“Without a full spectrum of voices from partisan political elites, though, anxious citizens in search of protection from threats to their health and way of life may support charlatans or madmen who offer bodily protection while destroying the body politic.”

There are plenty of reasons to be anxious about the state of the nation: the coronavirus pandemic, the economy, climate instability, physician burnout, an endless war on terrorism, returning to the classroom (or not), and racism, among other societal and personal stressors. All these major dangers are on top of the still-looming nuclear risk that could blot out human life on earth in virtually an instant. No wonder some individuals are calling 2020 “the worst year ever.”

As if that were not enough, now we have a presidential election happening in the midst of partisan political warfare, civil unrest, and frightening conspiracy theories on TV and the internet. The stakes seem sky high, perhaps because the president has so much influence on how we address every other crisis.
**NOW APPROVED**

SPRAVATO®, IN CONJUNCTION WITH AN ORAL ANTIDEPRESSANT, IS NOW APPROVED FOR THE TREATMENT OF DEPRESSIVE SYMPTOMS IN ADULTS WITH MDD WITH ACUTE SUICIDAL IDEATION OR BEHAVIOR (MDSI).  

Limitations of Use:

- The effectiveness of SPRAVATO® in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of SPRAVATO® does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO®.

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

The most common adverse reactions with SPRAVATO® plus oral antidepressant (incidence ≥5% and at least twice that of placebo nasal spray plus oral antidepressant) were: dissociation, dizziness, sedation, blood pressure increased, hypoesthesia, vomiting, euphoric mood, and vertigo.

Learn more at www.spravatohcp.com

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**Indications:**

SPRAVATO® (esketamine) CIII Nasal Spray is indicated, in conjunction with an oral antidepressant, for the treatment of:

- Treatment-resistant depression (TRD) in adults.
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.

**Limitations of Use:**

- The effectiveness of SPRAVATO® in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use of SPRAVATO® does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose of SPRAVATO®.

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

MDD=major depressive disorder.


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**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 SPRAVATO® prior to use in patients at higher risk of abuse. Monitor for signs and symptoms of abuse and misuse (5.3).

- SPRAVATO® is only available through a restricted program called the SPRAVATO® 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. SPRAVATO® is not approved for use in pediatric patients (5.5).

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

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Important Safety Information (continued)

CONTRAINdications
SPRAVATO® 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.

WARNINGS AND PRECAUTIONS
Sedation: In clinical trials, 48% to 61% of SPRAVATO®-treated patients developed sedation and 0.3% to 0.4% of SPRAVATO®-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 SPRAVATO® with CNS depressants [see Drug Interaction (7.1)].

SPRAVATO® is available only through a restricted program under a REMS.

Dissociation: The most common psychological effects of SPRAVATO® were dissociative or perceptual changes (including distortion of time, space and illusions), derealization and depersonalization (61% to 84% of SPRAVATO®-treated patients developed dissociative or perceptual changes). Given its potential to induce dissociative effects, carefully assess patients with psychosis before administering SPRAVATO®; treatment should be initiated only if the benefit outweighs the risks. 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.

SPRAVATO® is available only through a restricted program under a REMS.

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 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.

SPRAVATO® is available only through a restricted program under a REMS.

SPRAVATO® Risk Evaluation and Mitigation Strategy (REMS): SPRAVATO® is available only through a restricted program called the SPRAVATO® REMS because of the risks of serious adverse outcomes from sedation, dissociation, and abuse and misuse. Important requirements of the SPRAVATO® REMS include the following:
• Healthcare settings must be certified in the program and ensure that SPRAVATO® is:
  • Only dispensed and administered in healthcare settings.
  • Patients treated in outpatient settings (e.g., medical offices and clinics) must be enrolled in the program.
  • Administered by patients under the direct observation of a healthcare provider and that patients are monitored by a healthcare provider for at least 2 hours after administration of SPRAVATO®.
  • Pharmacies 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 adult and pediatric patients, the incidence of suicidal thoughts and behaviors in patients age 24 years and younger was greater than in placebo-treated patients. SPRAVATO® is not approved in pediatric (<18 years of age) patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. Monitor all antidepressant-treated patients for clinical worsening and emergence 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. Consider changing the therapeutic regimen, including possibly discontinuing SPRAVATO® and/or the concomitant oral antidepressant, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Increase in Blood Pressure: SPRAVATO® causes increases in systolic and/or diastolic blood pressure (BP) at all recommended doses. Increases in BP peak approximately 40 minutes after SPRAVATO® administration and last approximately 4 hours. Approximately 8% to 19% of SPRAVATO®-treated patients experienced an increase of more than 40 mmHg in systolic BP and/or 25 mmHg in diastolic BP in the first 1.5 hours after administration at least once during the first 4 weeks of treatment. A substantial increase in blood pressure could occur after any dose administered even if smaller blood pressure effects were observed with previous administrations. 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 SPRAVATO®, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of SPRAVATO® outweigh its risk. 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 SPRAVATO® therapy should take into account the balance of benefit and risk in individual patients.

BP should be monitored for at least 2 hours after SPRAVATO® administration. Measure blood pressure around 40 minutes post-dose and subsequently as clinically warranted until values decline. If BP remains high, promptly seek assistance from practitioners experienced in BP management. Refer patients experiencing symptoms of a hypertensive crisis (e.g., chest pain, shortness of breath) or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, seizures, diminished consciousness, or focal neurological deficits) immediately for emergency care.

Closely monitor blood pressure with concomitant use of SPRAVATO® with psychostimulants or monoamine oxidase inhibitors (MAOIs) [see Drug Interactions (7.2, 7.3)]. In patients with history of hypertensive encephalopathy, more intensive monitoring, including more frequent blood pressure and symptom assessment, is warranted because these patients are at increased risk for developing encephalopathy with even small increases in blood pressure.

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

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. SPRAVATO®-treated subjects required a greater effort to complete the cognitive tests at 40 minutes post-dose. Cognitive performance and mental effort 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 beyond one year.

Impaired Ability to Drive and Operate Machinery: Before SPRAVATO® administration, instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep. Patients will need to arrange transportation home following treatment with SPRAVATO®.

Ulcereative or Interstitial Cystitis: Cases of ulcerative or interstitial cystitis have been reported in individuals with long-term off-label use or misuse/abuse of ketamine. In clinical studies with SPRAVATO® nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in SPRAVATO®-treated patients than in placebo-treated patients. No cases of esketamine-related interstitial cystitis were observed in any of the studies, which involved treatment for up to a year.

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®, 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 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 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 endpoints 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 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 “spaced out.” Monitoring for signs of abuse and misuse is recommended.

ADVERSE REACTIONS

The most common adverse reactions with SPRAVATO® plus oral antidepressant (incidence ≥5% and at least twice that of placebo nasal spray plus oral antidepressant) were:

TRD: dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.

Treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior: dissociation, dizziness, sedation, blood pressure increased, hypoesthesia, vomiting, euphoric mood, and vertigo.

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

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SPRAVATO® (esketamine) nasal spray, CIII

Brief Summary

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

• Patients are at risk for sedation after administration of SPRAVATO [see Warnings and Precautions].
• Patients are at risk for post-SPRAVATO administration.

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].

Spravato Risk Evaluation and Mitigation Strategy (REMS) called the SPRAVATO REMS [see Warnings and Precautions].

Suicidal Thoughts and Behaviors

Adverse events increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Close monitoring on 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
• Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior

Limitations of Use:
• The effectiveness of SPRAVATO in preventing suicide or in reducing suicidal ideation or behavior has not been established [see Clinical Studies (14.2) in Full Prescribing Information] Use of SPRAVATO does not preclude the need for hospitalization if clinically warranted, even if patients experience a transient improvement in suicidal ideation or behavior immediately after administration of SPRAVATO. SPRAVATO is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established.

CONTRAINdications

SPRAVATO is contraindicated in patients with:
• Anomalous vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformations [see Warnings and Precautions]
• History of hemorrhagic stroke [see Warnings and Precautions]
• Hypersensitivity to esketamine, ketamine, or any of the excipients.

WARNINGS AND PRECAUTIONS

Sedation

In clinical trials, 46% to 61% of SPRAVATO-treated patients developed sedation based on the Modified Observer’s Assessment of Alertness/Sedation scale [MOAA/S] [see Adverse Reactions], and 0.3% to 0.4% of SPRAVATO-treated patients experienced loss of consciousness (MOAA/S score of 0). 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 [see Doseage and Administration (2.4) in Full Prescribing Information].

Closely monitor for sedation with concomitant use of SPRAVATO with CNS depressants [see Drug Interactions].

SPRAVATO is available only through a restricted program under a REMS [see Warnings and Precautions].

Dissociation

The common psychological effects of SPRAVATO were dissociative or perceptual changes including distortion of time, space and illusions, derealization and depersonalization (61% to 84% of SPRAVATO-treated patients developed dissociative or perceptual changes based on the Clinician-Administered Dissociative States Scale [C-ADS]; see Adverse Reactions). Given esketamine's ability to induce dissociative effects, as well as its ability to induce a dissociative state, physicians should carefully assess patients with psychosis before administering SPRAVATO; treatment should be initiated only if the potential benefits outweigh 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 [see Doseage and Administration (2.4) in Full Prescribing Information].

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 dependence. 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 state-controlled substances authority for information on how to prevent and detect abuse or diversion of SPRAVATO. Individuals with a history of drug abuse or dependence are at greater risk; therefore, use considerable caution in prescribing SPRAVATO to individuals with a history of substance use disorder and monitor for signs of abuse or dependence [see Drug Abuse and Dependence].

SPRAVATO is available only through a restricted program under a REMS [see Warnings and Precautions].

SPRAVATO Risk Evaluation and Mitigation Strategy (REMS) (1.10)

SPRAVATO is available only through a restricted program under a REMS called the SPRAVATO REMS because of the risks of serious adverse outcomes from sedation, dissociation, and abuse [see Based Warnings and Precautions]. Important requirements of the REMS REMS include the following:

• Healthcare settings must be certified in the program and ensure that SPRAVATO is:
  – Only dispensed and administered in healthcare settings.
  – Only dispensed and administered in healthcare settings.
  – Only dispensed and administered in healthcare settings.
  – Only dispensed and administered in healthcare settings.
  – Only dispensed and administered in healthcare settings.
  – Only dispensed and administered in healthcare settings.
  – Only dispensed and administered in healthcare settings.
  –只有在医疗保健机构中分发和使用SPRAVATO
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Further information, including a list of certified pharmacies is available at www.SPRAVATOrems.com or 1-855-382-4022.

Table 1: Risk Differences of the Number of Patients with Suicidal Thoughts or Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>Comparator</th>
<th>SPRAVATO Increased Compared to Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>14 additional patients</td>
<td>4 cases more than placebo</td>
</tr>
<tr>
<td>18-64</td>
<td>3 additional patients</td>
<td>1 case more than placebo</td>
</tr>
<tr>
<td>≥65</td>
<td>1 fewer patient</td>
<td>4 cases less than placebo</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 four months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with MDD that antidepressants delay the relapse of depression and that depression is itself a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for clinical worsening and emergence 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. Consider changing the therapeutic regimen, including possibly discontinuing SPRAVATO; and/or the concomitant or concurrent antidepressant, in patients with depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Increase in Blood Pressure

Increases in systolic and/or diastolic blood pressure (BP) at all recommended doses. Increases in BP peak approximately 40 minutes after SPRAVATO administration and last approximately 40 minutes [see Adverse Reactions].

Approximately 8% to 16% of patients treated with SPRAVATO and 1% to 4% of placebo-treated patients experienced an increase of greater than or equal to 40 mm Hg in systolic BP and/or 25 mm Hg in diastolic BP in the first 1.5 hours after administration at least once during the first 4 weeks of treatment. A substantial increase in blood pressure could occur after any dose administered even if smaller blood pressure effects were observed with previous administrations.

SPRAVATO is contraindicated in patients for an increase in BP or intracranial pressure poses a serious risk (e.g., aneurysmal vascular disease, arteriovenous malformation, history of intracerebral hemorrhage) [see Contraindications].

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

Assess BP prior to administration of SPRAVATO. In patients whose BP is elevated prior to SPRAVATO dosing, a general guide is to delay SPRAVATO therapy should take into account the balance of benefit and risk in individual patients.

BP should be monitored for at least 2 hours after SPRAVATO administration [see Doseage and Administration (2.1, 2.4) in Full Prescribing Information]. Measure blood pressure around 40 minutes post-dose and subsequently as clinically warranted until values decline. If BP remains high, promptly seek assistance from practitioners experienced in BP management. Refer patients experiencing symptoms of a hypertensive crisis (e.g., chest pain, shortness of breath) or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, seizures, dimmed consciousness or focal neurologic deficits) immediately for emergency care.

Closely monitor blood pressure with concomitant use of SPRAVATO with psychostimulants or monoamine oxidase inhibitors (MAOIs) [see Drug Interactions].

Patients with history of hypertension, coronary artery disease, cerebrovascular disease, or hypertensive encephalopathy, more intensive monitoring, including more frequent blood pressure and symptom assessment, is warranted because these patients are at increased risk for developing encephalopathy with even small increases in blood pressure.

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 treatment resulted in a greater effort to complete cognitive tests at 40 minutes post-dose. Cognitive performance and mental effort 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 beyond one year.

Impaired Ability to Drive and Operate Machinery

Two placebo-controlled studies were conducted to assess the effects of SPRAVATO on the ability to drive and operate machinery. In one study (Clinical Studies (14.3) in Full Prescribing Information), 14.8% of SPRAVATO-treated subjects required a greater effort to complete 40 minutes post-dose. Cognitive performance and mental effort were comparable between SPRAVATO and placebo at 2 hours post-dose. Sleepiness was comparable after 4 hours post-dose.

Impairment of Cognitive Functioning

Corticosteroids and/or interferon beta-1a has been reported in individuals with long-term off-label use or misuse/abuse of ketamine. In clinical studies with SPRAVATO nasal spray, there was a higher rate of primary motor tract symptoms [see Warnings and Precautions], which may include numbness, weakness, and paresthesias in SPRAVATO-treated patients than in placebo-treated patients [see Adverse Reactions]. No cases of esketamine-related interstitial cystitis were observed in any of the studies, which included treatment for up to one year.

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

Neurotoxicity

Based on published findings from pregnant animals treated with ketamine, the racemate mixture of ketamine and esketamine, SPRAVATO may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an fetus exposed to SPRAVATO in utero. Advise women of reproductive potential to consider pregnancy planning and prevention [see Use in Specific Populations].
Clinical Trials Experience

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

Treatment-Resistant Depression

SPRAVATO® was evaluated for safety in 1,700 adults diagnosed with treatment-resistant depression (TRD) (see Clinical Studies (14.1) in Full Prescribing Information) from five Phase 3 studies (3 short-term and 2 long-term) and one Phase 2 dose-ranging study. Of all SPRAVATO-treated patients in the completed Phase 3 studies, 479 (30%) received at least 6 months of treatment, and 178 (11%) received at least 12 months of treatment.

Adverse Reactions Leading to Discontinuation of Treatment

In short-term studies in adults < 65 years old (Study 1 pooled with another 4-week study), the proportion of patients who discontinued treatment because of an adverse reaction was 4.6% in patients who received SPRAVATO plus oral AD compared to 1.4% for patients who received placebo nasal spray plus oral AD. For adults ≥ 65 years old, the proportions were 6.6% and 3.1%, respectively. In Study 2, a 1-long term study, the discontinuation rate because of an adverse reaction was similar for patients receiving SPRAVATO plus oral AD and placebo nasal spray plus oral AD in the maintenance phase, at 2.6% and 2.1%, respectively. Across all Phase 3 studies, adverse reactions leading to SPRAVATO discontinuation in more than 2 patients were (in order of frequency): anxiety (1.2%), depression (0.8%), blood pressure increased (0.6%), diziness (0.4%), suicidal ideation (0.3%), dissociation (0.4%), nausea (0.4%), vomiting (0.4%), headache (0.3%), muscle weakness (0.3%), vertigo (0.2%), hypertension (0.2%), panic attack (0.2%) and sedation (0.2%).

Most Common Adverse Reactions

The most commonly observed adverse reactions in patients treated 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, hypotension, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.

Table 2 shows the incidence of adverse reactions that occurred in patients treated with SPRAVATO plus oral AD at any dose and greater than patients treated with placebo nasal spray plus oral AD.

Table 2: Adverse Reactions Occurring in ≥2% of Adult TRD Patients Treated with SPRAVATO® Oral AD at Any Dose and at a Greater Rate than Patients Treated with Placebo Nasal Spray plus Oral AD

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo Nasal Spray + Oral AD</th>
<th>Placebo + Oral AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td><strong>Tachycardia</strong></td>
<td>6 (2%) 1 (0.5%)</td>
</tr>
<tr>
<td><strong>Ear and lymphatic disorders</strong></td>
<td><strong>Vertigo</strong></td>
<td>78 (23%) 6 (12%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td><strong>Nausea</strong></td>
<td>98 (28%) 19 (9%)</td>
</tr>
<tr>
<td></td>
<td><strong>Vomiting</strong></td>
<td>33 (9%) 4 (2%)</td>
</tr>
<tr>
<td></td>
<td><strong>Diarrhea</strong></td>
<td>22 (7%) 13 (6%)</td>
</tr>
<tr>
<td></td>
<td><strong>Dry mouth</strong></td>
<td>19 (5%) 7 (3%)</td>
</tr>
<tr>
<td></td>
<td><strong>Constipation</strong></td>
<td>11 (3%) 3 (1%)</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td><strong>Feeling drunk</strong></td>
<td>19 (5%) 10 (5%)</td>
</tr>
<tr>
<td></td>
<td><strong>Feeling abnormal</strong></td>
<td>12 (3%) 0 (0%)</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td><strong>Blood pressure increased</strong></td>
<td>36 (10%) 6 (2%)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td><strong>Dizziness</strong></td>
<td>101 (29%) 17 (8%)</td>
</tr>
<tr>
<td></td>
<td><strong>Sedation</strong></td>
<td>79 (23%) 21 (9%)</td>
</tr>
<tr>
<td></td>
<td><strong>Headache</strong></td>
<td>70 (20%) 30 (14%)</td>
</tr>
<tr>
<td></td>
<td><strong>Gnusia</strong></td>
<td>66 (19%) 20 (14%)</td>
</tr>
<tr>
<td></td>
<td><strong>Hypersomnia</strong></td>
<td>63 (18%) 5 (2%)</td>
</tr>
<tr>
<td></td>
<td><strong>Lethargy</strong></td>
<td>37 (11%) 12 (6%)</td>
</tr>
<tr>
<td></td>
<td><strong>Dyshoria</strong></td>
<td>15 (4%) 0 (0%)</td>
</tr>
<tr>
<td></td>
<td><strong>Tremor</strong></td>
<td>12 (3%) 2 (1%)</td>
</tr>
<tr>
<td></td>
<td><strong>Mental impairment</strong></td>
<td>11 (3%) 2 (1%)</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td><strong>Depression</strong></td>
<td>142 (41%) 21 (9%)</td>
</tr>
<tr>
<td></td>
<td><strong>Anxiety</strong></td>
<td>45 (13%) 14 (6%)</td>
</tr>
<tr>
<td></td>
<td><strong>Insomnia</strong></td>
<td>29 (8%) 16 (7%)</td>
</tr>
<tr>
<td></td>
<td><strong>Euphoria</strong></td>
<td>15 (4%) 2 (1%)</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td><strong>Pollakiuria</strong></td>
<td>11 (3%) 1 (0.5%)</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td><strong>Nasal discomfort</strong></td>
<td>23 (7%) 11 (5%)</td>
</tr>
<tr>
<td></td>
<td><strong>Throat irritation</strong></td>
<td>23 (7%) 9 (4%)</td>
</tr>
<tr>
<td></td>
<td><strong>Oral pharyngeal pain</strong></td>
<td>9 (3%) 5 (2%)</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td><strong>Hyperhidrosis</strong></td>
<td>14 (4%) 5 (2%)</td>
</tr>
</tbody>
</table>

* The following terms were combined:
  - Anxiety includes: agitation; anticipatory anxiety; anxiety; fear; feeling jittery; irritability; nervousness; panic; attack; tension
  - Blood pressure increased includes: blood pressure diastolic increased; blood pressure increased; blood pressure systolic increased; hypertension
  - Dissociation includes: disorientation; depersonalization/derealization disorder; derealization; delusion; dysphoria; dissociation; dysesthesia; feeling cold; feeling hot; feeling of body temperature change; hallucinations; auditory; hallucination; visual; hypervigilance; illusion; ocular symptom; oral dysesthesia; paresthesia; paresthesia oral; pharyngeal paresthesia; photophobia; time perception altered; tinnotes; vision blurred; visual impairment

SPRAVATO® (esketamine) nasal spray, CIII

ADVERSE REACTIONS

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

- Sedation (see Warnings and Precautions)
- Dissociation (see Warnings and Precautions)
- Increase in Blood Pressure (see Warnings and Precautions)
- Cognitive Impairment (see Warnings and Precautions)
- Impaired Ability to Drive and Operate Machinery (see Warnings and Precautions)
- Ulcerative or Intestinal Cystitis (see Warnings and Precautions)
- Embryo-fetal Toxicity (see Warnings and Precautions)

- Gastrointestinal disorders
- Nervous system disorders
- Respiratory, thoracic and mediastinal disorders
- Skin and subcutaneous tissue disorders
- Skin and subcutaneous tissue disorders

**Most Common Adverse Reactions**

The most commonly observed adverse reactions in patients treated 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, hypotension, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.

