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IN THIS ISSUE

Focus of the Month: **Issues in Psychopharmacology**

Learning objectives for this issue:
1. Detail the causes and disease course of tardive dyskinesia. **2.** Describe management and treatment options for tardive dyskinesia. **3.** Explain psychodynamic psychopharmacology and how to use it in your practice. **4.** Summarize some of the current findings in the literature regarding psychiatric treatment.

The Facts on Tardive Dyskinesia

Olga Waln, MD
Neurologist
Houston Methodist Neurological Institute, Department of Neurology

Dr. Waln has disclosed that she has no relevant relationships or financial interests in any commercial company pertaining to this educational activity.

We're all aware that neuroleptics and other dopamine-receptor blocking agents (DRBAs) can cause a variety of movement disorders, often referred to as extrapyramidal syndromes (EPS).

Many EPS, such as acute dystonia, akathisia, or drug-induced parkinsonism, typically manifest within hours or days (sometimes a few weeks) after patients start neuroleptics, or after the dose is increased. Fortunately, these neuroleptic-induced movement disorders are reversible, and the symptoms resolve soon after the causative medication is discontinued.

This is not the case with tardive

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In Summary

- Tardive dyskinesia is characterized by delayed-onset, drug-induced movement disorders that persist for months or even years after the drug is discontinued.
- Prevention of TD is paramount. If you must use a neuroleptic, choose atypicals if possible and take action as soon as you notice any sign of TD.
- Dopamine-depleting drugs such as tetrabenazine are the most effective medications for TD.

Q&A With the Expert

Psychodynamic Psychopharmacology
David Mintz, MD

Fellow, American Academy of Psychoanalysis and Dynamic Psychiatry
Staff psychiatrist, Austen Riggs Center, Stockbridge, MA

Dr. Mintz has disclosed that he has no relevant relationships or financial interests in any commercial company pertaining to this educational activity.

TCPR: Dr. Mintz, what is psychodynamic psychopharmacology?

Dr. Mintz: Psychodynamic psychopharmacology is a way of thinking about treatment—treatment resistance in particular. When patients don't respond to medications, it asks what else might be the problem besides just the wrong diagnosis or the wrong medications. It addresses the central role of meaning and interpersonal factors in psychopharmacologic outcomes. It doesn't tell you *what* to prescribe, but it gives guidance about *how* to prescribe to get the best results. Whereas evidence-based practice looks at how the patient is like other patients, psychodynamic psychopharmacology encourages consideration of what is unique about the patient (Mintz D & Belnap BA, *J Amer Acad Psychoanalysis Dynamic Psychiatry* 2006;34(4):581–601; Mintz D & Flynn D, *Psychiatr Clin North Am* 2012;35(1):143–163).

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The Facts on Tardive Dyskinesia

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dyskinesia (TD), a fascinating disorder, or rather a group of drug-induced movement disorders with distinct clinical presentations. The main differences between TD and other drug-induced movement disorders are:

- the delayed onset of the symptoms, hence the name "tardive," and
- persistence of the symptoms for months or years after a causative drug was discontinued.

According to *DSM-5*, TD can develop after neuroleptics are used for at least a few months, or an even shorter period in older patients, and lasts "at least a few weeks." TD can also result from sudden discontinuation or dose reduction of a neuroleptic, emerging within four to eight weeks of withdrawal and persisting for longer. When the symptoms last fewer than four to eight weeks after discontinuation of the offending drug, it's called withdrawal-emergent dyskinesia (American Psychiatric Association. *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing;2013).

Epidemiology

Up to 20% to 50% of patients treated with neuroleptics might develop TD, especially if they are treated with first generation, or "typical" antipsychotics. Second generation neuroleptics are associated with lower risk of TD (Correll CU et al, *Am J Psychiatry* 2004;161:414–425), although this has been contested (see *TCPR*, January 2013).

Middle-age and elderly patients have about a 10-fold higher risk of developing TD after one year of treatment compared to younger patients. Although both genders can develop TD, postmenopausal women might be at higher risk. Tardive dystonia is the only exception as it occurs more often in younger males.

Clinical Course and Types of TD

Tardive dyskinesia has an insidious onset with evolution into a full syndrome over days and weeks, and a waxing and waning course. The symptoms persist for years or decades in most patients, even after discontinuation of an offending drug. The severity of TD can range from mild movements that the patient might not be aware of, to a very severe, disabling disease.

