THE CARLAT REPORT PSYCHIATRY

A CME Publication

AN UNBIASED MONTHLY COVERING ALL THINGS PSYCHIATRIC

Daniel Carlat, MD
Editor-in-Chief
Volume 15, Number 3
March 2017
www.thecarlatreport.com

IN THIS ISSUE

Focus of the Month:
Pharmacogenetics

Learning Objectives
After reading these articles, you should be able to:
1. Describe the evolution of pharmacogenetic testing and its impact on clinical practice.
2. Evaluate the benefits and challenges of current pharmacogenetics research as applied to clinical prescribing patterns.
3. Summarize some of the current findings in the literature regarding psychiatric treatment.

Pharmacogenetic Testing: An Update

Daniel Carlat, MD, Publisher, The Carlat Psychiatry Report

Dr. Carlat has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Given how many essentially equivalent medications we have to choose from, how great would it be to have a test that tells us which drug to prescribe for which patient? Everybody wants personalized medicine, and in some other specialties, such as oncology, this is becoming a standard part of treatment. In this article, we'll review some of the basics of pharmacogenetic testing and examine in more detail the commercial genetic tests that are currently available.

Continued on page 2

In Summary

- The Genesight and Genecept tests haven't been proven effective in determining a patient's metabolizer response to specific psychiatric medications and side effects.
- Initial results of the CNSDose test, which relates to medications currently prescribed, show promise but warrant further replication of results to be clinically useful.
- Although pharmacogenetic tests do not require FDA approval, the agency does supply pharmacogenetic recommendations for certain psychiatric medications.

Q&A With the Expert

Understanding Pharmacogenetics Research

Rudolf Uher, MD

Professor, Department of Psychiatry, Dalhousie University School of Medicine, Halifax, Nova Scotia

Dr. Uher has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

TCPR: Dr. Uher, you have been a co-investigator on the major studies of pharmacogenetics in psychiatry. It's a complicated field, and I thought you could explain how the research is actually done.

Dr. Uher: The basic goal of this kind of research is to try to find an association between a genetic variant and the clinical response to a particular medication. Given that there are dozens of medications to choose from for any given disorder, it would be very helpful if we could do a genetic test that would tell us which drug is the best for a particular patient.

TCPR: All right, so we all have 23 pairs of chromosomes and many thousands of genes that might play a role in medication response. How does one go about solving this problem?

Dr. Uher: Traditionally, we've done these studies using the candidate gene method. The way this works is that you start by identifying a small number of promising candidates for genes that might be related to drug response. For example, the serotonin transporter is the target molecule of SSRIs, so a logically related gene would be the serotonin transporter gene, which encodes the protein that is responsible for serotonin

Continued on page 4

Pharmacogenetic Testing: An Update
Continued from page 1

The theoretical basis for pharmacogenetic testing

Genes are composed of specific sequences of nucleotide base pairs, and those base pairs form an alphabet that instructs our body to create amino acids, which are put together in various ways to create proteins. Many of these proteins are enzymes, which are defined as molecules that facilitate chemical reactions.

Of most relevance to pharmacogenetic testing in psychiatry, there is a specific group of enzymes called the cytochrome P450 enzymes (or CYP450), which are found in the liver and help our bodies metabolize drugs. They accomplish this by chemically transforming the drugs to make them more water-soluble. The more water-soluble a drug becomes, the more likely it is to dissolve in urine, and thence get cleared from the body.

The genes that encode CYP450 enzymes are called pharmacokinetic genes, and they vary among individuals. Some of these gene variants create versions of the enzymes that are inactive or much less active than normal, while other variants increase activity. This interindividual variability is termed polymorphism, from the Greek "poly" (many) and "morph" (form). Another term for a genetic variant is an allele, which refers to the particular form of a gene on one of two paired chromosomes. Based on the CYP450 polymorphisms, individuals are categorized in different ways with respect to specific enzymes:

- **Extensive metabolizers:** Otherwise known as "normal" metabolizers, these people have normally active CYP450 genes on both chromosomes, meaning that they see an average level of drug in the body.
- **Intermediate metabolizers:** These people metabolize drugs a bit more slowly than extensive metabolizers, but not dramatically so.
- **Poor metabolizers:** These people carry inactive or partially active CYP450 genes, and therefore metabolize drugs significantly more slowly than extensive metabolizers. This may result in more side effects since serum drug levels are higher.
- **Ultrarapid metabolizers:** With extra copies of certain genes, these people metabolize drugs more quickly than extensive metabolizers, sometimes requiring unusually high doses of medications to achieve a therapeutic level.

