COMMENTARY
How Reading Current Literature Stimulates Duh and Yawn Responses
An Analysis of Causes and Potential Interventions

Jerald Kay, MD, and Joel Yager MD

As (primarily) clinicians of a certain age, when picking up copies of mainstream and premier psychiatric journals these days, we, and many of our friends and associates, have increasingly experienced disturbing physiological phenomena best described as Duh and Yawn responses. Duh responses occur in reaction to reading scientific articles and commentaries that deliver old “ho-hum” news; despite all the time invested, readers gather sorrowfully little new clinically useful information or perspective. Yawn responses occur when articles are unreadable, opaque, and impose such enormous cognitive loads that seriously tackling them would risk developing cognitive hernias. Faced with these issues brimming with such articles, many of our colleagues—frustrated subscribers with limited time for professional

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Dismantle Racism in Psychiatry & Society

H. Steven Moffic, MD, Rahn K. Bailey, MD, Frank A. Clark, MD, Claire Cohen, MD, Catherine Friedman, MD, Jessica Isom, MD, MPH, Aekta Malhotra, MD—SPAR (Seven Psychiatrists Against Racism)

The racial dust that we often do not see has been in the air ever since our country’s beginning. As a result, the brutality of chattel slavery used for the economic growth of colonial settlers became embedded in the minds and bodies of all countrymen. That pollution, much of it still invisible, remains with us, woven into the structural, institutional, and individual racism of our nation.

CONTINUED ON PAGE 11
SPRAYATO™ (esketamine) CIII Nasal Spray is indicated, in conjunction with an oral antidepressant (AD), for the treatment of treatment-resistant depression (TRD) in adults.

SPRAYATO™ is not approved as an anesthetic agent. The safety and effectiveness of SPRAYATO™ as an anesthetic agent have not been established.

**Important Safety Information**

**WARNING: SEDATION, DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS**

See full prescribing information for complete boxed warning

- Risk for sedation and dissociation after administration. Monitor patients for at least two hours after administration (5.1, 5.2).
- Potential for abuse and misuse. Consider the risks and benefits of using SPRAYATO™ prior to use in patients at higher risk of abuse. Monitor for signs and symptoms of abuse and misuse (5.3).
- SPRAYATO™ is only available through a restricted program called the SPRAYATO™ REMS (5.4).
- Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. SPRAYATO™ is not approved for use in pediatric patients (5.5).

**CONTRAINDICATIONS**

SPRAYATO™ is contraindicated in patients with:

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation
- History of intracerebral hemorrhage
- Hypersensitivity to esketamine, ketamine, or any of the excipients


**INDICATION**

SPRAYATO™ (esketamine) CIII Nasal Spray is indicated, in conjunction with an oral antidepressant (AD), for the treatment of treatment-resistant depression (TRD) in adults.

**WARNINGS AND PRECAUTIONS**

**Sedation:** In clinical trials, 49% to 61% of SPRAYATO™-treated patients developed sedation and 0.3% of SPRAYATO™-treated patients experienced loss of consciousness. Because of the possibility of delayed or prolonged sedation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting. Closely monitor for sedation with concomitant use of SPRAYATO™ with CNS depressants (see Drug Interaction (7.1)).

SPRAYATO™ is available only through a restricted program under a REMS.

**Dissociation:** The most common psychological effects of SPRAYATO™ were dissociative or perceptual changes (including distortion of time, space and illusions), derealization and depersonalization (61% to 75% of SPRAYATO™-treated patients developed dissociative or perceptual changes). Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering SPRAYATO™; treatment should be initiated only if the benefit outweighs the risk. Because of the risks of dissociation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting. SPRAYATO™ is available only through a restricted program under a REMS.

**Abuse and Misuse:** SPRAYATO™ contains esketamine, a Schedule III controlled substance (CIII), and may be subject to abuse and diversion. Assess each patient’s risk for abuse or misuse prior to prescribing and monitor all patients for the development of these behaviors or conditions, including drug seeking behavior, while on therapy. Individuals with a history of drug abuse or dependence are at greater risk; therefore, use careful consideration prior to treatment of individuals with a history of substance use disorder and monitor for signs of abuse or dependence. SPRAYATO™ is available only through a restricted program under a REMS.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNINGS, on following pages.

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Long-term Cognitive Impairment: Long-term cognitive and memory impairment treated subjects required a greater effort to complete the cognitive tests at 40 minutes.

Short-term Cognitive Impairment: In a study in healthy volunteers, a single dose of SPRAVATO™ caused small increases in blood pressure.

Seizures, diminished consciousness or focal neurological deficits) immediately after administration of SPRAVATO™. Assess BP prior to administration of SPRAVATO™. In patients whose BP is elevated prior to SPRAVATO™ administration (as a general guide: >140/90 mmHg), a decision to delay administration of SPRAVATO™ is contraindicated in patients for whom an increase in BP or intracranial pressure poses a serious risk (e.g., aneurysmal vascular disease, arteriovenous malformation, history of intracerebral hemorrhage). Before prescribing, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of SPRAVATO™ outweigh its risk. Monitor for urinary tract and bladder symptoms during the course of treatment with SPRAVATO™ and refer to an appropriate healthcare provider as clinically warranted.

Embryo-fetal Toxicity: SPRAVATO™ may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO™ in utero. Advise women of reproductive potential to consider pregnancy planning and prevention.

Drug Interactions

CNS depressants (e.g., benzodiazepines, opioids, alcohol): Concomitant use may increase sedation. Closely monitor for sedation with concomitant use of CNS depressants.

Psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armadafinil): Concomitant use may increase blood pressure. Closely monitor blood pressure with concomitant use of psychostimulants.

Monoamine oxidase inhibitors (MAOIs): Concomitant use may increase blood pressure. Closely monitor blood pressure with concomitant use of MAOIs.

Use in Specific Populations

Pregnancy: SPRAVATO™ is not recommended during pregnancy. SPRAVATO™ may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO™ in utero. There are risks to the mother associated with untreated depression in pregnancy. If a woman becomes pregnant while being treated with SPRAVATO™, treatment with SPRAVATO™ should be discontinued and the patient should be counseled about the potential risk to the fetus.

Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including SPRAVATO™, during or after pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants.

Lactation: SPRAVATO™ is present in human milk. Because of the potential for neurotoxicity, advise patients that breastfeeding is not recommended during treatment with SPRAVATO™.

Females and Males of Reproductive Potential: SPRAVATO™ may cause embryo-fetal harm when administered to a pregnant woman. Consider pregnancy planning and prevention for females of reproductive potential during treatment with SPRAVATO™.

Pediatric Use: The safety and effectiveness of SPRAVATO™ in pediatric patients have not been established.

Geriatric Use: Of the total number of patients in Phase 3 clinical studies exposed to SPRAVATO™, 12% were 65 years of age and older, and 2% were 75 years of age and older. No overall differences in the safety profile were observed between patients 65 years of age and older and patients younger than 65 years of age.

The mean esketamine Cmax and AUC values were higher in elderly patients compared with younger adult patients. The treatment of TDO in geriatric patients was evaluated in a 4-week, randomized, double-blind study comparing flexibly dosed intranasal SPRAVATO™ plus a newly initiated oral antidepressant compared to intranasal placebo plus a newly initiated oral antidepressant in patients ≥65 years of age. At the end of four weeks, there was no statistically significant difference between groups on the primary efficacy endpoint of change from baseline to Week 4 on the Montgomery–Åsberg Depression Rating Scale (MADRS).

Hepatic Impairment: SPRAVATO™-treated patients with moderate hepatic impairment may need to be monitored for adverse reactions for a longer period of time.

SPRAVATO™ has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Use in this population is not recommended.

Drug Abuse and Dependence

Controlled Substance: SPRAVATO™ contains esketamine hydrochloride, the (S)-enantiomer of ketamine and a Schedule III controlled substance under the Controlled Substances Act.

Abuse: Individuals with a history of drug abuse or dependence may be at greater risk for prescribed misuse of SPRAVATO™ Abuse is the intentional, non-therapeutic use of a drug, even once, for its psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for which it was not prescribed. Careful consideration is advised prior to use of individuals with a history of substance use disorder, including alcohol.

SPRAVATO™ may produce a variety of symptoms including anxiety, dysphoria, disinorientation, insomnia, flashbacks, hallucinations, and feelings of floating, detachment and to be “spaced out.” Monitoring for signs of abuse and misuse is recommended.

Adverse Reactions

The most common adverse reactions with SPRAVATO™ plus oral AD (incidence ≥5% and at least twice that of placebo nasal spray plus oral AD) were dissociation, dizziness, nausea, sedation, vertigo, hypophoresis, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.

Please see Brief Summary of full Prescribing Information, including Boxed WARNINGS, on following pages.
SPRAVATO®

( esketamine) nasal spray, CII

Brief Summary

BEFORE PRESCRIBING SPRAVATO®, PLEASE SEE FULL PRESCRIBING INFORMATION, INCLUDING BOXED WARNING.

WARNING: SEDATION; DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

Sedation
• Patients are at risk for sedation after administration of SPRAVATO (see Warnings and Precautions).

Dissociation
• Patients are at risk for dissociative or perceptual changes after administration of SPRAVATO (see Warnings and Precautions).

Because of the risks of sedation and dissociation, patients must be monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting (see Warnings and Precautions).

Abuse and Misuse
• SPRAVATO has the potential to be abused and misused. Consider the risks and benefits of prescribing SPRAVATO to patients in this risk of abuse. Monitor patients for signs and symptoms of abuse and misuse (see Warnings and Precautions).

Because of the risks of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse, SPRAVATO is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the SPRAVATO REMS (see Warnings and Precautions).

Suicidal Thoughts and Behaviors

Antidepressant increases the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. SPRAVATO is not approved for use in pediatric patients (see Warnings and Precautions).

INDICATIONS AND USAGE

SPRAVATO® is indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults (see Clinical Studies (14.1) in Full Prescribing Information).

Limitations of Use

• SPRAVATO is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established.

CONTRAINDICATIONS

• Patients with active anesthetic agents have not been established.

SPRAVATO is contraindicated in patients:
• Anuric vascular disease (including thoracic and abdominal aorta, intraocular, and peripheral arterial vessels) or arteriovenous malformation (see Warnings and Precautions)
• History of intracranial hemorrhage (see Warnings and Precautions)
• Hypersensitivity to esketamine, ketamine, or any of the excipients

WARNINGS AND PRECAUTIONS

Sedation
• Clinical trials, 40% to 61% of SPRAVATO-treated patients developed sedation based on the Modified Observer’s Alertness/Sedation scale (MOAA/s) (see Adverse Reactions), and 0.2% of SPRAVATO-treated patients experienced loss of consciousness (MOAA/s score of 0).

Because of the risk of delayed or prolonged sedation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting (see Dosage and Administration (2.4) in Full Prescribing Information).

Closely monitor for concomitant use of SPRAVATO with CNS depressants (see Drug Interaction).

SPRAVATO is available only through a restricted program under a REMS (see Warnings and Precautions).

Dissociation
• The most common psychological effects of SPRAVATO were dissociative or perceptual changes (including somnolence, impaired time, space, and illusions), derealization and depersonalization (61% to 75% of SPRAVATO-treated patients developed dissociative or perceptual changes based on the Clinician Administered Dissociative Symptom Scale) (see Adverse Reactions). Given the potential to induce dissociative or perceptual effects, carefully assess patients with psychosis or a diagnosis of schizophrenia; treatment should be initiated only if the benefit outweighs the risk.

Because of the potential of dissociation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting (see Dosage and Administration (2.4) in Full Prescribing Information).

Closely monitor for concomitant use of SPRAVATO with CNS depressants (see Drug Interaction).

SPRAVATO is available only through a restricted program under a REMS (see Warnings and Precautions).

Abuse and Misuse
• SPRAVATO contains esketamine, a Schedule III controlled substance (CIII), and may be subject to abuse and diversion. Assess each patient’s risk for abuse or misuse prior to prescribing SPRAVATO and monitor all patients receiving SPRAVATO for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy. Contact local state professional licensing board or local state professional licensing board for more information on drug-related abuse, misuse, and diversion/abuse (see Warnings and Precautions).

SPRAVATO is available only through a restricted program under a REMS (see Warnings and Precautions).

SPRAVATO Risk Evaluation and Mitigation Strategy (REMS)

SPRAVATO is available only through a restricted program under a REMS called the SPRAVATO REMS because of the risks of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse (see Boxed Warning and Warnings and Precautions).

Important requirements of the SPRAVATO REMS include the following:
• Healthcare settings must be certified in the program and ensure that SPRAVATO is:
  • Only dispensed in healthcare settings and administered to patients who are enrolled in the program.
  • Administered by patients under the direct observation of a healthcare provider and that patients are not alone at any time during the 2-hour period.
• Healthcare providers must be certified in the REMS and must only dispense SPRAVATO to healthcare settings that are certified in the program.

Further information, including a list of certified pharmacies is available at www.SPRAVATOREms.com or 1-855-382-6022.

Suicidal Thoughts and Behaviors in Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,560 pediatric patients (SPRAVATO is not approved for these patients), the incidence of suicidal thoughts and behaviors in patients age 24 years and younger was greater in placebo-treated patients. There was a considerable variation

SPRAVATO® (esketamine) nasal spray, CII

in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in insurance reimbursement data. There were differences in absolute incidence of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD). The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

<p>| Table 1: Risk Differences of the Number of Patients with Suicidal Thoughts or Behaviors in the Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients |</p>
<table>
<thead>
<tr>
<th>Age Range (Years)</th>
<th>Drug-Placebo Difference in Number of Patients with Suicidal Thoughts or Behaviors per 1000 Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>&lt;1</td>
</tr>
<tr>
<td>18-24</td>
<td>5 additional patients</td>
</tr>
<tr>
<td>25-64</td>
<td>6 patients</td>
</tr>
</tbody>
</table>

* SPRAVATO is not approved in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond 4 months. However, there is substantial evidence from postmarketing studies in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors. Monitor all antidepressant-treated patients for clinical worsening and emerging of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider.

Between prescribing SPRAVATO, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of SPRAVATO outweigh its risks.

Because of the risks of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse, SPRAVATO is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the SPRAVATO REMS (see Warnings and Precautions).

Cognitive Impairment

Short-Term Cognitive Impairment

In a study in healthy volunteers, a single dose of SPRAVATO caused cognitive performance decline 40 minutes post-dose. Compared to placebo-treated subjects, SPRAVATO-treated subjects required a greater effort to complete cognitive tests at 40 minutes post-dose. Cognitive performance and mental effects were comparable between SPRAVATO and placebo at 2 hours post-dose. Sleepiness was comparable after 4 hours post-dose.

Long-Term Cognitive Impairment

Long-term cognitive and memory impairment have been reported with repeated ketamine misuse or abuse. No adverse effects of SPRAVATO nasal spray on cognitive functioning were observed in a one-year open-label safety study; however, the long-term cognitive effects of SPRAVATO have not been evaluated in clinical trials.

Impaired Ability to Drive and Operate Machinery

Two placebo-controlled studies were conducted to assess the effects of SPRAVATO on the ability to drive (see Clinical Studies (14.1) in Full Prescribing Information). The effects of SPRAVATO 84 mg were measurable on the ability to drive at 6 hours and 18 hours post-dose, however, two SPRAVATO-treated subjects required a greater effort to complete cognitive tests at 40 minutes post-dose.

Monitor for urinary and bladder symptoms during the course of treatment with SPRAVATO, and refer to an appropriate healthcare provider as clinically warranted.

Embryo-Fetal Toxicity

Based on published findings from pregnant animals treated with ketamine, the racemic mixture of esketamine and ketamine, SPRAVATO may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an embryo exposed to SPRAVATO in utero. Advise women of reproductive potential to consider pregnancy planning and prevention (see Use in Specific Populations).
Sedation was evaluated by adverse event reports and using the Modified Observer’s Alertness/ Sedation scale (MOAA/s). In the MOAA/s scale, 5 means “responds readily to name spoken in normal tone” and 0 means “no response after painful tapuszeesque.” Any decrease in MOAA/s from pre-dose is considered to indicate presence of sedation, and such a decrease occurred in a higher number of patients on esketamine than placebo during the short-term trials (Table 3). Dose-related increases in the incidence of sedation were observed in a fixed-dose study (see Warnings and Precautions).

Table 3: Incidence of Sedation (MOAA/s <5 in Double-blind, Randomized, Placebo-Controlled Fixed-Dose Study with Patients <65 Years of Age and Double-blind, Randomized, Placebo-Controlled Fixed-dose Study with Patients ≥65 Years

<table>
<thead>
<tr>
<th>Patients ≤65 years</th>
<th>Placebo + oral AD</th>
<th>SPRAVATO + oral AD</th>
<th>Placebo + oral AD</th>
<th>SPRAVATO + oral AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=112</td>
<td>N=113</td>
<td>N=116</td>
<td>N=65</td>
<td>N=72</td>
</tr>
<tr>
<td>Sedation (MOAA/s &lt;5)</td>
<td>11%</td>
<td>50%</td>
<td>61%</td>
<td>19%</td>
</tr>
</tbody>
</table>

*Patients who were evaluated with MOAA/s.

Disassociation/Perceptual Changes
SPRAVATO can cause disassociative symptoms (including derealization and depersonalization) and perceptual changes (including distortion of time and space, and illusions). In clinical trials, dissociation was transient and occurred on the day of dosing. Dissociation was evaluated by adverse event reports and the Clinician-Administered Dissociative States Scale (CADDSS) questionnaire. A CADDSS total score of more than 4 indicates presence of disassociative symptoms, and such an increase to a score of 4 or more occurred in a higher number of patients on esketamine compared to placebo during the short-term trials (see Table 4). Dose-related increases in the incidence of disassociative symptoms (CADDSS total score >4) were observed in a fixed-dose study. Table 4 shows the incidence of dissociation (CADDSS total score >4) in a double-blind, randomized, placebo-controlled, fixed-dose study in adults <65 years of age and a double-blind, randomized, placebo-controlled, fixed-dose study with patients ≥ 65 years of age.

Table 4: Incidence of Dissociation (CADDSS Total Score >4) in Double-blind, Randomized, Placebo-Controlled Fixed-dose Study with Patients <65 Years and Flexible-dose Study with Patients ≥65 Years

<table>
<thead>
<tr>
<th>Patients ≤65 years</th>
<th>Placebo + oral AD</th>
<th>SPRAVATO + oral AD</th>
<th>Placebo + oral AD</th>
<th>SPRAVATO + oral AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=113</td>
<td>N=113</td>
<td>N=116</td>
<td>N=65</td>
<td>N=72</td>
</tr>
<tr>
<td>CADDSS total score &gt;4 and change &gt;0</td>
<td>5%</td>
<td>61%</td>
<td>69%</td>
<td>12%</td>
</tr>
</tbody>
</table>

* Number of patients who were evaluated with CADDSS

Increase in Blood Pressure
The mean placebo-adjusted increases in systolic and diastolic blood pressure (SBP and DBP) over time were about 7 to 9 mmHg in SBP and 4 to 6 mmHg in DBP at 40 minutes post-dose and 2 to 5 mmHg in SBP and 1 to 3 mmHg in DBP at 1.5 hours post-dose in patients receiving SPRAVATO plus oral antidepressants (Table 5).

Table 5: Increases in Blood Pressure in Double-blind, Randomized-controlled, Short-term Trials of SPRAVATO + Oral AD Compared to Placebo Nasal Spray + Oral AD in the Treatment of TRD

<table>
<thead>
<tr>
<th>Patients ≤65 years</th>
<th>Patients ≥65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>DBP</td>
</tr>
<tr>
<td>SPRAVATO + oral AD</td>
<td>Placebo + oral AD</td>
</tr>
<tr>
<td>N=222</td>
<td>N=222</td>
</tr>
<tr>
<td>56 mg</td>
<td>84 mg</td>
</tr>
<tr>
<td>28 to 84 mg</td>
<td>28 to 84 mg</td>
</tr>
<tr>
<td>7/23/20</td>
<td>3:06 PM</td>
</tr>
</tbody>
</table>

Systolic blood pressure
≥180 mm Hg 9 (12%) 0 7 (6%) 0
≥160 mm Hg 29 (8%) 1 (0.5%) 12 (11%) 1 (2%)
Diastolic blood pressure
≥110 mm Hg 13 (4%) 1 (0.5%) 7 (6%) 0
≥95 mm Hg 48 (13%) 6 (3%) 10 (14%) 2 (3%)

Nausea and Vomiting
SPRAVATO can cause nausea and vomiting (Table 6). Most of these events occurred on the day of dosing and resolved the same day, with the median duration not exceeding 1 hour in most subjects across dosage sessions. Rates of reported nausea and vomiting decreased over time across dosage sessions from the first week of treatment in the short-term studies, as well as over time with long-term treatment (Table 6).

Table 6: Incidence and Severity of Nausea and Vomiting in Double-blind, Randomized-controlled, Fixed-dose Study

<table>
<thead>
<tr>
<th>Treatment (+ Oral AD)</th>
<th>N</th>
<th>All</th>
<th>Severe</th>
<th>All</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=222</td>
<td>116</td>
<td>37 (32%)</td>
<td>4 (3%)</td>
<td>14 (12%)</td>
<td>3 (2%)</td>
</tr>
</tbody>
</table>
SPRAVATO® (esketamine) nasal spray, CIII

Data

A placebo-controlled juvenile animal studies demonstrate that the administration of drugs that block NMDA receptors, such as ketamine, during the period of rapid brain growth or synaptogenesis, results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on the wide differences across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but this window may extend out to approximately 3 years of age in humans.

Females and Males of Reproductive Potential

Contraception

Based on published animal reproduction studies, SPRAVATO may cause embryo-fetal harm when administered to a pregnant woman (see Warnings and Precautions and Use in Specific Populations). However, it is not clear how these animal findings relate to females of reproductive potential treated with the recommended clinical dose, concomitant pregnancy planning and prevention for females of reproductive potential during treatment with SPRAVATO.

Pediatric Use

The safety and effectiveness of SPRAVATO in pediatric patients have not been established. Clinical studies of SPRAVATO in pediatric patients have not been conducted.

Geriatric Use

Of the total number of patients in Phase 3 clinical studies exposed to SPRAVATO, (N=1601), 194 (12%) were 65 years of age and older, and 25 (2%) were 75 years of age and older. No overall differences in safety profile were observed between patients 65 years of age and older and patients younger than 65 years of age.