Tardive dyskinesia can manifest as a variety of abnormal movements including stereotypy, dystonia, akathisia, tics, myoclonus, tremor, parkinsonism, or chorea (see box on this page) (Waln O & Jankovic J, *Tremor Other Hyperkinet Mov* 2013;3:1–11). Videos of these conditions can be found at http://1.usa.gov/1iWToMC.

Classic TD is the most common type of the disorder that manifests as repetitive oro-facial movements, or stereotypies, such as lip smacking, chewing, facial grimacing, tongue movements inside the mouth, and tongue popping out. Some patients with classic TD may also have stereotypic movements of the limbs or trunk such as foot tapping, piano-playing movements of fingers and toes, hands rubbing, trunk rocking, and swaying.

Tardive akathisia is a feeling of internal restlessness that is usually uncomfortable and can be disabling. These patients appear restless and fidgety. They often rock in a chair, cross-uncross legs when sitting, get up and pace on a spot, touch their face or scalp, or scratch themselves. Some can have repetitive moaning and grunting.

Tardive dystonia can be generalized or focal, usually affecting tongue and facial muscles, and it has very characteristic features. Patients with tardive dystonia typically have opisthotonic trunk arching, neck retrocollis, adduction and pronation of arms with extension of the elbows, and flexion of the wrists.

Tardive chorea in adult TD patients usually accompanies classic oro-facial dyskinesia. But in children, generalized chorea affecting mainly the trunk and limbs with no or minimal involvement of the oro-facial region, is a characteristic feature of ***withdrawal-emergent dyskinesia***, a self-limiting condition typically resolving over several weeks.

Tardive tics are clinically indistinguishable from motor and phonic tics of Tourette syndrome, but much older age at onset in conjunction with the history of chronic exposure to a DRBA would point towards tardive tics.

Tardive tremor manifests as a high amplitude and low frequency postural, kinetic, and resting tremor with no other parkinsonian features such as bradykinesia, rigidity, or gait changes.

Tardive myoclonus presents as postural jerk-like movements usually affecting upper extremities.

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Neuroleptic-Induced Movement Disorders

Acute/Subacute (hours–weeks)
- Acute dystonic reaction
- Acute akathisia
- Drug-induced parkinsonism
- Neuroleptic malignant syndrome (can also manifest after chronic exposure to neuroleptics)

Tardive (months–years)
- Classic tardive dyskinesia
- Tardive stereotypy
- Tardive dystonia
- Tardive akathisia
- Tardive tics (tardive tourettism)
- Tardive tremor
- Tardive myoclonus
- Tardive chorea
- Tardive parkinsonism
- Withdrawal emergent syndrome

The Facts on Tardive Dyskinesia
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Tardive parkinsonism can be diagnosed if parkinsonian features (ie, rest tremor, bradykinesia, rigidity, gait changes) persist for several months or years after discontinuation of a DRBA. Note that drug-induced parkinsonism typically resolves within a few weeks after stopping an offending drug. Both conditions should have normal dopamine transporter SPECT imaging (DaTscan), as opposed to Parkinson's disease.

About one third of TD patients might have a combination of two or more tardive syndromes.

Etiology/Pathophysiology

Although neuroleptics are the most common cause of TD, antiemetics, vasoactive medications, and other psychotropic drugs, such as antidepressants, can also cause TD (see box on this page).

The pathophysiology of TD is still poorly understood (Waln O & Jankovic J, *op.cit*). One of the most popular theories about pathogenesis of TD is that chronic blockade of dopamine receptors in basal ganglia, particularly D2 and possibly D3, leads to the receptors' upregulation (increasing in number) and supersensitivity to dopamine, producing a hyperkinetic movement disorder.

"Typical" antipsychotics bind to D2 receptors stronger and for a longer time than newer generation neuroleptics, and therefore they carry a higher risk of causing TD. "Atypical" neuroleptics, particularly clozapine (Clozaril) and quetiapine (Seroquel), have the lowest D2 receptor occupancy and therefore a lower risk of TD.

This receptor-supersensitivity theory makes sense if you recall that TD can manifest after sudden discontinuation of a neuroleptic, in which supersensitive dopamine receptors "crave the drug." We also know that *increasing* the dose of a neuroleptic in patients who develop TD can temporarily improve the symptoms, possibly because the higher dose saturates the increased number of the receptors.