Table 3: Adverse Reactions Occurring in ≥2% of Adult Patients with MDD and Acute Suicidal Ideation or Behavior Treated with SPRAVATO® Oral AD and at a Greater Rate than Patients Treated with Placebo Nasal Spray plus Oral AD

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>SPRAVATO + Oral AD (N=227)</th>
<th>Placebo + Oral AD (N=225)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td><strong>Tachycardia</strong></td>
<td>8 (4%) 2 (1%)</td>
</tr>
<tr>
<td><strong>Ear and lymphatic disorders</strong></td>
<td><strong>Vertigo</strong></td>
<td>14 (6%) 1 (0.4%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td><strong>Nausea</strong></td>
<td>61 (27%) 31 (14%)</td>
</tr>
<tr>
<td></td>
<td><strong>Vomiting</strong></td>
<td>26 (11%) 12 (5%)</td>
</tr>
<tr>
<td></td>
<td><strong>Constipation</strong></td>
<td>22 (10%) 14 (6%)</td>
</tr>
<tr>
<td></td>
<td><strong>Dry mouth</strong></td>
<td>8 (4%) 6 (3%)</td>
</tr>
<tr>
<td></td>
<td><strong>Tongue</strong></td>
<td>5 (2%) 2 (1%)</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td><strong>Feeling drunk</strong></td>
<td>8 (4%) 1 (0.4%)</td>
</tr>
<tr>
<td></td>
<td><strong>Feeling of relaxation</strong></td>
<td>5 (2%) 3 (1%)</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td><strong>Blood pressure increased</strong></td>
<td>34 (15%) 14 (6%)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td><strong>Myalgia</strong></td>
<td>5 (2%) 1 (0.4%)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td><strong>Dizziness</strong></td>
<td>103 (45%) 34 (15%)</td>
</tr>
<tr>
<td></td>
<td><strong>Sedation</strong></td>
<td>66 (29%) 27 (12%)</td>
</tr>
<tr>
<td></td>
<td><strong>Dysphoria</strong></td>
<td>46 (20%) 29 (13%)</td>
</tr>
<tr>
<td></td>
<td><strong>Hypoesthesia</strong></td>
<td>30 (13%) 4 (2%)</td>
</tr>
<tr>
<td></td>
<td><strong>Lethargy</strong></td>
<td>10 (4%) 4 (2%)</td>
</tr>
<tr>
<td></td>
<td><strong>Confusional state</strong></td>
<td>5 (2%) 0 (0%)</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td><strong>Dissociation</strong></td>
<td>108 (48%) 30 (13%)</td>
</tr>
<tr>
<td></td>
<td><strong>Anxiety</strong></td>
<td>34 (15%) 29 (13%)</td>
</tr>
<tr>
<td></td>
<td><strong>Euphoric mood</strong></td>
<td>17 (7%) 1 (0.4%)</td>
</tr>
<tr>
<td></td>
<td><strong>Intentional self-injury</strong></td>
<td>7 (3%) 3 (1%)</td>
</tr>
<tr>
<td></td>
<td><strong>Dysphoria</strong></td>
<td>5 (2%) 0 (0%)</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td><strong>Pollakiuria</strong></td>
<td>5 (2%) 2 (1%)</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td><strong>Oropharyngeal pain</strong></td>
<td>10 (4%) 3 (1%)</td>
</tr>
<tr>
<td></td>
<td><strong>Throat irritation</strong></td>
<td>9 (4%) 5 (2%)</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td><strong>Hyperhidrosis</strong></td>
<td>11 (5%) 5 (2%)</td>
</tr>
</tbody>
</table>

* The following terms were combined:
  - Anxiety includes: agitation; anxiety; anxiety disorder; fear; irritability; nervousness; panic attack; psychomotor hyperactivity; tension
  - Blood pressure increased includes: blood pressure diastolic increased; blood pressure increased; blood pressure systolic increased; hypertension
  - Dissociation includes: disorientation; depersonalization/derealization disorder; derealization; delusion; dysphoria; dissociation; dysesthesia; feeling cold; feeling hot; hallucination; hallucination, auditory; hallucination, visual; hallucination, visual; hypervigilance; mixed (hyperactivity, hypervigilance); paresthesia oral; pharyngeal paresthesia; photophobia; time perception altered; tinnotes; vision blurred
  - Dizziness includes: dizziness; dizziness exertional; dizziness postural; procedural dizziness
  - Dysphoria includes: dysphoria; dysphoria, visual
  - Headache includes: headache; sinus headache
  - Hypersomnia includes: hypersomnia; hypoglycemia oral, hypoglycemia, pharyngeal hypoglycemia
  - Lethargy includes: fatigue; lethargy; psychomotor retardation
  - Pollakiuria includes: mictonit urge and pollakiuria
  - Sedation includes: sedation, somnolence, stupor
  - Tachycardia includes: heart rate increased; at.

[See Warnings and Precautions]
Table 4: Incidence of Sedation (MOAA/S Score <5) in Double-Blind, Randomized, Placebo-Controlled Studies with Adult Patients <65 Years of Age with TRD and Flexible-Dose Study with Patients >65 Years of Age with TRD

<table>
<thead>
<tr>
<th>Patients &lt;65 years</th>
<th>Patients &gt;65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Oral AD</td>
<td>Placebo + Oral AD</td>
</tr>
<tr>
<td>56 mg</td>
<td>84 mg</td>
</tr>
<tr>
<td>N=112</td>
<td>N=114</td>
</tr>
<tr>
<td>Sedation (MOAA/S score &lt;5)</td>
<td>11%</td>
</tr>
</tbody>
</table>

Table 5: Incidence of Dissociation (CADSS Total Score >4 and Change >0) in Double-Blind, Randomized, Placebo-Controlled Studies with Adult Patients <65 Years of Age with TRD and Flexible-Dose Study with Patients >65 Years of Age with TRD

<table>
<thead>
<tr>
<th>Patients &lt;65 years</th>
<th>Patients &gt;65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Oral AD</td>
<td>Placebo + Oral AD</td>
</tr>
<tr>
<td>56 mg</td>
<td>84 mg</td>
</tr>
<tr>
<td>N=113</td>
<td>N=113</td>
</tr>
<tr>
<td>CADSS score &gt;4 and change &gt;0</td>
<td>5%</td>
</tr>
</tbody>
</table>

Table 6: Increases in Blood Pressure in Double-Blind, Randomized, Placebo-Controlled, Short-Term Trials of SPRAVATO® Oral Compared to Placebo Nasal Spray in Oral AD in the Treatment of TRD in Adult Patients

<table>
<thead>
<tr>
<th>Patients &lt;65 years</th>
<th>Patients &gt;65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPRAVATO + Oral AD</td>
<td>Placebo + Oral AD</td>
</tr>
<tr>
<td>N=346</td>
<td>N=222</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>38 mg Hg</td>
</tr>
<tr>
<td>≥ 180 mm Hg</td>
<td>9 (3%)</td>
</tr>
<tr>
<td>≥ 250 mm Hg increase</td>
<td>40 (12%)</td>
</tr>
</tbody>
</table>

Table 7: Incidence and Severity of Nausea and Vomiting in a Double-blind, Randomized, Placebo-Controlled, Fixed-Dose Study in Adult Patients with TRD

<table>
<thead>
<tr>
<th>Treatment (Oral AD)</th>
<th>N</th>
<th>Nausea</th>
<th>Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Severe</td>
<td>All</td>
<td>Severe</td>
</tr>
<tr>
<td>Placebo Nasal Spray</td>
<td>113</td>
<td>12 (11%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 8: Effect of SPRAVATO® on the Incidence of Nausea and Vomiting in a Double-blind, Randomized, Placebo-Controlled Study with Adult Patients >65 Years of Age with TRD

<table>
<thead>
<tr>
<th>Patients &gt;65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPRAVATO + Oral AD</td>
</tr>
<tr>
<td>N=67</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
</tbody>
</table>

Table 9: Effect of SPRAVATO® on the Incidence of Sedation in a Double-blind, Randomized, Placebo-Controlled Study with Adult Patients >65 Years of Age with TRD

<table>
<thead>
<tr>
<th>Patients &gt;65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPRAVATO + Oral AD</td>
</tr>
<tr>
<td>N=72</td>
</tr>
<tr>
<td>Sedation (MOAA/S score &lt;5)</td>
</tr>
</tbody>
</table>

Table 10: Effect of SPRAVATO® on the Incidence of Dissociation in a Double-blind, Randomized, Placebo-Controlled Study with Adult Patients >65 Years of Age with TRD

<table>
<thead>
<tr>
<th>Patients &gt;65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPRAVATO + Oral AD</td>
</tr>
<tr>
<td>N=67</td>
</tr>
<tr>
<td>Dissociation (CADSS total score &gt;4 and change &gt;0)</td>
</tr>
</tbody>
</table>
Female and Male 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. 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. 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 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 (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 newly initiated 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 56 mg or 84 mg administered twice-weekly. 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

The mean esketamine AUC 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 in this population 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 “spaced out”. Monitoring for signs of abuse and misuse is recommended.

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 ketamine. Ketamine, the racemic mixture of arketamine and esketamine, is a Schedule III controlled substance and has known abuse potential. In this study, the mean “Drug Liking at the Moment” and “Take Drug Again” scores for single doses of intranasal SPRAVATO (84 mg and 112 mg – the maximum recommended dose and 1.3 times the maximum recommended dose, respectively) were similar to scores in the intravenous ketamine (0.5 mg/kg infused over 40 minutes) control group. However, these scores were greater in the SPRAVATO and ketamine groups compared to the placebo group. The 112 mg dose of intranasal SPRAVATO was associated with significantly higher scores for “Hallucinating,” “Floating,” “Detached,” and “Spaced Out” than the 84 mg dose of intranasal SPRAVATO and the intravenous ketamine dose.

Dependence

Physical dependence has been reported with prolonged use of ketamine. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or significant dosage reduction of a drug. There were no withdrawal symptoms captured up to 4 weeks after cessation of esketamine treatment. Withdrawal symptoms have been reported after the discontinuation of frequently used (more than weekly) large doses of ketamine for long periods of time. Such withdrawal symptoms are likely to occur if esketamine were similarly abused. Reported symptoms of withdrawal associated with daily intake of large doses of ketamine include craving, fatigue, poor appetite, and anxiety. Therefore, monitor SPRAVATO-treated patients for symptoms and signs of physical dependence upon the discontinuation of the drug.

Tolerance has been reported with prolonged use of ketamine. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). Similar tolerance would be expected with prolonged use of esketamine.

Overdosage

Management of Overdose

There is no specific antidote for esketamine overdose. In the case of overdose, the possibility of multiple drug involvement should be considered. Contact a Certified Poison Control Center for the most up to date information on the management of overdose (1-800-222-1222 or www.poison.org). Manufactured for: Janssen Pharmaceuticals, Inc. Titusville, NJ 08560 © 2019 Janssen Pharmaceutical Companies cp-81105v6
The Importance of Learning

Albert Einstein once said, “Intellectual growth should commence at birth and cease only at death.” Nowhere is that truer than in medicine. As research uncovers new mechanisms of action for pharmacology and etiologies of disorders, physicians must keep up with the latest and most effective ways to help their patients.

John J. Miller, MD, sets the stage with his editorial, a personal reflection on a lifetime of learning. Even after nearly 30 years of practice, he admits he has mastered only the first 5 letters of the “psychiatric alphabet.” He exhorts colleagues to join him as he seeks a deeper understanding of the psychiatric ABCs. And Psychiatric Times® is honored to support you in that endeavor.

Perhaps the most exciting learning happens at the forefront of knowledge, where new discoveries are made. In this issue you will find clinical and commentary pieces that explore new research, outline novel strategies to overcome challenges, and share lessons from experiential learning. Our continuing medical education article, for example, discusses considerations surrounding medical cannabis. Although it is gaining medical acceptance and piquing patient interest, cannabis raises important medicolegal questions, and clinicians need to know what they are and how to answer.

At the same time, there is always something new to learn, even about the most familiar topics. Within these pages, we include articles that explore core clinical areas, including mood disorders, schizophrenia and psychosis, and neuropsychiatry. For example, Rajesh Tampi, MD, MS, FAPA, and colleagues take a close look at the variants of frontotemporal dementia (FTD). This disorder is the third most common type of dementia and the second most common among patients 65 years or younger, but it is often misdiagnosed as other psychiatric disorders. The authors provide the practical knowledge you need to better identify and manage FTD. Similarly, Kultaj Kaleka, RN, and Juliette M. Perzhinsky, MD, MSc, share insights into medication-assisted treatment, including the ethical dilemmas related to its use. They remind us that in learning the ABCs of psychiatry, it is important to reflect on the implications for patients.

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The Practice of Medicine

John J. Miller, MD | Editor in Chief

For me, the fall has always conjured excitement about a new odyssey of learning. With the first days of school came both excitement and fear, wondering if I had the ability to learn all that was expected of me. During the previous academic year, I had listened with awe as students in the grade ahead of mine discussed their subject matter, and each year I wondered how I could ever learn that complex material. One memory in particular remains alive and well, and it visits me a few times each year.

I was in the first grade at St James Elementary School, a parochial elementary school in Salem, MA. An intimidating nun informed us we would be learning the complete alphabet. Fear filled me as I anticipated what felt like the impossibility of learning all 26 letters of the alphabet. Somehow, I succeeded, and these 26 letters have served me well over the years.

Each academic year had its own curriculum to be mastered, and each course of study initially seemed impossible:

Learning to construct a sentence with nouns, verbs, and adjectives.

Understanding the history of the United States as it was taught at that time.

Playing a simple melody on a xylophone.

Becoming familiar with the periodic table of the elements in chemistry.

Writing a complete term paper, with references expected.

It was not until the second semester of my sophomore year of college at the University of Massachusetts Amherst that something shifted inside of me, and the fear of learning new material transformed into a passion to learn more. The class material transformed into a new side of me, and the fear of learning chemistry. Walking from my dorm was “Molecular Evolution,” the first course specific to my major of biochemistry. Walking from my dorm room to the classroom I felt energized and excited about what the next lesson would teach me. The course started with the accretion of the planet earth from stardust and moved through the theoretical processes that created the molecules that eventually would become the building blocks of life.

Reflecting on that experience, I realized that if the necessary elements were all present, learning could be fun, meaningful, and could actually be driven by passion. Several of these elements are unique to each person. Arguably, being exposed to a wide-ranging curriculum during the high school years increases the likelihood that each student will discover their passion, and hopefully they will be given the opportunity to follow it.

During my 12 years of study in college, medical school and psychiatry residency, I naively expected that I would ultimately learn all that I would need to become a competent clinical psychiatrist. Today, 29 years after completing my residency in psychiatry and applying great effort to keep up to date with our rapidly evolving field, I feel like I have only scratched the surface of learning all 26 letters of the alphabet. Psychiatry is a field where the key to success is curiosity and a willingness to keep learning.

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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, popular 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.
IT’S REAL PROGRESS.

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%).

Please see the accompanying Brief Summary of Prescribing Information on the following page.

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

**SEE ITS EFFICACY AT CAPLYTAHCP.COM**
CONTRAINDICATIONS

CAPLYTA is contraindicated in patients with history of hypersensitivity reaction to lumateperone, clozapine, olanzapine, risperidone, aripiprazole, quetiapine, or any excipients in the formulation, including Mannitol, citric acid, sodium bicarbonate, or black raspberry seed extract. It is also contraindicated in patients with recent history of serotonergic or sympathomimetic agent use (within 14 days) or with a history of seizure, head trauma, cerebrovascular disease, or cardiac disease. CAPLYTA is also contraindicated in patients with uncontrolled hypertension, pheochromocytoma, or uncorrected QT prolongation.

WARNINGS AND PRECAUTIONS

Increased Incidence of Tardive Dyskinesia

In placebo-controlled trials of adult patients with schizophrenia, the mean change in body weight was approximately -2 kg for CAPLYTA-treated patients, compared to 10% of placebo-treated patients. Patients with schizophrenia, on average, also had a mean decrease in weight of -1 kg (SD 5.6). The mean change in body weight was not significantly different between patients treated with CAPLYTA and those treated with placebo in a 15-week trial in patients with stable schizophrenia, in which the mean change in body weight was approximately -2 kg (SD 5.6) at Day 175 and approximately -3.2 kg (SD 7.4) at Day 365.

Leukopenia, Neutropenia, and Agranulocytosis

Neutropenia, including agranulocytosis, has been reported during treatment with antipsychotic agents, including CAPLYTA. Patients randomized to risperidone, paliperidone, and olanzapine had a higher frequency of leukopenia, neutropenia, and agranulocytosis than patients randomized to placebo. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS), a potentially fatal syndrome, has been reported in association with administration of antipsychotic agents, including CAPLYTA. Patients with NMS may have a common clinical presentation, including fever, muscle stiffness, dyskinesia, dystonia, muscle twitching, tardive dyskinesia, tremor, drooling, respiratory distress, and hyperthermia. The mean change in body weight was approximately -2 kg (SD 5.6) at Day 175 and approximately -3.2 kg (SD 7.4) at Day 365.

Body Temperature Dysregulation

Body Temperature Dysregulation: CAPLYTA-treated patients, compared to 10% of placebo-treated patients. Patients with schizophrenia, on average, also had a mean decrease in body weight of -1 kg (SD 5.6). The mean change in body weight was not significantly different between patients treated with CAPLYTA and those treated with placebo in a 15-week trial in patients with stable schizophrenia, in which the mean change in body weight was approximately -2 kg (SD 5.6) at Day 175 and approximately -3.2 kg (SD 7.4) at Day 365.

Hyperosmolar coma or death, has been reported in patients treated with antipsychotic agents, including CAPLYTA. Patients randomized to risperidone, paliperidone, and olanzapine had a higher frequency of leukopenia, neutropenia, and agranulocytosis than patients randomized to placebo. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis.

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letters, and I try to remain aware of their current contribution and application to clinical psychiatry, but in all honesty it is hard.

Hence the term practice of medicine. Even with all the right elements of interest, commitment, passion, and effort, my view is that it is not humanly possible to ever master psychiatry. We simply must keep on practicing, learning new information, and honing new skills.

