

IN SESSION with Anil Malhotra, MD

Pharmacogenetics of Schizophrenia



Dr. Malhotra is the Director of Psychiatry Research at the Zucker Hillside Hospital in Glen Oaks, New York, and professor of psychiatry at the Albert Einstein College of Medicine in Bronx, New York. His research group focuses on identifying the biologic underpinnings of schizophrenia and the mechanism of action of antipsychotics. They have identified numerous genes associated with increased risk for the disorder; determined their relationship with important clinical manifestations of illness, including cognitive impairment; and begun to examine the role of genetic factors in predicting individual responses to pharmacologic treatment.

What is the difference between genomics and pharmacogenetics?

The key difference is that pharmacogenetic studies are focused on trying to understand the variation in clinical response to medications. Clinical response to medications can be how well a patient does with antipsychotics, in terms of clinical efficacy; it can be the side effects that are associated with treatments with different agents; or it can be how well patients cognitively respond to pharmacotherapy. Whereas, genomics, or classical disease genetics, is focused on understanding the disease susceptibility genes that occur in the general population. Pharmacogenetics is really a much more specific subset of genomic or genetic studies focused on the drug response phenotype.

What are some of the key concepts involved in pharmacogenetic studies?

At its most basic level, pharmacogenetics can be really quite simple. If one considers the fact that in the population, at any given gene—for example, the dopamine (D)₂ receptor gene—there are multiple forms of the gene, called alleles. We look at the relationship to one form of a gene versus another form of the gene and

how that predicts or is associated with a clinical characteristic—in this case, drug response. For example, in the D₂ receptor gene, there are alleles that, in the general population, ~50% of people have one form and ~50% of people have another form of the gene. Thus, we have two groups of individuals, and we can examine their drug response patterns and the side effects. That, at its most basic level, is what we are trying to do in pharmacogenetics.

How important are “candidate genes”? Do physicians narrow it down to likely candidates on some basis and focus on those?

Yes, that has been the primary strategy in pharmacogenetics, where we look at a specific gene within the entire genome of ~25,000 genes. The question is how do you pick which gene to really focus on. The candidates are evaluated on a number of different perspectives. For the most part, in pharmacogenetics at least, those candidates have been selected based on knowledge of where the drug acts. For antipsychotics, we have pretty good data that the D₂ receptor is involved in the efficacy of these agents. Thus, the gene that codes for the D₂ receptor becomes a candidate gene.

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Similarly, other receptors, for example the serotonin (5-HT)_{2A} and 5-HT_{2C} receptors, become candidates because we know that most of the antipsychotics have relatively potent affinity for those receptor subtypes. There are other ways that genes become candidates, though. In some cases, a gene has been implicated in the pathophysiology of schizophrenia, from a disease-susceptibility study. Therefore, it has been argued that it could be a candidate gene for drug response and can be tested in a similar fashion.

Is there any area in psychiatry where researchers have come close or have already reached the point where they can conduct a study and, with relative certainty, predict the drug response or susceptibility to the side effects?

As yet we do not have a convincing, firm, replicated finding across a large data set that we would use to clinically predict drug response. Though I think, at this point, it is fair to argue that there are at least some very promising candidates, both in the treatment of depression and in the treatment of schizophrenia. Moreover, I think they are really promising results in the evaluation of clozapine-induced agranulocytosis.

How accurate is that test?

An article¹ about to be published describes a very high specificity for predicting clozapine-induced agranulocytosis. Nineteen subjects that carried the risk form of the HLA-DQB1 gene, and of those 19 subjects, 17 of them had developed clozapine-induced agranulocytosis. That is a relatively specific result. The downside is it is not as sensitive, in that a number of subjects who developed clozapine-induced agar acidosis did not carry the risk form of the gene, and thus you could not be sure that they were not going to get it. Yet, if patients were positive for the risk allele, there was a very, very high likelihood of developing the side effects.

In that case, would you avoid clozapine in those patients?

That is a clinical decision. The problem there, of course, is when a patient gets to the point where they may require clozapine treatment, what other choice do you have? I think, at the very least, there would be very careful monitoring of white blood cell count, and very careful counseling of the patient who might enter into such a trial.

According to the literature the risk of agranulocytosis, as we understand it, may have been overstated because it was a very homogenous population that carried the gene for this risk. Were any kind of particular subgroup of patients identified by their background?

