Hospital-Based Psychiatric Emergency Programs

The Missing Link for Mental Health Systems

Scott Zeller, MD

Boarding of psychiatric patients in medical emergency departments (EDs) for hours or even days is a serious issue plaguing hospitals across the country. Typically, the emergency physician has determined that the patient needs further psychiatric care. However, the sole option available is usually admission to an inpatient psychiatric facility. Unfortunately, few regions have enough inpatient psychiatric beds to meet the needs of a system predicated on admitting the majority of ED patients, especially since, in the past decade, behavioral health patients have risen to become one in every eight cases in EDs in the US. As a result, psychiatric patients can end up confined indefinitely in small ED quarters with a sitter or security guard, or restrained to a gurney in a back hallway, while they await admission. Many of these boarded patients receive little or no psychiatric treatment beyond sedation. Thus, sadly, the most highly acute patients in a
As we attempt to do so, we suffer impediments and harassments by various bureaucracies, including dwindling reimbursements, decreased time with patients, increased record-keeping requirements, and burdensome demands of specialty and other oversight boards. In short, we regularly interact with bureaucratic systems that pressure us to value money over health, screen time over face time, and record-keeping over people-helping.

Yet there is a reason that we become psychiatrists, and a reason that we remain in the field. For all its perils, psychiatry is filled with extraordinary moments of healing, honesty, insight, and human connection. With such a heady mix of costs and benefits, psychiatrists will always run the danger of being swamped by the negative as they seek to cultivate the positive.

As human beings, in fact as mammals, we are inherently prone to pay more attention to the bad than the good, and to demonstrate a negativity bias in most aspects of life.1 Gottman and colleagues2 have asserted it takes five positive interactions for every negative one to keep a relationship stable and happy. Positive psychology has taught us that we need to actively cultivate appreciation for the goods of life—gratitude—by regular and conscious practice.

Conscious emphasis on the positive does not mean denial of the negative, as if a naive Pollyanna-like attitude constitutes self-actualization. Rather, by emphasizing the good, we more accurately balance positive and negative in our emotional and intellectual lives. Or, more fundamentally, by focusing on the positive, we help keep ourselves from sinking into an ocean of negativity.

And so, in a spirit of gratitude, here are a few of the many extraordinary advantages of being a psychiatrist.

External goods
US psychiatrists earn an average of $273,000 a year, placing them in the top 2% of wage earners in the US.3 Regardless of their position in the salary range, psychiatrists earn more than enough to provide for themselves and their families. We are among the top 3% in educational attainment, with a doctorate and four years (plus) of post-graduate training. We also enjoy the tremendous prestige of being a physician, with instant respect, credibility, and social status wherever we go. Of course, positive psychology has confirmed that money, possessions, and social status are relatively superficial goods and are not the most important factors in happiness and well-being.4 So (being good psychiatrists) let us look more deeply.

Helping others
A profound and inescapable aspect of a meaningful, happy life is the ability to contribute to the good of others. As psychiatrists, helping others is the essence of our jobs. This truth is so familiar that it often feels trivial when it is in fact profound.5 We enjoy a social role that is ultimately about doing good for our patients, their families, and our society, and we will see tangible results of our efforts in both the short and long term. By the end of a psychiatric career (and in spite of mistakes and limitations), countless people and their families will be better off because of our work.

Being needed
Nationally and worldwide, there is a vast shortage of psychiatrists that will not end in the foreseeable future. Wherever we go, we will be needed and valued. We do not need to worry about being able to find work and support ourselves. Better than that, as an individual psychiatrist, I can contemplate the fact that if I were not filling the need I now fill, there would not be anyone else to make up for it.

Being significant
Obviously, we matter as psychiatrists. Yet how many of us have considered the strange fact that people rearrange their lives, schedules, and finances, all to receive the privilege of sitting with us in a room and talking?

Yes, they need medications, but realistically they can get medications elsewhere. They want to talk to us. They want to be heard, and they want to learn from our knowledge and wisdom. They actually believe (at least on some level) that time spent with us will make their lives better. This is extraordinary—after all, how many people in the rest of daily life approach us and offer us money for our sage advice, or re-arrange their day just to hear what we have to say about their lives? Do family members wait each day with bated breath for our words of wisdom? And yet there are people, every day, who commute, show up, sit, and wait just for the opportunity to talk to us, their psychiatrists.

Intellectual engagement
As we know, the human brain is the most complex object in the physical universe, bar none. Our job challenges us to understand the workings of the human brain and the human person on every level that we can, and to help people make use of this knowledge to live better lives. We help people understand and seek integration and healing on biological, psychological, social, and spiritual levels. Our patients teach us, our colleagues teach us, and every day new studies will come out to illuminate this most exquisite of all creations. We will never stop learning, and we need never be bored.6

Self-improvement
As a psychiatrist, whatever I learn applies to me. Every day, our work teaches us more about the human condition. We have access to the inner, intimate, and (generally) honest experiences of countless people, not the superficial Facebook-type self-advertising that goes on in much of our culture. Thus, we have a source of knowledge about the human condition that no one can better. And we have a daily motivator to practice our own self-care, self-improvement, and growth. As we understand our patients more deeply and help them, we simultaneously learn to understand and help ourselves.

Self-esteem
People who spend large amounts of time on social media appear vulnerable to feelings of inferiority and discouragement in the face of others’ relentless success.7 As the old Alcoholics Anonymous saying has it, “You are comparing your insides with other people’s outsides.” As psychiatrists, we have a rare view into the “insides” of countless people. We enjoy the privilege of seeing that self-doubt, inadequacy, guilt, stress, and illness are a normal part of individual and family life. Our profession allows us to better accept ourselves and our limitations, using adverse experiences for our own growth and the benefit of others.

Love
I consider love to be the “L-word” of our profession. We don’t often use it with patients, for obvious reasons. But psychiatrists create constructive relationships as the fundamental basis of their work. We are formally trained to do so, even with the most difficult patients. Though extreme levels of patience and skill are sometimes required, achieving such good and meaningful relationships is among the greatest joys of life. Better than most other professionals, psychiatrists understand that relationships are central to the good life and base their professional lives on nurturing such relationships.8 “Life is pain,” declares Dread Pirate Roberts in The Princess Bride. “Anyone who tells you differently is selling something.” If that is true, then thank goodness for psychiatry. And thanks to those who practice it. Because of them, human life is a little bit less painful.

Dr Morehead is a psychiatrist in private practice, and former Assistant Residency Director at the Karl Menninger School of Psychiatry. He is board certified in General Psychiatry (ABPN) and Neuropsychiatry (UCNS), maintaining interests in neuroscience, psychotherapy, spirituality, and advocacy for mental illness.

References
Throughout my life I have found myself reflecting on the philosophical question of how my life would be, or in fact would I be here at all, if a single event in history had occurred differently. Impersonal events like the extinction of the dinosaurs or a larger accretion of stardust resulting in the Earth orbiting the sun at a greater distance, incompatible with life, are obvious major events. However, it is the smaller and more personal events that bring up strong emotions and relief when I reflect on these.

My mother died on July 14th at the age of 83. She died peacefully after years of progressing medical ailments. My father, my 4 siblings, and I were all with her, and she had said her goodbyes to her extended family and friends. She welcomed her passing with relief, ready to join her parents in the heaven that had been such an important part of her life. It was during the ensuing days, with the telling of all the stories and remembrances of my mother’s life, that I found myself reflecting on the unpredictable web of events and decisions that easily could have eliminated me from this story. For brevity, I will share three.

Although my grandmother’s due date was Christmas Day, my mother was born on Thanksgiving Day in 1935 during a blizzard in Salem, MA. When my grandmother went into labor that day, my grandfather called the doctor, who informed them it was likely “false” labor, and he was unable to go to their home due to the severe weather. This weather also served to trap them in their home, unable to go to the hospital. Later that day, in the family home, my great grandmother delivered my mother, who was then placed in a drawer next to the wood stove in the kitchen to keep her warm. She weighed 4.5 pounds and was healthy.

My mother’s family was devoutly Catholic, and after attending an all-girl’s Catholic high school my mother wanted to become a nun. Wisely, my grandfather asked her to delay that commitment for a year, and to attend some type of post high school education. My mother joined her best friend in attending the Salem Hospital School of Nursing, where she discovered her passion for pediatrics, and she worked as a pediatric nurse until she retired. She married my father and gave birth to 5 children over 10 years.

In 1975, at the age of 39, my mother received a diagnosis of a rare cardiac anomaly that she was unknowingly born with. A fistula connected her coronary sinus with her left coronary artery, and it had slowly grown in diameter to the width of a pencil, shunting the oxygenated blood away from her heart muscle and back to her right atrium. During her 30s, as her heart enlarged, she became increasingly short of breath with minor activity; finally, a cardiologist made the correct diagnosis. The only treatment option was open heart surgery to close the fistula, which was very new medical technology at that time. In 1975 she became one of the first open heart surgery patients at the Massachusetts General Hospital in Boston.

These are but three of hundreds, likely hundreds of thousands of decisions that have had a direct impact on me in unknowable ways. And so, it is for each of us, reminding us of our responsibility to make each decision and choose each action wisely and thoughtfully, but simultaneously accepting the reality that an immense web of events have led us to this life, and this moment.

Mom, thank you for your choices and actions, and may you rest in peace.
INDICATION & USAGE
INGREZZA® (valbenazine) capsules is indicated for the treatment of adults with tardive dyskinesia.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
INGREZZA is contraindicated in patients with a history of hypersensitivity to valbenazine or any components of INGREZZA. Rash, urticaria, and reactions consistent with angioedema (e.g., swelling of the face, lips, and mouth) have been reported.

WARNINGS & PRECAUTIONS
Somnolence
INGREZZA can cause somnolence. Patients should not perform activities requiring mental alertness such as operating a motor vehicle or operating hazardous machinery until they know how they will be affected by INGREZZA.

QT Prolongation
INGREZZA may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. INGREZZA should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.

Parkinsonism
INGREZZA may cause parkinsonism in patients with tardive dyskinesia. Parkinsonism has also been observed with other VMAT2 inhibitors. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant parkinson-like signs or symptoms.

ADVERSE REACTIONS
The most common adverse reaction (≥5% and twice the rate of placebo) is somnolence. Other adverse reactions (≥2% and >Placebo) include: anticholinergic effects, balance disorders/falls, headache, akathisia, vomiting, nausea, and arthralgia.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch at www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see the adjacent page for brief summary of Prescribing Information and visit www.INGREZZAHCP.com/PI for full Prescribing Information.


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Brief Summary: for full Prescribing Information and Patient Information, refer to package insert.

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QT Prolongation
INGREZZA may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. In patients taking a strong CYP2D6 or CYP3A4 inhibitor, or who are CYP2D6 poor metabolizers, INGREZZA concentrations may be higher and QT prolongation clinically significant. For patients who are CYP2D6 poor metabolizers or are taking a strong CYP2D6 inhibitor, dose reduction may be necessary. For patients taking a strong CYP3A4 inhibitor, reduce the dose of INGREZZA to 40 mg once daily. INGREZZA should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.

Parkinsonism
INGREZZA may cause parkinsonism in patients with tardive dyskinesia. Parkinsonism has also been observed with other VMAT2 inhibitors. In the 3 placebo-controlled clinical studies in patients with tardive dyskinesia, the incidence of parkinson-like adverse events was 3% of patients treated with INGREZZA and <1% of placebo-treated patients. Postmarketing safety reports have described parkinson-like symptoms, some of which were severe and required hospitalization. In most cases, severe parkinsonism occurred within the first 2 weeks after starting or increasing the dose of INGREZZA. Associated symptoms have included falls, gait disturbances, tremor, drooling, and dyskinesia. In cases in which follow-up clinical information was available, parkinson-like symptoms were reported to resolve following discontinuation of INGREZZA therapy. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant parkinson-like signs or symptoms.

ADVERSE REACTIONS
The following adverse reactions are discussed in more detail in other sections of the labeling:

- Hypersensitivity
- Somnolence
- QT Prolongation
- Parkinsonism

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Variable and Fixed Dose Placebo-Controlled Trial Experience
The safety of INGREZZA was evaluated in 3 placebo-controlled studies, each 6 weeks in duration (fixed dose, dose escalation, dose reduction), including 442 patients. Patients were 20 to 85 years of age with moderate to severe tardive dyskinesia and had concurrent diagnoses of mood disorder (fixed dose, dose escalation, dose reduction), including 445 patients. Patients were 26 to 84 years of age with moderate to severe tardive dyskinesia and had concurrent diagnoses of mood disorder.

Other Adverse Reactions Observed During the Premarketing Evaluation of INGREZZA
Other adverse reactions of ≥3% incidence and greater than placebo are shown below. The following table does not include adverse reactions: 1) already listed in previous tables or elsewhere in the labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have clinically significant implications, or 5) which occurred at a rate equal to or less than placebo.

Endocrine Disorders: blood glucose increased
General Disorders: weight increased
Infectious Disorders: respiratory infections
Neuropsychiatric Disorders: drooling, dyskinesia, extrapyramidal symptoms (non-akathisia)
Psychiatric Disorders: anxiety, insomnia

During controlled trials, there was a dose-related increase in prolactin. Additionally, there was a dose-related increase in alkaline phosphatase and bilirubin, suggesting a potential risk for cholestasis.

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of INGREZZA that are not included in other sections of labeling. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders: rash

DRUG INTERACTIONS

Drugs Having Clinically Important Interactions with INGREZZA

<table>
<thead>
<tr>
<th>Table 2: Clinically Significant Drug Interactions with INGREZZA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monamine Oxidase Inhibitors (MAOIs)</strong></td>
</tr>
<tr>
<td><strong>Clinical Implication:</strong> Comitant use of INGREZZA with MAOIs may increase the concentration of monamine neurotransmitters in synapses, potentially leading to increased risk of adverse reactions such as serotonin syndrome, or attenuation of treatment effect of INGREZZA.</td>
</tr>
<tr>
<td><strong>Prevention or Management:</strong> Avoid concomitant use of INGREZZA with MAOIs.</td>
</tr>
<tr>
<td><strong>Examples:</strong> bocarizid, phenelzine, selegiline</td>
</tr>
<tr>
<td><strong>Strong CYP3A4 Inhibitors</strong></td>
</tr>
<tr>
<td><strong>Clinical Implication:</strong> Comitant use of INGREZZA with strong CYP3A4 inhibitors increased the exposure (Cmax and AUC) to valbenazine and its active metabolite compared with the use of INGREZZA alone. Increased exposure of valbenazine and its active metabolite may increase the risk of exposure-related adverse reactions.</td>
</tr>
<tr>
<td><strong>Prevention or Management:</strong> Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP3A4 inhibitor.</td>
</tr>
<tr>
<td><strong>Examples:</strong> ketoconazole, atorvastatin, clarithromycin</td>
</tr>
<tr>
<td><strong>Strong CYP2D6 Inhibitors</strong></td>
</tr>
<tr>
<td><strong>Clinical Implication:</strong> Comitant use of INGREZZA with strong CYP2D6 inhibitors may increase the exposure (Cmax and AUC) to valbenazine’s active metabolite compared with the use of INGREZZA alone. Increased exposure of active metabolite may increase the risk of exposure-related adverse reactions.</td>
</tr>
<tr>
<td><strong>Prevention or Management:</strong> Consider reducing INGREZZA dose based on tolerability when INGREZZA is coadministered with a strong CYP2D6 inhibitor.</td>
</tr>
<tr>
<td><strong>Examples:</strong> paroxetine, fluoxetine, quinidine</td>
</tr>
<tr>
<td><strong>Strong CYP3A4 Inducers</strong></td>
</tr>
<tr>
<td><strong>Clinical Implication:</strong> Comitant use of INGREZZA with a strong CYP3A4 inducer decreased the exposure of valbenazine and its active metabolite compared to the use of INGREZZA alone. Reduced exposure of valbenazine and its active metabolite may reduce efficacy.</td>
</tr>
<tr>
<td><strong>Prevention or Management:</strong> Consider using strong CYP3A4 inducers with INGREZZA is not recommended.</td>
</tr>
<tr>
<td><strong>Examples:</strong> rifampin, carbamazepine, phenytoin, St. John’s wort</td>
</tr>
</tbody>
</table>

Digoxin

**Clinical Implication:** Comitant use of INGREZZA with digoxin increased digoxin levels because of inhibition of intestinal P-glycoprotein (P-gp).