There are a number of CYP450 enzymes—for example, 1A2, 2D6, 2C19, and 3A4. One can be a poor metabolizer at one enzyme, but an extensive metabolizer at another.

In addition to pharmacokinetic genes, lab tests can also detect variations in "pharmacodynamic" genes that create proteins relevant to how drugs act on neurons in the brain. These include genes encoding for serotonin receptor and transporter proteins. Unfortunately, studies have not been able to consistently correlate variants in these genes with clinical response (see this month's Q&A for details). Nonetheless, this hasn't prevented companies from selling kits to test these genes, claiming that the results can tell patients which drugs are likely to be more or less effective.

Is metabolizer status clinically relevant?

It's clear that metabolizer status can affect blood levels of medications, as one would predict. Most of the studies demonstrating this have been completed with healthy volunteers taking a single dose of a drug. That's very different from the typical psychiatric patient, who takes more than a single dose and is often taking more than one medication at a time. So most studies are suggestive, but not necessarily applicable to our patients. There are several studies in real-world psychiatric settings that imply a person's metabolizer status does in fact affect both response to medications and side effects. They are mainly retrospective studies, meaning that researchers identify a group of patients, find their metabolizer status, and see whether there's any correlation between genotype and response or side effects. Some of these studies have shown such correlations. For example, in one study of hospitalized patients, those who were poor metabolizers for 2D6 were over three times more likely to have required a switch of antidepressants than extensive metabolizers (*Journal of Clinical Psychopharmacology* 2005;25:188–191).

These suggestive studies led many clinicians to become interested in the potential utility of pharmacogenetic testing. The only way to assess this utility is to randomize patients to a group in which their treatment is guided by such testing vs a group in which it is not. If genetic testing is useful, we should be able to see a measurable advantage in the guided group. We'll review these studies next.

Prospective clinical trials of genetic testing

The last time *TCPR* looked at pharmacogenetic testing (in our May 2015 issue), we focused specifically on studies done by Assurex, the company that markets the Genesight test. We concluded that the data didn't meet reasonable standards of clinical evidence. Since then, studies have been published regarding two other genetic testing packages.

These proprietary commercial tests are different from simply ordering P450 testing through a laboratory. The companies assemble multiple genetic tests into a multi-gene panel. For example, Assurex's Genesight test analyzes six CYP450 genes and two serotonin genes (https://genesight.com/patients/medications-and-genes-tested/). Genomind's Genecept test

Continued on page 3

Pharmacogenetic Testing: An Update
Continued from page 2

analyzes the same six CYP450 genes, but includes more pharmacodynamic genes—12 in all (see https://genomind.com/genes-analyzed/). CNSDose, a newer test out of Australia from a company called Baycrest Biotech, focuses exclusively on pharmacokinetic genes, including several that are not in Genesight's or Genecept's portfolio. There are many other commercial tests available—a recent review counted 22 (Bousman CA and Hopwood M, *Lancet Psychiatry* 2016;3(6):585–590)—but only the three included in this article have published data on the tests' clinical utility.

In January 2017, the *Journal of Clinical Psychiatry* published a systematic review of the literature on pharmacogenetic testing in patients with major depressive disorder (Rosenblat JD et al, *J Clin Psych* 2017, published electronically 1/3/17). The authors started by reviewing the same three Genesight trials we had reviewed in 2015, and like us, they were not impressed. They found that the non-randomized open-label studies had too many methodology problems to be convincing, and that the double-blind study failed in its quest to demonstrate a benefit of Genesight testing.

Rosenblat et al reviewed two more recent studies: one of the Genecept test (marketed by Genomind) and one of CNSDose. The test of Genecept was a 3-month naturalistic study in which 685 patients with depression or anxiety were enrolled. Everybody received the Genecept assay, and 77% of patients improved after 3 months (39% responded, 38% had remission). The numbers sound impressive at first blush, but unfortunately the study was open-label, without blinding and with no comparison group. As the authors point out, without a control group, we have no idea whether patients' improvement had anything to do with receiving the Genecept test. On a side note, Genomind's website provides a textbook case of marketing spin. In describing its uncontrolled study, Genomind states that "These data demonstrate that the incorporation of pharmacogenetic information into the treatment of patients with mood and anxiety disorders *produces benefits in depression and anxiety symptoms, side effects, and overall functioning"* (emphasis added). Caveat emptor.

