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Chris Aiken, MD
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IN THIS ISSUE

Focus of the Month:
Depression

Learning Objectives

After reading these articles, you should be able to:

1. Identify common misconceptions about disulfiram.
2. Describe best practices for documenting notes under the new open notes policy.
3. Understand the role of psychotherapy and pharmacogenetic testing in depression.
4. Summarize some of the current research findings on psychiatric treatment.

Disulfiram: An Underused Strategy for Alcohol Use Disorders

Stephen Wyatt, DO. Private practice psychiatrist with certification in addiction psychiatry,, Charlotte, NC.

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

Alcohol ranks third among preventable causes of death in the US, but it is by far the most undertreated. Fewer than 8% of people with alcohol use disorders (AUDs) receive treatment for their disease, and only a minority of them receive FDA-approved medications. Those medications are acamprosate (Campral), naltrexone (Vivitrol, ReVia), and disulfiram (Antabuse). Disulfiram is the oldest of the bunch, and it has accumulated a few myths over its 70-year career that have hindered its use.

Highlights From This Issue

A few genetic tests are ready for clinical practice, including CYP2D6, 2C19, 3A4, HLAs, and whole exome sequencing (WES), but only for certain patients and certain medications.

Antidepressants and psychotherapy both treat depression, but in different ways. Dr. Giovanni Fava describes how to harness those differences to prevent recurrent depression.

For the right patient, disulfiram (Antabuse) is a very effective treatment for alcohol use disorders. Low doses work just as well as high doses and are much safer.

Light therapy worked in a small randomized controlled trial of PTSD.

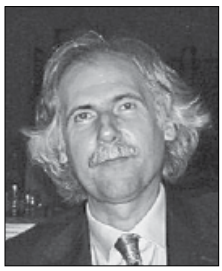
Continued on page 2

Q&A With the Expert

Psychotherapy and Medication in Recurrent Depression
Giovanni Fava, MD

Clinical Professor of Psychiatry at the State University of New York at Buffalo. Editor-in-Chief of the journal Psychotherapy and Psychosomatics *and author of over 500 scientific papers. His book,* Discontinuing Antidepressant Medications, *is due from Oxford University Press in 2021.*

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



TCPR: When depression is recurrent, we usually continue the antidepressant indefinitely. Has that practice come under challenge?

Dr. Fava: Yes. Antidepressant drugs are certainly important during the depressive episode, but what we are starting to question is whether they are as effective in preventing relapse. A meta-analysis from 12 years ago found that antidepressants are not as effective in recurrent depression as they are in single episodes (Kaymaz N et al, *J Clin Psychiatry* 2008;69(9):1423–1436).

TCPR: But there are studies showing preventative effects, right?

Dr. Fava: There are studies where remitted patients were taken off antidepressants, or randomized to stay on them, and they seem to favor the medication. The problem with these studies is that they did not differentiate between withdrawal and relapse (Baldessarini RJ and Tondo L, *Psychother*

Continued on bottom of page 3

Disulfiram: An Underused Strategy for Alcohol Use Disorders
Continued from page 1

How it works

Disulfiram's mechanism is primarily pharmacokinetic. It irreversibly blocks the enzyme that clears out acetaldehyde, a metabolite of alcohol that is responsible for the nausea, vomiting, and headaches known colloquially as a hangover. The result is that patients who drink while on disulfiram, even in small amounts, will suffer a severe hangover within 5–15 minutes. Depending on the dose of disulfiram and how much alcohol is ingested, this interaction may result in chest pain, weakness, difficulty breathing, and rarely death (Kristenson H, *Alcohol Alcohol* 1995;30(6):775–783).

Besides this metabolic effect, disulfiram also inhibits the metabolism of dopamine in the CNS. This dopaminergic effect does not seem to influence alcohol use, but it does reduce the rewarding effects of cocaine. Thus disulfiram is effective against both addictions in the often co-occurring alcohol and cocaine use disorders (Carroll KM et al, *Arch Gen Psychiatry* 2004;61(3):264–272).

The disulfiram effect was discovered in 1937 when workers exposed to this compound in the manufacturing of tires (where it was used to stiffen rubber) became ill after drinking alcohol. Clinical trials in AUDs ensued, leading to its FDA approval in 1951. Our understanding of disulfiram has evolved since then, but an early mishap—where doctors advised patients to drink on disulfiram—led to a lingering perception that the drug is too dangerous to use in practice.

Myth #1: Safety

At first, disulfiram was thought to work through aversive conditioning, and some physicians advised patients to drink on it in order to experience the aversive reaction. Rarely, the reaction can be fatal, so this practice was soon abandoned. Disulfiram's safety was further improved by lowering the daily dose from 1,000–3,000 mg to 250 mg. With these precautions, mortality from the disulfiram alcohol reaction has not been reported in many years (Chick J, *Drug Saf* 1999;20(5):427–435).

Outside of the alcohol interaction, the most common side effects on disulfiram are a maculopapular rash, bad breath, and fatigue. Disulfiram does have a few contraindications: cardiovascular and cerebrovascular diseases (the drug can raise blood pressure and there are rare reports of heart failure on it), significant hepatic impairment (disulfiram can be hepatotoxic), psychosis (which can worsen on disulfiram), and pregnancy (disulfiram is a teratogen). It should also be avoided in patients who are cognitively impaired because of the need to understand and follow the instructions. Initial liver enzymes (LFTs) should be obtained and monitored every 6 months during treatment, although most cases of elevated LFTs on disulfiram are due to alcohol itself (Iber FL et al, *Alcohol Clin Exp Res* 1987;11(3):301–304).

All this is not to suggest that disulfiram is as safe as, say, buspirone. However, its risks are many leagues lower than those of the disease it treats, and that's the kind of reasoning that should guide its use. But is it really effective for AUDs?

Myth #2: Efficacy

Disulfiram's efficacy is often doubted. The thinking is that a patient with mild AUD will stay on it (and may not need it), while a patient with significant AUD will simply stop the medication when they have the urge to drink. In fact, disulfiram's half-life is 2–5 days, and its alcohol interaction continues for up to 2 weeks after it is stopped, ensuring that there is some time for patients to reconsider their decision to relapse.