**Prevention or Management:** Digoxin concentrations should be monitored when coadministering INGREZZA with digoxin. Increased digoxin exposure may increase the risk of exposure-related adverse reactions. Dosage adjustment of digoxin may be necessary.

The indication potency of St. John’s wort may vary widely based on preparation.

Drugs Having No Clinically Important Interactions with INGREZZA
Dose adjustment for INGREZZA is not necessary when used in combination with substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A, or CYP3A4/5 based on in vitro study results.

OVERDOSAGE

Human Experience
The pre-marketing clinical trials involving INGREZZA in approximately 850 subjects do not provide information regarding symptoms with overdose.

Management of Overdose
No specific antidotes for INGREZZA are known. In managing overdose, provide supportive care, including close medical supervision and monitoring, and consider the possibility of multiple drug involvement. If an overdose occurs, consult a certified Poison Control Center (1-800-222-1222 or www.poisnon.org).

For further information on INGREZZA, call 84-INGREZZA (844-647-3992).
Debunking the Two “Chemical Imbalance” Myths (Again!)

And Moving Toward a Bio-psycho-socio-cultural Model of Major Depression

By whatever biological mechanisms, the clinical reality is that antidepressants are effective in many patients with severe, acute major depression.

Ronald W. Pies, MD

A little learning is a dangerous thing.

Alexander Pope

ike the legendary Count Dracula, who could be killed only by driving a stake through his heart, some myths seem almost immortal. For more than 8 years now, I have tried to drive a stake through the heart of two myths regarding the so-called “chemical imbalance theory”—but with only limited success, as a recent piece in the New Yorker brought home to me.1,2

And, yes, there are really two myths to debunk. The first holds that mental illnesses (psychiatric disorders) in general are caused by “a chemical imbalance in the brain”—the so-called “chemical imbalance theory.” The second myth holds that “Psychiatry” as a profession endorsed the first myth, deliberately and knowingly lying to countless, unsuspecting patients. Depending on which anti-psychiatry group, blogger, or website you investigate, you will find a number of corollaries to the second myth; for example, “Psychiatrists lied to patients in order to justify giving them medication,” or “Psychiatrists were corrupted by Big Pharma, and stood to make a lot of money by promoting the chemical imbalance theory” (Sidebar). Rebuttals of these claims are almost always disclaimed as, “Psychiatry defending its guild interests” (as if the purveyors of anti-psychiatry animus have no self-serving motives).

Ironically, anti-psychiatry groups are quite right in heaping scorn on the chemical imbalance theory of mental illness, but not for the reasons they usually give. (I hasten to add that debunking the chemical imbalance theory is not to deny that biological factors play an important role in serious mental illness, including but not limited to major depression, bipolar disorder, and schizophrenia). The fact is, there could never have been a scientifically based, chemical imbalance theory of mental illness, because a genuine theory requires an integrated network of well-supported, interlinked hypotheses. And yes, the frequently ignored distinction between a theory and a hypothesis is crucial. It is the key to understanding why claims by antipsychiatry bloggers regarding the chemical imbalance theory nearly always crash and burn.

The theory that never was

Scientifically speaking, there never was a network of validated hypotheses capable of sustaining a full-blown, global chemical imbalance theory of mental illness. Moreover—and here we come back to Myth 2—psychiatry as a profession and medical specialty never endorsed such a bogus “theory,” when judged by its professional organizations, its peer-reviewed publications, its standard textbooks, or its official pronouncements. Furthermore, the whole notion of some looming, monolithic “Psychiatry” is absurd on its face, as my colleague, George Dawson has argued.3

To be sure: what many psychiatrists in the 1980s and 1990s did promote was some version of the biogenic amine (or catecholamine) hypothesis of mood disorders, focusing mainly on the neurotransmitters norepinephrine and serotonin. (Schizophrenia was conventionally explained by the now outdated “dopamine hypothesis.”) And, in truth, the significance of serotonin was considerably over-emphasized—owing to what Roger S. McIntyre, MD has facetiously called, “Psychiatry’s High School Crush.”4

Furthermore, the SSRIs were accorded a rock-star status as effective antidepressants that they did not deserve. Most troubling from the standpoint of misleading the general public, pharmaceutical companies heavily promoted the “chemical imbalance” trope in their direct-to-consumer advertising. There was no concerted attempt by our profession to promote a causal or etiological theory of mental illness in general, based solely on chemical imbalances. Neither did the originators of the biogenic amine hypothesis—psychiatrists Joseph J. Schildkraut and Seymour S. Kety—promote such a view in the 1960s.5 Indeed, in 1965, Dr Schildkraut stated:

A rigorous extrapolation from pharmacological studies to pathophysiology clearly cannot be made. Clinical studies relevant to the catecholamine hypothesis are limited and the findings are inconclusive. It is not possible, therefore, to confirm definitively or to reject the catecholamine hypothesis on the basis of data currently available.

The closest thing we have to an “official” position on the etiology of psychiatric disorders is this 1978 statement from the American Psychiatric Association, which was approved by the APA Board of Trustees: “Psychiatric disorders result from the complex interaction of physical, psycho-logical, and social factors and treatment may be directed toward any or all three of these areas.”6

Critics of my thesis are inordinately fond of citing a dozen or so statements by various psychiatric luminaries—including two former APA presidents—that do, indeed, invoke the phrase, “chemical imbalance.” By cherry-picking quotes of this nature, anti-psychiatry groups and bloggers believe they have demonstrated that “Psychiatry” has defended a bogus chemical imbalance theory. These critics are simply wrong. Decontextualized quotes from a dozen—or even a hundred—famous psychiatrists do not represent an official professional consensus, much less the views of over 30,000 US psychiatrists.

Moreover, most of the quotes or statements usually cited by psychiatry’s critics use the term “chemical imbalance” in the specific context of antidepressants and their putative mechanism of action. For example, here is a quote from 2004:

Patients with neurotransmitter dysregulation may have an imbalance of serotonin and norepinephrine... Antidepressant medications that act as dual serotonin-norepinephrine reuptake inhibitors [SNRIs] . . . may aid in correcting the imbalance of serotonin and norepinephrine neurotransmission in the brain.8

The writer was hypothesizing a mechanism of action by which SNRIs may be helpful for patients who experience depression in the context of pain. He was certainly not propounding a causal chemical imbalance theory of depression, much less of psychiatric disorders in general. Note, as well, the careful use of the word “may.” Yes: with 20-20 hindsight, the imbalance claim has proved inaccurate and simplistic—but was not demonstrably false or mendacious when stated in 2004. (Even today, we simply do not have the sophisticated technology to verify or falsify, in real time, putative neurotransmitter “imbalance” in the human brain, during a patient’s depressive bout.) Indeed, with the benefit of further research, we now believe that the likely mechanisms of action of antidepressants are much more complicated than merely altering levels of neurotransmitters.
Growing evidence that various neuro growth factors, such as BDNF (brain-derived neurotrophic factor) are involved in the etiology of depression and the mechanism of action of some antidepressants. The rapid antidepressant effect of ketamine has also raised the possibility that the NMDA receptor, and possibly, the opioid system, are involved in the biology of depression.12

One important caveat, however: the DSM-5 construct of MDD is so broad and elastic, it almost certainly encompasses a multitude of underlying disease entities. As Dr Joel Paris has noted, “MDD is a highly heterogeneous category, leading to problems in classification and in specificity of treatment.”13

In the area of bipolar disorder, Maletic and Raison14 have described a “unified field theory” in which reduced brain volume in mood-regulating brain regions, dysregulation of glial-neuronal interaction, and abnormal hypothalamic-pituitary-adrenal function are interlinked with inflammatory activation. Such a sophisticated model cannot be reduced to chemical imbalances.

It is abundantly clear that biological factors are an important component of severe mood disorders. However, in recent years, psychiatrists have become increasingly interested in the environmental and sociocultural risk factors for depression. For example, the risk of post-partum depression is increased in the presence of a poor marital relationships, stressful life events, a negative attitude towards pregnancy, and lack of social support. A recent study has also shown that early life stress, such as childhood maltreatment, has a detrimental effect on brain structure, which increases the risk of an unfavorable disease course in major depression.21

Race and ethnicity are also possible risk factors for major depression. Bailey and colleagues22 report that “while minority populations are less likely to suffer from acute episodes of MDD than Caucasians, they are more likely to suffer from prolonged, chronic, and severely growing evidence that various neuro growth factors, such as BDNF (brain-derived neurotrophic factor) are involved in the etiology of depression and the mechanism of action of some antidepressants. The rapid antidepressant effect of ketamine has also raised the possibility that the NMDA receptor, and possibly, the opioid system, are involved in the biology of depression.12

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debilitating depression with heavy consequences on their level of daily functioning.23

Conclusion
In the 1980s, the 1990s, and beyond, pharmaceutical companies heavily promoted something resembling a chemical imbalance theory of mood disorders directly to consumers—or, at least, used the “chemical imbalance” trope to explain why antidepressants supposedly work. In recent years, as psychologist Dr John Grohol has pointed out, some non-professional websites have provided misleading graphics that reinforce the “chemical imbalance” trope.24 It is not surprising that the “Theory That Never Was” has taken hold in the minds of so many.

While some prominent psychiatrists have used the term “chemical imbalance” in their public comments about antidepressants—and possibly in their clinical practices (Sidebar)—there was never a unified, concerted effort within American psychiatry to promote a chemical imbalance theory of mental illness.

The original catecholamine hypothesis of mood disorders was carefully qualified by its originators in the 1960s, and has been recognized as significantly flawed and inadequate by US psychiatrists since at least 2003—and probably much earlier. The hypothesis has since been modified and corrected to reflect more complex biological mechanisms in major mood disorders. These disorders are best understood using a bio-psychosocial-cultural model, which has been the mainstream of academic psychiatry for over 30 years.

As with many other neuropsychiatric diseases, including Alzheimer disease, the precise causes of major mood disorders are still unknown. Almost certainly, there is a plethora of causal processes involved, depending on the diagnostic criteria and subtype of the illness (similar to the subtyping of anxiety). Fortunately, we have effective pharmacologic and psychosocial treatments for mood disorders. As for the bogus chemical imbalance theory and its mission to the profession of psychiatry, it is time to drive the stake into its misbegotten heart. We must focus on providing our patients greater access to holistic, comprehensive psychiatric care.

Dr Pies is Professor of Psychiatry, SUNY Upstate Medical University, Syracuse, NY and Tufts University School of Medicine, Boston. He is Editor in Chief of Psychiatric Times (2007 to 2010). He reports no conflicts of interest concerning the matter of this article.

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REFERENCES
The History and Value of Guidelines for Best Practices of Telemental Health

» Robert Caudill, MD and Jay H. Shore, MD, MPH

Telepsychiatry has moved from an esoteric curiosity to mainstream practice. It has been challenged along the way at many turns. Some degree of scientific skepticism is required when considering any health care innovation. While the utility of telepsychiatry seemed obvious to many, it was always necessary to develop a robust literature in support of its effectiveness and for acceptance of this health care innovation and associated technology. That task was achieved long ago.

An outgrowth of the supporting evidence has been the creation and adoption of guidelines to assist clinicians in the implementation of telepsychiatry. The efforts at guidelines began shortly after the earliest attempts at instituting telemedicine practices. Historically, the American Psychiatric Association (APA) was a slow adopter of telepsychiatry. To its credit, over time it has moved from skepticism to gradual embrace, to acceptance and enthusiastic promoter of telepsychiatry. Telepsychiatry has its origins in the 1950s. However, the more modern incarnation grew from Internet advances and the ubiquity of adequate bandwidth. As with any novel technology or practice, mainstream acceptance could only follow pilot projects and pioneering efforts. Protocols and processes were created from scratch for these initial programs. Those who are the first to put new tools into use do so without the benefit of established guidelines. However, it is only through such efforts that the data and evidence can be collected and the field refined to allow for the development of the standards that follow.

In this regard, telepsychiatry is no different from any other area of medicine where technical developments have moved from theory to established and routine practice. Activities, disciplines, and methods that are available to identify, implement, and monitor the available evidence in health care are called “best practices.” Such guiding principles must hold up to the scrutiny of those who are active in the field. Those protocols developed during the early adoption of a new technology must withstand repeated challenges if they are to garner wider acceptance and mainstream implementation. The evolution of telepsychiatry has followed this process. Specific technical organizations formed and grew to support such innovation. These groups then give back to the field through the aggregation of data followed by thoughtful synthesis and promulgation of this material to others who are prepared to follow.

Current best practices for videoconferencing-based telemental health

With suitable fanfare, the most recent version of Best Practices in Videoconferencing-Based Telemental Health was adopted by both the APA and the American Telemedicine Association (ATA) in the spring of 2018. The foundational texts were updated, streamlined, and harmonized and culminated in this co-branded document. While the chair of the APA telepsychiatry committee is a psychiatrist by definition, it is not a given that a psychiatrist, or even a physician necessarily, would happen to hold one of the two key ATA offices. This fortuitous arrangement of office holders and the opportunity to synchronize between the two organizations greatly facilitated the creation of this document.

When the writing committee convened to begin work on the new co-branded document, they drew upon precursor works that dated back to 1998. On the APA side, it required the merging and updating of ATA works from 2009 and 2013. A writing committee composed of 11 thought leaders from both organizations undertook an iterative writing process that produced the new document. Support staff from both organizations also contributed to the success of the final product. Once a working draft was completed, it was distributed to larger groups within the two organizations including the Telemental Health Special Interest Group (TMH SIG) of the ATA, the APA Committee on Telepsychiatry, the ATA Standards and Guidelines Committee, as well as both ATA and APA staff. Feedback from this extended review was incorporated into the final work, which has been received with widespread acceptance within the field.

The final product serves as an example of high level collaboration between large organizations working toward a common goal. The document became available online on the websites of both APA and ATA and was recently published in Teledermicine and e-Health, the leading journal of the teledermicine field.

The document itself stands as a succinct summarization of accepted best practices for deploying telemedicine technology in the service of mental health care.

The process by which the document came into existence, was refined, and ultimately promulgated should also serve as an example. Other areas of the medical field where multiple groups are working in an area with intrinsic and overlapping interests in the success and growth of that initiative could benefit from emulating this process. Writings on technology topics are prone to having relatively short shelf-lives as the technologies themselves rapidly evolve. This concern was embraced by the writing group through a focus on outlining principles and practices that are less likely to be subject to obsolescence in the face of technological progress. Hopefully the stage has been set for future collaborations of this sort. When the time for an inevitable updating of the document is required, perhaps a similar representative group of professionals will come together for that task as well.

