Advice to Young Psychiatrists
From a Very Old One

recently came across this compelling tweet: “An open question on mental health as a junior psychiatrist: What do you think I should learn and focus on to be a better doctor and advocate for my patients?” Could there possibly be a better question for all people starting out in any field to ask themselves, and others, as they embark on their careers? The 140-character limit imposed by Twitter forced me to offer only a brief reply containing five scant snippets of advice. This troubled me; his serious request deserved a more serious response. So, here it is—the 50 most important things I have learned in my 50 years studying psychiatry.

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SCHIZOPHRENIA AND PSYCHOSIS
Examining the Link Between the Immune System and Schizophrenia

Since prenatal and early life infections are associated with schizophrenia risk, there has been growing interest in an immune hypothesis of schizophrenia. For instance, a recent study found significantly increased neutrophils in patients with first-episode psychosis compared with controls, and higher neutrophil counts were associated with greater total and positive symptoms as well as reduced total brain gray matter volume on magnetic resonance imaging. Similarly, recent meta-analyses have found an increased ratio of neutrophils to lymphocytes and monocytes to lymphocytes in the blood of patients with psychosis.

To further explore this notion, Steiner and colleagues undertook a study of innate immunity in patients with first-episode psychosis and unmedicated schizophrenia compared with controls. The innate immune system—which includes monocytes and granulocytes—is the first line of defense and plays a key role in the body’s response to infection and injury. Understanding the role of the immune system in schizophrenia could provide new insights into the disease and potential therapeutic targets.

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

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

Important Safety Information

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

See full prescribing information for complete boxed warning

• Risk for sedation and dissociation after administration. Monitor patients for at least two hours after administration (5.1, 5.2).
• Potential for abuse and misuse. Consider the risks and benefits of using 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).

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, 49% to 61% of SPRAVATO™-treated patients developed sedation and 0.3% 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 75% of SPRAVATO™-treated patients developed dissociative or perceptual changes). Given its potential to induce dissociative effects, carefully assess patients with psychoses before administering SPRAVATO™; treatment should be initiated only if the benefit outweighs the risk.

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

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.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including boxed WARNINGS, on following pages.
SPRAVATO™ may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO™ in utero. Advise women of reproductive potential to consider pregnancy planning and prevention.

**Drug Interactions**

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

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

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

**Use in Specific Populations**

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

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

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

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

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

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

**Hepatic Impairment:** Spravato™ has not been studied in patients with severe hepatic impairment 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, dissociation, 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 AD (incidence 25% 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.

Please see Full Prescribing Information, including Boxed WARNINGS, on following pages.
SPRAVATO™ (esketamine) nasal spray, CIII

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

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

CONTRAINDICATIONS
SPRAVATO is contraindicated in patients with:
- Anorexymal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriosclerotic malformation (see Warnings and Precautions)
- History of intracranial hemorrhage (see Warnings and Precautions)
- Hypersensitivity to esketamine, ketamine, or any of the excipients.

WARNINGS AND PRECAUTIONS
Sedation
In clinical trials, 49% to 81% of SPRAVATO-treated patients developed sedation based on the Modified Observer’s Alertness/Sedation scale (MOAA/S) (see Adverse Reactions), and 0.3% of SPRAVATO-treated patients experienced loss of consciousness (MOAA/S score of 0). Because the effects of prolonged sedation in patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting (see Dosage and Administration (2.4) in Full Prescribing Information).

Closely monitor for sedation and concomitant use of SPRAVATO with CNS depressants (see Drug Interactions).

Dissociation
The most common psychological effects of SPRAVATO were dissociative or perceptual changes (including synesthesias of time, space and illusions), derealization and depersonalization (61% to 75% [see Adverse Reactions]).

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

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

Use in Specific Populations
Use in Pregnancy
There were differences in the incidence of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD). The drug had approximately a 6-fold increase in the number of cases of suicidal thoughts and behaviors per 1000 patients treated as provided in Table 1.

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
Age Range (Years) Drug/Placebo Difference in Number of Patients with Suicidal Thoughts or Behaviors per 1000 Patients Treated

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Drug/Placebo Difference in Number of Patients with Suicidal Thoughts or Behaviors per 1000 Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>Increases Compared to Placebo 14 additional patients 14 additional patients</td>
</tr>
<tr>
<td>18–24</td>
<td>Increases Compared to Placebo 5 additional patients 5 additional patients</td>
</tr>
<tr>
<td>25–64</td>
<td>1 fewer patient 1 fewer patient</td>
</tr>
<tr>
<td>≥65</td>
<td>6 fewer patients 6 fewer patients</td>
</tr>
</tbody>
</table>

* SPRAVATO is not approved in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors. Monitor all antidepressant-treated patients for clinical worsening and 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 (see Adverse Reactions).

Approximately 8% to 15% of SPRAVATO-treated patients and 1% to 3% of placebo-treated patients experienced an increase of more than 40 mmHg in systolic BP and/or 25 mmHg in diastolic BP in the first hour following 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) (see Contraindications).

BP should be monitored for at least 2 hours after SPRAVATO administration (see Dosage and Administration (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 hypereventilation) to emergency care.

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

Cognitive Impairment
Short Term Cognitive Impairment
In a study in healthy volunteers, a single dose of SPRAVATO caused cognitive performance decline 40 minutes post-dose. Compared to placebo-treated subjects, SPRAVATO-treated subjects required a greater effort to complete cognitive performance tests 40 minutes after treatment. 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 and memory impairment have been reported with continued 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 (see Clinical Studies (14.3) in Full Prescribing Information). The effects of SPRAVATO 84 mg were comparable to placebo at 8 hours and 18 hours post-dose. However, two SPRAVATO-treated subjects in one of these studies discontinued the driving test at 8 hours post-dose because of SPRAVATO-related adverse reactions.

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.

Ulcereous or Intestinal Cysts
Capsular or intestinal cysts have been reported in individuals with long-term off-label use of misuse/abuse of ketamine. In clinical studies with SPRAVATO nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, microntusion urgency, nocturia, and cystitis) in SPRAVATO-treated patients than in placebo-treated patients (see Adverse Reactions). No cases of esketamine-related intestinal cysts were observed in any of the studies, which included treatment of up to 2 years.

Counsel patients with a history of hyperactive encephalopathy, more intensive monitoring, including 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.