Finally, the authors reviewed the CNSDose test. Unlike Genesight or Genecept, CNSDose does not suggest specific drugs, but rather gives suggestions for how to dose medications that you may have already chosen. In a 12-week double-blind trial, patients with major depression were randomly assigned to either a genetically guided group (n = 74) or an unguided group (n = 74). The guided group had a remission rate of 72% vs. only 28% in the unguided group, a difference that was statistically significant. The results are pretty spectacular—perhaps too spectacular to be believed. As the *J Clin Psych* reviewers pointed out, the paper didn't specify exactly how the reports were used to guide prescribing, nor was it clear how the study achieved a remission rate higher than any other remission rate reported in clinical trials. Given that this was the first study ever published on the CNSDose test, and given how anomalous the remission rates were, we'd need a replication done with a different sample, and preferably one not conducted by the apparent owner of the company.

To sum up, at this point none of these tests inspire confidence, either because of poor methodology (Genesight, Genecept) or results that are so anomalous that they require replication (CNSDose). If you were to use them, any positive effect would likely be due more to the placebo-engendering effect of your enthusiasm than to any true scientific utility. Both the Genesight and Genecept tests are covered by Medicare and some private insurance companies; the criterion is a diagnosis of refractory major depression with at least one prior medication failure (for coverage details, see http://tinyurl.com/zfyh3t4).

Using FDA dosing recommendations as a guide

Pharmacogenetic tests do not require FDA approval, which might explain why so many are being marketed with limited evidence. Nonetheless, the FDA does require some pharmacogenetic information on some drug labels, and it publishes a handy table to allow you to look up which drugs have pharmacogenetic recommendations (see http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm). You can sort this table by therapeutic area to focus on psychiatric drugs, of which there are 27 listed. (See our summary of these recommendations in the table on page 6.)

Many of the recommendations are to lower starting doses in patients who are poor metabolizers. For example, in aripiprazole's label, you'll read: "Dosing recommendation in patients who are classified as CYP450 2D6 poor metabolizers (PM): The aripiprazole dose in PM patients should initially be reduced to one-half (50%) of the usual dose and then adjusted to achieve a favorable clinical response."

While the FDA does not specifically ask you to order genetic testing, you will not know whether your patient is a poor metabolizer unless someone has ordered it. Therefore, a case could be made for selectively ordering CYP450 testing to ensure you dose drugs in accordance with FDA labeling. Whether you do this is a judgment call; most of us are content to skip the genetic testing, and instead choose to start most medications at a low dose and titrate up gradually in order to prevent side effects.

Can genetic testing do more harm than good?

Genetic testing may be theoretically helpful in some cases, such as in patients with unexplained poor response or with unusually high vulnerability to side effects. But can ordering such tests paradoxically *worsen* treatment? There are various scenarios in which it might:

- **Poor medication switches.** Both Genesight and Genecept produce reports in which they assign certain recommended drugs to a green column labeled "use as directed" and others to a red or orange column labeled "use with caution." The company marketing literature paints a rosy picture of treatment resistant patients who have finally found the right medication as a result of these recommendations. But more skeptical press coverage has reported on patients who have done poorly, such as a man who was switched from venlafaxine (Effexor) to levomilnacepran (Fetzima) and

Continued on page 6

Expert Interview
Continued from page 1

reuptake. Different people have different gene variants that affect how much of the transporter is produced.

TCPR: And how might variations in the amount of serotonin transporter protein affect the response to antidepressants?

Dr. Uher: Let's assume that SSRIs work by blocking the reuptake of serotonin back into the neuron. They do this by disabling the serotonin transporter protein, making it harder to "vacuum" up excess serotonin and clear it from the synapse. That extra serotonin presumably helps to improve mood in patients with depression. If a person has a gene variant that causes the brain to make more serotonin transporters, that means the person's brain supplies more vacuum cleaners to clear out serotonin. If that person took an SSRI, it might not be as effective because all those extra transporters would counteract the serotonin reuptake inhibition. Conversely, if a person produces less transporter protein, the SSRI would be able to block most of it, leaving more serotonin in synapses and therefore leading to a better antidepressant response. This is a simplistic explanation, but it's the basic idea.