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References
Children Who Ask to Become Suicide Bombers
And Their Approving Parents: A Joyless Meditation

Lawrence H. Cline, MD

A

while back I was asked, as a psychiatrist, to weigh in on the topic of Arab children who ask to become suicide bombers, and their approving parents. I took a pass. I wasn’t ready to go down that path, to set aside my shield of labels, all variations of “brainwashed,” “fanatic,” and “crazy,” and put down my cleaver that splits the me from them and the them from their humanity.

Then, I remembered. If psychiatrists can stand ready to help survivors of cults and kidnappings, and returning POWs, how is a child suicide-bomber applicant with approving parents any different? I set aside my shield and put down my cleaver and asked myself the following question: “Face-to-face with such a child and the approving parents, what would I say? Where might I begin?”

For this I began pondering the familiar experience of letting oneself get carried away by a destructive impulse, remembering and reflecting on those dares and double-dares of childhood. I reflected on our readiness to tear down goal-posts following a victory on the gridiron in our youth and our joining a march as young adults and remaining even after it morphed into a destructive riot. A part of us knew there was more at risk than property; there was our health, reputation, and career. But, at such moments these aren’t our priorities, are they? “I don’t know why I did that,” you hear yourself telling a parent, teacher, or judge. Think of actor Mel Gibson who said as much following his drunken anti-Semitic rant after a traffic stop, or those youthful accusers during Salem’s witch trials in the 1690s and their subsequent apologies. Think of Pinocchio. They all had one thing in common; they came to their senses. They woke up, or grew up, as it were, and felt and expressed remorse.

So, the question becomes: where-in does the state of being carried away by group-think become one’s permanent state of mind, one from which one never wakes up or grows up and comes to one’s senses? It’s as if, for some, there simply isn’t a self to wake-up—a self-awareness, an awareness of self-with-agency. And never was. It’s as if for some children who’ve never had support for pondering and raising questions, only for doing and thinking as they were told, obedience has been their consistently reliable source for belonging, identity, appreciation, and love. And returning POWs, how is a child suicide-bomber applicant with approving parents any different?

What would it mean to such a child, now a youth, to be told, “Just be yourself”? And if that doesn’t carry meaning might the absence of affirmation of one’s individuality in early life account for that? Are we talking about a sense of Self that is not simply dark, it’s absent?

For us in the West, of course, submission to the will of a group is generally a conditional thing—temporarily, whereas in the Arab world it can be unconditional and permanent. What we might call a deprivation they might consider an asset wherein hope for redemption, for a recovery of lost honor and dignity, if not in this life then in the next, is bona fide. Obviously, the mention of fulfillment and becoming whole can have different meanings. It’s not so surprising, then, that people who approve of and sponsor suicide bombings by children never seem to use the word “death” in their justifications, promotions, and celebrations, preferring instead words like being (eg, being a martyr, being in Paradise) and becoming (eg, becoming a Hero), highlighting what is gained, not lost.

We’re uncomfortably close, here, to a distinctly un-Western version of “Born Again,” which, creepy as it feels, sheds sobering light on our task. In both cases— theirs and ours—we are talking about religious people, determined to faithfully do God’s will by doing the right thing, unafraid to sacrifice to make the world a better place.

I’m reminded of the Bible story of Eve in the Garden of Eden who bit into that apple even though she’d been told she would die if she did. I didn’t think she was thinking of dying back then, or even death. I don’t think she even knew what those words meant, nothing having ever died in the Garden. How could she know? So, like Eve, maybe for prospective child bombers and their parents it’s not death they have in mind but a state akin to transformation, of being “Born Again.”

There’s this story we tell of the psychiatrist becoming frustrated trying to talk his patient out of the delusional belief that he, the patient, is actually dead. “You’re alive!” the doctor finally begins shouting in abject frustration. “No, I’m dead!” the patient shouts back until, in desperation, the doctor grabs a letter-opener. “Do dead men bleed?” “No!” The psychiatrist stabs the patient’s arm and the patient, staring with disbelief at his bleeding arm, murmurs, “I was wrong. Dead men bleed.” We laugh, of course, never thinking to ponder what such a patient might have meant by “dead” or why his doctor never asked. Just because we don’t use words in the same way, doesn’t mean we’re not, in some sense, on the same page. Just because someone speaks of wanting to die, to suicide, doesn’t mean he or she is depressed, doesn’t rule out a motive of simply trying not to go mad, end pain, or not be a burden. How many people have, while psychotic, killed others, not from hate or anger as the media automatically assumes in their coverage, but from fear of harm and the urge to protect, to save themselves, or others. Or the world?

One can see where a would-be bomber and the parents, having made this decision, stand out among their peers in a new way, noticed and affirmed. One can see where this, for them, is a new experience, status, and identity that commands attention and respect. They have stepped forward to stand apart and are now special. Might their orchestrating and experiencing this new status represent an instinctual pull toward the completion of something that had been aborted years before, something that had never developed, that singular voice that no one would dare silence now? Might this be a manifestation of a wholeness with agency, long denied? Such a formulation would, of course, be a reach, but it’s not that hard to imagine these children and their parents trying, in this way, to realize something, complete and fulfill something. If not something in their lives, then something in the lives of their People or in the world of their Maker. Such behaviors, for child and parent both, might not be about anger, revenge, brainwashing, or madness. They may simply be about repair and redemption.

I can imagine myself now across the table from that child who asks to be a suicide bomber. His parents are with him. I am there as analyst, maybe designating healer. Where do I begin? I begin where they are, where both of us are. Healers trying to make the world a better place.

Dr Cline is the author of Psychiatrist on the Road: Encounters in Healing and Healthcare, an account of his Locum Tenens experience.
The Centers for Disease Control and Prevention estimates that autism affects 1 in every 59 children in the US. While the core features of autism impair functioning, a significant source of further impairment is comorbid psychiatric disorders. People with autism spectrum disorder (ASD) are more likely than the general population to have comorbid psychiatric disorders. Although prevalence rates vary widely, converging evidence suggests that anxiety disorders and ADHD are most prevalent.

Numerous factors contribute to the increased risk for comorbid psychiatric disorders. People with autism are at higher risk of being bullied and are more likely to experience adverse life events, which can increase stress and risk for depression and anxiety. Cognitive rigidity, problems with emotion regulation, and intolerance of uncertainty associated with ASD can predispose this population to higher levels of anxiety and depression. Emotional regulation deficits may be a transdiagnostic phenomenon that underlies features of ASD as well as anxiety and other psychiatric comorbidities.

The Autism Comorbidity Interview (ACI) is a semi-structured interview that utilizes the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) with adaptation to increase validity in the ASD population. Additional screening questions and coding options were added to the ACI to help distinguish core features of ASD from features of other psychiatric disorders.

The ACI was used to assess psychiatric comorbidity in 109 children with ASD aged 5 to 17 years. Findings indicate that 72% of the children had at least one additional DSM-IV psychiatric diagnosis. Anxiety disorders were most common, followed by ADHD (Figure).

Assessment of comorbid psychiatric disorders
Screening instruments designed for psychiatric conditions in the general population may not adequately differentiate features of ASD and can result in overdiagnosis. However, there are several validated disorder-specific tools that have been specifically developed to assess for comorbid disorders in children and adults with ASD (Table 1). Features of ASD can appear to overlap with symptoms of other conditions making it difficult to distinguish symptoms that relate to the core features of ASD versus symptoms of other psychiatric disorders (Table 2).

General considerations for assessing psychiatric comorbidity in ASD
1. Establish a baseline. It is important to establish an individual’s baseline for when he or she has functioned best. For psychiatric conditions that are episodic (eg, mood disorders) or those that appear later in development (eg, OCD, psychosis), it is important to distinguish baseline behaviors and functioning from distinct changes in symptoms that are expected with the onset of a co-occurring psychiatric condition.

2. Assess for medical comorbidity. Assess for medical problems that can exacerbate emotional and behavioral symptoms, particularly in less verbal people.

3. Factor in genetics. Some genetic syndromes are known to be associated with psychiatric conditions and behavioral phenotypes. This can help with more targeted screening (eg, fragile X syndrome has a higher prevalence of anxiety and ADHD, Williams syndrome has a higher prevalence of anxiety, and 22q11 deletion syndrome is associated with higher prevalence of psychosis).
4 Consider symptoms in the context of developmental level.

Comorbid conditions should be considered if there are symptoms that are beyond what would be expected for an individual’s mental age and developmental level.

**Anxiety disorders**

Using findings from their meta-analysis, van Steensel and colleagues estimated that 40% of youth with ASD have a comorbid anxiety disorder. Risk factors for developing anxiety that are prevalent in ASD include social skill deficits, sensory sensitivity, cognitive rigidity, heightened physiological arousal, and difficulties regulating stress.

**Specific phobias.** Specific phobia tends to have an onset in childhood. In most cases the phenomenology of specific phobia in ASD tends to be similar to typically developing youth. However, people with developmental disabilities may also develop fears to unusual objects or situations, such as elevators, vacuum cleaners, etc.

Common phobias found in youth with ASD include loud noises, needles, and crowds. Sensory sensitivities can contribute to specific fears in autism, some of which may not rise to the level of meeting criteria for specific phobia but can contribute to impairment. For example, anxiety about eating food due to food textures, avoidance of clothing due to tactile sensitivity, or fear of loud objects such as vacuums and hairdryers due to noise sensitivity.

**Generalized anxiety.** Worry related to intense preoccupations, schedules, and environmental changes may be atypical features of anxiety that are important to recognize and ask patients about. Some of these features are captured by Kerns’s summation that they represent an “intolerance of uncertainty,” which can mark atypical anxiety in ASD.

Anxiety can present as perseverative questioning and reassurance seeking about an anticipated event or other worry. Repetitive questions used to obtain more information about a restricted interest should be distinguished from questions that are triggered by anxiety. People with ASD can have difficulty verbalizing internal states of anxiety or triggers for anxiety. For those who are non-communicative, an anxiety disorder may have to be considered by inference based on observation, such as persistent resistance to entering crowded rooms.

**Obsessive compulsive disorder.** Repetitive behaviors and restricted interests in ASD can be difficult to distinguish from the compulsions and obsessions of OCD. In OCD, obsessions are recurrent, intrusive thoughts that are distressing, and compulsive behaviors in OCD are bothersome, unwanted, and serve the function of attempting to alleviate the obsession.

Repetitive behaviors in ASD (e.g., lining up objects, following the same routine, watching the same video) are generally a preferred or comforting activity, although they can lead to problematic behaviors or irritability when the person is interrupted or needs to stop. In addition, the most common forms of compulsions in OCD: hand washing, cleaning, making things “just right” are distinct from the typical repetitive behaviors of ASD, such as hand flapping, body rocking, and finger flicking.

People with ASD can have difficulty articulating obsessive thoughts and describing whether a behavior is aimed at reducing anxiety. The ACI adapted the criteria for OCD to allow caregivers to infer the mental experiences of people who exhibit compulsive behaviors. For example, caregivers could be asked if a compulsive behavior appeared to be aimed at reducing anxiety or linked to recurrent thoughts. Using this criteria Leyfer and colleagues found that 37% of their sample met criteria of OCD. In a different study by Simonoff and colleagues, the assessment tool did not allow for caregivers to make this inference and the prevalence of OCD was estimated at 8.2%.

**Social anxiety.** Diagnosis of social anxiety in ASD requires that a person with ASD is avoiding social interaction due to a fear of potential negative outcome rather than just a lack of interest in social interaction, which is a common core feature of ASD. In older higher-functioning youth social anxiety can develop as awareness of differences from peers increases.

**Attention deficit-hyperactivity disorder**

ADHD is a common co-occurring condition with ASD and as such DSM-5 no longer prohibits ADHD to be diagnosed with ASD. Diagnosis of co-occurring ADHD can be challenging because symptoms of inattention, executive functioning problems, and social cognitive deficits are common in both conditions. It is important to distinguish features of inattention and impulsivity that may be inherent in ASD, such as distractibility related to a special interest, sensory seeking behaviors, or processing problems, from those that warrant an additional diagnosis of ADHD in children with ASD. The hyperactive-impulsive subtype of ADHD can also manifest in people with ASD and is best assessed in the context of the youth’s developmental age, expected activity level, and environmental demands.

**Depression**

Diagnosis of depression in neurotypical youth typically relies on self-report of mood symptoms such as feelings of sadness, hopelessness, or decreased self-esteem. Describing these internal states can be difficult for many people with ASD, particularly those with limited verbal skills. Magnuson and Constantino developed a framework for assessment of depression in ASD. For people with limited verbal skills or difficulties verbalizing feelings, increased self-injurious behavior, decreased self-care, labile moods, decreased interest in special interests, and regression of skills were observable behaviors associated with depression. For verbal youth with ASD, insight into ASD symptoms and their impact on functioning, awareness of being teased or being different from peers, social rejection, and low self-efficacy were risk factors for depression.

**Psychosis**

While their co-occurrence is uncommon, autism and psychosis have some symptom overlap, which can raise diagnostic questions. Pragmatic language deficits in ASD can include abrupt changes in topic, failure to provide context, and tangential comments, which can contribute to what appears to be a disorganized quality of language and thought process. When people with ASD are under stress they can have more disorganized and tangential speech, which is typically attributable to anxiety, problems with cognitive control, and pragmatic language deficits rather than underlying psychosis.

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**Lifetime prevalence of psychiatric disorders in children with autism**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>MDE (&gt;1 episode)</th>
<th>Schizophrenia, other</th>
<th>Social phobia</th>
<th>Specific phobia</th>
<th>Generalized anxiety</th>
<th>OCD</th>
<th>ADHD</th>
<th>ODD</th>
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<tbody>
<tr>
<td>MDE (major depressive episode)</td>
<td>10.1%</td>
<td>13.8%</td>
<td>0.0%</td>
<td>7.5%</td>
<td>32%</td>
<td>44.3%</td>
<td>30.6%</td>
<td>8.9%</td>
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<td>DSM-IV</td>
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<td>Subsyndromal</td>
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MDE, major depressive episode; ODD, oppositional defiant disorder.
Adhansia XR is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older.1

ARE YOU TREATING YOUR PATIENT’S FULL DAY?

In adults, Adhansia XR significantly improved attention vs. placebo, as measured by mean PERMP-T scores averaged across all time points up to 16 hours post-dose.1,2*

*Randomized, double-blind, placebo-controlled, crossover design, adult workplace environment (AWE) study of Adhansia XR in 45 adults (18-58 years) with ADHD. Primary Endpoint: Mean PERMP-T scores of Adhansia XR vs. placebo, averaged across all time points on the AWE days. PERMP-T=Permanent Product Measure of Performance Total score.1

Important Safety Information

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including Adhansia XR, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy.

Please see Additional Important Safety Information on the following page.
Please read Brief Summary of Full Prescribing Information on the following pages, including Boxed Warning.
Important Safety Information (cont'd)

CONTRAINDICATIONS
Adhansia XR is contraindicated in patients with a known hypersensitivity to methylphenidate or other components of Adhansia XR. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other methylphenidate products. Adhansia XR is also contraindicated in patients receiving concomitant treatment with monoamine oxidase inhibitors (MAOIs), and also within 14 days following discontinuation of treatment with a MAOI, because of the risk of hypertensive crisis.

WARNINGS AND PRECAUTIONS
Potential for Abuse and Dependence
CNS stimulants, including Adhansia XR, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy.