There is some indication that the frequency might be a little bit higher in the Ashkenazi Jewish population. However, the frequency of clozapine-induced agranulocytosis does seem to be declining

over time. When clozapine was first developed the frequency was reported to be ~1%. In more recent work, the frequency seems to be dropping to closer to 0.4% or 0.5%. Whether that decrease is due to a different patient population receiving the drug may be an issue, or, it may be due to better monitoring.

There was a large-population Finnish study² where they actually showed that clozapine carried much lower risk of mortality, over time, than even some of the newer drugs. It seems to be counterintuitive.

I agree with you because I think clozapine is still really under-utilized. It does have a side-effect burden and we cannot underestimate the side effects of weight gain and the low risk for agranulocytosis. It is a difficult drug to use, from many perspectives, including the requirement for a blood draw. Still, I think most people would agree that the data we have over a 20–30-year period suggests that it is really the only agent that has been able to show superior efficacy, as compared to another agent, in treatment-resistant schizophrenia, at the least.

Our hope is that with pharmacogenetic studies we could increase the utilization of what we still think is a very effective drug. The Finnish data is very impressive in terms of mortality and morbidity, and clozapine, again, appeared to be the clear winner there.

It comes as a surprise, even specifically in terms of cardiovascular mortality and morbidity, given the fact that clozapine causes weight gain and has been included in diabetes.

Clozapine is certainly associated with a lot of weight gain. However, we published a paper in *JAMA*³ where we had looked at antipsychotic-naïve pediatric patients. And in those patients who had not been exposed previously to antipsychotics, even so-called “weight-neutral” antipsychotics caused really profound weight gain in a relatively short period of time. For example, aripiprazole was associated with a 4–5 kg weight change in 12 weeks of treatment in these antipsychotic-naïve patients. There were greater numbers for olanzapine, risperidone, and quetiapine.

Are there any current tests that show promise in predicting not only who will get agranulocytosis, but also who will gain weight or develop diabetes with antipsychotics?

At this point in time there is certainly no clinically available test, but there is a lot of research effort going into that area, including research in our own laboratory. We actually have some very promising data, suggesting that there are a few key genes that may be associated with the risk for antipsychotic-induced weight gain. The difficulty in doing these studies is, if you are looking at the weight gain in chronically treated patients, you are not really assessing the true weight liability of a drug. Some

patients have previously been exposed to three or four other drugs, all of which cause weight gain. While focusing on these antipsychotic-naïve patients and in those data sets, we have reported one specific gene, the D₂ receptor gene, that seems to influence weight gain in that population. However, we are now looking, on a genome-wide basis, for other genes, and we already have some very promising early data.

Is there anything that implicates anticholinergic or 5-HT_{2C}?

5-HT_{2C} has been implicated by Reynolds and colleagues⁴ in first-episode, antipsychotic-naïve patients. However, it was in a Han Chinese population, so it made it a little bit difficult to extrapolate to the United States or European populations. Those kind of genes have popped up.

What about tardive dyskinesia?

Tardive dyskinesia (TD) was, at least for the last decade, a real focus of investigation for pharmacogenetic studies. The D₃ receptor and one of the cytochrome P450 (CYP) genes have been linked. The difficulty there is similar to the weight gain situation, because you do not really know which drug caused the TD. In many cases, a patient who has developed it has probably been on multiple medications. The other issue being that the risk of TD certainly seems to be less with the second-generation antipsychotics, and they are harder and harder studies to do.

Are we able to test for susceptibility to schizophrenia or some of its deficits, so that we might initiate treatment early? Does it really matter if you start treatment before you have overt psychotic symptoms? Have we been able to identify susceptibility genes?

No, I do not think there is currently any gene that we use clinically, in terms of if you had a child or adolescent patient who was showing some prodromal signs of the illness, that we would genotype them and say it looks like they are at high risk. There are genes that have been relatively reliably identified that predict risk for schizophrenia, but the effect size or the odds ratio are very, very modest, and they do not provide any individual prediction ability at a given patient's level. At this point in time, those are really not ready for clinical prime time.

The issue of early treatment is another thorny issue. There are obviously numerous ethical issues around the issue of treating children who are at risk for disorder but may not go on to develop the disorder, with potent drugs like antipsychotics, which have again this liability of weight gain and other potential side effects. From the genetic perspective, I do not think anyone would argue, right now, that we should be using genetic tests to diagnose people who are at risk for schizophrenia.

Have there been any pharmacogenetic studies that have been helpful in predicting a response to one antipsychotic compared to another?

