

The future of pharmacotherapy for schizophrenia

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Although enormous progress has been made in the treatment of schizophrenia, and the use of existing pharmacologic agents can have a dramatic effect on the short- and long-term management of the disorder, enormous challenges and unmet needs continue to exist. Despite the introduction of a second generation of antipsychotic medications, many patients continue to derive inadequate benefits from available agents. Negative symptoms and cognitive dysfunction, and decrements in psychosocial and vocational functioning, often continue to persist despite our best available treatments. Medication adherence remains a constant challenge and has not been dramatically improved by the new-generation antipsychotic drugs. Since all currently marketed antipsychotic agents possess some degree of dopamine antagonist effects, the role of other neurotransmitters in the primary antipsychotic activity remains largely unclear. It is possible that different domains of disease effects might benefit from different specific classes of medications, yet research in this area is not highly developed. The promise of further discoveries in genetics leading to new treatment targets and better predictors of treatment response (both therapeutic and adverse) is enormously exciting, but these developments will require years of additional research. The field must balance the need to make the most informed and thorough use of available agents with a sense of both excitement and patience as we work toward other approaches.

Key words: Schizophrenia, pharmacotherapy, drug targets, pharmacogenetics

Enormous progress has been made in the treatment of schizophrenia. The introduction of antipsychotic medication has had a profound effect on the short- and long-term management of this disease, yet enormous challenges and unmet needs still exist. We will attempt to review some areas where future progress could occur, ranging from enhancing the effective use of existing medications to strategies for developing the next generation(s) of pharmacologic agents.

WHAT CAN BE DONE TO ENHANCE TREATMENT OUTCOME WITH EXISTING AGENTS?

Although second-generation medications offer some important advantages over conventional antipsychotics, the scope and long-term implications of these advantages still remain somewhat unclear, and cost is an important factor in many settings (1,2). Despite these gains, there are still large numbers of patients who fail to derive adequate benefit from new generation drugs and we do not have a sufficient research data base to guide decisions regarding alternative treatments. Many clinicians will raise dosage, switch to different agents or add adjunctive antipsychotics (first or second generation) or mood stabilizers, yet we do not have a sufficient number of randomized controlled trials to evaluate the effectiveness or to recommend specific timing and duration of such interventions (3). It is easy for clinicians to draw erroneous conclusions based on experience with individual patients. If dosage is raised or another medication is added, subsequent gains could be due to the passage of time, since response in schizophrenia is variable in both degree and time course.

Clozapine remains the only drug with proven efficacy in patients who are poor or partial responders (4-6). However many clinicians are hesitant to utilize clozap-

ine, because of both perceived risks and the burden of blood monitoring. For many patients this clinical reluctance is unfortunate, since the potential benefits might well outweigh the potential risks. There still remains debate as to whether or not clozapine should be a second-line or third-line treatment; however, it is most concerning when it is not used at all in patients who are persistently symptomatic. There is also mounting evidence that clozapine has advantages in the reduction of suicidal behavior in patients with schizophrenia, which provides another important rationale for more widespread utilization (7).

Although new-generation antipsychotic medications have demonstrated more efficacy on measures of negative symptoms and cognitive function, these results are inconsistent and modest (1,8), leaving substantial room for further improvement. As we will discuss in more detail subsequently, it is likely naïve to assume that a single intervention will have the desired effect across the broad range of signs and symptoms (positive, negative, affective, cognitive, behavioral, etc.) associated with schizophrenia.

The use of specific medications targeted to particular domains is beginning to be a focus of research. An example is the use of drugs shown to enhance cognitive functioning in other diseases in trials involving patients with schizophrenia. As yet there is an inadequate data base to draw conclusions and our understanding of the pathophysiology of cognitive dysfunction in schizophrenia is far less well developed than that in Alzheimer's disease.

Another area where further progress must be made is adherence to treatment. Although compliance with medication-taking is a challenge in any disease, the difficulties experienced by patients with schizophrenia add to the challenge. Noncompliance rates have been estimated to be 40% or higher within one or two years of follow-up (9,10). Given a better side effect profile it was hoped that

the new-generation medications would go a long way towards reducing rates of noncompliance. However, the gains in this regard have been modest (11,12).

There have been some positive effects observed with psychosocial strategies to enhance compliance (13), but those strategies are not completely effective and are not widely implemented. Given the established need for continuous pharmacotherapy in preventing relapse and rehospitalization, it is important to first apply available formulations (long-acting injectable antipsychotics) more consistently and also to develop other technological solutions to poor or partial compliance.