But such is the case in every field of study, and why should medicine be any different? Our primary responsibility is to do no harm. In many clinical situations this requires me to know what I know, know what I don’t know, and consult with a colleague who likely knows more than I do, when necessary. One of the many gifts of psychiatry as a field of medicine is its extreme diversity. The menu of specialty options we have in the field is vast, and each psychiatrist usually evolves into a specific area of practice that fits like a comfortable glove. It is our responsibility as psychiatrists, however, to remain up to date with what is happening in our field of psychiatry in general. Fortunately, there is no paucity of educational opportunities to support us in our ongoing, self-directed learning.

"Even with all the right elements of interest, commitment, passion, and effort, in my view it is not humanly possible to ever master psychiatry. We simply must keep on practicing, learning new information, and honing new skills."

"Transparency, and ultimately honesty, will help Americans make decisions based on data and facts, not fear and bias."

During past crises, we have seen how those moral failures have played out. Fear during the AIDS crisis led to rampant discrimination against the lesbian, gay, bisexual, transgender, and queer (LGBTQ) community, in addition to an irrational fear of individuals from specific countries, most notably Haiti. After September 11th, the nation saw an uptick in hate crimes against Sikhs, a religious group with no connection to the attacks on our country, in addition to attacks on Muslims, millions of whom are peaceful and productive American citizens. None of the fear and violence against these groups made Americans safer.

These irrational responses to unprecedented circumstances arise from fear, and they are unproductive at the end of the day. What is productive—and has been proven to work—is transparent and honest information. Historically, risk communication has been a challenge for the medical community, but big data and artificial intelligence (AI) can provide a useful channel for communicating COVID-19-related information to the public.

"Transparency, and ultimately honesty, will help Americans make decisions based on data and facts, not fear and bias."
Assessing Competency To Stand Trial

Barry Wall, MD, and Ruby Lee, MD

The United States legal system has long recognized that criminal defendants must be competent to stand trial (CST) prior to proceeding with the legal process to allow for fairness for the accused and protect the integrity of the justice system. Trying a defendant who is unable to assist in their own defense would call into question the dignity of the proceedings and render the adversarial process unfair. Psychiatrists and psychologists assist courts by evaluating defendants’ CST and, when necessary, providing treatment to restore competency in defendants initially found to be incompetent to stand trial (IST). The term competence restoration (CR) is used to describe the treatment and education process used to transform the defendants classified as IST to CST (Table 1).

CST, therefore, is a legal decision made by a judge that determines if a criminal defendant is able to proceed with the legal process. It is also called adjudicative competence or fitness to proceed. It is the most commonly conducted criminal forensic evaluation in the United States. There has been a surge in CST evaluation requests in recent years, with current estimates of 160,000 or more evaluation requests annually. This increase may be due to the criminalization of mental illness, substance abuse, and intellectual disability, all of which often stem from the lack of adequate access to civil treatment in the community. Thus, the gap in traditional treatment services in the community results in the overuse of the CST-CR system. Public mental health care systems are in crisis, and increasingly they must devote dollars to those facing criminal charges for costly forensic evaluations and lengthy state hospitalization stays.

The minimum legal standard for competency to stand trial was set by the US Supreme Court in Dusky v United States. In 1960, the court determined that “it is not enough for the district judge to find that ‘the defendant [is] oriented to time and place and [has] some recollection of events,’ but that the ‘test must be whether he has sufficient present ability to consult with his lawyer with a reasonable degree of rational understanding—and whether he has a rational as well as factual understanding of the proceedings against him.’”

Defense attorneys have concerns regarding their client’s competency in about 8% to 15% of felony prosecutions, and it is estimated that about 20% to 30% of evaluated defendants are found incompetent to stand trial. If a judge determines a defendant is CST, the legal case proceeds. If the judge determines a defendant is IST, the evaluation begins, typically in the form of both treatment of the defendant’s mental illness and competency education (Figure).

A CST evaluation is first and foremost a clinical evaluation. As with all psychiatric evaluations, a CST evaluation includes a review of medical records in addition to a thorough clinical interview. Police reports, medical records from jail, prior competency evaluations, and information shared by the lawyer are some of the data that are an integral part of the competency evaluation although they are not included in typical psychiatric evaluations.

In addition to assessing the defendant’s psychiatric, medical, and social histories, the defendant’s competence as it relates to trial-related tasks is evaluated. This includes assessing an understanding of the charges and their potential consequences, an understanding of the trial process, knowledge about the various participants in a trial, and whether the defendant has the ability to help in their own defense and make decisions about their case.

CST is a present tense evaluation, meaning it is an evaluation that determines the current mental state of the defendant, conducted after the alleged criminal incident has occurred. In contrast, a criminal responsibility evaluation determines the mental state of the defendant at certain point in the past, specifically at the time of the alleged criminal incident. Additionally, CST trial is moment specific. Therefore, a defendant could be initially recommended as CST and later, as the case progresses, may become IST. In fact, the issue of competency can be raised at any point in the court process.

Table 1. Important Competency Terms

<table>
<thead>
<tr>
<th>CST - Competent to stand trial</th>
<th>IST - Incompetent to stand trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental ability to stand trial; a person is mentally competent to stand trial if they are able to understand the character and consequences of the proceedings against them and is able properly to assist in their defense.</td>
<td>Mentally incompetent to stand trial; a person is mentally incompetent to stand trial if they are unable to understand the character and consequences of the proceedings against them or are unable properly to assist in their defense.</td>
</tr>
<tr>
<td>CR - Competence restoration</td>
<td>To be considered restored and competent to stand trial, a defendant must be able to consult with their defense lawyer and have a rational and factual understanding of the legal proceedings.</td>
</tr>
</tbody>
</table>

Case Example

“John,” a 35-year-old man with a history of schizoaffective disorder, is arrested; he has been treatment nonadherent for several months. Once detained, he is restarted on treatment. By the time the evaluators saw...
In the above scenario, the defendant was disorganized during the time of arrest, but by the time the CST evaluation was ordered, he was back on medications and was overall functioning well. Therefore, he was first recommended as CST. However, once he stopped taking his medications in jail, he became psychotic and became increasingly paranoid. He ultimately stopped taking his medicines. When his defense attorney tried to meet with him, John began muttering under his breath that the lawyer was conspiring with the judge and the police.

In such a case, a law student who is knowledgeable about the legal system would do well on scoring instruments. However, in undergoing a thorough CST evaluation, the evaluator would realize that the defendant is paranoid and likely unable to assist in her own defense despite having a strong factual base of knowledge. Therefore, while the law student has a factual understanding of the case (such as case travel, various pleas, etc), the law student’s ability to apply the information to her own case would be impaired, as she does not have a rational understanding of the situation. She is viewing the situation through a psychotic process. This defendant would also be recommended as IST, despite her in-depth knowledge of the law, as she was unable to comport her behavior appropriately in the civil mental health court. By extrapolation, if the criminal court judge ordered a CST evaluation, she would likely be recommended to the court as IST because she was unable to work with her attorney in civil court due to mental illness symptoms.

Although there are no diagnoses that equal IST, psychosis and intellectual disability are the 2 most common clinical reasons that defendants are found incompetent to stand trial. Nonetheless, a defendant with schizophrenia can be competent and, similarly, a defendant with intellectual disability can be competent. Consider the following case example.

“Jodi,” a 25-year-old law student with a long history of treatment nonadherence, once again stops her medications because they made her thinking “too slow.” She becomes increasingly paranoid. On a particularly bad day, Jodi calls the police for backup, as she believes that people are walking around downtown with bombs in backpacks. The police arrive as she is being arrested—she was trying to take a backpack from a passerby, believing a bomb to be inside.

Since she refuses medication, the treatment team requests the court to medicate despite objection. During the hearing in mental health court to determine treatment, Jodi, being a law student, starts to question the psychiatrist. She is well versed in the requirements that are needed for involuntary medication, and she insists on cross examining the psychiatrist, despite the judge advising her to defer to her attorney.

In such a case, a law student who is knowledgeable about the legal system would do well on scoring instruments. However, in undergoing a thorough CST evaluation, the evaluator would realize that the defendant is paranoid and likely unable to assist in her own defense despite having a strong factual base of knowledge.

Concluding thoughts

This case illustrates that an intellectual disability does not automatically equate with incompetence. Prior experience in the legal system would be an important factor in this case. The defendant had repeated exposure to the system, giving him a lot of practical experience. As such, it is likely that he would be competent to stand trial, even though he has an intellectual disability.


To illustrate how critical the clinical evaluation is in CST evaluations, and that a clinical evaluation cannot be replaced by a competency assessment instrument, consider the following case.

“Tony” is a 25-year-old man who has been in and out of the legal system since he was a teenager. He was not a high school graduate; he dropped out in the middle of tenth grade as he no longer wanted to go to school. He successfully worked with his attorney on several other misdemeanors, both in family court as a juvenile and in the criminal court system as an adult. He has never served time, as he always managed to get probation.

Tony violates a no contact order, and because of his history of intellectual disability, his competency to stand trial is questioned. After an evaluation, including a clinical evaluation and the CAST-MR, it is clear that he has an understanding of the charges and their potential consequences. Plus, as a result of years of experience in the court system, Tony also has a good handle on the trial process. He tells you that he is interested in accepting a deal, because it will allow him to avoid going to jail. Tony further explains he would prefer to admit to some form of guilt to be quickly paroled so that he can see his newborn child.

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Table 2. Common Competency Assessment Tools

<table>
<thead>
<tr>
<th>Tool</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAI</td>
<td>Competency Assessment Instrument, 13 areas of functioning, takes about 1 hour, scoring not standardized</td>
</tr>
<tr>
<td>GCCT</td>
<td>Georgia Court Competence Test, 21 items that fall into 3 domains, takes about 10 minutes</td>
</tr>
<tr>
<td>CAST-MR</td>
<td>Competence Assessment for Standing Trial for Defendants with Mental Retardation, 50 questions</td>
</tr>
</tbody>
</table>
being unable to admit IST defendants for CR services in a timely fashion. Better collaboration between the criminal justice and clinical care systems could improve services for persons with serious mental illness in the legal system.3,10,11

Dr Wall is a clinical psychiatrist, treating patients in the Providence, Rhode Island area. He is also a clinical professor at Brown University and provides expert witness consultations for medical-legal purposes. Dr Lee is clinical assistant professor of psychiatry at Brown University, and is the assistant program director of the Forensic Psychiatry Fellowship and assistant director of the forensic service at Slater Hospital, Rhode Island’s only state hospital.

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REFERENCES
Diagnosis
The gold standard instrument for assessing psychopathy is the Hare Psychopathy Checklist Revised or PCL-R. In the forensic setting, performance of the PCL-R is accompanied by extensive collateral investigation, psychiatric interview, and review of the individual’s medical, social, and criminal history. There is also a screening version of the PCL-R, the PCL-SV, which can be performed outside of the specialized forensic setting (Table). The PCL-R and its derivatives have demonstrated good interrater reliability and can potentially be useful when leveraged by objective and ethical evaluators who are trained to interpret the instruments and to provide honest and impartial professional opinions. However, concerns have been raised about the susceptibility of the tests to bias when performed by individuals who lack this expertise. These tools have also exhibited wide variability in their ability to predict future violence and their use in the assessment of risk must be approached with caution. There are significant ethical concerns regarding the potential misuse of these tests in legal and clinical decision making when the fate of an individual’s liberty or the safety of others is at stake.14,15 While the items in the PCL-R and PCL-SV may help guide formulation, the diagnosis of psychopathy in the general outpatient setting must be made carefully and only with substantial amounts of data gathered through the physician-patient relationship over time.

The differential diagnosis for psychopathy includes a personality disturbance due to another mental illness or physical condition. For example, individuals with frontotemporal dementia may present with impulsive behavior and an apparent lack of regard for others. Autism spectrum disorders may also present with impaired mentalization and apparent lack of empathy. Psychotic illnesses may produce a flattened affect with the appearance of shallow or blunted emotional responses. Patients who are dependent on a substance may exhibit manipulativeness and recklessness when their disorder is uncompensated and, then improve when receiving appropriate treatment.

The concept of psychopathy in pedi atric patients is complex and controversial. Psychopathy is similar to other personality disorders in that it is not diagnosed prior to adulthood, due to the fluidity of personality traits during early development and the inability to predict which children will go on to develop a disorder and which will not. Furthermore, multiple items in the adult diagnostic criteria are predicated on the patient having had sufficient years of life to fulfill them (such as parasitic lifestyle or multiple short-term marital relationships). Any assessment of psychopathic traits in a child or adolescent patient must be approached with extreme caution.

Treatment
A perilous belief once persisted in the scientific community that psychopathy was not only untreated, but that attempting to treat a psychopath was affirmatively harmful.16 While incarceration is the definitive “treatment” for some, psychopathy exists on a spectrum like any other mental disorder; more recent research suggests the condition is capable of responding to treatment.

“While incarceration is the definitive ‘treatment’ for some, psychopathy exists on a spectrum like any other mental disorder; more recent research suggests the condition is capable of responding to treatment.”

Table. Items in the Screening Version of the Hare Psychopathy Checklist-Revised (PCL-SV)

<table>
<thead>
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<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Superficial</td>
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<tr>
<td>2</td>
<td>Grandiose</td>
</tr>
<tr>
<td>3</td>
<td>Deceitful</td>
</tr>
<tr>
<td>4</td>
<td>Lacks remorse</td>
</tr>
<tr>
<td>5</td>
<td>Lacks empathy</td>
</tr>
<tr>
<td>6</td>
<td>Does not accept responsibility</td>
</tr>
<tr>
<td>7</td>
<td>Impulsive</td>
</tr>
<tr>
<td>8</td>
<td>Poor behavioral controls</td>
</tr>
<tr>
<td>9</td>
<td>Lacks goals</td>
</tr>
<tr>
<td>10</td>
<td>Irresponsible</td>
</tr>
<tr>
<td>11</td>
<td>Adolescent antisocial behavior</td>
</tr>
<tr>
<td>12</td>
<td>Adult antisocial behavior</td>
</tr>
</tbody>
</table>

Items are assigned scores 0 (does not apply), 1 (somewhat applies), or 2 (definitely applies), with a score > 18 considered indicative of psychopathy. Adapted from: Hare et al. (1990).

Dr Saleh is a child & adolescent and forensic psychiatrist. He is the director of the Sexual Violence Prevention & Risk Management Program at Beth Israel Deaconess Medical Center, and a Harvard Medical School faculty. His forensic practice focuses on criminal and civil cases including sex offender, threat, competency, and criminal responsibility assessments. Dr Burton is the fourth year psychiatry resident at Beth Israel Deaconess Medical Center in Boston, MA. She will be participating in the forensic psychiatry fellowship program at the University of Massachusetts Medical School.

REFERENCES
Presidential Election Anxiety

How might mental health professionals potentially assess and address this “election anxiety”? 

Election anxiety polls

The polls confirm our intuition: we are a nervous nation. Earlier this year, the American Psychological Association conducted a “Stress in America” survey, in which they found more than half (about 56%) respondents identified the 2020 election as a significant stressor. At the end of June, the Centers for Disease Control reported that the highest rising levels of anxiety were among young adults, as well as black and Latino people of all ages. The prevalence of anxiety symptoms among all populations was 3 times higher than the corresponding period in 2019.1

Certain groups of minorities, especially educated and higher-earning black males, are at risk for more anxiety.2 Of course, these sources of anxiety may be related to the higher implicit bias of white men.3

Anxiety also seems to differ along partisan party lines. About two-thirds of recent Joe Biden supporters say they are scared about the country’s future, compared to about one-third of President Donald Trump’s supporters.4 Of course, these sources of anxiety can change, and change quickly, depending on societal developments.

In our Psychiatric Times polls (Figures 1 and 2) inquiring about the upcoming elections, the trend was clearly slanted toward being very worried, with about half of respondents doing something productive about it and half not. As far as our patients are concerned, the second poll suggested a similarly strong degree of concern. If these trends hold up, the anxiety level would be even higher in our psychiatric world than in the greater society.

Varieties of anxiety

Anxiety refers to a prolonged state of apprehension brought on by uncertainty about future threats. Past threats logged in our memories and unconscious can also influence our view of upcoming risk. As such, anxiety is a natural emotion and vital for survival. In contrast to anxiety, fear is an acute or phasic response to an immediate and identifiable threat, as we explained in a prior article for Psychiatric Times titled “FDR, the Bene Gesserit, and the Psychiatry of Fear.”5

Figure 1. Psychiatrist Anxiety About the Upcoming Elections

I am very worried, and I am doing something about it 43%
I am very worried, but I am not doing anything about it 39%
I am concerned, but not terribly so 12%
I pay no attention to politics 4%

Figure 2. Patient Anxiety About the Upcoming Elections

My patients are very concerned 78%
My patients do not seem to be bothered or concerned 9%
I do not know; I avoid this topic 12%

Perception is a key for both anxiety and fear because the threat can be an imagined one. If anxiety is punctuated by acute episodes of fear, such as fear-mongering political campaign ads, it can feel like a one-two punch to our sense of security.

The physical and psychological symptoms of anxiety, such as feeling tense or having trouble concentrating, can be so uncomfortable that they cause behavioral changes. Fight or flight stress responses range from avoidance to aggression, as well as self-medicating with alcohol and street drugs. Peaceful protests in presidential elections can reflect a normal and appropriate expression of anxiety, such as is emerging virtually with the “Rage Moms,” who are fed up with being teacher, caregiver, employee, and parent all at the same time. When protests turn into riots, however, they may be a reflection in part of too much anxiety, an overreaction to perceived threats. Similarly, police may have appropriate anxiety for their role and risk, or not.

There are several kinds of anxiety. Given the power of the presidency, a presidential election may tend to elicit anxiety about one’s very existence and the meaning of one’s life. That is called existential anxiety.6

Figure 1. Psychiatrist Anxiety About the Upcoming Elections

Individuals who are more intolerant of uncertainty are especially vulnerable to excessive anxiety.7 The brain correlate of this intolerance is an increase in striata volume, particularly in the putamen. One brain model of subclinical and clinical anxiety is the uncertainly and anticipation model.8 This is a feedback model, in which there is either a disrupted cognitive estimation of probability and cost of a future threat, or heightened subjective feelings about negative future events. That is a feedback model suggests why it is difficult to stop until neuroplasticity develops new anxiety pathways.

Although many individuals are overly anxious, others may not be anxious enough given the circumstances. They suffer from inadequate anxiety. Inadequate anxiety can lead to ignoring various risks and, in this case, not voting. Those individuals who have sociopathic tendencies tend to have less anxiety, which in turn may allow them to manipulate individuals with higher anxiety levels.9

If there is an appropriate amount of anxiety, it would be an amount proportionate to the assessment of future danger, which in itself is difficult to predict and may change over time. Therefore, appropriate anxiety is a moving target. It needs regular monitoring and recalibration.

The deep history of anxiety

Anxiety has apparently persisted over human history, indicating that it has an important evolutionary role. Simply put, the evolutionary advantage of anxiety could be that it leads individuals to take fewer risks, seek safety, and focus on doing things well. On the other hand, anxiety can limit the risk-taking that advances human adaptability.

In terms of evolutionary psychology, anxiety would help us survive as a species. One way that anxiety can do this is to organize our cognitive functions quickly in response to danger. Additionally, another thesis is that chronic anxiety can be a driver of genius.10 Anxiety can also be a negative reinforcer that encourages the socialization necessary for survival and reproduction, because anxiety is generally most intense when we are isolated.11

A history of election anxiety

Reviewing some historical elections may be informative, and perhaps reassuring, as we approach this upcoming election.

A clear parallel can be drawn between our upcoming election and the election of 1920. It was during another devastating pandemic, the so-called “Spanish flu” that began in 1918. (President Trump’s grandfather died of this flue.) The worst of it was over by 1920, and the Republican nominee, Warren Harding, ran and won on a “return to normalcy” platform. His message resonated with the electorate, and he seemed to reduce the public’s fears. He was viewed positively while president but died only about 2 years into his term. Soon after he died, his reputation fell amid multiple scandals, stemming from his habit of giving government jobs to friends.

