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**Chris Aiken, MD**  
**Editor-in-Chief**  
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#### Learning Objectives

After reading these articles, you should be able to:

1. Identify parenting strategies that parents with psychiatric disorders can use to protect the mental health of their children.
2. Evaluate the effectiveness of genetic testing in antidepressant selection.
3. Summarize some of the current research on psychiatric treatment.

## A Second Look at Genetic Testing

Chris Aiken, MD, Editor-in-Chief of The Carlat Psychiatry Report. *Practicing psychiatrist, Winston-Salem, NC.*

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

Genetic tests are marketed with a bold claim: that a handful of genes can predict medication response. AssureRx's GeneSight is the most popular of these tests, and in 2015 we reviewed the evidence behind its panel. In short, it was lacking, but the company has just released new data that may move it a little closer to the mainstream.

#### What's in the test

GeneSight looks at two areas where genetics can influence medication response:

#### In Summary

- The largest clinical trial of pharmacogenetic testing to date was recently published, and it failed to confirm the utility of the popular GeneSight test.
- Only 1 in 5 patients in the study had genetic variations that were relevant to their treatment.
- Some of the tests on genetic panels are valid, but the rarity of relevant drug-gene interactions makes it difficult to prove their validity, even in a treatment-resistant population.

1. **Pharmacokinetics.** Around 20%–30% of people have genetic variations in their metabolic enzymes that can lead

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## Parenting Strategies for Patients With Mental Illness

### Marie Yap, PhD

Associate Professor of Psychology at Monash University in Australia.

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

*"To love and work" was how Freud saw the goal of psychiatric treatment. Mental illness robs people of many meaningful roles, from work to parenting. We spoke with Marie Yap, director of the award-winning Parenting Strategies program, to learn how to help our patients function better as parents and prevent psychiatric disorders in their children.*



#### TCPR: When a parent has a psychiatric disorder, how do you recommend they talk about it with their children?

**Dr. Yap:** Children do better when parents talk openly about the reality of the illness and its impact on the family. Openness can also dispel the stigma around mental health. The talk needs to be age-appropriate. In younger children, I would use analogies with physical illness: "It's like if Dad had a really bad case of flu. It would sap his energy, and he would be in bed most of the day." As the child gets older, for example after puberty, you can speak more directly about the condition.

#### TCPR: Would you use the actual diagnostic terms?

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Expert Interview—Parenting Strategies for Patients With Mental Illness  
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**Dr. Yap:** If they want to know a name, I think it's good to tell them, "This is what the doctor calls it. When you talk to your friends, you can just tell them, 'My mom has an illness. She is unwell.'" But more important is to address how the condition is affecting the family and to let children know that it's safe to talk about it within the family and with trusted adults. It's an ongoing conversation, and it involves practical matters. You might say, "So, during this time Mom won't be able to cook dinner; we might get takeout, or Grandma will come in and help."

**TCPR: What else can parents do in the face of active mental illness?**

**Dr. Yap:** They can talk about specific strategies to manage the effects on the family, such as, "I'll let you know when I'm feeling unwell and need to be alone. Here are some things you can do if that happens." Find age-appropriate ways for the child to help out. Children need to have a role, but the burden of the illness should not be their responsibility. It may not be appropriate for a 7-year-old to cook dinner, but a teenager could take that on. Also, draw on support from friends, teachers, counselors, and extended family.

**TCPR: What about more damaging effects, like when a parent yells or breaks things during a manic episode? How should this be addressed with children?**

**Dr. Yap:** I do think parents should address the effects of their illness openly with children. That doesn't mean the illness is an excuse. They could say something like, "I'm sorry. You don't deserve to be treated that way, and that's not how I want to treat you." Clearly, when the interaction was traumatic, it's more complicated. I'd want to make sure the parent is stable enough to have that conversation without getting triggered. If the parent doesn't feel ready, there could be a family meeting with a mental health professional there to mediate. That could contain any further explosiveness.

**TCPR: Often these families are worried that their children will grow up to have the same problems. Are there parenting strategies that can prevent psychiatric disorders?**

**Dr. Yap:** A lot of research has gone into that question, and if I had to boil it all down, it would be these words: *acceptance, support, and autonomy*. Parents need to develop an accepting and warm relationship with their children, while encouraging them to step out more on their own as they grow. A big challenge is to adapt as they age; to know how much to let go and when. Can they trust their 7-year-old to cross the road at a traffic light?