Serious Cardiovascular Events
Sudden death, stroke and myocardial infarction have occurred in adults treated with CNS stimulant treatment at recommended doses. Sudden death has occurred in pediatric patients with structural cardiac abnormalities and other serious cardiac problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during Adhansia XR treatment.

Blood Pressure and Heart Rate Increases
CNS stimulants cause an increase in blood pressure (mean increase approximately 2 to 4 mmHg) and heart rate (mean increase approximately 3 to 6 bpm). Individuals may have larger increases. Monitor all patients for hypertension and tachycardia.

Psychiatric Adverse Reactions
CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

CNS stimulants may induce a manic or mixed episode in patients. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression).

CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing Adhansia XR. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients, compared to 0% in placebo-treated patients.

Priapism
Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products, in both pediatric and adult patients. Priapism was not reported with drug initiation but has occurred during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

Peripheral Vascularopathy, including Raynaud’s Phenomenon
CNS stimulants, including Adhansia XR, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud’s phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud’s phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

Long-Term Suppression of Growth
CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients.

Careful follow-up of weight and height in pediatric patients ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated pediatric patients over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated pediatric patients (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including Adhansia XR. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Allergic-Type Reactions FD&C Yellow No. 5
Adhansia XR 45 mg capsules contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS
The most common (≥5% and twice the rate of placebo) adverse reactions occurring with Adhansia XR in adults are insomnia, dry mouth, and decreased appetite.

The most common (≥5% and twice the rate of placebo) adverse reactions occurring with Adhansia XR in pediatric patients are decreased appetite, insomnia, and weight decreased.

PREGNANCY EXPOSURE REGISTRY
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Adhansia XR during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychostimulants at 1-866-961-2388.

To report SUSPECTED ADVERSE REACTIONS, contact Purdue Pharma L.P. at 1-888-726-7535 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Please read Brief Summary of Full Prescribing Information on the following pages, including Boxed Warning.


For more information, visit AdhansiaXR-hcp.com
including Raynaud's phenomenon [see Warnings and Precautions (5.6)] - Long-term suppression of growth [see Warnings and Precautions (5.7)] - Allergic Reactions FDC® Yellow No.5 [see Warnings and Precautions (5.8)]. 

6. ADVERSE REACTIONS The following are discussed in more detail in other sections of the labeling:  

- Known hypersensitivity to methylphenidate or other components of ADHANSIA XR. 
- Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other methylphenidate products [see Adverse Reactions (6.2)]. 
- Receiving concomitant treatment with monoamine oxidase inhibitors (MAOIs), and also within 14 days following discontinuation of treatment with a MAOI, because of the risk of hypertensive crisis [see Drug Interactions (7.1)]. 

- Patients with a known hypersensitivity to methylphenidate or other ingredients of ADHANSIA XR. 
- Drug dependence [see Boxed Warning]. 

4. CONTRAINDICATIONS ADHANSIA XR is contraindicated in patients: • With a known hypersensitivity to methylphenidate or other components of ADHANSIA XR. 
- Hyperpyrexia 
- Other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy (see Warnings and Precautions [5.1], Drug Abuse and Dependence [9.2, 9.3]). 

5. WARNINGS AND PRECAUTIONS 5.1. Potential for Abuse and Dependence CNS stimulants, such as methylphenidate, have a high potential for abuse and dependence. Assessment of abuse potential is in at least part determined by the risk of abuse prior to prescribing, and monitoring for signs of abuse and dependence while on therapy (see Drug Abuse and Dependence [9.2, 9.3]). 

- Cardiovascular Events 
- Sudden death, stroke, and myocardial infarction have occurred in adults treated with CNS stimulant treatment at recommended doses. Sudden death has occurred in pediatric patients with structural cardiac abnormalities and other serious cardiac problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients known to have structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, coronary artery disease, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or unexplained cardiovascular signs and symptoms during treatment. CNS stimulants cause an increase in blood pressure (mean increase approximately 2 to 4 mmHg) and heart rate (mean increase approximately 3 to 6 bpm). Individuals may have larger increases. Monitor all patients for hypertension and tachycardia. 

- Psychiatric Adverse Reactions: Exacerbation of Pre-existing Psychiatric CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychiatric disorder. 

- Several days to weeks after first dosing. 

- Allergic-Type Reactions: FD&C Yellow No.5 are often subsequent to an increase in dose. 

- Priapism: Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products, in both pediatric and adult patients. 

- Peripheral Vasculopathy: CNS stimulants, including ADHANSIA XR, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. 

- Upper respiratory tract infection. 

- 2% of adults (12 to 17 years) treated with ADHANSIA XR had decreased appetite, nausea, and weight loss (mean difference approximately 2 to 4 kg for adult and pediatric populations). There were no deaths reported in this group. 

- 1 to 4% of adults treated with ADHANSIA XR had decreased appetite, nausea, and weight loss, with mean differences of approximately 1 to 2 kg and 1 to 2 cm for weight and height, respectively. 

- ADHANSIA XR was studied in adults (18 to 72 years) and pediatric patients (6 to 17 years) who met Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria for ADHD. The safety data for adults is based on two randomized, double-blind, placebo-controlled studies in doses of 25 mg to 80 mg per day. The tolerability of these patients exposed to ADHANSIA XR during 1-week long controlled treatment periods is 885, this included 434 adult patients and 449 pediatric patients (12 to 17 years), 93% (274) from two clinical trials in adults, one in pediatric patients ages 12 to 17 years, and one in pediatric patients ages 6 to 12 years [see Clinical Studies (14)]. 

- Adverse Reactions Leading to Discontinuation of Treatment in controlled adult trials for Study 1, 5% of both of ADHANSIA XR-treated patients and placebo-treated patients discontinued due to adverse reactions. In an adult workplace environment study (Study 2), 10% of ADHANSIA XR-treated patients discontinued due to adverse reactions compared to 0% of placebo-treated patients. The following adverse reactions led to discontinuation at a frequency of ≥1%: ADHANSIA XR-treated patients: nausea, bronchitis, gastrointestinal viral, viral infection, blood pressure increased, and hypomania. In a controlled trial (Study 3) in pediatric patients (12 to 17 years), 3% of ADHANSIA XR-treated patients discontinued due to adverse reactions compared to 0% placebo-treated patients. The most frequent adverse reactions leading to discontinuation in at least 1% of ADHANSIA XR-treated patients and at a rate greater than placebo was irritability (1%). Two patients taking ADHANSIA XR 70 or 85 mg had delirium leading to discontinuation. In a controlled trial (Study 4) in pediatric patients (6 to 12 years), 1% of ADHANSIA XR-treated patients discontinued due to adverse reactions compared to 0% of placebo-treated patients. Adult Patients with ADHD The most common adverse reactions (incidence of ≥1%) and at least twice placebo of ADHANSIA XR occurring in controlled trials in adults were insomnia, dry mouth, and decreased appetite. Table 1 lists the adverse reactions that occurred ≥2% of adult patients and greater than placebo among ADHANSIA XR-treated adult patients. 

- Pediatric Patients (12 to 17 years) with ADHD. The most common adverse reactions (incidence ≥5%) and at least twice placebo of ADHANSIA XR occurring in controlled trials in adults were insomnia, dry mouth, and decreased appetite. Table 1 lists the adverse reactions that occurred ≥2% of adult patients and greater than placebo among ADHANSIA XR-treated adult patients. 

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo</th>
<th>ADHANSIA XR</th>
<th>All doses ADHANSIA XR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=735</td>
<td>N=176</td>
<td>N=293</td>
<td>N=78</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4%</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Initial Insomnia</td>
<td>17%</td>
<td>11%</td>
<td>16%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>8%</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4%</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1%</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>4%</td>
<td>7%</td>
<td>15%</td>
</tr>
<tr>
<td>Feeling jittery</td>
<td>1%</td>
<td>3%</td>
<td>8%</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>3%</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0%</td>
<td>4%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Pediatric Patients (12 to 17 years) with ADHD. The most common adverse reaction (incidence ≥5%) and at least twice placebo of ADHANSIA XR occurring in controlled trials in adults were insomnia, dry mouth, and decreased appetite. Table 2 lists the adverse reactions that occurred ≥2% of pediatric patients (12 to 17 years) and greater than placebo among ADHANSIA XR-treated pediatric patients (12 to 17 years).
8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Pregnancy Exposure Registry. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADHANSIA XR during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychostimulants at 1-888-961-2388. Risk Summary. Published studies and post-marketing reports on methylphenidate use during pregnancy are insufficient to identify a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the fetus associated with the use of central nervous system (CNS) stimulants during pregnancy (see Clinical Considerations). No effects on morphological development were observed in embroyo-fetal studies with oral administration of methylphenidate to pregnant rats and rabbits during organogenesis. Doses up to 7 and 11 times, respectively, the maximum recommended human dose (MRHD) of 85 mg/day given to adolescents on a mg/m² basis. However, fetal spina bifida was observed in rabbits at a dose 36 times the MRHD given to adolescents. A decrease in pup body weight was observed in a pre- and post-natal development study with oral administration of methylphenidate to rats throughout pregnancy and lactation at doses 4 times the MRHD given to adolescents (see Data). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage among pregnancies is 2 to 4% and 16 to 20%, respectively. Clinical Considerations: Fetal/Neonatal Adverse Reactions. CNS stimulants, such as ADHANSIA XR, can cause vasoconstriction and therefore decrease placental perfusion. No fetal and/or neonatal adverse reactions have been reported with the use of therapeutic doses of methylphenidate during pregnancy. However, premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers. Data: Animal Data: In embryo-fetal development studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis. Malformations (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose which is approximately 36 times the maximum recommended human dose (MRHD) of 85 mg/day given to adolescents on a mg/m² basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (117 the MRHD given to adolescents on a mg/m² basis). There was no evidence of morphological development effects in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (7 times the MRHD given to adolescents on a mg/m² basis), which was also maternally toxic. The no effect level for embryo-fetal development in rabbits was 25 mg/kg/day (2 times the MRHD given to adolescents on a mg/m² basis). When methylphenidate was administered to rats through maternal inhalation in clitoral pregnancies, incidences of major birth defects and miscarriage were 2 to 4% and 16 to 20%, respectively. No effects on postnatal development were observed. The no effect level for pre- and postnatal development in rats was 15 mg/kg/day equivalent to the MRHD given to adolescents on a mg/m² basis.

8.2. Lactation

Risk Summary Limited published literature, based on breast milk sampling from five mothers, reports that methylphenidate is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.1 and 2.1. There are no reports of adverse effects on the breastfed infant and no effects on milk production. Long-term neurodevelopmental effects on infants from stimulant exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ADHANSIA XR and any potential adverse effects on the breastfed infant from ADHANSIA XR use. 8.3. Pediatric Use

Growth. Growth should be monitored during treatment with methylphenidate, including ADHANSIA XR. Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted (see Warnings and Precautions [5.7]). Juvenile Animal Toxicity Data: Rats treated with methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in spontaneous locomotor activity in adulthood. A deficit in acquisition of a specific learning task was observed in female only. The doses at which these findings were observed are at least 3 times the maximum recommended human dose (MRHD) of 85 mg/day given to children on a mg/m² basis. In the study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (postnatal day 7) and continuing through sexual maturity (postnatal week 10). When these animals were tested as adults (postnatal weeks 15-16), decreased spontaneous locomotor activity was observed in male and female previously treated with 50 mg/kg/day (approximately 3 times the MRHD of 85 mg/day given to children on a mg/m² basis) or greater, and a deficit in the acquisition of a specific learning task was observed in females exposed to the highest dose (6 times the MRHD given to children on a mg/m² basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (approximately 0.25 times the MRHD given to children on a mg/m² basis). The clinical significance of the long-term behavioral effects observed in rats is unknown. 8.5. Geriatric Use

ADHANSIA XR has not been studied in the patients over the age of 72 years.

9. DRUG ABUSE AND DEPENDENCE. 9.1. Controlled Substance

ADHANSIA XR contains methylphenidate, a Schedule II controlled substance. 9.2. Abuse

CNS stimulants including ADHANSIA XR are abused. Abuse includes the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving. Signs and symptoms of CNS stimulant abuse include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, suicidal or homicidal ideation have also been observed. Abusers of CNS stimulants may chew, snort, inject, or use other unapproved routes of administration which can result in overdose and death (see Overdosage [10]). To reduce the abuse of CNS stimulants including ADHANSIA XR, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants, monitor for signs of abuse while on therapy, and then consider the need for ADHANSIA XR use. Abuse is a state of dependence (after prolonged high-dose administration of CNS stimulants) which includes psychic and/or physical effects over time) may occur during chronic therapy with CNS stimulants including ADHANSIA XR. Dependence: Physical dependence (a state of adaptation manifested by a withdrawal syndrome precipitated by drug cessation, rapid dose reduction, or administration of an antagonist) can occur in patients treated with CNS stimulants including ADHANSIA XR. Withdrawal symptoms after abrupt cessation following prolonged high-dose administration of CNS stimulants include drowsiness, mood; depression, fatigue; vivid, unpleasant dreams, insomnia or hyperactivity, increased appetite, and psychomotor retardation or agitation.

10. OVERDOSAGE

10.1. Signs and Symptoms

Signs and symptoms of acute methylphenidate overdose, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: nausea, vomiting, diarrhea, restlessness, anxiety, agitation, tremors, hyperflexia, muscle twitching, convulsion (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, hypotension, tachypnea, mydriasis, dryness of mucous membranes, and rhabdomyolysis. 10.2. Management of Overdose

Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice on the management of overdose with methylphenidate. Provide supportive care, including close medical supervision and monitoring. Treatment should consist of general measures employed in the management of overdose with any drug. In the event of multiple drug overdosage, supportive and symptomatic measures. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures.

Healthcare professionals can telephone Adlon Therapeutics’ Medical Information Department (1-888-827-0618) for information on this product.
Psychiatric Disorders in Autism

Continued from page 15

Moreover, people with ASD may use idiosyncratic language or scripted phrases from favorite movies or songs that appear out of context to the listener and therefore may sound disorganized or delusional. Strong convictions and overvalued ideas about their special interests may seem delusional. Difficulties with theory of mind and understanding the intentions of others may lead to distrust and paranoia but are best understood as the downstream effects of ASD core deficits, rather than a co-occurring psychosis.

There are currently no validated measures for assessing psychosis in ASD. Taking a detailed developmental history is key to distinguishing features of these two conditions. When psychosis occurs in ASD, the onset of psychotic symptoms is typically in adolescence or early adulthood and is associated with a change in functioning from baseline. Symptoms such as restricted affect, repetitive behaviors, tendency to disorganize speech when under stress, self-talk, or magical thinking, which have been chronic and present from a young age are more likely to be consistent with ASD rather than psychosis.

When baseline restricted interests become more morbid, illogical, and delusional, it is important to recognize the benefit of early treatment and risk for life-threatening complications in severe cases. Diagnosis of catatonia in ASD can be challenging because echolalia, mutism, and stereotypic movements are common in both conditions.

Onset of catatonic symptoms in ASD may be gradual and in its early stages can present with a regression in self-care skills, reduction in speech, and difficulties initiating tasks. New onset of movement problems such as getting stuck part way through an action, difficulty initiating movements, immobility, increase in repetitive behaviors, difficulty crossing thresholds, and holding postures should raise suspicion for catatonia. Repetitive behaviors such as stereotypic movements and echolalia should not be counted toward a separate diagnosis of catatonia if they are consistent with an individual’s baseline symptoms of ASD.