Seizure-Induced Cerebral Reperfusion Injury
In a study in healthy volunteers, a single dose of SPRAVATO caused a 50% reduced cerebral blood flow in a healthy volunteer. No adverse effects were observed in any of the subjects.

Other Adverse Reactions
Other adverse reactions observed in clinical trials included increased salivation, paresthesias, flushing, dysgeusia (change in taste), and sweating. The most common adverse reactions in clinical trials were increased salivation, sedation, dissociation, and abuse and misuse.

Concomitant Use
Before prescribing SPRAVATO™, please see full prescribing information, including boxed warning.
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]
- Increased in Blood Pressure [see Warnings and Precautions]
- Cognitive Impairment [see Warnings and Precautions]
- Impaired Ability to Drive and Operate Machinery [see Warnings and Precautions]
- Ucercative or Intestinal Cystitis [see Warnings and Precautions]
- Embryo-fetal Toxicity [see Warnings and Precautions]

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.

Patient Experience
SPRAVATO™ was evaluated for safety in 1709 patients diagnosed with treatment resistant depression (TRD) [see Clinical Studies (14.1, 14.2) in Full Prescribing Information] from five Phase 3 studies (3 short-term and 2 long-term studies) and one Phase 2 dose-ranging study. Of all SPRAVATO-treated patients in the completed Phase 3 studies, 478 (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 proportion were 5.6% and 3.1%, respectively. In Study 2, a long-term maintenance study, the discontinuation rates because of an adverse reaction were 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 (0.9%), blood pressure increased (0.6%), dizziness (0.6%), suicidal ideation (0.5%), dissociation (0.4%), nausea (0.4%), vomiting (0.4%), headache (0.3%), muscle weakness (0.3%), vertigo (0.2%), hypotension (0.2%), panic attack (0.2%) and sedation (0.2%).

Most Common Adverse Reactions
The most commonly observed adverse reactions in TRD patients treated with SPRAVATO plus oral AD (incidence ≥ 5%) and at least twice that of placebo nasal spray plus oral AD were dissociation, anxiety, 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 or equals to patients treated with placebo nasal spray plus oral AD.

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo Nasal Spray + Oral AD</th>
<th>SPRAVATO + Oral AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia*</td>
<td>6 (2%)</td>
<td>78 (23%)</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertigo*</td>
<td>78 (23%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>11 (3%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23 (7%)</td>
<td>12 (6%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>19 (5%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>98 (28%)</td>
<td>19 (9%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>32 (9%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>General disorders and site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling abnormal</td>
<td>12 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Feeling drunk</td>
<td>19 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure increased*</td>
<td>36 (10%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness*</td>
<td>101 (29%)</td>
<td>17 (8%)</td>
</tr>
<tr>
<td>Dysarthria*</td>
<td>15 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Dysgeusia*</td>
<td>66 (19%)</td>
<td>30 (14%)</td>
</tr>
<tr>
<td>Headache*</td>
<td>70 (20%)</td>
<td>38 (17%)</td>
</tr>
<tr>
<td>Hypoesthesia*</td>
<td>63 (18%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Lethargy*</td>
<td>37 (11%)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Mental impairment</td>
<td>11 (3%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Sedation*</td>
<td>79 (23%)</td>
<td>21 (9%)</td>
</tr>
<tr>
<td>Tremor</td>
<td>12 (3%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety*</td>
<td>45 (13%)</td>
<td>14 (6%)</td>
</tr>
<tr>
<td>Disassociation*</td>
<td>142 (41%)</td>
<td>21 (9%)</td>
</tr>
<tr>
<td>Euphoric mood</td>
<td>15 (4%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>29 (8%)</td>
<td>16 (7%)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poliuria</td>
<td>11 (3%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal discomfort*</td>
<td>23 (7%)</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>9 (3%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Tooth irritation</td>
<td>23 (7%)</td>
<td>9 (4%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>14 (4%)</td>
<td>5 (2%)</td>
</tr>
</tbody>
</table>

*The following terms were combined:
- Anxiety includes: agitation; anticipation anxiety; anxiety; fear; feeling jittery; irritability; nervousness; panic attack; tension

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo + Oral AD</th>
<th>SPRAVATO + Oral AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Number of patients</em></td>
<td>N=112</td>
<td>N=114</td>
</tr>
<tr>
<td>Sedation (MOAA/s ≤ 5)</td>
<td>11%</td>
<td>50%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo + Oral AD</th>
<th>SPRAVATO + Oral AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Number of patients</em></td>
<td>N=113</td>
<td>N=116</td>
</tr>
<tr>
<td>CADSS total score &gt;4 and change &gt;0</td>
<td>5%</td>
<td>61%</td>
</tr>
</tbody>
</table>

*Patients who were evaluated with MOAA/s

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

Table 6: Incidence in Blood Pressure in Double-blind, Randomized-controlled, Short-term Trials of SPRAVATO + Oral AD Compared to Placebo Nasal Spray + Oral AD in the Treatment of TRD

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo + Oral AD</th>
<th>SPRAVATO + Oral AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥180 mmHg</td>
<td>9 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>≥290 mmHg increase</td>
<td>28 (8%)</td>
<td>12 (17%)</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥110 mmHg</td>
<td>13 (4%)</td>
<td>10 (14%)</td>
</tr>
<tr>
<td>≥25 mmHg increase</td>
<td>46 (13%)</td>
<td>10 (14%)</td>
</tr>
</tbody>
</table>

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

Table 7: Incidence and Severity of Nausea and Vomiting in Double-blind, Randomized-controlled, Fixed-dose Study

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo + Oral AD</th>
<th>SPRAVATO + Oral AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>7 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Placebo Nasal Spray</td>
<td>115</td>
<td>31 (27%)</td>
</tr>
<tr>
<td>Placebo Nasal Spray + Oral AD</td>
<td>84 mg</td>
<td>37 (32%)</td>
</tr>
<tr>
<td>Placebo + Oral AD + Placebo + Oral AD + Placebo + Oral AD</td>
<td>28 to 84 mg</td>
<td>12 (11%)</td>
</tr>
</tbody>
</table>
SPRAVATO™ (esketamine) nasal spray, CIII

Sense of Smell
Sense of smell was assessed over time; no difference was observed between patients treated with SPRAVATO plus oral AD and those treated with placebo nasal spray plus oral AD during the double-blind maintenance phase of Study 2 [see Clinical Trials (14.2) in Full Prescribing Information].