**TCPR: Sounds like it takes a lot of flexibility—not an easy task for someone with anxiety or depression.**

**Dr. Yap:** They have to try and think, "What's the worst thing that could happen if I don't step in and it turns out wrong?" The process of the child's learning is as important as the child's success. Encourage children for trying! When they make mistakes, it's an opportunity to talk about what happened. What led them to the decision? What could they do differently in the future? When there's a foundation of support and acceptance, children will know that the parent is available if they need to reflect or bounce ideas off someone, or if they need a shoulder to cry on.

**TCPR: Are there any counterintuitive findings in the parenting research?**

**Dr. Yap:** Not exactly, but we have found that overinvolvement, or "helicopter parenting," increases the risk of mental health problems in a child. It's quite a robust finding in depression and anxiety (Yap MB & Jorm AF, *J Affect Disord* 2015;175:424–440). It gets back to autonomy: "Am I doing things for my children that they could reasonably do themselves?"

**TCPR: What are some examples of appropriate involvement?**

**Dr. Yap:** Knowing where your children are when they're not with you. What are they doing? Who are they with?

**TCPR: Technology has made that easier. We've got web cameras and GPS trackers.**

**Dr. Yap:** I'd suggest that developing a relationship where the child is comfortable disclosing that kind of information is more important than accurate surveillance, particularly with teens. It's not just about the knowing, but wanting to know because of parents' interest in their child's life.

**TCPR: What about poor boundaries and emotional overinvolvement?**

**Dr. Yap:** That takes overinvolvement to another level, and it's also a predictor of poor outcomes (Yap MB et al, *J Affect Disord* 2014;156:8–23). An example is withholding affection or giving the cold shoulder if a child is not doing what the

**"Children do better when parents talk openly about the reality of mental illness. If they want to know a name, I think it's good to tell them, 'This is what the doctor calls it.'"**

Marie Yap, PhD

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Q & A  
With  
the Expert

## What Can Our Pregnant Patients Do to Prevent Mental Illness in Their Children? Robert Freedman, MD

Professor and Former Chairman, Department of Psychiatry, University of Colorado-Denver. Editor Emeritus, American Journal of Psychiatry.

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

**TCPR:** Expectant mothers often want to come off psychiatric medications. From their perspective, mental illness takes place in the brain and won't affect the fetus, while psychiatric medications are quite dangerous. What can we tell them?

**Dr. Freedman:** There are risks with psychiatric medications, but the only one that is contraindicated in pregnancy is valproate (Depakote), which has been linked to neural tube deficits and lower IQ. On the other hand, untreated mental illness also affects the developing baby, and this risk isn't limited to postpartum disorders. During pregnancy, untreated depression significantly increases the risk that the infant will fail to develop adequate levels of cerebral inhibition. That's a measure of the infant's ability to filter out irrelevant stimuli, and it's the first sign that development is not on an optimal track (Hunter SK et al, *Schizophr Bull* 2011;37(6):1200-1208).

**TCPR:** How do we know that problem is caused by prenatal depression, rather than depressive symptoms that continue after childbirth?

**Dr. Freedman:** The reason we study cerebral inhibition is that it can be measured very early—1 month after birth—and that helps separate out the effects of depression during pregnancy from the psychosocial consequences of living with a depressed mother. When depression is treated during pregnancy, even with antidepressants, we don't see this problem in development. So as best we can tell, it's depression during pregnancy that's causing it.

**TCPR:** What else can expectant mothers do to prevent psychiatric problems in the developing baby?

**Dr. Freedman:** Avoid drugs, including nicotine and marijuana. Good nutrition. Also flu shots, because infections are one of the leading risk factors for schizophrenia (Brown AS et al, *Am J Psychiatry* 2010;167(3):261-280). The shot comes as an inactivated virus formulated for pregnancy. And, of course, prenatal vitamins. Most of these have folate and vitamins A and D, which are critical to brain development and help prevent schizophrenia, but one nutrient they often miss is choline. In 2017, the American Medical Association (AMA) recommended adding choline.

