Schizophrenia is associated with impaired cognition, which persists despite current treatments, and is an important determinant of quality of life and overall function. There is limited evidence for the efficacy of pharmacological treatments for cognitive impairment in schizophrenia. Therefore, well-tolerated medications with efficacy for this indication represent a huge area of unmet need.

MIN-101 is a novel compound with equipotent affinities for sigma-2, serotonin 5-HT2A, and α1-adrenergic receptors, but weak dopaminergic antagonism. MIN-101 also does not have affinity for cholinergic or histaminergic receptors, which is...
Assistant Suicide

Continued from page 1

Physician-assisted suicide occurs when a physician facilitates a patient’s death by providing the necessary means and/or information to enable the patient to perform the life-ending act (eg, the physician provides sleeping pills and information about the lethal dose, while aware that the patient may commit suicide) . . . Physician-assisted suicide is fundamentally incompatible with the physician’s role as healer, would be difficult or impossible to control, and would pose serious societal risks.4

In essence, the two requests (officially known as Resolutions 15-A-16 and 14-A-17) asked the CEJA to consider, respectively, whether the AMA should take a “neutral stance” on physician “aid in dying;” and whether the phrase physician assisted suicide ought to be replaced by the phrase aid in dying in official AMA references to this practice. (I am condensing and paraphrasing for the sake of simplicity; the more technical language of the resolutions may be found in the actual CEJA report). The authors of the CEJA report wisely noted the critical role of language in this controversy, stating: “Not surprisingly, the terms stakeholders use to refer to the practice of physicians prescribing lethal medication to be self-administered by patients in many ways reflect the different ethical perspectives that inform ongoing societal debate.” Those who favor the practice just described generally prefer the terms death with dignity or medical aid in dying. Those who oppose physician provision of lethal medications generally favor the term physician-assisted suicide.

AFTER MUCH DELIBERATION, the CEJA report reached two main conclusions:

1. The AMA Code of Ethics should not be amended, effectively sustaining the AMA’s position that physician-assisted suicide is fundamentally incompatible with the physician’s role as healer.

2. With respect to prescribing lethal medication, the term physician assisted suicide describes the practice with the greatest precision.

On the second point, the Council noted that “The terms ‘aid in dying’ or ‘death with dignity’ could be used to describe either euthanasia or palliative/hospice care at the end of life; and this degree of ambiguity is unacceptable for providing ethical guidance.” Notably, the Council’s analysis and recommendations, if accepted by the AMA House of Delegates, would put the AMA squarely in the camp of the American College of Physicians, whose 2017 position on PAS (and on euphemistic alternative terms, like death with dignity) is crystal clear:

Physician-assisted suicide is neither a therapy nor a solution to difficult questions raised at the end of life. On the basis of substantive ethics, clinical practice, policy, and other concerns, the ACP does not support legalization of physician-assisted suicide . . . [Moreover], dictionaries define suicide as intentionally ending one’s own life. Despite cultural and historical connotations, the term is neither disparaging nor a judgment. Terms for physician-assisted suicide, such as aid in dying, medical aid in dying, physician-assisted death, and hastened death, lump categories of action together, obscuring the ethics of what is at stake and making meaningful debate difficult; therefore, clarity of language is important.5

What about the APA? The American Psychiatric Association’s code of ethics is based on that of the AMA; accordingly, official APA policy is opposed to PAS of any kind. However, in light of the emerging practice in Belgium and the Netherlands of euthanizing non-terminally ill patients—including psychiatric patients—the APA felt it important to craft a position explicitly addressing this population. And so, in December 2016, the APA Board of Trustees passed the following position statement, which originated in the APA Assembly and was unanimously supported by the APA Ethics Committee: “The APA, in concert with the American Medical Association’s position on Medical Euthanasia, holds that a psychiatrist should not prescribe or administer any intervention to a non-terminally ill person for the purpose of causing death.”69 The statement by the APA Trustees speaks forcefully to the slippery slope of medically authorized killing in countries like Belgium and the Netherlands, where psychiatric patients are now routinely (and legally) euthanized. As my colleague, Mark S. Komrad, MD, wrote:

People with non-terminal illnesses have been legally euthanized at their own request in several countries for nearly 15 years. This has included certain eligible patients who have only psychiatric disorders.

In 2002, Belgium, the Netherlands, and Luxembourg removed any distinctions between “terminal” and “non-terminal” conditions, and between physical suffering and mental suffering, for legally permitted PAS/euthanasia...

Between 2008 and 2014, more than 200 psychiatric patients were euthanized by their own request in the Netherlands (1% of all euthanasia in that country); 52% had a diagnosis of personality disorder, 56% refused one or more offered treatments, and 20% had never even had an inpatient stay (one indication of previous treatment intensity). When asked the primary reason for seeking PAS/Euthanasia, 66% cited “social isolation and loneliness.” Despite the legal requirement for agreement between outside consultants, for 24% of psychiatric patients euthanized, at least one outside consultant disagreed.7

These and many other shortcomings in the European regulation of PAS are vividly illustrated in a new documentary by Canadian filmmaker, Kevin Dunn, Fatal Flaws.89

Conclusion

The thorny issue of end-of-life care is likely to remain controversial in the US, with physicians themselves holding a wide variety of views.10 Critical in this debate is the finding that most persons requesting PAS are not actively experiencing extreme suffering or inadequate pain control. Data from the Washington and Oregon PAS programs show that most patients request PAS because they fear loss of dignity and control over their own lives.11 These are matters that lend themselves to psychiatric...
FROM THE EDITOR

Black and White and Red All Over
Allan Tasman, MD | Editor in Chief

I

my generation, a common riddle for 10-year-olds was, “What’s black and white and read all over?” Because you only heard it spoken, you thought the word “read” was actually the color “red,” and the first time around you didn’t know the answer was “newspaper.” Of course, when you were 10 that’s why it was funny the first 50 times someone asked you. Then it was just dumb. I used the word red in my headline because the news folks ought to be red-in-the-face embarrassed and that’s not funny either.

For example, a June 2018 editorial in The New York Times was titled “The Crazy Talk About Asylums.” They rightly aired concerns that the solutions to the wave of mass school shootings in the US was not to have more psychiatric asylums, as had been advocated by President Trump following the Parkland, Florida shootings.

The Times did say a number of things that make a lot of sense, but which are hardly “news” in the sense that these are new ideas that are worth attention. They cited the Parkland, Florida shootings. The Times editors who decide that the inadequacy of mental health care is such a public health emergency that ongoing investigative journalism is needed? A single editorial, no matter how righteous, is unlikely to have any effect on public policy. That’s why I think they ought to have any effect on public policy, because the news IS read all over, either online or in print, and journalism with a sustained focus can make a difference.

The other topic I want to emphasize regarding the absence of sustained news coverage is the epidemic of suicide in the US. I wrote about this in my February Psychiatric Times editorial, but that was before the CDC released their most recent data which shows that suicide rates in the US continue to climb, now with around 45,000 suicide deaths each year. The majority of those are from self-inflicted gunshots.

The National Suicide Prevention Lifeline provides 24/7, free and confidential support for people in distress: 1-800-273-8255

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From the Editor

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shots. And while the mass shoot-ings appropriately gain a great deal of coverage, there is little mention of that all the gun violence deaths in the US each year, most of them are suicides.

Until the suicide deaths of 55-year-old fashion designer Kate Spade and celebrity chef and TV star 61-year-old Anthony Bourdain in the same week in early June, I didn’t really see much coverage of the public health emergency that is represented not only by suicide, but by the approximately 10-fold greater numbers of attempts. Where’s the ongoing media cover-age of that? The week after those two celebrity deaths, NBC News at least showed the phone number for the National Suicide Lifeline on their nightly broadcast. But that’s about it from the media.

We’re in the middle of a long hot summer, likely to break a heat record, and the public interest in these topics understandably has waned. I was sad about Anthony Bourdain’s death, because I’ve been a fan of his TV shows. But my level of sadness can hardly be compared with the level of lasting distress suffered by friends, col leagues, and families of those who have committed suicide or been killed.

What psychiatrists can do about these ongoing problems is unclear beyond the care we provide for those in severe distress. In some cases, local training programs for police departments have had some salutary effects on individual cases of gun violence or potential suicide. But there obviously hasn’t been an effective national set of policies to address these problems, as I’ve said before.

These omissions are worth pondering, since these days, other than personality politics, there seems to be little beyond the 24-hour news cycle that gets sustained coverage. That’s not good for the body poli-tic, no matter what the issue.

References

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Forward your comment, along with your full name, title, and affiliation to: editor@psychiatrictimes.com

We may select your letter to appear in a From Our Readers feature in print, or at the end of the article online, with a response from the author. We’ll accept letters up to 4 weeks from the online publication date.

In the subject line, please include “Letter to the Editor” and the title of the article to which you’re referring.
Assisted Suicide

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By a 56-44 vote, the AMA House of Delegates decided to reject the CEJA report as it is now written, and to send it back to the Council for re-evaluation. However, as of now, the official AMA position remains opposed to physician-assisted suicide.

Cognitive Effects of MIN-101

Continued from page 1

important given negative effects of anticholinergic and antihistaminergic agents on cognition in severe mental illness. This raises the possibility that MIN-101 may have positive effects on cognition through sigma-2 and 5-HT2A antagonism.

Davidson and colleagues previously performed a 12-week phase 2b RCT of MIN-101 versus placebo in patients with symptomatically stable schizophrenia and chronic negative symptoms. Briefly, they enrolled 244 patients (age 18 to 60) with a DSM-5 schizophrenia diagnosis at 36 sites across 6 countries. Participants were randomized to placebo or oral MIN-101 at 32 or 64 mg/d in a 1:1:1 ratio for 12 weeks. Assessments were completed at baseline and weeks 2, 4, 8, and 12. They found significant improvements in negative symptoms in both MIN-101 groups at 8 weeks, with benefit maintained at week 12, that was not driven by improvements in mood.

Reefe and colleagues analyzed cognition as a secondary outcome measure from this trial. Inclusion criteria for the study were: clinically stable according to their psychiatrist; negative symptoms for at least 3 months and a baseline Positive and Negative Syndrome Scale (PANSS) negative subscale score of ≥ 20; and scores < 4 for PANSS excitement, hyperactivity, hostility, suspiciousness, uncooperativeness, and poor impulse control items; and extensive use of anticholinergic and antihistaminergic medications were discontinued 5 days before study baseline.

Cognition was measured using the Brief Assessment of Cognition in Schizophrenia (BACS) at baseline and weeks 4 and 12. BACS scores were standardized into age- and gender-adjusted z-scores and T scores. Data for the primary endpoint (change from baseline to week 12 in BACS composite and subscale scores) were analyzed using mixed-model repeated measures based on an intent-to-treat population. At baseline, the 3 subject groups did not differ based on age, sex, PANSS scores, Clinical Global Impression (CGI) scores, or BACS scores. Over 95% of subjects in each group completed the BACS at baseline. From baseline to study endpoint (week 12), subjects in the MIN-101 32 mg group had significant improvements in the BACS composite (effect size ~ 0.3 SD over placebo), token motor, and verbal fluency scores compared to the placebo group. There was a non-significant trend for improvement in the symbol coding, token motor, and verbal fluency scores from baseline to end-point for subjects in the MIN-101 64 mg group compared to placebo.

In the MIN-101 32 mg group, changes in cognitive functioning were not correlated with changes in negative symptoms at either week 4 or 12. By contrast, in the MIN-101 64 mg group, improvement in the PANSS negative factor score was significantly correlated with improvement in the BACS cognitive composite score at both week 4 (Pearson r = -0.29) and week 12 (r = -0.41).

The bottom line

The authors concluded that MIN-101 has a possible benefit on cognition in patients with stable schizophrenia symptoms and concurrent negative symptoms, potentially through sigma-2 and serotonin 5-HT2A receptor antagonism. Approximately 40% of patients in the MIN-101 32 mg group had a clinically meaningful improvement in cognition (defined as ≥ 0.5 SD improvement).

They note a limitation of the study is that in contrast to dose-related effects of MIN-101 on negative symptoms, the findings for cognitive performance are divergent. It is also not clear whether the same pattern of results would be observed for patients with a different profile of schizophrenia symptoms, or if MIN-101 was used as add-on therapy. Nevertheless, this study suggests that through an innovative mechanism of action, MIN-101 may address a key area of unmet need in the treatment of patients with schizophrenia.

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References

ADDRESSING DEPRESSION
The World’s Largest Health Problem

» James Murrough, MD, PhD

Depression is the world’s largest health problem, accounting for more disability than any other disease worldwide. Many patients with major depressive disorder (MDD) are never diagnosed, and those who are diagnosed may not receive adequate treatment due to factors that include stigma, a lack of understanding of the medical nature of depression in the community, and access to care. This is highly relevant to the current discourse surrounding the need to curb the rising worldwide suicide rate, since untreated MDD is a primary cause of completed suicides.

Similarly, the psychiatric community has grappled with problems related to stigma and the need for patient education on the pathophysiological explanations of depression and the deployment of effective treatments. Yet the field continues to suffer both from the lack of a complete mechanistic understanding of depression as well as from a therapeutic portfolio that is only partially effective. Only one in three patients will achieve remission following up to 12 weeks of treatment with a first-line antidepressant medication. These factors re-enforce a lack of clarity regarding the causes of depression and appropriate treatment strategies both within and outside of the medical community. This in turn unwittingly contributes to the stigma and confusion surrounding the world’s largest health problem.

Despite the scope and magnitude of the problem, the field may be witnessing a turning point in our capacity to understand and treat depression. Advances in functional neuroimaging have led to the identification of biological subtypes of depression and to the identification of specific moderators of treatment response to medication versus psychotherapy. Very recently, the advantages of pharmacogenetic-guided treatment compared to treatment as usual was shown in the first large-scale demonstration in a study that included more than 1,000 patients with MDD who were unresponsive to an initial first-line therapy. These developments may herald substantial progress towards personalized medicine for depression in the years to come. At the same time, clinical trials research is yielding positive results for compounds that act at therapeutics targets outside of the monoamine system, including glutamate, GABA, and opioid systems. In the very near future we may witness the first truly novel antidepressant agents to enter the clinic in decades. Therefore, despite the sobering scale of the problem, tangible progress in depression research and treatment should encourage optimism in clinicians and patients alike. With continued work, the future will continue to brighten.

Dr. Murrough provides consultation services to Allergan, Fortress Biotech, Novartis, Janssen Research and Development, Genentech, ProPhase, and Global Medical Education and has received research support from Avanir Pharmaceuticals. Dr. Murrough is named on a patent pending for neuropeptide Y as a treatment for mood and anxiety disorders.

References
The Psychopharmacology of Depression: Strategies, Formulations, and Future Implications

Dr Goldberg is Clinical Professor of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY.

With well over two dozen traditional antidepressants available in the US, and an ever-growing list of other psychotropics, the options for treating clinical depression today are broad and vast. However, recent findings suggest that the magnitude of efficacy for most antidepressants compared with placebo may be more modest than previously thought. Most depressed patients do not respond fully to a first antidepressant trial, and with each subsequent trial, there is less chance of symptom remission. About one-third of patients receiving long-term treatment report persistent moderate-to-severe depression. Hence, there remains more than a little room for improvement.

Since the late 1950s, the traditional view of treating depression has focused on the role of monoamines (serotonin, norepinephrine, and dopamine) as the main targets for medications. Newer treatments are looking beyond effects on monoamines as potential strategies to leverage depressive symptoms.

A major challenge for progress in novel pharmacotherapies is our lack of a full understanding about the causes of depression. Advances in functional neuroimaging and genetic markers have begun to shed new light on brain regions and pathways associated with aberrant neural functioning in depression, but not in ways that have led to treatments aimed at remedying its pathogenesis. This makes it hard to think of antidepressant medications as “treating” the pathophysiology of depression (as when antibiotics eliminate the cause of an infection); rather, antidepressant relief symptoms by counteracting or compensating for depression’s consequences (as when diuretics alleviate peripheral edema regardless of its etiology).