TCPR: Interesting. Are there any other gene variants that might affect antidepressant response?

Dr. Uher: Another example is cytochrome P450 genes (CYP genes) for liver enzymes that break down antidepressants. If there are too few of the enzymes, blood levels of the drug would go up, and this might cause more side effects. On the other hand, if there are too many enzymes, blood levels would be low, and there might not be enough response.

TCPR: What kinds of studies have been done with candidate genes?

Dr. Uher: There have been hundreds of studies done with various candidate genes to predict antidepressant response or toleratibility. Typically, you do genetic tests on a group of patients who have taken a particular antidepressant, you assess the response, and you do statistical analysis to see if there is any correlation between having certain gene variants and antidepressant response.

> **"It's appearing very unlikely that variations in candidate genes have any real effects on response to antidepressants."**
>
> Rudolf Uher, MD

TCPR: And what have these studies concluded?

Dr. Uher: Unfortunately, thus far, there is no consistent effect of any of the genes on either antidepressant response or side effects. The two largest pharmacogenetic studies, of response and side effects, both found equally negative results. One was STAR*D, and the other was GENDEP. Speaking as both a psychiatrist and a researcher involved in these trials, it was a huge disappointment. When we were planning the analyses, we thought these genes were safe bets. We predicted not only that we would find effects of these genes, but also that we would find out about other genes that would be promising. In fact, we ended up disconfirming the effects of the genes we had assumed would be shoo-ins.

TCPR: That's surprising—it seems that we often hear about findings showing some kind of association.

Dr. Uher: Yes. This was confusing, because there were many positive results, but none of them have been consistently replicated. We think the reason for this is that investigators typically test multiple candidate genes, but they tend to publish only the results that were positive. This selective reporting makes it appear that there are many positive results in the literature, but you are not seeing all the negative results. And if you run many different tests, it's possible that you will get some positive findings by chance alone. It's appearing very unlikely that variations in candidate genes have any real effects on response to antidepressants.

TCPR: Can you give us a bit more detail on the STAR*D and GENDEP studies?

Dr. Uher: STAR*D had genetic data on approximately 1,400 patients with depression, and GENDEP collected genetic data from over 800 patients with depression (*Am J Psychiatry* 2013;170(2):207–217. doi:10.1176/appi.ajp.2012.12020237). Both studies found important non-genetic predictors of outcome—for example, patients with symptoms of loss of interest, reduced activity, and anxiety were more likely to have poor outcomes. But the genetic results were largely disappointing. Both STAR*D and GENDEP examined comprehensive arrays of candidate genes, but could not replicate positive findings of previous smaller studies. STAR*D found a strong association in the serotonin receptor 2A gene, but this did not replicate in GENDEP. GENDEP found an association in the serotonin transporter gene, but it did not unequivocally replicate in STAR*D. In addition, both studies examined the CYP genes and found that they were unrelated to treatment outcomes or side effects.

TCPR: So what is your take on the commercial genetic tests that have been marketed? They certainly claim that their tests are predictive of both response and side effects.

Dr. Uher: I've looked at the studies done by one of the companies, Assurex, which markets the Genesight test. This test is based on a small number of candidate gene variants—the same ones that did not show replicable effects in large independent studies. The company did publish their own studies where they randomized patients to an active condition, which got the test, or to a control condition, which did not. They showed that people who get the test are slightly more likely to get better, but interpreting the meaning of this result is difficult. What they are doing in their studies is comparing a complex intervention against nothing.

TCPR: How does that make it trickier to interpret?

Dr. Uher: Let's think of how they recruited patients. They approached patients and essentially asked, "Would you be willing to be in a study? In it, you will either get a test that will predict the best antidepressant for you based on your genetic makeup, or you will not get the test." The people who got the test, and their psychiatrists, received a colorful printout that gave recommendations about which antidepressants would be best. Even if the testing that generates the recommendations is not valid, simply being in the active group generates a potential placebo effect. The treatment group feels like something special is being done for them. On the other hand, the patients assigned to the control group heard about the possibility of this cutting-edge gene

Continued on page 5

Expert Interview
Continued from page 4

test and they knew they were not getting it, so that generates disappointment, which can lead to potentially higher scores on depression scales.