In many countries, existing long-acting injectable medications are underutilized. Some clinicians believe that they can detect poor or partial adherence in their patients and reserve long-acting injectable medications only for those patients who have repeatedly demonstrated non-compliance. In reality, it is difficult to identify potentially noncompliant patients in advance, as such behavior is multidetermined and causes vary from patient to patient. Given the potentially serious consequences of relapse (loss of social support and/or job status, emergence of aggressive, violent or self-destructive behavior, increasing family burden, homelessness, greater societal costs), efforts to prevent relapse become critical.

Some physicians perceive long-acting injectable drugs as having more adverse effects, yet there is no evidence that this is the case, and in fact the potential to use doses associated with lower blood levels can actually reduce the risk of adverse effects (14).

Other clinicians assume that patients will not accept long-acting medication and that, even if they do, it by no means assures compliance, since the patient can fail to receive the injection at the appropriate time interval. Many patients will not welcome the suggestion of an injectable medication at first mention (often because of the fear of pain associated with injections). However, if the clinicians are willing to work through this reluctance, even if necessary by asking to administer one 'test' injection, patients often end up agreeing to using these medications. Once they do, they are often pleased with the results (15).

The notion that injectable medication doesn't guarantee compliance is partially true. However, the critical difference is that when a patient fails to receive the appropriate injection the clinical team is immediately aware of this and can initiate appropriate action (phone calls to patient and/or family, home visits, etc.). In addition, since long-acting medication provides a more gradual decline in blood levels than after stopping oral medication, the clinical team has some time to initiate appropriate steps before the patient is in fact without active medication.

Our impression regarding relapse prevention is that this aspect of treatment is often given inadequate attention in comparison to acute care. The course of an illness like schizophrenia will probably be determined more by what

strategies are employed (not just pharmacologic, but also psychosocial and vocational) during periods of relative remission than during periods of acute exacerbation.

Now that a long-acting, injectable, second-generation medication has been developed, one obstacle to the use of this particular strategy should be reduced, since the potential advantages of both can now be combined (16). The use of a new technology (a biodegradable microsphere encapsulation of an active drug) is also welcome in being water (not oil) based and therefore associated with less pain and local reaction at the injection site. It is hoped that other technological advances will increase our options to develop long-acting delivery systems of whatever type.

For some patients, even surgical implantation could be a beneficial alternative and would be consistent with a more widely accepted 'medical model' of managing a devastating illness like schizophrenia (17).

Some clinicians continue to argue that autonomy in medication-taking is a critical ingredient in disease management. However, when there are so many risks associated with covert noncompliance and the latter is so frequent, it would seem that other areas of autonomy and self care should be the focus while eliminating as many risks for relapse as possible.

THE DEVELOPMENT OF NEW AGENTS

There continues to be debate as to what factors account for the 'atypicality' of second-generation drugs, and as yet we do not have a clear understanding of why clozapine continues to display some relatively unique advantages. Therefore, questions remain as to what neuropharmacologic properties should be sought after in ongoing drug development. Have we taken the existing paradigm as far as it can go? And if so, what other strategies should be brought to bear?

Other dopaminergic drugs

Even within the traditional goal of optimal dopamine antagonism, new approaches are being developed. There has been considerable interest for many years in the use of agonists to modify dopaminergic function in a variety of ways. The idea is to combine antagonist and agonist effects in a way which could 'normalize' dopamine function rather than risk excessive blockade in some brain areas as the price for necessary blockade in other areas (18).

The development of a clinically effective and well-tolerated partial agonist (aripiprazole) has demonstrated that this strategy could be successful. It is the first of this class to demonstrate clinical efficacy comparable to conventional antipsychotics (19).

So far clinical data suggest few adverse effects. The very low rate of extrapyramidal side effects and lack of pro-

lactin elevation support the value of the partial agonist property. The extent to which this and other such compounds will provide significant advantages in terms of efficacy in general or in specific symptom domains remains to be seen. Theoretically, such compounds can 'normalize' or 'modulate' dopamine function by reducing dopaminergic transmission without completely blocking it when dopaminergic activity is excessive, or on the other hand stimulating dopamine transmission when it is reduced.

Compounds have also been developed as selective dopamine antagonists at receptors other than the dopamine D2 receptor. None of these compounds as yet has been shown to be clinically effective as an antipsychotic agent, but issues of appropriate dose finding remain potential concerns (20).

Serotonergic agents

Serotonergic receptor subtypes, particularly the 5-HT_{2A} receptor, have received considerable attention as playing a role in the 'atypicality' of second-generation antipsychotic medications (21,22). Attempts have been made to develop compounds with specific 5-HT_{2A} antagonist effects without also acting at dopamine receptors. However, the results to date with one such compound have not demonstrated adequate antipsychotic effects (23).