But wouldn't you expect the receptors eventually to undergo downregulation, or decrease in number, after not being exposed to a DRBA for months? If so, TD symptoms should resolve, but this doesn't happen in many cases. The neurodegenerative hypothesis and oxidative stress hypothesis of TD may explain why. According to these theories, neurons may be irreversibly damaged by neuroleptic-induced lipid peroxidation and free-radical formation, which causes persistent TD long after the discontinuation of the offending drug.

The most recent "maladaptive synaptic plasticity" hypothesis attempts to connect all previous theories and fill the gaps between them (Teo JT et al, *Mov Disord* 2012;27:1205–1215). According to this hypothesis, D2-receptor hypersensitivity and neuronal damage caused by increased oxidative stress can result in the formation of abnormal new connections between basal ganglia and brain cortex, leading to abnormal movements that persist even after the offending drug is removed.

The mechanism of TD caused by other, non-neuroleptic, medications is unclear. It is possible that increased levels of serotonin caused by SSRI and SNRI antidepressants can imitate an antidopaminergic effect on basal ganglia neurons similar to DRBAs, but this is not proven.

You've probably noticed from your own clinical experience that most patients taking antipsychotic medications for years do *not* develop TD, and the same medication regimen can cause different types and severity of TD. Does it mean there is genetic susceptibility for TD? Multiple gene candidates were recently found in association with TD, including genes coding for dopamine and serotonin receptors, antioxidative enzymes, and drug metabolism enzymes (Teo JT et al, *op.cit*). Therefore, although not a genetic disorder, TD might have a genetic predisposition.

Management of TD

Prevention of TD is paramount. Whenever you can, avoid DRBAs and choose alternative medications or "atypical" neuroleptics with lower potential to cause TD. If you decide to use DRBAs in your patient, frequently re-assess the need to continue treatment and watch for symptoms of TD at every visit.

Take action as soon as you notice signs of TD in your patient. The most important approach in treatment of TD is the removal of an offending drug as soon as possible. Remember, the longer patients with the symptoms of TD continue taking DRBAs, the lower their chances of recovery. But do not stop a DRBA abruptly; instead, taper it off slowly to avoid worsening of TD.

Although we know that increasing the dose of a DRBA can temporarily improve the symptoms of TD, this strategy should be avoided and used only in the most severe cases when immediate control of the disabling TD symptoms is required.

The dopamine-depleting drugs, reserpine (Serpalan) and tetrabenazine (Xenazine), are the most effective medications in any TD syndromes (see the table on page 5). Both medications prevent reuptake and recycling of the monoamines (including dopamine), thereby promoting their breakdown within the synaptic cleft. As a result, hypersensitive dopamine receptors receive reduced dopaminergic stimulation, thus improving hyperkinetic movements in the absence of dopamine-receptor blockade.

Tetrabenazine is currently considered a first-line treatment option in TD if the symptoms persist after discontinuation of a DRBA. Despite this, the use of tetrabenazine remains off label. So far, it is FDA-approved only for Huntington's chorea, and is only available in the USA from a specialty pharmacy (see the manufacturer's website, www.xenazineusa.com/HCP).

This medication is usually well toler-

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Medications Associated with Tardive Dyskinesia

Antipsychotics
- ***1st generation:*** haloperidol, loxapine, pimozide, chlorpromazine, thioridazine, trifluoperazine, prochlorperazine, perphenazine, fluphenazine, thiothixene
- ***2nd generation:*** ziprasidone, iloperidone, asenapine, clozapine, quetiapine, risperidone, paliperidone, olanzapine, amisulpride, aripiprazole

Antiemetics
- droperidol, metoclopramide, chlorpromazine, prochlorperazine

Antidepressants
- ***SSRI/SNRI:*** duloxetine, citalopram
- ***Tricyclic:*** amoxapine

Lithium

Calcium channel blockers
- flunarizine, cinnarizine

Expert Interview
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TCPR: What are some examples of those unique aspects of patients that influence outcomes?