TCPR: Sounds like there was a potential for biased results.

Dr. Uher: Exactly. It's also important to keep in mind that only one of the Genesight studies was blinded. This study was small (49 patients total) and it did not meet the standards for a well-designed clinical trial, because the researchers knew which patients were getting the test, which can lead to measurement bias (Winner JG et al, *Discovery Med* 2013;16(89):219–227).

TCPR: So the evidence was low-quality and not convincing. What do you conclude?

Dr. Uher: If you do something special for your patients, it will be on average beneficial. Although the genetic tests being marketed do nothing helpful for prediction, at least they are not harming anyone. The psychiatrists ordering the tests feel this is something special for their patients, and the patients feel that they are being given something special. "Genetic test" is an impressive-sounding phrase, and there is also a novelty effect. There's an old adage, "Drugs are most effective when they are first launched." For example, when Prozac was first launched, it seemed to work for everyone. People get excited by new technologies, and this boosts the placebo effect.

TCPR: All right, so there is likely an expectancy effect here. Are there any other reasons why people would be impressed with these tests?

Dr. Uher: Yes. The printout listing the genetic results includes other information, including general guidelines about which antidepressants are good options for patients with depression. When doctors see such guidelines at the point of care, they tend to practice more rationally. They end up appropriately changing treatment more often when the first medication doesn't work well, and this in itself leads to more effective practice. We have seen this in studies using measurement-based guidelines, which give the doctors tools to measure response and guidelines for what to prescribe in different circumstances. It's likely that any effect of the genetic tests works simply by providing doctors with commonsense treatment guidelines—and not via any genetic prediction.

TCPR: We've talked about gene candidate studies. What other methods are being used to find predictive genes?

Dr. Uher: The current standard of genetic research is the genome-wide association study (GWAS). About nine years ago, we began to have the molecular technology and computational power to measure and analyze a very large number of variants across genes. Using these techniques, we can get information about gene variants in the entire genome. Testing all of the genes in this way is a huge advantage, because we no longer have to guess on a small number of candidate genes for our focus. This means that we can get genetic testing on patients who have responded to drugs and search for any possible gene-response association. (Editor's note: For more information about GWAS, see https://www.genome.gov/20019523/.)

TCPR: And what sorts of findings have these studies yielded?

Dr. Uher: The first genome-wide significant finding came from the GENDEP study. We found a gene variant that predicted response to nortriptyline (Uher R et al, *Pharmacogenomics J* 2009;9(4):225–233. doi:10.1038/tpj.2009.12). It was on chromosome 6, and it is in the UST-1 gene. This gene is important for determining where newly generated neurons go in adulthood—it helps with adult neurogenesis. Unfortunately, over the past few years we still have not been able to replicate that finding, meaning it could still be a fluke. The problem is that since relatively few people use nortriptyline these days, it's hard to recruit enough subjects to do that kind of study.

TCPR: Any other GWAS findings?

Dr. Uher: Yes. Another study got published in September 2016 based on data collected through the consumer genomics test "23andMe" (Li QS, *Transl Psychiatry* 2016;6(9):e889. doi:10.1038/tp.2016.171). They did a GWAS of 40,000 people who were treated with antidepressants at some point in their lives. Nearly 10,000 were treated with SSRIs, and they had no significant findings. However, in one of the smaller analyses of 4,000 people who had taken Wellbutrin, they found one association: a weakly predictive variant in an area on a chromosome that was not a gene itself, but was between two other genes. The odds ratio was 1.35, meaning that having this variant increases the odds of achieving remission on Wellbutrin 1.35 times. It's a small effect size, and one may debate whether it should be considered statistically significant, because they conducted 12 different analyses and this was the only one that was positive. I am looking forward to seeing the results of replication, which should be easier to get for Wellbutrin, since it is commonly used.

TCPR: So overall, the results have been pretty underwhelming.

Dr. Uher: The message is clear that there is not a single variant that will predict response to antidepressants, but that response will be predicted by variants of numerous genes. The good news is that, given our more sophisticated research methods, we can now estimate what proportion of response from antidepressants is likely to be genetically determined, and it's about 42%.