It has also been speculated that, since clozapine has an agonist effect at 5-HT_{1A} receptors, this might contribute to its novel effects (22). However, as yet attempts to develop medications combining 5-HT_{1A} agonist effects with other receptor binding activities have not replicated clozapine's clinical profile.

Muscarinic agents

Since some cholinesterase inhibitors seem to be active on psychotic symptoms (as well as on cognitive dysfunction) in patients with Alzheimer's disease (24), it has been hypothesized that such agents might have potential for treating cognitive and/or psychotic symptoms in schizophrenia. As yet there are insufficient data from clinical trials to draw conclusions.

Muscarinic agonists or partial agonists might also have some useful clinical effects in schizophrenia based on animal models (25).

Glutamatergic agents

The observation that N-methyl-D-aspartate (NMDA) receptor antagonists can produce a range of schizophrenia-like symptoms has led to the hypothesis that some deficiency in NMDA function might play a role in the pathophysiology of schizophrenia (26). This has led to the development of animal models and the testing of relevant agents in man. If NMDA function is reduced in schizophrenia, then the hypothesis follows that drugs which

facilitate or enhance NMDA function might have some therapeutic potential. Glycine, in effect, serves as an agonist at the NMDA receptor and has been employed in clinical trials with some success, particularly on negative symptoms (26,27). D-cycloserine is a partial agonist at the glycine regulatory site on the NMDA receptor which has shown some efficacy on negative symptoms either alone or in combination with antipsychotic medications (28). The effects of these agents, however, are modest and not entirely consistent.

A variety of other strategies are currently being explored to modify NMDA receptor function or related glutamate release, including inhibition of glycine uptake and inhibition of glutamate release.

Other agents

Other potential classes of agents which might modify psychotic symptoms or the evolution of such symptoms include protein kinase C inhibitors, steroidal agents, agents intended to correct hypothesized abnormalities in membrane phospholipid composition and function, and agents which might have direct or indirect neurotrophic effects.

The evolution and pathophysiology of schizophrenia is no doubt complex, involving genetic risk and possible environmental factors contributing to problems in neurodevelopmental plasticity, connectivity and/or integration. The involvement of a varied and complex array of factors in determining appropriate neural development and ongoing functional capacity could provide opportunities for interventions (perhaps even prevention) as a better understanding of these possibilities emerge.

THE PROMISE OF GENETICS

The sequencing of the human genome and subsequent identification of common genetic variants in the form of single nucleotide polymorphisms (SNPs) provide another avenue for progress in the pharmacotherapy of schizophrenia. Comprehensive genomic information may pave the way for the identification of new drug targets, as well as provide the tools to identify biological predictors of response to currently available and newly developed antipsychotic drugs.

Identification of new targets

For the past three decades, intensive effort has been placed on genetic strategies to identify susceptibility genes for schizophrenia. For the most part, these studies have utilized 'linkage' analysis strategies that involve the ascertainment of families with multiple affected relatives or of sibling pairs in which both members of the pair are affected with schizophrenia. When successful, these studies suggest chromosomal regions that harbor susceptibility

genes, and positional cloning efforts may ensue to precisely localize the candidate gene. To date, there have been many linkage studies with nominally positive results, but the limitations of linkage analysis have hampered the actual identification of a susceptibility gene (29). A major problem with linkage analysis is that, although powerful for the detection of genes of major effect, it is less useful when genes of relatively modest effect interact to contribute to disease pathophysiology (30). Therefore, positive results have been difficult to replicate. Moreover, the chromosomal region implicated by a positive result may contain hundreds, if not thousands of genes, and identifying the actual genetic contribution may be difficult with current technology.

The new genomic information, however, may provide new means to identify susceptibility genes. It is now possible to fine map candidate regions more comprehensively with the new SNP information in order to better localize linkage regions. Moreover, genetic association approaches utilizing unrelated cases provide enhanced power to detect genes of modest effect (31), as well as to assess SNPs located within genes implicated in linkage analyses. For example, Straub et al (32) have recently reported that dysbindin, a gene located on the short arm of chromosome 6 identified in a linkage study completed in 1994, is associated with schizophrenia in a family-based case-control design using recently identified SNPs in the region. Several other groups are utilizing similar strategies and it is likely that multiple genes increasing risk for schizophrenia may soon be detected.

As these genes are identified, many of the proteins that they code for may represent new targets for drug development. Moreover, treatment strategies with new agents can be focused on subgroups of schizophrenia patients with specific susceptibility alleles, potentially enhancing the power of these treatment strategies. Finally, although an individual gene product may not be readily amenable to pharmacological intervention, it may be located within an anatomic or functional pathway that may suggest additional directions for new drug discovery.