There is a grain of truth in the lack of efficacy myth, however. Disulfiram is much more effective when given under supervision, either by a friend, relative, or clinical staff. In one meta-analysis, unsupervised disulfiram worked no better than control, while supervised disulfiram had a large effect size (0.8) compared to a similarly supervised non-disulfiram control group (Skinner MD et al, *PLoS One* 2014;9(2):e87366).

In practice, unsupervised disulfiram can work in highly motivated patients, such as professionals whose careers would be derailed by a relapse. But supervised delivery is the ideal. Clinically supervised treatment is available at some centers, and private practitioners can ask the patient to enlist a trusted friend or relative to ensure they remain adherent.

Disulfiram's efficacy is also questioned because it did not work when tested against a placebo, but that is an inevitable result of its mechanism. To ensure adequate blinding, subjects on placebo are issued the same stern warning about dangerous reactions with alcohol, and this leads them to cut back as much as the disulfiram group. It is also easy to break the blind by ingesting a small amount of alcohol. So how do we

Continued on top of page 3

Disulfiram: An Underused Strategy for Alcohol Use Disorders

Continued from page 2

know that it works? The main support comes from unblinded randomized trials that have compared disulfiram to psychotherapy, naltrexone, or acamprosate.

There are at least 17 of those trials, and in the majority of them disulfiram performed much better than the active comparator. For example, it surpassed acamprosate and naltrexone with a magnitude similar to the difference between stimulant and placebo in ADHD—ie, effect size of 0.8 (Skinner et al, 2014). These effect sizes are somewhat inflated, however, by the fact that disulfiram requires total abstinence, while other treatments succeed by merely reducing the use of alcohol.

Disulfiram: Quick Facts	
FDA Indication	Alcohol use disorders
Other Uses	Cocaine use (when comorbid with alcohol)
Dosing	Start 500 mg QD for 1 week (to rev up interaction) then lower to 250 mg QD
Side Effects	Most side effects resolve within 2 weeks: fatigue, headache, impotence, maculopapular rash, acne, dermatitis, bad breath, metallic or garlic-like aftertaste
Risks	Rare hepatitis (monitor LFTs every 6 months)
Interactions	Inhibits CYP2E1; may raise levels of warfarin, phenytoin, theophylline, desipramine, imipramine, caffeine, and some benzodiazepines (diazepam, oxazepam, and chlordiazepoxide)
Contraindications	Pregnancy, cardiovascular and cerebrovascular diseases, significant hepatic impairment, psychosis, and cognitively impaired patients who cannot follow the directions
Cost	$40/month

The ideal patient

The ideal candidate for disulfiram is a patient who has been unsuccessful in reducing alcohol and has experienced disastrous effects with its use. These are patients who resonate with the adage "one is too many, and a thousand is not enough." They understand the need for total abstinence and recognize they need external help in achieving it. They have a caring person in their life who can watch them take the medication, and they are hopefully involved in a 12-step program or psychotherapy for addiction. It's with these patients that I'll open up a discussion of disulfiram. After explaining how the drug works, I will tell the patient that it is most effective when taken in front of another person. This can also solidify mutual trust in that relationship.

Long-term therapy is the ideal for prevention, but some patients are successful taking disulfiram episodically. Patients with significant self-awareness and commitment to sobriety may benefit from taking disulfiram when, for example, they are faced with an event where alcohol will be freely flowing, presenting a significant risk of relapse.

All patients struggle with adherence, and this problem is compounded by addiction. For a person with AUD, cravings feel like a basic need. On the other hand, some healing takes place in these habitual pathways after patients have been sober for a couple of months. Cravings lessen and confidence improves. Their brain is recovering, and good things are starting to happen in their life, which is harder to let go of.

TCPR VERDICT: Disulfiram is very effective in AUDs, particularly when its delivery is supervised by a friend, relative, or clinical staff. Low doses are safer and work just as well as higher ones. As long as the patient does not have a contraindication, disulfiram is a relatively safe intervention for a disease that can be fatal when left untreated.

To learn more, listen to our 6/28/21 podcast, "The Rediscovery of Antabuse." Search for "Carlat" on your podcast store.

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Expert Interview — Psychotherapy and Medication in Recurrent Depression

Continued from page 1

Psychosom 2019;88(2):65–70). Withdrawal reactions are extremely common with SSRIs and SNRIs, and we have no way to know how many of the relapses in those trials were actually withdrawal and post-withdrawal syndromes.

TCPR: You've advocated for "sequential treatment" as an alternative to keeping these patients on antidepressants for the long term. Can you describe this approach?

Dr. Fava: Yes, it involves sequential use of antidepressants and psychotherapy. We first introduced sequential treatment in 1994 as a way to treat residual symptoms of depression. These are the low-grade depressive symptoms that patients suffer from after coming out of an episode, and they put the patient at risk for relapse. We start with an antidepressant. After 4–6 weeks we should have a good idea if that antidepressant is working, and if it is we'll keep them on it for another few months. Improvement on antidepressants is usually steady and progressive for the first 3 months of treatment. After 3 months we reassess the patient, this time looking for residual symptoms. Then we taper the antidepressant and start psychotherapy to address the residual symptoms. These residual symptoms, by the way, are tightly related to the prodromal symptoms that brought the patient into a full episode in the first place.

TCPR: So the clinician needs to understand the prodromal symptoms that led up to the depression in order to prevent the next episode?

Dr. Fava: Right, and the best time to assess for that is not in the acute phase of the illness; it is when the patient has gotten better. We can then ask, "What was going on before the depression began?" And they'll say, "Oh yeah, as a matter of fact, before becoming depressed I started avoiding social situations."

Continued on page 4

Expert Interview – Psychotherapy and Medication in Recurrent Depression
Continued from page 3

TCPR: It sounds like this requires more than running a depression screen like the PHQ-9.