**TCPR:** How did the AMA come to that decision?

**Dr. Freedman:** Choline has been studied in pregnancy for over a decade. It improves the infant's cognitive ability and has no side effects at the doses studied. Choline is an agonist at the alpha-7 nicotinic receptors, which are implicated in the development of schizophrenia. Our group has found that choline supplementation during pregnancy prevents early signs of future schizophrenia and other disorders, such as social isolation and attention problems, at 3.5 years of age. Another group has now found that choline supplements prevent early cognitive deficits in children of mothers who drink alcohol in pregnancy.

**TCPR:** Tell us more about what you found.

**Dr. Freedman:** With the FDA's approval, we conducted a randomized clinical trial of choline supplementation in 100 pregnant women. So far we've followed the children up to age 4, and the choline group has less social isolation and better attention. Those two areas tend to be abnormal in people at that age who later develop schizophrenia, but we don't know what will happen in 20 years (Ross RG et al, *Am J Psychiatry* 2013;170(3):290-298).

**TCPR:** Are the data good enough to start using choline clinically?

**Dr. Freedman:** I can't say. On the one hand, a fetus has only one chance at brain development, and deficits occurring in fetal life are not reversed after birth. For example, folic acid before birth prevents spina bifida. After birth, folic acid will not close the spine that failed to close during fetal development. So it's very important for people to be aware of choline. On the other hand, the evidence is still coming in. Other groups have found similar results, with improvements in cognition and behavior at ages 1 to 4 years.

**TCPR:** Are prenatal vitamins starting to add choline?

**Dr. Freedman:** Most popular brands, like One-A-Day Prenatal, do not. A few vitamin brands have it, but in very small doses like 10-50 mg. The FDA's recommendation for dietary choline is 550 mg daily, but the average Western



**“There are risks with psychiatric medications, but untreated mental illness also affects the developing baby, and this risk isn't limited to postpartum disorders. During pregnancy, untreated depression significantly increases the risk that the infant will have trouble filtering out irrelevant stimuli, which is the first sign that development is not on an optimal track.”**

Robert Freedman, MD



## A Second Look at Genetic Testing

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to levels of many psychiatric medications that are abnormally high (ie, slow metabolizers) or abnormally low (ie, fast metabolizers).

2. **Pharmacodynamics.** While *pharmacokinetics* is about serum levels, *pharmacodynamics* is about the brain's response to medications, which may be shaped by genetics.

GeneSight uses this information to create a stoplight with three categories of recommendations: Green (no worries—go ahead and prescribe this medication), Yellow (proceed with caution), and Red (best to avoid). Other companies present their results in a similar style, but each company's results are driven by different, proprietary algorithms, which limits the ability of independent investigators to evaluate their validity. In other words, we're stuck with industry-supported trials, and so far GeneSight has the largest number of them.

### What we know so far

Before this new study was released, GeneSight's clinical data had run into a brick wall. The positive studies were poorly designed, while the well-designed studies were negative. Two open-label, non-randomized studies with a total of 209 subjects suggested that GeneSight improved outcomes in depression. However, a randomized, double-blind trial failed to replicate that benefit (Zeier Z et al, *Am J Psychiatry* 2018;175(9):873–886). That negative study was small, involving 49 subjects, so the company undertook a larger study to see if they could demonstrate the value of their test.

### A new study

GeneSight's latest study is the largest to date, involving 1,167 subjects with moderate to severe treatment-resistant depression. They were randomized to receive antidepressant therapy that was guided either by GeneSight or by the clinician's usual care. Most patients had failed at least 3 antidepressants, although only 1 failure was required for study inclusion. After 8 weeks, there were no significant differences between the two groups

on the primary outcome measure, which was improvement on the Hamilton Depression Rating Scale (HAM-D). Although the study failed on the primary measure, results were marginally positive on secondary outcomes of response ( $\geq 50\%$  improvement on the HAM-D, achieved by 26% in the GeneSight group vs 20% in the controls) and remission (final HAM-D  $\leq 7$ , achieved by 15% in the GeneSight group vs 10% in the controls) (Greden JF et al, *J Psychiatr Res* 2019;111:59–67).