DRUG INTERACTIONS

Central Nervous System Depressants
Concomitant use with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation [see Warnings and Precautions]. Closely monitor for sedation with concomitant use of SPRAVATO with CNS depressants.

Psychostimulants
Concomitant use with psychostimulants (e.g., amphetamines, methylphenidate, modafinil, armodafinil) may increase the risk of hypertension and/or tachycardia [see Warnings and Precautions]. Closely monitor blood pressure with concomitant use of SPRAVATO with psychostimulants.

Monoamine Oxidase Inhibitors (MAOIs)
Concomitant use with monoamine oxidase inhibitors (MAOIs) may increase blood pressure [see Warnings and Precautions]. Closely monitor blood pressure with concomitant use of SPRAVATO with MAOIs.

USE IN SPECIFIC POPULATIONS

Pregnancy

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

Risk Summary
SPRAVATO is not recommended during pregnancy. There are insufficient data on SPRAVATO use in pregnant women to draw conclusions about any drug-associated risk of major birth defects, miscarriages, stillbirths, or fetal outcomes. No published findings from pregnant animals treated with ketamine, the racemic mixture of esketamine and ketamine, SPRAVATO may cause fetal harm when administered to pregnant women [see Data]. Advocate pregnant women of reproductive potential to avoid exposing to SPRAVATO in utero. There are risks to the mother associated with untreated depression in pregnancy (see Clinical Considerations). If a woman becomes pregnant while being treated with esketamine should be discontinued and the patient should be counseled about the potential risk to the fetus.

Published studies in pregnant primates demonstrate that the administration of drugs that block N-methyl-D-aspartate (NMDA) receptors during the period of peak brain development increases neuronal cell death and can result in learning and memory deficits. There are no data on pregnancy exposure in primates corresponding to periods prior to the third trimester in humans [see Use in Specific Populations].

In an embryo-fetal reproduction study in rabbits, skeletal malformations were noted at maternally toxic doses when ketamine was intranasally administered. In a No Observed Adverse Effect Level (NOAEL) study, 0.03 times the maximum exposure that the human would receive during pregnancy (MRHD) of 84 mg/day. In addition, intranasal administration of esketamine to pregnant rabbits during pregnancy and lactation at exposures that were similar to those at the MRHD resulted in a delay in sensorimotor development in pups during the preweaning period and a decrease in motor activity in the post-weaning period.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Diseases-Associated Fatal and/or Embryo-Fetal Risk
A prospective, longitudinal study followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. The women who discontinued antidepressants were more likely to experience a relapse of depression than those who continued antidepressants. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

Data

Animal Data
Based on published data, when female monkeys were treated intravenously with racemic ketamine at anesthetic levels in the third trimester of pregnancy, neuronal cell death was observed in the brains of their fetuses. This period of brain development translates into the third trimester of human pregnancy. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuropathological correlates with long-term cognitive deficits.

Racemic ketamine was administered intraperitoneally to pregnant rats during the period of organogenesis at doses of 15, 50, and 150 mg/kg/day. Estimating 50% of the exposure to be from esketamine, the NOAEL associated with esketamine plasma exposure (AUC) is 12-times the AUC exposure at the MRHD of 84 mg/day. In pregnant rabbits, racemic ketamine was administered intranasal gestational day 6 to 18 at doses of 10, 30, and 100 mg/kg/day. The high dose was lowered to 100 to 50 mg/kg after 5 days of dosing due to excessive mortality in the pregnant rabbits. Skeletal abnormalities were observed at doses of 30 mg/kg/day, which were maternally toxic. The NOAEL for skeletal malformations was associated with a plasma esketamine exposure (AUC) that was 0.3 times the AUC exposure at MRHD of 84 mg/day.

Administration of esketamine to pregnant rats during pregnancy and lactation at intranasal doses equivalent to 4.5, 15, and 45 mg/kg/day (based on a 200-gram rat) produced AUC exposures of 0.07, 0.5, and 0.7 times the MRHD of 84 mg/day, respectively. Maternal toxicity was observed at doses ≥ 15 mg/kg/day. In addition, a dose-dependent delay in the age of attainment of Przer Mobility response reflected the NOAEL for this delay in sensory/motor response observed in pups during the preweaning period. This sensory/motor developmental measure was tested starting on postnatal day (PND) 9, and the effect normalized by PND 19 in treatment groups as compared with PND 14 for the majority of the control animals. There is no NOAEL for maternal toxicity and decreased maternal motor activity during the postweaning period was 4.5 mg/kg/day which was associated with a plasma exposure (AUC) that was 0.07-the AUC exposure at MRHD of 84 mg/day.

Lactation

Risk Summary
Esketamine is present in human milk. There are no data on the effects of SPRAVATO on the breastfed infant or on milk production. Published studies in juvenile animals report neurotoxicity [see Data]. Because of the potential for neurotoxicity, advise patients that breast-feeding is not recommended during treatment with SPRAVATO.

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

Contraception
Based on published animal reproduction studies, SPRAVATO may cause embryo-fetal harm when administered at human efficacious doses to pregnant rabbits. [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 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 TD 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 in the proportion of change from baseline to Week 4 on the Montgomery-Asberg Depression Rating Scale (MADRS).

Hepatic Impairment
The mean esketamine AUC and IIV values were higher in patients with moderate hepatic impairment compared to patients 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.

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 health care 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, flashbacks, hallucinations, and feelings of floating, detachment and to be “spaced out.” Monitoring for signs of abuse and misuse is recommended.

Physical dependence has been reported with prolongation of 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 substances and have 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) were 6.5 and 1.3 times the maximum recommended dose, respectively. No scores in the intranasate 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 “Indulging,” “Floating,” “Detached,” and “Spaced Out” than the 84 mg dose of intranasal SPRAVATO and the intranasal ketamine dose.

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).

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sp-81105v2
GETTING DOWN AND DIRTY

In today’s busy world, everyone is stretched thin for time. Information is coming from all directions, and we are expected to respond at a moment’s notice.