Gone are the days of oversimplified theories that depression is caused by a “chemical imbalance.” More likely, depression involves changes in brain architecture and the interplay of complex circuits in which chemicals, or neurotransmitters, are the messengers of information, rather than the causes of faulty functioning. Table 1 summarizes some of the major conceptual shifts that have occurred in thinking about the probable causes of depression (or at least its neurobiological context), which sets the stage for new ways to consider innovative treatment strategies. Looking beyond the role of monoamines as treatment targets in depression, a number of novel therapeutic strategies have begun to receive growing interest in preclinical and clinical trials. Key points about emerging novel depression pharmacotherapies are summarized in Table 2, and described more fully below.

Glutamate modulating agents
Subanesthetically dosed intravenous (IV) ketamine currently represents perhaps the most dramatic and innovative antidepressant pharmacotherapy to emerge in decades. It is pharmacodynamically unique in its rapid onset (hours rather than days to weeks) and its potential ability to reduce suicidal ideation after a single dose, independent of its antidepressant properties. While both lithium and clozapine have been shown to reduce suicidal behaviors, neither has been shown to reduce ideation, much less in the same day after a single dose.) Meta-analyses suggest that 0.5 mg/kg IV ketamine produces nearly a 10-fold greater likelihood of response than placebo at day 1 and a 4- to 5-fold likelihood of sustained response after one week.

The exact psychotropic mechanism of action of ketamine remains elusive. Initial work focused on blockade of ionotropic N-methyl-D-aspartate (NMDA) receptors as accounting broadly for its antidepressant effects. However, subsequent negative randomized trials with other NMDA receptor antagonists (such as rituxolizate) redirected interest toward ketamine’s other, non-NMDA receptor-related mechanisms, such as sigma receptor agonism, mu opioid receptor antagonism, or midbrain monoaminergic inhibition. Other authors have suggested that at low doses, ketamine’s antidepressant effects may derive from an increase in glutamate transmission with increased t-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor expression, leading to increased release of brain-derived neurotrophic factor (BDNF). Murrough and colleagues recently observed the necessity of AMPA receptor activation for the antidepressant effects of ketamine. They reported that “directly targeting the NMDA [receptor] may not be required.” As noted by the American Psychiatric Association Council on Research Task Force on Novel Biomarkers and Treatments, future advances will depend on a better understanding of the many mechanisms of action relative to the antidepressant properties of ketamine.

Ketamine is currently not approved by the FDA as a treatment for depression. Uncertainty remains as to whether repeated dosing is safe, effective, and necessary to avoid relapse and, if so, when, at what frequency, and for how long. The aforementioned APA Council on Research Consensus Statement on ketamine treatment for depression stated that while some clinics already offer 2- to 3-week courses of ketamine delivered 2 to 3 times per week, “there remain no published data that clearly supports this prac-

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**TABLE 1. Changing perspectives about the pathophysiology of depression**

<table>
<thead>
<tr>
<th>Component</th>
<th>20th century</th>
<th>21st century</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assumed pathology</td>
<td>“Chemical imbalance”</td>
<td>Disorders of synaptic plasticity and neural interconnectivity*</td>
</tr>
<tr>
<td>Unit of interest</td>
<td>Neurotransmitter (especially monoamine) levels</td>
<td>Brain circuits and interconnections, glial support to neurons</td>
</tr>
<tr>
<td>Putative biomarkers</td>
<td>DST nonsuppression, peripheral (serum, CSF, urine) monoamine or metabolite levels, platelet MAO levels</td>
<td>SNPs/haplotypes from GWAS; markers of neuronal viability (eg, trophic and anti-apoptotic gene products, serum BDNF levels), fMRI/diffusion tensor tractography</td>
</tr>
<tr>
<td>Presumed vulnerability factors</td>
<td>Division of “endogenous” (within the body) depression attributed to “biological causes” and “neurotic” (mainly environmental causes, such as early life adversity or deprivation, actual or perceived loss or neglect)</td>
<td>Genetic susceptibility loci; diminished capacity for resilience when faced with adversity; inflammatory cytokines (theoretical, not proven); negative cognitive schemas; others</td>
</tr>
<tr>
<td>Role of genetics</td>
<td>Ill-defined contributor to “endogenous” depression</td>
<td>Non-Mendelian heredity; complex traits and multiple genes of small effect; penetrability of recurrent major depression ~37%*</td>
</tr>
<tr>
<td>Biological impact of pharmacotherapy</td>
<td>Rectify presumed monoamine deficiencies</td>
<td>Enhance neuroplasticity</td>
</tr>
</tbody>
</table>

*Genetics and/or epigenetics can produce receptor or neurotransmitter dysfunction that is the primary etiology for depression. BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; DST, dexamethasone suppression test; fMRI, functional magnetic resonance imaging; GWAS, genome-wide association studies; MAO, monoamine oxidase; SNPS, single nucleotide polymorphisms.
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tice, and . . . the relative benefit of each ketamine infusion [should] be considered in light of the potential risks associated with longer term exposure to ketamine and the lack of published evidence for prolonged efficacy with ongoing administration.” Thus far, studies of other pharmacotherapies to sustain an initial ketamine response (such as riluzole or lithium) have proven no better than placebo.

Enantimeric esketamine remains investigational as a possible easier-to-administer intranasal (IN) antidepressant, although IN bioavailability is only about half that of IV ketamine’s 100%. Two randomized multi-site trials of IN esketamine added to antidepressants showed dose-related better efficacy than placebo: Daly and colleagues found that 28 mg to 84 mg of IN ketamine twice weekly over two weeks produced significant improvement in depressive symptoms as compared to placebo beginning after 1 week and continuing through week 9 for the majority of responders. A study by Canuso and colleagues demonstrated a significant reduction in depressive symptoms within 4 hours of administration (56 mg to 84 mg insufflated over 15 minutes) and a medium to large effect size, sustained after 25 days; suicidal ideation reduced significantly at 4 hours but not beyond that time. Another recent randomized pilot trial of IN racemic ketamine (the mixture of S- and R-ketamine) was prematurely discontinued due to poor tolerability (including cardiovascular and neurological adverse effects) and highly variable absorption across subjects.

### TABLE 2. Summary of emerging novel pharmacotherapy approaches to major depression

<table>
<thead>
<tr>
<th>Agent</th>
<th>What’s known</th>
<th>What’s unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiglutamatergic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>Rapid antidepressive effect after IV administration in about 50% of depressed patients; antidepressant effects sustained for at least 1 week in about 1/3 of acute responders; apparent reduction of suicidal ideation after a single dose</td>
<td>Antidepressant mechanism of action (less compelling effects seen with other NMDA receptor antagonists); efficacy and safety of IN administration; necessity (and protocol) for repeated administrations to sustain response; long-term safety and efficacy; depression efficacy of esketamine, or ketamine’s metabolite norhydroxyketamine</td>
</tr>
<tr>
<td>Esketamine</td>
<td>“S” enantiomer of racemic ketamine, intranasally formulated; rapid onset of antidepressant and anti-suicide effects</td>
<td>Long-term safety and efficacy; how to maintain antidepressant and anti-suicide effects; abuse potential (eg, relative to IV ketamine)</td>
</tr>
<tr>
<td><strong>Opioid partial agonist</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALKS 5461</td>
<td>Preliminary evidence of antidepressant efficacy when added to inadequately-effective antidepressants; well tolerated</td>
<td>Possible robust effects; possible bioavailability of buprenorphine</td>
</tr>
<tr>
<td><strong>Anti-inflammatories</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>Preliminary evidence of antidepressant efficacy in depression with elevated hs-CRP; preliminary efficacy as monotherapy or adjunctive to antidepressants</td>
<td>Possible robust effects; possible efficacy in noninflammatory depressive subtypes</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Medium-to-large effect size observed in initial randomized trials for depression; well-tolerated</td>
<td>Both positive and negative trials have been reported; possible clinical profile for appropriate candidates; possible long-term gastrointestinal or cardiovascular safety</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Tetracycline antibiotic that also reduces oxidative stress, promotes neuronal growth; significant reduction in depressive symptoms with large effect size as adjunct to antidepressants versus usual treatment, dosed at 100-200 mg/day for 12 weeks; preliminary efficacy in unipolar and bipolar depression</td>
<td>Small number of studies limits generalizability</td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scopolamine</td>
<td>Three 15 minute 4 μg/kg parenteral infusions q3-5 days associated with significantly greater improvement in depression symptoms versus placebo, evident within several days; large effect sizes; possible greater effects in women than men; antimuscarinic adverse effects seem mild and transient</td>
<td>Small sample sizes require replication in larger randomized studies; possible utility/bioavailability of transdermal or other nonparenteral formulations</td>
</tr>
<tr>
<td>Brexanolone</td>
<td>Small, preliminary placebo-controlled trial data support efficacy in severe postpartum depression</td>
<td>Possible use in forms of depression other than postpartum (eg, premenstrual depression), long-term efficacy and safety; feasibility of IV administration; need for replication in larger randomized trials</td>
</tr>
<tr>
<td>PPARγ agonists</td>
<td>Preliminary support for mono- or adjunctive antidepressant efficacy in major depression independent of metabolic status; may cause weight gain</td>
<td>Not all studies are favorable; replication needed with larger sample sizes</td>
</tr>
</tbody>
</table>

**The opiate system**

Modulation of the endogenous opioid system has long been a target of interest in the treatment of mood disorders, but it is limited by safety risks, tolerance, and addiction potential. Recent work has focused on a proprietary combination of the μ-opioid partial agonist/kappa antagonist buprenorphine plus the μ-opioid receptor antagonist samidorphan (ALKS 5461). The potent blockade of μ-opioid receptors in samidorphan, which prevents buprenorphine access to these receptors, effectively renders buprenorphine a selective kappa opiate receptor (KOR) antagonist, which is its putative antidepressant mechanism. After initial favorable Phase II trials, in 2013 the FDA granted ALKS 5461 fast track status for accelerated regulatory review as an antidepressant adjunct. Subsequent randomized trials in treatment-resistant major depression revealed statistically significant differences from placebo on some, but not all, depressive symptom outcome measures and at some, but not all, doses studied. The FDA initially refused to review the new drug application for ALKS 5461 as an adjunctive therapy for depression because of concerns about bioavailability and lack of evidence, but then reversed its position. ALKS 5461 is
Antiinflammatories and immunomodulators
There has been growing recognition of complex interrelationships between depression and inflammation. Some but not all patients with clinically significant depression appear to have elevated serum markers of systemic inflammation, such as high sensitivity C-reactive protein (hs-CRP) and inflammatory cytokines. While causal relationships between depression and inflammation are poorly understood and questions remain whether depression causes inflammation or vice versa, randomized trial data suggest potential antidepressant value of nonsteroidal anti-inflammatory drugs (NSAIDs), particularly the COX-2 inhibitor celecoxib. A pooled meta-analysis of 5447 participants from 10 NSAID trials and 4 cytokine inhibitors (as mono- or add-on therapy for depression) revealed statistically significant advantages over placebo, with small to medium effect sizes, for response (odds ratio = 6.6; 95% confidence interval=2.2-19.4) or remission (odds ratio = 7.9; 95% confidence interval=2.9-21.1). It has not been established whether adding celecoxib or other NSAIDs to an antidepressant may be more useful only in the setting of elevated serum markers of inflammation. Elsewhere, preliminary studies reveal that inflammatory depressive subtypes (ie, high baseline hs-CRP) may respond better to a tricyclic than SSRI, or adjunctive L-methylfolate, or the tumor necrosis factor (TNF) antagonist infliximab (administered IV at 5 mg/kg over 3 doses).

Anticholinergic muscarinic agents
Harking back to the 1970s hypothesis that depression could reflect cholinergic-adrenergic dysregulation, interest has turned to the possible antidepressant effects of the muscarinic cholinergic antagonist scopolamine. Preliminary studies of intravenous scopolamine dosed at 4 μg/kg in both unipolar and bipolar depression have produced remission rates from 45% to 56% (Cohen’s d ranged from 1.2-3.4) typically within several days of administration, with persistence for 10 to 14 days. Antimuscarinic adverse effects such as sedation, dry mouth, and blurry vision are common but transient. Neurocognitive measures reaction time during selective attention tasks reveal no significant delays following IV scopolamine infusion. Analogous to IV ketamine, questions remain about the optimal number of infusions to minimize relapse as well as the use of nonparenteral formulations.

Neurosteroids
Brexanolone (SAGE-547), also known as allopregnanolone, is a positive allosteric modulator of GABA-A receptors. It is a progesterone metabolite that exerts neuroprotective, pro-cognitive, and possible antidepressant/anxiolytic properties. Precipitous drops in progesterone and allopregnanolone after childbirth prompted interest in the use of allopregnanolone specifically in postpartum depression. A small (N = 21) initial trial of brexanolone (administered intravenously because of its short half-life and poor oral bioavailability) or placebo for severe postpartum depression yielded a substantial reduction in depressive symptom severity within 60 hours (effect size = 1.2). Further data remain pending. SAGE-217 is reformulated brexanolone that has good oral bioavailability, allowing for oral administration, as well (CONTINUED ON PAGE 12)
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as a longer half-life allowing once-a-day dosing. It is currently being studied as an adjunctive agent for treatment resistant depression.

PPAR-γ agonists and incretins

Thiazolidinediones are insulin sensitizers that also demonstrate antidepressant properties in animal studies and appear to possess anti-inflammatory, neuroprotective, antioxidant and anti-excitatory properties. Pioglitazone, a PPAR-γ agonist thiazolidinedione, has been studied versus placebo or metformin in major depression, both as monotherapy and in combination with antidepressants or lithium. A meta-analysis of 4 trials revealed significantly higher remission rates than controls (27% versus 10%, respectively; odds ratio of remission in major depression = 5.9 (95% confidence interval=1.6-22.4), p = .009), with an NNT = 6.25 Even though PPAR-γ agonists can decrease insulin resistance, weight gain can be an undesired adverse effect that is possibly a result of a combination of fat cell proliferation, fluid retention, and increased appetite. Pioglitazone also carries serious adverse risks for congestive heart failure and bladder cancer.

Glucagon-like peptide 1

Another class of antidiabetic drugs known as glucagon-like peptide 1 (GLP-1) agonists mimic the action of insulin (so-called incretins) and are of interest as a potential target for depression. GLP-1 agonists such as li- raglutide possess neuroprotective and antiapoptotic properties, and animal studies suggest it has antidepressant and pro-cognitive effects, particularly involving reward and motivation. Human studies have thus far focused more on weight-reducing and possibly cognitive benefits of li- raglutide more than its potential antidepressant efficacy, but its mechanism represents a promising direction for further study.

Future directions

This brief overview has focused on emerging novel pharmacotherapies for depression. While the provisional nature of proof-of-concept studies may be encouraging, they are far from definitive. The aforementioned findings are largely preliminary and meant more to prompt larger randomized trials to establish efficacy, safety, and generalizability rather than inspire premature immediate uptake into clinical practice.

Given the focus on neuroprotection and enhanced neuroplasticity as proposed targets of treatment, it would seem remiss not to at least mention the neurobiological impact of depression-specific psychotherapies, mindfulness meditation, and related psychosocial interventions. Psychotherapy is, among other things, a behavioral learning paradigm, presumably rendering alterations in cognitive functions (memory, attention, and decision-making), fear extinction, and emotional processing. Evidence-based psychotherapies for depression have been shown to produce changes in brain network connectivity (recapitulating the idea of Hebbian synapses, where “neurons that fire together wire together”) and upregulation of intracelular transcription factors involved in neuronal plasticity. Enhanced neuroplasticity may represent a common denominator target for effective biological or psychosocial treatments for depression.

Increasingly, drugs we call antidepressants are diversifying to include broader classes of molecules. A more neuroscience-based nomenclature for psychotrophic drugs has already been proposed and will no doubt invoke more novel drug mechanisms, supplanting older concepts about depression as a chemical imbalance as perspectives continue to evolve about how antidepressants impact neuronal viability and brain microarchitecture.