Our society today is split along ideological, racial, and class lines. The same was true during the election of 1968. On March 31, 1968, President Lyndon Johnson announced that not only was he partially halting the United States bombing of Vietnam, but also that he would not seek the nomination for president. Although his withdrawal offered hope for reconciliation, that dissipated quickly. Only 5 days later, Martin Luther King Jr was killed. Only a couple of months after that, Robert F. Kennedy, who was running for the Democratic nominee, was murdered. The nomination of Hubert Humphrey occurred during a violent, conflictual convention in Chicago. Richard Nixon won the presidency with a law-and-order message and a (secret) plan to end the war in Vietnam. Nixon knew what millions of Americans were worried about, and he promised to eliminate the sources of their fear.

Another election that has a lesson to teach us is 1980. The incumbent, Jimmy Carter, was defeated in part because the economy was awful, which caused increased anxiety and unhappiness. In his infamous “crisis of confidence” speech, he tried to address the nation’s concerns, but the voting public concluded that President Carter was in over his head. Similarly, the COVID-19 pandemic has adverse...
ly affected our economy, although it remains to be seen if the electorate will hold the president accountable.

The concern about the economy also brings us to the picture. High unemployment levels contributed to Herbert Hoover’s landslide defeat. Franklin Delano Roosevelt led the recovery with federal work projects and mobilization for World War II. In his inaugural address, Roosevelt told Americans that they had “nothing to fear but fear itself.” He was effective because he at once calmed the nation’s nerves and tackled the underlying sources of its anxiety: poverty, unemployment, and hunger.

For psychiatrists in particular, perhaps the most anxiety-provoking election was in 1964. Answering a poll conducted by FiC magazine on whether Barry Goldwater was mentally fit to be president, about half of the replying psychiatrists provided what Freud would call “wild analysis.” Goldwater sued the magazine, won his case, and psychiatrists were embarrassed. The result was the 1973 Goldwater Rule, set by the American Psychiatric Association. The rule barred psychiatrists from diagnosing or analyzing a public figure, an admonishment stirring anxiety and debate among psychiatrists in our time.14 Goldwater lost the 1964 election to Johnson in part because the electorate feared he might overreact to a perceived Russian threat and start a nuclear war.

In the 2016 election, our Psychiatric Times poll found that two-thirds of responders preferred Hillary Clinton. We had a comment section then, and the discussion was passionate, suggesting some intense underlying anxiety in the mental health professional community.

Although less attention is given to vice presidents and vice-presidential nominees, they can make a difference, and their influence is not lost on voters or candidates. For instance, George McGovern initially added Thomas Eagleton as his vice president on the 1972 ticket. Upon learning that Eagleton had clinical depressive episodes, McGovern consulted with psychiatrists who apparently advised him that a recurrence of depression was possible and could endanger the country.2 As a result, McGovern dropped him from the ticket. Interestingly, Eagleton went on to be reelected to the senate and achieved other career successes, and McGovern lost in a landslide. McGovern may have been too anxious about Eagleton’s depressive episodes, which may have cost him the seat. And, as we psychiatrists know, recurrence may be a risk, but it is not a good reason to think an individual is incapable of serving in a public office.

The vice president can represent other personal qualities that are important to the public. Joe Biden, Donald Trump, and Mike Pence are all older white males. In contrast, Biden chose Kamala Harris as his running mate. In picking a woman who is the child of Indian and Jamaican immigrants, he may be trying to assure the younger and more ethnically diverse parts of the electorate that he shares their concerns with racism, sexism, and other forms of discrimination.

Looking back on this historical survey, it appears that Americans reward politicians who are able to acknowledge their anxieties and put forth credible plans to eliminate the sources of their fears. Politicians who appear to be overly anxious, or blithely unconcerned, fare poorly.

Potential interventions

Although you will not find “election stress disorder” in DSM 5, it has been described.14 This “disorder” leads to all-or-nothing thinking and defense mechanisms of blame, denial, and avoidance. These reactions can lead to cult-like, brainwashed adherence to a one-sided perspective. Should you or your patients feel overwhelmed or anxious, many of the traditional behavioral approaches may prove to be helpful (Table). We need to be especially cognizant of countertransference, reactions where our own anxiety and political beliefs intrude into the therapeutic arena.

After the election, another informal disorder may emerge: a so-called post-election stress disorder. This phrase was first coined when President Obama was elected as a result of conflict and rising anxiety, especially around the issue of race.21 Therefore, it was not surprising to see some post-election emotional fallout and backlash regarding the country’s first Black President. Did those reactions last and influence the election of President Trump?

Whatever the case, the period after the 2020 election may be more anxious still. There are already widespread fears of voter suppression, voter fraud, and delayed results. Post-election anxiety could escalate even more than in 2000, when a controversial Supreme Court decision ended the Bush-Gore race.

The role of psychiatry

At least going back to the time of Plato, philosophers have tried to reduce the role of emotions such as anxiety in politics and promote rationality alone.1 Given the importance of anxiety in our evolution, psychiatry should not be surprised at the limitations of that approach. Of course, undo anxiety about safety and security leads to vulnerability, a propensity to being manipulated instead of educated. Recent polls indicate that such groups as young adults, Blacks, and Latinos are becoming increasingly anxious, likely due to uncertainty about their future. Particular attention needs to be paid to the well-being of these groups in terms of family and community psychological support, which in turn can make them more resilient.

Charismatic leaders more concerned with themselves and their public image than with the public good are particularly problematic. With our 2-party system, political leadership can change suddenly, and the losing party is often afraid of what will happen to them under the new regime. Leadership for all is necessary to reassure the losing side that it does not need to panic or lash out.

Anxiety is an essential emotion that can help us assess and respond to future risks to our safety and security, a basic human psychological need as Maslow has taught us.14 However, to use anxiety successfully, people need to be able to assess risks rationally. Although the future is unknowable, educated estimates can still be made—if there are accurate information and facts. One of the psychiatric lessons from the Spanish flu and the public panic that accompanied it was the need for the government to be honest and open.21

Since psychiatry has expertise in distinguishing fantasy from reality, as well as managing anxiety, we are essential for making presidential anxiety useful, rather than harmful for the public, patients, and for ourselves. Our Psychiatric Times polls indicate that both we and our patients are quite worried, with the good news that about half of us are already trying to do something productive about it.

The role of psychiatry in politics has been limited by the Goldwater Rule against commenting on public figures that we have not evaluated. As a result, psychiatry has retreated to the margins of the political arena. How might psychiatrists play a larger, more productive role in American public life? Psychiatrists could be involved in routine mental health assessments of any presidential candidate and annually for the president. Additionally, there is no prohibition against educating the public and our patients about the role of anxiety in politics. Psychiatrists could help their fellow citizens hit the sweet spot of anxiety: enlightened participation, voting, realistic hope, and improved mental well-being. In fact, it is psychiatry’s ethical responsibility to contribute what we can “to the improvement of the community and the betterment of public health.”22

Concluding thoughts

Psychiatric Times has featured a series looking at the psychiatric challenges for the 2020’s, and it now seems that politics and psychiatry will be one of them. This is one of the social aspects of psychiatry.23 There are 2 more elections scheduled during this decade. Just like finding the right amount of anxiety, we need to find the right amount of political engagement, not too much and not too little, in the 2020s.

Dr Moffic is an award-winning psychiatrist who has specialized in the cultural and ethical aspects of psychiatry. A prolific writer and speaker, he received the one-time designation of being a Hero of Public Psychiatry from the Assembly of the American Psychiatric Association in 2002. He has recently been leading Tikun Olam advocacy movements on climate instability, burnout, Islamophobia, and Anti-Semitism for...
13. Dickinson MJ, Fava EA. Anxiety and depression may have an evolutionary role as negative reinforcers, encouraging socialization. Medical Hypotheses. 2006;66(6):796-800.
Mental Health Pandemic

Continued from Cover

without an established diagnosis. So, yes, many folks are indeed suffering. All this has led many outlets and even some psychiatrists to declare a “mental health pandemic” or “secondary pandemic” amidst the already devastating COVID-19 pandemic. I found about 145,000 results, searching the term "mental health pandemic" on Google. Indeed, several respected mental health professionals have taken to using this linguistically awkward term. Ironically, mental health pandemic understood in epidemiological terms would mean something like “a worldwide outbreak of mental health.” While well-intentioned, the casual and colloquial use of the term pandemic is not warranted in this context.

Tardive Dyskinesia (TD): Risk of TD and the likelihood that it will become irreversible increases with the duration of treatment and the cumulative dose of antipsychotic drugs, including SECUADO. TD can develop after relatively brief treatment periods, even at low doses, and may also occur after discontinuation of treatment. Prescribe SECUADO in a manner most likely to reduce the risk of TD. If signs and symptoms of TD appear, drug discontinuation should be considered.

Metabolic Changes: Atypical antipsychotic drugs, including SECUADO, have caused metabolic changes, including the following:

• Hyperglycemia and Diabetes Mellitus: Hyperglycemia, in some cases associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics. Hypoglycemia has been reported in patients treated with sublingual asenapine. Assess fasting plasma glucose before or soon after initiation of treatment, and monitor periodically during long-term treatment.

• Dyslipidemia: Atypical antipsychotics cause adverse alterations in lipids. Before or soon after initiation of antipsychotic medication, obtain a baseline fasting lipid profile and monitor periodically during treatment.

• Weight Gain: Weight gain has been observed with atypical antipsychotics, including SECUADO. Monitor weight at baseline and frequently thereafter.

Hypersensitivity Reactions: Hypersensitivity reactions, including anaphylaxis, angioedema, hypotension, tachycardia, dyspnea, wheezing, and rash have been reported in patients treated with asenapine, including SECUADO. In several cases, these reactions occurred after the first dose.

Orthostatic Hypotension, Syncope, and Other Hemodynamic Effects: Atypical antipsychotics cause orthostatic hypotension and syncope. The risk is greatest during the initial dose titration and when increasing the dose. Monitor orthostatic vital signs and patients who are vulnerable to hypotension. Use SECUADO cautiously with other drugs that can cause hypotension, bradycardia, respiratory or central nervous system depression. Consider a dose reduction if hypotension occurs.

Figure. Mental Health Symptoms During COVID

During late June, 40% of US adults reported struggling with mental health or substance use*

ANXIETY/DEPRESSION SYMPTOMS 31%
TRAUMA/STRESSOR-RELATED DISORDER SYMPTOMS 26%
STARTED OR INCREASED SUBSTANCE USE 13%
SERIOUSLY CONSIDERED SUICIDE† 11%

*Based on a survey of US adults aged ≥18 years during June 24-30, 2020
†In the 30 days prior to survey

SOURCE: CDC.gov
Of course, I understand that the intention underlying the term is to highlight a worldwide upsurge in mental health issues and symptoms, which is a valid concern. But problems often arise when we co-opt terms and apply them to psychiatry. For example, the same casual misuse of epidemiological terms has been commonly used in the popular press for years when referring to various “epidemics” of psychiatric illness in the United States—even though no credible evidence ever supported that bogus claim.3 And this is more than a semantic quibble. The use or misuse of language can have powerful effects on the public’s beliefs and perceptions—witness the benevolent effects of the “schizophrenogenic mother” or “chemical imbalance” tropes.6

Let us back up a bit and explore the definitions of these terms. An epidemic refers to an increase, often sudden, in the number of cases of a disease above what is normally expected in that population in that area. A pandemic refers to a disease epidemic that has spread over several countries or continents, usually affecting a large number of people.7 The critical term here is disease, and the critical point is that self-reported symptoms obtained from a screening survey do not establish the presence of a psychiatric disease, illness, or disorder. Many people can experience a new onset of—or an increase in—one or more symptoms of anxiety or depression, but not meet clinical criteria for a psychiatric disorder.

Upon careful, clinical evaluation, such self-reported symptoms may or may not turn out to be a clinically significant disease or mental illness. The CDC report itself notes this limitation of its survey, stating “a diagnostic evaluation for anxiety disorder or depressive disorder was not conducted.”8 Consider the diagnosis of generalized anxiety disorder (GAD). According to the DSM-5, symptoms must be present for at least 6 months—so no one who responded to the CDC sur-

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**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 leukopenia or neutropenia. Discontinue SECUADO at the first sign of a clinically significant decline in WBC and in severely neutropenic patients.

QT Prolongation: Sublingual asenapine was associated with increases in QTc interval from 2 to 5 msec versus placebo. There were no reports of QT prolongation exceeding 500 msec for SECUADO and placebo. Use SECUADO should be avoided in patients with a history of cardiac arrhythmias and in circumstances that may increase the risk of the occurrence of torsade de points 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).

Dry mouth: 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 wear 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.

Adverse Reactions: Commonly observed adverse reactions (incidence ≥5% and at least twice the rate of placebo) were extrapyramidal disorder, application site reaction and weight gain.

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 CYP1A2 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. Although antipsychotics are not thought to affect the fetus at therapeutic doses, caution should be exercised when antipsychotics are used during pregnancy. For more information, contact 1-866-980-2388 or getnews@noven.com.

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.


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SDD-2024-R1 1/20
vory in June 2020 would have met that criterion if their anxiety symptoms began, say, in March 2020. Furthermore, DSM-5 criteria for nearly all the major disorders require that the person demonstrates “clinically significant distress or impairment in social, occupational, or other important areas of functioning.”

Experiencing an uptick in some symptoms of anxiety or depression does not necessarily mean that you have reached that distress-meaning impairment threshold—much less, that you have a mental disorder. The difference between symptoms and disorder is not merely semantic. A formal, clinical diagnosis of a mental disorder has wholly different implications—medical, legal, and psychological—than those associated with, say, normal or adaptive response to the stress and strain of the COVID-19 pandemic.

The nebulous term depression may be misleading when considering many emotional reactions to the pandemic. I suspect—although I cannot prove—that many of the responders were reporting symptoms reflecting understandable demoralization and grief—and these are not mental disorders. On the contrary, as psychologist John F. Schumaker* has elegantly put it, demoralization is “an overarching psycho-spiritual crisis in which victims feel generally disoriented and unable to locate meaning, purpose, or sources of need fulfillment.” And grief, of course, is a normal, adaptive reaction to life’s “slings and arrows” and its manifold, painful losses.**

In my experience, only a careful clinical evaluation could distinguish profound demoralization and grief from major depressive illness among the CDC survey respondents. Screening instruments like the 4-item Patient Health Questionnaire (PHQ-4)—used in the CDC survey—simply cannot do the job.

None of this is to minimize the mental health challenges posed by the COVID-19 pandemic. Individuals

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with established psychiatric diagnoses (e.g., posttraumatic stress disorder, schizophrenia, or bipolar disorder) may be experiencing serious, pandemic-related exacerbation of their illness, and they may require immediate treatment or refinement of their current treatment. There is also strong, emerging evidence that COVID-19 may lead to severe and enduring neurocognitive complications.12 Care and treatment of these seriously affected individuals should be our priority. We must also carefully monitor the long-term psychological effects the pandemic may have on children and adolescents.13 Finally, we must remain vigilant regarding the numerous psychological and emotional toll the pandemic is taking on our physicians, nurses, and other frontline health care workers.14

And, let me clarify: the mere fact that someone may not meet full DSM-5 criteria for a mental disorder does not mean that the person is unprofessional or in need of mental health care. We undervalue insurance coverage for, say, telemedicine counseling. We know, for example, that subclinical depression—i.e., falling just short of the threshold for major depression—can nevertheless be a disabling condition that needs treatment, and may respond to psychotherapy.14 So, no—the term mental health pandemic is not really helpful or accurate. But that observation does not negate the distress and loneliness of so many who are enduring the COVID-19 pandemic, nor should it diminish our efforts at comforting and supporting them.

**Dr Pies is professor emeritus of psychiatry and director of the Center for Ethics in Psychotherapy and the Law.**

**Acknowledgments** — I wish to thank

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**Table 1: Adverse Reactions in <0.2% of Patients in Key SECUADO Dose Groups and With Occurrence at an Uncommon Rate in the Possible Group in Key Schizophrenia Trials**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo</th>
<th>3.8 mg/24 hours</th>
<th>7.6 mg/24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>4 (1.7%)</td>
<td>4 (3.1%)</td>
<td>4 (2.9%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (1.7%)</td>
<td>4 (3.1%)</td>
<td>4 (2.9%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8 (3.9%)</td>
<td>10 (7.6%)</td>
<td>10 (7.6%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>0 (0.0%)</td>
<td>2 (1.5%)</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

**Systemic Drug Class** | **Commonly Observed Adverse Reactions** | **Other Adverse Reactions Reported in Clinical Trials with Sublingual Asenapine** | **Other Adverse Reactions Observed During the Premarketing Evaluation of SECUADO**

- **Cardiovascular Disorders**:
  - **Hypertension**:
    - Blood pressure increased, diastolic hypertension
    - Hypertensive crisis
  - **Angina pectoris**:
  - **Arrhythmias**:
    - Atrial fibrillation
    - Atrial flutter
  - **Congestive heart failure**:
  - **Stenosis of coronary artery**:
  - **Myocardial infarction**:
  - **Cardiac dysrhythmias**:

- **Respiratory Disorders**:
  - **Respiratory depression**:
  - **Respiratory arrest**:
  - **Aspiration**:

- **Central Nervous System Disorders**:
  - **Seizures**:
  - **Dizziness**:
  - **Paroxysmal dyskinesia**:

- **Gastrointestinal Disorders**:
  - **Diarrhea**:
  - **Nausea**:

- **Skin and Appendages**:
  - **Urticaria**:
  - **Eczema**:

- **Metabolism and Nutrition Disorders**:
  - **Insulin resistance**:
  - **Hypoglycemia**:

- **Neurological Disorders**:
  - **Paranesthesia**:
  - **Paresthesia**:

- **Ophthalmic Disorders**:
  - **Blurred vision**:
  - **Night blindness**:

- **Endocrine Disorders**:
  - **Gynecomastia**:
  - **Premenstrual syndrome**:

- **Genitourinary Disorders**:
  - **Renal abnormalities**:
  - **Urinary retention**:

- **Other Adverse Reactions**
  - **Dyspepsia**:
  - **Vomiting**:

**Table 2: Changes in Fasting Glucose in Adult Patients in the 6-Week, Placebo-Controlled, Fixed Dose Schizophrenia Trial**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Endpoint</th>
<th>Change (Mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>5.9 ± 0.3</td>
<td>6.3 ± 0.2</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>3.8 mg/24 hours</td>
<td>5.7 ± 0.3</td>
<td>7.0 ± 0.2</td>
<td>1.3 ± 0.1</td>
</tr>
<tr>
<td>7.6 mg/24 hours</td>
<td>6.0 ± 0.3</td>
<td>7.9 ± 0.2</td>
<td>1.9 ± 0.1</td>
</tr>
</tbody>
</table>

**Table 3: Change in Body Weight in Adult Patients from Baseline in the 6-Week, Placebo-Controlled, Fixed Dose Schizophrenia Trial**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Endpoint</th>
<th>Change (Mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>70.5 ± 10.5</td>
<td>73.5 ± 10.5</td>
<td>3.0 ± 1.0</td>
</tr>
<tr>
<td>3.8 mg/24 hours</td>
<td>69.5 ± 10.5</td>
<td>75.0 ± 10.5</td>
<td>5.5 ± 1.0</td>
</tr>
<tr>
<td>7.6 mg/24 hours</td>
<td>70.0 ± 10.5</td>
<td>80.0 ± 10.5</td>
<td>10.0 ± 1.0</td>
</tr>
</tbody>
</table>

**Table 4: Changes in BMI at Baseline and Endpoint in Adult Patients in the 6-Week, Placebo-Controlled, Fixed Dose Schizophrenia Trial**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Endpoint</th>
<th>Change (Mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>23.0 ± 3.0</td>
<td>25.5 ± 3.0</td>
<td>2.5 ± 0.5</td>
</tr>
<tr>
<td>3.8 mg/24 hours</td>
<td>23.0 ± 3.0</td>
<td>27.5 ± 3.0</td>
<td>4.5 ± 0.5</td>
</tr>
<tr>
<td>7.6 mg/24 hours</td>
<td>23.0 ± 3.0</td>
<td>30.0 ± 3.0</td>
<td>7.0 ± 0.5</td>
</tr>
</tbody>
</table>

**Table 5: Changes in ALT in Adult Patients from Baseline in the 6-Week, Placebo-Controlled, Fixed Dose Schizophrenia Trial**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Endpoint</th>
<th>Change (Mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>25.5 ± 7.5</td>
<td>32.5 ± 7.5</td>
<td>7.0 ± 1.0</td>
</tr>
<tr>
<td>3.8 mg/24 hours</td>
<td>26.0 ± 7.5</td>
<td>34.0 ± 7.5</td>
<td>8.0 ± 1.0</td>
</tr>
<tr>
<td>7.6 mg/24 hours</td>
<td>26.5 ± 7.5</td>
<td>37.5 ± 7.5</td>
<td>11.0 ± 1.0</td>
</tr>
</tbody>
</table>
**ADVERSE REACTIONS**

**Metabolic Changes**

Tardive dyskinesia, a syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic medication, and monitor periodically during long-term treatment.