Treatment considerations

Treatment of comorbid psychiatric conditions in ASD warrants a multimodal approach with contributions from caretaker education (applied behavioral analysis); psychotherapy; pharmacology; sensory, speech, and language interventions; and other disciplines depending on the individual’s history and presentation. Although a review of all of these modalities is beyond the scope of this article, some of the evidence and resources for CBT and pharmacotherapy for psychiatric comorbidity in ASD follow.

Cognitive behavioral therapy. CBT has been shown to reduce anxiety in children with ASD and anxiety disorders. Effective modifications to traditional CBT for youth with ASD have included increased parent involvement to promote generalization, incorporation of visual aids, making sessions highly structured and predictable, increased practice of skills, and explicit teaching of social skills as part of the therapy. Use of the child’s restricted interests can make the therapy more salient, help explain therapeutic concepts, create concrete metaphors, and reinforce participation.

ASD-specific CBT programs for anxiety include Multimodal Anxiety and Social Skills Intervention (MAS-SI), Face Your Fears, and Behavioral Interventions for Anxiety in Children With Autism (BIACA). Programs targeting executive functioning, mindfulness, and emotion regulation have also been found to reduce anxiety.

Pharmacological interventions. There are currently no medications for the core symptoms of ASD. Pharmacologic interventions for comorbid psychiatric conditions may help to alleviate associated symptoms and allow better engagement for the individual in educational and psychosocial treatments.

Targets for medication may include but are not limited to anxiety, impulsivity, hyperactivity, sleep problems, mood instability, depression, aggression, and self-injurious behavior. The American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameter on ASD provides a summary of randomized controlled trials of medication treatments for comorbid psychiatric conditions in ASD; the AACAP provides an overview of medication approaches by symptom area and guidelines for parent-provider discussion. Both are available for free download at www.aacap.org.

Dr Siegel is Vice President Medical Affairs, Developmental Disorders Service, Maine Behavioral Healthcare.

<table>
<thead>
<tr>
<th>TABLE 1. Disorder-specific assessment tools for psychiatric comorbidity in ASD</th>
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<tbody>
<tr>
<td>▶ Children’s Yale-Brown Obsessive Compulsive Scale (CY BOCS) – PDD</td>
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<tr>
<td>▶ Repetitive Behavior Interview</td>
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<tr>
<td>▶ Repetitive Behavior Questionnaire</td>
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<tr>
<td>▶ Parent-Rated Anxiety Scale for Youth with Autism Spectrum Disorder (PRAS-ASD)</td>
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<td>▶ ASD – Comorbidity for Adult Scale (ASD-CA)</td>
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<tr>
<td>▶ Anxiety Scale for Children with ASD (ASC-ASA)</td>
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<tr>
<td>▶ Anxiety Disorders Interview Schedule with Autism Spectrum Addendum (ADIS-ASA)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 2. Symptoms of ASD that overlap with symptoms of other conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms of ASD</td>
</tr>
<tr>
<td>Idiosyncratic speech</td>
</tr>
<tr>
<td>Scripted phrases out of context</td>
</tr>
<tr>
<td>Lack of social motivation</td>
</tr>
<tr>
<td>Repetitive behaviors</td>
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<tr>
<td>Restricted interests</td>
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References


Clinical Characteristics of Chronic Traumatic Encephalopathy

Arman Fesharaki-Zadeh, MD, PhD

Chronic traumatic encephalopathy (CTE) occurs as a result of repetitive mild traumatic brain injury (TBI) with a progressive neurodegenerative pathology. CTE was first identified as “punch drunk” syndrome by Marland in 1928, who reported severe neuropsychiatric symptoms in a group of boxers.

The disease process involves accumulation of phosphorylated tau (p-tau) in the sulci and peri-vascular region, with accompanying gliosis. CTE neuropathological progression is described in four stages. In stage I, there are few loci of p-tau in the sulci of lateral frontal cortices. The advancement of the disease involves areas of the brain including the temporal and parietal lobes as well as the insula. By stage IV, there is global spread of p-tau, as well as phosphorylated 43 kDa TAR DNA binding protein (TDP-43).

Clinical characteristics

Although there is no consensus on the clinical characteristics of CTE, McKee and colleagues’ proposed a set of clinical symptoms corresponding to each of four neuropathological stages.

Stage 1. A typical CTE patient is either clinically asymptomatic or may complain of mild short-term memory deficits, or depressive symptoms. Mild aggressive symptoms have also been reported.

Stage 2. Mood and behavioral symptoms are more severe and may include explosive behavioral outbursts and more severe depressive symptoms.

Stage 3. Patients typically display more cognitive deficits, ranging from memory loss to executive and visuospatial functioning deficits as well as symptoms of apathy.

Stage 4. Patients have profound language deficits, psychotic symptoms such as paranoia as well as motor deficits and parkinsonism.

Further attempts at clinical classification of CTE patients were made by Stern and colleagues. The researchers looked at 36 male patients with pathologically confirmed CTE, who did not have any comorbid neurodegenerative diseases; histories were provided by next of kin informants retrospectively. There were two distinct emergent clinical subgroups: the younger group initially presented with behavioral/ mood symptoms, while the older group presented with mainly cognitive symptoms. Cognitive deficits eventually developed in the younger group, whereas there were significantly less mood and behavioral symptoms in the older group as time went by. Furthermore, the younger group of patients were significantly more physically violent and behaviorally disinhibited. It is important to note that approximately one-quarter of these patients did not have memory symptoms. However, as the researchers noted, these two clinical subtypes may not be representative of the wider spectrum of all CTE patients.

In a more extensive study, Mez and colleagues examined 202 American football players; 177 of these players had a confirmed CTE diagnosis. The mean age at the time of death was 67 years; the mean number of years of playing football was 15.1. Study subjects were divided into mild and severe neuropathology groups. The vast majority from both groups suffered from behavioral and mood symptoms, as retrospectively reported by next of kin (96% vs 89% from severe CTE subgroup). Similarly, most of the patients in both groups had cognitive symptoms (85% in the mild subgroup vs 95% in the severe subgroup). Moreover, 33% of patients in the first group displayed signs of dementia compared with 85% of the second group who had signs of dementia.

Findings suggest an association between cumulative repetitive head impacts and the development of neurodegenerative symptoms including depression, behavioral dysregulation, executive functioning deficits, and cognitive impairment in adulthood. The age at the time of exposure to repetitive head impacts is another distinct risk factor for development of neurocognitive deficits in later adulthood.

Mechanism of CTE pathogenesis

Although there are no treatments for CTE, preclinical studies provide a promising avenue for studying the mechanism of CTE pathogenesis as well as exploring possible treatment regimens under controlled laboratory conditions. The exact mechanism by which repetitive head impacts lead to CTE remains to be fully described, but one proposed mechanism is immunologic conversion of these cells from a non-destructive phenotype to a destructive one.

The development of new neuroimaging techniques such as diffusion-weighted magnetic resonance imaging (MRI), as well as positron emission tomography (PET) using tau ligands are promising new modalities for understanding the clinical progression of the disease. Patients with CTE are typically in their 4th or 5th decade of life and can present with new-onset mood or anxiety symptoms, which typically later involve memory and cognitive deficits. The patient’s history is of paramount importance, since a typical patient would have suffered multiple prior concussive and subconcussive hits occurring in a variety of different settings including playing sports or in a combat setting.

The patient’s history is of paramount importance, since a typical patient would have suffered multiple prior concussive and subconcussive hits occurring in a variety of different settings.

CASE VIGNETTE

Bob is a 59-year-old with a history of multiple concussions who has been having a series of neurocognitive symptoms for the past several years. He describes himself as an ex-football player, who played in high school and college, and had more than 20 concussions. He lost consciousness a few times for unknown durations. Significant memory and cognitive issues developed about 4 years ago. He experienced symptoms of depression and began to drink excessively to cope with work-related frustrations. His wife reports that there were a few episodes of noticeable behavioral changes, including unusual emotional reactivity in certain everyday situations, such as a simple family-related discussion. She started to notice that Bob was having difficulties following instructions, and retaining details from conversations. Bob continues to drive on a regular basis, although he has had an episode of not being able to navigate. Bob’s wife has taken over the family finances. She describes her husband...
as previously being a sociable person but now avoids public settings.

In addition, according to his wife, Bob has become overly passive in certain situations. He had been a heavy drinker but stopped drinking about 8 months earlier and has remained sober. He manages his basic activity of daily living without difficulties, but at times he forgets to complete various routine tasks and needs reminders.

Bob’s medical history includes hypertension and depression, for which he takes 60-mg duloxetine daily. The overall results of his laboratory tests are normal although his gait is cautious and slow with mild shuffling, and he walks with a cane. His score on the Montreal Cognitive Assessment (MOCA) is 13/30 (normal score ≥26/30). Bob has significant deficits in free recall, executive functioning, attention, and abstraction. Bob is well-groomed and dressed appropriately. His mood is euthymic, and his affect is reactive and congruent to his mood. His thought process is mostly linear, coherent, and goal-directed. He denies any suicidal/homicidal ideations/intents/plans and does not endorse any auditory or visual hallucinations. His insight and judgment are limited to fair.

Brain imaging indicates cavum septum pellucidum (CSP) involving the lateral ventricles (Figure 1). There is also significant asymmetrical left hippocampal atrophy, 11th percentile compared with his age-matched controls (Figure 2).

Prevention

Based on the nature and popularity of contact sports and the intrinsic component of head collisions, prevention of head trauma poses a paramount challenge and requires a paradigm shift. Education of athletes on safe techniques, such as safe tackling, could offer significant potential benefits.

Cultural changes must include the creation of a “stigma free” environment, in which athletes are encouraged to responsibly report symptoms to coaches, referees, and team physicians. This in turn would create opportunities for timely assessment, diagnosis, and symptom-based treatment. It is imperative for team physicians to intervene in cases in which athletes are prematurely encouraged to return to play in spite of persistent neuropsychiatric deficits. Such athletes are especially vulnerable to repetitive head impacts and new onset chronic neuropsychiatric symptoms.

Conclusion

CTE is increasingly entering the public discourse via mass media. The increasing number of younger retired athletes with CTE is especially alarming. Another population that is especially vulnerable to CTE are war veterans. There is a great deal of complexity regarding the possible etiology of CTE in this population. The rate of mild (m)TBI is exceedingly high, and it is highly comorbid with PTSD. Moreover, multiple mTBIs can increase the risk for PTSD progression adding to the complexity of their clinical interaction.

Omalu and colleagues11 reported a case of an Iraqi war veteran with a history of PTSD but no history TBI, whose brain showed characteristic signs of CTE upon postmortem neuropathological examination. However, it is unclear whether PTSD alone is an independent risk factor for CTE development. As the CTE clinical characterization continues to evolve, it is imperative to exercise vigilance. This is exceedingly important given the degree of symptom overlap between affective symptoms of CTE and other neuropsychiatric disorders (eg, PTSD, behavioral variant frontotemporal dementia).

The collective awareness of this devastating neurodegenerative disease will likely result in intensifying efforts to improve our understanding of disease pathology as well as exploring potentially a promising therapeutic regimen.

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References

Psychopathology of Tinnitus

Zeina Chemali, MD, MPH, and Romy Nehme, MD

Tinnitus is the perception of noise in the absence of any corresponding sound source. Physicians and patients tend to immediately assume that this disorder is mainly localized at the level of the auditory system. In the case of idiopathic tinnitus, patients are told that there is no treatment and they just need to “learn to live with it.” The aim of this article is to show that tinnitus is secondary to an aberrant brain circuitry affected by disorders such as mood, anxiety, and alcohol and substance abuse as well as executive dysfunction, migraine, sleep and stress. By treating these comorbidities, tinnitus tends to improve.

CASE VIGNETTE

A 55-year-old man (MR) presents with bilateral tinnitus and high-frequency sensorineural hearing loss. MR has a complex developmental history including global developmental delay, traumatic brain injury at the age of 5, and dyslexia diagnosed at age 16. MR works part-time as a train operator and is exposed to high levels of acoustic trauma. His brain MRI scan reveals an incidental finding of volume loss within the bilateral parietal lobes. He denies any significant decline in cognitive functioning. However, in the context of a language-based learning disability, he continues to struggle with several aspects of language, including problems with articulation, reading, writing, and spelling, consistent with his baseline.

MR reports no difficulty carrying out his job responsibilities and is fully independent for all activities of daily living. His mental status is consistent with expectations for an individual with a language-based learning disability, including deficits across several aspects of language. He also exhibits select weakness in aspects of the executive domain that overlaps heavily with language functions, including sequencing, word generation, and retrieval of unstructured verbal information.

The causes of his difficulties, although likely neurodevelopmental, were exacerbated by additional salient factors, such as tinnitus that in turn is directly related to and worsened by a lack of restorative sleep due to sleep apnea and a split shift work schedule, as well as a history of alcohol use. The goal of the evaluation and management of this patient was to treat his comorbid conditions, decreasing his perception of tinnitus. It was recommended that he use ear protection, wear sound cancellation devices, and taper off alcohol. He receives mindfulness training and cognitive behavioral therapy for dyslexia and attentional difficulties. A low dose of sertraline is started for anxiety and melatonin and continuous positive airway pressure (CPAP) for sleep regulation.

Epidemiology

Tinnitus is described as ringing, roaring, hissing, or pulsatile. It is classified as subjective and objective. Objective tinnitus is very rare and consists of a sound heard by both the patient and the physician such as arterial bruits, venous humps, and palatal and stapedial myoclonus. Subjective tinnitus is the most common and is only appreciated by the patient. It affects 50 million people in the US. About 5-2% of 2% of people request urgent medical assistance either for acute unbearable tinnitus or for chronic tinnitus that worsened suddenly. The number one culprit of tinnitus is hearing loss.

Causes and differential diagnosis of tinnitus

There is no standard diagnostic criterion for tinnitus. Self-report is the base for determining tinnitus presence. In a subset of psychiatric patients (eg, with schizophrenia) tinnitus may be confused with auditory hallucinations.

The causes of tinnitus could be peripheral or central. Peripheral causes usually involve cochlear pathologies associated with hearing loss (eg, noise-induced hearing loss or Meniere disease), acoustic neuroma or vestibular nerve damage due to infection, an autoimmune disorder, or diabetes. Central causes of tinnitus include stroke, demyelinating lesions, traumatic brain injury, and arteriovenous malformations. Other causes of tinnitus include the use of ototoxic drugs and neck trauma.

Pathophysiologically, tinnitus is understood as the result of an adaptive mechanism to a diminished input: when the neural output stemming from the cochlea is weakened, the auditory system automatically compensates the loss by augmenting its gain. In such situations, tinnitus is compared to that of phantom limb pain. Indeed, a strong positive correlation between the amount of cortical reorganization and the subjective strength of tinnitus was found in a study by Muhlnickel and colleagues. Other theories have also been described that are non-adaptive in nature and connect tinnitus to the somatosensory system or the hypothalamic-pituitary axis, specifically cortisol.

Interestingly in tinnitus, many brain areas are affected beyond the auditory system and pathway. In fact, electrophysiological data show that various electroencephalogram (EEG) abnormalities involving different brain areas are associated with tinnitus. Particularly, quantitative EEG showed unilateral localized focus of high frequency activity over the temporal lobe auditory cortex in tinnitus patients.

Other areas involved in tinnitus include the anterior cingulate cortex, dorsal lateral prefrontal cortex, insula, supplementary motor area, orbitofrontal cortex, parahippocampus, posterior cingulate cortex, and the precuneus.