In chatting with you, our readers, we realize you are not exempt from the seemingly limitless demands from work, family, friends, your conscience, and so on. Since 1985, Psychiatric Times has provided you, the psychiatrist, clinical information you can use to help your patients by distilling and synthesizing current research, guidelines, practice trends, and real-life experiences from experts and thought leaders from around the world. We also share your colleagues’ insights, thoughts, frustrations, and triumphs in today’s world, from exploring the impact of culture on psychiatry and mental health, to the environment, to politics, and even entertainment.

To further support your needs, we have identified six areas within psychiatry that seem to resonate most with you and your practice needs: Addiction and Substance Use Disorders, Schizophrenia and Psychosis, Mood Disorders, Anxiety and Stress Disorders, Neuropsychiatric Disorders, and Psychosomatics. Look for these areas highlighted throughout the book. We welcome your feedback on the topics and this new initiative—you are always welcome to drop us a note at PTEditor@mmhgroup.com.

With that in mind, we invite you to read a report about new research on the link between the immune system and schizophrenia, which is highlighted on the cover. Also in this issue, Editorial Board member David N. Osser, MD, provides a brief tutorial explaining the role of lamotrigine in treating bipolar disorder, and Mark A. Oldham, MD, and colleagues present two cases of patients with comorbid psychiatric and medical problems. Plus, to keep you up-to-date, you will find recent conference coverage, with the speakers sharing their insights and take-home messages to improve clinical care. Rounding out our clinical articles, you will find discussions on gun violence as well as a new installment of the thoughtful and acclaimed Critical Conversations in Psychiatry series with Awais Afsah, MD.

Of course, we will continue to bring you the columns and features to which you look forward every issue. This month, the Special Report explores infectious diseases and their direct and indirect effects on mental health and your patients. Look for the piece by Gjumrakch Aliev, MD, PhD, and colleagues that discuss a link between infectious burden and Alzheimer disease. The article, “Psychiatry, Outbreaks, and Pandemics: Lessons Learned,” by Nidal Moukaddam, MD, PhD, helps us understand how infectious outbreaks have shaped the psyche of humanity for centuries (and beyond). And to help you earn CME credit, you can read about the link between the immune system and schizophrenia, which is further supported by new research.

Foremost, we hope you continue to find Psychiatric Times as your source of clinical news and information!
FROM THE EDITOR

Be Here Now

John J. Miller, MD | Editor in Chief

In the early 1960s two prominent Harvard University clinical psychology professors, Timothy Leary, PhD, and Richard Alpert, PhD (also known as Ram Dass), were researching the effects of LSD and psilocybin in a study named the Harvard Psilocybin Project. Two of the experiments known as the Concord Prison Experiment and the Marsh Chapel Experiment observed the effect of these hallucinogens on prisoners and priests. Due to clear ethical professorial and research violations, both Leary and Alpert were fired from Harvard in 1963. After Leary’s departure from Harvard, he continued to lecture and write about the mind-altering effects of hallucinogens, which he himself had taken frequently with meaningful personal experiences. Alpert followed a different path. After several years of pursuing a pathway to “higher consciousness,” initially through continued experimentation with hallucinogens and then with spiritual practices grounded in meditation and yoga, Alpert decided to travel to India in 1967, where he underwent a personal transformation. Alpert was searching for a drug-free path to achieve the experiences of higher consciousness that he attained under the influence of hallucinogens. After studying under a guru in India and intensively practicing meditation, he felt personally transformed, and his guru gave him the new name Ram Dass. Upon returning to the US, he has spent the rest of his life teaching meditation, working with various non-profits, and promoting the practices of conscious living and conscious dying.

One of my favorite parts of Dass’s personal evolution is his relationship with his guide when he first travelled to India—still under the persona of Richard Alpert. Alpert would start to talk with his guide about how he had a PhD from Stanford University, was a professor of psychology and clinical researcher at Harvard University, and routinely bragged about his other personal achievements. Each time, his guide would interrupt Alpert and say, “none of that matters… just be here now,” the important lesson that Alpert would eventually internalize. This lesson later became the title of his first book as Dass “Be Here Now.”

I have been an explorer of philosophy, spirituality, and the world’s numerous religions since my high school years. However, not knowing the difference, this exploration was intellectual and not experiential. Unlike Dass, who underwent a tortuous journey to his discovery of the transformational power of meditation, I was fortunate to meet my teacher and mentor while a second-year medical student at the University of Massachusetts (UMass) Medical School in Worcester.

In 1979, Jon Kabat-Zinn, PhD, had started the first Mindfulness-Based Stress Reduction (MBSR) clinic in a US hospital at the UMass Medical Center to help medical patients with chronic pain and stress. He presented a lecture to my medical school class in 1983, teaching us about his MBSR program, and the impressive results he had demonstrated in these patient groups. I was impressed, as Jon seemed to have bridged the gap between the practice of mindfulness meditation and improved quality of life.
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Advice to Young Psychiatrists