Dr Goldberg has been on the speaker bureau for Merck, Neurocrine, and Sunovian, and Takeda-Lundbeck and has been a consultant for Neurocrine and Sunovian.

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Psychotherapeutic Interventions for Depression: Which Work Best?

Mary Beth Connolly Gibbons, PhD

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The American Psychological Association describes cognitive therapy (CT), behavioral activation (which can be administered alone but is also an important component of CT), interpersonal psychotherapy, and problem-solving therapy as having strong evidence of effectiveness in the treatment of major depressive disorder (MDD) using the criteria for evidence-based psychotherapies originally formulated by Chambless and Hollon. Short-term dynamic psychotherapy is listed as having only modest evidence of effectiveness.

In contrast, the American Psychiatric Association recommends CT, interpersonal therapy, problem-solving therapy, and psychodynamic psychotherapy as effective interventions for depression but limits the recommendation to only mild to moderate depression. Recent evidence on the effectiveness of psychotherapy in the treatment of depression suggests that another look should be taken at these guidelines. There is emerging evidence supporting the effectiveness of CT for severe depression and the effectiveness of dynamic psychotherapy for depression. In this article, I review some of the recent studies and possible changes to the guidelines that should be considered.

Cognitive therapy

The efficacy and effectiveness of CT for MDD has been well established in controlled efficacy trials as well as in real-world effectiveness trials. Given the substantial pain and suffering experienced by those who will encounter an episode of MDD in their lifetime, the research to date validating the effects of CT justify the time and costs necessary to implement this intervention in outpatient settings.

Hollon and colleagues demonstrated that CT reduced the risk of relapse after treatment was completed with continuation effects comparable to keeping patients on medication. The trial included only patients with severe depression, which indicates that the APA might reconsider its limited recommendation of psychotherapies for only mild to moderate depression.

Short-term dynamic psychotherapy

In contrast to the solid evidence base for CT in the treatment of depression, there has been substantial debate in the literature over the past 20 years regarding whether short-term dynamic psychotherapy, which targets maladaptive interpersonal patterns as the source of symptomatology, has sufficient research to support its dissemination as an intervention for MDD. Although dynamic psychotherapy has been and is currently practiced worldwide, the research literature across mental disorders is flooded with reviews that debate whether it has adequate evidence of effectiveness.

A comprehensive review concluded that dynamic psychotherapy has large pre-and post-effects that are maintained at 1 year and medium effect sizes relative to control conditions. Two trials provide strong evidence that dynamic psychotherapy combined with medication is superior to medication alone in the treatment of depression. These studies provide valuable insight into the utility of dynamic psychotherapy in real-world practice where psychotherapists are often combined with medication treatment.

A recent trial of longer-term psychoanalytic treatment demonstrated superiority over treatment as usual for treatment-resistant MDD. At the 2-year follow-up, 44% of patients in the psychoanalytic treatment no longer met criteria for MDD compared with 10% of those receiving treatment as usual.

Dynamic versus cognitive therapy

In describing the evidence needed to define a psychotherapy as evidence based, Chambless and Hollon assert that treatment efficacy is best demonstrated in controlled research. They suggest that studies with samples per condition of at least 25 that demonstrate an intervention is not significantly inferior to an already validated intervention can be considered evidence that treatments are equivalent. They warn that the interpretability of equivalence/non-inferiority trials is dependent on trials conducted with strong attention to internal validity.

To add to the emerging evidence supporting the effectiveness of dynamic psychotherapy in the treatment of depression, 2 large-scale noninferiority trials demonstrated that dynamic psychotherapy is statistically noninferior to CT in the treatment of MDD. Driessen and colleagues randomized 341 patients in outpatient settings to short-term dynamic psychotherapy versus CT using research methods that included manualized treatments, training protocols, and blind independent assessments. They found there were no differences between treatments at termination or follow-up on either patient-rated or observer-rated outcome assessments.

My colleagues and I conducted a randomized non-inferiority trial comparing short-term dynamic psychotherapy to CT in the treatment of MDD specifically in the community mental health setting. We developed and implemented our randomized noninferiority trial in the community setting with a focus on internal validity, including:

- Expert, intensive, individual and group supervision in each treatment modality on par with the training procedures implemented in efficacy trials
- Blind fidelity ratings to ensure that treatments were delivered adequately and could be discriminated
- Blind expert assessments of the primary symptom outcome

We found that dynamic psychotherapy was statistically noninferior to CT, building on the Driessen trial to indicate that dynamic psychotherapy may be broadly effective across settings. Our blind assessments of adherence and competence demonstrated that the cognitive and dynamic psychotherapies could be discriminated and that the CT delivered in the community setting had adherence and competence ratings comparable to those demonstrated in efficacy trials.

Our community trial also demonstrated that patients found both CT and short-term dynamic psychotherapy to be highly sensible, patients were very confident in the treatments, and patients would recommend these treatments to others.

CT focused on both behavioral activation techniques and cognitive restructuring techniques. Based on our blind expert adherence ratings, the specific techniques used most frequently included concrete activities like setting the agenda and assigning homework, as well as cognitive restructuring techniques that included encouraging the exploration of specific thoughts and beliefs and relating feelings to thoughts.

Short-term dynamic psychotherapy focused on both the supportive and expressive techniques described...
in the manual. Therapists used explicit alliance-enhancing techniques to build the collaborative relationship and used clarifications and interpretations of the relationship patterns interfering with patients’ goals in their current relationships. Based on our blind expert adherence ratings, the specific interventions used most frequently in our community implementation of dynamic psychotherapy included supportive techniques like using mutual affect, conveying a sense of respect and liking, and using a high level of comments, as well as expressive techniques including exploration of patient wishes towards others, perceived responses of others, and responses.

Predictors of effectiveness
To date, the evidence supports the effectiveness of both cognitive and dynamic therapies in the treatment of MDD, which suggests that the American Psychological Association should also consider revising their treatment guidelines. At the population level, both treatments offer a reasonable approach to helping alleviate the symptoms of depression. In practice, however, clinicians must decide which treatments are best suited to individual patients.

Despite decades of research on predictors of effectiveness within these treatments, we still do not have reliable indicators of which treatment to provide to which patients.

DeRubeis and colleagues have conducted innovative studies to evaluate a wide range of possible predictors of treatment effectiveness across CT and medication to build a comprehensive predictive model that could be used to personalize treatment for patients. They found chronicity of illness (more chronic), age (older), and intelligence (lower) were predictive of poor response across both CT and medication. Meanwhile, patients who had been married, unemployed, or had higher number of life events had significantly better outcomes with CT compared with medication. The researchers have developed an algorithm that produces a personalized advantage index that indicates which modality might provide better outcomes.

Such predictive models are sorely needed to help practicing clinicians decide which psychotherapeutic interventions are most likely to benefit any given patient. Most studies evaluate no more than a few predictors of treatment effectiveness within single treatment modalities. Since the prediction of which psychotherapy might benefit a specific patient is likely to be complex, studies are needed that can evaluate a range of possible treatment predictors and moderators across multiple evidence-based psychotherapeutic approaches. Such a personalized approach to matching patients with psychotherapy may improve patient satisfaction with services and improve outcomes.

Conclusion
As we move forward with research to improve our ability to personalize psychotherapies to meet the needs of specific patients, we also need to think through how best to dissemi-

ated the many psychotherapeutic techniques to practicing clinicians. Most training programs remain focused on one school of psychotherapy and many clinicians graduating from these training programs have strong allegiances to a specific psychotherapeutic modality. In spite of this, we have found that clinicians are interested in gaining expertise in a variety of psychotherapeutic techniques.

Despite interest in an eclectic approach to psychotherapy, clinicians are not interested in completely replacing their preferred therapeutic modality. Rather, they prefer to bring in elements of other psychotherapies that may further benefit their patients. As a result, research examining whether a brief focused psychotherapy module can address treatment personalization needs while meeting the practical needs of clinicians is needed to improve the effects of psychotherapies in clinical practice.

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Mental Illness, Civil Liberty, and Common Sense

From our beginnings, psychiatry has functioned at the intersection of medicine and the broader society—serving not only to treat psychiatric disorders but also to help prevent patients from harming themselves or others. When the father of modern psychiatry, Philippe Pinel (1745-1826), freed his patients from chains (at the Salpêtrière asylum in Paris) 220 years ago, he established a centuries-long precedent of attempting to appropriately balance the civil rights of the mentally ill with the occasional and carefully considered need for involuntary treatment. This requires finding a delicate balance in best serving the sometimes-conflicting values of patient welfare, protecting civil liberties, and public safety.

More than any other medical specialty, we sometimes feel compelled, and empowered, to treat patients against their will. With this comes two great responsibilities—to protect free choice and civil rights to the fullest degree possible, but also to restrict them on the very rare occasions when this is clearly necessary to protect the patient and/or society.

A system breaks down
The state-operated inpatient “asylums” in the US, originally intended as a respite for psychiatric patients, soon degenerated into overcrowded and degrading warehouses. Patients were deprived of liberty without due process, subjected to harmful neglect, and often locked up for years—sometimes for life—without any real treatment or normalizing interpersonal interaction. Rather than foster recovery, the social exclusion of hospitals often made patients much sicker.

As recently as the 1960s, there were more than 600,000 Americans involuntarily committed to psychiatric facilities that really functioned more like prisons than hospitals. False commitment was common. Hazardous and unproven treatments like lobotomy and insulin shock were sometimes imposed on unwilling patients for unclear indications.1,2

FIVE NODAL POINTS contributed to the massive deinstitutionalization of psychiatric patients that occurred in the 1960s and 1970s.

1. In 1946, Mary Jane Ward1 published The Snake Pit. This bestselling novel, that was made into an Academy Award winning film, exposed the dire plight of the mentally ill.

2. In 1961, psychiatrist Thomas Szasz2 published his classic book The Myth of Mental Illness. He described the destructive threats to civil liberties and a decent life posed by state “hospitals.”

3. Also in 1961, sociologist Erving Goffman3 described how the neglect and humiliation of asylums-turned-prisons made patients much more symptomatic and dysfunctional than they would be in real-life situations.

4. The availability of antipsychotic drugs in the 1950s and 1960s made feasible the closing of many state hospital beds and treatment in the more normal and socially inclusive community outpatient clinics.

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And finally, Jack Kennedy, the newly elected president, had a strong personal commitment to help people with mental illness based on his sisters’ disastrous experience with lobotomy.

The idea was to close the massive state hospitals and instead care for patients with mental illness in community settings that would end their isolation from the world and recognize their rights as citizens. When funded and practiced well, community psychiatry was an enormous success. But, sadly, the money saved from closing the custodial state hospitals was often misallocated to tax cuts and prison construction—depriving the mentally ill of adequate community treatment and housing. The result has been a broken American mental health “non-system” that over-treats the worried well and vastly undertreats the seriously mentally ill. Instead of 600,000 in state hospitals, we now have 350,000 mentally ill in prison and 250,000 homeless—because the vast majority is unable to obtain decent housing and access to treatment.

Funding for mental health continues to be cut by millions each year, long-term hospitalizations are virtually nonexistent, and many patients who desperately need short-term help are turned away because there really are no beds and no outpatient alternatives. This leaves them, and their families and loved ones, stranded without any recourse in a sea of neglect.

An all-too-common scenario in modern psychiatry is the person who can clearly benefit from psychiatry but receives no help because of unavailable access to treatment and/or too stringent commitment laws. If a (usually petty) crime is committed, often the only alternative is jail because there is no psychiatric treatment available in anything approaching a timely fashion. Occasionally, the seriously disturbed person will commit a major crime—one that could have been avoided had he received proper psychiatric care, counseling, and housing.

While the Szaszian position on involuntary commitment was valuable and much needed decades ago when coercive abuses of psychiatry were frequent, it has now mostly outlived its usefulness because psychiatric coercion is now so rare and almost always necessary when applied. Today the awful coercion of patients with severe mental illness occurs because so many have been relegated to prisons and back alley streets. Misplaced concern about psychiatric coercion often, and paradoxically, reduces freedom and gravely harms patients who are severely ill. In the name of protecting their rights from psychiatry, the person is liable to wind up in jail.

We need an approach that balances civil rights with
the common sense need for occasional involuntary treatment. Even Szasz acknowledged that government has a right—and duty—to protect citizens from dangerous people. While psychiatric commitment can be a terrible evil when done carelessly and too often, it can also be life- and freedom-saving, both for the patients themselves and for those around them, when done rarely and properly.

In weighing the civil liberties implications of involuntary treatment in psychiatry, one must distinguish between emergency holds (usually for 48 to 72 hours)—common and necessary to prevent imminent harm—from “commitment” in the sense of long-term institutionalization. The latter, now very rare, cannot be initiated by psychiatrists but may only be initiated by a judge or a magistrate. Most civil libertarians deem short-term psychiatric holds to be appropriate use of state power to guard against imminent dangerousness. Concerns about long-term commitment are now mostly moot points, since such hospitalizations have become rare.

**Balancing civil rights**

Every effort should be made by the clinician to enlist the patient’s cooperation in their care and treatment. A trusting, empathic therapeutic relationship almost always eliminates the need for court-ordered treatment. If the patient trusts you, he will take your carefully considered recommendation seriously. Involuntary treatment should never be initiated out of convenience or to avoid having the difficult discussion of the need for hospitalization.

If patients must be hospitalized involuntarily, they should be offered the opportunity to sign voluntary papers as soon as possible and afforded the constitutional right to refuse medication if they are competent and nondangerous. Even involuntary patients retain the right to refuse treatment as long as they are competent and there is no acute emergency situation.

Judicial protections must be firmly in place—not just rubber stamps that immediately grant the petitioning clinician’s or police officer’s request. In a free society, there are only two ways a person can legally be deprived of liberty: if he has committed or is suspected of committing a crime, or if he is psychiatrically committed (with the rare exception of the patient who poses a public health hazard due to a communicable disease).

Most court-ordered referrals should be for outpatient treatment in a pleasant environment that includes medication, decent housing, social inclusion, and vocational rehabilitation. Such outpatient commitment statutes exist in many states yet historically have been underutilized because necessary treatment and housing are unavailable.

Psychiatric advanced directives, allowing patients to agree to future treatment should they later become unwell again, should be encouraged whenever a patient has had more than one episode of severe illness.

**Conclusion**

Sixty years ago, Thomas Szasz did the profession—and the world—a great service by pointing out the gross abuses of power perpetrated in the name of psychiatric treatment. His influence on the humane treatment of the mentally ill forever changed the landscape of American psychiatry. But the current clinical and legal reality has reversed. The risks to freedom come from jails and homelessness, not from the now almost nonexistent psychiatric hospitals.

Common sense, compassion, and good clinical care all support the rare, and carefully guarded, use of involuntary treatment to protect the most vulnerable members of our society. As unsavory as involuntary treatment may seem from moral and legal perspectives, it is by far preferable to homelessness and imprisonment.

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What does it mean to be a virtuous psychiatrist? The answer might lie in the wisdom of the Greek philosophers. When it comes to happiness, success, and wellbeing, Aristotle speaks of *eudaimonia* (“flourishing”), a sort of moralized happiness, distinct from mere pleasure. *Arete* (“virtue/excellence”) signifies the qualities necessary to live well and to achieve *eudaimonia*. Moral virtue embraces the notion that if we fail to cultivate and exercise virtues such as wisdom, curiosity, intellect, aesthetic sensitivity, compassion, empathy, and generosity, we fail to exemplify human flourishing.

One is not likely to grow as a psychiatrist if one cannot flourish as a human. Professional success alone is no measure of *eudaimonia*, and one must be wary of paths to professional success that are littered with oppressive loneliness, alienation, apprehension, and self-indulgent greed. Flourishing will not be found in drudgery but in intellectually stimulating and fulfilling work that urges us to be our best selves.

As I graduate from my psychiatry residency program, these thoughts weigh heavily on me. I can think of no better gesture of goodwill to my fellow trainees and other psychiatric colleagues than to share some meditations or pieces of advice that I have found helpful in my own life and career. I certainly cannot claim any degree of *arete*. I aspire (and frequently fail) to live up to these ideals on a regular basis, but they have been valuable guides on an uncertain path.