Imaging studies also showed involvement of certain regions including auditory structures (auditory brain stem, medial geniculate nucleus, primary and secondary auditory cortex and temporo-parietal association areas) as well as cortical and subcortical areas found on positron emission tomography (PET) scan and functional MRI (amygdala, hippocampus, anterior cingulate, and orbitofrontal cortex). Comorbid psychiatric symptoms and syndromes

Alcohol consumption has been described as a risk factor for tinnitus; however, most results have not been significant. There is very limited literature on the relationship between tinnitus and substance use, and most results are inconclusive. However, it is still recommended that patients abstain from substance use including alcohol and tobacco because of their negative effects on overall health.

Impact on quality of life/level of distress

The Tinnitus Handicap Inventory (THI) is a good tool to assess the impact of tinnitus on quality of life and patients’ progress. Patients with tinnitus appear to have poorer quality of life compared with people who do not have tinnitus, notably in those with disabling hearing loss. Reported consequences include anxiety, concentration difficulties, depression, and irritability.

Similarly, reducing tinnitus intensity has a direct impact on the improvement in patients’ quality of life. It is interesting to note that children’s quality of life is affected less by tin-
Acoustic simulation during sleep has shown effectiveness over placebo.10 It could be that children exhibit depression and anxiety or insomnia and substance abuse as well as insomnia and stress, sleep, and trauma. Nonpharmacological treatment is the most studied approach to decrease the perception of tinnitus and improve the patient’s quality of life.12

Other interventions. Patients who received acupuncture treatments reported benefit compared with the control group that received sham treatment with fake needles.11 When the tinnitus is associated with sensorineural hearing loss, especially if unilateral, cochlear implantation may be indicated. Both low frequency and high frequency repetitive transcranical magnetic stimulation to the auditory cortex was studied in patients with tinnitus and showed promising results. Other areas studied are the frontal and parietal regions, as well as the dorsal cochlear nucleus, the inferior colliculus, and the medial geniculate body of the thalamus.16 Epidural stimulation has been shown to be safe and effective in small trials.17 Deep brain stimulation, although not used specifically for tinnitus but rather for other approved indications (eg, movement disorders) has shown benefit in patients who have comorbid tinnitus.18

Conclusions. We currently know that tinnitus is an aberrant brain–ear circuitry. The workup consists of a thorough history and physical exam including a cognitive assessment. Urgent referrals should be made when tinnitus is pulsatile or associated with neural deficits (facial weakness or paralyzis), unexplained sudden hearing loss, vestibular symptoms, or otalgia and drainage. In the case of tinnitus without the symptoms described above, other comorbidities such as psychiatric symptoms, stress, sleep, and trauma should be assessed and treated. There is no single treatment for tinnitus, and the goal is to target associated distress with CBT to decrease the perception of tinnitus and improve the patient’s quality of life.

References
Polypharmacy: A Challenge for Community Psychiatrists

The pharmacological management of psychiatric disorders has been revolutionized since chlorpromazine became available in 1955. Newer psychotropics have added years to the life of people suffering with mental illness, and they have enhanced the quality of life for patients. Psychopharmacology is responsible for the reduction in duration of inpatient care, and it has helped to provide recovery to millions of patients discriminated against because of the stigma of mental disorders. However, polypharmacy has been met with challenges because many practicing clinical guidelines and treatment algorithms prefer a monotherapy approach.

The challenge of polypharmacy is not only in clinical practice but also in the evidence for its effects. Polypharmacy in psychiatry is often a clinical need that reflects a clinician’s frustration. The main indication of polypharmacy remains nonresponse to monotherapy and persistent symptoms. These symptoms are seen in the domain of persistent positive, negative, cognitive, affective, or anxiety/phobias.

The prescribing of polypharmacy continues despite the evidence that monotherapy often works and non-drug therapies may be preferred options. Psychosocial interventions are seldom used because they are not easily accessible, and such limitations make it necessary to prescribe more medication in a hope to obtain symptom remission. In the presence of clear clinical evidence of serious adverse effects due to multiple medications, one argument in decision making is the effectiveness of polypharmacy in improving the outcomes for patients.1

When using polypharmacy, it is important to address adherence issues and to educate patients and their families. In doing so, medication dosages, the possible adverse effects of the medications, and drug-drug interactions are explained. Despite all the difficulties and complexities associated with polypharmacy, there has been an exponential rise in its use (based on clinical communication and experience sharing with colleagues). The primary reason for this is the advent of psychopharmacology that is receptor specific-based rather than a disorder-based medication.2

Although polypharmacy is often used in the management of psychiatric disorders, there is very poor awareness of its efficacy. In some situations, polypharmacy also lacks respect and acceptability. This arises out of the fact that most reputed textbooks and clinical guidelines advocate monotherapy and a single drug at high doses rather than clinical practice scenario where multiple drugs targeted at specific symptoms are prescribed.

There is a need for polypharmacy that is rational and judicious. Despite its limitations and lack of consensus, polypharmacy does improve overall outcomes for patients.3 The National Association of State Mental Health Programme Directors (NASMHPD) provides classification of polypharmacy (Table 1).4

Is there evidence to substantiate polypharmacy?

One of the major failings of polypharmacy is the lack of randomized controlled trials and an evidence base that can help clinicians decide what combinations and medications will work for psychiatry. Many reviews of polypharmacy look at drug combinations that are used in the treatment of schizophrenia and depression.4 Certain combinations are mentioned; however, none has been found to be superior to another. Moreover, because there are huge differences in prescribing styles among clinicians, there are many variations in the combinations of drugs prescribed. It is often concluded that polypharmacy is more calculated scientific guesswork than evidence-based treatment.4

It is important to remember that each prescribed drug has clear indications, has well-defined therapeutic goals, and as far as possible is evidence based. Clinicians need to evaluate whether polypharmacy enhances clinical outcomes or whether it promotes adverse effects. This is even more important when patients already on polypharmacy are shifted to a new combination of drugs and when patients are shifted from monotherapy to polypharmacy.4

The STAR*D and CATIE trials have focused on combination therapy but despite elaborate methodology and painstaking research, they have failed to elucidate what drug combination works in either depression or schizophrenia.5,6 Most of the combinations used in polypharmacy are based on the clinical judgment and experience of the treating psychiatrist and their experience with individual patients rather than clinical studies.

This raises several questions about prescribing patterns. Despite strict guidelines about clozapine, its use remains fairly complex in many countries. Was clozapine alone responsible for seizures or was this an additive effect of the various drugs prescribed with clozapine? Would clozapine do better as monotherapy of 300 to 400 mg with a response of 60% to 70% compared with polypharmacy that showed an improvement of 90% but may have additively caused seizures? Emergency physicians may not be aware of the adverse effects of psychiatric drugs, and in this case no serum clozapine levels were checked to determine whether clozapine toxicity resulted in the seizures. Polypharmacy, while viable in improving the quality of life, may have additive adverse effects that may go undetected when the patient presents to the emergency department.

Does polypharmacy enhance clinical outcomes?

Polypharmacy is paramount when treating comorbid psychiatric disorders (eg, depression and panic disorder; ADHD and enuresis).3,6 In polypharmacy we may use multiple drugs prescribed at lower to normal doses rather than one drug at a higher dose. Various

CASE VIGNETTE

Mr VD, aged 40 years, has a diagnosis of schizophrenia. He is being treated daily with 15-mg olanzapine in divided doses, 30-mg mirtazapine at night, and 300-mg clozapine at night. He also receives 10-mg zolpidem because of sleep disturbances. He was treated in the past with risperidone and haloperidol, but the drugs had to be withdrawn because of extrapyramidal reactions when he was initially started on these drugs. During his last relapse, Mr VD received clozapine during his inpatient stay. He had a 90% improvement in symptoms with clozapine.

After drinking alcohol at a family function, he became drowsy and started convulsing. He was taken to a nearby hospital and admitted in an intensive care unit; he died later that night due to seizure-related complications. The emergency physician was unable to ascertain which medication may have caused the seizures. The hospital did not have the facility for clozapine monitoring, and patient records were not available.

CONTINUED ON PAGE 35
Before Personality: Character Assessment and Its Troubled History

Greg Eghigian, PhD

The 20th century introduced a number of new concepts to psychiatry and clinical psychology. One of the most influential has been the notion of personality. Carl Jung, Gordon Allport, Abraham Maslow, Harry Stack Sullivan, and Carl Rogers are just a few of the early figures who, starting in the 1920s, developed theories and models designed to capture the inner core of human subjectivity (or the “self,” as Rogers put it). But while their names and ideas continue to resonate, time has proven less kind to another psychological project that played out at the same time. This was characterology.

Coined in 1867 by Julius Bahnse, a student of the philosopher Arthur Schopenhauer, characterology was associated primarily with Germany. It is there that it began to take hold and thrive, with the founding of the field’s two major journals in the mid-1920s: Jahrbuch für Charakterologie (Yearbook for Characterology) and Zeitschrift für Menschenkunde (Journal for Human Studies).

Characterology emerged as a type of character analysis following along the lines of the clinical assessment of functional disorders in the 19th century. This was an assessment that involved examining a patient for outward signs indicating a psychopathology or at least a proclivity toward some pathological state of mind. The approach was beholden in no small measure to the work of the France-based psychiatrist Bénédict Morel (1809–1873), whose theory of degeneration held that at least a proclivity toward some pathology of the mind was characteristic of the human character. This was an assessment that in time. This was characterology.

In Germany, characterology’s star began rising in the 1920s and 1930s, when industry and the public sector began seeing the value in applied psychology, with the founding of the Council on Intercultural Affairs and the assimilation of minorities in the 1950s and early 1960s. But times were changing. As West German researchers and clinicians increasingly turned to the US for inspiration, they found themselves drawn to “trait-and-factor” methods instead. The idea was no longer to uncover supposedly fixed character traits, but rather to identify the general aptitudes, adaptabilities, and interests of a person. As a result, a more dynamic and developmental concept of “personality” replaced “character” in academic and professional circles.

Dr Eghigian is Professor of History, Penn State University.

References
The Disabled Employee’s Manager
A Common Complicating Factor of Workplace Disability

Barbara Long, MD, PhD, Andrew O. Brown, MD, Sean Sassano-Higgins, MD, and David "Daven" E. Morrison, MD, for the Committee on Work and Organizations, Group for the Advancement of Psychiatry

One of the most perplexing challenges for psychiatrists who interact with the workplace is the competing forces for and against mental health. As previously argued, work is of paramount importance for the mental health of any person, especially an adult. Building off of what we have argued to this point, the intersection of work, health, the patient, and the doctor becomes decoupled as disability is considered. If returning to work is not thoughtfully planned for, the whole delicate web can fall apart.

We are a group of psychiatric professionals whose work varies. At times we are focused 100% on clinical, other times we are 100% focused on the work environment, and much of the time we are focused on the intersection. This Psychiatric Times exploration of work and disability focuses on the challenges of the workplace manager, the employee with whom there is a conflict related to performance, and the psychiatrist who is tasked with the challenge to determine disability.

For many of the cases we see there is a great deal of ambiguity or gray space. There are some cases where there is clear evidence of the onset of a mental illness independent of workplace dynamics, yet in many others there is not. As in all systems, there is a critical balance to find between what is pathological and what is supporting mental health.

How might the psychiatrist support mental health at work?
To the workplace organization, the mental health system seems fraught with traps to undermine productivity: decreased production, lost hours, and distracted and “on edge” supervisors all tracking back to performance issues of employees. For managers, the role becomes confusing and even frustrating. They most likely do not know what “toxic” means, much less how to handle “periods of irritability, down moods,” or how to grant “occasional time to be away from work.”

Many managers are not trained in the various regulations such as the Family and Medical Leave Act (FMLA), and they can be particularly perplexed by options for dealing with employees who are distressed to the point of distraction and deteriorating performance. In fact, although not always written explicitly, the manager feels incompetent because the psychiatrist or the plan generated by the Employee Assistance Program (EAP) carries with it many implicit requests “to be a therapist.”

On the psychiatrist’s side of things, the doctor is at risk of unspoken feelings of incompetence as well. Physicians are trained to be knowledgeable and confident in their point of view, and a treatment plan is the foundation of this training. Yet, most psychiatrists are quickly out of synch with the workplace as it relates to disability.

Here is an abbreviated list of why psychiatrists can also feel incompetent:

1. They have not been trained to see the workplace from the managers’ point of view.
2. They do not know how to analyze a system like a workplace or a work environment that can include interacting internationally or virtually, and to decide who is responsible for what aspect of the work flow.
3. The terms toxic, stress, and even PTSD are often used imprecisely in the workplace without the discipline or clarity typically used in medical assessments and treatment plans.
4. Their allotted time with patients is shrinking.
5. The expertise on the Internet to pursue disability is large and growing every day creating an asymmetric knowledge for the doctor compared with the employee.
6. Most psychiatrists do not understand effective and ineffective performance management systems or competent leaders of healthy workplace cultures.

In our preliminary survey-based research, “Psychiatry of Workplace Dysfunction—Tools for Mental Health Professionals, Managers, and Employees,” the findings indicate that psychiatrists generally feel incompetent addressing common psychiatric challenges to the workplace, such as how to compose a thoughtful return to work plan. Moreover, the survey findings suggest that residency training directors feel unprepared to design curricula that cover these shortfalls.

In the end, the patient’s anxiety about returning to work combined with direction from family, friends, or the Internet has the potential to cause the patient to single-mindedly pursue disability. The powerful emotional affects generated in the sessions about returning to work overwhelm the treating doctor and the worker patient.

The compounding forces to pursue disability create demands on the patient and on the psychiatrist. This combined with the distress of an overwhelmed manager leads to an adversarial and misaligned system that rapidly escalates. Thus, ironically the employee, psychiatrist, and manager all play a role in the decline of the overall mental health of patients. Specifically, it harms the ability of the patient and the manager to learn how to resolve conflict.

This is not new. Our committee has explored this dynamic for over 40 years with the original position paper, “What Price Compensation.”

Long absences from work make it difficult to return to work, for a number of reasons:

- The anxiety associated with being accepted back into the group
- The unconscious tendency of the group to exclude fellow members during their absence
- The concern about being able to perform one’s duties at excellent levels
- The effect of injury on one’s self-esteem during the period of “doing nothing and not contributing”

There is a missing piece that can help the manager, the psychiatrist, and the employee find common ground: a pathway to returning to work while managing mental illness and its sequela. Our larger mission is to support both the managers at work as well as psychiatrists with their patients to understand the forces leading to mental health.

In the previous article in our series on disability we highlighted the need to address the concept of functional assessment. It is important to note, however, that because symptoms are subjective, functional assessments don’t always provide a true picture of the patient’s disability. If the patient is being coached on how to respond to assessments, the problems affecting the doctor-patient and/or the employee-manager relationships are worsened. Psychiatrists must work with the patient to improve functioning gradually, paralleling the return to work plans that are regularly used by other medical practitioners (eg, orthopedists). The goal is to avoid permanently eliminating work from patients’ lives.

Dr Long is Committee Chair, Work and Disability Consultant Private Industry, the Courts, and the Legal Profession; Dr Brown is Department Psychiatrist, Boston Police Department, Consulting Psychiatrist, Boston Fire Department, Work and Disability Consultant, Private Industry and Government; Dr Sassano-Higgins is Adjunct Professor, Department of Psychiatry, University of Southern California; Dr Morrison is Clinical Assistant Professor of Psychiatry and Behavioral Sciences, Chicago Medical School.