1. Your patients will be your best teachers.
2. No meeting with any patient is ever routine for them, so it should never be routine for you.
3. Focus on establishing a strong therapeutic alliance and healing relationship. The most important goal of any first session is the patient’s returning for a second.
4. Helping serious mental illness is very much harder, but also much more gratifying, than treating mild illness or the worried well.
5. Validate that your patients are currently trying to do their best, but also set a tone of future expectations that they will find ways to change themselves, and their world, for the better.
6. Always inspire realistic hope and always reverse unrealistic demoralization.
7. Follow your patient—nay your preconceived notions, a supervisor, or a manual.
8. There are no bad or boring patients, but there are some bad and boring doctors.
9. Be as empathic, as caring, as involved, and as alert for the 10th patient each day as you did for the first.
10. Never lose sight of the practical struggles each patient faces in the real world and try to help them find practical solutions.
11. Do not be shy about giving advice when advice is needed.
12. Do not give advice when the patient can find his or her own way.
13. Include family, friends, other informants, and potential co-therapists whenever possible.
14. Be open ended enough in your questions to let patients tell their life stories and structured enough in your questions to get the specific information you need.
15. Try to create rare magic moments—things you say to patients that they will remember always and use in changing their lives.
16. Take your time and be careful. Small mistakes can have major consequences.
17. Know the patient, not just the diagnosis.
18. Diagnosis should almost always be written in pencil—especially in the young and the old. And, always err on the side of underdiagnosis—it is easier to later up-diagnose and almost impossible to erase a diagnostic error that can haunt the patient for life.
19. Use DSM, but do not worship it. Equally distrust clinicians who do not know DSM and those who only know DSM.
20. Educate patients about their symptoms, diagnosis, course, and the risks and benefits of plausible treatments.
21. Negotiate, do not dictate, the treatment plan: allow patients to pick whichever plausible treatment most suits them with awareness that no one size fits all.
22. Do not join the bandwagon of diagnostic fads. Whenever everyone seems to suddenly have a diagnosis, it is surely being way overdone (eg, attention deficit hyperactivity disorder, autism, bipolar disorder).
23. Watchful waiting is the best treatment whenever there is doubt or the symptoms are mild.
24. Placebo is the best “medicine” ever invented and responsible for most of what appears to be drug effect when milder symptoms improve.
25. Severe illness is usually easy to diagnose reliably and always requires urgent intervention.
26. Always rule out the real possibility that symptoms are caused by medications, alcohol, street drugs, or medical illness.
27. Don’t be a careless pill pusher, but do understand the great value of medications used wisely for proper indications.
28. Know the risks, not just the benefits, of medications.
29. Educate your patients on adverse effects, complications, and withdrawal symptoms.
30. Be alert to, and try to avoid, drug-drug interactions. Include in your consideration all the many non-psychiatric medications the patient is likely to be taking.
31. Start low and go slow especially with young and old patients.
32. De-prescribing requires much more skill than prescribing—learn it well and apply it often to reduce the harms caused by over-medication.
33. Avoid the current tendency toward irrational poly-pharmacy.
34. Learn about and use three treatments that are very effective, but relatively harder to use and thus very underutilized: lithium, clozapine, and electroconvulsive therapy.
35. Cautiously meet with drug sales people; be skeptical of their claims, but evaluate them carefully and educate patients to be critical of direct-to-consumer drug ads that misleadingly promote disease mongering.
36. Read the scientific literature with great skepticism and awareness that most studies do not replicate, positive results are always exaggerated, and negative results are usually buried. Do not be bewitched by genetic findings—so far, they have flopped in finding causes and have no place in planning treatments.
37. Uncertainty sure beats false certainty; Accept its inevitability; do not jump to conclusions, and help your patients deal with the anxiety it provokes.
38. Learn statistics, especially as they apply to medical decision making and think probable not rigid yes/no categories.
39. Have a rich, varied, and satisfying personal life.
40. Embark on a personal psychotherapy to help understand yourself better, solve any problems you may have, correct biases based on your personality and experiences, and discover what it is like to be a patient.
41. Learn from your supervisors, but do not follow them slavishly.
42. Read widely, especially the great classic novels, and see psychologically astute movies and plays.
43. Read history and try to deduce its recurring patterns.
44. Travel the world to understand the wide diversity of human experience.
45. Do not impose your cultural biases, your religious beliefs (or non-beliefs), or personal values on your patients.
46. For every complex question, there is a simple, reductionistic answer—and it is wrong. Do not expect or believe simple answers to complex questions, such as “What causes mental illness and how best to treat it?”
47. Instead, do have a well-rounded, four-dimensional bio/psycho/social/spiritual approach to understanding mental disorders and selecting treatments for them.
48. Be a vocal advocate for our patients. We must do all in our power to reverse the shameless neglect of the severely ill that has relegated 600,000 of them to jail or homelessness.
49. Be yourself—and grow into an even better version of yourself as you enjoy the special privilege of helping others better themselves.
50. FIRST, DO NO HARM!

Dr Frances is Professor Emeritus and former Chair, Department of Psychiatry, Duke University; Chair, DSM-IV Task Force. He is the author of Saving Normal and Essentials of Psychiatric Diagnosis. Twitter: @AllenFrancesMD.
FROM THE EDITOR

Be Here Now
Continued from page 6

life. I remind myself often of Jon’s definition of mindfulness: “Paying attention, on purpose, in the present moment, in the service of self-understanding,” and I frequently re-read sections of his first two books.²³

My third year of medical school was extremely stressful for me. After reveling in the first two years of medical school, which focuses on the basic sciences and lecture format classes in the many disciplines that are foundational to the practice of medicine, as you recall, the third year consists of clerkships where the medical student is immersed in the many basic specialties of medicine.

During my third year, we spent 10 weeks embedded in the hospital-based practices of internal medicine and surgery, and five weeks in pediatrics, obstetrics and gynecology, psychiatry, and family practice. Having no prior clinical experience and having been trained as a researcher in molecular genetics, I felt like a fish out of water—a very incompetent and highly stressed fish at that. Remembering Jon’s mindfulness program, I approached him and set up the first behavioral medicine fourth year medical student clerkship at Jon’s MBSR.

I attended the program as a participant, and quickly realized experientially the power of mindfulness meditation to provide me a tool to manage my own stress. Jon’s program had such an impact on me that I chose psychiatry as my specialty after medical school. I spent half of my fourth-year residency in psychiatry engaged in research at Jon’s clinic evaluating the benefits of MBSR in the treatment of anxiety disorders.

Realizing the time between the end of my psychiatry residency training program and beginning my life’s profession as a psychiatrist was a unique opportunity for an adventure that might otherwise have to wait until I retired, I attended a 90-day residential silent mindfulness meditation retreat at the Insight Meditation Society in Barre, Mass.—a meditation center I had frequented often during my years as a resident in psychiatry. From September through December 1991, I lived in a small 6- by 10-foot room with a futon mattress on the floor, living in silence with 100 co-retreatants who had also taken the 90-day vow of silence. The instructions were simple: be mindful of everything—formal meditation practice in the hall, eating meals, walking in the woods, judging oneself, judging others, pain, pleasure, boredom, sleepiness, joy, sadness, fun memories, painful memories—everything. These 90 days of silence in a small farming town in central Massachusetts were extremely difficult, with moments of significant insights into the nature of my own mind.

Since 1992, I have volunteered as the consulting psychiatrist at the Insight Meditation Society—a relationship that I greatly value on many levels. I continue to practice mindfulness on a daily basis, and I realize I am still a beginner. In next month’s editorial I will delve deeper into the practice of mindfulness, and how it has become a foundational treatment in the various mental health professions.

REFERENCES

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Gun Violence and Medical Professional Organizations: Political Business as Usual?