Dr. Mintz: There are dozens of psychosocial factors that affect medication outcomes. Patient preference is a potent one. It makes a huge difference if patients get the treatment that they want. For example, in one study, when patients with depression were randomized to a treatment they wanted—either psychotherapy or psychopharmacology, about 50 percent got better. However, when people who wanted medication were randomized to the psychotherapy group, only a quarter of them got better. And when people who wanted psychotherapy were randomized to the psychopharmacology group, only about seven percent of them responded (Kocsis JH et al, *J Clin Psychiatry* 2009;70(3):354–361). Another important factor is whether the patient is ready to get better. We know, for example that when patients who are not ready to change (based on a "readiness to change" battery) are given a medication, they do worse than patients who are ready to change, *even when these patients receive a placebo* (Beitman BD et al, *Anxiety* 1994;1(2):64–69).

Health isn't just about an absence of symptoms; health is about resilience and being in charge of yourself.

David Mintz, MD

TCPR: So we should be paying more attention to what our patients prefer.

Dr. Mintz: Absolutely. Sometimes, when people come to a psychiatrist, we have already made up their minds for them in a way. This can stand in the way of our patients getting better.

TCPR: What can you tell us about the doctor-patient alliance and its role in treatment?

Dr. Mintz: It is really about giving the patient greater authority, bringing them in as a partner rather than establishing yourself as the one who knows best, even before you know what the patient wants. We psychiatrists have to pay attention to the fact that our environment applies considerable pressures upon us to objectify patients or to think about them in a biomedically reductionistic way.

TCPR: Is there evidence that a good doctor-patient alliance improves outcomes?

Dr. Mintz: Studies have found that patients with a good alliance receiving placebo had greater reductions in depression than patients in a poor alliance receiving an active drug (Krupnick JL et al, *J Consult Clin Psychol* 1996;64(3):532–539). Psychiatrists are sometimes not familiar with the evidence for the profound effect of psychosocial factors on outcomes, so familiarizing oneself with that evidence base goes a long way toward helping resist pressures to treat patients as if they are neurotransmitter soup. Furthermore, I think we need to know the patient; what he or she really wants. This is where the psychodynamic aspect comes in. A person may want to be rid of their depression on the surface, but beneath that there are likely to be more potent motivations, like the desire to be loved, or to escape some crushing burdens. And you, the psychiatrist, need to try to understand what your patient is most trying to get, and not make the assumption that the important thing is to stop this or that symptom.

TCPR: But if we don't address symptoms and the underlying illness, but instead just give the patient what they want, then are we doing ultimately a disservice to the patient?

Dr. Mintz: That is an interesting question. There is no alliance if either participant is simply submitting to the will of the other. Rather than reflexively giving them what they want, I would say that we should support them in getting what they want. We have to be guided by therapeutic principles. I'm concerned, however, that we are not mental health professionals anymore; we have become mental *illness* professionals. Health isn't just about an absence of symptoms; health is about resilience and being in charge of yourself. It is useful to hold a developmental perspective, always asking what is it that will help the patient get where they want to go. And that may mean *not* treating symptoms at times because treatments can also get in the patient's way. For example, a patient who requires four milligrams of Klonopin a day to eliminate anxiety might be just too compromised to achieve their goals. To what extent do you want to really participate in that? We are not simply trying to get rid of symptoms; we are trying to help people get back into life.

TCPR: Can you tell us about the role of the placebo effect in psychopharmacology?

Dr. Mintz: Studies suggest that placebo effects may account for more than three quarters of the effects of medications, or at least antidepressants. The thing is, placebo effects are real. You can lower blood pressure, you can cure ulcers. Depression is often so difficult to treat that we should be using every tool in our armamentarium, including optimizing the relationship and mobilizing the placebo effect.

TCPR: You have written about patients being ambivalent about symptoms. Can you describe what that means, how to identify it, and then how to use that in our treatment?

Dr. Mintz: Patients are in conflict; they want many things at different levels. Patients are often ambivalent about taking their pills because they expect to be harmed, more even than they think they will be helped. Similarly, the most ill patients often have experienced profound powerlessness in their lives, and find that they can be more powerful in their illness than they ever were in health. So I always keep in mind that patients may become attached, consciously or unconsciously, to covert benefits of their illnesses.

TCPR: What are "counter-therapeutic" uses of medications, which you have also spoken about?

Dr. Mintz: One example is when the patient learns to rely on medication instead of relying on people. They have come to the

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The Facts on Tardive Dyskinesia

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ated; however it can cause or exacerbate depression, produce daytime somnolence, akathisia, and parkinsonism, especially in higher doses. Reserpine can cause the same side effects but also orthostatic hypotension and diarrhea; therefore it is used less often.