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Opioid Use in Pregnancy Affects Offspring Across Their Lifespan

Laurie Martin

Children exposed to opioids in utero are at significant risk for health problems, including preterm birth, neurodevelopmental issues in infancy, and psychological and medical issues in childhood, according to a study published in JAMA Network Open. Azuine and colleagues sought to determine risk factors for women who used opioids in pregnancy and found significant short- and long-term health consequences that may include emotional issues as well as conduct disorder and ADHD.

To investigate the issue, researchers looked at 8509 mother-newborn pairs from the Boston Birth Cohort (BBC), a large sample of an urban, low-income population from its inception in 1998. The cohort followed 3153 children throughout their lives until aged 21 years. Mothers’ self-reports and/or electronic health records determined that 454 (5.3%) children had in utero opioid exposure or neonatal abstinence syndrome (NAS). The researchers defined in utero exposure as “opioid use or a clinical diagnosis of neonatal abstinence syndrome for a child.”

The magnitude of poor health outcomes associated with in utero opioid exposure underscores the need for psychiatrists to look out for women at risk for opioid exposure. “The short- and long-term outcomes associated with opioid exposure are too dire to ignore. . . . We must act now. All hands must be on deck, and psychiatrists can be the leaders on this.”

Insights for psychiatrists

Although study authors do not make clinical recommendations per se, Dr Azuine notes that psychiatrists play a critical role in the screening, diagnosis, and treatment of substance use disorders and addiction. He also states that the findings have two key implications for psychiatrists.

Screening and treatment: The consequences of opioid exposure cut across the life span of women and their children. “Screening and treatment for opioid use disorder should be delivered within the context of the life course identifying and treating women before they become pregnant, when they are pregnant, and after they have had their babies. Health care providers must use every window of opportunity to prevent the harm of opioid use and exposure among mothers and children.”

The implications of the study as it relates to psychiatric treatment are to continue to provide compassionate care within a safe environment. “We found that there were sociodemographic risk factors for opioid exposure. Psychiatrists should consider these social and environmental factors when they see pregnant mothers suspected with opioid use disorders.”

Future studies should consider other factors outside the scope of this research that found patients who abuse opioids may also gravitate to other drugs (eg, marijuana, stimulants, alcohol, tobacco). “This tells us that there is probably no single substance of addiction,” said Dr Azuine.

References

Richard M. Berlin, MD

At a performance of Ravel’s “Piano Concerto for the Left Hand,” commissioned by Austrian pianist Paul Wittgenstein Who lost his right arm during World War I.

The moment the maestro flicks his baton, an orchestra thunders and the pianist suffers a stroke. But everyone plays on while we watch his left hand glissando the keyboard with so much force his thumb sprays blood.

I close my eyes to turn off the sight of his right hemiplegia, only to picture lesions on MRIs and clots busted with tPA. I crush my impulse to call 9-1-1 and lock in to 88 keys stroked by five fingers, confused by the illusion I hear the thunder of ten.

And when I let myself look again, half a man nails the climax, then vaults to his feet, cuff stained crimson, both palms held to his heart, the audience in tears, standing with “Bravos” for the soloist, for the thrust of Ravel’s impossible score, and for Wittgenstein’s first proof that a man can gather all the world’s notes in one hand and play them with the power of two.

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Making Your Practice Work for You

ASSUMPTIONS THAT MAY BE HOLDING YOU BACK

- There aren’t enough psychiatrists, I have to do it all
- Patients need me to work crazy hours
- To pay the bills I have to see [fill in the ridiculous number here] patients every week
- I don’t have anything to say to the world
- I don’t have to do any marketing, since psychiatrists are in demand
- I went into medicine, not business, learning about marketing, business, and technology won’t help me as much as doing clinical work
- I can do it best, so I should do almost everything

1. What would your perfect week look like? How much time would you have to work-out, meditate, and enjoy social activities? What time would you start/end work to have the healthiest family and social life? How much sleep would you get?

2. What experiment could you do to test a change in your assumptions? For example, could you block out Thursday afternoons for golf, commit to being home for dinner four out of five days, or drop off your kids at school every day? What if you tried it for a month or 3 months?

3. Then examine what fell apart during the experiment? An experiment like this will point out the systems and opportunities for change. For example, maybe you need to schedule a different on-call routine. Or maybe an assistant needs additional training on prescription refills.

Highly educated individuals often have a very concrete view of the world. There may be an assumption that if you start a new system, you will have to do it that way forever. But successful business people understand that you can always change and adapt. If, after a month, it is impossible to have dinner with the family four nights a week, change the systems or the experiment.

Examining strengths and productivity

Many psychiatrists get on the treadmill of seeing patients, keeping up with records, and putting out fires in their practice. In doing so, it is easy to miss the redundancies and inefficiencies in their practice. For example, if a front desk staff member needs to type a date every time a patient is billed after the appointment, what’s the one thing you can do such that by doing it everything else will be easier or unnecessary?

 Whether it’s an email, meeting, or denied insurance claim, tasks suck time and energy from you. Most of the time it is unnecessary. Even worse, it stops you from putting time into the ideas that could genuinely have an impact on the world, make your schedule easier, and create space to innovate. By asking, “What’s the very best use of my time?” you can clearly identify what you need to outsource to an assistant or virtual assistant.

Better than a new best friend— the virtual assistant

What is a virtual assistant? A virtual assistant (VA) does not physically work in your office. This could be a medical biller who lives in Houston, a scheduler who answers live but lives in Florida, or a graphic designer in South Africa. So, why hire a virtual assistant?

The clearest reason to hire someone virtually is that you save money. You don’t have to find a space for them. VAs typically have their own tools, like a computer and phone. Also, most VAs are paid by the project or only for time when they work. So, you’re not paying for someone to sit in an office for 40 hours a week. Instead, they may be in a shared workspace, a home office, or sitting at their dining room table. A typical private practice might have a four office suite with a reception area. If this were automated, the VA might answer phones, onboard new patients before their appointment.
and schedule additional appointments virtually. If that additional space is used, that could save 20% to 30% on rent. Then add the productivity side as well and that 40-hour week may only be 25 hours.

Before we go too far down this path, there are obvious objections:

- How do I know they are following HIPAA?
- What is the liability?
- Is it legal?
- What does the code of ethics say about this?

I’m not an attorney and as a rule you should never take legal advice solely on one article you read. Each state and city has its own laws, rules, and boards that may have a say in this, so consult an attorney on your model and contracts. Legal best practices abound for this. Something as simple as a Business Associate Agreement can outline the limits of HIPAA, disclosure to patients, and methods to ensure legal and ethical confidentiality. Assuming the legal and ethical side has been covered, how do you start outsourcing to take tasks off your plate?

In his book, *Virtual Freedom*, Chris Ducker outlines an exercise that is helpful. Take out a sheet of paper and make three columns:

- Don’t Like Doing
- Can’t Do
- Shouldn’t Do

In this activity, you identify tasks in your day that you don’t like doing, can’t do, or shouldn’t do. These are all opportunities to outsource work to another individual.

What types of tasks are private practices outsourcing? Here is a list of the most frequently outsourced tasks in a private practice:

- In-coming phone calls, reminder calls, and scheduling
- Insurance billing
- Social media marketing
- Maintenance of electronic health records
- Website updates
- Delivery of office supplies, water, or beverages for patients
- Monitoring and responding to emails
- Resource and video editing
- Case management and ancillary services
- Electronic prescription delivery
- Accepting and processing payment immediately

**Taking it to the next level: growing beyond your practice**

The opportunities for psychiatrists are immense if you can challenge the typical model. For example, numerous private practices have worked to grow billable services outside of the clinician’s hours. Here are some questions that allow you to identify key opportunities for your practice:

1. What other services are your patients already paying for (eg, mental health counseling, massage, acupuncture, health coaching)?
2. What lifestyle choices do you wish your patients would make (eg, increased exercise, changes in nutrition, improved sleep)?
3. What specialties could be developed that are needed in your community (eg, more focused work on trauma, EMDR, support groups)?

By collaborating with an assistant, it is possible to grow and scale your practice beyond your own time. The following example may be helpful.

Dr Matthews sees 50 patients per week. She focuses on teens with emerging mental health issues. However, several of the parents have requested to start seeing her. She has noticed an increase of mental health issues around anxiety and depression. She knows she can’t see more people because she has designed her schedule to accommodate her personal life. However, she doesn’t want to miss this opportunity.

She asks her assistant to design a survey for each patient to complete while waiting for their appointments. The survey has three main questions:

- What services are you currently using outside of our office that support your mental health (please include services you plan to use in the next 6 months such as mental health counseling, massage, or other mental health support services)?
- What services do you wish we offered here?
- How would your life be different if we offered these services here?

Based on this survey Dr Matthews discovers that her current patients would like to have mental health counseling and support groups to assist with psychiatric medication reviews. Over the next 6 months, Dr. Matthews hires two Master-level clinicians to run groups and offer counseling 10 hours per week. She also hires a virtual assistant through MoveForwardVirtualAssistants.com and a medical billing company to help manage patient calendars. Here’s what happens:

1. Each clinician does 8 individual or family sessions per week with an average reimbursement of $92 per session. $1472 per week x 4 weeks = $5888
2. Her new biller charges 5% collected: $294.40
3. Her new virtual assistant does scheduling and is paid when working. The cost is $395 per month through the company.
4. Dr Matthews optimizes her own office so that current space is used for the sessions, that way they occur in the evenings or on weekends, when she’s not in the office. No additional rent.

Dr Matthews makes an additional $5,888 gross minus the $689 administrative expenses to equal $5,199 per month or $62,388 gross annually. She compensates that master-level clinicians at 40%, which increases overall expenses by $24,955.20. This gives Dr Mathews an annual net profit of $37,432.80.

In the start-up phase, Dr Matthews had additional costs such as her attorney, accountant, and legal forms. As well, there might be additional costs such as a new EMR like Therapy Notes or additional phone lines or email. Dr Matthews also had to check state employment law to determine if the clinicians should receive 1099 or W2 forms. But you get the point. This is one example of how simply a practice can begin to shift beyond the face-to-face income earned by a psychiatrist.

**Moving forward to endless possibilities**

By releasing old assumptions and brainstorming, it is possible to break the old models of private practice and find new ways to be productive within your practice. The creativity and flexibility of virtual assistants and real assistants can help relieve burnout, increase happiness and fulfillment, and increase your income. Just imagine what your practice might look like if you fully optimized your time and thought about how to make an impact on the world beyond the walls of your practice.

Mr Sanok is the Founder of Practice of the Practice. He is a TEDx speaker, business consultant, and has the No. 1 podcast for private practices, The Practice of the Practice Podcast. Joe is passionate about helping practice owners to optimize their practices and launch big ideas, all within the context of designing their lifestyle. He offers the one-week intensive for practice owners, Slow Down School, and has numerous resources on his website. To schedule a time to talk with him go to www.PracticeofthePractice.com/apply.

Dr Sanok reports no conflicts of interest concerning the subject matter of this article.
Emergency Psychiatry

Continued from cover

Community crisis centers are most commonly staffed by therapists and social workers trained to counsel individuals while providing a safe and supportive environment. Psychiatrists or psychiatric nurse practitioners may also be available, though their hours are usually limited.

Most community crisis center patients self-present or are escorted voluntarily to the clinic by case managers, mobile crisis personnel, or police officers. Each patient typically receives a thorough psychosocial assessment and referrals to follow-up care. Some clinics also provide overnight crisis stabilization services.2

Yet while community-based programs provide many benefits, they are usually not equipped to care for patients with serious or dangerous psychiatric conditions. These centers commonly have a long list of exclusion criteria such as acute aggression, danger to self, involuntary status, or comorbid substance abuse disorders.2

Current and prospective patients who display these criteria are typically directed to hospital EDs or transported there by law enforcement or emergency medical services; indeed, many centers have required treatment algorithms for high-acuity patients that clearly end in “send to hospital emergency department or call 911.”

It is worth noting that these types of patients who would be excluded from community crisis centers likely make up a large percentage of the high-acuity individuals who end up boarding in EDs awaiting inpatient care. So, while community crisis centers can do fantastic work, they might have a negligible effect on ED utilization involving patients with high-acuity psychiatric conditions. In fact, expecting these organizations to handle the most acute psychiatric patients would be like expecting a private doctor’s office to treat heart attacks and severe car accidents.

Through no fault of their own, some community crisis centers have become victims of unrealistic expectations. State and county behavioral health leaders might assume that by creating these centers they will dramatically reduce the number of psychiatric patients presenting to EDs—and therefore put a dent in ED boarding. This is not only unfair to the centers, it also sadly underestimates how serious, debilitating, life-threatening, and unpredictable the emergency symptoms of severe mental illness can be, and how these require an elevated level of care.

This is where hospital-based psychiatric EDs fit in. Because emergency psychiatry programs are designed to work with highly acute individuals, they can typically accept the lion’s share of patients who would be excluded from community crisis centers. But rather than board patients for admission as would traditional medical EDs, hospital-based psychiatric EDs quickly assess and initiate prompt treatment, with a goal of stabilization in the emergency setting, and discharge to home or other less-restrictive levels of care rather than inpatient admission. And indeed, across many different locations and care models—rural and urban, academic and municipal—psychiatric EDs have proved very effective. The great majority of psychiatric ED patients in programs around the country, typically 70% to 80% or even higher, successfully stabilize and return home or to outpatient dispositions in less than 24 hours.

Treating high-acuity patients in psychiatric EDs rather than boarding them in general EDs just makes sense. Psychiatric cases are the only class of patients seen in EDs for whom the default treatment plan has traditionally been inpatient admission. An ED would not, for example, hold a patient having an asthma attack for transfer to an “inpatient asthma bed”; instead, they would treat the patient’s breathing difficulties as soon as possible. Psychiatric emergency patients are also experiencing urgent distress and deserve that same rapid approach.

Initiating prompt emergency care is exactly what the psychiatric EDs do. This is also completely consistent with the federal Emergency Medical Treatment and Labor Act (EMTALA) governing hospitals that considers high-acuity psychiatric emergencies to be equivalent legally to medical emergencies, deserving the same immediate attempts to evaluate and stabilize. Meanwhile, patients who may benefit most from community crisis centers might be unlikely to require the high-acuity approach of the emergency psychiatry sites and would perhaps be reluctant to go to hospital EDs in the first place—so these programs can optimally work together in an almost completely complementary way, which would rarely be redundant.

One historic distinction has been the idea that hospitals use the medical model while community crisis centers are more wellness and recovery focused, but this does not have to be the case when a hospital-based psychiatric emergency program is part of the system. Many psychiatric EDs—particularly newer designs like EmPATH Units—blend the wellness and recovery model with the medical model, hoping to bring the best of both approaches, where appropriate, to the unique challenges of high-acuity patients. The result is a supportive, calming, and home-like environment where patients can also receive the specialized medical attention and intervention needed. There is thus potential for a seamless continuity of care philosophy connecting hospital-based psychiatric EDs and community crisis clinics.

It is clear that to provide every patient experiencing acute psychiatric symptoms with timely, individualized, and an appropriate level of care, and to minimize ED boarding, mental health systems should endeavor to support both community crisis centers and hospital-based psychiatric EDs.

Dr. Zeller is Vice President for Acute Psychiatry with the physician partnership Vituity and Assistant Clinical Professor of Psychiatry, University of California, Riverside, CA. He is an Editorial Board Member of Psychiatric Times.