The mean esketamine Cmax and AUC values were higher in elderly patients compared with younger adult patients [see Clinical Pharmacology (12.3) in Full Prescribing Information]. The efficacy of SPRAVATO for the treatment of TRD in geriatric patients was evaluated in a 4-week, randomized, double-blind study comparing flexibly-dosed intranasal SPRAVATO plus a new initiators oral antidepressant compared to intranasal placebo plus a newly initiated oral antidepressant in patients ≥ 65 years of age. SPRAVATO was initiated at 28 mg twice weekly and could be titrated to a maximum of 56 mg twice weekly. By the end of the fourth week, there was a statistically significant difference between groups on the primary efficacy endpoint of change from baseline to Week 4 on the Montgomery-Asberg Depression Rating Scale (MADRS).

Hematopoietic

The mean esketamine Cmax and t1/2 values were higher in patients with moderate hepatic impairment compared to those with normal hepatic function [see Clinical Pharmacology (12.3) in Full Prescribing Information]. SPRAVATO treated patients with moderate hepatic impairment may need to be monitored for adverse reactions for a longer period of time.

SPRAVATO has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Use is not recommended [see Clinical Pharmacology (12.3) in Full Prescribing Information].

Drug Abuse and Dependence

Controlled Substance

SPRAVATO contains esketamine hydrochloride, the (S)-enantiomer of ketamine and a Schedule III controlled substance under the Controlled Substances Act.

Abuse

Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse of SPRAVATO. Abuse is the intentional, non-therapeutic use of a drug, even once, for its psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed. Careful consideration is advised prior to use of individuals with a history of substance use disorder, including alcohol.

SPRAVATO may produce a variety of symptoms including anxiety, dysphoria, disorientation, insomnia, flashback, hallucinations, and feelings of floating, detachment and to be “space out”. Monitoring for signs of abuse and misuse is recommend.

Abuse Potential Study

A cross-over, double-blind abuse potential study of SPRAVATO and ketamine was conducted in recreational polydrug users (n=34) who had experience with perception-altering drugs, including substances used for their psychological and/or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

Abuse Potential Study

A prospective, longitudinal study followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. The women who continued antidepressant treatments during pregnancy were more likely to experience a relapse of untreated depression during pregnancy than those who were euthymic and taking antidepressants at the beginning of pregnancy. The risk of untreated depression during pregnancy is important because, for the purpose of the study, the postpartum period was defined as 6 months after delivery. The results of this study indicate that continuation of antidepressant treatment during pregnancy may reduce the risk of postpartum depression.

Abuse Potential Study

A cross-over, double-blind abuse potential study of SPRAVATO and ketamine was conducted in recreational polydrug users (n=34) who had experience with perception-altering drugs, including substances used for their psychological and/or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

Abuse Potential Study

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THE GLASS IS HALF FULL

It is hard to believe it is already August. Soon children will return to school, in 1 form or another; the days will grow shorter and colder, and the leaves will change color. To some it marks the end of summer, and to others it marks the beginning of the autumn holidays and cozier days. It depends on how you look at it.

Several of this month’s contributors share these sentiments, reminding us that both the half-full and half-empty views can serve as important wake-up calls. In our Psycho-Oncology Special Report, the authors celebrate advances in cancer care, but they also recognize we can do more to help patients. For instance, Wendy G. Lichtenfeld, PhD, and colleagues explore how meaning-centered psychotherapy (MCP) can serve as a buffer against the depression and hopelessness reported by patients with metastatic disease. According to the authors, this brief, structured, manualized intervention enhances patients’ sense of meaning and purpose by reflecting on what matters most to them and facilitating reconnection, even during the most challenging of times. Similarly, Lawrence E. Kaplan, DO, sheds light on the lingering neuropsychiatric sequelae, either due to the specific cancer or adverse effects of treatment. With improved screening and awareness, interdisciplinary approaches and interventions can address these issues to improve patients’ lives.

Similarly, in the front cover article discussing racism, 7 psychiatrists come together to challenge the status quo. We can—and should—do better, they say. Not only do the authors identify areas that need to be addressed, but they provide measures to help us ensure we are indeed moving forward.

Also in this issue, leaders in psychiatry discuss the need to push the envelope to do more for patients. Jerald Kay, MD, and Joel Yager, MD, lament how potential cures, identify future steps to remedy the situation, and challenge the field to do better.

Although our editor in chief, John J. Miller, MD, agrees with many of those sentiments, he reminds us of the Wows and Awesomes. From pharmacogenomics to neuroimaging and brain circuitry, ever-evolving research propels psychiatry into new areas to improve patient care and outcomes. His “glass half full” assessment reminds us that while progress has been made, we need to continue pushing for more.

With everything going on in the world, this lesson has become abundantly clear—our attitudes will help us ride the ups and downs and the slings and arrows that present themselves and propel us to better times. And, we hope, this issue of Psychiatric Times® will provide you with the tools and knowledge to achieve success for you and your patients.

Mike Hennessy Sr
Chairman and Founder, MJH Life Sciences
My Wow and Awesome Responses While Reading the Psychiatric Literature

John J. Miller, MD  Editor in Chief

I thoroughly enjoyed reading this month’s cover story by Jerald Kay, MD, and Joel Yager MD, in which they share their assessment of the state of the vast psychiatric literature that regularly bombards us clinicians. The authors reflect on how journal publications have become less relevant to them as clinicians over the decades and describe 2 visceral responses—Duh and Yawn—when reading current journal articles. Overall I agree with their assessment, and I encourage reading their delightful article. Nonetheless, the scientist in me scowled at a few of their opinions. So, I thought it would be worthwhile to travel down a few side roads to share my reflections on the current psychiatric literature as well as the many accomplishments psychiatry has seen since the 1950s. Although I tend to agree with their statement that much of the current publications in psychiatric journals are either redundant with little new information (their Duh response) or overly technical to the point of being a remedy for insomnia (their Yawn response), I aimed to get some perspective.

After logging into PubMed, I entered the following search terms, applied the “limit to articles published in the past 5 years” filter, and I was actually not surprised by the results:

- ANTIDEPRESSANTS: yielded 24,811 publications;
- ANTI-Psychotics: yielded 16,393 publications;
- PHARMACOTHERAPY: yielded a whopping 580,107 publications.

It would be naïve and foolish of me to consider reading even 1% of these articles, and I am in full agreement that the vast majority of them would illicit either a Duh or Yawn response. However, every month I find at least 20 or more papers from which I learn something. Every psychiatrist—clinician, academician, researcher, consultant, or some combination thereof—has a unique interest and specialty in our vast and diverse field of psychiatry. Sometimes I find an obscurely titled article from a not-so-famous journal that becomes one of my favorite articles of the month; I would never have stumbled upon such gems without a strategy to enrich the pool of articles that I take the time to read. For each psychiatrist, that strategy will be different, but such a method to whittle down the literature can make the process somewhat of an adventure—often rewarded with a much-appreciated article.

New drugs: cardiology versus psychiatry

I was also intrigued by the article’s comparison of new pharmacological treatments since 1950 in cardiology (the article’s reference noted 14) versus psychiatry (3 according to the article). The reference, it turns out, was an excellent TED talk from which I learned a lot. However, the source of the cardiac versus depression/schizophrenia new treatments was a graph without a published source reference. The presenter showed a slide titled: “Development of New Treatments for Mental Illnesses Compared with Heart Disease,” with the Y axis labeled “# of Mechanistically Distinct Drugs.” The X axis showed bar graphs of “Distinct Drugs” that existed in the 1950s compared to those available today for depression, schizophrenia, and heart disease. The reference for the slide was “Courtesy of: Bill Carlezon and Ed Skolnick.” This is a case where context is critical.

As psychiatrists, we should be so lucky that the anatomy and functionality of the brain is the same as the heart. Comparing a pump—which has been exhaustively studied and is extremely well understood—with the human brain—which is the seat of human consciousness, allowing me to write this editorial while simultaneously and automatically managing all of my bodily functions, allowing for emotional responses, and containing the circuitry of language, culture, ethics, and morality—is like comparing our understanding of a meteor with that of a black hole. We find ourselves empathizing with Isaac Newton’s famous quote:

“I do not know what I may appear to the world, but to myself I seem to have been only like a boy playing on the seashore, and diverting myself in now and then finding a smoother pebble or a prettier shell than ordinary, whilst the great ocean of truth lay all undiscovered before me.”

Despite this limited understanding of the human brain, I find it remarkable that we have made so much progress since the 1950s. It was in 1954 that we began using chlorpromazine, our first antipsychotic, and in 1958 and 1959 we started using our first 2 antidepressants, imipramine and iproniazid, respectively. As a psychopharmacologist who relishes understanding psychotropics and their putative mechanisms of action, I continue to be amazed by how much we have learned about pharmacology and the brain since I began medical school in 1982. Although the mechanisms of action of current US Food and Drug Administration-approved drugs for the treatment of depression are limited to 4 neurotransmitter systems (eg, serotonin, norepinephrine, dopamine, and glutamate), the diverse subcomponents of these 4 systems targeted by FDA-approved antidepressants is vast. When you add to this the drugs that we use “off label,” the list of mechanisms of action expands greatly.

Novel drugs in psychiatry

In the past 35 years, our portfolio of new pharmacological agents in psychiatry has grown tremendous-
ly, providing patients with many new options. Although we certainly have mountains of new information and understanding to explore and based on the common occurrence of novel breakthroughs in psychiatry, it is important to consider our significant advances (Table).

Table

Sadly, there are challenges in developing novel agents for the many—arguably all psychiatric diagnoses—that have either no or sub-optimal current FDA-approved treatments. As such, the pharmaceutical industry has virtually abandoned new drug development in neuroscience with a few exceptions.

Pharmacogenomics

Remarkably, it was a publication in Scientific American by Francis Crick in 1954 that first suggested that “DNA alone, free of protein, may be able to carry genetic information.” In a mere 46 years, the world scientific community announced the completion of the first map of the entire human genome, and by 2003 they completed the sequencing of all 3 billion base pairs. This remarkable accomplishment paved the way to identify the polymorphic families of genes that code for receptors for a particular neurotransmitter. Today, just for the neurotransmitter serotonin, we have characterized in detail 7 different families of serotonin receptors and approximately 18 different subfamilies—all with unique and divergent roles in our brain’s neuro-circuitry. Many of our newer antidepressants and antipsychotics have unique molecular binding affinities at these 18 different targets for serotonin, which I would argue are structurally and functionally different medications.

Pharmacogenomics is in its infancy, whereas evidence-based genes in the psychiatrists’ clinical toolbox (i.e., CYP2D6, CYP2C19, HLA-B*15:02, and HLA-A*31:01). Over the next 10 to 20 years, we will likely see a continued expansion of psychiatric pharmacogenomics that will include an array of clinically relevant genes for receptors, cytochrome P450 enzymes, uridine 5’-diphosphate glucuronosyltransferases (UGT) enzymes, promoter sequence variations, and more.

In parallel to this genetic research is the increasing understanding of the complexities of the human genome. We are learning that many psychiatric disorders can have a synergistic risk or protection for unmasking based on the contributions of numerous genes, often across many different chromosomes. In the case of the approximately 100 genes with varying degrees of risk for (or protection from) the development of schizophrenia, there is one of these genes on almost all the 23 different human chromosomes. Additionally, genome-wide association studies have shown that regions of DNA which contain an increased risk for schizophrenia also contain regions of DNA that increases the risk of metabolic disorders.

Neuroimaging, brain circuitry

As a first-year medical student in 1982, I recall seeing my very first human CT scan—the chest, abdomen, and brain. I was blown away by the detail, and I continue to be amazed by the clinical information that can be extracted by the new numerous neuroimaging tools available: computed tomography (CT) or computed axial tomography (CAT), positron emission tomography (PET), magnetic resonance imaging (MRI), functional MRIs, functional ultrasound imaging, single-photon emission computed tomography, magnetoencephalography, and others. I have treated patients for whom these techniques have been a primary source of information in differential diagnosis and treatment planning.

In 2011, the FDA approved the imaging agent DaTscan in conjunction with SPECT to determine the density of dopamine transporters to aid in the diagnosis of Parkinson disease. More recently, in May 2020 the FDA approved Tauvid, an imaging agent used with PET scanning to evaluate patients for Alzheimer disease. This agent is approved for adults with cognitive impairment to quantify the density and location of aggregated tau neurofibrillary tangles to assist in the differential diagnosis of possible Alzheimer. The future of neuroimaging looks very bright!

Concluding thoughts

In this editorial, my goal was to provide a “glass half full” assessment of where we are in psychiatry and the importance of a vast psychiatric literature that can elicit the Duh and Yawn responses.

The fascinating history of medicine, which rests on the shoulders of the giants in science, has shown us that we can never predict what obscure research observation or serendipitous finding will open a door to advancements in medicine. For this reason, I am happy to tolerate articles that elicit the Duh and Yawn responses, knowing that somewhere tucked in that vast ocean of publications, I will continue to stumble upon articles that elicit Wow and Awesome responses.

REFERENCES

Important Safety Information

Boxed Warning: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis.

Contraindications: CAPLYTA is contraindicated in patients with known hypersensitivity to lumateperone or any components of CAPLYTA. Reactions have included pruritus, rash (e.g. allergic dermatitis, papular rash, and generalized rash), and urticaria.

Warnings & Precautions: Antipsychotic drugs have been reported to cause:

- **Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis**, including stroke and transient ischemic attack. See Boxed Warning above.
- **Neuroleptic Malignant Syndrome**, which is a potentially fatal reaction. Signs and symptoms include: hyperpyrexia, muscle rigidity, delirium, autonomic instability, elevated creatinine phosphokinase, myoglobinuria (and/or rhabdomyolysis), and acute renal failure. Manage with immediate discontinuation of CAPLYTA and provide intensive symptomatic treatment and monitoring.
- **Tardive Dyskinesia**, a syndrome of potentially irreversible, dyskinetic, and involuntary movements which may increase as the duration of treatment and total cumulative dose increases. The syndrome can develop after a relatively brief treatment period, even at low doses. It may also occur after discontinuation of treatment. Given these considerations, CAPLYTA should be prescribed in a manner most likely to reduce the risk of tardive dyskinesia. Discontinue CAPLYTA if clinically appropriate.
- **Metabolic Changes**, including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, has been reported in patients treated with antipsychotics. Measure weight and assess fasting plasma glucose and lipids when initiating CAPLYTA and monitor periodically during long-term treatment.

- **Leukopenia, Neutropenia, and Agranulocytosis** (including fatal cases). Perform complete blood counts in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Discontinue CAPLYTA if clinically significant decline in WBC occurs in absence of other causative factors.
Choose CAPLYTA to help control your patients’ symptoms with low rates of side effects¹

- In clinical trials, the most common adverse reactions were somnolence/sedation (24%) and dry mouth (6%)¹

**Orthostatic Hypotension and Syncope.** Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension.

**Falls.** CAPLYTA may cause somnolence, postural hypotension, and motor and/or sensory instability, which may lead to falls and, consequently, fractures and other injuries. Assess patients for risk when using CAPLYTA.

**Seizures.** Use CAPLYTA cautiously in patients with a history of seizures or with conditions that lower seizure threshold.

**Potential for Cognitive and Motor Impairment.** Advise patients to use caution when operating machinery or motor vehicles until they know how CAPLYTA affects them.

**Body Temperature Dysregulation.** Use CAPLYTA with caution in patients who may experience conditions that may increase core body temperature such as strenuous exercise, extreme heat, dehydration, or concomitant anticholinergics.

**Dysphagia.** Use CAPLYTA with caution in patients at risk for aspiration.

**Drug Interactions:** Avoid concomitant use with CYP3A4 inducers, moderate or strong CYP3A4 inhibitors and UGT inhibitors.

**Special Populations:** Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Breastfeeding is not recommended. Avoid use in patients with moderate or severe hepatic impairment.

**Adverse Reactions:** The most common adverse reactions in clinical trials with CAPLYTA vs. placebo were somnolence/sedation (24% vs. 10%) and dry mouth (6% vs. 2%).

**Orthostatic Hypotension and Syncope.** Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension.

**Falls.** CAPLYTA may cause somnolence, postural hypotension, and motor and/or sensory instability, which may lead to falls and, consequently, fractures and other injuries. Assess patients for risk when using CAPLYTA.

**Seizures.** Use CAPLYTA cautiously in patients with a history of seizures or with conditions that lower seizure threshold.

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**Reference:** 1. CAPLYTA prescribing information, 2019.

**SEE ITS EFFICACY AT** CAPLYTAHCP.COM
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) of antipsychotic drugs in the treatment of patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. In pooled data from short-term (4- to 6-week), placebo-controlled trials of patients treated with drug A, the rate of death was 4.5% compared to 2.6% in placebo-treated patients. Elderly patients treated with antipsychotics are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) of antipsychotic drugs in the treatment of patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis: Elderly patients treated with antipsychotics are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) of antipsychotic drugs in the treatment of patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

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Psychiatrists should be experts at hearing and seeing what is not visible. We are taught to listen with a third ear for hidden or unconscious meanings. We look to nonverbal messages to understand what is not stated. And that is exactly what we need to do to let the sun shine through the racist dust. We have to use racial hearing aids and racial visual lenses so we do not forget to look for the racism. We need to leverage our experiences to improve the experiences of those who come after us.

Antiracism as an ethical priority

This is one of those times that try our souls. Or should try our souls—psychiatrists and everybody else.

You may recall those paraphrased words of Thomas Paine during other revolutionary times. In 1776, George Washington rallied his freezing and faltering troops, and the United States went on to win the war of independence. However, not everybody received the promised freedom of independence. African Americans did not. With the deaths of Mr. George Floyd and others as well the persecution of so many others, we have been tragically reminded that we are still trying to unite and win the 400-year war against racism and discrimination. This unfortunate truth has been made clear not only by the recent police tragedies but also the overrepresentation of minorities among pandemic deaths, the destruction from climate-related disasters, and the continued urban gun violence.

The American Medical Association’s Principles of Medical Ethics states, “A physician shall recognize a responsibility to participate in activities contributing to the improvement of the community and the betterment of public health.” Since racism harms everyone, from the victims to the perpetrators, and causes harm on multiple levels, we are ethically bound to address and reduce in order to improve public health and better our communities.

The history of racism in psychiatry

Psychiatry’s history in addressing racism has been spotty at best, sometimes promoting advances and sometimes stagnating, even in surprising places. Benjamin Rush, MD, (1745-1813) often called “the father of American psychiatry,” exemplifies the twists and turns of psychiatry’s stand on racism.

Rush was an abolitionist, even though he owned a slave. In fighting for freedom for African-Americans, he also developed the diagnostic theory of “Negritude,” which was considered to be similar to a mild form of leprosy. The only cure for this disorder was to become white. (A possible medical explanation for this hypothetical genetic defect was that it was the fairly rare disease of vitiligo, in which the skin loses its pigment and appears to get lighter.) Do the good deeds make up for the racist actions?

Meanwhile, the field did not see the first Black psychiatrist, Solomon Carter Fuller, MD, until around 1900, more than 50 years after organized psychiatry began in the United States. Gradually, the numbers of Black psychiatrists grew and contributed their expertise to the field, including efforts to address racism. These psychiatrists introduced ideas like labeling the psychological and health effects of interpersonal racism via the concept of microaggressions. Their targeted literature contributions led to a reduction of the misdiagnosis of Black Americans. And, psychiatry had to wait until 2019 before it saw its first Black president—Altha J. Stewart, MD.

Despite the small advances, there have been difficulties and hurdles. Black psychoanalysts experienced challenges while navigating institutes that deemed Black patients as unanalyzable and weaponized theory to perpetuate racist stereotypes. Many of these psychiatrists had to make Campbellian heroic journeys to overcome racial obstacles along the way.

Unfortunately, these microaggressions are still common. Despite her experience, expertise, and position of authority in psychiatry, Danielle Hairston, MD, director of psychiatry residency at Howard University, noted she is still routinely questioned and doubted. She shared this experience of a white colleague ignoring her at a patient’s bedside:

“He’s like, oh, well, the psychiatrist will be here to speak to you soon. And I was like, I’m right here. And he’s like, oh, my gosh. Like, I thought you were the sitter. And he’s like, oh, my God; I don’t know why I said that. And I was like, oh, it’s because I’m Black. And I don’t even necessarily think that he’s racist. It’s just that that’s the bias.”

The APA is not the only psychiatric organization that has missed the boat. Not only has the American Association of Community Psychiatrists (founded in 1935 and recently renamed as the American Association for Community Psychiatry), not had a Black president, it has not had one of any ethnic minority of color background. Yet, it is generally considered to be more liberal than the APA.

Similar racial challenges and contributions emerged for psychiatrists outside of the United States. The most prominent international Black psychiatrist was Frantz Fanon, MD, who practiced in Tunisia and Algeria in the 1950s. He espoused that colonialism had a direct negative psychic effect and that the political and psychic are intertwined. To address this with his patients, he came up with the concept of institutional psychotherapy, meaning the environment and activities of an inpatient ward should be culturally congruent and positive.

Leveraging psychiatry to understand and address racism

Fanon’s ideas help us to understand the 3 main centers of racism in the US. His work on institutional psychotherapy highlighted 1 of the 3 centers; the others are structural and personal. All of these can have different degrees of intensity and prevalence. Institutional racism, which Fanon aimed to address, involves institutions’ policies, practices, and procedures that have a disproportionately negative effect on minorities’ access to quality goods, services, and opportunities. Structural racism relates to how it is imbedded within every aspect of the country as a consequence of chattel slavery more than 400 years ago. Internalized personal racism reflects the finding that we all have some degree of racism as a consequence of structural racism, some of which is unconscious and can be discovered by taking an Implicit Bias Test and/or feedback from others.

All 3 of these centers of racism can be addressed in various ways. From the very first model curricula on cultural psychiatry education for residents in training, self-reflection of one’s cultural background has been deemed essential in psychiatry. Even so, the onus is on those with the most power, which means so-called white-Americans who have benefited from the unearned advantages captured by the term White privilege. Interestingly, intermittent attempts to psychopathologize severe racism as a DSM disorder have failed thus far, in part due to disagreements on where to draw the line. (To learn more, it is helpful to read the allegorical gardener’s tale by Camara Jones, MD, PhD, MPH.) Black patients and psychiatrists are not alone in facing racial-ethnic disparities. Other minority groups, especially Native Americans, have also been affected. Why do these disparities and racism tendencies exist? The disparities may reflect our hard-wired brain tendencies of human nature to fear those who seem different, which contributes to tribalism and our modern ingroups. This reaction is almost like a psychological immune system but, like the physical immune system, it can go awry at times. When it does, it provides a substrate for racism, Islamophobia, anti-Semitism, and related group discriminations. Moreover, we tend to project our inadequacies onto others, scapegoating them in an attempt to feel better and gain power.