**1 Invest in a community of colleagues and friends**

No one succeeds alone. Even if that were possible, what meaning does success have in a vacuum? For the ambitious, there will never be enough awards, presentations, and publications. These are hollow achievements by themselves. Kept in the confines of one’s CV, accolades are meaningless, a collector’s obsession. It is only in the context of one’s relationship with a community that these become meaningful: a community that one has contributed to and a community that takes pride in one’s achievements. What is left psychologically of one’s success without this embrace of community and family, except hauteur and snobbery?

**2 Be wary of the psychological costs of empty ambition**

Professional success and personal happiness do not have to be a zero-sum game, but success pursued blindly often is. A healthy degree of ambition is necessary for success in life, but it needs to be tempered by other values in the context of meaningful life goals. As identified by David Foster Wallace:

If you worship money and things—if they are...
where you tap real meaning in life—then you will never have enough. Never feel you have enough . . . Worship your intellect, being seen as smart—you will end up feeling stupid, a fraud, always on the verge of being found out.

3 Be radically honest with yourself
We cannot run from ourselves without great cost. If my experience with psychotherapy as a trainee has taught me one thing, it is our need to be honest with ourselves. We all have aspects in us that are dark, shameful, or embarrassing, and they would be frowned upon by society if they were ever to be revealed. Yet, we do great damage by refusing to acknowledge these fragments of our psychological lives. We should extend to our hidden selves the same non-judgmental understanding and compassion we extend to our patients.

4 Seek honesty in relationships with others
It is better to have fewer, deeper friendships than to have many superficial ones. Those who have achieved some degree of self-honesty will understand and recognize how emotionally constricted our social relationships can be. Ethical considerations are valid restraints to self-expression, but social prejudice and mindless etiquette should not be. Seek honesty in friendships the same way you seek honesty in your relationship with the self.

5 Express your opinions with a measure of humility
It is easy to identify biased thinking and behaviors in others, but we are largely unaware of our own biases. Intelligence is no refuge against this; in fact, a higher cognitive ability may even be associated with a larger bias blind spot. Intelligence fails to protect from other kinds of cognitive biases as well. For instance, it has been shown that the magnitude of my-side bias shows very little relationship to intelligence.

This highlights to me the need for immense humility: we need to be continuously mindful of our own vulnerability to self-deception. In other words, don’t take yourself too seriously.

6 Be charitable to your fellow sufferers
We are all damaged, even the best of us. The facts of life have tarnished us. Arthur Schopenhauer said:

. . . the appropriate form of address between man and man ought to be, not monsieur, sir but fellow sufferer, compagnon de misères. However strange this may sound it corresponds to the nature of the case, makes us see other men in a true light and reminds us of what are the most necessary of all things: tolerance, patience, forbearance and charity, which each of us needs and which each of us therefore owes.

7 Accept the inevitability of failure and loss
Success is never guaranteed, even to those who may “deserve” it. And certainly, even the most accomplished people do not always succeed in everything they do. Accept that no matter how intelligent, powerful, or resourceful you are, you will fail, at one point or another. Life is fragile, and we are all helpless in the face of entropy of existence.

Instead of allowing disappointment to turn us into bitter, base, and vengeful “creatures,” we can transform ourselves for the better. We can do so by answering hardship...
Flourishing

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with hope and courage, and by cultivating compassion, humility, and sensitivity when confronted with suffering. How we respond to pain and evil impacts our moral character, as expressed by Elisabeth Kübler-Ross.6

The most beautiful people we have known are those who have known defeat, known suffering, known struggle, known loss, and have found their way out of the depths. These persons have an appreciation, a sensitivity, and an understanding of life that fills them with compassion, gentleness, and a deep loving concern. Beautiful people do not just happen.

Ask questions. Seek out answers. Be curious about yourself and others. Take delight in the discoveries of shared curiosity.

Be curious. Approach the world with an open mind

Curiosity is a remarkably undervalued virtue. Life is vast and complex, and it deserves to be approached with awe. There is intrinsic value in our attempts to understand this existence. Ask questions. Seek out answers. Be curious about yourself and others. Take delight in the discoveries of shared curiosity. According to Bertrand Russell:7

The happy man is the man who lives objectively, who has free affections and wide interests, who secures his happiness through these interests and affections and through the fact that they, in turn, make him an object of interest and affection to many others.

Choose to grow

We are imperfect, and there is always room for improvement—personally, professionally, morally, emotionally, artistically, and intellectually. Meaningful success is rarely achieved by staying within one’s comfort zone. Be inspired by leaders in your field. Although one may feel miniature in comparison, aspire to see the world from their vantage point and build from there. As expressed by Sir Isaac Newton,8 “If I have seen further it is by standing on the shoulders of giants.”

Seek solace in our limitations

Wisdom is in making peace with our finitude in a potentially infinite world. We find meaning in the pleasures that come our way, in being our better selves, and in generative concerns to leave this world a better place.

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References

Major Depressive Episode: Is It Bipolar I or Unipolar Depression?

When a new patient presents with DSM-5 criteria for a major depressive episode, clinicians should attempt to differentiate between BD and unipolar depression. The treatment of these 2 disorders differs significantly.

- Unipolar depression has many treatment options, including approximately 29 FDA-approved antidepressants and 3 FDA-approved medications, all of which are atypical antipsychotics (one is a combination drug).
- Antidepressants pose significant hazards to patients with BD, especially when used as monotherapies.
- A comprehensive psychiatric evaluation can provide information to assist the clinician in differentiating a unipolar major depression from BD, facilitating optimal treatment of the patient’s affective disorder.
- Correctly identifying and appropriately treating the underlying affective disorder (unipolar versus bipolar depression) may significantly improve the patient’s short-term and long-term response to treatment and maximize the likelihood of effective mood stabilization.

**The DSM change**
A novel change in DSM-5 is the elimination of the DSM-IV-TR diagnosis of Bipolar I Disorder, Mixed Episode (the current episode meets criteria simultaneously for a major depressive episode and a manic episode for at least one week). This was replaced by a new specifier for both bipolar disorder and unipolar depression called mixed features.

**The antidepressant question**
Since the publication of the 2007 New England Journal of Medicine Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study comparing treatment of depressed patients with bipolar disorder on a mood stabilizer (e.g., lithium or divalproex), there is a risk for destabilizing the patient’s mood into a manic state, a depressive state with mixed features, or a manic state with mixed features, all of which can result in considerable morbidity and possibly mortality. Additionally, chronic antidepressant treatment in a patient with bipolar disorder can accelerate mood instability.

**Tools to get to the right diagnosis**
When a new patient presents for treatment of a major depressive episode, it is prudent for the clinician to spend time in the clinical interview obtaining history that may aid in the differentiation of a bipolar depression from a unipolar depression. Differentiating BD depression from unipolar depression can be straightforward if the patient (or their family/advocate/guardian) is an accurate historian or if they can provide comprehensive past treatment records of mood episodes. If the patient has a past episode of mania or hypomania with mixed features, the diagnosis of BD can be made and antidepressant medications should be avoided. Unfortunately, getting a comprehensive and accurate psychiatric history can be difficult for many reasons. In addition, it is common for patients to not view episodes of hypomania as problematic (in fact, patients may experience hypomania as a productive and enjoyable mood state). This may result in lack of reporting.

Although laborious, a detailed initial psychiatric evaluation is needed and should include: a family history and med

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Major Depressive Episode

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(evenly in first degree relatives), details of any prior mood episodes, past treatments that may have unmasked symptoms suggestive of mania or hypomania, symptoms that may have preceded substance use disorders, effects of any past treatment with antidepressants (ie, for previously treated depression, anxiety disorders, premenstrual dysorphic disorder, obsessive compulsive disorder, posttraumatic stress disorder, or other disorders). Similarly, obtaining additional history from a partner, family member or friend can assist in a more informed clinical assessment as to what the primary psychiatric disorder may be.

The Mood Disorder Questionnaire (MDQ), developed by Hirschfeld and colleagues, can serve as a screening tool and should be given to depressed patients to evaluate the likelihood of a prior manic or hypomanic episode. The MDQ consists of 13 yes/no questions derived from the DSM-IV criteria for bipolarity and clinical experience. If the patient checks off seven or more “yes” answers, several of these “yes” symptoms co-occurred, and this resulted in at least moderate psychosocial impairment, then there is a good likelihood of a past manic or hypomanic episode. The MDQ was validated in a study of 198 patients being treated in outpatient psychiatry clinics and demonstrated that patients with a screening score of 7 or more “yes” answers achieved a sensitivity of 0.73 and a specificity of 0.90 for identifying patients with bipolar spectrum disorder. Thus, although the MDQ is not diagnostic for bipolarity, it can help guide the evaluating clinician as to how to direct the clinical interview.

A recent study demonstrated the importance of obtaining a good family history. The study was designed to identify characteristics that would predict conversion from unipolar depression to bipolar depression and followed 91,587 Danish patients diagnosed with unipolar depression from 1995 through 2016. During the follow-up period, which included 702,710 person-years, a parental history of bipolar disorder was the strongest predictor of conversion. If the past psychiatric history reveals prior episodes of mania, mania with mixed features or significant hypomania, the current major depressive episode should be treated as a BDI depression and antidepressant medications should be avoided. If the patient has never had a prior manic/hypomanic episode, differentiating BDI from unipolar depression is more challenging.

Over the past two decades, researchers have attempted to identify additional risk factors that may tip the evaluation scale more toward a likely diagnosis of either a unipolar depression or a BDI. The Table lists risk factors that should be assessed that would support a diagnosis of BDI depression as opposed to unipolar depression. However, it is important to note that none of these risk factors are diagnostic for bipolarity.

Concluding thoughts

Ultimately, the decision to treat a patient who presents with a DSM-5 major depressive episode as an episode of unipolar depression versus BDI depression is made after factoring all of the information available at the time of treatment initiation. It is helpful to think of a balanced scale, with one side containing information suggesting the diagnosis of unipolar depression and the other side BDI depression. After adding all of the elements of the evaluation to the appropriate end of the scale, the likely diagnosis often becomes clear.

A patient who presents with a well-defined DSM-5 major depressive episode may have the primary diagnosis of either unipolar major depression or BDI depression. Since the choice of treatments are significantly different, obtaining a comprehensive initial history, utilizing scales like the MDQ, obtaining additional history from previous psychiatric treatment or from people that know the patient well can provide the clinician with an increasing degree of confidence in how to proceed. Unless hospitalization is indicated, or in the presence of other complicating factors, there is nothing wrong with delaying treatment for a day or a week while additional history is obtained. In the long run, it will pay off to begin a treatment that is more appropriate for the patient’s primary affective diagnosis.

Dr Miller notes he serves as a speaker/consultant for Sunovion and Otsuka/Lundbeck, and on the speaker’s bureau for Allergan and Teva. He is also on an advisory board for Alkermes and Janssen Virtual Feedback Committee, and has consulted for Align2Action.

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Suicides and Psychiatrists

H. Steven Moffic, MD

Dr. Moffic is an editorial board member and regular contributor to Psychiatric Times. Before he retired from clinical work for the underserved population, he was a tenured Professor at the Medical College of Wisconsin.

As I distressingly read about the recent celebrity suicides, as well as the research that suicide rates have been climbing once again over the past couple of decades, I had a sense of déjà vu. We had been here before. I was reminded of Robin Williams, about which a blog for Psychiatric Times drew an unprecedented amount of attention and discussion.1 His, too, was seemingly a surprise, even though he publicly disclosed a history of mental illness and substance abuse.

The usual reminders were trotted:

- The warning signs of suicide
- Patients (and friends) seem to improve or worsen suddenly without sound reason
- Probably half of potentially suicidal patients need good treatment or don’t seek help at all
- Stigma surrounds patients with psychiatric disorders and ultimately, this adversely affects acceptance of mental illness
- Medications (eg, low-dose lithium) are useful and potentially life-saving
- We still need more resources and research
- Guns are dangerous (although these celebrities died by hanging)

For psychiatrists, the suicide of one of our patients is probably the most distressing event in our careers, despite the saying that “You are not a real psychiatrist until you have a patient that commits suicide.” It is intended to mean that a patient’s suicide—as undesired and painful as it is—can be an irreplaceable learning situation that tests our resilience.

Of course, we psychiatrists are not immune to suicide. On the contrary, psychiatrists and other physicians have the highest rates of suicide of any profession.2,3 Paradoxically, we do not fit many of the limitations spelled out for the public:

- We have resources to get the best care (just as celebrities do)
- We have knowledge of what leads to suicide
- We know the implied risk of suddenly feeling better or worse without sound psychological reason
- We are stigmatized, too, but that is offset by the value of our profession

What this suggests is that we should pay attention to reducing suicide in ourselves and among our colleagues. If we find ways to do so, we may learn new innovations for the public. We need to create an atmosphere that enhances self-disclosure to colleagues as well as systems that do not adversely punish the psychiatrist for having a mental illness.

We need to ensure that psychiatrists from various backgrounds (eg, transgendered persons) do not get discriminated against in medicine and psychiatry

(CONTINUED ON PAGE 18B)
We need systems that empower clinical psychiatrists so that our burnout rate diminishes.

We may need to revive the traditional recommendation to receive our own psychotherapy as a learning experience.

Like the song *New York, New York*, if we can succeed in reducing suicide in psychiatrists, perhaps we can do it anywhere. Despite this positive reframing, there should be no other goal than to reduce suicides.

Our ability to predict suicide is still in its infancy. Yet, the psychological pain that is the substrate of a suicide seems so much more common than actual suicides.

Meanwhile, what gives me hope and even amazes me is that there are not more suicides. Our ability to predict suicide is still in its infancy. Yet, the psychological pain that is the substrate of a suicide seems so much more common than actual suicides. It seemed to me that the vast majority of my own patients—dominated by high-risk patients—might potentially want to commit suicide, but only one “succeeded” early in my residency training. I did have some who only survived serious attempts by apparent chance yet ended up being grateful that they survived.

It may be a testimony to both the human spirit as well as the effectiveness of psychiatric treatment that there is not a much higher rate of suicide. Focusing mainly on the negative will only reinforce the stigma. Both psychiatrists and the public need periodic reminders of how well we are doing.

References


Parkinson Disease Psychosis: Evaluation and Treatment

*Neal Hermanowicz, MD*

The symptoms experienced by people with Parkinson disease (PD) are extensive, and it can be daunting even for an experienced clinician to sort through the diverse symptoms that patients present with. In addition to problems with mobility...
patients often experience fatigue, weight loss, sleep disorders, bladder and bowel dysfunction, mood disturbance, cognitive decline, and psychosis.

During these visits, providers must prioritize and be especially attentive to those symptoms that have the potential to be particularly disruptive to the patients and their caregivers. Although the list of problems associated with PD is long, only a small number may be especially and acutely derailing. Although this includes falls and associated injuries, infections, stool impaction and bowel obstruction, in this article, I focus on psychosis.

### Hallucinations and delusions

Psychosis symptoms in PD consist of hallucinations and delusions. The hallucinations are most commonly visual but may involve any of the senses. When hallucinations are initially present, they typically manifest as a sense that someone is standing beside or behind them, or that someone or something has passed through the periphery of their vision. Patients may also have visual illusions, seeing an object differently than what it truly is. A roadside fire hydrant might appear to be a child, or a potted plant appears to be an animal.

Although initially infrequent and non-threatening, over time the hallucinations generally occur more often, are more complex, involve other senses and become distressing. Patients with PD psychosis symptoms may buy food and set their table for hallucinated guests; refuse to enter their bedrooms or their bathrooms because of their perception that strangers are lurking there; flee their homes to escape, call the police, or arm themselves because the hallucinated intruders are perceived as intending to harm them.

**Recommendations for evaluation and treatment of Parkinson disease psychosis**

1. Regular inquiry with patient and caregiver about PD psychosis symptoms.
2. Evaluate and treat acute illness (eg, urinary tract infection, pneumonia, stool accumulation, subdural hematoma).
3. Reduce or eliminate non-essential medications (eg, diphenhydramine, anticholinergics for over-active bladder, anxiolytics, analgesics).
4. Reduce or eliminate Parkinson medications (eg, anticholinergics, amantadine, COMT-inhibitors, MAO-inhibitors, dopamine agonists, levodopa).
5. Initiate medication to specifically address PDP symptoms (pimavanserin, clozapine).