### How impressive are these results?

A glance at GeneSight's new brochure would have you believe the results are quite impressive. The secondary outcomes are on the cover, magnified to accentuate a small difference. In reality, you'd need to test 20 patients with treatment-resistant depression to bring 1 patient to remission. The results look a little better when limited to those patients who were switched from medications that were poorly matched with their genes to those that, according to the test, were a better fit. In this group, you'd need to test 8 patients to bring 1 to remission. That's still fairly modest, and keep in mind that only 1 in 5 patients entered the study on medications that did not match their genes.

A bigger problem is that the primary measure was negative, and in a large study like this, such a failure is fairly definitive. Secondary measures are meant to explore possibilities, not confirm the truth, because every time one is added, it increases the chance of a false positive. No one should boast about secondary measures, and these aren't even much to boast about.

Also, the study was not truly double-blind, a flaw shared by all the controlled trials in this field. Patients and raters were blinded to the presence of genetic testing, but the doctors who chose the antidepressants were not. It's possible that these physicians conveyed a little more enthusiasm about their choices when they knew those choices were guided by a genetic test.

### Other contenders

GeneSight is one of over 40 commercially available tests. Three of their competitors have randomized controlled trials:

NeuroIDGenetix, Neuropharmagen, and GeneCept.

NeuroIDGenetix uses a genetic panel similar to GeneSight's and just released a 12-week double-blind randomized controlled trial in 685 patients with depression or anxiety. Their paper boasts positive results, but they selectively reported the data, including only half of the sample (those with moderate to severe depression) in their final results (Bradley P et al, *J Psychiatr Res* 2018;96:100–107).

Neuropharmagen employs a much broader array of genes in their algorithm and recently released two major studies. As with GeneSight, the more rigorous the study, the less impressive the results. Neuropharmagen has two randomized controlled trials in depression, one from Korea ( $n = 100$ ) and the other from Spain ( $n = 316$ ). The Korean study was positive across the board, but it was single-blind; raters were not blinded to the use of the test. The Spanish study was double-blind, but like the GeneSight trial, it was positive only on secondary measures (Pérez V et al, *BMC Psych* 2017;17:250; Han C et al, *Clin Psychopharmacol Neurosci* 2018;16:469–480).

GeneCept takes a different approach, focusing on genes that regulate the transport of medications across the blood-brain barrier. If that transport is slow, higher doses may be needed. GeneCept's panel only tells us about the dosing of medications, not their selection. However, it is the only test that has a positive, well-designed study without major flaws. In their 12-week randomized controlled trial of 148 patients with depression, the remission rate was 2.5 times greater in the gene-guided group: 28% vs 72% (Singh AB, *Clin Psychopharmacol Neurosci* 2015;13:150–156).

### A few good tests

These clinical trials test proprietary algorithms, with results that are promising but not yet definitive. There's another way to use genetic testing, though—you can skip the summary and look at the individual tests. Two groups, the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the FDA, keep a running

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## A Second Look at Genetic Testing

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tally of the drug-gene interactions that are valid and reliable. So far only a handful of pharmacokinetic genes have met their standards: CYP2C19, CYP2D6, and with flibanserin (Addyi), CYP2C9. The groups have also weighed in on which medications are reliably altered by those genes, and they're listed in the "Actionable

Drug-Gene Interactions" table below. These are the drug-gene interactions worth paying attention to in a genetic panel.

What about pharmacodynamic genes? The serotonin transporter gene is the most researched of these and is part of the GeneSight panel. Supposedly, the short version of this gene predicts lower response

and more side effects with SSRIs, but the actual evidence on those points is mixed. The data on side effects did not hold up in a meta-analysis (Crawford AA et al, *Eur Neuropsychopharmacol*, 2013;23:1143–1150). For response to SSRIs, one meta-analysis found no relationship, while another concluded that the association was weak and only held up in European patients (Porcelli S et al, *Eur Neuropsychopharmacol* 2012;22:239–258; Taylor MJ et al, *Biol Psychiatry* 2010;68:536–543).

**TCPR VERDICT:** Most genetic tests add a marginal benefit that is barely detectable in clinical trials. We don't recommend them for routine use, but they may have a role in patients with moderate to severe depression who have failed multiple antidepressants. GeneCept has promising data to guide antidepressant dosing, but not selection, and that study needs confirmation. When interpreting genetic tests, take heed of the drug-gene interactions supported by good evidence, mainly the CYP2D6 and CYP2C19 genes.