The solution, therefore, lies in our prefrontal cortex and our ability to think rationally and carefully to control our emotional tendencies and reframe our thinking, as is done formally in cognitive behavioral therapy. For optimal antiracist impact, we must start with parents and their children, and use the tools currently at our disposal.

Clinical care and racism

All things considered, Black patients more often trust Black clinicians than those of other races. Unfortunately, Black patients have a much smaller chance than white or Asian-American patients of finding culturally similar clinicians. Whenever there is a cross-cultural match of patient and physician, building a positive therapeutic relationship is that much more important. In addition to providing welcoming access, careful evaluation, and appropriate treatment, this also necessitates making race and racism an open and accepted topic to discuss. Similarly, when staff and leadership reflect the cultures of the patients and communities, it sends a comforting message. Inservice training on racism should be ongoing to further promote a welcoming and appropriate environment. Moreover, the patient’s preferences in terms of racial and cultural terminology should dictate how things are discussed. Whenever the alliance is not going well, consultation with colleagues from the treatment team with
“If I love you I have to make you conscious of things you don’t see.” — James Baldwin

Racism and Professional Wellness

Frank A. Clark, MD

Burnout remains an important topic of discussion in psychiatry, both because of its possible deleterious effects on our own well-being and its impact on the quality of care of our patients. Although a 2017 Medscape Psychiatrist Lifestyle Report found a rate of burnout among Black psychiatrists at 32% compared with 43% among White respondents, these statistics are misleading. My opinion is that the percentage of burnout among Black psychiatrists is likely higher than reported because of the pervasive ethnics in the room that were not assessed—structural racism and racial microaggressions.

There must be a call to action if Black psychiatrists are to flourish professionally and personally in a system that has historically invalidated their concerns related to racial injustices, both in the form of health care disparities and exclusion from leadership positions. Proposed strategies include transforming the physician workplace to better resemble communities of color; redesigning medical education curriculum to emphasize the importance of diversity, inclusion, equity, and social determinants of health; and recognizing the value and contributions that Black psychiatrists have made to the field.

Composing the piece: integrating the authors

Racism is clearly a psychological and social phenomenon in which a particular group is viewed as superior or inferior to another. Yet, race may not be something intrinsic and immutable, and the judgements and groupings may be fluid, illusory, imposed, or sometimes insurgent concept. For instance, in World War II, the Aryans touted a so-called “master race.” Similarly, the 2020 US Census has a haphazard listing of races: White; Black or African American; American Indian or Alaska Native; Asian; and Native Hawaiian and Pacific Islander. Neither Hispanic or Latino, nor Jewish are listed as a race, but there is a write-in area for “Some Other Race,” acknowledging the fluidity and self-defining nature of the term race.

With that in mind, our challenge is to assemble the various voices to contribute to the dialogue. Accordingly, a multi-racial group of co-authors crafted this piece. Even so, we grappled with how to pull together our expertise and experience, especially since there has been some controversy over who has the right to have a voice in the discussion. At first, we tried to write a typical review article on racism and psychiatry. However, not only was it difficult to come to consensus on some matters, but we found our personal voices got lost. Fortunately, our secondary thinking processes of our reflective ego managed any tension, which is one of the reasons psychiatry can and should play an important role in this discussion.

Once we decided that each co-author should present on themes important to them, complete with their own race-related terminology, the project moved along quickly. In turn, once our individual voices were preserved, returning to more general themes in the surrounding material was easier. We view this as a model for leadership and cooperation in the antiracism movement. We learned how to hear each other’s racial messages, viewed psychiatry through a racial lens, and tried to portray a variety of experiences and learned lessons.

In many ways, this structure is like an integrated jazz band playing a prototypical song: we play together in the beginning sections, then go on to different instrumental solos backed up by our colleagues, and finally conclude together. (Interestingly, Jazz America’s contribution to the music world, was developed and led by Black musicians.) Thus, without further ado, we present the musical style of our diverse and passionate group.

Police and Criminal Justice Reform

H. Steven Moffic, MD

Blue genu salivates with anticipation for the kill.

Dark vessels begging for mercy while lying still.

Tick-tock, tick-tock!

Blue genu consciously aware of lifeless prey.

Witness’s souls weep as they relive flashbacks of Freddie Gray.

Tick-tock, tick-track!

Blue genu imposes historical privilege to the black slain.

Dysphoric chocolate seeks justice for fatigued hearts bloodied with pain.

Tick-tock, tick-tock!

Tick-tock, tick-tock!

Black longevity has a premature clock.

– Genophobia by Frank Clark, MD

With one tick-tock, one of my patients’ lives was ended prema-
We must—and can—do better.

There are also 109 public schools named after Confederate leaders, despite the fact that one fourth of students attending these schools are African Americans. Many in white America argue that these symbols represent their heritage. However, multiple studies show the primary factor of maintaining these symbols is racial resentment.21

For our country to truly heal, we must not glorify prior racist remnants. We must not embellish the symbols of white supremacy by encouraging their adverse racist principles. There has been some progress on this front. For instance, Governor Nikki Haley removed the Confederate flag after the 2015 shootings at the AME Church in South Carolina. New York State Senator Todd Kaminsky introduced a bill to include education on hate symbols and their effects in school curricula. There is a petition, once again, in Rhode Island to remove “Providence Plantations” from the official state name. This name, incidentally, is on every professional medical license, which is often hung on the walls in doctors’ offices and potentially noticed by Black patients.

We need everyday citizens and leaders to promote fairness, equity, and a greater sense of shared humanity across our nation.

Crucial and Productive Conversations About Racism

Aekta Malhotra, MD

Borrowed from the management world, the term crucial conversations is one of many helpful communication tools when the stakes are high and emotions may get the best of us. Alas, none of these tools will emancipate us from our intellectual cages or ease our psychological discomfort. Fortunately, British psychoanalyst Wilfred R. Bion, MRCS, LRCP, can help us in this endeavor. For instance, he wrote: “If the learner is intolerant of the essential frustration of learning he indulges phantasies of omniscience and a belief in a state where things are known.”22 Language that alienates, shames, and intimidates can be seen as a subconscious attempt to avoid the greater discomfort of challenging systems that oppress, while other individuals, prone to faltering as humans, become the subjects of our outrage. Bridging racial groups then becomes too uncomfortable.

As an Indian-American, I have faced plenty of racism in my personal and professional life. Yet, I have still been the beneficiary of privilege that is not afforded to my African American colleagues. I accept that with much humility. It is time we reframe systemic racism as not only a problem for those who have been oppressed, but rather a societal problem warranting solutions driven by those who have been the beneficiaries of the flawed systems. Because systemic racism has been interwoven in our lives for generations, we require active aliyshap to mitigate its effects. We collectively must find ways to become comfortable with being thrust into unfamiliar territory.

Examining Racial Blind Spots in Psychiatric Practice

Jessica Isom, MD, MPH

As we are trained to drive, the importance of paying attention to blind spots on the road is constantly underscored. We are taught to acknowledge this phenomenon and make necessary corrective actions. Like drivers, psychiatrists have the ability to reposition themselves and their tools so as to avoid collisions, maintain safety, and continue on course.

Unconscious biases dominate our everyday life. Addressing unconscious bias, however, is not outside of our control.

As physicians, we are charged with mitigating the effects of racial bias so our behaviors may mirror our conscious egalitarian values. Unfortunately, we continue to do exactly the opposite in many cases, resulting in a racially inequitable health care system supported by racialized medical decision-making that burdens non-White patients. Race is one of the primary drivers of physician behaviors, and it has been shown to contribute to medical decisions, despite lack of a biological basis. Psychiatric training both nourishes and negates unconscious racial bias by refusing to acknowledge its presence and dismissing its influence on medical judgement.

We must mitigate the impact of unjust racial biases on our practice of psychiatric medicine. Zestcott and colleagues offers a starting point for reducing the influence of implicit bias on medical decision-making. Common-group, counter-stereotyping, and bias awareness opportunities (such as leveraging the Harvard Implicit Association Test) have shown promise in reducing the impact of implicit bias and/or increasing the motivation to do so.

Only by acknowledging the blind spots can we start to make meaningful course improvements.

Visual Symbols of Racism

Rahn K. Bailey, MD

After World War II, when the Allied nations conquered Nazi Germany, all Nazi statues and monuments were destroyed. Why is there resistance to doing the same in America? Nearly 700 remaining monuments of Confederate “heroes” stand as a reminder to African Americans of the slavery, bigotry, animosity, and the frank hatred that still exists today.
Lifelong Education on Race in Psychiatry

Catherine Friedman, MD

What baseline working knowledge of the impact of racism and other sociocultural factors on health is needed to be an effective psychiatrist in the United States?

Graduate and continuing medical education need to begin to address communication barriers caused by personal bias and ignorance. This process should include increased trainee and workforce diversity; required knowledge of and reflections on history and social sciences regarding race, and racism; diverse supervision; and explorations of unconscious bias.

Yet, graduate psychiatric training only captures psychiatrists for a short period at the beginning of their careers. Psychiatrists continue to practice for decades, and thus need refreshers and continuing education opportunities via formal and informal learning opportunities. Maintenance of Certification (MOC) requirements can and should provide tools, encouragement, and motivation for practicing psychiatrists to increase their understanding of race issues as well as guidance in working with people of diverse racial backgrounds. By increased knowledge and awareness with lived experiences, we afford more opportunities to make a difference.

Save the Children!

H. Steven Mofic, MD

“Could the police kill me, too?”

These were the words of a 9-year-old Black male child in his parent’s care awaiting the start of a car-caravan protest. Inevitably, it seems, all the current racial trauma combined with the intergenerational transmission of trauma will psychologically harm our children’s future, especially Black children.

The challenges are many. How do we best talk to children about the trauma and the racism? To what should they be exposed? How can we prevent future posttraumatic symptoms and instead foster resilience and growth? We will need support, hope, and many uncomfortable talks.

I am reminded of the traditional Masai warriors greeting, “How are the children?” We know many are not fine.

A 2020 report looked at counties across the US to determine where children were most and least protected and prioritized. Specifically, the study looked at the factors that cut short childhood, including food insecurity, high school graduation rates, teen pregnancy, and child homicide and suicide rates. Although results varied greatly across the country, Black and Native American children were overrepresented in the many poor counties. The authors noted, “This report uncovers an unacceptable reality in America, where one child can be exponentially more likely than another to succeed in life based solely on the county where they grow up.”

If things stay the way they are, will we ever be able to answer the Masai’s question with “They are well?”

Intersectionality in Psychiatry

Rahn K. Bailey, MD

“Intersectionality” refers to overlapping or interdependent systems of discrimination. It is a theoretical framework for understanding how various aspects of a person’s social and political identities might create unique vulnerabilities to discrimination. Race can be combined with gender, sexuality, class, nationality, ableism, and age. Using intersectionality as an analytic tool can shine a light on those who are most vulnerable to discrimination. Most likely, the more sociocultural differences each individual has, the more vulnerable they will be to discrimination, and the more difficulties they will endure.

A myriad of patients are similarly burdened with multiple issues that impact their mental health, which in turn can lead to anxiety, depression, substance abuse, and suicide. Thus, understanding intersectionality is essential for psychiatrists. It allows us to better understand our patients, their specific needs, and how best to manage their concerns for better outcomes, including offering crucial support for those who feel abandoned.

Racially Based Criminalization of Substance Abuse Disorders

Catherine Friedman, MD

For centuries, racial biases in communication have presented people of color as having inherent characterological deficits that make them seem irresponsible, lazy, and criminal. This has resulted in ideas of “weakness” and “depravity” when discussing substance misuse in this patient population.

In contrast, substance misuse by white individuals is more likely to be attributed to non-characterological traits, such as socioeconomic status, external environment, and mental health issues. This dichotomy manifests in the legal system, where Blacks are more likely to be arrested, jailed, denied bail, and charged with felonies than whites—although rates of drug use and selling/distribution are similar among both groups.

Similarly, crack cocaine possession (primarily used by Blacks) in the 1980s were associated with much harsher criminal penalties than powder cocaine possession (primarily used by whites). And, when opioid use disorder began to affect many whites in the 2000s, instead of seeing increased criminal penalties, a public health emergency was declared.

It is time we look at all substance use disorders as similar diseases and aim to address their root causes instead of penalizing people based on the substances commonly used by a select population.

Racial Lessons Learned in Rural Psychiatry

Claire Cohen, MD

As I sit here watching the demonstrations against racial oppression, I am flooded with feelings and thoughts of my experiences as a Black person, a Black woman, and a Black female psychiatrist practicing in Western Pennsylvania—in and around Pittsburgh and the edge of Appalachia.

I work with patients of all races and have gotten very positive patient reviews over the years. I tend to be stoic in the face of adversity. But sometimes I wonder if I partly rely on unhealthy denial to help deal with racism on the job.

Some of the things I have been told are jaw-dropping. I have patients and parents of patients who tell me I am the best doctor they ever had, and in the same breath they let me know they are glad I speak English. Oh, they say that since I am Black, I understand what it is like to be down-and-out; or, they feel they can reveal their most embarrassing thoughts and actions to a Black doctor, but they want a White doctor who they are sure would be more competent. The scariest experience was when an agency that asked for my services told me they were sending me to areas where there are no psychiatrists to perform evaluations—and that they were sending someone to accompany me because “it is Klan country.”

In order to practice effectively and safely in rural areas that are vastly underserved, it is important to have better support.
### Table. Addressing Issues in Racism

<table>
<thead>
<tr>
<th>Issue</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professional wellness</td>
<td>Monitor burnout percentages of Black psychiatrists on an annual basis with implementation of anti-burnout studies.</td>
</tr>
<tr>
<td>Police and criminal justice reform</td>
<td>Infuse mental health professionals into culturally diverse safety and security institutions, providing guidance and education.</td>
</tr>
<tr>
<td>Visual symbols of racism</td>
<td>Monitor annually the number of racist symbols and names that remain as well as the number of changes and removals made.</td>
</tr>
<tr>
<td>Examining racial blind spots in psychiatric practice</td>
<td>Observe the proportion of psychiatry grand rounds, medical education offerings, professional meetings, and professional development that address racial bias in psychiatric and medical decision-making.</td>
</tr>
<tr>
<td>Lifelong education on race in psychiatry</td>
<td>Active learning and experiences can be guided, measured, and encouraged through Performance in Practice Assessment modules that focus on race in all its dimensions.</td>
</tr>
<tr>
<td>Life the Children</td>
<td>Annual traumatic symptoms prevalence and resilience monitoring of children across cultures.</td>
</tr>
<tr>
<td>Intersectionality in psychiatry</td>
<td>Identify different groups to which people belong and start collecting data of cases of discrimination against them annually.</td>
</tr>
<tr>
<td>Racially based criminalization of substance abuse disorders</td>
<td>Annual measurement and tracking of racial disparities in drug-related arrests and sentencing as well as referrals to appropriate treatment for substance-related crime.</td>
</tr>
<tr>
<td>Racial lessons learned in rural psychiatry</td>
<td>Monitor the number of Black American psychiatrists practicing in rural areas and the supports offered for retention as well as safety.</td>
</tr>
</tbody>
</table>

### Concluding thoughts

Because racism has been part of our country since its founding, it is everywhere and in everyone. Psychiatrists, in particular, should have the knowledge, attitudes, and skills to see where racism is hidden both externally and intrapsychically—in, for instance, symbols, terminology, aversive behavior, and micro-inequities—and then how to process it therapeutically.

We are encouraged by the work of anti-racism scholars who have outlined a strategic approach to shining light on racism. And, we encourage the reader to use this piece as a potential roadmap for your own personal journey in addressing racism in psychiatry and our nation. Since it is important to do this work systematically with mechanisms for accountability, we offer suggestions to measure outcomes and success levels (Table).

We represent a small group of psychiatrists with various staked interests in this subject. We acknowledge and honor the efforts of those valued experts before us and after us who have—and will—enrich the resources necessary for these efforts to be successful. Similarly, we recognize that your joining in this work is voluntary and important. We invite you to contact the authors should you wish to continue this discussion and share in the journey with us.

### References

30. Save the Children USA. The Land of Inopportunity: Closing the Childhood Equity Gap for America’s Kids. 2020.
How Reading Current Literature Stimulates Duh and Yawn Responses

Continued from Cover

reading—simply let piles of journals accumulate unread.¹

Not entirely jaded, and perhaps slightly privileged by our station to be blunt, professional duty demands that we call it as we see it. Decades ago, we recall looking forward to each new issue, anticipating it would likely contain at least several reasonably understandable, clinically relevant, informative articles. Not now. Paradoxically, although revenue sustaining these journals come in large part from pharmaceutical, medical device, and services advertising aimed at practitioners, the journals publish fewer and fewer clinically pertinent, readable articles. Overall, we feel we have not left the journals; the journals have left us.

Our impressions are regularly verified by colleagues and students. Many practitioners report they never read journals because they find them largely to be a waste of time since so many published articles fail the clinical relevance test.

We are not inclined to be anti-scientific nor whining complainers. In fact, understanding the multiple functions that journals serve in academic life, we appreciate the remarkable efforts and contributions of editors. Still, if these journals are to remain reasonably relevant to practicing psychiatrists, as they once were, we feel obligated to explore what has transpired and to suggest remedies.

To start, Duh responses (Table 1) are activated by a variety of article types, including but not limited to:

- Articles hawking certain psychotropic agents as effective and efficacious, despite mountains of modest findings and scientific evidence to the contrary, are unwarranted, irritating, and dishonest.
- Reports hyping newly FDA-approved “me-too” drugs that are superior to their predecessors.
- Articles promising more than can be delivered.
- Articles touting unwarranted enthusiasm for the effectiveness and efficacy of psychotherapies.
- Studies on genome-wide analyses, neuroimaging, personalized psychiatry, and artificial intelligence, biomarkers, and the like.
- Papers propounding that childhood neglect, abuse, and other adverse experiences profoundly impact development.
- Articles advocating the integration of neurology with psychiatry in residency training and practice.

Compared with heart disease over the past 70 years, the lack of meaningfully new treatments for two of psychiatry’s principle concerns, depression and schizophrenia, is striking. Since 1950, cardiology has had more than 14 new pharmacological treatments compared to approximately one quarter of that number for mental illness.

- Enthusiastic reports hyping newly FDA-approved “me-too” drugs that are no better than garden-variety generics in clinical practice, and that upon methodological scrutiny are promoted based on subtly corrupted research methodology favoring the new guy.
- Articles promising more than can be delivered, for example showing unbridled optimism for medications and compounds with high risk of abuse.²

Table 1. The Duhs

- Articles hawking certain psychotropic agents as effective and efficacious regardless of evidence.
- Reports hyping newly FDA-approved “me-too” drugs that are superior to their predecessors.
- Articles promising more than can be delivered.
- Articles touting unwarranted enthusiasm for the effectiveness and efficacy of psychotherapies.
- Studies on genome-wide analyses, neuroimaging, personalized psychiatry, and artificial intelligence, biomarkers, and the like.
- Papers propounding that childhood neglect, abuse, and other adverse experiences profoundly impact development.
- Articles advocating the integration of neurology with psychiatry in residency training and practice.
Similarly, articles touting unwarranted enthusiasm for the effectiveness and efficacy of a variety of psychotherapies despite years of scientific evidence to the contrary, including “me too” therapies based on subtly corrupt research methodology. As well, the continued overreliance on meta-analyses to ascertain efficacious treatment has proven to be an unhelpful substitute for new head to head comparison of specific psychotherapies.

Studies focused on genome-wide analyses, neuroimaging, personalized psychiatry, and artificial intelligence, enduring search for biomarkers and a slew of other basic science and epidemiologically remote studies, which, while of potential intellectual interest to subsets of psychiatrists, are of dubious clinical relevance, generating mountains of “so what” associationals, not causal, findings that yield little of value for either educating or treating patients. Topol, Verghese, and Ofri's dialogue, titled "AI may save some time, but it can't listen to a patient" captures the clinician’s sentiment. The history of American psychiatry is replete with big promises but failed expectations, most recently the premature sanctifications of personalized psychiatry and artificial intelligence.

Papers propounding that childhood neglect, abuse, and other adverse experiences profoundly impact development, not only in childhood, but throughout the entire life cycle. How many times and in how many ways does this need to be repeated? Since thousands of publications on the neurobiology of trauma, from conception to grave, have unfortunately produced no clinically relevant treatment advances, practitioners at best might conclude the research findings are consistent with their clinical experiences but offer little new practical value.

Intermittently erupting articles advocating integrating neurology with psychiatry in residency training and practice, which, aside from constituting a credible subspecialty, seems entirely unwarranted given current basic science and clinical services research. Some of these articles cite the promise of NIMH’s Research Domain Criteria (RDoC) as providing a new paradigm for understanding mental disorders. While RDoC’s aspirational goals to improve psychiatry are laudable, at this time research based on RDoC paradigms does not appear to translate readily into clinical innovation.

In contrast, Yawn responses (Table 2), undoubtedly more frequent when tired clinicians peruse journals at the end of busy days, are activated by a variety of article types, including but not limited to those containing:

- Turgid and obscure writing, a cross between legal-ese, technical engineering manuals and Jacques Lacan.
- Hyperversive lengthiness, where take-away lessons could be transmitted in a paragraph or 2.
- Lengthy, excessively technological, scientifically super-specialized sections suitable for Cell or Nature Biotechnology.
- Displays of statistical virtuosity, understanding of which might require a post-doc in mathematics.
- Authorships by a multinational consortium of at least 100 authors.

What accounts for the flood of Duh and Yawn-ogenic publications?

Editorial boards and publishers are conflicted in attempting to serve several masters concurrently. Consequently, their changing determinations regarding journals’ purposes, intended audiences, and “customers” contribute to increasing numbers of Duh and Yawn-ogenic publications. Guarding their profession’s sacred knowledge, journals archive new discoveries. Obligated to keep financially afloat, journals accommodate governing boards and advertisers. Finally, possibly in last place, serving educational needs of professional organizations’ members-at-large, journals attempt to inform and teach to increase clinicians’ knowledge and skills.