Dr. Fava: Yes, that's totally inadequate. What we need to do is to interview the patient after a course of pharmacotherapy as if they were a new patient—starting from the very beginning and tracking all of the possible symptoms. We might say, "When I first saw you, you were off the road. I prescribed an antidepressant and now you are back on the road. However, if you drive the way you did before the depression, you will go off the road again sooner or later." Then we start psychotherapy while tapering the antidepressant.

TCPR: Why wait? Why not just add psychotherapy from the start?

Dr. Fava: Because when we look at studies that combine the two, adding the therapy does very little to change the outcome. It's with this intensive, two-stage approach that we see the difference, and we've recently confirmed that in a meta-analysis of 17 randomized controlled trials (Guidi J and Fava GA, *JAMA Psychiatry* 2021;78(3):261–269).

TCPR: What type of psychotherapy do you use in sequential treatment?

Dr. Fava: In the first studies we used CBT to address residual depression, which usually involves symptoms such as anxiety, irritability, avoidance, giving up easily, and interpersonal difficulties like friction in relationships and inhibited communication. Then we realized traditional CBT was not enough. Now there are three main models for preventing depression—well-being therapy (WBT), preventive cognitive therapy, and mindfulness-based CBT. These build from CBT and can be delivered in group or individual sessions.

TCPR: You helped develop well-being therapy (WBT). Tell us about what it is.

Dr. Fava: WBT is a manualized, short-term psychotherapeutic strategy that emphasizes self-observation, with the use of a structured diary, homework, and interaction between patient and therapist. It does not have to be intensive; in our studies we used 1 session every other week for a total of 8–10 sessions. To borrow a phrase from Jerome Frank, WBT is essentially guided self-therapy.

TCPR: What happens in the sessions?

Dr. Fava: One thing that sets WBT apart from many other therapies is that we don't just look at what is wrong. We want patients to experience positive affect, not simply the absence of depression. This involves self-observation. We ask them to look for times that things are going well and record them in a diary. Patients with recurrent depression often lack what we call *transfer of experiences*. In other words, they do not pull from past successes, such as a time when they successfully coped with a problem that they are once again struggling with. For example, take a university student who has intense anxiety about a test. He does better than he expected on it, and over the next year he grows in his academic skills. But when exam time comes around again, he has the same intense anxiety as though he has learned nothing in the past year. So in WBT, we help patients become more aware of their strengths.

> **"When I see a patient who is unable to engage in regular psychotherapy for various reasons, I always write two prescriptions. One is the medication. Then, on a second pad, I will make some simple lifestyle suggestions and discuss the evidence supporting those ideas. Then I will say, 'The medication will likely help you 50% if things go really well; the other 50% is up to you.' "**
>
> Giovanni Fava, MD

TCPR: And the diary of positive experiences helps them develop that awareness?

Dr. Fava: Yes, but that's not the diary's only purpose. It's also the basis for identifying and overcoming obstacles (thoughts and behaviors) to well-being. At first the patient may say, "Well, my diary will be blank. I never have positive experiences." That's never true—they may feel bad 90% of the time, but there might still be 10% when they feel well. The problem is that these moments are fleeting, and we address that in the next session. When they bring in their diary, I will ask, "OK, so you felt good in that situation, but then you stopped feeling good; why?" And for the next assignment I'll ask them to write down what kept those moments from continuing.

TCPR: What are some common responses?

Dr. Fava: Often it is unrealistic expectations or opportunities that are not pursued. For example, "I was able to solve a problem at work. I felt good. But then I thought about other things I'm not able to do and the moment stopped." Then the therapist will make practical suggestions and problem-solve ways to keep those moments going.

TCPR: I often hear patients dismiss their success by focusing on their feelings, such as "Yes, I was able to get through that, but it was miserable. I felt anxious." Does part of this work involve shifting their focus from emotions to functioning?

Dr. Fava: Yes. And it is not simply a matter of making the patient more aware cognitively. It is also a matter of behavioral activation; changing how they are living in some way. The aim is to build resistance to stress (ie, resilience, frustration tolerance, adaptability, and flexibility) and a unifying outlook that can consistently guide their actions toward their values and goals and—ultimately—a more meaningful life *(Editor's note: A WBT manual is available at www.well-being-therapy.com)*.

TCPR: Many patients are unable to engage in regular psychotherapy for various reasons. What can we do for them?

Dr. Fava: When I see a patient, I always write two prescriptions. One is the medication. Then, on a second pad, I will make some simple lifestyle suggestions and discuss the evidence supporting those ideas. Then I will say, "The medication will likely help you 50% if things go really well; the other 50% is up to you." And I tell them, "This is more important than the medication." Sometimes the patient comes back and they don't feel sufficiently better, but they say, "Probably your medication worked, doc, but I didn't do my 50%."

Continued on bottom of page 6

How to Write an Open Note

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

"A physician should at all times deal honestly and openly with patients." —AMA Code of Medical Ethics

Beginning April 4, 2021, the Department of Health and Human Services (DHHS) instituted a new policy stating that all clinical notes must be open to patients for their review in a timely fashion. Since that announcement, I have heard physician colleagues from various specialties voice concerns over what this means for us, our patients, and the future of our field. In this article, we'll take a close look at this new regulation and how it might affect our clinical practices.

The new rules

The new rules are part of the 21st Century Cures Act, which aims to modernize various aspects of medicine, from clinical trials to electronic health records (EHRs). The intent of the ruling is to remove obstacles to patient records so they can be viewed by patients and shared more easily across health care systems. The mandate is handed down by Medicare, Medicaid, and DHHS.

The first part of the ruling applies mainly to developers of EHRs. It requires them to adopt a standardized interface so that electronic records can be shared across platforms. This will take time, and the ruling allows developers 3 years to prepare this rollout.

The second part is the open notes provision, which pertains more directly to clinicians. Under this provision, clinicians must allow patients full access to their medical information without charge or delay. The information must be available to patients through an electronic portal so that they can read it without having requested it.

The exact time frame of a "delay" is not defined, but DHHS does give an example that gets the point across. If a practice withholds labs from a patient to allow their physician time to review and comment on the results, that would be considered a delay.

There are four exceptions to this transparency rule, and I'd suggest clinicians treat them as rarities, not goals.