**Actionable Drug-Gene Interactions**

Gene	Newer Antidepressants	Tricyclics	Antipsychotics	Other
CYP2C19	citalopram escitalopram sertraline	amitriptyline clomipramine doxepin imipramine trimipramine		diazepam flibanserin
CYP2D6	<i>fluoxetine</i> <sup>1</sup> fluvoxamine <i>paroxetine</i> <sup>1</sup> sertraline duloxetine <i>venlafaxine</i> <sup>1</sup> mirtazapine vortioxetine	amitriptyline clomipramine desipramine doxepin imipramine nortriptyline protriptyline trimipramine	aripiprazole brexpiprazole iloperidone <i>risperidone</i> <sup>1</sup> perphenazine pimozide <sup>2</sup> thioridazine clozapine	atomoxetine methylphenidate modafinil donepezil <i>galantamine</i> <sup>1</sup> flibanserin <i>propranolol</i> <sup>1</sup>
CYP2C9				flibanserin

<sup>1</sup>According to the FDA, these drugs are informative but not actionable <sup>2</sup>The CYP2D6 test is required in the FDA labeling for pimozide  
Source: <https://cpicpgx.org/genes-drugs>

## Expert Interview—Parenting Strategies for Patients With Mental Illness

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parent wants. Saying things like, "If you love me, you would do this" or making the child feel guilty for having a different point of view is about psychological control. It's manipulative, but I don't think most parents do it intentionally.

**TCPR: Boundaries can break down when the parent has an active mental illness.**

**Dr. Yap:** Yes. That's an important factor when children feel responsible for taking care of their mentally unwell parent. That's hard to process, even when the parent is supportive, because a young child is going to feel responsible when the parent is depressed: "It's my fault that Mom's in bed all day because I disobeyed her and made her upset." Teens may react the other way and just blame the parent.

**TCPR: What else do we know about prevention?**

**Dr. Yap:** There's quite a lot of evidence that diet, physical activity, and sleep play an important role. Sleep is not as much of a challenge with younger kids, but when puberty hits, the circadian rhythm goes out of whack a bit (Dolsen MRJ et al, *J Physiol Paris* 2016;110(4 Pt B):467–479). Young people need to get enough sleep, but they also need consistency in their sleep and wake times, including weekends. Parents can set rules, like staying away from screens a half hour before bed.

**TCPR: What do we know about alcohol use in the home?**

**Dr. Yap:** To start with, providing the child or teen with alcohol is not a good idea. Nor is it helpful to model excessive drinking or to drink as a way to manage stress (Yap MBH et al, *Addiction* 2017;112(7):1142–1162). But should the parent abstain completely? The way I interpret the evidence is that it goes back to the child's autonomy. If you take the extreme view that alcohol is an absolute no, end of discussion, then the child has no opportunity to make an autonomous decision. That's what matters. Making it an open discussion allows children to learn to weigh the pros and cons on their own.

**TCPR: Final thoughts?**

**Dr. Yap:** There is no inoculation against mental illness, but there is reason to be hopeful. There are things that parents can do to reduce those risks in their children, and they don't need to be perfect parents to do it. Many parents, including parents with mental illness, have strengthened their parenting skills and benefitted their child's mental health by doing parenting programs (Yap MBH et al, *Clin Psychol Rev* 2016;50:138–158).

**TCPR: Thank you for your time, Dr. Yap.**

*Editor's note: Parents can find Dr. Yap's free guides at [www.parentingstrategies.net](http://www.parentingstrategies.net). Another useful resource is Triple-P Parenting ([www.triplep-parenting.com](http://www.triplep-parenting.com)), which offers free training in parenting strategies in many states.*

## Research Updates IN PSYCHIATRY

### ADHD

#### **Amphetamines Stand Out in ADHD**

**REVIEW OF:** Cortese S et al, *Lancet* 2018;5:727-738

**TYPE OF STUDY:** Meta-analysis

With so many medications available to treat ADHD, wouldn't it be nice to know if some are better than others? In this comprehensive meta-analysis, researchers sought to compare the relative efficacy and tolerability of both stimulant (methylphenidate and amphetamines) and non-stimulant (atomoxetine, bupropion, modafinil, clonidine, and guanfacine) medications for ADHD in children and adults.