Other, less studied medications showed some symptomatic improvement in TD according to small studies and case reports. Among those medications are amantadine (Symmetrel), clonazepam (Klonopin) and other benzodiazepines, baclofen (Lioresal), valproic acid (Depakene), zolpidem (Ambien), donepezil (Aricept), lithium, antioxidants, zonisamide (Zonegran), vitamin B6, and melatonin. Anticholinergic medication like trihexyphenidyl (Artane) and benztropine can be effective in tardive dystonia but can exacerbate other types of TD.

Botulinum toxin injections are often used for treatment of focal dyskinesia and tardive dystonia. In the most severe and refractory cases of TD, surgical treatment such as pallidotomy or deep brain stimulation can be considered.

TCPR'S VERDICT: TD can manifest as a variety of movement disorders and can be caused by medications other than first-generation antipsychotics. Early recognition of TD symptoms and discontinuation of the offending drug can improve prognosis in TD patients. Tetrabanazine is the first-line in treatment of any type of TD.

Treatment of Tardive Dyskinesia

Medication	Dose (starting / maintenance)	Comments
Slowly taper off an offending drug		Depending on the dose, taper off over a few weeks.
Dopamine-depleting drugs:		
Tetrabenazine	12.5–25 mg / 50–75 mg (sometimes up to 200 mg daily)	First line drug in TD but monitor for worsening of depression, drug-induced parkinsonism (dose-dependent).
Reserpine	0.25 mg / 0.75–8 mg	Rarely used now due to peripheral side effects.
Amantadine	100 mg / 100–300 mg	Mild effect if any. Possibly works by blocking glutamate receptors (Angus S et al, *J Clin Psychopharmacol* 1997;17(2):88–91).
GABA-ergic drugs:		Mild effect if any, side effects might outweigh benefits (Alabed S et al, *Cochrane Database Syst Rev* 2011;Apr 13(4):CD000203). Of benzodiazepines, clonazepam is most commonly used (Thaker GK et al, *Arch Gen Psychiatry* 1990;47(10):980).
Baclofen	5–10 mg / 20–120 mg	
Benzodiazepines	0.5 mg / 1–4 mg for clonazepam	
Valproic acid	500 mg / 900–1500 mg	
Anticholinergic drugs:		Use only in tardive dystonia. Can worsen other types of TD.
Trihexyphenidyl	1 mg / 4–32 mg	
Benztropine	0.5 mg / 1–2 mg	
Botulinum toxin	Variable doses	Use especially in focal dyskinesia/dystonia. Can be combined with oral drugs.
Zolpidem	5 mg / 10–40 mg	Does not cause drowsiness in some patients with TD (Waln O & Jankovic J, *Mov Disord* 2013;28(12):1748–1749).
Other medications: (donepezil, vitamin E, vitamin B6, lithium, melatonin)	Variable doses	Very questionable effectiveness, rarely used in clinical practice.

Expert Interview

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conclusion that you can't count on people, but your pills will be there for you. And so they get upset and they turn to their medications; their world becomes increasingly depopulated because they turn less and less to people, and they are caught in a depressing vicious circle. This person is never going to stop being depressed because of the way he uses medications to avoid healthy developmental steps.

TCPR: Many outside influences keep us from approaching our patients in the ways you're talking about. Can you talk about some of these factors?

Dr. Mintz: The concept of the 15-minute med check is probably the most destructive thing in psychiatry, because it already presupposes that all you are there to do is check the meds, and the person is left out of it. Our whole idea of the 15-minute med check is a massive experiment. There is no evidence base whatsoever for working this way. Most drug trials are done in environments where there is a tremendous amount of human contact. Patients are seen weekly, often with additional supports like nurses. To the extent that psychosocial factors matter, it is totally unfounded for us to be generalizing from that environment to the environment of the 15-minute med check.

TCPR: How, then, can we build this alliance?

Dr. Mintz: I don't think it is so much about the time, but about the stance you take: that you and your patient are partners.

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Research Updates IN PSYCHIATRY

Section Editor, Glen Spielmans, PhD

Glen Spielmans, PhD, has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

DEPRESSION

Has Research Found a Reliable Depression Biomarker in Boys?

A major obstacle in the prevention of depression is the lack of a predictive biomarker in individuals who later develop the disorder. British researchers have shown that the combination of a physiological biomarker—salivary cortisol—and the presence of depressive symptoms might be used to predict the development of major depression in adolescents.