PD psychosis delusions often have content that is paranoid or consists of spousal infidelity. Theft of money or possessions, poisoning by food or medications, including by spouses, family members, or care-
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sides, are recurrent themes of delusions. Spousal infidelity with hired caregivers, friends and neighbors is a common delu-

The psychosis symptoms can turn a difficult situation of coping with PD into an untenable one. They worsen quality of life for patients and caregivers, they are a common reason that PD patients leave their homes for continued care in a skilled nursing facility.

Prevalence and causes
Psychosis symptoms are common in patients with PD. Reported prevalence of psychosis is variable and time depen-
dent—it increases with the duration of illness. One relatively small prospective multicenter study reported that 74% of PD patients experienced visual hallucinations at the 20-year follow up.1

Although psychosis symptoms were previously regarded as adverse effects of dopaminergic medication, it has become clear that this is not entirely correct. Medications do play a role, but neither the medication type nor dosage are clearly corre-
lated with psychosis. Moreover, psychosis symptoms have been reported in patients who have not received any medications for PD.2

The brain substrate enabling hallucinations appears to include parkinsonism with Lewy body pathology, and an increased density of serotonin receptors in the temporal cortex.

Although psychosis symptoms were previously regarded as adverse effects of dopaminergic medication, it has become clear that this is not entirely correct. Medications do play a role, but neither the medication type nor dosage are clearly correlated with psychosis. Moreover, psychosis symptoms have been reported in patients who have not received any medications for PD.2

The brain substrate enabling hallucinations appears to include parkinsonism with Lewy body pathology, and an increased density of serotonin receptors in the temporal cortex. Risk factors identified for PDP include REM sleep behavior disorder, dementia, depression, patient age as well as duration and severity of PD.

Interestingly, patients and caregivers do not necessarily report these symptoms during their appointments with their treating provider. There are several possible expla-

PD, embarrassment about mental health issues, or that there are too many PD symptoms to discuss in a visit with time constraints.

Treatment strategies
Nonpharmacological treatments for PD psychosis such as reassurance and discussion with the patient are being explored but have not yet been firmly estab-

lished. Some basic points are worth considering. One of the most important things is making sure that the patient does not have access to guns or other weapons. In addition, it is important to keep in mind that another acute or subacute illness may cause these symptoms to emerge or increase—
symptoms may be due to a simple problem such as a urinary tract infection or something more complex such as a subdural hematoma. Since hallucinations tend to occur in the evening and nighttime with lower light, well lighted rooms and a nightlight may provide some benefit.

Another important factor to consider is how medications are contributing to PD psychosis. Anti-

cholinergic medications (eg, diphenhydramine, oxybutynin) that enter the CNS should be avoided.
When possible, reduce or eliminate Parkinson medications, all of which may have a provocative effect on psychosis. Opinions vary on which medications to reduce or discard, but most experts agree anticholinergics such as trihexyphenidyl and benztropine mesylate should be the first to go.

There is less agreement about the sequence for reduction/elimination of other medications such as amantadine, dopamine agonists, and MAO and COMT inhibitors. Levodopa is generally regarded as the centerpiece for treatment of motor symptoms of PD, and therefore is usually the last medication to be reduced, but seldom, if ever, removed. The method of addressing psychosis symptoms by PD medication adjustment has not been examined in a large clinical study and therefore the success rate, complications, and time course have not been reliably established.

Pharmacological choices to actively treat PDP symptoms have historically included quetiapine and, less commonly, clozapine. Although quetiapine has been commonly prescribed for PD psychosis, studies have been small and short in duration with mixed results regarding efficacy. Clozapine, on the other hand, has demonstrated efficacy for psychosis in two clinical trials, although, again, relatively small and of short duration.

Although clozapine was found to be efficacious for PD psychosis, there is insufficient evidence to support efficacy of quetiapine. Clozapine is infrequently prescribed, presumably because of the burdensome requirement for monitoring blood counts for the small but potentially fatal risk of neutropenia. Many people, including experienced clinicians, feel that quetiapine has been beneficial for PD psychosis. The discrepancy between formal studies and anecdotal observations is difficult to explain.

Pimavanserin was developed specifically to treat PD psychosis by its action at serotonin receptors, a quality shared by quetiapine and clozapine. Pimavanserin was also developed to avoid interactions with other neurotransmitters, particularly dopamine. Pimavanserin has a relatively long half-life of 57 hours, compared with about 6 hours and 14 hours for quetiapine and clozapine, respectively. This means clinical response to pimavanserin may require several weeks to fully assess its efficacy. On the other hand, the long half-life allows for once daily dosing, which is attractive for patients who may be taking several other medications numerous times daily.

In the single, 6-week study that led to FDA approval of pimavanserin for PD psychosis, mean improvement of psychosis symptoms of 37% was seen with the active treatment compared with 14% for placebo. Adverse effects included confusion, peripheral edema, and increased hallucinations. As with quetiapine and clozapine, and, for that matter, all antipsychotic medications, pimavanserin has a black box warning about increased risk of death in elderly patients with dementia-related psychosis. However, unlike other antipsychotics, the warning further states that pimavanserin is approved only for hallucinations and delusions associated with PD psychosis. The FDA label also carries a warning regarding QT interval prolongation.

At the time of this writing, the lay press was reporting that a number of patients with PD psychosis had died after being treated with pimavanserin. It has not been established that pimavanserin played a causative role in these deaths—no additional cautions have been issued by the FDA regarding associated risks. PD psychosis itself is an independent risk factor for PD mortality.

Conclusion
Routine querying of patients and caregivers about PDP symptoms is essential for optimal care of patients with PD. Identification of PD psychosis symptoms and earlier treatment may prevent escalation to
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When I first read this quote, my initial impression was that it came from Freud. If pressed, I would have guessed from his late-life despairing opus, *Civilization and Its Discontents*. But I was wrong. These were among the last words written by Walter Benjamin, months before his suicide in 1940. In fact, these words are engraved on his tombstone. Even more oddly, and perhaps profoundly befitting his somewhat scattered career, this German-Jewish atheist who died by suicide was allowed burial in consecrated Catholic soil in Spain.

Walter Benjamin was one of the founding fathers of the so-called Frankfurt School of Philosophy in the 1920s and 1930s, which included Theodor Adorno, Max Horkheimer, Erich Fromm, Hannah Arendt, and Herbert Marcuse. The members were German neo-Marxists and psychoanalytically influenced scholars who were openly critical of the German people who allowed the National Socialists to come into power. The group introduced the concept of applying multidisciplinary study and dialectical methods to the bigger questions of history, psychology, economics, philosophy, and art—even to medicine, long before there was any discussion of a “bio-psycho-social” ap-
who took it and did nothing to stop him from overdosing on morphine. She destroyed the note and convinced the authorities that Benjamin’s death was the result of heart failure, concerned that if the authorities discovered Benjamin’s death was a suicide it would weaken the entire group’s chances of obtaining exit visas.

The standard historical interpretation of Benjamin’s death is one of tragic pseudo-irony. Benjamin, with the help of his expatriated colleagues, Adorno and Horkheimer, had undertaken a desperate flight from Marseilles to Port Bou in Spain with several other refugees. Benjamin carried a single attaché case reportedly containing an unknown manuscript, and “enough morphine to kill a horse.” He had already abandoned his brother and sister to their own devices (as German-Jewish exiles with no citizenship; as did Gurland, who abandoned her prisoner-of-war second husband, only to marry Fromm 4 years later, and to commit suicide herself in 1952). Once in Port Bou, the group was told that Spain was no longer issuing exit visas to undocumented French refugees, and this was the pretext for Benjamin’s suicide. The next day, this decision was reversed, and the group was allowed to leave for neutral Portugal, and eventually for New York.

Walter Benjamin’s suicide is especially interesting as a bridge from the Freudian psychosocial era of hysteria-neuroses to the current era of the borderline-narcissist. Psychoanalysis was foundational to the Frankfurt School, and philosophically they were really a marriage of Marx and Freud. All the founding members were sons of wealthy Jewish businessmen who turned their backs on the capitalism of their fathers (often able to do so, ironically, with the financial support of their fathers), but who frequently, especially Benjamin, wrote nostalgically, almost longingly, of their childhoods.

Benjamin especially refused to grow up. His entire historical worldview in fact was that we all march through history backward, that we all greet the imminent future with our backs turned. In other words, the future is a constant reappraisal of the past, a constant atonement, a series of ruminations and regrets, a wistful clinging to prior accomplishments.

The biggest target of Benjamin and his colleagues, and the root of their almost paradoxical nostalgia, was the so-called “culture industry,” the manufacture of products than of wants and desires by, as they saw it, vast capitalistic machines. They frequently compared Hollywood to the Nazi propaganda machine, and they harbored little doubt that Hitler and his lieutenants’ primary motivation was less ideological than financial.

(America was under the sway of “monopoly capitalism”; Germany and the Soviet Union under “totalitarian capitalism.”) They feared less that the Nazis would militarily conquer the world than that the rest of the world would link arms in capitalistic solidarity with the Nazis.

In this context Walter Benjamin became the 20th-century iteration of the “wandering Jew.” While his colleagues settled in Frankfurt, at least until it became too dangerous, he remained restless, taking up residence variously along the Mediterranean and in Germany and Paris, intermittently moving back home with his parents. He was married, but he had frequent affairs, often quite intense relationships that left him temporarily suicidal. He seemed to care little for his only son.

(CONTINUED ON PAGE 18H)
What is especially significant here is Benjamin’s comparison of the what he calls “destructive character,” what we might more euphemistically call the “cluster B personality,” with the “consciousness of historical man.” In his 1931 essay, The Destructive Character, he sums it up in this way: “The destructive character lives from the feeling not that life is worth living, but that suicide is not worth the trouble.”

This reads like a blithe shrugging off of the slightly later Algerian-French existentialist philosopher Albert Camus’ famous admonition that whether to commit or not commit suicide is the only legitimate philosophical question remaining.

So why go on?
This is where the German critical theorists and French existentialists agreed. Because there is always work to be done.

Arthur Schopenhauer, perhaps the most miserable 19th-century philosopher who ever lived, in his cheerily titled On the Suffering of the World, ironically provided what may be the best admonition against suicide, and the one repeatedly resorted to by the critical theorists and existentialists: “The only cogent argument against suicide is that it is opposed to the achievement of the highest moral goal, inasmuch as it substitutes for a true redemption of this world of misery a merely apparent one.”

In other words, suicide is inauthentic. The redemption sought through suicide is illusory. As Benjamin himself put it, “The destructive character sees nothing permanent. But for this very reason he sees ways everywhere. Where others encounter walls or mountains, there, too, he sees a way. . . . Because he sees ways everywhere, he always stands at a crossroads. . . . What exists he reduces to rubble—not for the sake of rubble, but for that of the way leading through it.”

Benjamin’s essay was 10 to 11 years before Camus’ seminal work, The Myth of Sisyphus, in which he elaborates upon the “absurdity” of existence, the inescapable contradiction between the human faculty of reason and an unreasonable world. He bemoans the inevitable “philosophical suicide” that results from any attempt to provide an overarching metaphysical structure to existence: all conclusions invariably contradict their (absurd) premises. His conclusion? We must continue on. We must find our path. Sisyphus was damned to a hell on a treadmill. But even he eventually acknowledges the truth of his absurd situation, of his own personal tragedy, and there is meaning in that.

That is, even in the midst of hell, there is still, or even especially, work to be done.

References
Multimodal Markers and Biomarkers of Treatment

**Rebecca Strawbridge PhD**

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The emergence of precision approaches to treating depression could hardly be more essential: depression is now deemed to have the highest disability burden worldwide of all illnesses, and inadequate response to treatment compounds the issue. A substantial minority of patients experience multiple treatment-resistant depression (TRD) and consequential chronic and/or recurrent illness. The burden of TRD is challenging to quantify but extensive, partly due to the associations with increased physical as well as psychiatric morbidity and mortality that in turn present excessive costs to health care and economic sectors, in addition to being detrimental to individual and care-giver wellbeing. Despite this, TRD has received little attention; as a result, treatment guidelines have struggled to provide evidence-based recommendations for TRD, and we are unable to proactively prevent treatment-resistance.

The field of precision medicine has initiated significant advancements in the treatment of various physical illnesses in recent years. Psychiatric research is currently looking at ways to predict response to treatment for a range of disorders including major depressive disorder (MDD) because of the multitude of treatment options and relatively poor response rates to commonly prescribed interventions.

**Types of therapeutic markers**

The use of biomarkers to assist with optimizing treatment decisions for depression has been receiving increasing attention. Streams of biomarker “omics” may be representative of one or more biological systems and may be measured directly or indirectly in humans. “Omics” describes biomarkers that can be measured across the whole of each level (see Figure). Findings of abnormal genomic, epigenomic, transcriptomic, proteomic, and metabolomic and microbiomic profiles in individuals with psychiatric diagnoses—particularly MDD—have been widespread. Although the findings represent potential diagnostic biomarkers, inconsistencies between studies render single biomarkers ineffective as replacements for current diagnostic tools. Indeed, the potential for a diagnostic biomarker (or biomarkers) for depression are viewed with much skepticism, not least because it is difficult to see how they could ever outperform current diagnostic criteria. For example, neither diagnosis nor antidepressant treatment would be recommended for a patient who biologically scored positive for depression but manifested no discernible psychological or functional symptoms.

“Prognostic” biomarkers might be useful for detecting patient vulnerabilities for TRD or chronic depression regardless of which treatment is selected, while “predictive” biomarkers assess the likelihood of success with a specific intervention. Both prognostic and predictive therapeutic markers for depression have been explored for a wide variety of biological and non-biological factors.

It is outside the scope of this article to detail which markers in particular can be used as aids for finding optimum treatment strategies for number of reasons: there are too many potential markers; we have not nearly enough evidence or knowledge to make useful prediction estimates; and, it is likely that the most accurate prediction models will be of such considerable complexity that they cannot be practically applied with current approaches. Instead, I first look at a few recent findings that indicate promise for this field and follow with an overview of the challenges and barriers that must be overcome before therapeutic markers can effectively be utilized in practice.

**The inflammation revolution**

The most widespread biological research in the last decade has focused on inflammation. One of the most striking findings has been regarding macrophage migration inhibitory factor and interleukin-1β (IL-1β) mRNA. Cattaneo and colleagues specified cut-off values for biomarker levels; the highest levels were categorized as non-responders. Data showed a positive predictive value and specificity of 100% (as well as negative predictive values of ~85% and sensitivity of ~55%). Following the article release, news reports suggested that a blood test could be used to predict response to antidepressants in this way. This inference was premature inference for a number of reasons: limitations in sensitivity, sample size, and lack of replication.

The findings might be explained by the existence of a modifying factor such as chronicity: elevated IL-1β has been indicated in patients with chronic depressive episodes and high risk for treatment resistant symptoms. If these two gene expression markers are established as predictors of escitalopram or nortriptyline response (as Cattano et al. found) in future studies, many questions remain; for instance, do these biomarkers represent prescriptive predictors of specific antidepressants or prognostic markers of response regardless of treatment?

Another unanswered question is how gene expression relates to other streams of biomarker (see Figure). Increasing attention is being paid to the microbiome. In support of the findings of Cattaneo and colleagues, elevations in circulating inflammatory proteins have been widely linked to poorer treatment response to various antidepressant treatments but a better response to anti-inflammatory treatments than those with normal inflammatory activity.

SIGNIFICANCE FOR PRACTICING PSYCHIATRISTS

This article provides an update on the research evidence for predictors of response to treatments for patients with depression. Biomarkers have attracted research and media attention for their potential to progress the path towards precision psychiatry, but it is important to highlight that the evidence is far from consistent enough in methodology or results at present. The article proposes that identifying homogenous subgroups of patients with depression and utilizing new multimodal predictive modelling techniques will help facilitate advances in precision approaches to treatment for depression. In doing so, we can hope for an optimized answer to the question “what works for whom?”