1. **Serious imminent harm.** Clinicians can withhold records if releasing them could cause imminent harm to the patient or others. However, the ruling states that "emotional damage" does not qualify as harm, and it allows patients the right to an independent review of this exclusion.

2. **Psychotherapy process notes.** Since the early days of HIPAA, therapists have been allowed to keep private psychotherapy process notes separate from the medical record. The new ruling still allows this, but it specifies that medical information pertaining to symptoms and diagnoses cannot be cloistered in a psychotherapy note.

3. **Legal notes.** Information that is "compiled in reasonable anticipation of, or for use in, a civil, criminal, or administrative action or proceeding," can be withheld, such as communications with a lawyer around a malpractice suit or documentation pertaining to a civil commitment hearing.

4. **Off the grid.** Clinicians who do not use an EHR are exempt from this legislation for now.

Next I'll look at ways that open notes can improve the physician-patient relationship.

From HIPAA to open notes

While the new ruling expands patient access to the medical record, it is not the first to open up the notes. That

Continued on top of page 6

Top Ten Items to Consider When Documenting Your Notes	
1.	Compose notes as if you had to read them aloud in a courtroom—not to a jury of your peers, but to a jury of lay persons.
2.	Avoid writing that the patient "is noncompliant" (instead, try "is not taking the medication"), "refused treatment" (try "declined treatment"), or "failed the medication" (try "the medication failed").
3.	Convey hope in your assessment and plan, and list specific behavioral changes the patient can make to engage them in their recovery.
4.	Substitute more objective language for items that can be misinterpreted (eg, instead of "cry for help" or "suicidal gesture," write "a suicide attempt that was high in psychological significance but low in medical significance").
5.	Record all the sources of information you utilized to form your decisions, such as patient interview, nursing records, past visits, and collateral sources. This helps avoid allegations of hasty conclusions.
6.	Document the rationale behind your diagnosis, such as specific criteria, mental status exam, and associated signs.
7.	Avoid documenting identifying information about other people in the patient's life (eg, family, coworkers, etc).
8.	Use patient quotations where appropriate, especially when the patient's language is more effective than medical terminology in relating the moment.
9.	Discuss controversial areas with the patient in person before they read them in the note. Examples might include substance use disorders, personality disorders, delusional material, and secondary gain.
10.	Read notes aloud to see if unintended emotions are conveyed when the words are enunciated. Avoid exclamation points, asterisks, and other symbols that could convey negative emotions. When countertransference is strong, ask a peer to review your note before signing off.

How to Write an Open Note

Continued from page 5

started with HIPAA, which broke new ground in the 1990s by requiring medical providers to release notes to patients upon request, unless releasing them could potentially be harmful. The problem was that "harm" was never defined, and some providers interpreted it broadly in a way that precluded the release of most records.

Research over the past decade has shown that opening up notes to patients can improve health care significantly. For example, studies have noted that open records lead to greater medication adherence and help to solve a long-standing issue of patients either feeling confused by their physician's directions or simply not remembering what was asked of them (DesRoches CM et al, *Ann Intern Med* 2019;171(1):69–71).

Open notes can improve diagnostic accuracy, diminish stigma, and engage patients in their care. Psychiatric diagnoses have historically suffered from poor inter-rater reliability and could benefit from the patient's input (Matuszak J and Piasecki M, *Psychiatric Times* 2012;29(10):12). When patients understand the thinking behind their diagnosis, they are more likely to follow through on treatment and maintain hope in their recovery. Having the patient directly involved in medical decision-making can foster trust, lower demoralization, and increase their sense of control (Thom RP and Farrell HM, *AMA J Ethics* 2017;19(3):253–259).

On the other hand, open notes can also lead to miscommunication, complaints, or unspoken resistance between us and those we serve. In the table (page 5), I've outlined 10 ways to reduce this risk as you compose your notes in the open era.

"Either write something worth reading or do something worth writing." —Benjamin Franklin

TCPR VERDICT: New legislation allows patients nearly complete access to their medical record. Open notes are an opportunity to improve patient education, treatment adherence, and the therapeutic relationship. At the very least, write your notes as though your patients will read them.

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Expert Interview – Psychotherapy and Medication in Recurrent Depression

Continued from page 4

TCPR: How do you choose that advice?

Dr. Fava: It has to be personalized, based on what is learned through the clinical interview. I generally write very simple things, like doing something outdoors because otherwise they will sit on the couch all day and stew in negative thoughts. I might recommend they pursue things that create optimal experiences for them.

TCPR: What are "optimal experiences"?

Dr. Fava: These are the things that they do well; that they enjoy and gain satisfaction from (see table at right). Some call it being "in flow" or "in the zone." These experiences are characterized by the perception of high environmental challenges and environmental mastery, deep concentration, control of the situation, clear feedback on the course of activity, and intrinsic motivation. They might include activities like sports, school, or projects. What matters is that they are challenging enough to hold the patient's attention and bring a sense of accomplishment, but not so challenging as to be overwhelming.

Qualities of Optimal Experiences	
Challenging	Challenging enough to hold your attention, but not so challenging as to be overwhelming
Transcendent	You are less preoccupied with yourself and more focused on the activity itself—time flies while you do it
Sensory	It directly engages your senses of sight, touch, smell, taste, or hearing
Feedback	It provides clear goals and quick feedback
Rewarding	The more you do it, the more you want to do it
Purposeful	It is in line with your values and goals in life; you do it for its own sake, regardless of the outcome

TCPR: Once you shift from the antidepressant to the psychotherapy, do you continue the antidepressant or taper it off?

Dr. Fava: That has to be a shared decision, but we strongly encourage patients to taper and discontinue their antidepressant. Tapering goes better when they have the support of a therapist. Otherwise it is very difficult.

TCPR: So even though they have residual symptoms, you would still consider tapering the antidepressant?