Liza H. Gold, MD

In November 2018, the National Rifle Association (NRA) taunted physicians by tweeting, “Someone should tell self-important anti-gun doctors to stay in their lane.” In response, physicians, including psychiatrists, insisted that firearm death, suicide, injury, and trauma are indeed our lane. Both before and after the NRA warned us not to cross their imaginary line, physicians and our professional organizations increasingly have been calling for gun violence to be addressed as a public health crisis and have been proposing interventions to stem the tide of blood.

The American Psychiatric Association has been a leader in confronting the problem of gun violence, the leading cause of preventable injury and death in the US. Each year, firearms kill close to 40,000 people and injure another 70,000. Two thirds of all firearm deaths, the largest single category, are firearm suicides.

In 2014, the APA issued a position paper (and updated it in 2018) calling gun violence a public health problem in need of immediate action. In 2015, the APA along with eight other professional medical organizations jointly issued a “Call for Action,” advocating policies intended to mitigate the rate of injuries and deaths due to firearms. In 2019, the APA participated in a medical summit of 44 major medical and injury prevention organizations to address the gun violence problem.

The APA and other medical, injury prevention, and public health organizations have advocated for a number of actions: expanding background checks; requiring waiting periods on all gun transactions; requiring safe storage of all firearms in the home; banning assault weapons and high-capacity magazines; and allocating funding for federal firearms research. Many of these measures are widely supported by the American public across party and demographic lines. A September 2019 poll found that 86% of Americans support implementing red flag provisions allowing law enforcement to temporarily seize guns from people in crisis. Similarly, 89% support expanding federal background checks to cover private sales and gun-show transactions.

Although the cultural status quo on gun reform is shifting, the political status quo, at least on the federal level, continues to block any legislative intervention. The nonpartisan Center for Responsive Politics (opensecrets.com) estimated that during the 2016 election, the NRA and its affiliates spent a record $54 million to secure Republican control of the White House and Congress, including at least $30 million to help elect Donald Trump. Thus, these politicians’ investment in (and defense of) the political status quo from which they personally benefit may have become more obvious but is hardly surprising.

In contrast, most psychiatrists are likely to be surprised to find that the APA’s Political Action Committees (PAC) contributes more money more often to the campaigns of federal politicians whose positions do not align with the APA’s stated public health policy on firearm regulation reform compared with those who do. In their study of the PAC donation patterns of the 25 largest professional medical organizations regarding firearm safety, Schuur and colleagues found that the APA PAC donated $172,500 to NRA A-rated candidates for Congress, and $154,500 to candidates with any other rating (B-F) in the 2016 election cycle. Politicians with NRA A ratings can be counted on to oppose evidence-based firearm regulation, to vote reflexively against gun reform legislation, to blame gun violence on people with mental illness, and to continue to deny federal funding for firearm research.

The APA PAC is not alone in undermining its organization’s public position on firearm safety reform. By all measures investigated, almost all of the 25 medical organization PACs evaluated by Schuur and colleagues demonstrated a similar pattern of donations. This includes the American Medical Association (AMA; $574,500 to $420,500), the American College of Surgeons (ACS; $257,500 to $185,500), and the American College of Emergency Physicians (ACEP; $716,900 to $344,500).

In 2016 alone, health organization PACs donated about $5.5 million to NRA A-rated candidates as opposed to $4 million to candidates with any other rating. Schuur and colleagues concluded that their findings demonstrate a donation pattern on the part of 20 out of 25 PACs that “appears to be inconsistent with and a barrier to effective public health advocacy for firearm safety.”

In a related study, Neufeld and colleagues compared 2018 donations to individual politicians from physician organization PACs and the National Rifle Association Victory Fund (NRA PVF), focusing on seven organizations with published firearm injury prevention policies, including the APA, the AMA, the ACS, and the ACEP. Of the 141 members of Congress who received donations from both physician organization PACs and the NRA PVF (political victory fund), the NRA PVF rated 139 candidates as having greater than 90% NRA approval rating; 70.2% of the candidates received more funds from the medical organization PACs than from the NRA PVF, despite their votes against policies endorsed by the physician organizations themselves.

Overall, combined physician organization PACs donated about $1.5 million to NRA backed candidates; the NRA PVG contributed a total of about $420,000 to these members of Congress. The authors concluded that donations make an impact on NRA-backed members of Congress and to align with their organization’s public health policies regarding firearms “Organizations wishing to make firearm violence and injury prevention a priority must consider redistributing political donations.”

Notably, Steven Sharfstein, MD, a past President of the APA, found similar donation patterns by the AMA’s PAC in 1994 and concluded that this practice belied the AMA positions on these important public health issues. Medical organization PACs also contribute to politicians who support firearm reform legislation. Donating to politicians on both sides of any issue is business as usual in Washington. However, as pointed out in the article, this does not explain why any PAC, including the APA PAC, would give significantly more money to representatives who disagree with their organizations’ official positions than to those who support them.

Nevertheless, political business as usual regarding gun violence is no longer acceptable, particularly for medical organizations. The APA PAC’s pattern of political contributions in direct opposition to the APA’s stated positions on firearm reform undermines our professional credibility. More importantly, the APA PAC is supporting a deadly status quo. The fact that politicians’ obstructionist stance invariably includes reflexively blaming gun violence on individuals with mental illness makes the APA PAC’s contributions...
Introduction

INFECTIOUS DISEASES AND PSYCHIATRY

The “Lumpers” and the “Splitters”

Jason Caplan, MD

During my fellowship training, an esteemed mentor distilled the chief philosophical difference between those of us in the specialty of psychiatry and our cousins in the specialty of neurology as the dichotomy of “lumpers” and “splitters.” He clarified that we psychiatrists see a group of symptoms (like hallucinations, delusions, social withdrawal) and lump them into a diagnosis (i.e., schizophrenia). Neurologists, on the other hand, tend to take a group of patients with similar symptoms and divide them among a multitude of diagnoses based on the order that the symptoms presented, the most predominant symptom, or other such criteria.

From a theoretical standpoint, he offered no judgment as to which was the most appropriate of these approaches. Pragmatically, though, he did underscore that the problem we face on the lumping side is that our bailiwick is constantly being whitewashed by our splitting counterparts. There is no clearer illustration of this issue than the interplay between mental illness and infectious disease.

The history of psychiatry is littered with examples of groups of patients considered mentally ill who were later found to have an infectious cause of their symptoms. Perhaps the chief landmark of this type of diagnostic transition is now well over a century old as the term general paralysis of the insane gave way to the diagnosis of neurosyphilis.