TCPR: How is that number determined, given that no particular gene has been associated with response?

Dr. Uher: While no single variant shows a signal that is strong enough to be predictive of response, the number of weak signals is larger than what would be expected by chance. There is a statistical procedure (called genome-wide complex trait analysis) that allows us to estimate from the numerous weak signals how large the overall genetic contribution will likely be. From these data, we believe a large portion of antidepressant response is genetically based, and eventually we will figure out a genetic test to predict that. But we're not there yet.

TCPR: Thanks for your time, Dr. Uher.

CME Post-Test

To earn CME or CE credit, you must read the articles and log on to www.TheCarlatReport.com to take the post-test. You must answer 75% of the questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be taken by January 31, 2018. As a subscriber to *TCPR*, you already have a username and password to log onto www.TheCarlatReport.com. To obtain your username and password, please email info@thecarlatreport.com or call 978-499-0583.

The Carlat CME Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Carlat CME Institute is also approved by the American Psychological Association to sponsor continuing education for psychologists. Carlat CME Institute maintains responsibility for this program and its content. Carlat CME Institute designates this enduring material educational activity for a maximum of one (1) AMA PRA Category 1 Credit™ or 1 CE credit for psychologists. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity.

For those seeking ABPN Self-Assessment (MOC) credit, a pre- and post-test must be taken online at http://thecarlatcmeinstitute.com/self-assessment/

Below are the questions for this month's CME/CE post-test. This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Note: Learning Objectives are listed on page 1.

1. Individuals that carry inactive or partially active CYP450 genes, which may result in more side effects since serum drug levels are higher, are categorized as: (LO #1)
   - [ ] a. Extensive metabolizers
   - [ ] b. Intermediate metabolizers
   - [ ] c. Poor metabolizers
   - [ ] d. Ultrarapid metabolizers

2. What was one weakness in the Genesight study of pharmacogenomic guided treatment? (LO #2)
   - [ ] a. The control group did not show a negative effect
   - [ ] b. Researchers knew which patients were getting the test
   - [ ] c. There was a lack of multiple positive controls
   - [ ] d. Researchers did not minimize the effects of confounding variables

3. You are considering prescribing medication to a patient who is of Asian descent. Based on pharmacogenetic recommendations, you should test for the HLA-B*1502 allele before prescribing which drug? (LO #1)
   - [ ] a. Lamotrigine
   - [ ] b. Carbamazepine
   - [ ] c. Nortriptyline
   - [ ] d. Quetiapine

4. The Genome-based Therapeutic Drugs for Depression (GENDEP) study discovered a gene variant that predicted response to which antidepressant? (LO #2)
   - [ ] a. Protriptyline
   - [ ] b. Amoxapine
   - [ ] c. Imipramine
   - [ ] d. Nortriptyline

5. According to studies, after a follow-up period of 4 to 12 weeks, patients who switched antidepressants after 2 weeks of non-response had which of the following results compared to those who continued on the same medication? (LO #3)
   - [ ] a. A 5% better response rate in the depression scale score as well as secondary outcomes of response rate and remission rate
   - [ ] b. A 5% better response rate in the depression scale score but no change in secondary outcomes of response rate and remission rate
   - [ ] c. No change in the depression scale score but a 5% increase in secondary outcomes of response rate and remission rate
   - [ ] d. There were no significant differences between patients who continued and those who switched medications

Pharmacogenetic Testing: An Update

Continued from page 3

soon became acutely suicidal and was admitted to a hospital (https://tinyurl.com/hxkoyh8).

- **Inappropriate medication avoidance.** Testing reports list many commonly used drugs in the red column. Practitioners may then avoid use of these meds, even though they may have ultimately proven useful for patients.
- **Unwarranted patient skepticism.** Patients who read their reports will likely be skeptical of any drug in the discouraged category, making it difficult for you to prescribe them that drug in the future.
- **Misleading implications of being a "normal" metabolizer.** If a patient's genotype results show the patient to be a normal metabolizer (eg, extensive or intermediate), you may be inclined to believe that you can dose the patient more aggressively without side effects. But in real-world patients, even normal metabolizers can end up with high serum levels. For example, in one study a large group of patients who took venlafaxine were genotyped, and 4% of them were poor metabolizers at CYP450 2D6. Researchers then focused on the 96% of patients who were not poor metabolizers, and surprisingly, 27% of them had high ratios of venlafaxine