Dr. Fava: Yes, if there is at least partial remission and no depressed mood, because psychotherapy in the sequential model will take care of that. The results for this model are rather robust: It significantly decreases the likelihood of relapse compared to clinical management or treatment as usual even with long-term follow-up, such as 6 years (Guidi and Fava, 2021). There are randomized controlled studies that indicate sequential treatment is significantly better than treatment as usual, even when you taper and discontinue medications. No other approach does that.

TCPR: So why taper? Why not just keep them on the antidepressant?

Dr. Fava: Antidepressants were developed to treat severe episodes of depression, and this is still where we have the best evidence for their use. It is only as the drugs became more tolerable that we stretched their original indications to milder forms of mood disturbances and relapse prevention. However, if treatment is prolonged beyond 6 months, phenomena such as loss of clinical efficacy, episode acceleration, and switch into bipolar illness may ensue. There are also long-term side effects such as weight gain, gastric toxicity, and sexual dysfunction, as well as withdrawal symptoms if you try to discontinue them. Those hidden costs may outweigh their apparent gains in some patients, particularly when we lack good evidence of their maintenance effects.

TCPR: Thank you for your time, Dr. Fava.

Q&A With the Expert

Genetic Testing: What You Need to Know in 2021

John Nurnberger, MD, PhD

Vice Chair for Preclinical Research, Department of Psychiatry, Indiana University, Indianapolis, IN.

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

TCPR: Is there a role for genetic testing in clinical practice?

Dr. Nurnberger: I think the evidence is growing that there's a place for this in clinical practice. The meta-analyses of pharmacogenetic tests are actually looking pretty favorable recently, at least for some genes, particularly CYP2D6 and 2C19 (Bousman CA et al, *Pharmacogenomics* 2019;20(1):37–47). These code for metabolic enzymes in the liver and predict whether the patient will have unusually high levels of certain medications (ie, a poor metabolizer) or low levels (ie, a rapid metabolizer). Other genetic markers have not panned out as well, like the S and L allele of the serotonin transporter.

TCPR: That's interesting that the meta-analyses are positive, because most of the individual studies were not, except on secondary outcome measures.

Dr. Nurnberger: Yes. What seems to be happening is that there is a trend toward positive results in the depression trials, and those trends create a more positive signal when added together in a meta-analysis. But this isn't a slam-dunk. It's not the kind of evidence that the FDA would like to approve a drug.

TCPR: When would you order genetic testing?

Dr. Nurnberger: It's not at all routine in my practice, and I don't think it should be routine in anyone's practice. Where you might consider it is for patients who have failed a couple of antidepressant trials or have had very unusual responses to medications. Sometimes those results will guide treatment, and patients also appreciate knowing that there is a reason behind the experiences they've had with medications.

TCPR: Most genetic panels look at one or two dozen genes. Which genes are most useful?

Dr. Nurnberger: The ones I pay attention to are the CYP genes that affect antidepressant metabolism and, to a lesser extent, antipsychotic metabolism. Those are CYP2D6 and 2C19, and sometimes 3A4. I also pay attention to the summary recommendations, particularly the part about medications to avoid, but I take those recommendations with a grain of salt. You have to look at where that evidence comes from. If a panel says to avoid a medication because of 2D6 or 2C19 results, it's more solid.

TCPR: So you put more weight on those genes than you do on the summary results in the panel.

Dr. Nurnberger: Yes. The evidence is much stronger for those individual genes than it is for the summaries. Those summaries are based on algorithms that are not made public, so there's a little bit of a black box going on, and each company uses a different algorithm. Companies may also differ in how they present results of individual genes because there is no consensus on which combinations of alleles translate to rapid or slow metabolizer status.

"It's not at all routine to order genetic testing in my practice, and I don't think it should be routine in anyone's practice. Where you might consider it is for patients who have failed a couple of antidepressant trials or have had very unusual responses to medications. The genetic panels I pay attention to are the CYP genes that affect antidepressant metabolism and, to a lesser extent, antipsychotic metabolism."

John Nurnberger, MD, PhD

HLA genotyping

TCPR: Are there other genes worth paying attention to on these panels?

Dr. Nurnberger: Another one that can be critical is HLA genotyping. The FDA requires this test before starting carbamazepine in patients of Asian descent, because a positive result means they have a very high risk—around 90%—of allergic reactions like Stevens-Johnson syndrome on carbamazepine *(Editor's note: A positive HLA-B*1502 carries the highest risk).*

TCPR: How would you interpret a positive HLA in someone who's not of Asian descent?

Dr. Nurnberger: I'd interpret it as a warning signal and would not use carbamazepine. The original FDA warning requires the test in Asian populations because that is where the yield is highest, but subsequent studies have shown it is relevant to others as well. The original HLA subtype was identified in people of Han Chinese descent, but since then, we've identified other subtypes in other populations that convey a similar risk. In test results you'll see these as HLA-A and HLA-B, and a positive result on either is a good reason to avoid carbamazepine (Mullan KA et al, *HLA* 2019;93(6):417–435).

Continued on page 8

Continued from page 7

TCPR: Does HLA subtyping predict rashes on other anticonvulsants, like oxcarbazepine or lamotrigine?
Dr. Nurnberger: It does for oxcarbazepine. We now have enough data that the Pharmacogenomic Implementation Consortium recommends avoiding oxcarbazepine in people with a positive HLA result. With lamotrigine it is not yet as useful.
TCPR: Do you have to use the commercial panels to test for these genes?
Dr. Nurnberger: No. You can order them directly through most clinical laboratories, either with a blood draw or cheek swab. I have a little more confidence in results from an academic laboratory than a commercial panel. In terms of cost, it's difficult to say, as that will depend on the patient's insurance, but it may be more cost effective to test for individual genes that are relevant.
TCPR: The CYP genes predict serum drug levels, so why not just test the drug level directly if you're concerned?
Dr. Nurnberger: Nothing wrong with that. The only disadvantage is that you can't test the drug level until the patient is on the drug. With genetic testing, you can avoid the problem altogether, which may be relevant for a drug like citalopram where slow metabolizers are at risk for QTc prolongation and torsades de pointes when the dose goes beyond 20 mg a day.
TCPR: One topic that patients often bring up is the MTHFR gene, which is supposed to predict response to l-methylfolate augmentation in depression.
Dr. Nurnberger: My reading is that the evidence is not that great for MTHFR. There may be unusual circumstances in which genetic information on MTHFR may be clinically useful (such as a patient with multiple mutations), but there's no evidence that it is generally relevant. These tests can steer clinicians in the wrong direction, causing them to avoid medications that could be useful.
TCPR: Are there risks of over-testing with genetic panels?
Dr. Nurnberger: I think the risk is blind adherence to recommendations. If a patient is doing well on a medication, they should not be taken off it just because the genetic panel recommends avoiding it. Clinicians should not limit themselves to the medications that are recommended by the panel. They have to look at the whole picture like the patient's age, comorbidities, and whether the patient's depression is bipolar or has atypical, melancholic, or mixed features. The evidence is just not strong enough to base everything on the genetic test.