The investigators combed through published and unpublished databases and

located 82 double-blind, randomized controlled trials in children and adolescents, and 52 such trials in adults. Together, they included over 10,000 children and adolescents, and over 8,000 adults. The primary outcome was change in clinician-rated ADHD symptoms, while teacher ratings were also evaluated for children. "Tolerability" was defined as the percentage who dropped out because of side effects, while the broader term "acceptability" referred to those who dropped out for any reason. Outcomes were evaluated through 12 weeks of treatment.

In children and adolescents, all medications were superior to placebo. Amphetamines emerged as the most effective ADHD medication, superior to modafinil, guanfacine, atomoxetine, and

methylphenidate. Methylphenidate was superior to atomoxetine. Based on teacher ratings, only methylphenidate and modafinil separated from placebo (none of the amphetamine trials included teacher ratings). With respect to tolerability, amphetamines and guanfacine both displayed significantly more adverse effects than placebo; amphetamines also significantly increased diastolic blood pressure. Methylphenidate was better-tolerated than the amphetamines, and it was the only medication with better acceptability than placebo.

In adults, amphetamines emerged not only as the most efficacious agents but also the only ones with better acceptability than placebo. Methylphenidate, atomoxetine, and bupropion all had similar effect

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### Ask the Editor

#### Should You Prescribe Lithium to Suicidal Patients?

**Dear Dr. Aiken:** You recommended lithium for suicidal patients in the TCPR 2018 summer issue, but isn't there a risk of overdose with this strategy?

**Dr. Aiken:** From firearms to bridges, the suicide rate goes down when we erect barriers to the means. Barriers work because suicidal impulses are brief, lasting only 1-2 hours on average. It would seem intuitive, then, that withholding lithium, which is toxic in overdose, from a suicidal patient is a safe move. However, intuition doesn't match up with the evidence here.

Lithium stands in stark contrast to most other psychiatric medications, which carry a widely debated black box warning about increased suicidality. There is no evidence that lithium raises the suicide risk, and there is strong evidence that it does the opposite. People with mood disorders carry a risk of suicide that's 10-20 times higher than the general population, but when they take lithium, that risk falls to a level that is indistinguishable from the norm. This is true for completed and attempted suicide, in both unipolar and bipolar disorders, and is based on data encompassing over 110,000 person years (Tondo L et al, *Curr Psychiatry Rep* 2016;18(9):88).

That's impressive, but it's just observational data, and it could hide a bias. Perhaps doctors steer away from lithium in suicidal patients, which would explain the low suicide rates in patients treated with lithium. Randomized controlled trials (RCTs) suggest otherwise. In a meta-analysis of RCTs involving 2,400 patients, lithium reduced the risk of completed suicide by 60% compared to placebo (Smith KA et al, *Bipolar Disord* 2017;19(7):575-586). Those results were quickly followed by a case-controlled study of 50,000 patients, which confirmed

that this protective effect was unique to lithium and not seen with other mood stabilizers (Song J et al, *Am J Psychiatry* 2017;174(8):795-802).

Though it's a counterintuitive leap to prescribe lithium to a patient with a history of overdose attempts, it may be the only medication that can prevent those attempts. Lithium doesn't seriously change access to suicidal means given that a lethal dose of Tylenol—about 50 pills—is available in most medicine cabinets. That's why I prescribe lithium to suicidal patients, even if they've overdosed in the past. As a precaution, I tell them that lithium is rarely fatal in overdose, although often disabling. If a patient's risk is acute, I engage the family to dispense the medicine one night at a time.

On the other hand, I've had a number of patients overdose on benzos, and in those cases I don't give a second chance. True, anxiety is a risk factor for suicide, so intuitively one would expect benzodiazepines to lower this risk. Suicide, however, is not rational, and once again the data fly in the face of intuition. Both controlled and naturalistic studies suggest that benzodiazepines don't lower the suicide risk and may actually raise it (Dodds TJ, *Prim Care Companion CNS Disord* 2017;19(2). doi:10.4088/PCC.16r02037).

Though they shake my intuition, these findings also remind me that the highest aim for psychotropics is to improve functioning, not feelings. Lithium, with its anti-impulsive effects, comes close to that goal. Patients may feel better with benzos, but their functioning rarely improves, and the disinhibition these agents cause can do the opposite, at least when it comes to suicide.





