism, and spectrum of therapeutic actions (Creese *et al*, 1975).

After more than 40 years of experience with typical antipsychotic drugs, their therapeutic limitations have become painfully apparent to clinicians and patients alike. This is because typical antipsychotic drugs are not effective in all patients. Between 30% and 50% of patients with chronic schizophrenia are either unresponsive or only partially responsive (defined as a substantial reduction or remission of positive symptoms) to their antipsychotic drugs (Kane & Marder, 1993). In addition, antipsychotics are ineffective against other dimensions of schizophrenic pathology, namely the negative symptoms of the deficit state and neurocognitive deficits (Strauss & Carpenter, 1977; Carpenter & Buchanan, 1989). Lastly, typical antipsychotic drugs have an extensive side-effect profile, with the majority of patients experiencing one or more of the three acute extrapyramidal syndromes (Kane & Lieberman, 1992). These limitations place clinicians and their patients in an unenviable position in which they can expect only some symptoms to respond to treatment, along with uncomfortable and possibly disabling side-effects.

Given these circumstances, it is easy to see how those in the field of psychopharmacology were eager for therapeutic advance. Strategies for new drug discovery had stagnated. Clinicians were frustrated with the limitations of available treatments (Gardos & Cole, 1976). The field had outgrown the old paradigm, that is, the dopamine hypothesis of schizophrenia (Snyder *et al*, 1974). This prompted a renaissance of interest in clozapine, a drug that was originally developed in the 1960s (Baldessarini & Frankenburg, 1991; Lieberman, 1993). Following a host of new studies, this compound is now considered the prototype for a new class of compounds termed 'atypical antipsychotics'. (Atypical antipsychotics are variably defined and include the following features: efficacy in refractory patients and against negative symptoms, and reduced capacity to induce extrapyramidal side-effects, tardive dyskinesia, and elevate prolactin.) The novel effects of clozapine have catalysed a transformation in the field and provided a watershed in schizophrenia research. This has resulted in an array of novel strategies for drug development and provided a new window into the pathophysiology of schizophrenia. Risperidone has been introduced in the wake of clozapine (Marder & Meibach, 1994), and many other new putative atypical antipsychotic compounds are currently in various stages of development. These developments have raised three major questions that are currently being examined in the field. What is the mechanism of action of atypical antipsychotic drugs? What is the full extent of their therapeutic efficacy? What are the efficacies of the new atypical drugs relative to each other?

The articles of this supplement, which are based on information originally presented in a symposium, Current Issues in the Development of Atypical Antipsychotics, at the XIX Collegium Internationale Neuro-Psychopharmacologicum, June 1994, in Washington, DC, examine these questions from different perspectives. Drs Meise and Fleischhacker remind us that pharmacotherapy is only one component of the network of services that is required to treat and maintain schizophrenic patients successfully. Indeed, even the most effective drug treatments are dependent on the organisation and efficiency of the health-care system in which they are administered. At the least, the issue of cost and pharmacy budgets will be a determining factor in the availability of new and better treatments. In addition, rehabilitation and social support services are required to sustain and expand the therapeutic effects of drug treatment.

Dr Carpenter describes the pathological domains of schizophrenia, focusing on the primary and

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secondary negative symptoms, one of the most debilitating and pernicious aspects of the disease. He points out why most traditional study designs are unable to determine adequately drug efficacy against primary negative symptoms and suggests potential pharmacological treatment strategies. His bottom line is that we currently have no proven effective treatment for negative symptoms.

Dr Meltzer reviews the pre-clinical pharmacological mechanisms and considers his hypothesis (Meltzer *et al*, 1989) that atypical antipsychotic drugs have as their signature property less D_2 receptor affinity and greater 5-HT_2 receptor affinity in the light of recent studies. However, he also acknowledges the potential role of other neuroreceptors and neurochemical systems, including α_1, α_2, glutamate, D_1, D_4, 5-HT_4, 5-HT_7, and muscarinic receptor subtypes (specifically M_4) in contributing to their atypical mechanism of action.

Dr Casey describes how a non-human primate model can identify atypical compounds, distinguish true atypical antipsychotics from 'quasi-atypicals', and help to elucidate their mechanism of action. Of all the pre-clinical screening paradigms currently in use, the non-human primate model might have the highest degree of predictive validity thus far.

Dr Nyberg *et al* present results from an elegant series of studies of clozapine, risperidone, and typical antipsychotic drugs by the positron emission tomography group at the Karolinska Institute. Their findings suggest that the level of 5-HT_2 receptor occupancy may be a critical factor in mitigating D_2 receptor effects in the striatum, while at the same time supplementing them in the limbic and cortical regions.

The studies of a new putative atypical antipsychotic drug, ICI 204,636, reported by Dr Hirsch *et al*, indicate the emergence of yet another novel compound for the treatment of schizophrenia. Based on its pre-clinical profile and the results of these phase II studies, the drug appears to have antipsychotic efficacy comparable to that of typical drugs, but also efficacy against (secondary) negative symptoms, and few to no associated acute extrapyramidal side-effects. It also does not appear to elevate prolactin or cause endocrine side-effects as do typical drugs. We will await the results of additional studies of ICI 204,636 (along with the results of other new antipsychotic drugs currently in development) that further define its clinical properties and determine its optimal clinical use.

Thus, it appears that the long drought in schizophrenia treatment advances, whose end was signalled by the re-introduction of clozapine, has indeed come to an end. New treatments must, of course, wend their way through the development and the regulatory processes, but it appears certain that before the end of this decade psychiatrists will have new pharmacological tools with which to treat their patients more effectively and safely.

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