Balancing these diverse agendas, editors have been particularly sensitive to several trends:

- Impact factors: Based on the number of times its articles are cited, a journal’s impact factor constitutes its prime claim to fame. The more scientifically citable, the bigger the impact factor. Invented in 1975 and invigorated and more widely promulgated in 1992, impact factors have played increasingly large roles among journal editors.
competing for the best submissions. No surprise, journal editors compare the size of their impact factors. Questing for prestige, editors have tended to favor manuscripts with the most scientific gravitas—the most consortium-authored, "basic science," mathematically obscure, complex, and unintelligible manuscripts.7

Increasing numbers of academic scientists and clinician-educators are obliged to publish for promotion, to get grants funded and refunded, and for narcissistic strokes. Accordingly, authors increasingly publish in conglomerates (the number of authors per publication is rising substantially), publish numerous papers on the same data-sets, and publish their findings and opinions concerning the same clinical problems facing hundreds of other investigators across the world, not surprisingly most often with similar outcomes and similar hesitant conclusions. Hence, "endemic publishisism."8

For commercial enterprises (important journal advertisers such as pharmaceutical companies, device-makers, software, and other proprietary program developers), publication in major journals provide outlets for publishing gold-standard randomized controlled trial data necessary for FDA approvals. As important, these articles help companies disseminate infomercials targeting clinicians concerning their products, programs, and services, in the gorp of scientific publications. Similarly, "Me Too" psychotherapy outcome studies often serve to promote psychotherapy "brands," despite significant shortcomings in generalizability.

Potential cures for the duhs and yawns

Remedies must address 2 distinct considerations: First, what might journals do to better address the needs of clinician subscribers? Second, perhaps more important, how should today’s clinicians satisfy their needs to keep informed and current? Clearly, it is not just about journals.

What journals might do

Journal editors know they need to offer non-super-specialized, working clinicians enough in each issue to keep them coming back (Table 3). Accordingly, they try to include clinically focused commentaries and, intermittently, clinically case-oriented discussions, explanatory podcasts, and occasional videocasts designed to translate highly technical papers into plain English. Still, these efforts usually constitute a small percentage of each issue’s material.

Journals could also

- Use science writers to convey clearly important messages for clinicians. High-visibility journals (consider Science, Nature, and JAMA), admittedly work with larger budgets. They employ banks of science writers who recast each issue’s most significant findings into articles akin to the reading level of Scientific American summaries that convey much more information and guidance than brief abstracts but which are less wordy than the Manhattan phone book. Most clinicians would welcome more of these pieces, especially those that clearly detail clinical implications and applications. Science writers could succinctly provide no-nonsense critiques of faulty research designs, from randomized trials through meta-analyses.
- Next to each title in the table of contents

### IMPORTANT SAFETY INFORMATION, Continued

**Falls:** SECUADO may cause somnolence, postural hypotension and motor or sensory instability, which may lead to falls, and consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

**Leukopenia, Neutropenia, and Agranulocytosis:** Leukopenia, neutropenia, and agranulocytosis (including fatal cases) have been reported with antipsychotics, including asenapine. Monitor complete blood count in patients with pre-existing low white blood cell count (WBC) or absolute neutrophil count or history of drug-induced leukenopia or neutropenia. Discontinue SECUADO at the first sign of a clinically significant decline in WBC and in severely neutropenic patients.

**GT Prolongation:** Sublingual asenapine was associated with increases in QTc from 2 to 5 msec versus placebo. There were no reports of QT prolongation exceeding 500 msec for SECUADO and placebo. The use of SECUADO should be avoided in patients with a history of cardiac arrhythmias and in circumstances that may increase the risk of the occurrence of torsades de pointes and/or sudden death in association with the use of drugs that prolong the QT interval.

**Hyperprolactinemia:** SECUADO can elevate prolactin levels and the elevation can persist during chronic administration. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

**Seizures:** Use SECUADO with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

**Potential for Cognitive and Motor Impairment:** Somnolence was reported in patients treated with SECUADO. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that SECUADO does not affect them adversely.

**Body Temperature Regulation:** Use SECUADO with caution in patients who will experience conditions that increase body temperature ( strenuous exercise, extreme heat, dehydration and concomitant anticholinergics).

**Dysphagia:** SECUADO should be used cautiously in patients at risk for aspiration. Esophageal dysmotility and aspiration have been associated with antipsychotic drug use.

**External Heat:** Avoid direct external heat sources while wearing SECUADO.

**Application Site Reactions:** During warm time or immediately after removal of SECUADO, local skin irritation may occur. Instruct patients to select a different patch application site each day to limit the occurrence of skin irritation.

**Drug Interactions:** Monitor blood pressure and adjust antihypertensive drugs when taken with SECUADO. Based on clinical response, SECUADO dose reduction may be necessary when used with strong CYP3A4 inhibitors. (fluvoxamine). Reduce paroxetine (CYP2D6 substrate and inhibitor) dose by half when taken with SECUADO.

**Pregnancy:** Studies have not been conducted with SECUADO in pregnant women. Advise patients to notify their healthcare provider of a known or suspected pregnancy. The National Pregnancy Registry for Atypical Antipsychotics monitors pregnancy outcomes in women exposed to antipsychotics, including SECUADO, during pregnancy. For information, contact 1-866-961-2388 or http://womensmentalhealth.org/clinical-and-research-pregnancyregistry/.

To report suspected Adverse Reactions, contact Noven at 800-455-8070 or FDA at 800-FDA-1088 or www.fda.gov/medwatch.

Please see brief summary of full prescribing information on following pages.

were extrapyramidal disorder, application site reaction and weight gain. Instruct patients to select a different patch application site each day to limit the occurrence of skin irritation.

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**TABLE 5: ADVERSE REACTIONS IN SECUADO PLACEBO-CONTROLLED CLINICAL TRIALS**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>SECUADO 3.8 mg/24 hours</th>
<th>SECUADO 7.6 mg/24 hours</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>9.3% (19/204)</td>
<td>9.8% (20/204)</td>
<td>8.3% (17/204)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.0% (4/204)</td>
<td>2.4% (5/204)</td>
<td>1.9% (4/204)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>19.3% (39/204)</td>
<td>14.6% (30/204)</td>
<td>14.7% (30/204)</td>
</tr>
</tbody>
</table>

**Commonly Observed Adverse Reactions**

- Nausea
- Vomiting
- Dry mouth
- Weight gain

**Drug Interactions**

- Asenapine is metabolized by CYP1A2. Concomitant use of SECUADO with a CYP1A2 inhibitor increases AUC and time to reach peak concentration (t_{max}) by 50%.
- Concomitant use of SECUADO with a CYP1A2 inducer decreases AUC and t_{max} by 50%

**Dosage and Administration**

- The recommended dose of SECUADO is 3.8 mg/24 hours for the treatment of schizophrenia in adults.
- The recommended dose for the treatment of acute mania associated with bipolar I disorder is 5 mg twice daily.

**Contraindications**

- SECUADO is contraindicated in patients with:
  - Known hypersensitivity to the active ingredient or any of the excipients.
  - Significant abnormality in any QT interval.

**Warnings and Precautions**

- SECUADO is a complete serotonin receptor antagonist.
- SECUADO should be used with caution in patients with a history of seizures or with a current seizure disorder.
- SECUADO should be used with caution in patients with a history of a seizure disorder.
- SECUADO should not be used in patients with a history of seizures.

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**What might clinicians do to keep up?**

Although we believe that it is too early for clinicians to give up on journals, certain strategies might improve their overall reading experiences. As most clinicians already do, skim through the contents of the journal on the first page or two, and if there is a topic that you are not interested in, go on to the next article. Additionally, if you are reading a journal for the first time, consider reading the abstracts or the summary of the article before deciding whether to read the full article. Finally, if you are reading an article for the second or third time, consider skipping the introduction and reading directly to the conclusion of the article.
Cytochrome P450: You’ve Come a Long Way

John R. Miller, MD

What happens at the molecular level in patients after they ingest a medication? Over the past 30 years, psychiatry has come a long way, especially in better understanding the importance of considering the cytochrome P450 (CYP) system when prescribing medications.

To better understand these issues, it is helpful to look at clinical examples. Consider a patient who has been diagnosed with breast cancer and is being treated with tamoxifen. Tamoxifen, a prodrug, binds poorly to the estrogen receptor, which is the treatment target. The drug has to undergo metabolism through the cytochrome P450 2D6 (CYP2D6) pathway to be transformed into its active metabolites: 4-hydroxytamoxifen and endoxifen. Both metabolites have approximate 100 times more potent estrogen receptor than tamoxifen and are considered active treatment molecules.

In psychiatry, we have 3 commonly prescribed antidepressants—fluoxetine, paroxetine, and bupropion—that potentially inhibit CYP2D6. If a patient is on 1 of these 3 antidepressants as well as tamoxifen, the drug-dose interaction prevents the conversion of the tamoxifen to its active metabolites. In other words, the patient will not receive the benefits of treatment. If the patient also is genotypically an extensive intermediate, a poor metabolizer at the CYP2D6 pathway and 1 of these 3 antidepressants has been prescribed, the CYP2D6 pathway is completely knocked out. The result is no clinical activity from the tamoxifen, and any benefits of the treatment is negated. This is one dramatic example of how understanding drug-drug interactions at the CYP system can be clinically relevant.

Another example can be found in the underappreciated opioid medication arena. We know that codeine has very little activity at the mu opioid receptor, when codeine goes through the cytochrome P450 metabolic pathway, it gets metabolized to morphine, which is roughly 20 times more potent than codeine. The FDA product insert for codeine has a black box warning stating that if a patient is an ultra-rapid metabolizer (approximately 1% of the population) in CYP2D6, the patient is then at risk of respiratory depression and death due to the rapid metabolism of codeine to the much more potent morphine. If a patient is prescribed codeine and they are a poor metabolizer at CYP2D6, or if they are simultaneously taking 1 of those 3 antidepressants that inhibit CYP2D6, most of the codeine will not be metabolized to morphine and the patient may report no analgesic effect. This is important considering some patients engage in malingering and drug-seeking behaviors; the decreased analgesia described by the patient may simply be the consequence of not receiving adequate blood levels of morphine.

This pharmacology extends to 2 other commonly prescribed anxiolytics: hydrocode and oxycodone. Both are prodrugs with some anxiolytic properties, but they are both metabolized by the CYP2D6 enzyme system to their most potent active metabolites hydromorphone and oxymorphone, respectively. As with codeine and morphine, the patient’s CYP2D6 phenotype as well as the presence or absence of any fluoxetine, paroxetine, or bupropion can create a wide range of analgesia that can differ dramatically from patient to patient.

Thus, it is always important to consider the cytochrome P450 pathways when prescribing medications, as the results can be widely different than what you expect. Want to learn more? Visit psychiatrictimes.com/view/cytochrome-p450-youve-come-a-long-way

For the full article, log in to psychiatrictimes.com
ACP Releases Ethical Guidance for Electronic Communication With Patients

**Keith A. Reynolds**

The American College of Physicians (ACP) released a position paper aimed at ensuring that electronic communication between patients and physicians is thoughtful and effective while also maintaining standards of ethics and professionalism.

The position paper, “American College of Physicians Ethical Guidance for Electronic Patient-Physician Communication: Aligning Expectations,” appears in the *Journal of General Internal Medicine* and was developed by the ACP Ethics, Professionalism and Human Rights Committee (EPHRC). It makes recommendations for physicians navigating these new forms of communication with an emphasis on ethics and professionalism, privacy and confidentiality, and price considerations.

While the paper looks at using email, patient portals, text messaging, and video applications used by patients and physicians, it does not examine telemedicine, telephone, video, or other applications, according to a press release. The paper also does not discuss communication during appointments between clinicians, the release says.

The recommendations for the paper include:

- Physicians should not take the place of in-person communications.
- Physicians should only take part after discussion with the patient about expectations and appropriate uses, and with the patient’s consent.
- Physicians should use ethical and other concerns, they can help improve patient care, satisfaction, and clinical outcomes.
- Electronic communications should be used by physicians and institutions to promote health equity and proactively address the socioeconomic and demographic factors that can lead to disparities in uptake and utilization.
- Physicians, patients, and institutions should recognize and address increased workload associated with electronic communication and the impact that can have on physician well-being.

“This paper is particularly timely given the CO-VID-19 pandemic,” Jacqueline W. Fincher, MD, MACP, president of ACP, said in the release. “Electronic communications have become necessary and powerful tools that have the potential to help improve quality, patient satisfaction and access to health information and clinicians but they must be used with care and clear and mutual understanding of patients and clinicians.”

The paper also noted that the ACP Ethics Manual says that physicians must act in the best interest of their patients and should take care to extend standards for maintaining professional relationships and confidentiality.

Mr Reynolds is a staff writer with Medical Economics.
The field of psycho-oncology is evolving in important and meaningful ways. Screening for distress in patients with cancer is now a concept that is accepted and expected; how this is achieved, however, may vary. Some countries and cancer centers have a uniform system, whereas other countries and centers—and sometimes even clinics within the same center—allow for autonomy in terms of which scales or instruments are used, frequency of screening, and different protocols for various levels of distress.

The next several years will present challenges and opportunities for psycho-oncology to improve care for our patients. For example, it is important that we determine which evidence-based treatments should be provided to which patients and at which points in their trajectories of care. Similarly, how we provide care is certain to evolve, as it is likely telepsychiatry options will become more prevalent. With COVID-19, we have gained experience with the technology, and insurance companies and governmental payers have become more flexible about how we deliver services to patients. For all fields, and psycho-oncology in particular, this could be a positive aspect to come out of a very difficult time. It will be important for us to study and test various ways to provide needed services in this format.

Likewise, the articles in Part II of this Special Report provide a glimpse into the ways the field is evolving. For instance, Wendy G. Lichtenthal, PhD, and colleagues share insights into meaning-centered psychotherapy; our ability to translate such important work to greater numbers of patients is essential.

Psycho-oncology also has gotten firmly incorporated in fellowship training in consultation liaison psychiatry. The articles by Carey J. Myers, MD, PhD, and Carolina Retamero, MD, on suicide and cancer and by Lawrence E. Kaplan, DO, FACLP, on lessons learned provide opportunities to recognize the importance of framing major psychiatric topics and providing the best care possible.

Through our work with the World Psychiatric Association (WPA) as co-chairs of the WPA Section on Psycho-Oncology and Palliative Care, we recognize that these issues are important for psychiatrists and other mental health clinicians throughout the world. We appreciate that *Psychiatric Times* has recognized the importance of bringing these topics to you by leading authors, and we hope this inspires you to learn more. We also thank you, the reader, for your interest in these meaningful clinical topics. And, we thank our patients, who continue to inform and educate us so that we can provide better care.

Dr Riba is Professor, Department of Psychiatry, and Director, PsychOncology, University of Michigan Rogel Cancer Center, Ann Arbor, MI; she also is Deputy Editor in Chief Emeritus of *Psychiatric Times*. Dr Grassi is Professor and Chair of Psychiatry, University of Ferrara, Department of Biomedical and Specialty Surgical Sciences, and Director, University Hospital Psychiatry Unit, S. Anna University Hospital and Health Authorities Ferrara, Italy. They report no conflicts of interest concerning the subject matter of this Special Report.

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Finding Meaning in the Face of Suffering
Meaning-Centered Psychotherapy and Cancer

Wendy G. Lichtenthal, PhD, Kailey E. Roberts, PhD, Hayley Pessin, PhD, Allison Applebaum, PhD, and William Breitbart, MD

Cancer can lead to suffering in many forms: physical, emotional, spiritual, and existential. It limits patients’ ability to plan for the future and, too often, their lives. How can we help patients cope with their suffering and existential distress in the face of such challenges? Meaning-Centered Psychotherapy (MCP) may have something to offer. MCP is a brief, structured, manualized intervention that organizes and distills existential concepts so that they are more accessible and relevant to patients’ lives. Born out of research demonstrating that meaning can serve as a buffer against the depression and hopelessness that many patients with metastatic disease report, Breitbart and colleagues developed MCP to help enhance patients’ sense of meaning and purpose in the face of advanced cancer.

Theoretical framework underlying MCP
Inspired by the work of Viktor Frankl, MD, PhD,1 on logotherapy and the work of Irvin Yalom, MD,9 specific concepts highlighted in MCP include:

**MEANING OF LIFE:** There is always the possibility of creating or experiencing meaning, even in the last moments of life. The feeling that “life is meaningless” therefore reflects a disconnection from what gives our lives meaning.

**WILL TO FIND MEANING:** The desire to find meaning in our existence is a primary motivating force in human behavior that drives us to search for and create meaning throughout our lives.

**FREEDOM OF WILL:** We have the freedom to choose how to think about and respond to what comes our way, including limitations, challenges, losses, and uncertainty. This is a core concept in MCP, as the ability to choose our attitude toward suffering is something we always have control over, even in the worst of circumstances.

**SOURCES OF MEANING:** A sense of meaning can be derived from connecting to sources of meaning, including those described in MCP as historical, attitudinal, existential, and experiential (see Table for details).

Guided by structured questions in each session, MCP helps patients systematically reflect on what matters most to them and how sources of meaning can be accessed during challenging times. If a given source of meaning is not accessible, because of physical limitations or concerns about contracting COVID-19, for example, MCP therapists brainstorm with patients about how to tap into the meaningful aspects of these activities or experiences in adapted forms. Therapists repeatedly highlight sources of meaning in the patient’s life that can be used as resources to buoy the patient during difficult moments.

This is the sentiment behind Nietzsche’s quote, “He who has a Why to live can bear almost any How” that Frankl often referenced. In essence, MCP helps patients connect to their “Whys”—that is, their reasons for living—despite the suffering they endure. Frankl viewed suffering as a potential springboard for seeking and finding meaning. Patients’ drive to make sense of the challenges they face may lead to growth and identification of positive sequelae that can emerge as a byproduct of their adversity. However, therapists should be

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*In the 7-session Individual Meaning-Centered Psychotherapy, Sessions 3 and 4 are combined into a single session on Historical Sources of Meaning.*
Research demonstrating the efficacy of MCP

MCP has demonstrated efficacy in enhancing meaning in the lives of patients with advanced cancer in several large-scale trials and has been designated a National Cancer Institute Research-Tested Intervention Program. In 2 randomized controlled trials (RCTs) with patients who had advanced cancer, Meaning-Centered Group Psychotherapy (MCP; an 8-session version of MCP) demonstrated efficacy over supportive group psychotherapy in improving spiritual well-being, quality of life, and sense of meaning, as well as decreasing logical and existential distress among patients with advanced cancer.

Clinical applications

MCP should be delivered in the context of a supportive therapeutic relationship; an exploration of how to find meaning in suffering can only work effectively when the therapist acknowledges, supports, and validates the patient’s suffering. The structured nature of MCP, which includes a combination of didactics, experiential exercises, and guided discussion, enables the deep exploration of powerful concepts in a short period of time (Table; MCP treatment manuals12,13). MCP capitalizes on its time-limited format to propel patients to engage with emotionally provocative topics and take steps toward addressing unfinished business. Each MCP session introduces key existential concepts followed by an experiential exercise to help patients experience meaningful connection and share their “living legacy.” Therapists are encouraged to offer genuine reflections throughout MCP about patients’ meaningful impact on them, which can be particularly powerful for socially isolated patients.

Because MCP focuses on the universal struggles with existential distress in illness, it is not linked to a specific psychiatric diagnosis. MCP is not designed to treat acute psychiatric symptoms (eg, severe depression); therapists should refer patients to first-line stabilizing treatment (eg, medication) prior to attempting MCP. Patients with sufficient physical or cognitive limitations (eg, advanced dementia) to preclude participation in psychotherapy are not suited for this intervention.

In research, MCP has demonstrated particular efficacy in improving outcomes in patients with moderate to severe distress (scoring 4 or higher on the Distress Thermometer).14 The individual and group formats of MCP are nearly identical in content but differ in length. MCP has 8 sessions, providing additional time to focus on the historical sources of meaning, which involves patients sharing about their past, present, and future legacy. In MCP, group members each share responses to the experiential exercises and commonalities are emphasized. Group facilitators acknowledge the “co-creation of meaning” between themselves and group members; everyone present becomes witnesses, or repositories of meaning, for each other, and thus how a meaningful legacy created within the group.

In facilitating MCP groups, the basic tenets of group processes remain important.15 Facilitators should intentionally honor each member’s unique values. IMCP is structured similarly yet affords more flexibility and the opportunity to deepen the meaning-centered work with fewer time constraints. Ideally patients should attend all sessions to get the maximum benefit, as there is a logical progression of content. However, in-person attendance is not necessary as MCP has been successfully delivered via telehealth.16,17

CASE VIGNETTE

“Dr Smith” was a 40-year-old, married physician with one child who began MCP shortly after he received a diagnosis of advanced pancreatic cancer. Although skeptical of how meaning could help him, Dr Smith was hoping for relief from the overwhelming distress he was experiencing about his diagnosis. He was particularly upset by changes in his ability to work as a physician and fulfill responsibilities to his wife, children, and aging parents.

During Session 2, Identity Before and After Cancer, it became clear that being suddenly thrust into the patient role threatened Dr Smith’s sense of identity as someone who provides care for others and strives for perfection. While Dr Smith acknowledged gaining a greater understanding of the existential nature of his distress through discussion, he expressed frustration that there was no way to “fix” this suffering.

In Session 3, Historical Sources of Meaning, the concept of legacy proved to be the key to shifting the meaning Dr Smith made of his current struggles. He realized the distress he perceived changes to his identity were connected to the legacy he was given, as he had been encouraged by his family to be perfect and “fix things.” He realized he could choose to respond differently to the legacy he was given, leading to changes in how he parented and allowing things to be imperfect and messy more often.

As sessions progressed, ways that Dr Smith creatively responded to the physical challenges he faced were identified, reinforcing the concepts of choice and courage in how he faced
Conclusions and future directions
Given its demonstrated efficacy, efforts are underway to disseminate MCP by training clinicians who work with cancer patients through a National Cancer Institute-funded training program. Additionally, many replication and adaptation studies are ongoing, including efforts to adapt MCP for cancer survivors, parents bereaved by cancer, cancer caregivers, and patients in hospice. Cultural and linguistic adaptations have also been conducted. 4

MCP may be especially helpful in working with patients struggling with adversity and situations that feel beyond their control. This may be more relevant than ever in context of the COVID-19 pandemic, which, in threatening lives and imposing limitations on access to sources of meaning, has increased existential distress for patients, caregivers, and health care providers. Patients living through the pandemic are facing isolation, restrictions on their freedom, personal losses, and even greater threats to their and their loved ones’ mortality than they have previously experienced.