Continued on page 8

FDA Label Information Relevant to Pharmacogenetic Testing for Psychiatric Drugs

Medication	Pharmacogenetic Recommendations
Aripiprazole, iloperidone, perphenazine, atomoxetine, brexpiprazole, vortioxetine	Reduce dose in CYP2D6 PMs[1]
Desipramine, clomipramine, imipramine, amitriptyline, doxepin, nortriptyline, protriptyline, trimipramine, clozapine	Monitor levels in CYP2D6 PMs
Citalopram	Maximum recommended daily dose of 20 mg (rather than 40 mg) for CYP2C19 PMs, due to risk of QT prolongation
Thioridazine	Contraindicated in 2D6 PMs, due to risk of QT prolongation
Pimozide	In CYP2D6 PMs, dose should not exceed 4 mg/day in adults
Carbamazepine, oxcarbazepine	Avoid or use cautiously in individuals with the HLA-B*1502 allele (applicable to Asians)

[1]PM = poor metabolizer

Research Updates IN PSYCHIATRY

DEPRESSION

Switching Antidepressants May Be No Better Than Staying the Course

REVIEW OF: Bschor T, Kern H, Henssler J, Baethge C. Switching the antidepressant after nonresponse in adults with major depression: A systemic literature search and meta-analysis. *J Clin Psychiatry* 2016. doi:10.4088/JCP.16r10749. [Epub ahead of print]

STUDY TYPE: Meta-analysis

Clinical trials have shown that the response rate of major depression to a course of antidepressants is 50% to 70%. After a non-response, what should we do? Increase the dose? Switch to another medication? Augment with a different one? Unfortunately, we have remarkably little to guide us in the way of empirical studies. The largest "real-world" study of antidepressants, the oft-cited STAR*D trial, enrolled plenty of patients and compared various strategies. Unfortunately, that study was not very informative, because there was no placebo group, and patients were not fully randomized to group assignments.

The authors of this meta-analysis sought evidence to answer a specific question: Is it better to stay the course with the original antidepressant, or is it better to switch? They searched the literature for studies that enrolled patients with major depressive disorder who did not respond to at least a 2-week trial of an antidepressant. These patients were then randomly assigned to either continuation of the same medication or a switch to a different one. They found eight relevant studies, and combining them, 783 patients were randomized to continuation arms while 844 were assigned to switching arms. Some of the studies blinded participants to their treatment, but others did not; the follow-up lasted from 4 to 12 weeks, depending on the study.

The studies spanned a long time period, with the oldest published in 2001 and the most recent in 2014. Medications compared included the following (listed in order of continuation medication, switched-to medication): fluoxetine, mianserin; nortriptyline, fluoxetine; venlafaxine, fluoxetine; escitalopram, duloxetine (two studies); various SSRIs, duloxetine; various SSRIs, mirtazapine; desipramine or citalopram, desipramine or citalopram.

RESULTS

There were no statistically significant differences between patients who continued vs those who switched medications. This was true both for the primary outcome of change in depression scale score and for the secondary outcomes of response rate and remission rate.

TCPR'S TAKE

This is the largest and best study yet looking at whether it's better to switch antidepressants or stay the course, and the implication is that there is no advantage to switching.

PRACTICE IMPLICATIONS

When patients do not respond to an antidepressant, you may be tempted to switch to another one and then rotate through your list of favorites. But given the surprising finding that switching antidepressants incurs no discernible benefit, you may want to instead consider augmentation strategies or a psychotherapy referral.

Meditation: An Effective Treatment for Depression?

REVIEW OF: Sharma A, Barrett M, Cucchiara A, Gooneratne N, Thase M. A breathing-based meditation intervention for patients with major depressive disorder following inadequate response to antidepressants: A randomized pilot study. *J Clin Psychiatry* 2016 Nov 22. doi:10.4088/JCP.16m10819. [Epub ahead of print]