- There is an urgent need for tools that can help inform which treatment patients with depression should receive.
- This field is progressing and extensive biological and non-biological factors have shown the potential to predict response.
- Advances in ‘big data’ and statistical modelling hold promise for translating research into clinically useful approaches to treatment selection in the future.

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It’s not all about inflammation
Promising biomarkers have been posited across a range of biological systems, including neurotransmitter, cell proliferation, and metabolic and endocrine systems (which in themselves operate across omics levels). Cortisol levels could be a prognostic or prescriptive therapeutic marker. Depressed patients with higher levels of cortisol respond less well to psychological (and to serotonergic) therapies than those with lower levels. This relationship has not been consistently found in all studies and many other biological markers have predicted response to various treatments for depression (ie, inflammatory cytokines, c-reactive protein, brain-derived neurotropic factor, genetic and other biological markers).

Moreover, numerous nonbiological constructs have preceded poor antidepressant response and have been associated with many biomarkers, such as childhood trauma, personality disorder, psychosocial stress, chronicity and treatment resistance of depressive illness. Taken together, it appears improbable that a single marker of response to any treatment for depression can be identified without accounting for multiple factors. And modelling these variables together to understand the interactions between treatment mechanisms and outcome is a huge challenge that requires large patient samples and advanced computational models.

The search for homogeneous subtypes
Across biological and non-biological research one factor that is discussed again and again, but has not been fully addressed, is the heterogeneity of depression. One patient can present strikingly differently from another, but on the whole depression is viewed as a single disorder. Despite attempts, clinically homogeneous subgroups have not been identified that map on to which treatments people respond to, or even that consistently associate with specific biomarkers, which need to be delineated before therapeutic markers can be established.

Some subtypes have been commonly used such as atypical or melancholic features and these have, to some extent, been linked with biological features: patients with atypical depression may present with attenuated baseline cortisol levels but higher inflammatory activity. A somatic subtype may comprise patients with more prominent biological abnormalities, particularly related to inflammation (with prominent symptoms associated with sickness behavior), and this subgroup population might be at increased risk for non-response to monotherapy or low-intensity treatments for depression. This may exemplify the need for multimodal modelling of therapeutic markers in depression, specifically through combining clinical and biological factors. As well as proving useful for guiding a precision medicine “what works for whom” agenda, multimodal examination might also help to solve some of the other problems discussed above.

Clinician versus computer: clinical implications
In the absence of precision markers for treating depression, in contrast with a wide array of potential interventions to select from, clinicians are left to use their own clinical insight and intellect (in addition to communication with patients) to select the treatment most likely to achieve remission. This can work well; for example, a specialist national inpatient service in the UK for patients with severe TRD has utilized clinical expertise alongside multidisciplinary treatments to achieve very high rates of treatment response that have been sustained one year after discharge. While this indicates that even for complex affective disorders, considering a patient’s illness holistically and insightfully can reach a successful outcome for many individuals, this does not come without significant time investment and domain-specific expertise. Furthermore, findings suggest that statistical models consistently outperform clinical decision making in predicting response.

Predictive models are not yet sophisticated enough to be clinically useful and statistical modelling has its own challenges, including but not limited to overfitting of data, underpowered sample size, or poor quality data from large studies. Many researchers and clinicians believe that “big data” will catalyze basic science into translational use through mining datasets with large numbers of patients and variables (both biological and nonbiological) and employing machine learning strategies to determine clinically useful algorithms.

What works for whom: a conclusion?
Especially now that exciting interventions are beginning to surface, caution is urged. Not only are there thousands of potential therapeutic markers for depression (and more being proposed all the time), these often do not consider clinical heterogeneous presentations. Additionally, there are many putative reasons for non-response to treatments, including inaccurate diagnosis, life events, comorbidities, concurrent treatments, adherence or tolerability issues, duration and dose-related factors, thousands of permutations of depressive symptom combinations (and treatment combinations).

Research on therapeutic markers aspires to facilitate a means of maximizing treatment response early in the course of illness and bring enhanced care to patients more widely, quickly and cheaply. Although this is a noble goal that has the potential to enhance treatment and lessen the burden of this complex illness for many individuals, it is not straightforward: Depression is a complex phenomenon that co-occurs frequently with many diagnoses and for every triumphant anecdote there are a legion of other less-resolved cases.

In order to identify prognostic markers of response to treatment for depression, a multimodal model will almost certainly be required, with its components not yet ascertained. Models of prescriptive markers of response—predicting who will respond well to specific individual treatments—are likely farther away. Extensive work is ongoing in this area, and advancements in prediction modelling will accelerate progress. To accurately answer the question “what works for whom,” we need to maintain hope, patience, and determination.

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References
Pseudobulbar affect (PBA) is a neurologic condition that is characterized by brief episodes of uncontrollable crying or laughing, which usually is incongruent with the patient’s mood. Unfortunately, these involuntary emotional outbursts may be mistaken for symptoms of a mood disorder, such as major depression. Pseudobulbar affect often occurs secondary to a neurologic disorder, such as stroke, Alzheimer disease, traumatic brain injury, multiple sclerosis, and amyotrophic lateral sclerosis.

The prefix pseudo in ancient Greek language is used to represent something that is false. Pseudobulbar affect is appropriately named to describe an affect that may be incongruent with internal emotional states. This disorder was previously called emotional incontinence, pathological crying, and emotional lability. A likely reference to PBA appeared in Charles Darwin’s 1872 book, The Expression of the Emotions in Man and Animals. Charles Darwin stated, “Certain brain diseases, such as hemiplegia, brain-wasting, and senile decay, have a special tendency to induce weeping.” Although PBA has been documented in the literature for centuries, it continues to be misdiagnosed and underdiagnosed.

CASE VIGNETTE
Mr. A, aged 52 years, was admitted to the ICU following an ischemic stroke. During the hospitalization he began having sudden, brief, uncontrollable crying episodes. A psychiatric consultation was obtained, and he was started on sertraline for MDD. Unfortunately, he had minimal response to the medication. He continued to have crying episodes at home and was unable to identify a trigger for these outbursts.

Mr. A had no previous psychiatric history; he had a family history of major depression in an aunt. He reported a depressed mood that began shortly after the onset of his unexplained emotional outbursts. Mr. A’s wife was present at all medical visits and insisted that he was depressed as a consequence of the stroke. She believed that he was in denial about his feelings. Mr. A reported that he previously enjoyed spending time with family, friends, and outdoors. However, he began spending all of his time at home and declined family gatherings. Mr. A attributed these behavioral changes to wanting to avoid the embarrassment of an uncontrolled crying episode in public.

These symptoms persisted for months, and he obtained a second consultation. During this consultation, his symptoms were further elucidated. The crying outbursts were sudden, involuntary, unpredictable, excessive, and incongruent with mood. Pseudobulbar affect was diagnosed and Mr. A was started on a new treatment regimen. The symptoms decreased in frequency and intensity. His family and friends were educated about the condition, which decreased his embarrassment when an outburst occurred. Mr. A was able to resume spending time with family, friends, and restarted his outdoor activities.

Etiology
The exact cause of PBA is unknown. It is estimated that approximately 1.8 to 7.1 million individuals are affected in the US. An accurate estimate is difficult to obtain because of variable diagnostic criteria and patient populations. Research suggests that PBA affects up to 50% of patients who have experienced a stroke or have amyotrophic lateral sclerosis.

Pseudobulbar affect is caused by lesions of the medulla oblongata. Although, bulbar refers to the brain stem, the insult does not need to occur in the brain stem to cause PBA. Since PBA is often secondary to a wide variety of neurologic insults or injuries, the focus of research is not on identifying a specific lesion, but on identifying a common circuit. Current evidence suggests that PBA results from the disruption of the cerebro-ponto-cerebellar circuit, which decreases the threshold for the expression of emotion. It is proposed that damage to this circuit, such as from a stroke, may result in a disconnect. This condition has been classified as an affective disinhibition syndrome. The use of neuroimaging and neurophysiological studies of patients with PBA provides a neurological basis of PBA.

The dysfunction of the cerebro-ponto-cerebellar circuit is implicated in PBA. This circuit controls limbic and motor descending pathways to the brainstem and cerebellum. According to this theory, the cerebellum automatically controls emotional expression in response to information received from the cerebral cortex. This was tested using event-related potentials, which is a method to measure transient voltage waveforms in brain tissue. This work supported the prevailing gate control theory of PBA, which consists of sensory and motor abnormalities that result in disinhibition of the cerebellum’s ability to function as a gate control for motor expression of emotions. The cortical inputs to this circuit normally serve to inhibit inappropriate affect.

Research also suggests that abnormal glutamnergic and serotonergic neurotransmission may contribute to PBA. However, numerous other neurotransmitters may also be involved given their impact on emotion, such as dopamine, norepinephrine, and acetylcholine. We know that serotonin has many projections throughout the brain, and cell bodies originate in the brainstem raphe nuclei. Glutamate is the main excitatory neurotransmitter in the CNS. The exact etiology of PBA is unknown, but research supports a dysfunction of neural circuits and neurotransmitters that modulate the motor expression of emotion.

Diagnosis of pseudobulbar affect
The diagnosis of pseudobulbar affect is made upon clinical presentation and patient self-report of symptoms. The following are key diagnostic criteria: involuntary episodes of laughing and/ or crying that are sudden, unpredictable, excessive, and exaggerated.

There is a wide differential diagnosis for PBA, but the most challenging aspect is differentiating (CONTINUED ON PAGE 23)
Babble on Revisited

» Harvey Roy Greenberg.

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The ubiquitous compulsion to binge on TV coverage of the 2017 presidential race prompted me to fabricate, and anatomize the diagnosis of “Election Addiction Disorder.” I predicted the enormous craving for pre-election news would quickly dissipate after the polls closed, saving a few disgruntled true believers—presumably those unable to grieve a Trump smashing defeat.

Of course assumption of a Clinton triumph proved utterly wrong. Party favoritism played no part in my misread: I wasn’t much enamored of either candidate. But the London bookies had been uncannily spot-on about previous elections in the colonies, their chief aim only being to amass a mountain of quid. Brit oddsmakers predicted a Clinton victory as certain as Big Ben’s chime—so who was I to disagree?

Bingeing on news about the latest White House rumpus has escalated exponentially since the election, stoked—inter alia—by the Mueller investigation; the possibility of a disastrous trade war; and the threat of exchanging missiles with a North Korean adversary who sports the same bellicosity and gonzo hair-do. The Korean adversary who sports the same bellicosity and gonzo hair-do.

In my practice, I’ve been encountering despair, anxiety, and insomnia related to coverage of the West Wing rumpus room, augmenting patients’ previous difficulties. Spouses complain about sleep deprivation caused by a mate binge-watching into the wee hours. The addict often insists upon his or her partner’s presence for argument, solace, or simply being on the other side of the mattress as an irritated transitional object.

Whatever their political views, victims are haunted by an inchoate sense that the wheels are coming off the car, with nary a mechanic in site. Some sort of Yeatsian second coming seems looming just over the horizon. Patients who lived through 9/11 report dreaming about the fallen towers. “The best lack all conviction, while the worst are filled with passionate intensity,” said Yeats. I hear these sentiments echoed frequently in and outside the office.

CNN, MSNBC, and Fox News had addressed every quiddity and quoddity of the tumultuous campaign scene to vast profit. Eighteen months into the New Order no end to the Oval Office hurly-burly is in sight. Network honchos appear convinced that their mandate to keep viewers glued to the tube will continue indefinitely, as well as the tsunami of cash.

In this setting, tropes and technology reinforcing the feedback loop between coverage and consumer during the campaign have been cleverly enhanced. Now the news breaks from one nanosecond to the next. Whether the subject is ominous or trivial, it’s portentously trumpeted.

In the green and salad days of Murrow, Huntley and Brinkley, a chief anchor commented on the day’s events, then switched to a colleague as occasion dictated. Simultaneous splitscreening of multiple commentators roughly paralleled the rise of news-as-infotainment and pervaded the 2017 campaign coverage.

A pair of simultaneous talking heads originally sufficed. The number increased during the campaign, then escalated exuberantly to 6 or even more. Daily shows like “Morning Joe” and “Fox and Friends” feature a bevy of “regulars,” joined by one or more expert of every stripe, live and splitscreened. These continue breeding like rabbits.

Some are current or former high office holders: generals; diplomats; attorneys. Even mental health professionals have had a say. Some are respectable and bear attention; others are dubious bloviators, hack lobbyists; party-line speck-chuckers, and so forth.

Discourse ranges from collegial to acrimonious. The attack mode increasingly prevails. On the small screen as in the halls of power, going low commands higher recognition than common courtesy and civility.

Inevitably several commentators have become major celebrities themselves, in this culture of celebrity. The majority wear their laurels lightly; but others ooze smug self-satisfaction—especially off-putting when the broadcaster was once reasonably modest. As a function of ego-bloatting, subjective opinions are frequently stated as received truths.

I AM HARDLY THE FIRST TO OBSERVE THAT POLITICAL COVERAGE NOW COMPRIS ES AN ONGOING REALITY SHOW. The reasons why so many stay riveted to the screen are complex. Speculations on individual motives follow.

1 The pleasure principle certainly plays a role for junkies and ordinary viewers. Key broadcasters on the left and right can be genuinely informative and entertaining. The morning show coffee-klatches generate a comfortable, if totally spurious camaraderie—the bogus warmth of being in the know with Mika and Joe.

2 Uncertainty has never sat well with the species since the first caveman worried whether a wild wind or a wild beast was howling in the stygian night outside his cave. Addicts are particularly angst-ridden about being caught off-guard, if deprived of the network clanging, especially when the event at hand threatens life, limb, or stock market account.

The 16th century philosopher Thomas Hobbes’ posited that humanity’s native state was unremittingly savage. For Hobbes there was no Eden, only homo homini lupus—man is wolf to man. From his dank perspective, society was constituted lest we rend each other to pieces.

Freud echoed Hobbes’ pessimism about the human condition in Civilization and Its Discontents. He described the process of acculturation as the induction of a mass obessional state. Governments, laws, codes of conduct, served uneasily to keep a lid on the collective id. Civic and religious rituals reassured one that the status quo would remain perpetually in place. In this context, one speculates that the bigger’s incessant “checking in” may comprise a paradoxically comforting ritual: if the talking heads weren’t there whenever we tune in, then neither would we. (Freud also argued that “surplus aggression” was an inevitable consequence of keeping up the illusion of stability. With characteristic irony, he conceived that bloody warfare would be an inevitable consequence of projecting that surplus upon whatever convenient enemy.)
Throughout the centuries, during times of uncertainty before one or another calamitous prospect, those who felt—or were in fact—powerless, instinctively looked to charismatic others. Leaders temporal or secular, sundry prophets, sadhus, gurus, believed they possessed potent, indeed omnipotent power to head off apocalyptic or lead their acolytes out of it. One wonders if celebrity commentators now have acquired the cachet of the pseudo-messiahs of yore. The media guru may also be perceived as an avatar of a higher political power, confirming viewer/follower belief in the stupidity, evil, or elitism of a detested “other.”

I believe news programming is pitched at sustaining analogous ten-"other." pidity, evil, or elitism of a detested viewer/follower belief in the stu-

ning: intimating that a resolution is near vis-à-vis North Korean nuclear sabbre rattling, construction of a Mexican Wall, or the Stormy Dan-

nels scandal. Clearly, no such closure is in sight for the cascade of problems under endless scrutiny by the news sachsens. Instead of Murder on the Orient Express, we have Schehe-

razade. The moguls and their fellow travelers aim to keep the game afoot, the audience mesmerized, while enormous wealth continues to flow from hawking car insurance or psoriasis remedies.

My previous column cited Extraordinary Popular Delusions and the Madness of Crowds, the classic study of mob behavior by 19th cen-
tury journalist Charles Mackey.1 Mackey famously concluded that we go mad en masse about stock market bubbles or fashion fads, then recover our wits singly and slowly.