MCP empowers patients to focus on the choices they have in the face of limitations, helping them to connect to what matters most. It reaffirms the idea that meaning is always possible. When we are feeling disconnected, MCP facilitates reconnection. Therapists from a variety of theoretical orientations may find it helpful to draw on MCP concepts to support individuals through these uncontrollable and extraordinary circumstances. In turn, we derive meaning from the uniquely reciprocal nature of MCP, in that, as we accompany patients in their exploration of meaning, we co-create meaningful connection and our own personal legacies.

Dr Lichtenthal is Assistant Attending Psychologist, Department of Psychiatry & Behavioral Sciences, Memorial Sloan Kettering Cancer Center, and Assistant Professor of Psychology, Department of Psychiatry, Weill Cornell Medicine; Dr Roberts is Postdoctoral Research Fellow, Department of Psychiatry & Behavioral Sciences, Memorial Sloan Kettering Cancer Center; Dr Pessin is Research Project Manager, Department of Psychiatry & Behavioral Sciences, Memorial Sloan Kettering Cancer Center; Dr Applebaum is Assistant Attending Psychologist, Department of Psychiatry & Behavioral Sciences, Memorial Sloan Kettering Cancer Center, and Assistant Professor of Psychology, Department of Psychiatry, Weill Cornell Medicine; and Dr Breitbart is Chair, Department of Psychiatry & Behavioral Sciences, Memorial Sloan Kettering Cancer Center, and Professor of Clinical Psychiatry, Department of Psychiatry, Weill Cornell Medicine. The authors report no conflicts of interest concerning the subject matter of this article.

REFERENCES
The article serves as an introduction to the field of psycho-oncology for the practicing psychiatrist, from a brief background and history, identifying common cancer and treatment-related neuropsychiatric sequelae, to evidenced-based interventions and treatments, presented in a case-based format. While not comprehensive, given the exponentially evolving field, a list of selected readings will direct the reader to more in-depth reading relevant to specific cancers.

Figure 1

Contemporary role of the psycho-oncologist

PREVENTION DETECTION DIAGNOSIS ACTIVE TREATMENT SURVIVORSHIP PALLIATIVE CARE END OF LIFE

SELECTED FURTHER READINGS

Breast Cancer

Depression in Cancer Patients

Given her increased risk for recurrence of anxiety and depression, Laura was referred by her oncologist to psycho-oncology psychiatry because of her inability to tolerate tamoxifen, which is generally recommended for period of 5 to 15 years. Upon evaluation, Laura acknowledged anxiety and mood symptoms dating back to childhood, with a strong family history of anxiety and depression, and revealed she was a “perfectionist.” She was overwhelmed by both her diagnosis and treatment effects and worried about recurrence, concurrent with mood changes, hot flashes, body image, low libido, fatigue, poor concentration, passive suicidal ideation, and challenges working as an international recruiter for a Fortune 500 company.

Laura felt that she was a burden to her family. She was also overwhelmed with guilt and believed her work stress contributed to an immunosuppressed state resulting in her cancer diagnosis. Her husband, as her primary caregiver and caregiver for their 2 young children while working from home, was experiencing burnout. While raised as a Catholic, Laura had begun to question her faith, believing her diagnosis was a form of punishment from God.

Although her anxiety and depression were relatively well-controlled on fluoxetine prior to her cancer diagnosis, a switch from fluoxetine to a selective serotonin-norepinephrine reuptake inhibitors such as venlafaxine was recommended, given fluoxetine cytochrome P-450 (CYP) 2D6 strong inhibition in the conversion of tamoxifen.
(the pro-drug) to endoxifen (the active metabolite). By contrast, venlafaxine is a weak CYP2D6 inhibitor (Figure 3). With indications for anxiety and depression, venlafaxine is used off-label for hot flashes and neuropathies. Despite concerns about prescribing medications with marked CYP2D6 inhibition (eg, paroxetine, fluoxetine) for patients receiving tamoxifen for adjuvant treatment of breast cancer, recent studies are mixed regarding a relationship between CYP2D6 activity and cancer recurrence. Laura was given referrals to psychology, breast cancer support groups, palliative care (for pain and other symptom management), nutrition, chaplaincy services, and integrative medicine as well as caregiver support resources for her husband.

Over time, anxiety and depression were better controlled on venlafaxine, in addition to better targeting hot flashes, neuropathies, and myalgias, which allowed Laura to resume tamoxifen. What persisted were changes to her concentration, which she described as “mental clouding and fatigue,” often referred to as “chemo-brain,” from the effects of anti-estrogen therapy-induced menopause. Because some studies have shown benefits from psychostimulants (modafinil and armodafinil), Laura was prescribed methylphenidate, which improved concentration and focus and allowed her to return to work. However, it is important to consider metastasis and CNS involvement on the differential when evaluating for any cognitive or behavioral status changes, with a low threshold for neuro-psychological testing, neurological workup, and imaging.

Laura was better able to accept the treatment-related changes to her body, the cancer diagnosis, and the fears of recurrence through acceptance and commitment therapy (ACT), and cognitive behavioral therapy (CBT) helped with sleep and fatigue. She derived excellent peer support in her breast cancer support group and was strongly encouraged to modify her work schedule by other members of the group.

Given emerging evidence supporting the influence of diet and exercise on the neuroendocrine and inflammatory pathways, a nutrition consultation recommended a ketogenic diet as well as integrative approaches such as yoga, acupressure, and acupuncture. Chaplaincy was instrumental in helping her reframe and realign her religious beliefs and values, effectively assuaging underlying guilt related to her diagnosis. Her husband engaged in caregiver support groups and adopted a more balanced approach in his various caregiving and work roles, which resulted in increased support at home and with childcare. Ultimately, the couple was able to engage in couple’s therapy to improve interpersonal functioning.

(Continued on page 30)
With the emergence of new therapeutic strategies, we now have more options for improving the quality of life for people diagnosed with psychiatric disorders. As the field continues to progress it is important for you and your colleagues to understand the current clinical data and best practices when caring for your patients.

The Annual Psychiatric Times® World CME Conference™ is an event specifically designed to help you apply new evidence-based clinical concepts in psychiatry to real-world clinical practice. This 3-day meeting will feature expert presentations and panel discussions addressing emerging psychiatric treatments and newest clinical trial data, and best practices for managing challenging psychiatric diagnoses including mood disorders, anxiety disorders, eating disorders, postpartum depression, substance abuse disorders, and more. This experience provides the ideal curriculum with a focus on challenging patient case scenarios, integrating relevant evidence into real-world patient management, and comparing your practices with those of experts and peers.

Overview:

Agenda:

Thursday, October 15, 2020
12:00 PM Registration and Lunch
12:45 PM Presession Survey
1:00 PM Interventions for Sleep Disturbances in Psychiatric Disorders Karl Doghramji, MD
1:15 PM The Interplay of Migraines and Psychiatric Disorders: Treatment Implications Heidi Moawad, MD
1:30 PM Clinical Psycho-Oncology: Assessment and Management Guy Maytal, MD
1:45 PM Postsession Survey and Audience Q&A
2:10 PM BREAK
2:25 PM Hot Topics Presession Survey
2:35 PM Cannabis in Psychiatry: Clinical, Legal, and Ethical Issues David A. Gorelick, MD, PhD, DLFAPA, FASAM
2:55 PM The New Role of Psychedelics Shannon Clare Carlin, MA, AMFT
3:15 PM Postsession Survey and Audience Q&A

Benefits of Attending:

Learn About Emerging Treatments
Interact With Psychiatric Experts
Understand Strategies for Early Diagnosis

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### Friday, October 16, 2020

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<td>Presession Survey</td>
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<td>Diagnostic Issues in Mood Disorders</td>
<td>Sidney Zloof, MD</td>
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<td>8:45 AM</td>
<td>State-of-the-Art Treatment in Major Depressive Disorder</td>
<td>Sheldon H. Pfeffer, MD</td>
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<td>9:10 AM</td>
<td>Treatment Resistant Depression</td>
<td>Michael Thase, MD</td>
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<td>9:25 AM</td>
<td>Treating Major Depressive Disorder: Beyond MAOIs and SSRIs</td>
<td>Roger McIntyre, MD</td>
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<td>Postsession Survey and Audience Q&amp;A</td>
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<td>10:15 AM</td>
<td>Plenary Session: Special Report on Bipolar Disorder</td>
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<td>10:25 AM</td>
<td>State-of-the-Art Treatment in Bipolar Disorder</td>
<td>Melissa DeBello, MD, MD</td>
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<td>10:55 AM</td>
<td>Medical Crossfire®: Should Bipolar Depression Be Treated With Antidepressives?</td>
<td>Chris Aknin, MD; Nassir Ghaemi, MD; and Joseph F. Goldberg, MD</td>
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<td>11:10 AM</td>
<td>Combination Therapy in Bipolar Disorder</td>
<td>Nassir Ghaemi, MD</td>
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<td>Maintenance Therapy in Bipolar Hyperthymia</td>
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<td>Major Depressive Disorder</td>
<td>Rajaip Magi, MD</td>
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<td>1:45 PM</td>
<td>Bipolar Disorder</td>
<td>Daniel N. Swart, MD</td>
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<td>2:30 PM</td>
<td>Treating Major Depressive Disorder in a Primary Care Setting</td>
<td>Saraje Roes, MD</td>
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<td>3:00 PM</td>
<td>Treating Anxiety in a Primary Care Setting</td>
<td>Jeffrey R. Strain, MPH, FAACAP</td>
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<td>Plenary Session: Hot Topics, Special Report on Psychiatry, and Women's Health</td>
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<td>Treatment Strategies for Attention-Deficit/Hyperactivity Disorder</td>
<td>Anthony L. Rostain, MD, MD</td>
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<td>5:25 PM</td>
<td>Symptoms, Causes, and Treatment of Binge Eating Disorder</td>
<td>Carlos Grilo, PhD</td>
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<td>Practical Psychoneuroendocrinology: How the Brain, Nervous System, and Endocrine System Interact</td>
<td>Anita Clayton, MD</td>
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<td>Psychosocial and Psychopharmacological Options for Postpartum Depression</td>
<td>Jennifer L. Payne, MD</td>
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<td>7:00 PM</td>
<td>Effective Strategies for Hypoactive Sexual Desire Disorder</td>
<td>Anita Clayton, MD</td>
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SPECIAL REPORT

SELECTED READINGS CONTINUED

Neurocognitive


Neuroendocrine Tumors


Parenting and Family


Prostate Cancer


unexpectedly, Jonathan had been very close to his mother, and she inspired him to follow his dream of becoming an attorney; she had also been his dedicated caregiver since his initial diagnosis. As his second surgery and hospital course immediately ensued following his mother’s death, he did not have the opportunity to process his grief, not to mention grieving for his own loss of identity.

It was apparent Jonathan was suffering from a complicated grief reaction, demoralization, symptoms of PTSD, and neurocognitive and functional impairments that required a multi-disciplinary approach. Working closely with neuro-oncology, the recommendation was to transition from levetiracetam, given its neuropsychiatric effects, to a mood stabilizing antiepileptic medication such as lamotrigine. Other psychopharmacological interventions included sertraline for anxiety and symptoms of PTSD and prazosin for nightmares. Referrals were made for neurocognitive rehabilitation, trauma informed therapy, grief and loss counseling, and a caregiver support group for patients with brain tumors.

Eventually, Jonathan’s symptoms of PTSD improved with both trauma informed therapy and medication interventions. Through neurocognitive rehabilitation, he was able to employ adaptation strategies that improved his memory recall, interpersonal communication, self-esteem, and sense of autonomy. In turn, his family learned to adapt to his specific needs, while feeling supported by caregiver support groups and services.

Discussion
At our institution, we are fortunate to have a family camp that is sponsored by the neuro-oncology department; it allows patients and their family members, medical, nursing, and support staff to engage in numerous activities, while enjoying respite outside the medical setting. This case illustrates the multiple and complex psychosocial stressors and neuropsychiatric sequelae inherent to the brain tumor population, which requires a concerted multidisciplinary approach and extensive resources to improve and maintain quality of life.

The 2 cases represent general clinical approaches to breast and CNS cancers. Accordingly, there are nuanced clinical approaches to other cancers, including hematologic-oncological, head and neck, lung, gastrointestinal, genitourinary, gynecological, prostate, neuroendocrine, sarcoma, and melanoma (see Selected Readings).

Improvements in cancer care continue an upward trajectory; however, psychosocial and quality of life measures are not always synchronous.

References

Therapies

Symptom Management
BIPOLAR UPDATE

Topiramate in Bipolar Disorder and Comorbidities: The Myths and the Evidence

David N. Osser, MD

There appears to be some confusion regarding the efficacy of topiramate in bipolar disorder. Some prescribers think it is effective for mania, depression, or simply for “mood.” The evidence does not support this: all studies found no efficacy. Also, topiramate has a significant adverse effect burden, including the infrequent but serious problems of kidney stones (in more than 2% of patients), glaucoma, and suicidal ideation, and the more common problems (disliked by patients) of cognitive and memory impairment, numbness and tingling in the extremities, and hyperchloremic acidosis (present in up to 40% of patients)—check electrolytes and you will see—which can give a variety of non-specific symptoms that include dizziness, nausea, and fatigue. Topiramate is FDA approved for seizures and for migraine prophylaxis.

There are some off-label proposed uses for topiramate in comorbidities that are common in patients with bipolar disorder. It has been used as an adjunct to olanzapine to mitigate or even prevent weight gain. This is not recommended as something to do routinely (because of all those adverse effects), but at times this can be helpful and worth the risks. Topiramate in low doses (up to 92 mg) is a component of a weight loss combination product (with phentermine) that is on the market.

Topiramate has not been found effective for any phase of bipolar disorder.

Some patients with bipolar disorder who experience weight gain also have binge eating disorder (BED). There is only one FDA-approved medication for this: lisdexamfetamine. However, patients with bipolar disorder not currently on a good dose of a mood stabilizer and who have comorbid BED would likely not benefit from lisdexamfetamine or any other stimulant (nor with any antidepressant, some of which also have positive studies in BED). Topiramate has 2 positive studies in BED with good results so you might think of it for them.

Some substance abuse disorders (SUDs) may benefit from topiramate for prevention of relapse. There may be mild benefit in alcohol use disorder, and there are 2 positive studies of patients with cocaine use disorder, only 1 of which showed benefit at end point—at doses up to 300 mg daily. Note that all of these studies used substantial doses of topiramate. One encounters patients on low doses like 25 mg twice a day. These may be placebo-level doses for any of the possible SUD indications.

Several trials have examined the effect of topiramate on posttraumatic stress disorder (PTSD). In 2 studies, there was no difference from placebo, but 1 study conducted in Brazil on 70 civilian patients found a good effect size. The reduction in the Clinician-Administered PTSD scale was 58 on topiramate and 32 on placebo, p = 0.008.

Three small placebo-controlled trials of topiramate at up to 200 mg daily in patients with borderline personality disorder (BPD) are all from the same research group in Germany/Austria. Large improvements in hostility, interpersonal sensitivity, and anxiety symptoms were reported, larger than have been seen in other psychopharmacology studies of BPD. Although the papers identify no funding source, the UK NICE Guidance Development Group (GDG), suspicious about the large effect sizes, attempted without success to get more information about the funding from the authors and the publishing journals. Their interesting conclusion was “... as the GDG were unable to gain clarity in this regard, they took the decision not to consider their trials when drawing up their conclusions.” Clearly, these studies need replication.

Dr Osser is Associate Professor of Psychiatry, Harvard Medical School, and Consulting Psychiatrist, US Department of Veterans Affairs, National Telemental Health Center, Bipolar Disorders Telehealth Program, Brockton, MA. The author reports no conflicts of interest concerning the subject matter of this article.

REFERENCES

The Valkyrie

-in Norse mythology Valkyries were female figures who decided who would live or die in battle.

Richard M. Berlin, MD

Six-four, three hundred pounds, she rouses each sleepless post-op patient curled in sheet-tossed Hill Rom beds, their minds blurred from pain and Percocet when she belts out her sunrise chant:

Good morning, Honey, I’m Miss Dee, and I’m gonna bring the most beautiful breakfast you’ve ever seen. Why Honey, I’ve got grits, biscuits, bacon, and ham, flapjacks, waffles, omelets, and eggs, coffee, croissants, and a selection of teas.

So what will it be that you want from Miss Dee?

And the patients she has chosen to live squat into her sunlight and groan their orders, hungers revived, arous to do battle with a sweet and tempting world.

Dr Berlin is Instructor in Psychiatry, University of Massachusetts Medical School, Worcester, MA.
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Addiction & Substance Disorders

5 Steps to Improve Outcomes in Substance Abuse in Older Patients

Rajesh R Tampi, MD, MS, Deena J Tampi, MSN, MBA-HCA, RN, and Michel Farivar, MD

The population of older adults with substance use disorders (SUDs) is increasing in the United States. It has been postulated that by the end of 2020 there will be approximately 5.7 million older adults with SUDs when compared with 2.8 million individuals in 2006; the number of emergency department visits for drug misuse on an average day for older patients can be seen in Figure 1. Older adults tend to preferentially abuse alcohol, nicotine, and prescription medications while younger individuals use marijuana, cocaine, and heroin. There is a considerable scarcity of data regarding SUDs among older adults despite concerns of this issue being a major public health concern.

Older adults are considered at-risk population for using psychoactive drugs, as aging is associated with an increased burden of health-related issues and psychosocial stressors that can increase the risks due to use of psychoactive drugs. It is estimated that at least 1 in 4 older adults has used psychoactive medications within a pattern of substance abuse.

The 2005-2007 National Surveys on Drug Use and Health indicated that approximately 43% of individuals aged 65 years or older admitted to using alcohol in the past year with approximately 6.7% of these individuals reporting a pattern of alcohol abuse or dependence symptoms. The 2008-2009 US National Surveys on Drug Use and Health indicated that 14.1% of individuals aged 65 years or older reported past-year tobacco use when compared with 30.2% individuals aged 50 to 64 years. The 2005 and 2006 National Surveys on Drug Use and Health found that among adults aged 65 years or older, 0.7% had used marijuana and 0.04% had used cocaine in the past year. The rates of past-year use of inhalants, hallucinogens, methamphetamine, and heroin were also at less than 0.2%. Among individuals aged 50 years or older, the past-year non-medical use of prescription opioids at 1.4% is more prevalent than the non-medical use of prescription sedatives (0.14%), tranquilizers (0.46%), and stimulants (0.16%). In this age group, the past-year prevalence of prescription opioid use disorders was low at 0.13%, but the risk of prescription opioid dependence was higher at 7.6%. Of concern is that in the US, 8.7% of individuals aged 65 to 80 years filled at least one prescription for benzodiazepines in a 1-year period with 31.4% of these individuals receiving benzodiazepines for longer than 120 days in a year. These data suggest a population at increased risk for SUDs and associated comorbidities.

Risk factors

Risk factors for the development of SUDs among older adults include a history of substance use, comorbid psychiatric disorders, and the presence of cognitive impairment. Factors that mitigate the development of SUDs include being married, no previous history of substance use, and a religious affiliation. SUDs are moderately to highly heritable; findings indicate that an individual’s risk would be proportional to the degree of genetic relationship to the relative with SUDs. For reference, the heritability rates for hallucinogen use disorder is 0.39 and for cocaine use disorder is 0.72.

Consequences

SUDs among older adults is associated with worse medical outcomes and increased economic burden of care. The long-term use of psychoactive substances can result in adverse neurological outcomes even at therapeutic doses. These adverse effects include drowsiness, confusion, slowed psychomotor functioning, impaired reaction time, incoordination, ataxia, falls, and amnesia. The sustained use of psychoactive drugs often results in the development of physiological and physical dependence. Abrupt discontinuation of these drugs may result in serious withdrawal symptoms including delirium and seizures. The use of these substances may also result in problematic drug interactions with other prescribed medications or over the counter medical products.

Chronic use of psychoactive drugs can result in multiple medical complications including cardiac, hepatic, and renal impairments leading to greater rates of disability, morbidity and mortality. Approximately one-fifth of older adults who are hospitalized due to psychiatric disorders have a comorbid substance use disorder. Older adults with SUDs have higher rates of depression and suicide than age matched controls. The overall economic burden of substance use disorders among older adults is higher owing to greater risks for and rates of comorbidities, longer inpatient hospital stays and also the subsequent greater need for more intense outpatient programs to manage symptoms when compared with age matched controls.

Assessments

Available evidence indicates that SUDs among older adults are often underdiagnosed and poorly treated. The reasons for this underdiagnosis and poor treatment include lack of awareness regarding these disorders, denial of the disorder, the shame and stigma of using addictive substances, reluctance to seek professional help, lack of financial resources, the lack of social supports, the presence of comorbid conditions, limited time spent with primary care physicians, and the ageist attitudes toward mental health disorders among older individuals.

The use of standard diagnostic criteria (eg, DSM-5), which are validated for use among younger adults tends to underestimate the prevalence of SUDs when among older adults. The Consensus Panel of the Treatment Improvement Protocol (TIP) recommends screening for alcohol and prescription drug use disorders as part of a regular physical examina-

Figure 1. Number of Emergency Department Visits for Drug Misuse on an Average Day for Patients Aged 65 or Older

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Number of Emergency Department Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription or nonprescription pain relievers</td>
<td>118</td>
</tr>
<tr>
<td>Narcotic or pain relievers*</td>
<td>80</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>48</td>
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<tr>
<td>Alcohol in combination with other drugs</td>
<td>25</td>
</tr>
<tr>
<td>Antidepressants or antipsychotics</td>
<td>23</td>
</tr>
<tr>
<td>Cocaine</td>
<td>13</td>
</tr>
<tr>
<td>Heroine</td>
<td>7</td>
</tr>
<tr>
<td>Marijuana</td>
<td>5</td>
</tr>
<tr>
<td>Illicit amphetamines or methamphetamines</td>
<td>2</td>
</tr>
</tbody>
</table>

* by selected types of drugs; 2011 DAWN study

Narcotic pain relievers are a subset of prescription or nonprescription pain relievers.