Two cohorts (n=660 and 1,198) of British students (mean ages 13.7 and 14.5 years, respectively) participated in this longitudinal study. At baseline, early-morning salivary cortisol was measured daily over a four-day period; subjects also completed the Moods and Feelings Questionnaire (MFQ) and a battery of other neuropsychological tests. Follow-up interviews were conducted one to three years later.

Subjects were fairly evenly distributed among four classes, representing "high cortisol" (mean approximately 4–6 ng/ml) or "low cortisol" (2–3 ng/ml), as well as high or low depressive symptoms. The odds of developing major depression increased across the four classes, with the lowest risk in class 1 (low cortisol and low depressive symptoms, 31% of the sample) and the highest in class 4 (high cortisol and high depressive symptoms, 17%).

Sex differences were also apparent. Male students who had both elevated depressive symptoms and elevated cortisol levels had significantly greater odds of developing a diagnosis of MDD compared to boys with low symptoms and low cortisol (OR=14.7, 95% CI: 6.1–35.0). In girls, only depressive symptoms were significantly correlated with the onset of depression (OR=3.5 or 3.9 for high or low cortisol, respectively).

The researchers also found that the students (both male and female) with elevated depressive symptoms and high cortisol demonstrated more "overgeneral memory," a tendency to recall general features of autobiographical events rather than specific details, and suggest that efforts to enhance the specificity of memories in such individuals may be one way to intervene and, perhaps, prevent the onset of depression (Owens M et al, *Proc Natl Acad Sci US* 2014;111(9):3638–3643).

TCPR's Take: This study is another in a recent wave of research to identify biomarkers of mental illness. Notably, this study takes into account multiple features (cognitive, emotional, endocrine) to define a specific depressive phenotype, something lacking in the present *DSM*, and develops testable hypotheses for the prediction and possible prevention of major depression, even though it remains unclear why this particular combination increases the odds of depression in boys only. This research also identifies a possible nonpharmacological approach—namely, cognitive training to target overgeneral memory—to prevent later onset of depression.

Expert Interview

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Research in primary care settings has found that eliciting patient preferences takes no extra time. So a lot of this is a false assumption that you need hours and hours to build this kind of alliance.

TCPR: Many of us are being asked to perform measurement-based care, where we might be measuring outcomes that are just not relevant to the patient. Is this reality of practice still compatible with establishing a decent alliance with the patient?

Dr. Mintz: That is definitely a problem. Psychopharmacologic treatment resistance has doubled every five years since the early '80s. There has been a 3,200 percent increase in references to treatment-resistant psychiatric conditions during that time period. And I think it is in part due to a shift in the delivery of care, which promotes an objectifying approach to the patient. Now this includes things like engaging with a computer screen instead of a patient. However, since about 2009 there has been an increasing amount of attention to psychosocial factors in the prescribing process.

TCPR: What was special about 2009?

Dr. Mintz: The philosopher of science Thomas Kuhn said that scientific revolutions occur because the science gets better and better until it starts encountering its limits. The paradox of our focus on evidence-based practice is that it became clear that far too few of our patients are recovering on medications. So, in 2009 and the beginning of 2010 you started to see a slew of articles coming out into popular media—*Time, Newsweek, The Wall Street Journal,* and *The New York Times*—about the limitations of antidepressants and stating that there is a lot more for us to do to address the problems that our patients have.

TCPR: You are proposing that there is a lot of treatment resistance and it might be due to the failed alliance between the prescriber and patient, and that when done properly, the medications plus the alliance together will be successful.

Dr. Mintz: At least *more* successful. Obviously, I am not claiming it is a panacea. Our medications remain limited in terms of their biological effectiveness and our psychosocial approach may support effectiveness or detract from it. Treatment resistance is a real problem, and so we should be using every evidence-based tool we have to help our patients get better.

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CME Post-Test

This CME post-test is intended for participants only seeking AMA PRA Category 1 Credit™. For those seeking ABPN self-assessment (MOC) credit, a 13 question pre- and post-test must be taken online. For all others, to earn CME or CE credit, you must read the articles and log on to www.TheCarlatReport.com to take the post-test. You must answer at least four questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be taken by April 30, 2015. As a subscriber to *TCPR,* you already have a username and password to log on www.TheCarlatReport.com. To obtain your username and password or if you cannot take the test online, please email info@thecarlatreport.com or call 978-499-0583.