We have seen groups of patients cross the theoretical bridge from what many of us were taught to call primary mental illness to organic brain disease as the tools available to medicine allowed us to split off a specific causative mechanism for their symptoms. Some benefited from treatment directed at their pathogen, others endured the provision of an explanation without hope of improvement. Many found themselves outside the reach of psychiatric care regardless of whether their symptoms had changed.

We are now in an era where the acceleration of our ability to identify in vivo pathology of the central nervous system has birthed entire new diagnostic entities (see the burgeoning number of antibody-specific subtypes of autoimmune encephalitis). To avoid psychiatry being left as “the specialty of emotional or behavioral symptoms that we do not have an explanation for (yet),” it behooves us to expand our diagnostic repertoire beyond the lumping constructs of symptom groupings.

To that end, in this Special Report we offer articles that address the interplay of psychiatric and infectious disease. The articles address the potential infectious causes of neuropsychiatric symptoms, the potential neuropsychiatric adverse effects of drugs used in the treatment of infectious diseases, and the role of psychiatry in the management of pandemics. All include information vital to maintaining our ability to provide timely diagnoses and effective treatment to the patients we serve.

Dr Caplan is Chair of Psychiatry, St Joseph’s Hospital and Medical Center, Phoenix, AZ. He reports no conflicts of interest concerning the subject matter of this Special Report.
SPECIAL REPORT

Psychiatric Disorders Are Infectious Agents to Blame?

Robert Volkken, MD, Cameron Quanbeck, MD, and Lisa Shwartz, NP, RN

The association between infection and psychiatric disorders was one of the milestones of early 20th century medicine. The identification of Treponema pallidum in the brains of individuals with “general paresis of the insane” by Noguchi and Moore in 1913 established the role of tertiary syphilis and showed that bacterial infections can cause long-term changes in both neurological and psychiatric functioning. The eventual development of treatments for syphilis and the subsequent curing of individuals with general paresis also showed that the discovery of an infectious cause of a neuropsychiatric disorder could be followed by effective treatment. The association between infection and some cases of psychiatric disorders was further solidified by the identification of an increased rate of encephalitis lethargica following the influenza epidemic of 1918-1919. Influenza control measures might be partially credited for the rarity of encephalitis lethargica in the modern era.

Since that time and until recently, the association between infection and psychiatric disorders has received less attention than other causes of psychiatric disorders such as emotional stress and genomics. However, there has been a resurgence of interest in the role of infections in psychiatric disorders because of a number of scientific advances in the understanding of how infectious agents and the immune response can alter brain functioning and affect human behavior.

“Alterations in gut-based immune markers have been found in several psychiatric disorders including schizophrenia, bipolar disorder, and MDD.”

One advance that has rekindled interest in a role for infectious agents is an increased understanding of the mechanisms by which a range of microorganisms can enter the central nervous system and establish long-term persistence within the human brain. It had been previously thought that infection of the brain would lead to characteristic signs of inflammation such as white cell infiltration, granulomas, and tissue destruction. Postmortem examination revealed that these features are uncommon in the brains of individuals with serious psychiatric disorders, thus suggesting that infection is uncommon in persons with these disorders. However, recent discoveries have shown that many neuropathic infectious agents have complex mechanisms that allow them to lie dormant within the brain for extensive periods with little evidence of classical inflammatory reactions. This concept is consistent with recent studies indicating that there is substantial immune activity in the brains and systemic circulation of individual with psychiatric disorders.

Microorganisms capable of his latency include a diverse range of taxa including viruses such as the herpesviruses herpes simplex virus types 1 and 2, cytomegalovirus, and Epstein Barr virus as well as retroviruses such as human immunodeficiency virus, measles virus, bacteria such as Chlamydiae and Borreliae, and protozoa such as Toxoplasma gondii.

Microglial activation

There has been an increased understanding of the workings of the immune system within the CNS. It is now clear that the immune system in the brain utilizes specialized cells and mechanisms not found in other parts of the body. This difference is best exemplified by the microglia, which are specialized cells within the brain that form during fetal development and are present from birth. While microglia have multiple biological activities, their main function is the monitoring of infections agents and the generation of a controlled immune response.

Microglia are activated following infection with viral, bacterial, fungal, and protozoan agents through a complex and highly refined process of signaling that is mediated by pattern recognition molecules called toll-like receptors. Microglial activation has been documented in a wide range of psychiatric disorders including schizophrenia, bipolar disorder, and autism. Because the pattern of response to infectious agents is similar, microorganisms from widely diverse taxa can cause similar activation of immune processes and, hence, similar clinical pictures.

The list of infectious agents with neuropsychiatric potential includes a diverse set of taxonomic kingdoms including viruses, bacteria, and protozoa, largely overlapping with the microorganisms capable of establishing latency within the brain. The concept that different microorganisms can cause similar clinical disorders represents a divergence from the usual conceptualization of infectious diseases: that each disorder is caused by a specific infectious agent and that each agent has an identifiable clinical effect.

This understanding, derived from Koch’s famous postulates, is useful for the study of many infectious disease. However, this concept has been less useful for the study of complex brain disorders due to the substantial overlap in the immune response to infectious agents within the brain. The role of the immune system also opens the possibility of immune-based therapies for psychiatric disorders, although these are mostly in the stages of development and evaluation.

Microglial activation can be measured in patients using neuroimaging techniques such as PET scanning. However, the optimal method for employing these scans and their sensitivity and specificity in clinical practice have not yet been defined. The pharmacological targeting of microglial activation remains a promising approach in terms of novel therapeutic interventions for a range of psychiatric disorders.

The gut-brain axis

Another advance in understanding the potential role of infections and inflammation in brain disorders are research findings that suggest the brain does not exist as an isolated organ but rather interacts with many other organ systems in the body. The gastrointestinal tract is the best characterized brain-interacting organ system. Numerous studies indicate that the gastrointestinal tract and the brain interact with each other by means of a series of networks categorized as the gut-brain-axis.

Clinical manifestations of the gut-brain axis have been long noted by clinicians who observed a high rate of gastrointestinal symptoms in individuals with psychiatric disorders.