STUDY TYPE: Randomized, rater-blind, waitlist-controlled study

Complementary and alternative medicine is gradually becoming more mainstream, and we covered some of these treatments in a recent issue of *TCPR,* but we didn't cover yoga and meditation. Sudarshan Kriya yoga (SKY) is a meditation technique that combines yoga poses, sitting meditation, and breathing exercises. Past small studies have shown that SKY is effective for dysthymic disorder, depression due to alcohol dependence, and major depressive disorder in inpatients. In this trial, 25 adult outpatients with depression were recruited from the University of Pennsylvania Mood and Anxiety Disorders Treatment and Research Program. These patients had been on antidepressants for at least 8 weeks without a response. They were randomly assigned to either the SKY active (n = 13) or waitlist control (n = 12) group. The study lasted 8 weeks and consisted of 2 phases. Phase 1 (week 1) included six 3.5-hour sessions of the SKY program. Phase 2 (weeks 2–8) consisted of weekly follow-up sessions (of 3.5 hours) and daily at-home practice sessions of 20–25 minutes. While 3.5 hours of yoga might sound like a lot, only a small portion of the sessions involved yoga postures; these sessions included rhythmic breathing exercises, sitting meditation, and stress education. Clinical raters conducted 3 assessments: baseline, at the 1-month visit, and at the 2-month visit. The primary outcome was change in patients' HDRS-17 scores from the baseline to the 2-month visit.

RESULTS

Patients in the SKY active group had a mean reduction in their HDRS-17 score of 9.77 points, whereas the waitlist control group had a small increase in their score of 0.50 points (p = 0.032). SKY patients also showed greater improvement on two secondary outcomes: the Beck Depression Inventory and the Beck Anxiety Inventory. No patient in the SKY group reported any adverse reactions.

TCPR'S TAKE

The study was limited by the small sample size and by the lack of an active comparator control group. In addition, the treatment was pretty resource-intensive—it's unlikely that most patients will be able to find a program offering 3.5 hours of yoga and meditation per day for 6 days, much less be able to afford it, either in terms of time or money. Nonetheless, given that several other small studies have endorsed the SKY approach for depression and other conditions, it looks like SKY meditation has some promise as an augmenting treatment for patients with treatment resistant major depressive disorder.

PRACTICE IMPLICATIONS

This is a promising preliminary study, and we look forward to larger ones in the future that hopefully will replicate these results. In the meantime, *namaste!*

THE CARLAT REPORT: PSYCHIATRY

P.O. Box 626
Newburyport, MA 01950

PRSRT STD
US Postage
PAID
Nashville, TN
Permit 989

REMINDER!

Lock in your current rate today!

Our last price increase was 13 years ago, but the costs of printing and postage have finally caught up to us.

Subscription rates are increasing from $109 per year to $129 per year on **May 1, 2017.**

Lock in your current rate for 1 or 2 years by renewing today, even if your subscription isn't due to expire until after the price increase.

Renew at your current rate of:

- $109 for 1 year (savings of **$20** compared to increase)
- $209 for 2 years (savings of **$40** compared to increase)

Renew online at
www.thecarlatreport.com
or by phone at 978-499-0583.

This Month's Focus:
Pharmacogenetics

Next month in *The Carlat Psychiatry Report:* High Yield Therapy Techniques

Pharmacogenetic Testing: An Update

Continued from page 6

to its metabolite—the pattern you'd expect in poor metabolizers. Something other than genetics rendered these patients poor metabolizers. In some cases patients were taking other drugs that decreased venlafaxine metabolism, but in other cases there was no clear explanation. The authors point out that genetic testing can be misleading, and that a person's actual metabolic abilities will vary based on nongenetic factors (Preskhorn SH et al, *J Clin Psychiatry* 2013;74(6):614–621).

TCPR's Verdict on Pharmacogenetics

1. Avoid Genesight and Genecept. They aren't proven, and they might lead you to make inappropriate or potentially harmful prescribing decisions.
2. Keep your eye on CNSDose. If its initial spectacular results can be replicated, the test may be worth trying.
3. If you are the type of practitioner who likes to follow every FDA recommendation to the T, you might consider selectively ordering genotyping for specific enzymes, depending on the drug you are prescribing. But slow dose titration will accomplish the same purpose more cheaply.
4. If you are considering prescribing carbamazepine or oxcarbazepine to a person of Asian descent, you should test for the HLA-B*1502 allele. This is not a metabolic gene, but rather a gene that encodes for proteins on cell surfaces. Research has shown that Asians who have this allele are at high risk for serious rashes such as Stevens-Johnson syndrome if they take carbamazepine or oxcarbazepine.