**A dyskinesia syndrome may include the following symptoms:** dystonia, chorea, ballismus, tremor, myoclonus, abnormal movements, and gait disturbances. The syndrome may impair the ability to perform daily activities.

**Serious,...**

**Other possible adverse reactions include:** 
- Peripheral edema
- Constipation
- Dry mouth
- Hypertension
- Hypotension

**Safety and effectiveness of SECUADO in pediatric patients have not been established.**

**Infections and Infestations**

Infections have been reported in patients treated with SECUADO.

**Fetal/Neonatal Adverse Reactions:**

Patients who are planning a pregnancy or who become pregnant should not use SECUADO. If a patient becomes pregnant while taking SECUADO, she should be advised to discontinue SECUADO and use an alternative method of contraception. Her healthcare provider should be advised of the potential for drug exposure to the fetus.

**Neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately.**

**Fetal/Neonatal Adverse Reactions:**

The risk of adverse effects in the neonate is not known. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies. The risk associated with SECUADO cannot be directly compared with the risk of other antipsychotic drugs because there are no comparable data from trials in pregnant women. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

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What to Do When Being There Means Being Vulnerable

Eva C. Ihle, MD, PhD

In the early days of the shelter-in-place edict that was established in the San Francisco Bay Area in response to the COVID-19 pandemic, there was some debate about whether clinical services for patients with psychiatric illness were “essential.” The department of psychiatry at my home institution installed a COVID-19 Task Force for patient care, appointed by departmental leadership and composed of clinicians, researchers, and administrative staff. A remarkable number of departmental meetings were held to eventually conclude that patients with psychiatric symptoms could still receive care from behavioral health clinicians, psychiatrists included, who were now expected to be working from home, even though it has been argued that psychiatry is an essential medical service and should be delivered in person if and when necessary.1 The strategy adopted for accomplishing this goal in the outpatient setting was conversion of all office-based appointments to telehealth visits on a secure internet platform.

The deliberation was more complicated and the decisions more controversial (and less universally adopted) in the hospital setting, for patients, both children and adults, who were psychiatrically hospitalized, or who were receiving care in general medical (non-psychiatric) hospitals and had psychiatric symptoms and/or comorbid psychiatric illness that required consultation-liaison psychiatric care. Directives from departmental leadership were rapidly evolving in the first few weeks of shelter-in-place, and included such decisions as not psychiatrically hospitalizing any patient aged 60 years or older or not having psychiatry residents interact directly with patients in emergency rooms. Fortunately, directives such as these were quickly revised, presumably through an iterative process between clinicians and leadership. What took longer to establish were the policies for providing psychiatric consultation-liaison (C/L) service to medically hospitalized patients. These policies were hospital-specific and ultimately diverged on the basis of the philosophies held by the leaders of the respective C/L services. Each university-affiliated hospital was tasked with developing the protocols that would allow for consultations to be provided while taking into account the patient’s COVID-19 status. The solution that was adopted by the psychiatry C/L services of the 2 hospitals where I attend (a university-affiliated tertiary care center and a public safety net hospital) was a version of remote consultation via telehealth.

Most medical specialists who were still providing care and meeting the expectation of social distancing and infection control protocols in these hospitals embraced this technologic solution. Arguments in favor of this version of consultation were made to suggest that the quality of remote consultation would be adequate for the care provided. That may be true for straightforward cases. However, more often than not, there are cases that are far from straightforward, which diminuishes clinician efforts to use communication-enabling technology. The university hospital where I am an attending on the adult C/L service had years of experience with remote psychiatric consultation long before the COVID-19 pandemic. Our team provides consultation to multiple affiliated hospitals within the university health network but is headquartered in just one of them. From where we are stationed, our efforts to provide psychiatric consultations via technology have been and remain fraught with challenges, both technologic and patient-based. This experience demonstrated the shortcomings of being far afield from patients.

We are dependent on: the hardware and software functioning adequately; the hospital staff designated as “resource nurses,” who serve as our bridge to the patient by wheeling in the computer cart on which the technology runs and being present with the patient while our team engages with them; and our clinical acumen to detect subtle changes in facial expression, affect, and engagement on a small screen. These technologic factors are moost when patients refuse to interact with their consultant over the computer or to even consent to such an intervention. Even when patients consent to a virtual visit, there may be circumstances when their level of disorganization, paranoia, distractibility, agitation, or distress prevents them from interacting in a meaningful way with their consultant.

The experiences of the adult psychiatry C/L service described above informed the child and adolescent psychiatrists (CAPs) providing con-

Figure. Flowchart of Workflow and Decision Tree for Inpatient Psychiatric Consultations

(Daylight 8am-5pm, Weekdays) Inpatient C/L Service (Nighttime 5pm-8am, Weekends)

Embedded Child & Adolescent Psychiatrist

Non-urgent

Urgent

Emergent

Cross-Site Coverage

Curbside Consultation (with Peds MDs, NPs)

Telehealth Consult w/Pt

(no SI/HI or COVID-19+)

(+SI/HI, regardless of COVID-19 status)

In-Person Consult w/Pt

Behaviorally Appropriate and Verbal?

Nursing staff informs pt of impending Consult with Psych; wheels in iPad Cart (or ensures phone works)

Psychiatrist dons PPE and scrubs to engage directly with patient, caregiver

C/L Psychiatry completes consultation, communicates recommendations to consulting team, documents in chart
sultion to our different pediatrics units, but in different ways. At one site, the patients in the children’s hospital were evaluated through remote consultations using strict clinical criteria (altered mental status or suicidality if not COVID-19 positive) were met to justify in-person consultation (COVID-19 positive patients were not offered in-person psychiatric consultation). This algorithm required the primary pediatrics teams to engage with COVID-19 positive patients or their caregivers as a proxy for the CAPs (in the case of behavioral dysregulation or other symptoms that precluded the use of the telehealth device that the CAP C/L team relied on). Furthermore, the protocol did not accommodate patient preference. The COVID-19 negative patient confronting her cancer diagnosis had to engage with the team psychologist through a device and had to forego the opportunity for human contact.

The justification for remote consultation was the effort to minimize the number of staff exposed to COVID-19 and thus the likelihood of further contagion (presuming staff acted as vectors). However, the technology still needed human agents to manipulate it. Those humans were the same frontline staff who were expected to do the other tasks of patient care. Not only did this expectation suggest that their workload could be increased for the sake of supporting the CAP C/L team, but also that the safety of front-line staff could be forfeited for the safety of the consultants.

Another benefit that was touted was improved communication and/or collaboration between psychiatry consultants and primary teams. For those of us doing proactive consults, and those who are fortunate enough to be integrated into inpatient teams, communication to telehealth would have meant “retreating” from the frontlines and from our role as teammates. Instead, at the hospital where I am the CAP consultant to the inpatient Pediatrics unit, we developed a protocol (Figure) for conducting remote consultations for patients who were COVID-19 positive but not suicidal or homicidal to minimize interactions with the patient. We continued in-person consultations for everyone who was COVID-19 negative and “persons under investigation” (ie, patients whose test results were pending) or who were suicidal or homicidal (regardless of COVID-19 status). The difference between these circumstances would be the personal protective equipment (PPE) we would don (surgical masks and face-shields for COVID-19 negative patients; N95 respirators, face-shields, gowns, and gloves for COVID-19 positive patients). Of course, this protocol required the consumption of PPE.

Resources have been scarce, but hospitalized psychiatric patients are just as entitled to medical care as any other hospitalized patient, and those psychiatrists providing care need to be protected in the same way as other medical specialists. Physicians have always recognized that there are risks inherent in treating patients with medical illness, and we have accepted this risk as a hallmark of our professional duties.

The protocol that we developed recognized the importance of being present for the inpatient teams and the challenges that telepsychiatry can pose for our patients who are acutely (psychiatrically) symptomatic. The first patient I evaluated using this protocol was an adolescent manifesting symptoms of excited catatonia; she paced throughout her room during the entirety of the interview and could barely attend to me while in the room with her. It is highly unlikely that I could have engaged her and redirected her over a video monitor.

It came as no surprise that in response to the COVID-19 pandemic a number of remarkable policy changes occurred, perhaps more quickly than they otherwise would have. Several innovative programs arose at my home institution to meet the mental health needs of medical center staff; resilience and emotional well-being videos and webinars; self-care apps; family support programs; and direct assessment and treatment for faculty, staff, and trainees. What seemed to be missing from these efforts was comparable attention to the emotional and functional well-being of our patients with psychiatric illness.

It is becoming all too clear that additional support for the increasing mental health needs of patients, especially those with pre-existing psychiatric illness, will be necessary. So far, such support has been surprisingly limited. One program, our autism clinic, pivoted by establishing a virtual “coffee chat” support group function for the parents of patients with autism.

More data seem to be collected about the clinicians’ experiences of transitioning their services to telehealth platforms than the patients’ experiences of not being seen in person. Professional service organization list-servers have become repositories for institutional strategies for converting (in-person) inpatient C/L services to telehealth. Ambitious members of these organizations have constructed methods papers about these strategies.

Attention is slowly beginning to shift from the process of providing telehealth to its consequences, especially in the area of patient satisfaction and mental health care delivery. The consequences of these policy changes on the patients’ well-being are likely to be profound, and so far the impact of these changes on the needs of this vulnerable population has not been adequately explored. It makes no sense to deprive patients of the valuable service of our consultation if there are no clinical imperatives to do so. It can, of course, be a reasonable alternative to no care at all for patients who cannot access psychiatry through conventional means.

Technology is a fickle ally. It promises support but it fails short of authentic connection. In our efforts to open new vistas for consulting on medically hospitalized patients with psychiatric symptoms, we should not lose sight of what our duty to them was meant to be. Dedicating ourselves to the principles of social distancing may have resulted in the perceived abandonment of our patients. As our subspecialty comes to terms with the new normal of life in the post-COVID-19 era, it will be important to ensure that the emotional well-being of our patients is given at least as much attention as the mental health needs of our colleagues. Access to genuine care should not be relegated to virtual visits.

Dr Ilhe has no disclosures regarding the subject of this article.

Acknowledgements—Thank you to James Alan Bourgeois, OD, MD, for his support and mentorship, and to all of the physicians on the front lines providing medical care for patients during the COVID-19 pandemic.

REFERENCES

I Don’t Want to Die Here in Timbuktu

Richard M. Berlin, MD

I want to die in Gettysburg, PA

on the soft green flank of Little Round Top

where General Pickett led his charge.

I was happy there one afternoon

before I turned thirteen, the year

my father’s body launched its own Civil War,

trees glowing pumpkin and scarlet,

my mink-coated mother beaming

at her husband in his houndstooth jacket.

We were at peace, ten thousand dead

and thirty thousand wounded

as impossible to imagine as the carnage

my father would braze a few months later,

distant drums stirring the first steps

in my long march to become a doctor,

my battle to save him, a surgeon’s scalpel

trained on his belly like a bayonet.

Ihle is Health Sciences Clinical Professor in the Departments of Psychiatry & Behavioral Sciences and Pediatrics, Langley Porter Psychiatric Hospital and Clinics, UCSF Weill Institute for Neurosciences, University of California San Francisco, and Zuckerberg San Francisco General Hospital, San Francisco, CA. Dr Ilhe has no disclosures regarding the subject of this article.

Dr Berlin is Instructor in Psychiatry, University of Massachusetts Medical School, Worcester.
CASE STUDY

Documenting Recovery in Delusional Disorder With the MMPI-2

» Alan D. Blotcky, PhD

Delusional disorder is a major psychotic illness that is enigmatic and poorly understood. It is often difficult to treat because of the individual’s denial of a problem, difficulties in establishing a therapeutic alliance, and interpersonal and social conflicts. Unfortunately, many individuals with this disorder refuse treatment altogether. Available research suggests that 50% of patients who are adequately treated achieve a symptom-free recovery, while 90% of patients demonstrate at least some improvement. It has been found that persecutory delusions respond least well to treatment, with 50% improvement rates and no reports of complete recovery. Only a handful of studies have used objective outcome measures to evaluate patient improvement during treatment for delusional disorder. The best objective measure of patient recovery during treatment for delusional disorder is the Minnesota Multiphasic Personality Inventory-2 (MMPI-2). There have been hundreds of studies on the MMPI-2 and the treatment of psychiatric disorders. Up until now, there has been nothing in the literature that addresses the utility of the MMPI-2 in tracking or documenting treatment effects in delusional disorder.

This case illustrates the effectiveness of the MMPI-2 in documenting patient recovery during treatment for delusional disorder. Practical implications for psychiatrists and other mental health professionals are discussed.

“Mary,” a 42-year-old white female, temporarily lost custody of her 3 children to her ex-husband 18 months ago due to apparent psychotic-level functioning. I was appointed by the court to arrive at a definitive diagnosis and to provide appropriate guidance about her parenting abilities and custody status. (Mary, a pseudonym, has given written informed consent for her case to be included in this presentation. Identifying information about her has been altered to protect her privacy.)

Mary’s primary symptoms included both persecutory delusions and somatic delusions. Her delusions had been present for about 2 years. She believed that her colleagues at work were concocting a scheme to have her fired. She believed that her mother was not her biological parent. Mary also believed that drones were hovering over her home and that someone had installed a camera in her car to follow her. She reported unrelenting somatic symptoms that she attributed to an alien virus that had been planted in her water at home. Because of her delusional thinking, Mary had recently quit her job and was residing with her parents.

Prior to the onset of her delusions, Mary had obtained 2 master’s degrees and had a full-time position. She had a boyfriend, many friends, and her family relationships were intact. She was described as a smart and sweet person. She had been given primary custody of her 3 children at the time of her divorce 4 years earlier; it was not a highly adversarial divorce proceeding. She had no medical problems. She had no family history of psychosis or other psychiatric disorder.

Mary had been seeing a psychiatrist for several months prior to my involvement in the case; I obtained her records from him. Mary was described as having depression and anxiety. Psychosis was not noted. She was being treated with fluoxetine 20 mg and bupropion hydrochloride extended-release tablets 150 mg, but she was not improving. Mary had not divulged any delusional material to her psychiatrist.

Clinically, Mary was appropriately attired and well-groomed for her sessions with me. She wore make-up and jewelry. She was pleasant with me and made good eye contact. Mary’s cognitive abilities were intact. Her affect was slightly dysphoric but within normal limits. She was not manic or hypomanic. Mary’s delusions were prominent, and she had little or no insight into their nature and severity. She was also suspicious of me; she thought I might be involved in the conspiracy with her colleagues at work.

I asked Mary to provide a urine screen to rule out substance abuse. Her urine screen the same day was negative for illicit drugs.

Mary completed the MMPI-2, answering all 567 questions in 90 minutes. Her responses were scored on 3 validity scales, 10 basic clinical scales, and the PSY-5 supplementary scales.

Mary showed considerable distress but in the context of normal validity scales. She approached the test in an open and honest fashion. She did not exaggerate her symptoms. She was not defensive or guarded. Her responses were considered valid. She was to be believed.

Ten basic clinical scales were developed to assess different psychiatric conditions and symptoms. See Table below for a description of the...
Mary’s MMPI-2 after 4 months of treatment was remarkable as well. It indicates schizophrenia, Mary’s history reflects a significant cognitive disorder that requires the MMPI-2 as well. Mary’s MMPI-2 profile was consistent with that illness. In my view, Mary’s MMPI-2 profile was reflective of her persecutory delusions (scales 1 and 3), both components in her psychotic illness.

Supplementary scales are available on the MMPI-2 as well. Mary’s PSY-5 scales showed a significant elevation on the scale having to do with psychosis. This was corroborative of Mary’s history. Mary’s MMPI-2 test data, I diagnosed Mary with delusional disorder. Her delusional disorder was primary. She did not have a comorbid condition, such as bipolar disorder or schizophrenia. Mary did not have major depressive disorder or an anxiety disorder nor was she abusing alcohol or drugs.

No specific stressors were identified that contributed to the onset of Mary’s delusional disorder. However, she was feeling “pressure” from the law, her delusions had dissipated. PSY-5 scales were normal as well. All 10 basic clinical scales were normal; there were no suggestive signs of psychosis had dissipated. Mary’s delusions had remitted. She had no signs of psychosis had dissipated.

Mary completed the MMPI-2 again, and I obtained updated records from her psychiatrist. After 4 months on ziprasidone, Mary was remarkably improved. She was tolerating it well, and her delusions had remitted. She had developed important insight about her resolved delusions. They now seemed foreign and distant to her; they did not make sense to her. She could not even recall her suspiciousness about me. Mary’s affect was bright. She was talkative and expressive. She was appreciative of everyone’s concerns. Mary was looking for a full-time job and planned to get her own apartment.

Mary’s MMPI-2 after 4 months of treatment was remarkable as well. It was completely normal. Her validity scales were normal. All 10 basic clinical scales were normal; there were no significant elevations. In fact, there were no near-significant elevations. Her PSY-5 scales were normal as well. All signs of psychosis had dissipated.

Mary will be maintained on ziprasidone for the foreseeable future. She will have monthly to quarterly visits with her psychiatrist. Cognitive behavior therapy has been added to her treatment regimen, since it is regarded as a critical component in the maintenance of recovery. Mary’s legal case is closed to resolution. With her regained parenting abilities, the parties are approaching a compromised settlement.

**Discussion**

This case study illustrates many important clinical and practical points. Mary’s persecutory delusions and somatic delusions both abated with treatment. This result is consistent with the literature that reports that 50% of patients treated adequately achieve a symptom-free recovery. Delusional disorder in this case was treated successfully with antipsychotic medication (ziprasidone 20 mg). This finding is contrary to the data that suggest that persecutory delusions are recalcitrant. Mary did not have a comorbid condition, and the absence of comorbid conditions may make successful treatment of delusional disorder more attainable.

Overall, Mary’s recovery was likely due to a combination of the relatively short duration of her delusions (about 2 years), the lack of a comorbid condition, the use of an antipsychotic medication, the discontinuance of bupropion, and her high level of premorbid functioning.

The MMPI-2 proved to be a sensitive outcome measure in evaluating this patient’s improvement. Using the MMPI-2 at the time of diagnosis and later during treatment is an objective, data-driven way to assess a patient’s response to treatment. The MMPI-2 can be administered easily and is not overly intrusive.