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*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](http://www.TheCarlatReport.com). Note: Learning Objectives (LO) are listed on page 1.*

- According to a recent study, what effect did choline supplementation during pregnancy have on children's attention through the age of 4 years? (LO #1)
  - a. Children had less social isolation but slightly more attention challenges
  - b. Children had more social isolation with no difference in attention challenges
  - c. Children had less social isolation and better attention
  - d. There was no change in children's social isolation or attention
- Which of these genetic tests is considered a valid predictor of drug-gene interactions by expert consensus groups? (LO #2)
  - a. COMT
  - b. CYP3A4
  - c. Serotonin transporter gene
  - d. CYP2D6
- Emotional overinvolvement and poor boundary-setting by parents can increase the risk of mental health problems in a child. (LO #1)
  - a. True
  - b. False
- In a 2019 study, patients with moderate to severe treatment-resistant depression randomized to receive antidepressant therapy guided either by GeneSight or by the clinician's usual care showed which of the following results? (LO #2)
  - a. No significant differences between the two groups in improvement on the Hamilton Depression Rating Scale (HAM-D) (the primary outcome measure)
  - b. A non-significant trend toward improvement in the GeneSight-guided group on the HAM-D and on secondary outcome measures
  - c. No significant differences between the groups on any outcome measures
  - d. Significant improvement in the GeneSight-guided group in improvement on the HAM-D
- According to a 2018 study, ADHD medications are more efficacious and better-tolerated in adults than in children and adolescents. (LO #3)
  - a. True
  - b. False

## Research Update

Continued from page 6

sizes. Clonidine and guanfacine did not have data in adults, and modafinil was ineffective in this population, despite having positive results in children. Tolerability was similar among the agents. In contrast to their effects on children, amphetamines did not increase diastolic blood pressure in adults. Overall, ADHD medications were less efficacious and less well-tolerated in adults than in children and adolescents.

What are the weaknesses? There was a dearth of head-to-head trials, so these comparisons could only be made indirectly.

The dropout rate was used as a proxy for acceptability, and this is a rough estimate. Finally, while the large sample sizes instill greater confidence in the results, they also risk finding significant differences that may not necessarily be clinically meaningful.

### TCPR'S TAKE

It's rare for one medication to stand out in its class, but the amphetamines clearly emerged as the most effective option in both children and adults. That does not mean they should always be first choice,

though. Methylphenidate was a more tolerable option in children, and there will always be patients who respond better to the methylphenidate varieties. Non-stimulant options take longer to work, but they performed fairly well in this meta-analysis, sometimes rivaling methylphenidate's benefits. The only failure was modafinil, which worked in children but not adults.

—*Michael Posternak, MD.* Dr. Posternak has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

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Expert Interview—What Can Our Pregnant Patients Do ...  
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diet only yields about 300 mg of choline. So most women—about two-thirds—are choline-deficient. (*Editor's note:* Dr. Freedman has no financial or other interest in choline products.)

**TCPR: How would you supplement choline in pregnancy?**

**Dr. Freedman:** We actually use a precursor, phosphatidylcholine (PIP), and the dose we use in pregnancy is 6,300 mg daily. That converts to 900 mg of choline. PIP is the main dietary source of choline, and there are no known risks with PIP (eg, Country Life Phosphatidylcholine, 600 mg capsules, dose = 10 capsules/day, \$375/pregnancy). The pure form, choline bitartrate, is cheaper, but it can sometimes form a bolus in the large intestine, where bacteria metabolize it into a foul-smelling and sometimes toxic product (eg, Nature's Way Choline Bitartrate, 500 mg capsules = 204 mg choline, dose = 5 capsules/day, \$98/pregnancy).

**TCPR: When is the optimal time to supplement?**

**Dr. Freedman:** Earlier is better. A woman could start while trying to become pregnant. If she does start early, she should understand that spontaneous abortions are common and not something that's caused by supplementation.

**TCPR: Can a woman get choline from diet alone?**

**Dr. Freedman:** Yes, but it's not easy. It would take a serving of calf's liver every day, or 6 hard-boiled eggs a day, or 1–2 servings of steak a day.

**TCPR: Thank you for your time, Dr. Freedman.**

*Editor's note: Dr. Freedman maintains an educational site for patients at [www.prenataldoctoradvice.com](http://www.prenataldoctoradvice.com).*

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