Genes and diagnosis

TCPR: Which psychiatric disorders have the strongest genetic basis?
Dr. Nurnberger: Bipolar disorder, schizophrenia, and autism are the most heritable of the adult psychiatric disorders, with a heritability of 80% or greater. That means when it comes to the variance as to whether somebody is going to be affected or not, about 80% is determined by genetic factors. OCD is a little less—around 70%. The ones that are not as heritable are major depression, anxiety disorders, ADHD, and alcohol and substance use disorders; these have more like 40%–50% heritability.
TCPR: Can genetic testing inform diagnosis?
Dr. Nurnberger: Yes, but primarily for cases that result from copy number variants (small insertions or deletions) or rare sequence variants. This is relevant for intellectual disability and autism (and to a lesser extent for schizophrenia and bipolar disorder). However, in the future we may get more information from polygenic risk scores. To construct these, one looks at all the genetic markers in the genome that seem to differentiate cases from controls. Then you weigh each marker by the strength of its association (ie, effect size), and when you put all this together you have a score that tells you the genetic risk for a particular disorder. This could be very useful. Let's say you are treating a teenager with depression. If the polygenic risk score showed a high probability of bipolar disorder, you might avoid or be very careful with antidepressants.
TCPR: Are polygenic risk scores ready for practice?
Dr. Nurnberger: Close, but not yet. One problem is that the results do not apply equally across all ethnic groups. Although we have large samples—tens of thousands of patients and hundreds of thousands of controls—most of it is from people of European ancestry. But genetic testing is ready for clinical practice in autism and intellectual disability. This type of testing is recommended by all the major medical organizations that are involved in the care of persons with these disorders: psychiatry, neurology, and pediatrics (Fullerton JM and Nurnberger JI, *F1000Res* 2019;8(F1000 Faculty Rev):1293).
TCPR: Tell us about that.
Dr. Nurnberger: The specific test is "whole exome sequencing" (WES), which is a chromosomal microarray that looks at a panel of gene variants. The results do not tell you if a patient has autism. Instead, they test for specific chromosomal conditions that are associated with autism and intellectual disability. For example, there is the 22q deletion, which is associated with a particular syndrome that involves heart defects as well as autism and other physical stigmata.
TCPR: Do the results change practice?
Dr. Nurnberger: They can in several ways. First, they open the door to groups that offer support for families that have these syndromes, such as the Prader-Willi Association (Prader-Willi syndrome is associated with a deletion on the long arm of chromosome 15). The tests are also useful clinically because they tell us about other organ systems that may be affected, and in some cases lead to specific treatments. We test children primarily but also adults. The results are positive around 15% of the time in autism and 25% in intellectual disability *(Editor's note: The WES test is not recommended for mild autism spectrum disorders, such as high-functioning Asperger's disorder)*. We are also seeing more of these genetic abnormalities

Continued on page 9

Expert Interview – Genetic Testing: What You Need to Know in 2021

Continued from page 8

in schizophrenia, but here the rate is lower, around 5% (Nurnberger JI et al, *J Clin Psychiatry* 2018; 80(1):17nr12046).

TCPR: If the child is positive for one of these disorders, does that mean the parent is a carrier?

Dr. Nurnberger: Not necessarily. These genes can be inherited or can arise de novo. Mutations can occur from environmental factors or the aging process, which is why advanced paternal age is a risk factor for these disorders. It is also a risk factor for schizophrenia.

TCPR: How do you order WES testing?

Dr. Nurnberger: One way is through the department of medical genetics if you are near an academic medical center. Commercial labs also offer it, and it can be done through blood or saliva. The test is usually called "WES for autism spectrum disorders."

TCPR: Are there other promising genetic tests on the horizon?

Dr. Nurnberger: We are getting closer in some areas, like genes that predict agranulocytosis and clozapine or weight gain on antipsychotics. Lithium response is another area where there's been a lot of work, but this is more complex and will probably involve other markers besides genes. For example, we are developing ways to test for lithium response using cell lines that are grown in the laboratory. I think lithium is unfortunately underutilized in the US, and a test like that might be one way to enhance its use.

TCPR: Thank you for your time, Dr. Nurnberger.

To learn more, listen to our 7/5/21 podcast, "The Serotonin Transporter Gene: An Interview With Vladimir Maletic" and our 8/2/21 podcast, "Pharmacogenetic Testing: An Interview With John Nurnberger." Search for "Carlat" on your podcast store.