Figure 1. Number of Emergency Department Visits for Drug Misuse on an Average Day for Patients Aged 65 or Older

Prescription or nonprescription pain relievers
Narcotic or pain relievers
Benzodiazepines
Alcohol in combination with other drugs
Antidepressants or antipsychotics
Cocaine
Heroine
Marijuana
Illicit amphetamines or methamphetamines

by selected types of drugs; 2011 DAWN study

Narcotic pain relievers are a subset of prescription or nonprescription pain relievers.
treatment among adults aged 60 years or older. The routine use of standardized screening instruments like the Michigan Alcohol Screening Test-Geriatric (MAST-G), the CAGE screening test, and computerized screening tools like the Drug and Alcohol Problem Assessment for Primary Care (DAPA-PC) can assist with the appropriate diagnosis of SUDs among older adults.

Treatments

Available evidence indicates that treatments for SUDs among older adults are as successful as treatments for substance use disorders among younger adults. Programs that improve outcomes among older adults with SUDs include those that emphasize age-specific treatments, use of supportive and non-confrontational approaches that build self-esteem, emphasize cognitive-behavioral approaches, assist in development of skills to improve social support, use counselors who are trained and motivated to work with older adults and use of age-appropriate pace and content. Additionally, older adults have better outcomes when they are enrolled in programs where there is close monitoring for drug interactions and adverse effects of medication treatments. This is especially true among individuals withdrawing from alcohol and other drugs in which the withdrawal symptoms may be severe and prolonged.

Buprenorphine, disulfiram, and naltrexone are approved by the US Food and Drug Administration for the treatment of alcohol use disorder and buprenorphine is approved for the treatment of opioid use disorder among adults. However, the data on the use of these medications for the treatment of SUDs among older adults is limited. A review of the literature indicates that there are only two randomized controlled trials (RCTs) that evaluated the use of pharmacologic agents for SUDs among older adults. One trial evaluated the use of naltrexone when compared with placebo for the treatment of alcohol use disorder among individuals who were aged 50 to 70 years. The other trial evaluated the use of naltrexone or placebo as adjuncts with sertraline in the treatment of alcohol use disorder among individuals aged 55 years or older. Both trials showed that the use of naltrexone reduced the rates of relapse among older adults with alcohol use disorder. There are no RCTs that evaluated the use of buprenorphine, acamprosate, or disulfiram for SUDs among older adults. Figure 2 illustrates the 5 steps that can ensure success in the treatment of substance use disorders among older adults.

Conclusions

The number of older adults with an SUD will increase appreciably in the near future. The currently available diagnostic criteria that have been developed to identify SUDs among younger individuals are less sensitive in identifying SUDs among older adults. The use of standardized screening tools and specific diagnostic criteria will improve the identification of older individuals with SUDs.

Older adults with SUDs respond well to treatments, if these programs are specifically designed to meet the needs of the older adult population. However, additional studies are needed because there is a dearth of evidence regarding pharmacotherapy for SUDs among older adults.

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REFERENCES


This Month in Psychiatry

The Walking Cure

David A. Sasso, MD, MPH, for the Group for the Advancement of Psychiatry Committee on the Arts and Humanities

On August 26, 1910, 2 men were taking a long stroll through the streets of Leiden in Holland, engaged in deep conversation. The participants in this Friday afternoon promenade were Gustav Mahler and Sigmund Freud. And far more than a casual chat, it was a single extended 4-hour therapy session: the brief psychoanalysis of Mahler by Freud.

What can we learn from this encounter, especially about treating patients during our current experiences in COVID?

Learn more about this extraordinary encounter and what it means for present-day psychiatry here: https://www.psychiatrictimes.com/view/walking-cure
Hypothetical patient portrayal. Individual results may vary.

• Prior to and during treatment assess for the presence of cardiac disease. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulants at recommended doses, as well as sudden death in children and adolescents with structural cardiac abnormalities and other serious heart problems while taking CNS stimulants at recommended doses. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias while taking Vyvanse.

• CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients (monitor weight and height). Treatment may need to be interrupted in children not growing or gaining weight as expected.

• CNS stimulants cause increases in blood pressure (mean increase about 2-4 mm Hg) and heart rate (mean increase about 3-6 bpm). Monitor all patients for tachycardia and hypertension.

• Exacerbation of Pre-existing Psychosis: May exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder. Induction of a Manic Episode in Patients with Bipolar Disorder: May induce a mixed/manic episode in patients with bipolar disorder. Prior to initiating treatment, screen for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms, or a family history of suicide, bipolar disorder, and depression). New Psychotic or Manic Symptoms: At recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients with no prior history of psychotic illness or mania. Discontinue if symptoms occur.

• CNS stimulants are associated with a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

• CNS stimulants (amphetamines and methylphenidate-containing products), including Vyvanse, have a high potential for abuse and dependence. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of Vyvanse for the treatment of obesity have not been established.

Vyvanse demonstrated significant improvement in attention in adults with ADHD.†

Vyvanse is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in patients ages 6 and above. Vyvanse is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of Vyvanse for the treatment of obesity have not been established.

Learn more at VyvansePro.com/Start

Vyvanse® (lisdexamfetamine dimesylate) capsules, 10, 20, 30, 40, 50, 60 mg

Her improved focus started with Vyvanse. Vyvanse started with you.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
• Known hypersensitivity to amphetamines or other ingredients of Vyvanse. Anaphylactic reactions, Stevens-Johnson Syndrome, angioedema, and urticaria have occurred.
• Use with monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping MAOIs (including MAOIs such as linezolid or intravenous methylene blue), because of an increased risk of hypertensive crisis.

WARNINGS AND PRECAUTIONS
• Prior to and during treatment assess for the presence of cardiac disease. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulants at recommended doses, as well as sudden death in children and adolescents with structural cardiac abnormalities and other serious heart problems while taking CNS stimulants at recommended doses. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias while taking Vyvanse.

INFORMATION AND LIMITATION OF USE
Vyvanse is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in patients ages 6 and above. Vyvanse is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of Vyvanse for the treatment of obesity have not been established.
Hypothetical patient portrayal. Individual results may vary.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

- Use with monoamine oxidase inhibitors (MAOIs) or
- CNS stimulants (amphetamines and methylphenidate-containing products), including Vyvanse, have a

**WARNINGS AND PRECAUTIONS**

- Increased risk of serotonin syndrome when co-administered with serotonergic agents (e.g., SSRIs, SNRIs, triptans) and CYP2D6 inhibitors, but also during overdosage situations. Discontinue Vyvanse if it occurs and initiate supportive treatment.

**ADVERSE REACTIONS**

- The most common adverse reactions (≥5% and at least twice the rate of placebo) reported in clinical trials were:
  - Children aged 6 to 12: decreased appetite, insomnia, upper abdominal pain, irritability, vomiting, decreased weight, nausea, dry mouth, and dizziness;
  - Adolescents aged 13 to 17: decreased appetite, insomnia, and decreased weight;

- Adults: decreased appetite, insomnia, dry mouth, diarrhea, nausea, anxiety, and anorexia.

**PREGNANCY AND LACTATION**

Vyvanse may cause fetal harm. Breastfeeding is not recommended during Vyvanse treatment.

Please see Brief Summary of Full Prescribing Information, including Boxed WARNING regarding Potential for Abuse and Dependence, on following pages.

References:

3. Data on file; SPD489-066; Shire US Inc.

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US-LIS-0241 v1.0 05/20
**WARNING: ABUSE AND DEPENDENCE**

CNS stimulants (amphetamine and methylphenidate-containing products), including VYVANSE, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy.

**CONTRAINDICATIONS**

VYVANSE is contraindicated in patients with:

- Known hypersensitivity to amphetamine products or other ingredients of VYVANSE. Anaphylactic reactions, Stevens-Johnson Syndrome, angioedema, and urticaria have been observed in postmarketing reports.
- Patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs (including MAOIs such as linezolid or intravenous methylene blue), because of an increased risk of hypertensive crisis.

**WARNINGS AND PRECAUTIONS**

**Potential for Abuse and Dependence (See Above)**

Serious Cardiovascular Reactions

Sudden death, stroke, and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in children and adolescents with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during VYVANSE treatment.

Blood Pressure and Heart Rate Increases

CNS stimulants cause an increase in blood pressure (mean increase about 2-4 mm Hg) and heart rate (mean increase about 3-6 bpm). Monitor all patients for potential tachycardia and hypertension.

Psychiatric Adverse Reactions

**Exacerbation of Pre-existing Psychosis**

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

**Induction of a Manic Episode in Patients with Bipolar Disorder**

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

**New Psychotic or Manic Symptoms**

CNS stimulants, at recommended doses, may cause psychotic or manic symptoms, e.g. hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychiatric illness or mania. If such symptoms occur, consider discontinuing VYVANSE.

In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in 0.1% of CNS stimulant-treated patients compared to 0% in placebo-treated patients.

**Suppression of Growth**

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including VYVANSE. In a 4-week, placebo-controlled trial of VYVANSE in patients ages 6 to 12 years old with ADHD, there was a dose-related decrease in weight in the VYVANSE groups compared to weight gain in the placebo group. Additionally, in studies of another stimulant, there was slowing of the increase in height.

**Peripheral Vasculopathy, including Raynaud's Phenomenon**

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

**Serotonin Syndrome**

Serotonin syndrome, a potentially life-threatening reaction, may occur when amphetamines are used in combination with other drugs that affect the serotonergic neurotransmitter systems such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, bupropion, and St. John's Wort. Amphetamines and amphetamine derivatives are known to be metabolized, to some degree, by cytochrome P450 2D6 (CYP2D6) and display minor inhibition of CYP2D6 metabolism. The potential for a pharmacokinetic interaction exists with the co-administration of CYP2D6 inhibitors which may increase the risk with increased exposure to the active metabolite of VYVANSE (dextroamphetamine). In these situations, consider an alternative non-serotonergic drug or an alternative drug that does not inhibit CYP2D6. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, excitement, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

Discontinue treatment with VYVANSE and any concomitant serotonergic agents immediately if symptoms of serotonin syndrome occur, and initiate supportive symptomatic treatment. Concomitant use of VYVANSE with other serotonergic drugs or CYP2D6 inhibitors should only be used if the potential benefit justifies the potential risk. If clinically warranted, consider initiating VYVANSE with lower doses, monitoring patients for the emergence of serotonin syndrome during drug initiation or titration, and informing patients of the increased risk for serotonin syndrome.

**ADVERSE REACTIONS**

**Clinical Trial Experience**

Based on data from 4-week parallel-group controlled clinical studies of VYVANSE in pediatric and adult patients with ADHD.

**Adverse Reactions Associated with Discontinuation of Treatment**

In the controlled trial in patients ages 6 to 12 years, 8% (18/218) of VYVANSE-treated patients discontinued due to adverse reactions compared to 1% (1/72) of placebo-treated patients. The most frequently reported adverse reactions leading to discontinuation (1% or more and twice the rate of placebo) were ECG voltage criteria for ventricular hypertrophy, tic, vomiting, psychomotor hyperactivity, insomnia, decreased appetite and rash [2 instances for each adverse reaction, i.e., 2/233 (1%)]

In the controlled trial in patients ages 13 to 17 years, 3% (7/233) of VYVANSE-treated patients discontinued due to adverse reactions compared to 1% (1/77) of placebo-treated patients. Most frequent adverse reactions leading to discontinuation were irritability (3/233; 1%), decreased appetite (2/233; 1%), and insomnia (2/233; 1%).

In the controlled adult trial, 6% (21/358) of VYVANSE-treated patients discontinued due to adverse reactions compared to 2% (1/62) of placebo-treated patients. The most frequently reported adverse reactions leading to discontinuation (1% or more and twice the rate of placebo) were insomnia (8/358; 2%), tachycardia (3/358; 1%), irritability (2/358; 1%), hypertension (4/358; 1%), headache (2/358; 1%), anxiety (2/358; 1%), and dyspnea (3/358; 1%)

Adverse Reactions Occurring at an Incidence of ≥5% or More Among VYVANSE Treated Patients with ADHD in Clinical Trials

Most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) reported in children, adolescents, and/or adults were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting.

Adverse Reactions Occurring at an Incidence of ≥2% or More

Adverse reactions reported in the controlled trials in pediatric patients ages 6 to 12 years, adolescent patients ages 13 to 17 years, and adult patients treated with VYVANSE or placebo:

Adverse Reactions Reported by ≥2% of Children (Ages 6 to 12 Years) with ADHD Taking VYVANSE and at least Twice the Incidence in Patients Taking Placebo - VYVANSE (n=358); Placebo (n=233), Placebo (n=77):

- Decreased Appetite (39%, 4%), Insomnia (22%, 3%), Abdominal Pain Upper (12%, 6%), Irritability (10%, 9%), Vomiting (9%, 4%), Weight Decreased (9%, 1%), Nausea (6%, 3%), Dry Mouth (5%, 0%), Dizziness (5%, 0%), Affect Lability (3%, 0%), Rash (3%, 0%), Pyrexia (2%, 1%), Somnolence (2%, 1%), Tic (2%, 0%), Anorexia (2%, 0%)

Adverse Reactions Reported by ≥2% of Adolescent (Ages 13 to 17 Years) Patients with ADHD Taking VYVANSE and at least Twice the Incidence in Patients Taking Placebo - VYVANSE (n=233), Placebo (n=77):

- Decreased Appetite (34%, 5%), Insomnia (13%, 4%), Weight Decreased (9%, 0%), Dry Mouth (4%, 1%), Palpitations (2%, 1%), Anorexia (2%, 0%), Tremor (2%, 0%)

Adverse Reactions Reported by ≥2% of Adult Patients with ADHD Taking VYVANSE and at least Twice the Incidence in Patients Taking Placebo - VYVANSE (n=358), Placebo (n=62):

- Decreased Appetite (27%, 2%), Insomnia (27%, 8%), Dry Mouth (26%, 3%), Diarrhea (7%, 0%), Nausea (7%, 0%), Anxiety (6%, 0%), Anorexia (5%, 0%), Feeling Jittery (4%, 0%), Agitation (3%, 0%), Increased Blood Pressure (3%, 0%), Hyperhidrosis (3%, 0%), Restlessness (3%, 0%), Decreased Weight (3%, 0%), Dyspnea (2%, 0%), Increased Heart Rate (2%, 0%), Tremor (2%, 0%), Palpitations (2%, 0%)

**BRIEF SUMMARY:** Consult the Full Prescribing Information for complete product information.
In addition, in the adult population erectile dysfunction was observed in 2.6% of males on VYVANSE and 0% on placebo; decreased libido was observed in 1.4% of subjects on VYVANSE and 0% on placebo.

Postmarketing Experience
The following adverse reactions have been identified during post approval use of VYVANSE. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events are as follows: cardiomyopathy, mydriasis, diplopia, difficulties with visual accommodation, blurred vision, eosinophilic hepatitis, anaphylactic reaction, hypersensitivity, dyskinesia, dysgeusia, tics, bruxism, depression, dermatomyositis, alopecia, aggression, Stevens-Johnson Syndrome, chest pain, angioedema, urticaria, seizures, libido changes, frequent or prolonged erections, constipation, and rhabdomyolysis.

DRUG INTERACTIONS
Clinically Important Interactions with Amphetamines

MAO Inhibitors (MAOI)
Clinical Impact: MAOI antidepressants slow amphetamine metabolism, increasing amphetamines effect on the release of norepinephrine and other monoamines from adrenergic nerve endings causing headaches and other signs of hypertensive crisis. Toxic neurologic effects and malignant hyperpyrexia can occur, sometimes with fatal results.

Intervention: Do not administer VYVANSE during or within 14 days following the administration of MAOIs [see Contraindications].
Examples: selegiline, isocarboxazid, phenelzine, tranylcypromine

Serotonergic Drugs
Clinical Impact: The concomitant use of VYVANSE and serotonergic drugs increases the risk of serotonin syndrome.

Intervention: Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome, particularly during VYVANSE initiation or dosage increase. If serotonin syndrome occurs, discontinue VYVANSE and the concomitant serotonergic drug(s) [see Warnings and Precautions].
Examples: selective serotonin reuptake inhibitors (SSRI), serotonin norepinephrine reuptake inhibitors (SNRI), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John’s Wort

CYP2D6 Inhibitors
Clinical Impact: The concomitant use of VYVANSE and CYP2D6 inhibitors may increase the exposure of dextroamphetamine, the active metabolite of VYVANSE compared to the use of the drug alone and increase the risk of serotonin syndrome.

Intervention: Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome particularly during VYVANSE initiation and after a dosage increase. If serotonin syndrome occurs, discontinue VYVANSE and the CYP2D6 inhibitor [see Warnings and Precautions and Overdosage].
Examples: paroxetine and fluoxetine (also serotonergic drugs), quinidine, ritonavir.

Alkalizing Agents
Clinical Impact: Urinary alkalizing agents can increase blood levels and potentiate the action of amphetamine.

Intervention: Co-administration of VYVANSE and urinary alkalizing agents should be avoided.
Examples: Urinary alkalizing agents (e.g. acetazolamide, some thiazides).

Acidifying Agents
Clinical Impact: Urinary acidifying agents can lower blood levels and efficacy of amphetamines.

Intervention: Increase dose based on clinical response.
Examples: Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methamphetamine salts).

Tricyclic Antidepressants
Clinical Impact: May enhance the activity of tricyclic or sympathomimetic agents causing striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.

Intervention: Monitor frequently and adjust or use alternative therapy based on clinical response.
Examples: desipramine, protriptyline

Drugs Having No Clinically Important Interactions with VYVANSE
From a pharmacokinetic perspective, no dose adjustment of VYVANSE is necessary when VYVANSE is co-administered with guanfacine, venlafaxine, or omeprazole. In addition, no dose adjustment of guanfacine or venlafaxine is needed when VYVANSE is co-administered.

From a pharmacokinetic perspective, no dose adjustment for drugs that are substrates of CYP1A2 (e.g. theophylline, duloxetine, melatonin), CYP2D6 (e.g. atomoxetine, desipramine, venlafaxine), CYP2C9 (e.g. omeprazole, lanosoprazole, clozapam), and CYP3A4 (e.g. midazolam, pimozide, simvastatin) is necessary when VYVANSE is co-administered.

USE IN SPECIFIC POPULATIONS
Pregnancy
The limited available data from published literature and postmarketing reports on use of VYVANSE in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers dependent on amphetamines. Monitor infants born to mothers taking amphetamines for symptoms of withdrawal such as feeding difficulties, irritability, agitation, and excessive drowsiness.

Lactation
Lisdexamfetamine is a pro-drug of dextroamphetamine. Based on limited case reports in published literature, amphetamine (d-or d,-)- is present in human milk, at relative infant doses of 2% to 13.8% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.9 and 7.5. There are no reports of adverse effects on the breastfed infant. Long-term neurodevelopmental effects on infants from amphetamine exposure are unknown. It is possible that large dosages of dextroamphetamine might interfere with milk production, especially in women whose lactation is not well established. Because of the potential for serious adverse reactions in nursing infants, including serious cardiovascular reactions, blood pressure and heart rate increase, suppression of growth, and peripheral vasculopathy, advise patients that breastfeeding is not recommended during treatment with VYVANSE.

Pediatric Use
Safety and efficacy in pediatric patients below the age of 6 years have not been established.

Geriatric Use
Clinical studies of VYVANSE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Renal Impairment
Due to reduced clearance in patients with severe renal impairment (GFR <15 mL/min/1.73 m²), the maximum dose should not exceed 50 mg/day. The maximum recommended dose in ESRD (GFR <15 mL/min/1.73 m²) patients is 30 mg/day.
Lisdexamfetamine and d-amphetamine are not dialyzable.

Gender
No dosage adjustment of VYVANSE is necessary on the basis of gender.

DRUG ABUSE AND DEPENDENCE
VYVANSE contains lisdexamfetamine, a prodrug of amphetamine, a Schedule II controlled substance.

OVERDOSAGE
Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice for treatment of overdose. Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses. Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultsiveness, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. Serotonin syndrome has been reported with amphetamine use, including VYVANSE. Fatigue and depression usually follow the central nervous system stimulation. Other reactions include arrhythmias, hypertension or hypotension, circulatory collapse, nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma. Lisdexamfetamine and d-amphetamine are not dialyzable.
Anxiety & Stress Disorders

CLINICAL

Conventional and Integrative Approaches to Treating Anxiety in Pregnancy

Nina T. Ballone, MD, Casey Moffitt, and Madeleine A. Becker MD, FACLP

Anxiety is not unusual during pregnancy and postpartum for new mothers. However, for some women, anxiety symptoms are more severe, and cause distress, avoidance of activities, interfere with their ability to function at home or at work, or care for their children. One-third of women will suffer from an anxiety disorder in their lifetime. Perinatal anxiety is common and often underreported, with the prevalence ranging from 4% to 33.4% (Figure 1, Figure 2). Multiple factors may contribute to anxiety during the perinatal period, including rapid hormone fluctuations, biological predispositions, as well as psychosocial challenges that accompany the transition to parenthood.

The American College of Obstetrics and Gynecology (ACOG) recommends screening women for depression and anxiety at least once during the perinatal period followed by appropriate referral and treatment when necessary. Although common and impairing, much less attention has been focused on the treatment of perinatal anxiety, both in the literature and in the media. Untreated mood and anxiety disorders during pregnancy have been associated with multiple adverse outcomes for both the mother and baby, including a worsening of medical conditions, lack of medical care, substance use, smoking, suicide, and infanticdie. Anxiety itself is a strong predictor of postpartum depression. Anxiety disorders have also been associated with negative birth outcomes such as preterm birth, lower birth weight, earlier gestational age, increased odds for being small for gestational age, and smaller head circumference.

Treatment

Current treatment recommendations for perinatal anxiety disorders include psychotherapy alone or in combination with pharmacotherapy. A variety of therapeutic modalities, such as cognitive behavioral therapy (CBT), have been shown to be both safe and effective for treating mild to moderate perinatal mood and anxiety disorders as an adjunctive measure or as monotherapy. Unfortunately, less resourced and geographically isolated communities may experience cultural, logistical, and financial barriers to accessing psychotherapy services.

Findings indicate that exercise during pregnancy can be an important component of mental health treatment in addition to psychotherapy or medication management.