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

1. Classic tardive dyskinesia is characterized by which of the following (Learning Objective #1)?
   [ ] a) A feeling of internal restlessness that is usually uncomfortable and can be disabling
   [ ] b) Repetitive oro-facial movements, or stereotypies, such as lip smacking, chewing, facial grimacing, tongue movements inside the mouth, and tongue popping out
   [ ] c) High amplitude and low frequency postural, kinetic, and resting tremor with no other parkinsonian features such as bradykinesia, rigidity, or gait changes
   [ ] d) Postural jerk-like movements usually affecting upper extremities

2. The most effective medications in treating any TD syndromes include which of the following (LO #2)?
   [ ] a) Tetrabenazine (Xenazine) and reserpine (Serpalan)
   [ ] b) Haloperidol (Haldol) and loxapine (Loxitane)
   [ ] c) Amantadine (Symmetrel)
   [ ] d) Donepezil (Aricept) and lithium

3. Studies have found that patients with a good doctor-patient alliance who received placebo had what outcome when compared to patients in a poor alliance receiving an active drug (LO #3)?
   [ ] a) Patients with a good alliance receiving placebo had similar changes in depression scores when compared to patients in a poor alliance receiving active drug
   [ ] b) Patients with a good alliance receiving placebo experienced worsening of depression, compared to patients in a poor alliance receiving active drug
   [ ] c) Patients with a good alliance receiving placebo had greater reduction in depression than patients in a poor alliance receiving active drug

4. According to Dr David Mintz, research in primary care settings has found that eliciting patient preferences takes how much extra time per visit (LO #3)?
   [ ] a) 30 minutes [ ] b) 15 minutes [ ] c) 10 minutes [ ] d) eliciting patient preferences takes no extra time

5. In the Owens M et al study of biomarkers for depression, male students in which group were at the greatest risk of developing depression (LO #4)?
   [ ] a) High depressive symptoms and high cortisol [ ] b) High depressive symptoms and low cortisol
   [ ] c) Low depressive symptoms and high cortisol [ ] d) Low depressive symptoms and low cortisol

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News of Note

Stem-Cell Research Reveals Differences in Bipolar Disorder Neurons

A team of scientists from the University of Michigan Medical School studied a line of stem cells derived from patients with bipolar disorder to determine what, if any, differences could be found between these and the cells of people without the disorder.

The cells, called induced pluripotent stem cells (iPSC), were created by converting skin cells from patients or controls into stem cells. The team then allowed these cells to develop into neurons *in vitro*. The team found that the cells from patients with bipolar disorder were different in how they "express certain genes, how they differentiate into neurons, how they communicate, and how they respond to lithium," said scientist Sue O'Shea, PhD, in a statement.

Specifically, the cells showed significant differences in their expression of cell-surface receptors and calcium channels, and in how the cells behaved when treated with lithium. The cells also differentially expressed genes involved in migration to certain brain areas during development.

The scientists say they hope this research helps pave the way for studying treatments at a cellular level rather than through trial and error in human subjects, and that the "iPSC cell lines themselves provide an important resource for comparison with other neurodevelopmental disorders." Their findings were published online on March 25 in the journal *Translational Psychiatry* (http://bit.ly/1mUG1Qk).

TCPR: This all sounds great from a theoretical standpoint. But does this require anything extra to practice this way?

Dr. Mintz: There are a lot of simple things that anybody can do, beginning with resisting pressures to think reductionistically about patients. Ask patients what they want, ask what they might stand to lose if treatment works, and understand something about their lives and their relationships. If you know, for instance, that this person is scared of dependency in relationships, you could anticipate that if a medication works, it might frighten them. Then you can begin to address that fear with them, before it leads to treatment discontinuation. That, I think, any psychologically-minded person can do. I have begun to regret the term psychodynamic psychopharmacology because my other acronym for it would be JPOGCC (just plain old good clinical care), and I think that is something that is ideally a part of doctoring, whatever you are doing. I am optimistic that with the pendulum swinging we will see more research on psychosocial aspects of medications, and as the ball gets rolling, the field of psychiatry will be in a better position to resist care delivery models that really promote an objectification of the patient.

TCPR: Thank you, Dr. Mintz.

This Month's Focus:
Issues in Psychopharmacology

Next month in *The Carlat Psychiatry Report*: Psychiatric Diagnosis—DSM-5 and Beyond