Pharmacogenetics

Pharmacogenetic strategies may also enhance treatment strategies for schizophrenia by providing easily accessible biological, or molecular, predictors of antipsychotic drug response. A priori identification of the patients who respond well to a particular antipsychotic drug, or who are at increased risk for development of adverse side effects, may reduce lengthy ineffective medication trials and limit patient's exposure to adverse drug effects. Moreover, enhanced predictability of treatment response early in the course of a patient's illness may result in improved patient compliance and willingness to rapidly seek treatment upon symptom exacerbation or recurrence.

Pharmacogenetic studies in psychiatry have almost

exclusively utilized the candidate gene 'case-control' association design - an approach that is particularly well suited for pharmacogenetic studies in which unrelated individuals may be all that are available (29).

The candidate gene pharmacogenetic strategy has been successful in complex diseases such as asthma. For example, Kotani et al (33) found that the beta2-adrenergic receptor (B2AR) polymorphism Arg16Gly was significantly associated with the airway responsiveness of Japanese asthma patients (n=92) treated with the B agonist salbutamol. Similarly, Drazen et al (34) examined the association between improvements in forced expiratory volume in the first second (FEV1) in a placebo-controlled trial (n=221) of the anti-asthma drug ABT-761 and a polymorphism in the 5-lipoxygenase (ALOX5) gene. ALOX5 genotype was not associated with overall disease severity, but patients who were homozygous for the rare allele failed to respond to ABT-761. In fact, these patients' response to active drug treatment was indistinguishable from the patients who received placebo treatment.

The majority of pharmacogenetic studies of antipsychotic drug efficacy have focused on clozapine. These studies have primarily utilized SNPs within the genes for the neurotransmitter receptors to which clozapine has affinity. These include the dopamine D2, D3 and D4 receptor genes, as well as the serotonergic 5-HT2A, 5-HT2C, and 5-HT6 receptor genes (35,36). Thus far, the associations between SNPs in the 5-HT2A-receptor gene and clozapine response have been the strongest. Several studies have yielded weakly positive results and a meta-analysis of all of the published studies of the two 5-HT2A polymorphisms T102C and His452Tyr indicates that this gene may have a significant, albeit small, effect on the variation in clozapine response (37).

Another application of pharmacogenetic techniques has been in the domain of adverse effects. A dopamine D3 receptor SNP, Ser9Gly, which may alter dopamine-binding affinity (38) has been reported to alter susceptibility to tardive dyskinesia (TD). Moreover, there have been a number of reports suggesting that polymorphisms within the cytochrome p450 enzyme CYP2D6, a major enzyme in the oxidative metabolism of many antipsychotic drugs, are associated with development of TD (39-41), as well as reports indicating that an intronic polymorphism in the CYP1A2 gene may contribute to TD risk (42,43).

Clozapine-induced agranulocytosis is another side effect that has been studied in a number of populations. The high incidence of recurrence of agranulocytosis following clozapine rechallenge has suggested that genetic factors play a role in this adverse effect. To date, the focus of investigation has been the major histocompatibility complex (MHC) and human leukocyte antigen (HLA) variants, with specific HLA haplotypes being associated with agranulocytosis in Ashkenazi Jewish and in non-Jewish populations (44,45). These studies are limited by the infrequency of clozapine-induced agranulocytosis and

resultant small sample sizes for examination. Nevertheless, with the preponderance of data suggesting a link between HLA alleles and this important side effect, further work in this area could have significant clinical implications.

Finally, as discussed above, relapse following noncompliance with treatment is a critical limitation in the treatment of patients with schizophrenia. Molecular genetic approaches may be useful by providing the means to identify patients at especially high risk for rapidly relapsing following drug discontinuation. In a preliminary study of 41 schizophrenia patients, we found that serotonin transporter genotype predicted rapid relapse following antipsychotic drug discontinuation (46). 56% (9/16) of patients who were homozygous for the long allele (II) of a serotonin transporter polymorphism (5-HTTLPR) reported significant increases in psychotic symptoms within four weeks of drug discontinuation, in comparison to 16% (4/25) of subjects with the other two genotypes (Is and ss). These preliminary data suggest that it may be feasible to utilize molecular genetic techniques to provide individualized risk-benefit information to patients with schizophrenia and, perhaps, provide specialized interventions for those patients at higher risk of relapse.

With the increased interest in molecular genetics, many groups in academia and in industry are currently pursuing pharmacogenetic studies. The next generation of studies will employ markedly greater number of genes and SNPs and, with the concomitant reductions in genotyping costs, the potential to screen large portions of the genome for genes that influence response to antipsychotic agents may soon be feasible. Positive results may result in diagnostic tests to enable the individualization of treatment, or may point to the underlying molecular substrates of antipsychotic efficacy and thus present new targets for antipsychotic drug development.

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