### Available research suggests that

**50% of patients who are adequately treated achieve a symptom-free recovery, while 90% of patients demonstrate at least some improvement.**

**Concluding thoughts**

Lessons learned from this case study are clinically interesting, but only suggestive. Well-designed research is needed to study the proposition that the MMPI-2 is a highly effective instrument for evaluating treatment outcome in delusional disorder. Mary’s psychiatrist and I worked independently but in a cooperative fashion. This was quite helpful in facilitating Mary’s evaluation and treatment with minimal delays and roadblocks. The sharing of findings and conclusions between us led to an excellent result after much initial confusion.

Mary was fully adherent with her evaluation and treatment, whereas many patients with delusional disorder refuse treatment. Mary’s successful treatment was largely attributable to her therapeutic alliance with her psychiatrist and me. Her motivation to get well superseded any desire to resist intervention. Therapeutic alliance is a critical building block in adequate treatment.

Whether Mary will have a recurrence in her delusional disorder is unclear. Longitudinal research is needed to address the question of incidence recurrence in this specific illness. With other types of psychotic disorders, recurrences are often expected and even inevitable. As such, maintenance treatment in delusional disorder becomes extremely important. Treatment should include a combination of psychiatric medication and individual therapy.

The impact of psychotic disorders on child custody cases is a delicate matter. It should be recognized by all parties that a parent’s recovery from a psychotic disorder may be less than permanent. Child custody decisions need to be made with that psychiatric reality in mind. Maintenance treatment for the parent with a psychotic disorder is the vehicle by which parenting abilities can be regained and sustained.

**Dr Blotcky** is a clinical psychologist in private practice in Birmingham, Alabama. He is clinical associate professor, department of psychology, University of Alabama at Birmingham. Much of his clinical practice is devoted to forensic cases, including child custody, personal injury, and criminal cases.

**REFERENCES**

Managing Distress in Health Care Workers During COVID-19: Lessons From a Disaster Trauma Lens

Gertie Quitangon, MD

Coronavirus disease 2019 (COVID-19) blindsided the world. It exposed gaps in public health emergency planning at every level, including in the strategic planning to support mental health and wellness. Studies of the SARS and Ebola epidemics as well as natural disasters have taught us lessons about the importance of planning for and responding to the mental health needs of health care and frontline workers. Thus, this is a pivotal moment, a chance to implement systems and structures for staff support in every organization and advance staff wellness and resilience initiatives.

Disaster literature

The literature on disasters and public health emergencies describes pervasive emotional distress, feelings of extreme vulnerability, uncertainty, and threats to life, particularly during the rapid spread of an outbreak.1 A recent COVID-19 web-based survey supports this finding. More than 40% of respondents reported symptoms of depression, anxiety, traumatic stress, substance use, and suicidal ideation. Symptoms were notably exacerbated among older adults, essential workers, unpaid adult caregivers, and those with psychiatric conditions. Fortunately, evidence from disaster trauma research has shown that, ultimately, most people are resilient even after the most severe traumatic event.2 In the immediate aftermath of large-scale catastrophes, a majority of negative mental health symptoms are recognized as distress reactions to intense and overwhelming events. They are not pathologized or labeled psychiatric disorders. The disaster literature emphasizes the importance of acknowledging the normality of distress reactions, identifying high-risk populations, promoting effective coping and adaptation strategies, and encouraging overall wellness and resilience.3 Disaster mental health assistance during the acute phase is often more practical than psychological in nature. In this case, such assistance includes Centers for Disease Control information and updates, access to food and cleaning supplies, access to COVID-19 testing, protective equipment, financial assistance, and links to community resources.

After the acute phase of the disaster, long-term stress responses can emerge. Lancee et al.4 found that 2 years after the SARS outbreak, health care workers who treated these patients had elevated rates of smoking and drinking, absenteeism due to stress or illness, decreased face-to-face contact with patients, and decreased work hours. Yet rates of depression, posttraumatic stress disorder, and other mental illness were not elevated. This is consistent with existing research, which has found that the long-term impact of massive disasters is predominantly in the range of subsyndromal stress responses rather than an increase in psychiatric morbidity. Limited long-term studies suggest that post-disaster symptomatology peaks in the first year and then declines, but the course of recovery is variable.5 The challenge for mental health clinicians is to distinguish normal distress reactions to catastrophes from exacerbation of existing mental health susceptibilities or new-onset disaster-related pathology.

Disaster trauma is characterized by exposure to personal loss and community disruption. Cultural, political, and socioeconomic factors all influence the shared experience of major disasters.6 Looking through a disaster trauma lens, a better understanding of the emotional stages of public reaction can help: anticipate community responses to large-scale catastrophic events (Figure 1), identify the changing goals of recovery at different phases (Figure 2), and inform mitigation strategies. It is important to note that the timing of the phases is fluid. They do not occur in an exact sequence. Phases can overlap and move forward or back across a timeline, depending on the type of disaster.

Figure 1 depicts the stages of public reactions to natural disasters like 2012’s Hurricane Sandy and even the 9/11 terrorist attacks in 2001, but the community response to a pandemic seems more unpredictable. The immediate COVID-19 experience in New York state in the spring of 2020 was marked by safety concerns, deaths in the thousands, food and job insecurity, financial hardships, and anger at government response. We do, however, see a heroic phase exemplified by the emergence of heroes, such as Anthony Fauci, MD, on the national level and Governor Andrew Cuomo in New York state. We then witnessed community cohesion typical of the honeymoon phase as New Yorkers connected with each other from stoops, windows, terraces, and rooftops, all cheering for frontline workers at 7:00 PM each night to show gratitude and appreciation.

New York successfully flattened the curve by the summer. The number of daily deaths fell dramatically, from a peak of nearly 800 per day across the state down to none in New York City by June. Now the focus is shifting to economic recovery, while keeping community viral transmission low and bracing for a potential second wave. This could be the beginning of the reconstruction phase: figuring out a new normal and how to live with a persisting virus. Disillusionment is certainly felt when other states are unable to control the virus, in spite of the availability of immense resources and clear and concrete directions from world-class health experts to wear masks, avoid crowds, maintain social distance, and wash hands.

Supporting staff

Studies indicate that during an infectious disease outbreak, the operational response of an organization is likely the single most important factor influencing staff perception of both stress and safety.1 Traumatic events can disrupt feelings of safety, trust, control, esteem, and intimacy. As a result, staff can exhibit maladaptive behaviors or experience traumatic stress symptoms.8 Best practices to mitigate the disruptions and support staff during a pandemic involve 4 key elements: leadership, communication, education, and social support.

LEADERSHIP. Strong leadership and supportive teams influenced the resilience of health care workers during
the SARS and Ebola outbreaks.29,30 Capable and effective leadership over the course of a major disaster makes staff feel safe and supported by the organization. Best practices include:

- Visible and prepared leaders at organizational, departmental, and team levels.
- Setting the tone for a positive and supportive organizational culture.
- Skilled assessment of team strengths and weaknesses.
- Proactive outreach and crisis support from all levels of leadership.
- Creativity and innovation in increasing staff resilience and reducing stress.
- Role modeling infection control and safety practices—wear masks, practice physical distancing, and wash your hands.

COMMUNICATION. The cornerstone of infectious disease management is communication, coordination, and collaboration.31 Delivery of clear, transparent, timely, trustworthy information in a rapidly evolving situation is essential. Organizations should be prepared to:

- Acknowledge and normalize feelings of anxiety related to the pandemic.
- Communicate efforts to address the negative impacts of the pandemic, including financial concerns.
- Communicate supportive organizational practices (eg, working from home, flexible work schedule, reduced hours, job rotation, location rotation, availability of PPE, testing).
- Widely disseminate available self-care and wellness information and resources.

EDUCATION. Training and education on the issues of infection control, disaster mental health, and the disaster response system increases confidence and moderates the risk of stress. Just as Federal Emergency Management Agency (FEMA) provides appropriate resources and training for disaster responders before deployment, organizations have a responsibility to provide education and training to better prepare for and respond to a pandemic. Organizations should be prepared to offer staff:

- General information on disasters and pandemics.
- Education on infection control and universal precautions.
- Overview of disaster mental health.
- Targeted education on key sources of distress from COVID-19 (eg, quarantine-related distress, fear of contagion, concern for family, job stress, financial concerns, interpersonal isolation, stigma).

SOCIAL SUPPORT. Studies indicate that social support, both personal and professional, is a consistent protective factor and a strong mitigator of emotional distress in the wake of a massive disaster.11,12 Unfortunately, the battle against COVID-19 calls for decreased interpersonal contact. Quarantine, physical distancing, and remote and virtual work have all increased social isolation. This unprecedented public health crisis requires creativity and innovation to restore a sense of community and connectedness. In order to provide much-needed social support during difficult times, organizations should prepare to:

- Hold virtual meetings and virtual lunch/coffee breaks/happy hours to improve team cohesion and morale.
- Build in formal time during work hours for peer consultation to reduce feelings of isolation and increase feelings of efficacy.
- Use in-person or virtual service meetings and huddles to build relationships and improve responsiveness.
- Establish buddy system to check and balance each other’s stress level.

The scarcity of existing research on staff support and mitigation strategies during pandemics presents an opportunity to develop new programs that can be tailored to specific organizational contexts and cultures. Evaluation of best practices and robust analysis of the impact and sustainability of staff support plans during COVID-19 can inform future strategic planning and policy recommendations for staff wellness and resilience.

Dr Quitangon is clinical assistant professor of psychiatry, New York University School of Medicine and psychologist at the Department of Veterans Affairs New York Harbor. Dr Quitangon discloses that she receives royalties from Routledge for her book Vicarious Trauma and Disaster Mental Health: Understanding Risks and Promoting Resilience.

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BIPOLAR UPDATE

Oxcarbazepine: Does It Have a Role in Bipolar Disorder?

David N. Osser, MD

Oxcarbazepine (formerly branded as Trileptal) is an anticonvulsant that is structurally very similar to carbamazepine, which is US Food and Drug Administration-approved for acute or mixed mania but not well studied for depression. Both are thought to work by the same mechanism(s). The drug came to market as an anticonvulsant with very little time left on its patent protection, and it very quickly became a generic product. There was not enough time to do any significant studies on other possible uses such as in bipolar disorder before the patent ran out. Hence, there are very little data pertinent to its efficacy or effectiveness for bipolar mania or depression. What data are available are at best inconclusive,1 but Maudsley Prescribing in Psychiatry, citing 8 pertinent reports, rate it as “probably effective” for mania—the only medication with that rating in a table of 13 off-label possible alternative treatments.2

The only placebo-controlled study was in children and adolescents.3 The study included a total of 116 patients with symptoms of mania aged 7 to 18 years who were randomized to oxcarbazepine or placebo. There was no significant difference on the Young Mania Rating Scale, nor on rate of response defined as a 50% improvement in the scores. However, the response rates were 42% with oxcarbazepine and 26% with placebo, which looks like it could have become a significant difference if the cohort had been larger.

Oxcarbazepine has a somewhat milder adverse effect profile compared with carbamazepine. Probably the most significant risk with oxcarbazepine is hyponatremia; this most often occurs in the first 3 months of use, but it can occur later. Although few head-to-head comparisons are available,3 the incidence might be higher in oxcarbazepine than with carbamazepine. The overall rate is about 2% to 3%, but concomitant selective serotonin reuptake inhibitors (which can lower sodium by a different mechanism) probably increase this risk. Sodium monitoring should occur monthly for the first 3 months and every 3 to 6 months thereafter. Adverse effects that appear less often with oxcarbazepine include liver enzyme elevations (it is not metabolized and is renally excreted), serious rashes including Stevens-Johnson syndrome, leukopenia, sedation, and other rashes. It is a weaker inducer of cytochrome P450 3A4 compared with carbamazepine and thus has fewer drug interactions. Both oxcarbazepine and carbamazepine are weight-neutral, but they can cause double vision and vertigo. Slower titration may minimize these and other adverse effects. Teratogenicity is a severe problem with carbamazepine; the incidence is unclear with oxcarbazepine but it probably should be considered to be an equally high risk in women of child-bearing potential.

Dosage of oxcarbazepine is about one-third higher than with carbamazepine. The same dose has been used for bipolar mania as is used for seizure disorders; begin with 300 mg bid and increase every 3 days by 300 mg to the maximum dose of 2400 mg, if needed and tolerated. Serum levels are not available.

In conclusion, it seems that oxcarbazepine could be a consideration for patients who you want to treat with carbamazepine for mania (as monotherapy or adjunct) but for whom it would be unsafe or who have been unable to tolerate it. It is unlikely to be of value for someone who had an adequate trial of carbamazepine and has not responded. The evidence base for treating or preventing bipolar depression is very weak for both.

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The term frontotemporal dementia (FTD) describes a group of neurodegenerative disorders that are characterized by the clinical syndrome of progressive dysfunction in executive functioning, behaviors, and language. FTD is thought to be the third most common type of dementia after Alzheimer disease (AD) and dementia with Lewy bodies. FTD is also a common type of early-onset dementia (occurring among individuals 65 years or younger). FTD was noted in 1892 by Arnold Pick, MD, when he described an individual who presented with aphasia, temporal lobar atrophy, and presenile dementia. In 1911 the association between Pick bodies and FTD was described by Alois Alzheimer, MD, PhD, who named the disorder “Pick’s disease.” The term Pick’s disease became synonymous with FTD, referring to both the clinical syndrome and the pathological diagnosis. Currently, “Pick’s disease” is used only to describe the pathological diagnosis. In 1982, M. Marcel Mesulam, MD, identified the language subtype of FTD: primary progressive aphasia (PPA).

Available evidence indicates that FTD is the second most common cause of dementia among individuals 65 years or younger. The prevalence of FTD among individuals with early-onset dementia is between 3% and 26%. The population prevalence of FTD varies between 1 to 26 per 100,000. These numbers probably underestimate the true prevalence, as the disorder is often missed or misdiagnosed.

Subtypes
FTD has 2 main subtypes, based on their predominating presentations: the behavioral variant of FTD (bvFTD), and the language variant, i.e., PPA. Based on the localizations and underlying cerebral dysfunction, the language variant can be further subdivided into the nonfluent variant of PPA (nfvPPA) and the semantic variant of PPA (svPPA). Male predominance has been noted in the bvFTD and svPPA variants and female predominance in the nfvPPA variant. Table 1 details the diagnostic criteria of FTD’s 3 variants. A third variant of PPA has been described as logopenic PPA (lvPPA), in which individuals exhibit specific impairment with confrontation naming or word-finding difficulties and impaired sentence repetition. Neuroimaging studies among these individuals demonstrate predominant left posterior perisylvian or parietal atrophy/hyperorfusion/hypometabolism. Definite histopathologic evidence or the presence of a known pathogenic mutation allow for a definite diagnosis of FTD.

Evidence indicates that approximately 12.5% of individuals with bvFTD have concomitant motor neuron disease. In addition, 27.3% of individuals have features of minor motor system dysfunction,
including occasional fasciculations and mild muscle wasting or weakness. As the disease evolves, the clinical presentation of the 3 variants overlap with each other and with syndromes of atypical parkinsonism, including progressive supranuclear palsy (PSP) and corticobasal degeneration syndrome (CBD).1

Compared with AD, patients with FTD tend to have a shorter duration of survival from diagnosis and more rapid decline of cognition and function.1 The average survival time with FTD depends on the subtype; the average survival time is approximately 3 years for bvFTD and motor neuron disease and 12 years for svPPA.

**Neurobiology**

Current evidence indicates that FTD is a highly heritable disorder, with familial FTD accounting for approximately one-third to half of cases.2 Most cases of familial FTD present as the bvFTD variant. A family history of dementia is found in 25% to 50% of FTD cases, and about 10% have a clear autosomal-dominant inheritance.1 Mutations in the microtubule-associated protein tau (τ), progranulin, and chromosome 9 open reading frame 72 expansion are found in 25% to 50% of FTD cases, with one-third to half of cases.1 Most cases of familial FTD present as the bvFTD variant, with approximately half the post-mortem cases of FTD have abnormal deposition of transactive response DNA-binding protein 43 (TDP-43).

**Table 3. Neuroimaging Findings in FTD**

<table>
<thead>
<tr>
<th>Type of neuroimaging study</th>
<th>bvFTD</th>
<th>nfvPPA</th>
<th>svPPA</th>
<th>lvPPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volumetric MRI</td>
<td>Atrophy in the frontal and temporal lobes, especially in the prefrontal cortex, anterior temporal regions, the insula, anterior cingulate, striatum, and thalamus</td>
<td>Atrophy occurs in the left cerebral cortex, including the inferior frontal gyrus, especially pars opercularis, dorsolateral prefrontal cortex, superior temporal gyrus, and insula</td>
<td>Asymmetric temporal lobe atrophy especially in the anterior and inferior regions, with the most common presentation being prominent left-sided atrophy</td>
<td>Early left temporoparietal and posterior cingulate atrophy</td>
</tr>
<tr>
<td>Functional MRI</td>
<td>Reduced connectivity in the salience network: the frontal lobe, anterior cingulate, insula, amygdala, medial thalamus, and ventral striatum</td>
<td>Reduced functional connectivity in the frontal operculum, primary and supplementary motor areas, and inferior parietal lobe</td>
<td>Reduced functional connectivity in the semantic network involving the left anterior temporal lobe, inferior and ventral regions of the temporal lobe, bilateral frontal cortex, left amygdala, hippocampus, caudate, and occipital regions</td>
<td></td>
</tr>
<tr>
<td>18-fluorodeoxyglucose PET and SPECT</td>
<td>Hypometabolism in the frontotemporal regions, especially the orbitofrontal, dorsolateral, and medial prefrontal cortex and anterior temporal poles</td>
<td>Greater hypometabolism in the left inferior frontal and superior temporal regions</td>
<td>Temporal lobe hypometabolism with asymmetrical left hemisphere involvement in the entorhinal and perihipocampal cortex, inferior temporal poles, and amygdala</td>
<td>Left frontoparietopolar hypometabolism, especially in the lateral frontal and posterior lateral temporal lobes, caudate, posterior cingulate, and precuneus regions</td>
</tr>
</tbody>
</table>
a family history of dementia, movement disorders, and/or psychotic disorders, genetic counseling and a search for genes that cause FTD are both recommended.2

**Treatments**

Currently there are no US Food and Drug Administration (FDA) approved disease-modifying drugs for the treatment of FTD.14 In a systematic review, Nardell and Tampi found a total of 9 randomized, controlled, double-blinded clinical trials that evaluated various drugs for the treatment of FTD.15 These included 2 trials of the selective serotonin reuptake inhibitor paroxetine, 1 trial of trazodone, 2 trials of stimulants (methylphenidate and dextroamphetamine), 1 trial of the acetycholinesterase inhibitor galantamine, 2 trials of the N-methyl-d-aspartate (NMDA) antagonist memantine, and 1 trial of the neuropeptide oxytocin. The investigators concluded that SSRIs, trazodone, and the amphetamines may be effective in reducing some behavioral symptoms. None of these medications, however, improved cognition among individuals with FTD. Available data also indicated that these medications were well tolerated.