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Dosing Adjustments for CYP Genes

Result	What It Means	Dosing Adjustment
Poor (slow) metabolizer	Metabolic clearance is severely slowed, raising the levels of drugs that go through the pathway	Lower the dose by 30%–70%
Intermediate metabolizer	Metabolic clearance is moderately slowed, which may or may not raise the levels of drugs that go through the pathway	Watch carefully, as dose reductions may or may not be in order; the patient will be more prone to drug interactions if they take medications that further inhibit the enzyme
Extensive (normal) metabolizer	Metabolic clearance is unchanged	Nothing different
Ultrarapid metabolizer	Metabolic clearance is accelerated, lowering the levels of drugs that go through the pathway	Raise the dose by 135%–180%

Pharmacogenetic Recommendations From the FDA

	Medication	Gene	Risk	Action
Testing Required	Carbamazepine (and possibly oxcarbazepine)	HLA-B*1502	Stevens-Johnson syndrome (SJS)	In patients of Asian descent, test is required before starting carbamazepine and recommended (but not required) before oxcarbazepine; a positive result in this population means they are 80 times more likely to develop SJS on carbamazepine and 30 times more likely on oxcarbazepine
	Pimozide	2D6	Arrhythmias	Test is required before dosing pimozide above 4 mg/day (or 0.05 mg/kg/day in children) because of risk of arrhythmias; in poor metabolizers, wait 14 days between dose adjustments
Testing Recommended[1]	Thioridazine	2D6	Arrhythmias	Contraindicated in poor metabolizers
	Citalopram	2C19	Arrhythmias	Max dose of 20 mg/day in poor metabolizers
	Deutetrabenazine	2D6	Arrhythmias	Max dose 18 mg BID in poor metabolizers (must be divided BID)
	Valbenazine	2D6	Arrhythmias	Lower the dose by 50% and divide it twice a day in poor metabolizers
Adjust Dose if Testing Results Are Known	Atomoxetine, clozapine, perphenazine, venlafaxine, vortioxetine, and various tricyclics (amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2D6	Various	Lower the dose by 50% in poor metabolizers; for clozapine and tricyclics, adjust based on serum levels; for venlafaxine, keep in mind that the active metabolite (desvenlafaxine) will be low in poor metabolizers and high in rapid metabolizers
	Aripiprazole, brexpiprazole, iloperidone	2D6, 3A4	Various	Lower the dose by 50% in poor metabolizers at either enzyme, or by 75% if both enzymes are poor
	Flibanserin	3A4	Syncope	Lower the dose in poor metabolizers

[1]In these cases, the FDA does not require the test but does require dose adjustment if the test was done and an abnormality found (a slightly inconsistent recommendation). Sources: www.cpicpgx.org/genes-drugs; www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

Research Updates IN PSYCHIATRY

PTSD

Two Negative Studies of Mirtazapine and Riluzole for PTSD in Veterans

REVIEW OF: Davis LL et al, *J Clin Psychiatry* 2020;81(6):20m13267; Spangler PT et al, *J Clin Psychiatry* 2020;81(6):20m13233

TYPE OF STUDIES: Randomized, placebo-controlled trial; randomized controlled trial

Medications for posttraumatic stress disorder (PTSD) don't have a great track record, particularly in combat-related trauma. Prazosin, risperidone, psychotherapy, and the FDA-approved sertraline have all failed in this population (Raskind MA et al, *NEJM* 2018;378(6):507–517). These two trials shed light on the struggle to find more effective treatments.

Davis' team hypothesized that mirtazapine, which has both noradrenergic and serotoninergic effects, would improve PTSD by decreasing sleep problems and, maybe, fear and arousal. Mirtazapine has some evidence of efficacy in PTSD, with support from a few controlled but flawed trials (ie, they lacked randomization and placebo). Spangler's team looked at riluzole, a glutamatergic modulator, as an augmenter to an SSRI. Riluzole has open-label data in treatment-resistant depression and anxiety, and is related to glutamatergic agents we already use in psychiatry like lamotrigine, ketamine, and N-acetylcysteine.

Both studies were done with American veterans with combat-related PTSD, mostly men; only 3 subjects in the mirtazapine trial had PTSD from other trauma. Other psychiatric and substance diagnoses were excluded from the riluzole trial, but the mirtazapine study allowed comorbid depressive, anxiety, or substance use disorders.

In the riluzole study, 79 subjects already on SSRIs or SNRIs for 8 weeks were randomized to receive riluzole augmentation (mean dose 126 mg/day) or placebo. The mirtazapine study randomized 78 subjects to get the active drug (mean dose 39 mg/day) or placebo for 8 weeks as monotherapy. The primary outcome measure in both was change in PTSD symptoms as measured by the Clinician-Administered PTSD Scale (CAPS) (for riluzole) or the Structured Interview for PTSD (for mirtazapine). Both studies used standard rating scales to track secondary outcomes for depression, anxiety, sleep, disability, and global function.

Both drugs failed on the primary PTSD measures. Among secondary measures, riluzole was only positive on the hyperarousal subscale of the CAPS, and mirtazapine only made a significant difference on global functioning. Surprisingly, mirtazapine did not help sleep and appeared to increase nightmares in some subjects. Both medications were well tolerated. Riluzole's main side effects were impaired concentration and fatigue, while mirtazapine tended to cause sedation, nightmares, and irritability.

TCPR'S TAKE

We note no significant flaws with these studies, which found no significant benefits for riluzole or mirtazapine in PTSD. It's worth noting that riluzole was tested in a more treatment-resistant population, and both studies were conducted in combat-related PTSD, a group that tends to be less responsive to medication.

—Richard Moldawsky, MD. Dr. Moldawsky has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

To learn more, listen to our 7/19/21 podcast, "5 New Findings on Mirtazapine." Search for "Carlat" on your podcast store.

Shining a Light on PTSD

REVIEW OF: Youngstedt SD et al, *Mil Med* 2021 (Epub ahead of print)

STUDY TYPE: Randomized, sham-controlled trial

As stated in the previous brief, PTSD is difficult to treat, and numerous interventions for PTSD have failed with veterans. This study took a different approach; it is the first randomized controlled trial of light therapy for PTSD.

Conducted at the VA Medical Center in Columbia, South Carolina, this study randomized 69 veterans with combat-related PTSD (from Afghanistan and/or Iraq) to 4 weeks of morning bright light treatment or a placebo. Those with a history of winter depression were excluded.

Light therapy consisted of 30 minutes of 10,000 lux ultraviolet-filtered white light within one hour of arising. The placebo was an inactivated negative ion generator, which has been used to control for light therapy in other studies. Participants were blindly rated on the Clinician-Administered PTSD Scale (CAPS) and Clinical Global Impressions scale (CGI). Self-reported measures of depression, anxiety, side effects, and sleep were elicited at baseline and upon completion of the study. Sleep variables were indirectly measured via continuous wrist actigraphic recording. Approximately two-thirds of the participants in the study were simultaneously receiving other treatments for PTSD. The study was funded by the VA.