References

Caffeine requires no introduction as it is the most commonly consumed psychotrop drug in the world. It is primarily used for its predictable psychostimulant properties on the CNS. As with many drugs found in nature, it naturally occurs in select plant species located in Africa, East Asia, and South America. For these plants, it serves as an insecticide and a fungicide. It is commonly found in the leaves, seeds, and/or nuts of coffee, tea, and cocoa plants.

Caffeine is a member of the molecular class methylated xanthines, which also includes theophylline, theobromine, and paraxanthine. All four molecules are remarkably similar in structure, and the non-caffeine members vary only in the placement of their two methyl groups (CH3). Caffeine uniquely has a third methyl group and is metabolized by the liver to varying percentages of the other three. All have psychostimulant properties but vary in other physiological effects. Theobromine also functions as a bronchodilator, and, not surprisingly, is used in the treatment of asthma and chronic obstructive pulmonary disease. Theobromine has significant diuretic properties in addition to its weak psychostimulant effects. Paraxanthine does not exist naturally in any plants but is the most common metabolite of caffeine in humans.

The coffee bean, which seems to have originated in Yemen, has only caffeine. It was first described around 1450, at which time Sufi monks used the coffee bean to make a beverage to help with wakefulness while praying in their monasteries in Yemen.1 Tea leaves contain primarily caffeine, but also have varying degrees of theophylline and theobromine. The use of tea as a beverage is described as far back as 3000 BCE, and tea leaves are found throughout East Asia.1 The cocoa bean contains primarily theobromine, with some caffeine and virtually no theophylline. Cocoa bean residue has been found in a Mayan pot dating back to 600 BCE.1 Historically, it has been challenging to elucidate the mechanism of action of caffeine as a CNS psychostimulant. Previous competing theories included: increase in calcium release; inhibition of the enzyme phosphodiesterase that results in an increase in the secondary messenger cAMP; and interaction with adenosine receptors. This third theory is now believed to be the primary mechanism by which caffeine acts as a psychostimulant.

Caffeine, which is similar in structure to adenosine, is a competitive antagonist of adenosine A1 and A2A receptors (AIR and A2AR). The psychostimulant effects of caffeine can be neurobiologically...
dissociated into psychomotor activation and increased arousal. Both pharmacological properties are responsible for the wide use of caffeine. The increased arousal is related to the caffeine-mediated counteraction of the effect of adenosine on homeostatic sleep. Caffeine counteracts the adenosine-mediated sleepiness induced by prolonged wakefulness, mostly by acting on A1R that control the activity of ascending arousal systems. On the other hand, caffeine produces psychomotor activation by acting preferentially on A2AR, by indirectly controlling striatal dopaminergic transmission.

**Pharmacokinetics of caffeine**

After drinking a beverage containing caffeine, it takes from 30 minutes to 2 hours to reach its maximum serum concentration on average. Because of its property of solubility in both lipids and water, it is rapidly distributed evenly in all tissues throughout the body. It readily crosses the blood-brain barrier, allowing rapid access to receptors in the brain.

There are a number of factors that can affect the metabolism of caffeine in humans, and hence its pharmacokinetics. The average half-life of caffeine in humans is 2 to 6 hours. Caffeine is metabolized by the liver in first pass metabolism through the cytochrome P450 1A2 enzyme (CYP450 1A2). In addition to being a substrate for CYP450 1A2, caffeine is also a moderate inhibitor of this enzyme.\(^1\,^2\)

These properties have significant consequences for how the metabolism of caffeine is affected by some drugs, and how other drug metabolisms are affected by caffeine. The most common drug-drug interaction, which can have a clinical effect on how much caffeine is required to achieve a psychostimulant effect, is related to smoke. It is well established that smoke from any source (nicotine cigarettes or cigars, cannabis cigarettes, lengthy and prolonged exposure to smoke from a wood fire) induces the liver’s CYP450 1A2 enzyme—gradually increasing the activity of this enzyme by continuous smoke exposure over 2 weeks. This induction results in increased metabolism of caffeine by the CYP450 1A2 enzyme, requiring more caffeine to attain the same blood level as would be required in a non-smoker.\(^1\,^2\)

Estradiol inhibits the metabolism of caffeine; hence taking estradiol on a regular basis requires less caffeine to achieve the same level as being off estradiol. During pregnancy—a high estrogen state—the half-life of caffeine can be increased up to 15 hours in the third trimester. The SSR1 fluvoxamine, FDA approved to treat obsessive compulsive disorder, is a potent inhibitor of CYP450 1A2 and has been shown to increase caffeine’s half-life 10-fold.\(^1\,^2\)

Moreover, caffeine can elevate blood levels of some medications that can have significant clinical effects. Through its activity as a moderate inhibitor at the CYP450 1A2 enzyme, caffeine can increase the serum levels of clozapine and warfarin. Patients who are taking clozapine can be challenging to maintain at a steady serum level, as smoking cigarettes will decrease clozapine levels and drinking caffeinated beverages will increase clozapine levels.\(^1\,^2\)

**Adenosine-dependent modulation of striatal dopamine and glutamate neurotransmission**

Psychomotor activation is a major pharmacological effect of psychostimulants and classically implies a behavioral activation in response to specific stimuli, more specifically, to reward-related stimuli (rewards, conditioned rewards, or discriminative stimuli that signal the proximity of rewards). Psycho-stimulants also have reinforcing properties—the psychostimulant, itself, acts as a “reward” (ie, rewarding stimulus or reinforcer), implying that it elicits an approach and work to obtain it.

These properties of psychostimulants are similar to those of dopamine in the brain, and, particularly, in the striatum, the brain area with the highest dopamine innervation and the highest density of dopamine receptors. Thus, activation of the central dopamine system is involved with increasing responsiveness to reward-related stimuli—with orienting and approaching responses to those stimuli—thus reward-oriented behavior. Concomitantly, dopamine is directly involved with the learning (“stamping-in”) of stimulus-reward and reward-response associations that follows the receipt of reward.

Stimulus-reward associations lead some stimuli to acquire discriminative properties that signal the proximity of the reward or even to acquire rewarding properties (ie, conditioned rewarding stimulus), which become themselves behavioral attractors. The stamping-in of reward-response associations promotes positive reinforcement, the learning of the optimal sequential response—the action skill—that leads to the reward.

Dopamine cells increase their activity by the cues that predict the occurrence of the reward (discriminative/conditioned reward stimuli) and when the reward is better than expected (positive reward prediction error), in which case there is a phasic increase in striatal dopamine. This dopamine increase promotes activation of excitatory dopamine D1 receptors (D1R) and inhibitory dopamine D2 receptors (D2R), which have low and high affinity for dopamine, respectively. D1R and D2R are separately localized in the striatal cells that respectively constitute the “Go” (excitatory) and “No Go” (inhibitory) striatal efferent neuronal outputs.

The respective activation and inhibition promote the elicitation and learning of positively reinforced behaviors (approach behaviors). But dopamine cells also receive signals related to aversive stimuli and increase their activity with cues that predict the successful avoidance of an aversive stimulus. Consequently, there is elicitation and learning of negatively reinforced behaviors.

On the other hand, aversive stimuli (or cues that predict a non-avoidable aversive stimulus) produce inhibition of dopamine cell activity, which leads to the loss of a tonic activation of the high affinity D1R by endogenous dopamine. The consequent increase in the activity (by release of the D1R-mediated neuronal inhibition) of the “No Go” neuronal output, which is represented by the striatopallidal neurons, leads to freezing/withdrawal/escape behaviors.\(^1\,^2\)

Classic psychostimulants, such as cocaine, methylenidate, and amphetamine, activate the dopamine system by increasing the concentration of extracellular dopamine. In contrast, caffeine potentiates the effects of dopamine by counteracting adenosine neurotransmission. Blockade of A1R and A2AR in the striatum by caffeine releases the brake that endogenous adenosine exerts on dopamine activation, which is related to the ability of both adenosine and dopamine to facilitate a switch in the A2AR-mediated activation versus D1R-mediated inhibition of the striatopallidal neuron. In fact, A2AR activation is responsible for the increase in the activity of the striatopallidal neuron and the consequent freezing/withdrawal/escape behaviors induced by release of the D1R-mediated neuronal in-
Adenosine-dependent modulation of glutamate neurotransmission in the amygdala

The striatum is not the only localization of A1R and A2AR in the brain; adenosine also controls glutamate neurotransmission in other brain areas, such as the amygdala. Hence, the segregated presynaptic A1R versus A2AR, and postynaptic A1R and A2AR (expressed with significantly lower levels than in the striatum). The amygdala is the critical substrate of Pavlovian aversive conditioning, and it largely controls aversive stimuli in the lateral nucleus, where a variety of cellular events transform a neutral stimulus into an aversive conditioned stimulus.

The central nucleus of the amygdala is the major amygdalar output. For instance, its projections to the periaqueductal gray are involved in conditioned stimulus-induced freezing. Information from the lateral to the central nuclei is conveyed by the basal nucleus and the intercalated cell masses. The adenosine control of glutamate transmission onto the pyramidal neurons in the central nucleus of the amygdala is particularly critical. The A1R-mediated inhibition or an A2AR-mediated activation of the pyramidal cells in the basal nucleus leads to a respective decrease or increase in fear conditioning.6,8

The opposite effects of A1R and A2AR blockade have been documented experimentally, with A1R agonists facilitating, while A2AR antagonists decrease fear conditioning.8-10 Therefore, adenosine-mediated modulation of glutamate transmission in the amygdala represents a potential mechanism for the documented effects of caffeine on anxiety.

Caffeine and implications for anxiety

Anxiety disorders are common in psychiatry, and anxiety is a common symptom in many other psychiatric disorders. It is generally known that low doses of caffeine can be anxiolytic and high doses can be anxiogenic, particularly in susceptible individuals. Several studies indicate that a common block of polymorphisms of the A2AR gene (grouped by linkage disequilibrium) is associated with an increased expression of A2AR in the brain, predisposing to panic attacks and to the anxiogenic effects of caffeine.11-13 Based on the role of amygdalar A1R and A2AR in fear conditioning, A1R blockade, and not A2AR blockade, should lead to anxiogenic effects, making it difficult to explain the role of A2AR gene polymorphisms in anxiety and caffeine-induced anxiety. But the involvement of A2AR localized in the most posterior and medial part of the ventral striatum, with its putative role in fear extinction—the suppression of fear (more appropriately threat) conditioning—provides a possible way out of this conundrum.

Apart from the dopamine neurons that respond with a decrease in their activity upon presentation of an aversive and punishment-related stimulus, a specific population of dopamine cells increases its activity. In rodents, this neuronal subpopulation seems to be mostly localized in the most medial and posterior part of the ventral tegmental area (VTA), which specifically projects to the most posterior-medial part of the ventral striatum, the posterior-medial shell of the nucleus accumbens (NAc).14,15 This area of the striatum is mostly innervated by the rodent infralimbic cortex, equivalent to the rostral anterior cingulate cortex (ACC) in humans.

The infralimbic cortex innervates the interconnected posterior-medial portions of the VTA and shell of the NAc, the amygdala, and the insular cortex, and this circuit plays a key role in fear extinction. Specifically, the amygdalar input from the infralimbic cortex corresponds to the intercalated masses. These correspond to GABAergic inhibitory neurons also innervated by the pyramidal neurons of the basal nucleus and their activation leads to active inhibition of fear conditioned responses, to fear extinction. According to LeDoux and colleagues,16 active avoidance learning, with the elicitation of a behavioral response that avoids the interaction with the aversive stimulus, requires the suppression of fear conditioning. This system provides a significant additional mechanism by which dopamine promotes negative reinforcement during the establishment of an avoidance behavior—the switch “from fear to safety.”

Although still speculative, the anxiolytic effects of low doses of caffeine could be mostly mediated by blockade of striatal postsynaptic A2AR (in the A2AR-D2R heteromers) and presynaptic A1R (in the A1R-A2R heteromers) in the posterior-medial shell of the NAc, which should be expected to potentiate fear extinction. With higher doses of caffeine or with an increased expression of A2AR, as in the presence of anxiety susceptibility A2AR gene polymorphisms, striatal presynaptic A2AR blockade (in the A1R-A2AR heterodimer) would promote anxiety.

Conclusion

Caffeine is a naturally occurring psychotropic drug that has been used for its psychostimulant effects by humans for thousands of years. It is legal and requires no regulation, ubiquitous in most cultures, and consumed daily by all age groups. Although found naturally in coffee beans, tea leaves, and cocoa beans, it is also added to many beverages that are consumed daily for its psychostimulant effects.

Caffeine is also used in a variety of over-the-counter medications to treat various symptoms, ranging from headaches to somnolence. Furthermore, caffeine has a wide array of other physiological effects that we continue to discover and characterize. There is now a solid body of research that supports caffeine’s mechanism of action as a psychostimulant resulting from it being a non-competitive antagonist on adenosine receptors, in part through their ability to interact with dopamine receptors.

However, much work remains to be done, particularly in relation to the psychiatric implications. Clinical studies are needed that specifically evaluate the role of caffeine and A2AR antagonists in persons with anxiety. In order to establish the therapeutic versus anxiogenic doses of caffeine, studies should control for the role of anxiety susceptibility of A2AR gene polymorphisms, as well as polymorphisms of the gene for CYP450 1A2, which determine significant individual pharmacokinetic differences of caffeine.

However, this would still provide an incomplete picture because of the large variety of exogenous and endogenous factors, such as age, sex, hormonal status, diet, smoking, and exposure to drugs that influence caffeine intake, absorption, metabolism and pharmacological effects. An additional complication is the recent discovery of the psychomotor effect of paraxanthine, the main metabolite of caffeine in humans, which is related to its additional specific ability to inhibit a cGMP-prefering phosphodiesterase.17

Figure 2. The A2AR-D2R heterotetramer-AC5 complex.

Schematic slice-representation, viewed from the extracellular side of the minimal functional unit of the A2AR-D2R heterotetramer in complex with Gs (more specifically Go11) and Gi proteins (with Ga1 and Ga12/13 subunits) and adenyl cyclase (subtype AC5).

Adapted from Ferré et al.13
Polypharmacy

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neurotransmitters are implicated in psychiatric disorders and polypharmacy can target several receptor sites simultaneously. This led to many psychiatrists prescribing clozapine in combination with other drugs without blood monitoring; other psychiatrists did not use the drug, thus depriving patients of possible better outcomes.

There is a need for proper clinical titration, sound treatment algorithms, and well-defined protocols to effectively reduce irrational polypharmacy. An important clinical issue is when a patient on multiple drugs presents to a psychiatrist who wants to change the prescriptions to another multi-drug combination. It is important that certain drugs from the previous prescriptions be retained so that a switch can be made. Tapering medication must be done at a gradual rate while closely monitoring for withdrawal/rebound symptoms. When changing a medication, it is wise to switch the medication with one that has a similar half-life to enhance continuity of action.

Conclusions and recommendations

We are clearly living in an era where polypharmacy is necessary and where monotherapy often provides insufficient symptom improvement. The dilemma is the number of overwhelming drug possibilities available and the need to be aware of the right permutations and combinations. This perplexing decision is left to the clinician where rational prescribing is needed. Clinicians must regularly review scientific journals, clinical trial data, research on drug safety, latest neurobiological research, and update their knowledge of drug interactions to enable them to become scientific yet judicious, rational polypharmacy users. The most important point is the decision of whether to opt for polypharmacy or stick to monotherapy. Psychiatrists who prescribe multiple drugs may see better results; they may see an increase in adverse effects but have better clinical outcomes compared with monotherapy.

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References


TABLE 2. The evidence for polypharmacy

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