The evidence for the use of antipsychotics for the treatment of behavioral symptoms in FTD comes mainly from case reports and uncontrolled studies. 6 In addition, the use of antipsychotics can worsen the risk of extrapyramidal adverse effects, to which individuals with FTD are especially vulnerable. Furthermore, the boxed warning for the risk for death with the use of antipsychotics among individuals with dementia holds true also for individuals with FTD. For the treatment of behavioral symptoms in FTD, the evidence for the use of anticonvulsants—including valproic acid, topiramate, and carbamazepine—is limited to case reports. Evidence indicates that individuals with FTD and parkinsonism often do not respond to dopaminergic drugs, including levodopa and carbidopa, although some case reports indicate some benefits with these agents. Table 5 summarizes the pharmacotherapy for FTD.15,16

**Trials of α aggregation inhibitors, α acylation inhibitors, α-active vaccine, anti-α mononclonal antibodies, anti-human soritin mononclonal antibody, microtubule-stabilizing drugs, and proruranil expression activators have been completed or are currently in various phases of trials.17 Unfortunately, available results indicate that none of these drugs have yet been found to be beneficial.**

Available evidence indicates that nonpharmacological management techniques are helpful among individuals with FTD.14 These interventions include environmental approaches that assist individuals who struggle to accurately interpret, understand, and react to their environment. In addition, behavioral modification techniques and providing familiar activities appear to reduce different types of behaviors. Evidence indicates that educational services and coping strategies that are focused on problem-solving are effective in managing behavioral symptoms and reduce caregiver burden. The development of individualized regimens incorporating environmental and behavioral strategies have been proven to be highly beneficial in assisting individuals with FTD. The family caregivers who use these strategies become more competent in managing patients’ challenging behaviors. Speech therapy has been found to be beneficial among individuals with FPA.18

**Concluding thoughts**

The clinical syndrome of FTD is characterized by executive dysfunction, behavioral disturbances, and language impairment. FTD is often misdiagnosed or underdiagnosed due to the heterogeneity of its clinical presentation and the overlap of its clinical symptoms with those of other common neuropsychiatric disorders. Although there are no FDA-approved medications for the treating FTD, some agents have shown modest efficacy in improving behavioral but not cognitive symptoms. Nonpharmacological techniques can be beneficial in managing behavioral symptoms. Many newer therapies are currently under trial, although their benefits are not yet certain.

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The Case for Medication-Assisted Treatment: An Ethical Priority

Kultaj Kaleka, RN, and Juliette M. Perzhinsky, MD, MSc

Substance use disorder (SUD), including opioid use disorder (OUD), affects a significant proportion of the American population—20.3 million (7.4%) of Americans aged 12 years or older had a SUD in the past year. Of these, 2 million people had an OUD from heroin and/or misuse of prescription pain relievers. Although medication-assisted treatment (MAT) with methadone, buprenorphine, or naltrexone for OUD is the most efficacious, evidence-based treatment that is recommended by the National Institute of Health, Substance Abuse and Mental Health Services Administration (SAMHSA), and the World Health Organization, only 11% of patients with an OUD are prescribed approved treatment.

Limited access to MAT has been cited as a substantial barrier for patients with OUD; inequities across ethnic and sociodemographic groups speak to the health disparities evident in society. The provision of appropriate treatment and lack thereof are even more troublesome when considering the vulnerable populations that bear the disproportionate burden of SUDs and OUDs—namely, those involved with the corrections system and those with serious mental illness (SMI). It is no secret that a significant proportion of the criminal justice population has an SUD.1

Justice in criminal justice
Between 62% and 86% of individuals arrested test positive for recent drug use,2 and 64% to 76% of arrestees meet diagnostic criteria for SUD. More than half of individuals with a prescription OUD or heroin use in the past year report contact with the criminal justice system.2 Similarly, in terms of mental illness, 9.2 million Americans over 18 years old, or 3.7% of American adults, had co-occurring SUD and any mental illness in 2018.3

In line with the goal of reducing recidivism, a proportion of the criminal justice population is often diverted to drug courts. According to SAMHSA, there are currently 2,700 operational drug courts in the United States.4 These courts adjudicate cases involving substance-involved offenders, or individuals who were arrested for a drug-related offense and/or are eligible to enter a drug court program. Typically, an offender is followed by a drug court for 12 to 18 months. The National Drug Court Institute reports that more than 116,000 criminal offenders were served by a drug court program in 2009.4 However, only 56% of drug courts offer MAT to participants.5 Additionally, most individuals with SUD do not receive treatment while they are incarcerated, or they are forced to withdraw from treatment they were receiving before incarceration (Figure).6

Ethical considerations around MAT in caring for these patients are apparent through lenses of health care as a source of harm, paternalism, and violation of rights; through a refusal to provide access to appropriate care; or through the intersection of medicine and epidemiology. These considerations include issues around access to MAT and the context in which consent to MAT is obtained from those to whom it is offered. MAT is an approved treatment for OUD by the US Food and Drug Administration. The underlying pharmacology of drugs used in MAT and their physiological effects on individuals are well understood. MAT is known to assist in diminishing cravings, and some agents can alleviate the withdrawal symptoms associated with OUD. However, many drug courts and prison facilities do not offer provisions for MAT for incarcerated individuals.2,5

In the absence of MAT, individuals with OUD are forced to undergo detoxification with full exposure to the negative physiological and psychological withdrawal symptoms that they could easily avoid with MAT, including nausea, vomiting, diarrhea, agitation, anxiety, and suicide likelihood.6 This lack of access to approved and indicated therapy for a disease process could be construed as a punitive measure and borderline cruel and unusual punishment. In fact, detoxification in the absence of MAT is less efficacious than MAT and harmful to human health.7

Surveys of drug courts and the US prison systems do find practical reasons for not providing MAT, namely, the cost and lack of access to local providers. However, there are courts that do not permit MAT because of a lack of knowledge and stigma around OUD. Many drug court teams are uncertain about the underlying physiological mechanisms of opioid receptor agonists used in MAT and their efficacy in treating OUD. Some report they believe that patients with OUD use MAT to get high and not for treatment of OUD.2 Further, others think

Justice in drug courts
Between 29% and 45% of state and federal prisoners had an OUD in 2009. In the U.S. provided referrals for community buprenorphine providers in 2009, 45% of state and federal prisoners in the U.S. received methadone or buprenorphine maintenance after release in 2009. Without MAT, there was a 10-40X higher risk of death from overdose within 2 weeks of release from prison in a 2018 study.4

In a 2018 study, participants with OUDs were 80% less likely to graduate from drug court. Approximately 50% of drug courts required participants to discontinue methadone or buprenorphine within 30 days of a 2017 study. In jails and prisons, 30% of 5,100 parolees referred for opioid use disorder treatment in 2018 by probation, parole or court authorities received methadone or buprenorphine compared to 41% referred by non-criminal justice sources

that MAT use for OUD is essentially replacing one addictive substance with another.4 The false narrative that MAT reinforces addiction or replaces an illicit substance (heroin) has a negative impact on individuals.3 Additionally, the intersection of medicine and epidemiology is evident when those with SUDs/OUDs who do not have access to MAT turn to unsafe practices, such as the use of unclean needles to inject impure heroin or heroin laced with synthetic fentanyl. This, in turn, leads to increased morbidity and mortality as well as to public health issues of increased transmission of infectious diseases.3

The dangers of coercion The other side of the coin: being processed by a drug court and given the option of either incarceration or MAT. Asking an individual with a mentally incapacitating illness to consent to treatment brings in to question autonomy and validity of consent. Informed consent, by definition, should be voluntary and free of coercion.6,11 It should be obtained from someone with the capacity to make a decision after they have an understanding of the risks and benefits of available options. Consent under the threat of incarceration, or while incapacitated, is not informed consent and compromises individual autonomy.5,7 Many individuals with OUDs/ SUDs choose Narcotics Anonymous, peer support, drug-free detoxification, or treatment modalities other than MAT.3 Assuming a binary disposition, MAT versus drug-free detoxification is overly punitive and a violation of voluntariness and self-determination of these individuals.

Patients with SUDs/OUDs often contend with unfavorable correctional system interactions as well as SMI, and they predominantly comprise minorities from low-income or limited educational backgrounds and with reduced social support. They are a vulnerable population whom society has largely marginalized.5 Their rights are threatened, and they are afforded subpar and borderline unethical care. The underlying reasons behind this unsettling phenomenon is a lack of health literacy around MAT and stigma associated with OUD in nonclinical settings.

Concluding thoughts An ethical framework is needed, as well as best practice guidelines highlighting the efficacy of and science behind MAT specifically directed at the correctional system. Addressing limitations in knowledge base and highlighting shortcomings in protecting the rights of incarcerated individuals are both essential, in partnership with all stakeholders (including incarcerated patients, rights groups, judges, the correctional system, and medical bodies).

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Behind Closed Doors

Omar Reda, MD

Not only in America, but throughout the world, difficult conversations are taking place in many homes. Behind closed doors, children are exposed at early ages to discussions about heavy topics like violence, hate, and human cruelty.

I am blessed to have three daughters. I try to create a safe and sane home for them, but I have never imagined engaging them in some of these talks, especially here in the United States, and in the 21st century.

When I moved to Portland, Oregon in 2009, I thought the city’s nickname (the Rose City) was a sign that things would be much safer and more comfortable for my family. Similarly, my wife believed that moving from the southern to the northwestern part of the country would make things easier for us as Muslims and people of color.

But shortly after arriving, a young Somali boy was accused of planning a terrorist attack in one of the city’s busiest spots, the Pioneer Square. We found ourselves working with community leaders and the Muslim youth on topics like emotional safety and well-being, how to be a proud American Muslim, strengthening family ties, and improving the relationship between the community and its neighbors and law enforcement agencies.

Fast forward to 2011, a bloody civil war started in my home country Libya. I left my small immediate family behind to care for my extended family overseas, trying to heal some of the many psychosocial wounds of that protracted conflict. I lost friends and loved ones to violence and extremism. My wife and children had to live through periods of uncertainty and high anxiety every time I boarded a plane and returned in that dangerous journey.

We thought and prayed the new decade would bring a better energy, but the year 2020 has been one of the most challenging years of all. Here in Oregon we have been struggling to breathe, literally and metaphorically. It is not only the threat of the coronavirus disease 2019 (COVID-19) to our respiratory system, but also the systemic knee of injustice on the necks of our black brothers and sisters and the wave of hate facing minorities and people of color. The mask can help with the former crisis, but unmasking is what is needed for the latter.

It became the norm to talk with kids about their identity and self-worth, about micro- and macro-aggressions, about speaking up on behalf of the voiceless, but also about how they can defend themselves when someone decides to attack them verbally or physically. After the Portland max train stabbing incident and the New Zealand mosque shooting, we spent time and energy brainstorming ways on how to stay alive and feel safe at our places of social gatherings and worship. Trauma steals precious moments and impacts the potential for beauty.

I recently participated on a panel discussion about combating hate. A young black female stated that, “at least [things] are not as bad for this generation as it was for our fellow citizens in the 1950s and 60s.” That really broke my heart. Just because hate and violence are “not as bad,” does not mean things are OK. Children should not have to settle for a dysfunctional world.

“The talk” we thought we would have with our children is about how to survive the emotional turmoil of puberty. In the black community, that talk is also about how to stay alive in America. In the Latino community, it may be about the immigration system. In the Muslim community, it may be about terrorism. Hate is horrible, and it not only makes surivors doubt their own beauty, but it also makes us miss out on each other’s beauty.

We thought COVID-19 was only going to impact our ability to breathe, but then Mr Floyd’s death reminded us of the ugly pandemic of oppression. In Oregon, the smoke of the wildfires stirs different discussions about existential themes, like our relationship with God and the meaning of life.

Is it bad that our children are growing up very quickly and having these mature conversations at a young tender age, or is that the new norm? My hope is that trauma will eventually produce a more resilient generation and a more compassionate and cohesive society. I believe that many trauma survivors become better humans not despite, but because of their trauma stories.

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Julia is a 31-year-old female with depression and posttraumatic stress disorder (PTSD) who presents to your outpatient psychiatry clinic. She is married with 2 children and works as a store manager. Julia has been taking a selective serotonin reuptake inhibitor for the last 2 years, which alleviated her depressive symptoms. However, Julia continues to experience PTSD symptoms including nightmares, flashbacks, and avoidant behavior. She has tried various augmenting agents with little relief; she currently engages in therapy.

A friend of Julia’s recently told her that medical marijuana has been a panacea and has made it much easier to function. Intrigued, Julia researched cannabis online and found it might be beneficial for her PTSD symptoms. Julia smoked marijuana occasionally during her early 20s and found it to have a relaxing effect. She has not used marijuana since becoming pregnant with her first child about 8 years ago. She has many questions about medical cannabis including its risks, benefits, and how to obtain it, and she is looking to you for advice.

History of medical cannabis

The concept of cannabis as medicine has existed for millennia, but its legal recognition has only begun to gain traction with western medical practitioners in the last 2 decades. California became the first state to legalize medical cannabis in 1996 with the passage of Proposition 215-Compassionate Use Act, and many states have followed suit. As of May 2020, all but 3 states (Idaho, South Dakota, and Nebraska) have enacted legislation regarding the use of either medical cannabis or cannabis-derived (ie, cannabidiol-containing) products (Figure). This trend mirrors the worldwide trend of increasing acceptance of medical cannabis. Mexico, Australia, and much of Western Europe and South America have legalized medical cannabis.

ACTIVITY GOAL

The goal of this activity is to explore the medicolegal aspects of medical marijuana.

LEARNING OBJECTIVES

After engaging with the content of this CME activity, you should be better prepared to:

• Understand the basic concepts of medical marijuana including its history and legislation.
• Review possible indications and potential side effects of medical marijuana with patients.
• Discuss the social barriers associated with medical marijuana use.
• Understand the potential areas of liability physicians may encounter surrounding medical marijuana.

TARGET AUDIENCE

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

ACCREDITATION/CREDIT DESIGNATION/FINANCIAL SUPPORT

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Physicians’ Education Resource®, LLC and Psychiatric Times. Physicians’ Education Resource®, LLC is accredited by the ACCME to provide continuing medical education for physicians. Physicians’ Education Resource®, LLC designates this enduring material for a maximum of 1.5 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This activity is funded entirely by Physicians’ Education Resource®, LLC. No commercial support was received.

OFF-LABEL DISCLOSURE/DISCLAIMER

This CME activity may or may not discuss investigational, unproven, or off-label use of drugs. Participants are advised to consult prescribing information for any products discussed. The information provided in this CME activity is for continuing medical education purposes only and is not meant to substitute for the independent clinical judgment of a physician relative to diagnostic or treatment options for a specific patient’s medical condition.

The term cannabis refers to a genus of flowering plants belonging to the family cannabaceae. Two common species—sativa and indica as well as their hybrids—are consumed in the United States for medical and recreational purposes. A third rarer species, ruderalis, is endemic to Asia and Eastern Europe. The cannabis plant contains approximately 500 known chemical compounds. Sixty-six of these compounds are cannabinoids that are unique to cannabis; cannabinoids tetrahydrocannabinol (THC) and cannabidiol (CBD) are responsible for its psychoactive and purported medicinal properties, respectively. The remainder of the chemicals, such as nitrogenous compounds, amino acids, and terpenes, can be found in other plants and account for cannabis’ non-psychoactive properties including its color, flavor, and odor.

Although there are 3 main species of the cannabis plant, nearly 800 cultivars or strains are believed to exist. Cultivars are often described in terms of their cannabinoid content and specifically their CBD-to-THC ratios, as these account for their advertised medicinal properties. High CBD-to-THC strains are believed to have anti-inflammatory and calming properties; they are thought to be effective for pain and muscle spasticity.
for the treatment of autoimmune, mood, and anxiety disorders. In contrast, high THC-to-CBD strains are advertised as being helpful for pain and nausea.3 (These statements have not been evaluated by the US Food and Drug Administration. The FDA has not approved a marketing application for cannabis due to its federally illegal status and classification as a Schedule I drug.)

Legislation

Laws governing cannabis cultivation and use have not always been so favorable. While cannabis was a popular ingredient in medicinal compounds touted as a cure for a variety of conditions (eg, gonorrhea and “childbirth psychosis” in the late 19th and early 20th centuries), laws limiting and prohibiting its use were enacted as early as the 1920s. By 1931, 29 states passed legislation explicitly barring possession of cannabis. In the decades that followed, there were harsher penalties for possession, including mandatory minimum sentences for charges of possession of cannabis.

In 1971, the Controlled Substances Act (CSA) created the Drug Enforcement Agency’s drug schedules that still exist today. The CSA placed cannabis in the Schedule I category of drugs along with heroin, LSD, ecstasy, and psilocybin, all of which are believed to have no current medical use, high abuse potential, and lack of accepted safety data for use under medical supervision.4 The CSA dealt perhaps the hardest blow to cannabis’ potential use as a therapeutic agent by prohibiting the use of federal funds for any research into its efficacy and safety.

Cannabis legislation remained at a standstill for 25 years after the CSA, until the passage of Proposition 215 in California, which allowed patients with a valid doctor’s recommendation to possess and cultivate cannabis for personal use. In direct response to the proposition’s passage, the federal government also issued a policy in 1996 indicating that a physician’s recommendation or prescription of Schedule I substances was not in line with the public interest and threatened to revoke the prescribing privileges of those physicians who did not comply with the policy.9 The 1996 federal policy led to a landmark legal case Conant v Walters (United States Court of Appeals for the Ninth Circuit, 2002). The class action lawsuit was filed by patients with seriously medical illness and their doctors against John P. Walters, director of the White House Office of National Drug Control Policy and others. The court ultimately ruled that the existing federal policy violated a physician’s first amendment right to free speech by threatening censure for discussions held in the sanctity of the doctor-patient relationship; it further found physicians may discuss the pros and cons of medical marijuana with their patients and issue oral or written opinions recommending its use. However, the court explicitly stated that physicians may not prescribe or dispense marijuana or “aid and abet” the patient in the purchase, cultivation, or possession of marijuana. This landmark decision was the first to outline a physician’s right to recommend, but not prescribe, cannabis and provided a basis for legal protection from sanctions against their license.10

In 2014, Congress passed the Rohrabacher-Farr amendment as part of Commerce, Justice, Science, and Related Agencies Appropriations Act. This amendment, initially introduced in 2001, prohibits the use of federal funds to interfere with the implementation of state medical cannabis laws. The Rohrabacher-Farr amendment is considered a significant victory for proponents and consumers of medical cannabis because it allows state medical cannabis dispensaries to operate without fear of prosecution by the federal government, which still considers cannabis to be illegal due to its classification as a Schedule I drug.11

Legislation to reclassify cannabis from a Schedule I to a Schedule II drug and decriminalize it at a federal level was introduced in the Marijuana Opportunity, Reinvestment, and Expungement (MORE) Act of 2019. The Act was passed by the House Judiciary Committee, but Congress has not yet voted on it.12,13 If passed, the MORE Act would be another significant victory because scientists could apply for federal funds to formally research the potential medical benefits of cannabis.

Presently, as there is no federal legislation legitimizing its use, medical cannabis laws have been crafted at the discretion of individual states.14 As a result, there is significant variation from state to state (Table 1). Given the significant variation in medical cannabis laws amongst states and the continually shifting legal landscape regarding its use, medical cannabis presents a unique challenge for medical professionals who consider recommending it to their patients or who treat patients who receive it from other professionals. It is important that clinicians familiarize themselves with state laws to ensure compliance since deviation can have serious consequences for their licensure.

Indications

Marijuana has long been a part of popular culture. When smoked, vaped, or ingested, THC can produce sought-after effects such as euphoria, heightened senses, a distorted sense of time, alterations in physical movements, and decreased inhibitions. With 38 states allowing for the use of THC-containing medical marijuana compounds (Figure), it stands to reason that it may be effective for treating physical and mental ailments. By far, the most common psychiatric diagnosis listed by these states is PTSD, but others include Tourette syndrome, Alzheimer, and autism. As psychiatrists, we may be approached to diagnose some of these conditions in our patients as part of their interest in obtaining medical marijuana.

Adverse effects

It is important to consider what can go wrong when using THC. Common short-term side effects include conjunctival injection (often a tell-tale sign of intoxication), hyperphagia (or, in common parlance, “the munchies”), xerostomia (“cottonmouth”), dyspnea, tachycardia, and slowed motor response leading to delayed reaction time (which is particularly concerning while driving or operating heavy machinery). One of the most common psychiatric side effects is paranoia; this may be worth noting when discussing marijuana with patients who have a history of paranoid beliefs.