No, not as of yet. We do not have any individualized prediction ability. Our own data with the D₂ receptor, unfortunately, is across the entire class of medications, so it does not suggest that there is any one specific medication that's related to D₂ receptor variation. This is not surprising, since all of these drugs were developed to bind to the D₂ receptor. If we had a drug that did not act via the D₂ receptor, perhaps then we could test that question. As yet, we do not have the individualized prediction that we would like to see for antipsychotic treatments.

Is there any way to predict whether or not a particular side effect will be more problematic with one drug than another?

I mentioned the clozapine test, but that is a side effect that is relatively specific to clozapine. If that study is replicated in a larger cohort of subjects, and you were relatively sure that patients who carried the risk allele were going to develop clozapine-induced agranulocytosis, I think then you would be able to make an individualized prediction, such that the patient probably should not be treated with clozapine and should be considered for treatment with another antipsychotic that is not at risk for agranulocytosis.

Similarly, if the weight gain data plays out, we believe at least some of the antipsychotics are less likely to cause clinically significant weight gain and in patients who carry risk alleles, we would probably suggest that, all other things being equal, they be treated with a lower-liability drug.

My understanding is there was some effort made to try to specifically predict who would respond to newer antipsychotics. What do you know of these studies?

Yes, I think there are some efforts in some of the industry-sponsored, clinical trials, where they collected DNA samples. They are still ongoing in terms of trying to predict the response to some of those medications now being developed. The most recent one that was really linked to this was iloperidone, which was developed initially by a number of different companies, but Vanda Pharmaceuticals was the company that sought and received Food and Drug Administration approval for that drug. They have published a series of studies with iloperidone suggesting that there were some genetic predictors of clinical response to the medication.

Right now, almost everything is sort of on the cusp of maybe becoming clinically relevant.

Yes. I think we are very much on the cusp. Pharmacogenetic studies with really robust methodologies and robust genotyping

technologies only started ~10 years ago. The way genomics has moved from a technologic perspective over the last 5–10 years is really remarkable. Also, when you think about the information that is now available, in terms of the Human Genome Project, the HapMap project, and others, we are in a position where we can start to consider whether the studies we can conduct now will impact clinical care in the not-too-distant future. There is always the challenge of over-promising with any kind of new technology. I think we are beginning to see some hope that we will be able to actually impact clinical care by the use of these genomic technologies, in the not-too-distant future.

What has you most excited?

If one looks at other branches of medicine, in the past couple of years there have been very robust pharmacogenetic predictions of side effects, such that they have made it into clinical care and clinical practice. These are some rare side effects; in some cases, more common side effects. The question I would ask is where do you see the greatest possibility for promise in pharmacogenetics, and I think it is in the prediction of adverse events associated with treatment. Efficacy is a little bit more difficult to predict, due to many of the issues around the measurement of clinical efficacy in a clinical trial. In many cases, we can measure side effects very reliably and with very good accuracy, ie, weight gain, white blood cell count, prolactin levels. With these we have a pretty good sense of what we are measuring. Those phenotypes or those clinical characteristics are really probably more robust for pharmacogenetic studies. I would think that is the area, as we have seen in other branches of medicine, where we will start to see some traction with pharmacogenetic studies, again, in the not-too-distant future.

Were subjects in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study⁵ evaluated with respect to either tolerability or treatment response?

Yes, they were. The challenge in the pharmacogenetic studies of CATIE, as opposed to the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, was that patients were

initially randomized to numerous different medications. Thus, from a genetics perspective, the treatment arms are relatively small; ~100 patients in each of the treatment arms had DNA samples available. That has been a bit of a challenge.

In STAR*D, all of the patients were treated with citalopram in level one, and the sample size there is actually quite robust for pharmacogenetic studies. However, there are a group of investigators looking at the CATIE DNA samples for prediction of response, prediction of side effects, and discontinuation from the trial.

Are there any other aspects of pharmacogenetics you would like to mention?

CYP genotyping is actually a clinically available test. For example, you certainly can predict who is a poor metabolizer of CYP2D6 substrates. Patients who are really having a lot of side effects—eg, patients receiving low doses of risperidone, which is a CYP2D6 substrate—should be genotyped for CYP2D6 and evaluated for their metabolic status, because there you could actually make the case that a dosage reduction might be in order in those patients who are poor metabolizers. No one has conducted a prospective study of that question, as yet, and that is part of the problem. My colleagues and I are conducting a study but it will take a while until we have a sample size sufficient enough to make any real arguments or any results available. I think that kind of test does show some real promise for prediction of side effects. *PP*

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