For women with moderate to severe anxiety disorders that do not respond to psychotherapy and/or that is impairing functioning, ACOG recommends considering the initiation or re-initiation of pharmacotherapy with a selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI). These medications are well studied and can be very helpful and, in some cases, necessary for managing symptoms. The choice to use medications is very personal; the woman’s obstetrician and/or psychiatrist should discuss this option with her. The decision should be based on risks and benefits, weighing the risk of exposure to medication on the unborn baby against the severity and risk of untreated illness.

The most common risks associated with antidepressant medications exposure are low birth weight, preterm birth, poor neonatal adaptation syndrome, and persistent pulmonary hypertension of the newbron (Table). Among women taking antidepressants, more than 50% will discontinue these medications during pregnancy. However, women should be encouraged to continue treatment during pregnancy and be provided with a variety of options, including non-pharmacological approaches. An increasing number of women consider complementary and integrative approaches for alternatives or as adjunctives for treatment options during pregnancy. Complementary and integrative medicine emphasizes a holistic approach to health care and interventions and described the practices as enjoyable, valuable, and beneficial. Specifically, becoming aware of the causes of anxiety and the ability to reflect on thoughts and emotions were reported as beneficial by women across all categories of interventions.

Some of the most common forms of integrative practice are mindfulness-based interventions. Mindfulness-based stress reduction (MBSR) provides training in mindfulness meditation techniques as a self-regulation approach to stress reduction and emotion management. Mindfulness-based cognitive therapy is an adaptation of cognitive behavioral therapy with a focus on developing mindfulness skills learned in MBSR. The use of various forms of meditation such as those used in mindfulness-based interventions has increased more than three-fold in the past 5 years. Multiple studies of mindfulness-based interventions have demonstrated significant reductions on multiple measures (self-reported and interview screening scales) of anxiety in pregnant women.

Yoga is a mind and body practice with origins in ancient Indian philosophy that combines postures, breathing, and meditation. Yoga has been associated with a reduction in sympathetic activity, balancing heart rate variability, normalizing HPA axis activity, and influencing monoamine changes. Over the past decade, yoga has become increasingly popular for promotion of fitness and relaxation, and prenatal yoga classes have become widely available both in...
Anxiety & Stress Disorders

Figure 2. Prevalence of Anxiety Disorders in Pregnancy

<table>
<thead>
<tr>
<th>Anxiety Disorder</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized anxiety disorder</td>
<td>1.4%–5.2%</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>1.2%–3.3%</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>15</td>
</tr>
<tr>
<td>Posttraumatic stress disorder</td>
<td>15</td>
</tr>
</tbody>
</table>

Source: www.psychiatrictimes.com/view/issues/treating-anxiety-disorders-pregnancy

studies and online.

The 2017 National Health Interview Survey (NHIS) found that yoga is the most common complementary practice used by US adults.14 Studies looking specifically at the practice of yoga in pregnant women have shown that anxiety symptoms (self-reported and interview screening scales) were significantly decreased in response to even a one-20 minute yoga session, and participants continued to show improvements in anxiety symptoms with ongoing, regular practice. An instructor registered and trained in prenatal yoga is necessary for practice during pregnancy, as certain positions and over-heating, “Hot Yoga” should be avoided during pregnancy.

Regular physical activity has also been shown to be beneficial for pregnant and postpartum women for both physical and mental health. ACOG recommends that healthy pregnant women should aim to get at least 2.5 hours of moderate-intensity activity per week. Physical activity has been associated with reduction of pregnancy-related complications, including the risk of weight gain and gestational diabetes, as well as enhancing overall psychological well-being.16 During pregnancy, exercise may reduce anxiety symptoms and increase overall quality of life. Women who report exercising more frequently during pregnancy have lower than average anxiety symptoms (self-report measures).17 Findings indicate that exercise during pregnancy can be an important component of mental health treatment in addition to psychotherapy or medication management.18

Conclusion

Anxiety is common during the perinatal period and can have negative effects on mother and neonate. Women should be provided with multiple options for treatment and encouraged and supported to engage in care during this critical period. The high prevalence of perinatal anxiety disorders indicates a need to broaden the evidence base for treatment interventions. Therapy and medications are evidence-based and effective options for treating anxiety disorders in pregnancy. However, it is important to take into account patient preferences regarding treatment during pregnancy.

Complementary approaches are becoming increasingly used by women and may provide benefits for mental health treatment. Available evidence suggests that complementary approaches, specifically mindfulness-based interventions, yoga, and exercise have shown benefit for improving symptoms of perinatal anxiety disorders. Reductions in anxiety symptoms with mindfulness-based interventions, yoga, and exercise suggest an expanding and adjunctive role for complementary approaches to perinatal mental health treatment. More research is needed to systematically evaluate the use of nonpharmacological, integrative modalities for maternal mental health.

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REFERENCES

To Scan or Not to Scan: Brain Imaging in First-Episode Psychosis

Brian Miller, MD, PhD, MPH

An important clinical conundrum in the diagnosis of new-onset psychosis is the role of neuroimaging—including CT or MRI—to rule out medically or surgically treatable causes of illness. Current American Psychiatric Association guidelines recommend brain imaging in first-episode psychosis (FEP), favoring MRI or CT; however, other national guidelines do not make similar recommendations. Although some studies have reported abnormal CT scan findings in a percentage of participants with FEP (some of which were incidental), many others have found minimal diagnostic value of neuroimaging. To further explore such, Andrea and colleagues performed a retrospective chart review of neuroimaging in adolescents and young adults with FEP.

The study authors reviewed charts from 1998 to 2016 from an Early Psychosis Program in Calgary, Alberta, Canada. They included participants aged 15 to 24 years with a first-episode psychotic disorder diagnosed by a consulting psychiatrist using DSM-IV or DSM-5 criteria, normal neurological examination, and available neuroimaging. For participants who underwent neuroimaging, the treating physician determined the decision to obtain a CT versus MRI scan. Neuroimaging results were trichotomized into: (1) normal study, (2) abnormal study with routine follow-up, and (3) abnormal study necessitating urgent follow-up and intervention. A positive scan was defined as findings that caused a change in clinical management (eg, neurologic or surgical intervention). Accordingly, the authors defined diagnostic yield as a neuroimaging finding that caused a change in clinical management.

A total of 443 patients were referred during the study period. The most common diagnoses were schizophrenia (n = 156) and unspecified schizophrenia spectrum and other psychotic disorders (n = 191). Other diagnoses included nonaffective, affective, and substance-induced psychoses. In the sample, 351 (79%) participants received a CT scan, 63 (14%) received an MRI scan, and 29 (6.5%) received both CT and MRI scans. Of these, 25 (5.6%) had incidental findings, most commonly an arachnoid cyst (n = 7) or nonspecific hyperintensity (n = 7 on MRI), or hypodensity (n = 4 on CT). The prevalence of incidental findings was 4.7% for CT and 14% for MRI. None (0%) of the neuroimaging findings were found to cause or contribute to a FEP, and none required urgent follow-up for intervention. Therefore, the authors concluded that neuroimaging provided no diagnostic yield for work-up of FEP.

The authors additionally concluded that the role of structural neuroimaging in FEP remains controversial, but findings suggest that there is inadequate diagnostic and clinical efficacy to justify its routine use. They emphasized that their findings are limited to a population of young patients with FEP in the context of a normal neurologic examination, and that the rates of incidental abnormalities in the present study are similar to that observed in the healthy general population.

They also noted that the costs and risks associated with neuroimaging should be considered. A strength of this study was the large sample size of patients with FEP, while its limitations included the absence of a healthy control group, unknown inter-rater reliability among radiologists, and differences in equipment and imaging protocols.

The bottom line
Findings suggest that neuroimaging does not play a role in the diagnostic workup on FEP in patients with a normal neurological exam. However, in patients with an abnormal neurologic exam or clinical picture, neuroimaging may be warranted. In such cases, advantages of MRI include better gray/white matter differentiation, lack of radiation exposure, and better prognostication.

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CASE REPORT
A Double Whammy: Psychosis and Huntington Disease

Horacio A. Capote, MD, and Nicole E. Miller, PA-C

The challenges of a busy neuropsychiatric practice give us opportunity to further explore real world applications of our current armamentarium. This is true regarding both pharmacology as well as other procedural interventions. The following case will hopefully highlight some of these challenges as well as opportunities.

The patient originally presented as a 33-year-old man with a history of polysubstance abuse and mood disorder. He had been referred for neuropsychiatric assessment by our migraine clinic. Unfortunately, he received his third driving while intoxicated citation and failed drug court, and he was slated for incarceration. A few days prior, he received a diagnosis of Huntington disease (HD) by one of our movement disorder specialists. He was placed in a medium security facility where his condition was treated with a combination of aripiprazole, duloxetine, and hydroxyzine. Nonetheless, he described experiencing both visual and auditory hallucinations. The visual hallucinations were quite dramatic, involving zombies with pieces of their flesh falling off. The auditory hallucinations were not of a command nature and involved deprecating, condescending, and derogatory statements regarding the patient.

He was released after approximately 2 years, with 3 years of probation. His medications were abruptly discontinued 3 months before his release, and he was placed on haloperidol. The patient reported that these had not been particularly effective. Fortunately, he was also involved in the recovery process, and attended Narcotics Anonymous meetings twice weekly and visited an outpatient addiction clinic at least weekly.

His movement disorder specialist then prescribed deutetrabenazine for HD. The neuropsychiatry team discontinued haloperidol and began treatment with 34-mg pimavanserin daily. After 4 weeks, he noted an amelioration of the auditory hallucinations. Mood continued to be a problem (PHQ-9 = 20); lamotrigine was started with the customary 5-week titration schedule. After 2 more weeks, the patient reported amelioration of auditory and visual hallucinations. The vicissitudes of life continued to take their toll on the patient, including some conflicts regarding custody of his 6-year-old son. The patient began to experience drug cravings and was started on naltrexone. At the time, he began to describe ideas of reference, receiving messages through the television. The decision was made to increase pimavanserin to 51 mg daily. The patient was made aware that this was above the usual US Food and Drug Administration dosing guidelines; after a discussion of the benefits, alternatives, and risks, he decided to proceed.

Four weeks later, the patient reported a significant amelioration of his psychosis. He also indicated he was essentially more sociable, was taking his medications and was participating in community activities. In fact, his parole officer extended the time between reporting from weekly to every 3 weeks. The auditory hallucinations resolved completely; the visual hallucinations continued to ameliorate and resembled illusions.

The treatment was managed with 17-mg pimavanserin samples. When manufacturing of 17-mg pimavanserin samples stopped, the patient’s dose was reduced to 34 mg daily. Subsequently, the patient experienced an exacerbation of both auditory and visual hallucinations. Due to a lack of available samples and repeated denials of coverage by his insurance company, pimavanserin was discontinued and he was treated with other antipsychotics. Trials of adequate dose and duration with quetiapine and cariprazine did not result in amelioration of psychotic symptoms. The patient also began to miss visits and to follow-up less frequently.

Eleven months later, through a combined effort of both neuropsychiatry and movement disorder neurology, the patient once again was treated with 34-mg pimavanserin. Eight weeks later, he described the near resolution of auditory hallucinations, a significant amelioration of visual hallucinations, and some occasional paranoid thought content. His regimen was augmented with 25-mg clozapine daily. One month later, during a follow-up visit, the patient described complete resolution of auditory hallucinations and delusions. His visual hallucinations, although greatly ameliorated, persisted. Clozapine was increased to 50 mg, which resulted in full resolution of symptoms.

A variety of studies were conducted during the early course of his evaluation and treatment, including an electroencephalogram, multiple sleep latency test, extensive lab work, and electromyography, and neuroimaging of the brain and spine. Most results were within normal limits or essentially benign. He had a polysomnography indicative of sleep apnea and a positive DNA test for HD.

Discussion
This patient exemplifies the complicated nature of neuropsychiatric practice. Taking into account the preexisting movement disorder with rather significant comorbid psychiatric problems (including a higher risk of suicide) associated with HD, we were not eager to treat him with the usual dopamine blockade. Pimavanserin seemed ideally suited for the situation. When that medication is not enough to eradicate psychosis and some form of dopaminergic agent is inevitable, the data direct us to clozapine or quetiapine.

An argument can certainly be made that 68-mg pimavanserin would be preferable to the addition of a dopamine blocking agent. However, this would undoubtedly precipitate a conflict with the patient’s managed care insurance carrier.

Treatment utilizing the biopsychosocial model, including 12-step programs and addiction counseling, is indispensable. In addition, incarceration in this case dovetailed with recovery. In other words, the neuropsychiatric skill set must not be devoid of humanism. While science and technology expand our abilities, our goals still revolve around the patient and maximizing function.

“The visual hallucinations were quite dramatic, involving zombies with pieces of their flesh falling off.”

Here, we see the role of the clinician as a patient advocate and navigator of a rather complicated medical system. This included interactions with the legal system as well as various substance treatment providers.

In the final analysis, this patient’s life continues to be difficult. However, he is able to function and to act positively in terms of his commitment to others, particularly his son.

Dr Capote is Medical Director, Division of Neuropsychiatry, Dent Neurologic Institute; he is also Medical Director, Addiction Services, Byron Hospital, Buffalo, NY; Ms Miller is Physician Assistant, Dent Neurologic Institute. The authors report no conflict of interest concerning the subject matter of this article. The patient has agreed to have his case discussed in this article.

REFERENCE
A Challenging Psychotherapeutic Journey

Natan P.F. Kellermann, PhD

Early in 2020, when I first met “Rona” in my psychotherapeutic practice, I was struck by his contradictory impression. On the one hand, he was almost invisible with a timid appearance. On the other, he had an impressive crown-like outer shell with spikes that could explode if one bumped into them. But Rona, a master of disguise and transformation, was trying to evade any careful scrutiny. It was only when my patient presented himself as the silent killer responsible for the COVID-19 pandemic that he evoked my curiosity.

Accepting Rona as a patient was a difficult decision. I previously had worked with patients for whom I felt some amount of sympathy and for whom I wanted to help. Now, I was faced with an adversary I ultimately might want to eradicate.

When Rona entered my office, I immediately felt nauseated with breathing difficulties. I didn’t make much of it until I gradually became aware of the various symptoms he caused me—fatigue, sore throat, dry cough, nasal congestion, and fever. These were warning signs of central importance to get a deeper understanding of who he actually was. Building suspicious of his intentions for coming to therapy in the first place, I decided to keep some distance from him to protect myself.

As it turned out, people keeping a distance from him was his main presenting problem. He felt chronically lonely. “Everyone relates to me as if I were some kind of pest,” Rona said, “as if I have no birthright.” While sobbing heavily, he added: “Nobody has ever told me they love me.”

Not being in close contact with others also made him feel detached from himself. As long as he could remember, he said he searched for his real identity and for his genuine “self.” There was no “core” within him, no nucleus that gave him a sense of grounding.

Sometimes, he even doubted if he was alive at all. He felt empty in his solitude and thrived only when gaining entry into another person’s cells through his spike protein. That is when he could obtain some sense of self-actualization and multiply. At that moment, he said, he got a kick from causing a kind of blast in himself and the other person. It took some time before I understood he was talking about the cytokine storm when the immune system starts to attack its own cells and tissues rather than just fighting off the virus. Every time this happened, he felt exhilarated and was willing to go to extreme lengths to repeat the experience.

Before embarking on treatment, I administered a Rorschach test, which seemed to enjoy tremendously. Watching the inksblots, he often responded with loud laughs. He saw a lot of animals, but also many details of inner organs. In Card 8, he was visibly thrilled when he recognized some bats. They were at the center of his most urgent longing. The responses revealed a complex personality structure with internal conflicts.

Much of Rona’s psychopathology was exposed during these intake sessions, and it helped me to suggest a tentative diagnosis. He was addicted to spreading his vibes, contaminating as many people as possible. Besides his psychopathic and sociopathic behavior, he was also suffering from a severe narcissistic personality disorder. To emphasize his superiority over others, he had taken the nickname Corona, which means crown and implies sovereignty. Apparently, Rona had an inflated sense of his own importance, a deep need for admiration, and a lack of empathy for others. All these traits created troubled relationships. In short, he was a genuine example of an insidious egotistical parasite, someone who clings to another for personal gain without giving anything in return.

Interestingly, Rona had higher than normal intelligence. He was so clever that he had been able to outsmart many known drugs and vaccines. He presented a completely new kind of psychopathology that nobody had come across before. Viral immune...
nologists observed that he could harm all the major organs via blood vessel cells. Scientists were still trying to figure out what to do with him. Rona had already infected millions, and he had killed hundreds of thousands. The consequence of his activities also caused catastrophic worldwide economic damage. As a result, researchers from all over the world were searching for ways to eradicate Rona. Despite the efforts of so many, being invisible to the naked eye gave Rona an upper hand, and he succeeded to escape being caught. As a result, there was an overwhelming sense of powerlessness among governments all over the world. I was well aware of the urgent need to find better ways to cope with the threat he posed.

I had misgivings from the very beginning. I thought an individual approach would perhaps be insufficient in dealing with a global problem that demanded a worldwide concerted struggle. Even if I succeeded to “cure” Rona, the contamination would continue to be spread by his offspring. My hope was that if I could understand him better, I could perhaps help to end his lethal mission. If I could let him feel what he did to others, he might be able to gain some insight and change his ways.

Alternatively, I wanted to find the best strategy to destroy him.

Therapeutic process

Even though I tried to establish a therapeutic alliance with Rona, the sessions remained scary. When getting close to him, I was afraid he might infect me, and it was hard to build a sense of trust between us. Concurrently, I felt sad for the people who were dying and for their loved ones. What did it take? Why was he affecting their offspring? My hope was that if I could understand him better, I could perhaps help to end his lethal mission. If I could let him feel what he did to others, he might be able to gain some insight and change his ways.

The last thing I wanted to do was to help Rona strengthen his self-esteem and to “find himself” within a relationship of “unconditional positive regard.” More importantly, I felt, was to cultivate some amount of reality-testing in him.

Therefore, I decided to focus on his identity by asking him, “Who do you think you are?”

Every time I asked Rona that question, he had a different answer. One day, he said, “I am the Angel of Death to some. To others, I just come and visit with a breeze. Most children don’t sit still long enough for me to get under their skin.”

Another day he bragged, “I am Corona! Nobody knew my name only a few months ago. Now, I am world famous, and everybody knows me. I am a celebrity, with pictures shown on all TV stations and everybody talks about me. Is there someone more recognized than I am? Should I not be proud of my achievements?” He had been quite offended by my genetic setup. That doesn’t mean I am less intelligent than you, however. You still can’t stand this fact. With all your 20,000 or more genes and your big brains, you are still incapable of realizing the fact that I am more powerful than you. It blows your mind that I can kill you by a simple bump!”

Enraged, I repeated the same question again with a fiercer tone: “Who do you think you are? What gives you the right to spread your poison around and harm people? You are just a dangerous, cruel organism! What gives you the right to play God? You can’t do that! Don’t you have any sense of compassion?” He looked at me as if he was unable to understand.

It became more obvious to both of us that I began to relate to him more as a foe than a friend. But as I looked for the best strategy to eradicate him, it struck me that his existence was ultimately based on a very basic (and eternal) question of survival, adaptation, and evolution that had always found a battlefield within biochemistry. And it was now materializing in my treatment room. I had read somewhere that parasites are intrinsic to biological evolution and that they drive its complexity at multiple levels. All living things are trying to survive and multiply either through fight or through cooperation, and they change a little during this process. Taking this aspect into consideration made me a little more accepting of him.

As I had now expressed some of my anger, it became easier for me to continue to stay in contact with Rona. The next time I asked him, “Who do you think you are?” it was in a more friendly voice, and he was willing to open up more.

“I do not think who I am. I just exist. I am a chemical structure with a set of proteins that perform specific functions. It is not something I decide to do, neither is it something I have any conscious control over. In fact, I am not sure if I am conscious of anything at all. Consciousness is a privilege for humans and not for viral beings like me. You know you exist,
while we just exist. At the end of the day, that’s why I came to you for treatment. I also want to think and know I have a self. I get so tired of just floating around and multiplying.”

To my surprise, Rona turned his head towards me and added an important piece of information: “Look at me, doctor . . .” I looked at Rona and saw he was choked up with emotion. “Self-replication is a central part of being me. I am, after all, just a virus.”

That was a smart thing to acknowledge, I thought, for such a primitive molecular creature. He began to recognize he felt bound by his body and had no conscience, no free will, and no self-control. Self-replication was apparently an expression of his libido; his fundamental life instinct. Gaining a sense of self in the form of an inner nucleus would perhaps help him to better control his previously destructive behavior.

It seemed as if we were making some progress in the therapeutic process.

**Being there**

From this point on, my respect for Rona gradually grew. Discovering new parts of his personality also helped me ask Rona more frankly about his motives for killing so many people. He assured me: “I don’t kill the people who die. I just enter their organs to multiply. When that happens, some of them can’t tolerate it. They can’t breathe and their lungs stop functioning. Or their cardiovascular systems go caput, and they develop blood clots. It is just a sad result of me being there. But it’s not my original purpose.”

“What I want is simply to multiply; to stay ‘virent,’ and to be able to co-create. When people get too sick, and especially when they die, I am left not only with a loss of virulence, but also with a new awareness. By trying to answer his question, “Who do you think you are?” referring to humankind in general. “What do you think you are doing to the Earth where we all live?”

After that session, he suddenly disappeared in a droplet carried away by the wind.

I was left not only with a loss of smell but also with a new awareness. By trying to answer his question, “Who do you think you are?” referring to humankind in general. “What do you think you are doing to the Earth where we all live?”

**I realized human beings are not so different from Rona. We are only infinitely more destructive. I stopped to wonder if the present pandemic will become a ‘corrective emotional experience’ for those who survive it.”**

“Inside the cells, I must prevent their white blood cells from becoming ‘corrective emotional experiences’ for those who survive it.”

His answer to this question surprised me more than anything he had previously shared. Rona looked at me with distrust, as if he were unsure of how much to reveal. Hesitantly, he said: “While you are looking at me with your fancy electron microscope, you don’t realize I am also looking at you with my own viral magnifying glass.”

**Our roles were suddenly reversed**

Taken aback, I asked him suspiciously, “So what do you see in your magnifying glass?”

“I see you are scared of me and you try to keep a safe distance from me,” he replied.

Somewhat embarrassed, I nodded and asked in as offhand a way as I could, “And . . . ?”

“I see the chaos I have created in your world—the social distancing, the lockdowns, and the panic all around . . . I see how you struggle with existential dilemmas, with protecting your health versus saving the economy.”