There are also long-term issues that have been associated with THC. These may include cannabinoi d hyperemesis syndrome/cyclic vomiting syndrome and amotivational syndrome.15,16 There are potential consequences in pregnant woman, including a negative impact on fetal brain development and decreased birth weight.17 Finally, some argue that marijuana serves as a gateway drug, placing users in circumstances where they find themselves compelled to use more dangerous drugs with a higher potential for addiction. Doctors may also be called upon to answer questions about CBD. As it is readily available in multiple forms (eg, gummies, oils, pills) at numerous locations (eg, pharmacies, health food stores, gas stations), one may conclude that it is relatively benign. The FDA, however, warns that CBD may cause somnolence, gastrointestinal distress, irritability, and/or agitation.18 Regarding its efficacy as
a treatment option for serious mental illness, the results appear inconclusive.24,25 There is much discussion regarding the relationship between marijuana and psychosis, as there is some overlap between cannabis intoxication and primary psychotic disorders. For those experiencing a psychotic episode with concomitant marijuana use, the etiology of the symptoms becomes complex. If a patient who uses marijuana is later diagnosed with schizophrenia, the marijuana can further complicate the picture. For instance, in their resistance to accept the schizophrenia diagnosis, the patient and family may prefer to attribute the psychotic symptoms to marijuana. Unfortunately, this may lead to delays in receiving the appropriate antipsychotic treatment.

According to a 2016 meta-analysis, increased exposure to THC increases the odds of being diagnosed with schizophrenia.26 Additionally, THC use is associated with poor medication response, medication noncompliance, and higher frequency and temporary worsening of psychotic symptoms.27,28 This information should be tempered when discussing marijuana use with patients; while a clinician may share concerns about marijuana use with their patients, an absolute intolerance could potentially damage the therapeutic alliance.

Employment

After reviewing Julia’s medical history and discussing the potential side effects of medical marijuana, Julia begins to share concerns over the use of medical marijuana for her PTSD. She asks about anticipated employer problems, but she is unaware of her workplace’s policies. Julia further questions how it may affect other facets of her life.

Employment restrictions are delineated at the state level with varying degrees of stringency. The exception is federal employees who are prohibited from using both medical and recreational marijuana. The medical cannabis laws of Nevada and Washington will be used for illustrative purposes due to their contrasting laws. However, each state has slight nuances that need to be reviewed before discussing medical marijuana with patients.

The pre-employment job process may involve a drug screen and/or a questionnaire inquiring about marijuana (medical or recreational) use. The employer, according to their own policies, must choose how to handle a positive drug screen. Some may recognize medical marijuana as a legitimate treatment and disregard a positive test. Others may have a zero-tolerance drug policy.

A zero-tolerance policy was unsuccessfully challenged by a Washington state employer in Roe v. Teletech (Washington Supreme Court, 2011). The Washington Supreme Court upheld a ruling that an employer does not have to accommodate an employee’s use of medical marijuana, even when the employee is in a non-safety-sensitive position and uses medical marijuana exclusively off-site.29 In contrast, Nevada recognized the quandary of allowing medical marijuana while simultaneously permitting employers to discriminate against its use. Thus, Assembly Bill 32 was passed, making Nevada the first state to prohibit employers from discriminating against applicants for a positive marijuana test.30 It should be noted that some jobs are exempt from the Nevada bill.

Once employed, on-duty use of medical marijuana is almost universally prohibited. However, some states (eg, Massachusetts and Nevada) may require employers to reasonably accommodate an employee’s medical needs for off-duty/off-site use.31,32 This could entail allowing the employee to work shifts that do not interfere with medical marijuana use. Since on-duty use and related impairment are prohibited, employers may implement policies to determine impairment in a variety of different ways. For example, suspected impairment may be confirmed with a drug screen or via observation of behavioral changes. However, for chronic medical marijuana users, a drug screen is likely to be a poor indicator of impairment, as the non-psychoactive components of marijuana can stay in the body for weeks.33 The state of Arkansas recognized this issue and ruled that an employer cannot use a drug test as the sole indicator of impairment.34 Other states have allowed the employer autonomy over the methodology of determining impairment. Regarding off-duty use, restrictions are again variable. Some states force employers to recognize medical marijuana status, while others do not.35

Driving

Similar to employment, states have struggled with issues regarding people who use medical marijuana and drive due to the difficulty of identifying suspected impairment and corroborating it with objective measures that will hold up in court. Currently, there are 4 main testing methods: urine, blood, saliva, and breathalyzer. While urine and blood are the most commonly employed testing methods, they are also the poorest measures of impairment. Depending on the amount, frequency, and mode of marijuana use, THC may be metabolized by the liver within hours of ingestion.36 However, the non-psychoactive metabolites can remain in the system for weeks. A problem with generic urine and drug tests is that they do not evaluate for psychoactive versus nonpsychoactive metabolites. Rather, they only test for the presence of cannabinoids, which may be present for hours to weeks depending on the chemical compound. Thus, someone could ingest medical marijuana, have multiple days go by where they are no longer actively intoxicated, but still test positive on a drug or urine test. This is currently the case in Pennsylvania where a person using medical marijuana can be automatically issued a driving under intoxication notice after a crash if they fail a drug test.37

Some states have recognized this conundrum and sought alternative testing methods. The breathalyzer is a method being explored.38 A saliva test, which is currently being used in Europe, Alabama, and Oklahoma, is also being investigated as an option. However, the issue remains that neither test can determine impairment as there is no universal standard. Arizona and Michigan have remedied this issue by ruling that a positive blood or urine test alone is not sufficient evidence to prove intoxication.39 Therefore, the burden of proof is on the police officer alleging that a driver was intoxicated.

Gun ownership

Under the Gun Control Act of 1968, any unlawful user of a controlled substance is prohibited from purchasing or owning a gun.40 The key words at issue are “controlled substance.” Since marijuana is classified as a Schedule I controlled substance, it is illegal for anyone who uses medical marijuana to purchase a gun.41 Gun shops screen for marijuana compliance with federal laws and state laws.

Table 1. Areas of State-by-State Variation in Medical Cannabis Laws

<table>
<thead>
<tr>
<th>Qualifying conditions: Diagnosable medical conditions that qualify a patient to use medical cannabis</th>
<th>Most states outline qualifying conditions, but a minority allow physicians to use their discretion about constitutes such.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common: Severe, life-limiting illness such as cancer, HIV/AIDS, movement disorders/multiple sclerosis, amyotrophic lateral sclerosis, seizure disorders, and terminal illness</td>
<td></td>
</tr>
<tr>
<td>Psychiatric illnesses: PTSD, Tourette disorder, and autism</td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric disorders: Parkinson disease, Alzheimer disease, traumatic brain injury, and Huntington disease</td>
<td></td>
</tr>
<tr>
<td>Approved recommenders</td>
<td>In most states, only physicians can make a medical cannabis recommendation. However, several states allow nurse practitioners and physician assistants to recommend medical cannabis.</td>
</tr>
<tr>
<td>Recommender training</td>
<td>Some states require recommenders to complete an online training course, while others only require that recommenders have an active DEA license.</td>
</tr>
<tr>
<td>Home cultivation of medical cannabis</td>
<td>Most states do not allow home cultivation of medical cannabis, except for 7 states and Washington, DC. Some states only allow home cultivation under certain circumstances (eg, if a patient lives too far from a dispensary); there are generally quantity limits on the number of plants that can be grown.</td>
</tr>
<tr>
<td>Formulation</td>
<td>While cannabis is available in numerous formulations, including edibles, oils, smokable herb, tinctures, sprays, and topicals (eg, lotion, salve, etc), some states explicitly prohibit some formulations for medicinal purposes. For example, several states prohibit smoking of the dried herb.</td>
</tr>
<tr>
<td>Possession quantities</td>
<td>Some states indicate a specific quantity of dried herb or oil that a patient can possess at any one time, while others allow a patient to possess the quantity they use in a specific timeframe (usually 1-3 months).</td>
</tr>
<tr>
<td>Chemical composition</td>
<td>About one-half of all states that have legalized medicinal cannabis have restrictions on the percentage of THC, excluding those states with legalized recreational use. In those states that allow only “low THC” formulations, THC percentage limits range from 0.3% to 5%.</td>
</tr>
</tbody>
</table>

Further reading:

Although there are no known cases in which a state medical board and, rarely, criminal charges. In other words, they may be concerned about the possible risks. In states where marijuana is legal, there are no known cases in which a state medical board and, rarely, criminal charges.

**Education**

Finally, due to the difference between state and federal laws, schools are left to make their own decisions regarding medical marijuana use. Most schools receive state and federal funding, leaving them with the difficult task of trying to balance obeying laws that allow them to procure funding and accommodating their students’ needs. In Oklahoma, medical marijuana is legal. However, the University of Oklahoma ruled marijuana is prohibited on campus, regardless of medical status.39 This has forced students who use medical marijuana to live off-campus and find alternative times of use.

**Finances**

In addition to the various social constraints, price may be the ultimate decider of consumption. Medical marijuana tends to cost more than marijuana procured for recreational use.39 Price is dependent on location, supply and demand, method of consumption, and THC content. The cost of an ounce of medical cannabis in Colorado is well over $200 plus taxes compared to approximately $150 for medical grade street cannabis.39-40 This could lead individuals to pursue other methods for obtaining cannabis.

**Areas of risk for physicians**

At the conclusion of your appointment with Julia, she decides that it may not be the most opportune time to pursue medical marijuana, due largely to workplace concerns. She schedules a follow-up appointment to discuss this again at a later time. After the meeting, you converse with colleagues about the potential liability associated with medical marijuana from a physician perspective.

Some physicians argue that the lack of data about the efficacy of marijuana for treating various conditions stems from the severe research limitations that have lasted decades in the United States. They would like to provide their patients with a potentially helpful treatment recommendation, but they may be concerned about the possible risks. In general, medical risks associated with the practice of medicine can be divided into 3 broad categories: malpractice, disciplinary action by state medical boards and, rarely, criminal charges.

**Malpractice**

Although there are no known cases in which a physician was sued for malpractice related to their recommendation of medical marijuana treatment, the potential exists. Consider a patient who presents seeking a marijuana card for chronic pain of 6 months duration. If the physician recommends marijuana as a treatment, fails to review past records, examine the patient, or consider diagnostic studies to work up the pain complaint, there is potential for a missed serious diagnosis underlying the pain (e.g. malignancy). An expert could argue that the physician deviated from the standard of care by failing to gather sufficient information and by failing to perform necessary diagnostic workup or referral, which resulted in delayed diagnosis and proper treatment. Another example, perhaps more relevant to psychiatry, involves a physician who misses a diagnosis of schizophrenia in a patient (either due to failure to review records, gather relevant history, or conduct a mental status examination) and recommends medical marijuana to treat PTSD. Later, the treatment results in an exacerbation of psychosis that leads to violence toward self or others. In both examples, a medical malpractice case would likely hinge on whether the doctor breached the standard of care.

It is important to keep in mind that although medical marijuana is a legal treatment in a number of states, legal is not synonymous with meeting the standard of care. The legalization of medical cannabis prohibits criminal prosecution of the physician for recommending medical marijuana provided the physician complies with the state-specific regulations regarding recommending medical cannabis. Conversely, “standard of care” provides a benchmark with which to measure the conduct of the physician in assessing for negligence in their medical management. It is possible for a physician to prescribe a medication that is not against the law but goes against what an ordinary or reasonably prudent physician would prescribe in such circumstances (e.g., haloperidol as first line treatment for childhood attention-deficit/hyperactivity disorder). Courts may seek guidance from expert testimony, treatment guidelines, journal articles, facility policies, and position statements by professional organizations to establish the standard of care in a given scenario. Many professional medical and psychiatric associations do not presently recommend medical marijuana due to insufficient data, concern about negative effects, and lack of regulation. This could bolster the plaintiff’s argument that a physician’s recommendation of medical marijuana did not meet the standard of care.

**Medical board discipline**

In contrast to malpractice liability related to medical marijuana, which is mostly hypothetical at this point, there are several documented cases of medical board discipline against physicians recommending medical marijuana. According to the Federation of State Medical Boards (FSMB), 4081 physicians across the United States were disciplined by state medical boards in 2017.40 This represents less than 1% of physicians with active licenses (958,026), according to a 2018 census conducted by the FSMB.41 To our knowledge, no analysis has been published regarding disciplinary actions by state medical boards related specifically to medical marijuana.

There are, however, several examples from news articles and case law. In 2016, for example, 4 doctors in Colorado had their licenses suspended for recommending excessive marijuana plant counts.42 At that time, the standard plant count was 6 per patient, yet these doctors approved 75 or more plants for many patients. In 2017, a Michigan physician faced medical board discipline for certifying medical marijuana without conducting a physical examination.43 After appealing the medical board determination, the Michigan Court of Appeals upheld his discipline, citing statements by American Society of Addiction Medicine and Federation of State Medical Boards that recommend examining the patient prior to certifying medical marijuana. In 2019, a naturopath had his license suspended after recommending marijuana cookies as a treatment for ADHD and bipolar disorder in a 4-year-old boy.44 In 2019, a physician in New Jersey lost his license...
Criminal charges

In addition to state medical board discipline, doctors have rarely faced criminal charges related to medical cannabis certificates. In 2013, a Michigan doctor was convicted of health care fraud for selling signed medical cannabis certificates to a middleman for resale.10 In 2016, the Arizona Supreme Court reviewed a case in which a physician was indicted on forgery and fraudulent schemes related to allegedly lying about reviewing a patient’s medical records when he certified her for medical marijuana.11 Although medical board discipline and criminal charges related to marijuana certifications are likely rare, these situations can have serious and long-lasting implications for a physician’s career. Losing one’s medical license involves a loss of opportunities for liability on the part of physicians.12

In addition to state medical board discipline, doctors need to be considered. In addition, due to the in-fancy of medical marijuana, there are also several opportunities for liability on the part of physicians.

For indiscriminately prescribing medical cannabis to patients at hotels conferences that he hosted. The doctor was accused of failing to establish bona fide physician-patient relationships, gather comprehensive histories and examine patients, assess patients’ qualifying conditions every 3 months, and keep accurate and complete records.13

REFERENCES


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Renee.Theobald@hackensackmeridian.org or call: 732 751-3597
INDICATION AND USAGE
INGREZZA® (valbenazine) capsules is indicated for the treatment of adults with tardive dyskinesia.

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

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

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

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

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

- Hypersensitivity
- Somnolence
- QT Prolongation
- Parkinsonism

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

Variable and Fixed Dose Placebo-Controlled Trial Experience
The safety of INGREZZA was evaluated in 3 placebo-controlled studies, each 6 weeks in duration (fixed dose, dose escalation, dose reduction), including 445 patients. Patients were 26 to 84 years of age with moderate to severe tardive dyskinesia and had concurrent diagnoses of mood disorder (27%) or schizophrenia/schizoaffective disorder (72%). The mean age was 56 years. Patients were 57% Caucasian, 39% African-American, and 4% other. With respect to ethnicity, 20% were Hispanic or Latino. All subjects continued previous stable regimens of antipsychotics; 85% and 27% of subjects, respectively, were taking atypical and typical antipsychotics. Of the 445 patients who entered the studies, 261 patients were treated with INGREZZA (40 mg once daily). The mean time from the last dose of antipsychotic agent to baseline was 6 days. Patients on chronic antipsychotics were allowed to remain on their current antipsychotic regimen, including those who had not been treated with a neuroleptic for at least 14 days. All regimens of antipsychotics were considered at stable levels (±10% of target dose). Patients on a single antipsychotic agent were required to be on stable dosing ±10% for at least 1 month prior to baseline.

Adverse Reactions Leading to Discontinuation of Treatment
A total of 3% of INGREZZA-treated patients and 2% of placebo-treated patients discontinued because of adverse reactions.

Common Adverse Reactions
Adverse reactions that occurred in the 3 placebo-controlled studies at an incidence of ≥2% and greater than placebo are presented in Table 1.

Table 1: Adverse Reactions in 3 Placebo-Controlled Studies of 6-week Treatment Duration Reported at ≥2% and Greater than Placebo

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>INGREZZA (n=262) (%)</th>
<th>Placebo (n=139) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence (somnolence, fatigue, sedation)</td>
<td>10.9%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticholinergic effects (dry mouth, constipation, disturbance in attention, vision blurred, urinary retention)</td>
<td>5.4%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Balance disturbance (fall, gait disturbance, dizziness, balance disorder)</td>
<td>4.1%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Headache</td>
<td>3.4%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Alkaline (alkalosis, renitenseness)</td>
<td>2.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Musculoskeletal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2.3%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Within each adverse reaction category, the observed adverse reactions are listed in order of decreasing frequency.

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

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

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

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

Infectious System Disorders: hypersensitivity reactions (including allergic dermatitis, angioedema, pruritis, and urticaria)
Skin and Subcutaneous Tissue Disorders: rash

DRUG INTERACTIONS
Dosing has Clinically Important Interactions with INGREZZA

Table 2: Clinically Significant Drug Interactions with INGREZZA

<table>
<thead>
<tr>
<th>Monamine Oxidase Inhibitors (MAOIs)</th>
<th>Clinical Implication</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use of INGREZZA with MAOIs may increase the concentration of monamine neurotransmitters in synapses, potentially leading to increased risk of adverse reactions such as serotonin syndrome, or attenuated treatment effect of INGREZZA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention or Management</td>
<td>Avert concomitant use of INGREZZA with MAOIs.</td>
<td></td>
</tr>
<tr>
<td>Examples</td>
<td>isocarboxazid, phenelzine, selegline</td>
<td></td>
</tr>
</tbody>
</table>

Strong CYP3A4 Inhibitors

Clinical Implication
Concomitant use of INGREZZA with strong CYP3A4 inhibitors increased the exposure (Cmax and AUC) to valbenazine and its active metabolite compared with the use of INGREZZA alone. Increased exposure of valbenazine and its active metabolite may increase the risk of exposure-related adverse reactions.

Prevention or Management
Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP3A4 inhibitor.

Examples | troleandomycin, voriconazole, clarithromycin |

Strong CYP2D6 Inhibitors

Clinical Implication
Concomitant use of INGREZZA with strong CYP2D6 inhibitors increased the exposure (Cmax and AUC) to valbenazine’s active metabolite compared with the use of INGREZZA alone. Increased exposure of valbenazine and its active metabolite may increase the risk of exposure-related adverse reactions.

Prevention or Management
Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP2D6 inhibitor.

Examples | quinidine, paroxetine, fluoxetine, quinidine |

Strong CYP3A4 Inducers

Clinical Implication
Concomitant use of INGREZZA with a strong CYP3A4 inducer decreased the exposure of valbenazine and its active metabolite compared to the use of INGREZZA alone. Reduced exposure of valbenazine and its active metabolite may reduce efficacy.

Prevention or Management
Concomitant use of strong CYP3A4 inducers with INGREZZA is not recommended.

Examples | rifampin, carbamazepine, phenytoin, St. John’s wort |

Dopamine

Clinical Implication
Concomitant use of INGREZZA with dopamine increased dopamine levels because of inhibition of intestinal P-glycoprotein (P-gp).

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

Other Adverse Reactions Observed During the Premarketing Evaluation of INGREZZA

Dosing adjustment for INGREZZA is not necessary when used in combination with substrates of CYP1A2, CYP2B6, CYP2C9, CYP3A4/5 based on in vitro study results.

OVERDOSAGE

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

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

For further information on INGREZZA, call 844-INGREZZA (844-647-3992).

Distributed by: Neurocrine Biosciences, Inc.
San Diego, CA 92130

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IN ADULT PATIENTS WITH TARDIVE DYSKINESIA (TD)
Choose INGREZZA for results you can see¹

INGREZZA® (valbenazine) capsules reduced TD severity at 6 weeks, with results you can start to see as early as 2 weeks¹ ³

Important Information

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WARNINGS & PRECAUTIONS (continued)

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ADVERSE REACTIONS

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

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

Please see the adjacent page for Brief Summary of Prescribing Information and visit www.Neurocrine.com/INGREZZAPI for full Prescribing Information.

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