Bright light significantly improved CAPS and CGI scores, with a large effect size (1.1) compared to placebo. Additionally, significantly more subjects receiving bright light achieved a response (reduction > 33%) compared to placebo (44.1% vs 8.6%). However, no participant achieved remission from PTSD. Remarkably, scores for depression, anxiety, and sleep did not differ between treatment and control. There were no significant side effects with light therapy, though headache and eye strain can occur and it should be used with caution in ocular disease. Although the subjects were not blinded to their treatment, there was no significant difference in expectation of improvement between treatment and control.

Most mental illnesses, including PTSD, are associated with circadian rhythm abnormalities, which may explain some of these benefits. Light therapy also modulates serotonin. However, this doesn't explain why sleep and depression did not improve with light therapy.

We reached out to the lead author

Continued on page 11

CME Post-Test

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For those seeking ABPN Self-Assessment (MOC) credit, a pre- and post-test must be taken online at http://thecarlatcmeinstitute.com/self-assessment/
This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Learning Objectives (LO) are listed on page 1.

1. In a 2014 study of AUD, what was the effect size of supervised disulfiram, compared to a similarly supervised non-disulfiram group (LO #1)?
   [ ] a. 0.35 [ ] b. 1.21 [ ] c. 0.80 [ ] d. 0.52
2. According to the 21st Century Cures Act, psychotherapy notes pertaining to symptoms and diagnoses cannot be excluded from a patient's medical record (LO #2).
   [ ] a. True [ ] b. False
3. Which of the following best describes well-being therapy (LO #3)?
   [ ] a. A type of long-term psychoanalytic therapy that focuses on early childhood traumas
   [ ] b. A short-term psychotherapeutic strategy that emphasizes self-observation to build resistance to stress
   [ ] c. A form of CBT that addresses anxiety surrounding daily activities
   [ ] d. A long-term psychotherapy that focuses on reducing insomnia through meditation and mindfulness
4. In recent studies of combat-related PTSD, what was concluded about the efficacies of riluzole and mirtazapine on the primary outcome of change in PTSD symptoms (LO #4)?
   [ ] a. Mirtazapine improved PTSD symptoms but riluzole did not
   [ ] b. Both drugs significantly improved PTSD symptoms on the primary outcome
   [ ] c. Riluzole improved PTSD symptoms but mirtazapine did not
   [ ] d. Both drugs failed to improve PTSD symptoms on the primary outcome
5. Disulfiram is effective against AUD with which other co-occurring substance use disorder (LO #1)?
   [ ] a. Methamphetamine use disorder [ ] c. Cocaine use disorder
   [ ] b. Opioid use disorder [ ] d. Hallucinogen use disorder
6. In recent studies, what effect did open medical notes have on clinical care (LO #2)?
   [ ] a. It increased patients' demoralization [ ] c. It decreased patients' sense of control
   [ ] b. There was no effect on diagnostic accuracy [ ] d. It increased medication adherence
7. According to Dr. Nurnberger, genetic testing for the CYP2D6 or 2C19 genes can help you predict what about a certain medication for a patient (LO #3)?
   [ ] a. Likelihood of response
   [ ] b. Whether they are a poor or rapid metabolizer of a medication
   [ ] c. Likelihood of developing Stevens-Johnson syndrome
   [ ] d. Whether they will benefit from l-methylfolate supplementation
8. Which of the following is true about bright light treatment, compared to placebo, for combat-related PTSD (LO #4)?
   [ ] a. It significantly improved scores on the CAPS, with a small effect size
   [ ] b. It improved anxiety and sleep scores
   [ ] c. It significantly improved scores on the CGI with a medium effect size
   [ ] d. It significantly improved scores on the CGI and CAPS with a large effect size

Research Updates

Continued from page 10

(Youngstedt), who shared his impression that light therapy improved symptoms unique to PTSD.

TCPR'S TAKE

This well-designed study found bright light therapy made a meaningful difference in veterans with combat-related PTSD. Although it's only one study, we don't have many options for this population, and light therapy has a good safety record in depression. Consider it in patients who want a non-medication approach, and in those with seasonal depression (see *TCPR* Feb 2019 for directions on light therapy).

—Edmund Higgins, MD. Dr. Higgins has disclosed no relevant financial or other interests in any commercial companies pertaining to this educational activity.

To learn more, listen to our 7/26/21 podcast, "How to Use a Light Box." Search for "Carlat" on your podcast store.

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Depression
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Next Issue:
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Note From the Editor-in-Chief

Black-and-white ideas don't fit well in psychiatry, but they sometimes seep into my work nonetheless. There they nestle into some corner of uncertainty, making things a little more comfortable than they ought to be. In this issue, I expunge a few of them, with a little help from our friends.

Take genetic testing. People often ask the all-or-nothing question, "Is it useful or not?" That's a bit like asking, "Is laboratory testing useful?" As John Nurnberger shows us, the answer depends on the test and the patient.

Then there's long-term antidepressant therapy. Nassir Ghaemi has argued that a great fallacy of modern psychiatry is our belief that what is good for the short term must be good for the long term. With antidepressants in recurrent depression, this idea has become dogma, but Giovanni Fava describes an alternative view in this issue. He argues that antidepressants do their best work in the acute phase of the illness and ought to be followed by something with more lasting power, like psychotherapy, which may even replace them.

Next, Stephen Wyatt revives an old drug that some of us had put out to pasture—disulfiram. I had actually taken it off my electronic prescription list at one point, thinking it was too dangerous. But two things changed my mind. Alcohol-related problems rose to one of the top causes of death in the US, and disulfiram revealed itself to hold a larger effect size than other medications for alcohol use disorders in a few meta-analyses. Disulfiram isn't right for everyone, but it's not the deadly poison it's sometimes made out to be.

Finally, we learn that light therapy is not just for seasonal depression, and open medical notes may not be such a bad thing, and may even do some good. Or is that "finally"? Read on, and maybe you'll find a few sacred cows of your own to put out to pasture.

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