For some viewers the sheer amount of yackety about crucial or jejune issues comprises one great clot of undifferentiated, indigestible verbiage. They’ve recovered their wits, totally turning off an avalanche of blather that may yet generate its own extinction. One hopes that the awakening will spread. But as of now, there seems no end to the extra-

dinary popular delusion manufac-
tured by political broadcasting.

I haven’t heard of 12-step pro-

grams for news junkies. I can only advise my bingeing patients to fol-

low the lead of the healed; turn off the babbles absolutely, lest your brain turn to Swiss cheese: get down and get cognitive; commence deconditioning. Confine viewing the daily jabberwocky to a few moments; watch only those weekend shows that offer calm reprises. I ad-

vise sleep deprived mates to slum-

ber elsewhere until the afflicted partner gets the message. Instead of watching the incessant babble, I suggest reading the news in peace and relative sanity, over decaf or cocoa or Jack Daniels. I recommend publications like The Economist, although that suggestion would cer-
tainly consign me to the rack, thumbscrew and flame in certain quarters.

Finally, one is reminded of the story of the Boston grand dame, who was asked whether she would be voting for Franklin Roosevelt or Wendell Wilkie. “Neither,” was her tart reply, “It only encourages them!!”

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atric Times. 34(11);37.


Book Review
Millard Salter’s Last Day

Reviewed by Susan Hatters-Friedman, MD

Dr Hatters-Friedman is Associate Professor, University of Auckland, New Zealand.

n this novel by psychiatrist Jacob M. Appel, we join New York consultation-liaison psychiatrist Dr Millard Salter for what he intends to be his final day on earth. He has plans to hang himself at the end of the day (his 75th birthday), so that he doesn’t end up growing old and dependent. He has had one loving marriage and had fallen in love again in his widow-

hood. Three of his 4 children are successful, and he has had a productive career. As a psychiatrist, he will have, like the rest of us, spent much of his working life doing suicide risk assess-

ments and envisioning risk reduction plans. “Had he been one of my own patients, he’d have phoned 911 immediately.”2 Yet Dr Salter is not depressed; rather he has rationally planned out his suicide at length.

While the topic sounds like it could be nothing but morose, Appel tells Millard’s story with warmth and wit. Millard’s swansong of a day is not as expected. It is filled with a medical student who needs a letter of recommendation, VIP pa-

tients, and a hilarious malingerer (who rents his NYC apart-

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I believe news programming is pitched at sustaining analogous tension. From this perspective, the commentators’ long and loud debating engenders a sense of cliffhanging: intimating that a resolution is far from hand. The moguls and their fellow travelers aim to keep the game afoot, the audience mesmerized, while enormous wealth continues to flow from hawking car insurance or psoriasis remedies.

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References
Silver Linings After Abuse and Neglect

The neuroprotective role of resilience in patients with schizophrenia who experienced early childhood trauma is evaluated in this brief update.

>> Brian Miller, MD, PhD, MPH

**Childhood trauma and schizophrenia**

- Childhood maltreatment is associated with multiple adverse mental and physical health outcomes, and has an increased prevalence in schizophrenia.
- Schizophrenia is associated with increased cardiometabolic morbidity and mortality.
- Childhood trauma may be associated with metabolic dysfunction in schizophrenia.

**Resilience**

- Psychological resilience—mental health despite experiencing adversity—may positively impact mental and physical health and mortality.
- No previous studies have investigated whether resilience has a moderating effects on the negative impact of childhood trauma on health in patients with schizophrenia.

**Study Aim**

- Lee and colleagues investigated the association of childhood adversity on mental and physical health outcomes in patients with schizophrenia and healthy controls, including moderating effects of resilience.
- No previous studies have investigated whether resilience has a moderating effects on the negative impact of childhood trauma on health in patients with schizophrenia.

**Methods**

- The authors included 114 patients with schizophrenia and 101 controls.
- The diagnosis of schizophrenia or schizoaffective disorder was confirmed with SCID interviews; controls were screened with the MINI.
- Subjects with non-tobacco substance use disorders in the past 3 months, dementia, intellectual disability, or major neurologic disorders were excluded.
- Patients with schizophrenia were assessed with standard rating scales for psychotic disorders.
- Resilience was assessed using the 10-item Connor-Davidson Resilience Scale.
- Mental and physical well-being were assessed using the Short Form Health Survey, and measurement of height and weight.
- Participants also completed the Childhood Trauma Questionnaire.
- Blood samples were collected for fasting glucose and insulin, and hemoglobin A1c.
- General linear models were used to analyze the effects of subject group, trauma, and resilience on mental and physical health measured and metabolic biomarkers.

**Results**

- Patients with schizophrenia had worse self-reported mental and physical well-being, higher levels of trauma, higher BMI, and worse cognition and metabolic biomarkers than controls.
- In both patients and controls, childhood trauma was significantly associated with physical well-being, fasting insulin, and insulin resistance.
- In patients with schizophrenia, childhood trauma was not associated with worse mental health.

**Key Findings**

- Higher resilience was associated with better mental well-being (regardless of trauma severity) and better physical well-being and metabolic biomarkers.
- Patients with schizophrenia, high resilience, and high trauma had physical and mental well-being scores comparable to controls with low resilience and high trauma.

**Discussion**

- Patients with schizophrenia have higher levels of childhood trauma than controls, which is associated with worse physical, but not mental, health.
- Resilience was associated with better mental and physical health.

**Take-home**

- Resilience plays an important role in mental and metabolic health in patients with schizophrenia and controls.

**REFERENCES:**

Pseudobulbar Affect

Continued from page 22

PBA from MDD (Table). The differential diagnosis should also include the following: frontal lobe disorders, behavioral disturbances associated with Alzheimer disease, stroke, epilepsy, traumatic brain injury, and essential crying, all of which may be the underlying neurologic disorder that has created the cerebro-ponto-cerebellar circuit dysfunction that is the cause of the pseudobulbar effect.

The initial criteria for PBA were established by Poeck in 1969, which included: an emotional response inappropriate to a situation, affect is not congruent with emotions, inability to control the duration and severity of symptoms, and emotional expression does not result in relief for the patient. These criteria were expanded by Cummings in 2006 to include the following: a change from baseline emotional reactivity, not due to another disorder, not secondary to drug use, causes significant impairment, and affect is incongruent or exaggerated with patients’ subjective experience of their emotions.

Scales used to further characterize the diagnosis and symptoms of PBA include the Center for Neurologic Study—Lability Scale (a self-report instrument) and the Pathological Laughing and Crying Scale (PLACS), which is administered by a provider and measures sudden episodes of crying or laughing. The major clinical challenge is recognizing the symptoms of PBA, which is often misdiagnosed as a mood disorder.

Differentiating pseudobulbar affect from depression

Pseudobulbar affect is a disorder of affect and major depression is a disorder of mood. The key to differentiate these two disorders is understanding the difference between affect and mood (Table). Affect is an outward expression of a subjectively experienced emotion. A mood is experienced internally. Affect has been defined as “the subjective and immediate experience of emotion attached to ideas or mental representations of objects. Affect is an outward manifestation that can be classified as restricted,blunted,flattened,broad,labile,appropriate,or inappropriate.”

PBA is characterized by a lack of voluntary control over affective expression, a disorder of disinhibition. It is distinguished from MDD by its duration of symptoms. PBA symptoms last seconds to minutes, but major depression lasts weeks to months.

Patients with PBA will describe sudden,brief,intense,and uncontrollable displays of emotion. The emotional response or affect is considered inappropriate to a situation, exaggerated, involuntary, and often incongruent with mood. The emotional outbursts in PBA do not result in any relief for the patient and are not consistent with previous baseline emotional responses. The diagnosis of PBA is often secondary to neurologic disease, insult, or injury. PBA may occur comorbid with depression, but it is a distinctly different disorder.

MDD presents with symptoms that occur over weeks to months. The affect, such as crying, is consistent with the perceived depressed mood. Those with depression may have discrete emotional outbursts, but these are often elicited by known emotional triggers. Those with depression can identify their psychological triggers and modulate their affective responses, voluntarily. The diagnosis of MDD also includes a history of sleep disturbance, changes in appetite, changes in energy, feelings of guilt and hopelessness. These somatic symptoms are not directly associated with PBA. Major depression is thought to involve numerous and wide spread neural pathways and neurotransmitter systems, but PBA may involve more specific networks that determine the motor control of affect expression.

Treatment

There is no cure for PBA, but treatment can reduce the intensity and frequency of symptoms with the goal of improving well-being. The first step is to provide education to both the patient and his or her family. This will decrease the embarrassment associated with uncontrollable episodes and improve social functioning.

Until recently, the main treatment for PBA was antidepressants. Tricyclic antidepressants, and selective serotonin reuptake inhibitors/serotonin and norepinephrine reuptake inhibitors have been used off-label for treatment. The evidence for increasing serotonin to improve PBA symptoms has been limited to mainly case reports and small trials. It is thought that increasing levels of serotonin may decrease emotional lability and improve PBA symptoms.

The first treatment for PBA was FDA approved in 2010. Nuedexta is a fixed combination dosage capsule with 20 mg of dextromethorphan hydrobromide and 10 mg of quinidine sulfate. Normally,dextromethorphan is rapidly metabolized by CYP2D6 to dextorphan,which appears to have a similar receptor binding profile. Although the mechanism of how dextromethorphan decreases the number of episodes of involuntary laughing and crying is unknown,it is putatively related to dextromethorphan’s competitive low-affinity antagonism at the N-methyl-D-aspartate (NMDA) glutamate ion channel and/or its potent agonism at the sigma-1 receptor. Moreover,dextromethorphan inhibits the re-uptake of both serotonin and norepinephrine, which may also contribute to its mechanism of action.

The role of low dose quinidine,an antiarrhythmic medication,is to utilize its potent inhibition of the CY-P2D6 metabolic enzyme that slows down the metabolism of dextromethorphan and increases brain exposure. Pharmacokinetically, this increases the half-life of dextromethorphan from roughly 2 hours to 13 hours,hence allowing for a low dose and a BID daily dosing schedule.

A 12-week,double-blind,randomized, controlled trial of dextromethorphan/quinidine reported a reduction in the PBA episode rate of 46.9% to 49.0%, depending on dextromethorphan dose, compared with placebo. The exact mechanism is unknown, but it likely reduces sympto- mptoms of PBA through modulation of excitatory neurotransmission in disrupted neural circuits.

Concluding thoughts

PBA is a neurologic condition that is characterized by brief episodes of sudden and uncontrollable emotions. These involuntary outbursts of emotion may be mistaken for symptoms of a mood disorder,such as major depression. PBA is characterized by a lack of voluntary control over affective expression, a disorder of disinhibition. Major depression is thought to involve numerous and wide spread neural pathways, but PBA may involve more specific networks that determine the motor control of affect expression. The recognition and diagnosis of PBA is necessary to ensure appropriate treatment and improved quality of life.

References

5 Ways to Ask About Hypomania

Hypomania is critical to rule out, but hard to pin down.

Chris Aiken, MD

Dr Aiken is Instructor in Clinical Psychiatry at the Wake Forest University School of Medicine and the Director of the Mood Treatment Center in Winston-Salem, NC. He reports no conflicts of interest concerning the subject matter of this article.

Have fun, and don’t worry about your work. As long as you don’t give an antidepressant to a patient with hypomania, you can’t go wrong.” It sounded easy at the time, as the attending welcomed us to the outpatient module of psychiatric residency. Fifteen years and over 10,000 structured interviews later, I can only attest to how hard it is to diagnose hypomania. Here are the top pearls I’ve learned along the way.

1. Calibrate your index of suspicion

Expert interviews suggest that hypomania is common among patients with depression. The rates range from 20% to 30% in primary care, 30% to 40% in psychiatric clinics, and, in those with treatment-resistant depression, 40% to 60%. Those numbers might suggest you need to raise your index of suspicion, or they may just trigger disbelief. My first reaction was the later, but when I started applying structured interviews to my work in a general adult private practice, I arrived at the same frequency: 40%.

2. Use a structured interview

Instruments like the MINI and the SCID are the closest we have to a gold standard in psychiatric diagnosis. Their hypomania sections, however, tend to suffer low reliability, so it’s helpful to augment them with paper-and-pencil screens that both the patient and a relative can complete. There are links to the SCID, MINI, and 3 screening tests (see http://www.moodtreatmentcenter.com/measurement).

3. Follow the clues

Psychologically, hypomania has a lot in common with addictions. Denial, lack of insight, and a tendency to minimize or forget these altered states get in the way of diagnosing them. When asking structured questions such as, “Have you ever had a period of time when you felt high, hyper, or full of energy?”, pay attention to vague answers like “not really,” “only when I’m excited,” or “not in a long time.” If your index of suspicion is high, those answers should prompt you to dig further.

4. Don’t explain away symptoms

Patients tend to experience mood symptoms as natural responses to life, whether depressive or hypomanic. Their explanations can leave us wondering: Was it the normal glow of romance, or did a hypomanic drive prompt that new relationship? Was it just an all-nighter during final exams in May, or springtime hypomania? Was it youthful folly, or did bipolar strike at the usual age of onset (15 to 20)? I have never found definitive answers to those questions, but ambiguous answers remind me to keep looking for clues as I get to know the patient better.

5. Comorbidities are a soft sign of bipolar, not a reason to dismiss it

All the symptoms of hypomania are common in other disorders:

- ADHD: hyper, distracted, racing thoughts, talkative, impulsive
- Borderline personality disorder: labile, impulsive, irritable
- PTSD: irritable, reckless behavior
- OCD: hyperactive around compulsions
- GAD: racing thoughts, distracted, irritable
- Addictions: impulsive, euphoric, decreased need for sleep

The problem is that 60% of patients with bipolar disorder have at least one of the comorbidities I just listed, so their presence should raise—not lower—the index of suspicion.

Uncertainty is the rule with hypomania. I’ve followed some patients for 10 years before recognizing it. It’s humbling work, not unlike the type of dilemma Hippocrates wrestled with when he wrote that “Life is short; the art is long; opportunity fleeting; experience perilous; and decision difficult.” Tune in next month for part two of this guide, and never stop looking for clues.

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Addressing the Challenges of Treatment Resistant ADHD in Adults

The prevalence of ADHD in adults is estimated to be 4.4% in the general population with ranges of 12% to 40% in patients with other psychiatric disorders, depending on the primary diagnosis. Increasing recognition of ADHD as a source of functional impairment in adults has meant that its treatment is moving from the domain of specialists into the office of general psychiatrists. But what happens when the initial treatment approach does not provide adequate results? Through discussion of three cases, in this article we identify sources of treatment resistance and provide suggestions for optimizing treatment.

CASE VIGNETTE 1

John was a 19-year-old college freshman with a diagnosis of ADHD established in middle school who presented to the Penn ADHD Program with concerns that his stimulant medication was no longer working. He had been on the same daily dose of extended release mixed amphetamine salts (MAS) 20 mg in the morning along with 10 mg immediate release MAS in the afternoon since 11th grade, with generally good results until recently. John was enrolled in a very rigorous program in college that required him to read 250 to 300 pages of technical writing and to write up 2 lengthy lab reports and multiple homework assignments on a weekly basis. While he expressed a great deal of interest in his courses, it quickly became clear to him that the academic load was more than he had expected.

During his intake, John reported difficulty staying focused during lectures and lab sessions, often to the point that he would lose track of the course material. After class, John had trouble getting started on his assignments, often spending long periods of time internet surfing and chatting online with friends. He admitted that he had been spending excessive amounts of time socializing with his roommates and playing his favorite video games until late at night. He reported some continued benefit from the medication but noted that it was wearing off by the end of the morning instead of lasting through his afternoon classes and study sessions.

Despite recommendations for improving his scheduling and sleep hygiene plus an increase in MAS dosage to 20 mg of extended release twice daily, John continued to fall behind on his assignments and struggled to pass his courses. He had begun missing his morning classes because of his late-night gaming activities. When asked how the medication was working, he admitted to having increased his dose to 80 mg daily including a 20 mg dose at 8 PM. Much of the time, he was going to bed after 2 AM and not waking until after 10 AM, thereby missing many of his early morning classes.