He smiled at me briefly, and added in a stammering low voice: “Well, what I see . . . what I also see when I look at you human beings . . .”

He closed his eyes and opened them slowly. “I see what you are doing. I see what you do all the time, even behind your silly bandito face masks. I see what you are doing with everything around you, with nature, with the planet, with the earth. I see how you contaminate the air you breathe and poison the water you drink. I see how you destroy nature at a faster pace than it can restore itself. I see how you burn its resources, and how you fail to give it back.”

I kept silent, waiting for him to continue.

“Also, I see how you spread your kind all over at the expense of others—the mass extinction of other creatures, all the mammals, the birds, the reptiles, and the fish that have been killed by people.”

He paused again, and whispered with his eyes closed as if he doubted I would understand what he talked about. “You assume supremacy over all kinds of biological organisms you move around and annihilate.”

Then, he added with a more accusing tone: “Who do you think you are?” referring to humankind in general. “What do you think you are doing to the Earth where we all live?”

**Dr. Kellermann is a retired psychologist from Jerusalem, Israel. His website is http://peterfelix.weebly.com/”**
**Exploring N-Acetylcysteine in Psychiatry**

Anna Giménez-Palomo, MD, Seetal M. Dodd, PhD, Olivia M. Dean, PhD, Chiara Bortolasci, MSc, PhD, and Michael Berk, MD, PhD

**N-Acetylcysteine (NAC)** is a synthetic derivative of the endogenous amino acid L-cysteine (Figure 1) and a precursor of glutathione. It is known for its role in modulating oxidative stress and several pathophysiological processes, such as apoptosis, inflammation, mitochondrial dysfunction, and neurotransmission. The clinical benefits of NAC have been widely studied.

NAC is available in oral, inhalation, and intravenous (IV) formulations. When it is orally administered, NAC reaches peak plasma concentrations between 30 minutes and 1 hour. After being absorbed in the small intestine, NAC undergoes first-pass hepatic metabolism to be finally hydrolyzed to cysteine and available to synthesize glutathione, especially in the liver. Its oral bioavailability is poor, and that is the reason why IV formulation is preferred in acute paracetamol (acetaminophen) overdose.¹

The first clinical use of NAC was in the 1960s for cystic fibrosis. In the 1970s, its efficacy for the treatment of paracetamol overdose was discovered. Since then, a great number of applications have been attributed to NAC mainly due to its implication in oxidative stress. Recent studies suggest potential implications of NAC in several psychiatric disorders.

**NAC and oxidative stress**

Reactive oxygen species, such as superoxide radical, hydrogen peroxide, and the hydroxyl radical, are products from oxidative phosphorylation of the mitochondria, where water is produced from molecular oxygen and also from peroxisomes, which degrade fatty acids into hydrogen peroxide. These oxidant agents can produce oxidative stress, which occurs when oxidants exceed the antioxidant capacity.

Glutathione exerts a protective effect on cells as an antioxidant defense, since its free sulfhydryl group provides a source to reduce equivalents to scavenge harmful reactive oxygen species. The antioxidant activity of glutathione peroxidase, a defense mechanism against peroxides, is also allowed by the reducing equivalents that glutathione provides.

Regarding NAC, its free sulfhydryl group and its role as a glutathione precursor make it an antioxidant agent. The mechanisms of NAC on its most studied therapeutic effects are well known. Regarding mucolysis, NAC breaks the disulfide bonds of mucus glycoproteins, thereby reducing mucus viscosity. As an antidote to paracetamol poisoning, NAC restores the hepatic glutathione pool depleted in the drug detoxification process. Current evidence shows that NAC can potentially improve the course of many other illnesses related to oxidative stress.¹

**NAC in non-psychiatric disorders**

Apart from its efficacy as a mucolytic agent for the treatment of respiratory diseases, NAC has been found to increase alveolar surfactant, to have antioxidant, antimicrobial, and anti-inflammatory properties.²,³ This may explain why several clinical trials have assessed NAC for the treatment of chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis.
In clinical practice, NAC is commonly used as an antidote to paracetamol poisoning. Paracetamol is over 90% metabolized through phase II conjugation reactions, and a small part by cytochrome P450 2E1 to produce the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI). After that, NAPQI is conjugated and detoxified with cellular glutathione, and a minimum quantity binds to proteins. When the amount of NAPQI is greater, protein adduct formation increases, including mitochondrial production, which promotes oxidative stress. Reactive species are responsible for acute liver injury induced by paracetamol overdose. Oxidative stress also activates a mitogen-activated protein (MAP) kinase pathway, which amplifies mitochondrial oxidative stress, leading to cell necrosis.

Considering that paracetamol hepatotoxicity is based on glutathione depletion, NAC can be considered a good antidote for paracetamol overdose, which is the treatment of choice according to the established nomogram for paracetamol toxicity. It acts as a protector agent by scavenging NAPQI and by preventing protein adduct formation. Excess NAC not being used for glutathione synthesis is converted to Krebs cycle intermediates and supports mitochondria in order to produce higher ATP levels in hepatocytes and to avoid mitochondrial dysfunction, which is crucial in paracetamol-induced liver injury.

NAC has also been suggested to act as an antidote to other drugs, such as paracetamol, mushroom toxins, essential oils, chloroform, carbon tetrachloride and heavy metals, but evidence is still limited.

The use of NAC has also been studied in cardiovascular diseases and in the prevention of contrast-induced nephropathy, but researches have yielded controverted results. NAC has shown favorable results in small clinical trials in ophthalmology. Regarding retinitis pigmentosa, cone photoreceptor death occurs due to the accumulation of oxygen in the retina as a product of rod cells death. Animal studies assessing NAC effects showed that it promoted cone cell function and survival in mice with retinitis pigmentosa.

Findings from animal models suggest that NAC has the potential for the treatment of chronic neurodegenerative disorders, heavy metal neurotoxicity, and Alzheimer disease, which is produced at least in part by increasing neuronal glutathione levels and by the maintenance of glutamate homeostasis.

**NAC in psychiatric disorders**

The role of NAC in a great number of psychiatric disorders has been extensively studied. Many of these have a strong relationship with cognitive dysfunction, which is enhanced by oxidative stress. Some studies have shown that NAC significantly improves cognitive function in patients with neurologic or psychiatric diseases, but the clinical relevance of the effects is still unclear. A great part of preclinical evidence has reported that NAC may be involved in glutamate homeostasis modulation.

Glutamate is the most abundant excitatory neurotransmitter in the CNS and participates in learning and memory processes. Its action enhances the influx of extracellular Ca^{2+}, which is mediated by neuronal and glial membrane transporters in order to maintain the homeostasis of extracellular glutamate. NAC has demonstrated to activate presynaptic system Xc− (Sxc−) receptors, which mediate the exchange of extracellular cysteine and intracellular glutamate. When these presynaptic receptors are activated, glutamate release from excitatory nerve endings is inhibited. NAC also induces the expression of glutamate transporter-1 (GLT1) in astrocytes, which clears synaptic and extra-synaptic glutamate and enhances the maintenance of glutamate homeostasis.

In drug-naive states, glutamate binds to postsynaptic receptors and glia clears excess of glutamate through the transporter GLT-1. The glia receptor Sxc− also enhances glutamate release by its exchange with cysteine, thereby glutamate binds to presynaptic metabotropic receptors (mGluRs), which provides inhibitory feedback for further release (Figure 2).

Clinical data have supported the underlying hypothesis of imbalances in glutamate homeostasis in addictive brains by showing reductions in GLT-1 levels and of the catalytic unit of Sxc−. This leads to an increase of extrasynaptic glutamate and thus the activation of postsynaptic N-methyl-d-aspartate (NMDA) receptors, which increases the risk of relapse. Another consequence is the reduction of presynaptic inhibition through mGluR2/3 receptors. When NAC is converted to cysteine, it is exchanged into the glia for glutamate, which provides inhibitory feedback on presynaptic receptors, thereby limiting the release of glutamate. NAC has also been shown to increase the expression of GLT-1 and Sxc− transporters. Given that NAC has been shown to help to reach the glutamatergic homeostasis, most investigations of NAC in psychiatry focus on the treatment of addictions.

Psychiatric and neurodegenerative disorders are known to be associated with excessive release of glutamate and impaired glutamate homeostasis. Current evidence suggests that NAC may be effective in treating various psychiatric conditions.

**Addiction**

The hypothesized mechanism of action of NAC in substance use relies on the glutamate homeostasis hypothesis of addiction, where glutamate signaling in the nucleus accumbens has been disrupted. Psychiatric and neurodegenerative disorders are known to be associated with excessive release of glutamate and impaired glutamate homeostasis. Current evidence suggests that NAC may be effective in treating various psychiatric conditions.

In drug-naive states, glutamate binds to postsynaptic receptors and glia clears excess of glutamate through the transporter GLT-1. The glia receptor Sxc− also enhances glutamate release by its exchange with cysteine, thereby glutamate binds to presynaptic metabotropic receptors (mGluRs), which provides inhibitory feedback for further release. Clinical data have supported the underlying hypothesis of imbalances in glutamate homeostasis in addictive brains by showing reductions in GLT-1 levels and of the catalytic unit of Sxc−. This leads to an increase of extrasynaptic glutamate and thus the activation of postsynaptic N-methyl-d-aspartate (NMDA) receptors, which increases the risk of relapse. Another consequence is the reduction of presynaptic inhibition through mGluR2/3 receptors. When NAC is converted to cysteine, it is exchanged into the glia for glutamate, which provides inhibitory feedback on presynaptic receptors, thereby limiting the release of glutamate. NAC has also been shown to increase the expression of GLT-1 and Sxc− transporters. Given that NAC has been shown to help to reach the glutamatergic homeostasis, most investigations of NAC in psychiatry focus on the treatment of addictions.

A randomized clinical trial showed that NAC reduced cannabis use in adolescents, but this was not evidenced in adults. This improvement did not seem to be related with craving changes. Regarding smoking cessation, an open-label-study assessing the combination of NAC and varenicline showed a reduction of cigarettes consumption as well as a reduction in craving and smoking reward. A few clinical trials showed a significant reduction in cigarette consumption after...
12 weeks as well as increased rates of abstinence and reduced craving with NAC.23 However, other studies did not show a significant decrease in tobacco use. In a double-blind, placebo-controlled, 4-day study of 23 young adults NAC produced no difference in nicotine craving but reduced withdrawal scores and measures of the rewarding properties of the first cigarette posttreatment.17

A clinical trial showed contrary results regarding the reduction of methamphetamine craving with NAC.24 Another trial found benefits of NAC in gambling disorder.25

A systematic review of 9 studies confirmed the potential efficacy of NAC in obsessive-compulsive disorders. A small placebo-controlled clinical trial and one case series suggest the potential efficacy of NAC in nail biting.13,37,38 Larger controlled trials should be conducted to confirm the advantages of NAC in impulse-control disorders. A large quantity of trials has assessed NAC in impulse-control disorders. A small placebo-controlled clinical trial and one case series suggest the potential efficacy of NAC in nail biting.37,38 Greater evidence has shown the benefit of NAC in excoriation and in trichotillomania.39,40 The use of NAC is recommended in these cases. Larger controlled trials should be conducted to confirm the advantages of NAC in impulse-control disorders.

Autism spectrum disorder

Regarding the pathophysiology of autism spectrum disorders, evidence suggests mitochondrial dysfunction, oxidative stress and abnormalities in redox regulation, immune dysfunction and inflammation, environmental toxicants and disruption in other metabolic processes, including folate and cobalamin.2 Although some controlled trials failed to show improvements on clinical outcomes in autism, one of them showed improvement in oxidative stress, and others to have benefits in irritability, social abilities, and aggression.26-30 Larger clinical trials are needed to assess the response of core autism symptoms to NAC.

Bipolar disorder

Bipolar disorder has been related to oxidative stress, mitochondrial dysfunction, and immune dysregulation. High-quality studies have demonstrated that NAC can improve depressive symptoms during maintenance phase treatment, the scores in MADRS and Bipolar Depression Rating Scale (BDRS), response rate, symptom remission, quality of life, and functioning.19 Time to a new mood episode has not shown significant differences with the use of NAC versus placebo.

Depression

Animal studies have shown reductions in hippocampal mGlu2 receptors in mice that were not resilient to stress and higher susceptibility to stress in mice lacking mGlu2 receptor.28 A decrease in mGlu2 receptors and in the catalytic subunit of Sx-c in chronic stress was also reported.29 As mentioned, NAC enhances the activation of Sx-c, which has been linked to resilience to stress in animal studies. Antidepressant effects of NAC were blocked by antagonists of the inotropic glutamate receptor AMPA in mice studies, which suggests the involvement of AMPA receptors in the antidepressant-like effects of NAC.34 Use in depression is also supported by the presence of oxidative stress in depression.

Clinical trials are overall in the same line, suggesting a potential of NAC as adjunctive treatment in depression. Although no differences in depressive symptoms assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) were found in a clinical trial comparing NAC with placebo, differences were significant and in favor of NAC at the 16-week post discontinuation endpoint, which was also seen in other clinical outcomes.35 Reduction in depressive symptoms and benefits in quality of life were also found in secondary analysis of other studies. A recent meta-analysis including 5 studies assessing depressive symptoms with a follow-up of 12 to 24 weeks revealed significantly greater improvements in MADRS and functionality with NAC compared with placebo.36

Impulse-control disorders

A large quantity of trials has assessed NAC in impulse-control disorders. A small placebo-controlled clinical trial and one case series suggest the potential efficacy of NAC in nail biting.13,37,38 Greater evidence has shown the benefit of NAC in excoriation and in trichotillomania.39,40 The use of NAC is recommended in these cases. Larger controlled trials should be conducted to confirm the advantages of NAC in impulse-control disorders.

Obsessive-compulsive disorder

OCD’s pathophysiology relies on excessive glutamatergic activity and altered dopamine reward system signaling, which worsens oxidative stress. The ability of NAC to modulate glutamate and dopamine neurotransmission and its antioxidant properties have led to the study of NAC as an adjunctive therapy in OCD. One clinical trial found improvements in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and the Clinical Global Impressions (CGI) Severity Scale after 12 weeks, compared with placebo, although not on the CGI Improvement Scale.39 However, evidence regarding the treatment effects of NAC in OCD is still limited, and further research is needed.

Schizophrenia

Along with genetic predisposition and environmental factors, oxidative stress, mitochondrial dysfunction and immune abnormalities seem to be implicated in the etiopathology of schizophrenia. Some clinical trials have reported positive results with NAC, especially for negative symptoms, assessed with PANSS and the CGI, but not for positive symptoms.38-41 The benefits of NAC could be based on the regulation of glutamate homeostasis with NAC. Further clinical trials are needed to confirm these findings.

Precautions

Clinical studies and use in clinical practice have shown that treatment with oral NAC is well tolerated and safe, even at high doses. The most com-
mon adverse effect of NAC is gastrointestinal discomfort (eg, emesis, diarrhea). Severe skin reactions have been seen in very rare cases, and a reduction in platelet aggregation has been also observed. Antifusives medicines should not be administered concomitantly with NAC due to the decrease in the cough reflex, which could enhance the accumulation of bronchial secretions. The administration of oral antibiotics and NAC should be spaced by at least 2 hours, because the coadministration may be associated with decreased antibiotic activity. The concomitant administration of NAC and nitroglycerin should be avoided or at least monitored, because it induces hypotension.

Regarding patients with bronchial asthma, NAC should be discontinued in cases of broncho-spasm. NAC is contraindicated in patients aged younger than 2 years because mucolitics can cause bronchial obstruction. Caution is advised for patients with a history of peptic ulcer. NAC is contraindicated in patients with hypersensitivity to the active substance or any of the excipients, during pregnancy and breastfeeding.

Conclusions
Clinical research and clinical practice have shown that NAC is effective, safe, and mostly well tolerated. The therapeutic activity of NAC relies on several mechanisms of action, such as the reduction of oxidative stress, modulation of mitochondrial dysfunction, apoptosis, inflammatory processes, and modulation of glutamate homeostasis. This has led researchers to assess its potential use in several fields, including many different psychiatric disorders, as an adjunctive therapy.

Preclinical studies with NAC are promising, but clinical evidence is lacking in some areas. Clinical studies assessing NAC in depression suggest the efficacy of NAC in symptom improvement as an adjunctive therapy. The role of NAC in addictions is the most studied, particularly in cannabis or cocaine users, with mixed results in terms of relapse prevention, but suggesting that NAC might be more effective at preventing psychostimulant relapse than promoting initial cessation. Although further large studies are needed to increase the accuracy of current recommendations, NAC has shown to be a potential adjunctive treatment for many different disorders.

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• San Jose, CA: Schedule; 8-40 hours per week available. Pay Rate: $291,200 - $364,000 per year! Excellent Benefits.
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For additional listings, please visit: www.telecarecorp.com/physician-jobs/

You will work as part of a multidisciplinary team. The staff is all very friendly and it is a supportive working environment.

Please email your resume to: Psortraining@telecarecorp.com
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NORTH CAROLINA

NRP

Practice Opportunity in Raleigh, NC

Thriving outpatient practice looking to add fifth doctor. Excellent benefits, competitive salary with goal of partnership after one year. Congenial, low key atmosphere. Excellent support staff. Spacious offices. Raleigh has been ranked a top ten place to live year after year!

If interested, contact Kelly Stutler at kstutler@raleigh.twcweb.com or 919-782-9554.
SOUTH CAROLINA

Prisma Health, the largest healthcare provider in South Carolina, currently seeks BC/BE Psychiatrists to join our growing psychiatry department. The department is expanding our clinical, education, and research missions and is seeking candidates in all specialties. Successful candidates will have the opportunity to develop specialty outpatient clinics and/or programs, and work across disciplines with other departments. Ideal candidates will have an interest in teaching and be eligible for faculty appointment at University of South Carolina School of Medicine Greenville.

*Public Service Loan Forgiveness (PSLF) Program Qualified Employer*

Qualified candidates should submit a letter of interest and CV to: Natasha Durham, Physician Recruiter, Natasha.Durham@PrismaHealth.org, ph: 864-797-6114

Prisma Health is an equal opportunity employer which proudly values diversity. Candidates of all backgrounds are encouraged to apply.

Virginia

**Department of Psychiatry**

**Adult Admission Psychiatrist Opportunity**

Southwestern Virginia Mental Health Institute, in Marion, Virginia, sitting in the heart of the Blue Ridge Mountains is seeking a skilled Psychiatrist for our in-patient Adult Admission Unit. We invite you to consider working in a picturesque small town with abundant outdoor activities with shopping and airports nearby.

Training for this specialty area is available. Full time medical physicians are on staff for rounding, physical/histories and consultation.

Our 179-bed behavioral health facility offers an exciting career in a wide range of interesting pathology while providing a highly desirable work-life balance. No on-call required, with compensated on-call available. After hours, weekends and holidays are covered by dedicated full and part-time staff.

This is an employed position offering:

- A competitive salary with generous state benefits
- Paid malpractice Insurance
- Loan repayment up to $140,000 tax free for a 4 year commitment
- Another $10,000 paid toward loan debt
- CME stipend/leave
- Sign-on Bonus plus sign-on Vacation time
- Retocation allowance
- $10,000 employer contribution to a Virginia 529 College Savings Plan

If you are licensed or eligible for licensure in Virginia, and have completed a psychiatric residency, please send your current CV to kim.sayers@dbhds.virginia.gov, or phone 276-783-1204 to discuss this opportunity.

We invite you to join a team of dedicated physicians and loyal staff who are committed to promoting a life of possibilities for all Virginians.

For more information, please visit:

- www.swvmh.dhbs.virginia.gov
- www.smithcounty.org
- www.abingdon-va.gov

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Hackensack Meridian Health is a leading not-for-profit health care network in New Jersey offering a complete range of medical services, innovative research, and life enhancing care aiming to serve as a national model for changing and simplifying health care delivery through partnerships with innovative companies and focusing on quality and safety.

Through a partnership between Hackensack Meridian Health and Seton Hall University, the School of Medicine will re-define graduate medical education, research, and clinical practice; reverse the critical physician shortage in both the New York/New Jersey metropolitan area and the nation; and stimulate economic development in northern New Jersey.

The School of Medicine will be the anchor in the development of a comprehensive health sciences campus that will also include research facilities and biotechnology endeavors – all in service of educating tomorrow’s doctors, discovering novel therapies, and facilitating compassionate and effective healthcare that will meet the ever-changing needs of tomorrow’s patients.

The School of Medicine will be the cornerstone of a dynamic venue for the exchange of ideas, the development of healthcare and research thought leaders and practitioners, and the discovery of novel therapies to meet the medical challenges of the future.

“Ocean Medical Center’s psychiatry program will be a community-based program,” said Ramon Solikhah, M.D., program director for psychiatry as well as founding Chair of Psychiatry & Behavioral Health at the Hackensack Meridian School of Medicine at Seton Hall University.

“Our new psychiatry residency program will improve clinical care and ultimately encourage future health care leaders to build practices in the Jersey Shore area,”

As the area’s premier provider of psychiatric services, Hackensack Meridian Behavioral Health Services has provided comprehensive mental health and substance abuse services to the residents of Monmouth, Ocean, Middlesex, and Bergen Counties for over forty years. Due to continued growth and expansion, we are currently accepting applications for Psychiatrists to join our Mental Health and Addiction Interdisciplinary Teams in the following positions:

- **Carrier Clinic -Inpatient Attending**
  Child/Adolescent and Adult/Geriatric--Carrier Clinic (Belle Mead, NJ)

- **Child & Adolescent Section Chief**
  Includes Pediatric CL: Jersey Shore University Medical Center, (Neptune NJ)

- **Consultation Liaison Psychiatrists**
  Hackensack University Medical Center (Hackensack, NJ), Raritan Bay Medical Center (Perth Amboy, NJ), JFK Medical Center (Edison, NJ), Ocean Medical Center (Brick, NJ)

- **Outpatient**
  Ocean Medical Center (Brick, NJ)

- **Staff Psychiatrist for Adult Inpatient Unit**
  Riverview Medical Center (Red Bank, NJ) & Hackensack University Medical Center (Hackensack, NJ)

- **Outpatient Child & Adolescent Psychiatrist**
  Hackensack University Medical Center (Hackensack, NJ)

- **Geriatric Psychiatry**
  Hackensack University Medical Center (Hackensack, NJ)

Renee.Theobald@hackensackmeridian.org or call: 732 751-3597

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