ACTIVITY GOAL

To goal of this activity is to understand the sources of treatment-resistance in ADHD and how to ameliorate them by optimizing treatment.

LEARNING OBJECTIVES

At the end of this CE activity, participants should be able to:

- Identify the sources of treatment-resistant ADHD in adults
- Prevent misdiagnosis
- Optimize treatment

TARGET AUDIENCE

This continuing medical education activity is intended for psychiatrists, psychologists, primary care physicians, physician assistants, nurse practitioners, and other health care professionals who seek to improve their care for patients with mental health disorders.

CME INFORMATION

CME Credit (Physicians): This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of CME Outfitters, LLC, and Psychiatric Times. CME Outfitters, LLC, is accredited by the ACCME to provide continuing medical education for physicians.

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The following information is for participant information only. It is not assumed that these relationships will have a negative impact on the presentations.

Ben Hunter, MD, has no conflicts to report.
Source of treatment resistance
Nonadherence and executive functioning difficulties
College students with ADHD face multiple challenges with respect to self-regulation, time management, and completion of complex academic tasks. The supportive “scaffolding” they were provided at home is no longer available in the college setting. Moreover, the perpetual distractions of social life and online activities make it difficult for college students like John to complete their assignments in a timely fashion. In response to his executive functioning challenges, John began overusing his stimulant medication partially out of the mistaken assumption that it would help him get organized and do his work more consistently, and partly out of a wish to extend his workday. Unfortunately, this strategy did not work because medication alone cannot overcome executive functioning deficits and unhelpful habits like procrastination and poor sleep hygiene. John was advised to make use of the college’s learning center services including tutoring and ADHD coaching.

Mary and her husband, ADHD inattentive type was diagnosed, and Mary was started on methylphenidate ER.

Despite a less strenuous cognitive workload, she continued to feel inefficient and overwhelmed her inefficient learning habits. Mary failed several liberal arts classes and dropped out after less than one year.

CASE VIGNETTE 2
Mary was 46 years old when she presented at an outpatient intake appointment. She reported longstanding difficulties with attention, task-completion, and organization. Looking back, she recalled these symptoms as early as grade school, describing herself as a “daydreamer” who would occasionally be punished by her teacher for lapses in attention. Through middle school and high school, she sensed that it took her significantly longer than her peers to complete assignments, particularly those requiring extensive reading, which often took multiple passes for Mary to comprehend. However, she was generally successful until college, when the course demands at a challenging private university overwhelmed her inefficient learning habits. Mary failed several liberal arts classes and dropped out after less than one year.

Mary met her husband soon after leaving college and became a homemaker. They both eventually sought treatment in the form of methylphenidate medication. Mary tolerated methylphenidate and was titrated to 36 mg with 50% improvement in symptom reports, but further titration was limited by “jitteriness.” Mary’s sense of despair was palpable on her subsequent visit. Her psychotherapist corroborated a theme of feeling fundamentally flawed and “broken,” more prominent over the past 3 to 4 weeks. Mary noted that she was having increasing difficulty starting tasks, and on several days over the past week, she had returned to bed after getting the children off to school.

Comorbid diagnoses
ADHD is highly comorbid, showing particularly strong associations with mood and anxiety disorders. Clinically, it is often difficult to differentiate between depression or anxiety causing executive dysfunction versus untreated ADHD causing disorders of mood and anxiety. In Mary’s case, it initially appeared that her past depressive symptoms had been secondary to the self-esteem issues and sense of unmet expectations that result from functional impairment as a result of poor attention modulation. However, with Mary’s stimulant dosed adequately and improvement in symptoms specific to the diagnosis of ADHD, the imperative became addressing residual depressive symptoms. Mary was started on sertraline and titrated to a dose of 150 mg, at which point she noted significant reduction in both her depressive and inattentive symptoms. Notably, Mary’s self-esteem, motivation, and ability to initiate tasks improved markedly.

Clarifying diagnosis, changing area of study, managing expectations
John began taking advantage of college student support services and with the help of an ADHD coach, he began attending classes regularly, developed a more effective time management system, and was able to establish a healthier sleep-wake cycle. Despite these interventions, John remained overwhelmed with the high demands of his academic course of study. He was unable to maintain an adequate GPA to remain in the program and was asked to take an academic leave of absence. During his time away from school, he underwent psychoeducational testing and was found to have dyslexia and mild auditory processing difficulties. He was able to use this information to change his area of study and to receive academic accommodations when he returned to school. John took advantage of the school’s learning resources, developed better ways of getting started on his work in a timely fashion, and began to get better grades in his new major.

CASE VIGNETTE 3
James was a 38-year-old consultant in the alternative energy industry transferring care from his primary care doctor, who felt unable to adequately treat James’s multiple psychiatric comorbidities. James’s history revealed ADHD, combined type, diagnosed and treated with multiple different classes and doses of medications beginning in elementary school. He was currently prescribed lisdexamfetamine (LDX) 40 mg daily with marginal reported improvement. In addition, James met criteria for persistent depressive disorder and generalized anxiety disorder with panic, stating that his current dose of fluoxetine 20 mg, started one month earlier, “did nothing.” It was noted that James was boisterous and challenging during the interview. He openly expressed irritation at the psychiatrist’s refusal to add immediate release stimulants to his LDX without first optimizing long-acting therapy.

Key Point
Mary tolerated methylphenidate and was titrated to 36 mg with 50% improvement in symptom reports, but further titration was limited by “jitteriness.” Mary’s sense of despair was palpable on her subsequent visit. Her psychotherapist corroborated a theme of feeling fundamentally flawed and “broken,” more prominent over the past 3 to 4 weeks. Mary noted that she was having increasing difficulty starting tasks, and on several days over the past week, she had returned to bed after getting the children off to school.

Key Point
Stimulants are highly effective in treating “uncomplicated” adult ADHD. In the case of treatment resistance, re-screen for comorbid medical or psychiatric disorders and treat underlying/comorbid disease optimally before making further adjustments to stimulants.

Key Point
When patients exhibit learning and executive functioning difficulties, it is important to re-evaluate the underlying diagnosis and to encourage them to make professional decisions on the basis of new clinical information in order to optimize their likelihood for success and mastery.

Key Point
If patients report difficulty falling asleep due to “racing thoughts,” inability to shut down the mind,” or other similar complaints, consider extending dosing into the evening to cover reemerging inattentive symptoms driving insomnia. Stimulants have been demonstrated to positively affect architecture in the often-disrupted sleep of patients with ADHD.

Key Point
John began taking advantage of college student support services and with the help of an ADHD coach, he began attending classes regularly, developed a more effective time management system, and was able to establish a healthier sleep-wake cycle. Despite these interventions, John remained overwhelmed with the high demands of his academic course of study. He was unable to maintain an adequate GPA to remain in the program and was asked to take an academic leave of absence. During his time away from school, he underwent psychoeducational testing and was found to have dyslexia and mild auditory processing difficulties. He was able to use this information to change his area of study and to receive academic accommodations when he returned to school. John took advantage of the school’s learning resources, developed better ways of getting started on his work in a timely fashion, and began to get better grades in his new major.

Mary met her husband soon after leaving college and became a homemaker. They both eventually sought treatment in the form of methylphenidate medication. Mary tolerated methylphenidate and was titrated to 36 mg with 50% improvement in symptom reports, but further titration was limited by “jitteriness.” Mary’s sense of despair was palpable on her subsequent visit. Her psychotherapist corroborated a theme of feeling fundamentally flawed and “broken,” more prominent over the past 3 to 4 weeks. Mary noted that she was having increasing difficulty starting tasks, and on several days over the past week, she had returned to bed after getting the children off to school.

Comorbid diagnoses
ADHD is highly comorbid, showing particularly strong associations with mood and anxiety disorders. Clinically, it is often difficult to differentiate between depression or anxiety causing executive dysfunction versus untreated ADHD causing disorders of mood and anxiety. In Mary’s case, it initially appeared that her past depressive symptoms had been secondary to the self-esteem issues and sense of unmet expectations that result from functional impairment as a result of poor attention modulation. However, with Mary’s stimulant dosed adequately and improvement in symptoms specific to the diagnosis of ADHD, the imperative became addressing residual depressive symptoms. Mary was started on sertraline and titrated to a dose of 150 mg, at which point she noted significant reduction in both her depressive and inattentive symptoms. Notably, Mary’s self-esteem, motivation, and ability to initiate tasks improved markedly.

Clarifying diagnosis, changing area of study, managing expectations
John began taking advantage of college student support services and with the help of an ADHD coach, he began attending classes regularly, developed a more effective time management system, and was able to establish a healthier sleep-wake cycle. Despite these interventions, John remained overwhelmed with the high demands of his academic course of study. He was unable to maintain an adequate GPA to remain in the program and was asked to take an academic leave of absence. During his time away from school, he underwent psychoeducational testing and was found to have dyslexia and mild auditory processing difficulties. He was able to use this information to change his area of study and to receive academic accommodations when he returned to school. John took advantage of the school’s learning resources, developed better ways of getting started on his work in a timely fashion, and began to get better grades in his new major.

CASE VIGNETTE 2
Mary was 46 years old when she presented at an outpatient intake appointment. She reported longstanding difficulties with attention, task-completion, and organization. Looking back, she recalled these symptoms as early as grade school, describing herself as a “daydreamer” who would occasionally be punished by her teacher for lapses in attention. Through middle school and high school, she sensed that it took her significantly longer than her peers to complete assignments, particularly those requiring extensive reading, which often took multiple passes for Mary to comprehend. However, she was generally successful until college, when the course demands at a challenging private university overwhelmed her inefficient learning habits. Mary failed several liberal arts classes and dropped out after less than one year.

Mary met her husband soon after leaving college and became a homemaker. Despite a less strenuous cognitive workload, she continued to feel inefficient and disorganized. Mary described a daily routine of “fitting from one thing to the next” without actually completing any individual project, often forgetting to address multiple items within a given day if not explicitly recorded in a to-do list. After neuropsychological testing confirmed the results of scales completed by Mary and her husband, ADHD inattentive type was diagnosed, and Mary was started on methylphenidate ER.

CASE VIGNETTE 3
James was a 38-year-old consultant in the alternative energy industry transferring care from his primary care doctor, who felt unable to adequately treat James’s multiple psychiatric comorbidities. James’s history revealed ADHD, combined type, diagnosed and treated with multiple different classes and doses of medications beginning in elementary school. He was currently prescribed lisdexamfetamine (LDX) 40 mg daily with marginal reported improvement. In addition, James met criteria for persistent depressive disorder and generalized anxiety disorder with panic, stating that his current dose of fluoxetine 20 mg, started one month earlier, “did nothing.” It was noted that James was boisterous and challenging during the interview. He openly expressed irritation at the psychiatrist’s refusal to add immediate release stimulants to his LDX without first optimizing long-acting therapy.
Unrealistic expectations of medications and/or physician

James made numerous phone calls between psychiatric appointments, requesting increased doses of stimulants in each case, clearly expressing anger that he would be required to schedule office visits for such changes. During these phone calls, he was encouraged to allow time for adequate trial of each dose and was reminded of the initial treatment agreement stating that doses would not be increased over the phone. James responded well to the established boundaries, and his demanding behavior ceased relatively quickly.

Through further discussion, it became clear that James was expecting more coverage than any regimen could reasonably achieve. A review of his dosing and daily activities revealed that he was attempting to work, or otherwise remain highly cognitively engaged, for 16 to 18 hours every day. James was disabused of this misguided treatment goal and reminded of the substantial benefits of healthy diet, exercise, sleep, and general self-care. A more modest expectation of 12 to 14 hours of daily coverage was set.

Underdosing

Despite improvements in his daily routine, James continued to demonstrate residual symptoms at the current dosage of stimulant. His LDX was titrated in 10 mg increments until he reached a dose of 100 mg (100 mg LDX is equivalent to 40 mg MAS delivered over 12 hours), which James felt was effective and resulted in demonstrably less irritability. James was examined closely for adverse effects at each dosage, and none were observed, including at the highest dose.

A commonly-observed phenomenon in patients referred to our clinic for treatment resistance is underdosing of stimulants. There is little evidence to corroborate the concern many clinicians feel in titrating these medications. As with antidepressants or other psychiatric medications, there is wide variation in the metabolism of these compounds and it is sometimes beneficial to exceed FDA dosing recommendations, i.e., the benefit of increased doses continue to outweigh adverse effects and health risks.

Key Point

- Inability to extend focus and concentration past normal human capacity is not treatment resistance. Early discussion of appropriate expectations for stimulant therapy, along with clear prescribing boundaries, are critical when treating challenging patients.

Key Points

- Close monitoring is paramount when prescribing high doses of stimulants; check vital signs, consider an EKG, and screen closely for side effects.
- If not already attempted, a “class switch” (from amphetamine salts to methylphenidate, or vice versa) should be considered before moving to supra-FDA dosing.

Discussion

Treatment resistance in adult ADHD can stem from several sources including treatment nonadherence, misdiagnosis, patient misconceptions, insufficient use of environmental restructuring and psychosocial interventions, and symptom persistence despite adequate treatment trials (bona fide resistance). Non-adherence in adult ADHD is extremely common and is linked to the symptoms of the disorder itself: namely, forgetfulness, disorganization, and difficulties with self-control. As it has been observed, the key problem facing adults with ADHD is “turning intentions into actions,” so even the most motivated patients often have trouble following through on medical instructions.

Misdiagnosis often involves overlooking factors besides ADHD that may be impairing an individual’s ability to function. As the first case illustrates, hidden impairments like learning disabilities and auditory processing problems can significantly hinder academic success in college or graduate school. The second case exemplifies how comorbidities like depression and anxiety can interfere with optimal treatment. It is easy for clinicians to underestimate the extent to which patients’ distorted thinking about ADHD and its treatment can influence outcomes, as the third case illustrates. Providing ongoing psy

References


Post-tests, credit request forms, and activity evaluations must be completed online at www.cmeoutfitters.com/PT (requires free account activation), and participants can print their certificate or statement of credit immediately (80% pass rate required). This Web site supports all browsers except Internet Explorer for Mac. For complete technical requirements and privacy policy, visit www.neurosciencecme.com/technical.asp.

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- UMass Memorial Health Care: https://www.umassmemorialhealthcare.org/careers/physician-opportunities
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Sheldon Benjamin, MD
Interim Chair of Psychiatry
University of Massachusetts Medical School
UMass Memorial Medical Center
c/o: Adriana Dietlin, Physician Recruiter
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J1 / HIB VISA POSITION FOR CHILD/ ADOLESCENT PSYCHIATRIST IN MO – located in the Delta Regional Authority, J1 Waivers can also be obtained through the DRA as well as the state. Position can be inpatient, or inpatient and outpatient.

Please contact Terry Good, Horizon Health, at 804-684-5661; terry.good@horizonhealth.com; Fax: 1-804-684-5663.

OKLAHOMA

TELEMEDICINE OPPORTUNITY

Horizon Health is seeking a Psychiatrist to provide telemedicine coverage for a 12-bed geriatric inpatient psychiatric program in Oklahoma. The Psychiatrist will provide round-the-clock and treatment on patients for the inpatient program, as well as program administration and oversight services regarding service line policies, practice, development, compliance, and performance improvement. Some on-site coverage is preferred, but 100% telemedicine is available and will be considered for daily rounding and call coverage. Excellent compensation. For more information contact:

Mark Blakney, Voice: 979-420-7473, Fax: 979-420-8233; email: mark.blakney@horizonhealth.com

EOE

PA

OPENINGS IN PHILADELPHIA AND DARBY – Mercy Philadelphia Hospital, Philadelphia – opening on 16-bed Dual Diagnosis Unit. Mercy Fitzgerald Hospital, Darby – Crisis Service, Day and Night shifts available.

Please contact Terry Good, Horizon Health, at 804-684-5661; terry.good@horizonhealth.com; Fax: 1-804-684-5663.