SIGNIFICANCE FOR PRACTICING PSYCHIATRISTS

Ongoing research has identified multiple infectious diseases that may play a role in the development of neuropsychiatric disorders, particularly in people predisposed to genetic and environmental factors. Patient outcomes could improve as psychiatry expands to include the screening and treatment of these underlying infections, providing more precise treatment pathways for patients who are refractory to standard care.

Recent advances in understanding how the microbiome, the immune system, and the CNS interact have led to the identification of pathogens that play a role in psychiatric symptoms.

Psychiatric disorders share many genetic regions with genes that also encode for parts of the immune system (ie, the HLA network). This may explain why psychiatric symptoms have been associated with an altered immune response to several infectious diseases.

Further research is needed to improve methods for detecting brain inflammation and to identify pharmacological treatments to effectively manage persistent brain infections.

INFECTIOUS DISEASES AND PSYCHIATRY

November 2019

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and a correspondingly high rate of psychiatric symptoms in individuals with gastrointestinal disorders, particularly immune-based gastrointestinal disorders such as inflammatory bowel diseases. Alterations in gut-based immune markers have been found in several psychiatric disorders including schizophrenia, bipolar disorder, and major depressive disorder as well as in individuals who had a recent suicide attempt.

Recent studies have also shown that genetic differences can modulate the individual response to infectious agents. Many components of the immune system display individual variation based on genetic elements that comprise the human leukocyte antigen (HLA) and other immune networks. This immune variation is likely to explain much of the individual variation in response to infectious agents. For example, not every person who is exposed to the protozoan Toxoplasma gondii is at an increased risk for a psychiatric disorder—some of the variation apparently results from genetic differences.

In the case of Epstein Barr virus, increased risk of schizophrenia appears to be associated with an altered immune response to viral proteins, some of which is likely to be under genetic control. Furthermore, many microbial agents also have their own genomes, which can vary and define differing degrees of pathogenicity. For example, some strains of Toxoplasma gondii appear to be more associated with psychiatric disorders than others.

Interestingly, many of the genetic regions associated with increased risk of psychiatric disorders have been shown to encode components of the immune system and other immune active proteins. This finding suggests that some of the genetic risk of psychiatric disorders lies in variations in the immune response to infectious agents. In this scenario, many cases of psychiatric disorders represent an environmental exposure occurring in a genetically susceptible individual in a manner characterized as representing gene-environment interactions.

The microbiome

Microbes can also interact with each other within the gastrointestinal tract and other mucosal sites. This combination of microbes within the gastrointestinal tract has been characterized as the microbiome. Each person’s microbiome is established in early life and is determined by genetic and environmental factors. Environmental factors that shape the microbiome include exposure to microbial agents through breast feeding and household contacts, exposure to viruses and other agents that infect the gastrointestinal tract, exposure to allergens and diet.

The microbiome can also be altered by antibiotics and other pharmacological agents including many medications that are used to treat psychiatric disorders. Numerous studies have documented altered microbial composition in samples from individuals with a range of psychiatric disorders including schizophrenia, recent onset psychosis, bipolar disorder, and autism.

The microbiome can also affect the metabolism and pharmacokinetics of orally administered therapeutic agents. Person to person differences in the microbiome might thus explain some of the individual variation noted in the response to orally administered psychotherapeutic agents.

Another intriguing aspect of the microbiome is that it can be manipulated therapeutically by low-toxicity modalities. One type of intervention involves the administration of non-pathogenic microorganisms that can colonize the gastrointestinal tract, generally termed probiotics. Another intervention involves the administration of substances, generally non-digestible sugars called oligosaccharides that are nutrients for non-pathogenic bacteria in the diet and hence can indirectly alter the microbiome. Such probiotics can also be combined with probiotics to generate what has been characterized as synbiotic preparations.

The potential role of probiotic agents in psychiatric disorders is evidenced by some recent research. One study documented that the administration of a probiotic preparation administered with standard medications prevented relapse in individuals dissatisfied after hospitalization for acute mania. Another study showed that a similar probiotic preparation improved gastrointestinal symptoms and decreased markers of inflammation in individuals with schizophrenia, although psychiatric symptoms were not significantly altered.

Additional studies are needed to define the optimal dosage and composition of probiotic regimens as well as optimal treatment regimens. In addition, methods for documenting potency and shelf life of different commercially available preparations are needed. For these reasons, probiotic or previous preparations are not currently recommended for general use in the prevention or treatment of psychiatric disorders.

Antibiotics have been shown to increase the incidence of psychiatric disorders when administered in childhood, and the administration of antibiotics has been shown to be increased before hospital admission for a psychiatric disorder. These studies suggest that alterations in the microbiome might also have adverse effects and that the judicious use of antibiotics and the normalization of the microbiome following antibiotic use might be way to prevent some cases of psychiatric disorders.

Conclusion

The resurgence of interest in the role of infections and inflammation in serious psychiatric disorders provides exciting opportunities in terms of novel diagnostic methods and therapeutic interventions.

“The resurgence of interest in the role of infections and inflammation in serious psychiatric disorders provides exciting opportunities in terms of novel diagnostic methods and therapeutic interventions.”

REFERENCES

Psychiatric Adverse Effects of Antibiotics

» Megan K. Skelly, PharmD, Bethany A. Wattengel, PharmD, Kaitlyn E. Starr, PharmD, John A. Sellick, Jr, DO, MS, and Kari A. Mergenhagen, PharmD

Central nervous system effects of clarithromycin, beta-lactams, and fluoroquinolones occur because of their GABA-A antagonist action. Agents that have dose-dependent activity include: Linezolid, which can exhibit CNS activity via its monoamine oxide (MAO) inhibitor activity; metronidazole, which causes neuropsychiatric effects with cumulative or supratherapeutic levels; and tetracyclines, which are more likely to cause CNS effects in patients with reduced CYP2C19 activity. Nearly all antibiotic agents have been associated with CNS effects. Although uncommon, these events can be severe. Once the antibiotic is discontinued, effects are usually reversible. It is important for mental health care providers to recognize antibiot-
cic effects as a potential cause of neuropsychiatric adverse effects, as discontinuation often leads to rapid recovery.

Beta-lactams
Beta-lactams include penicillins, cephalosporins, and carbapenems. Generally, they are considered broad spectrum antibiotic agents that may act as GABA-A antagonists in a dose-dependent fashion to produce neurotoxicity. The beta-lactam ring is structurally similar to the GABA antagonist bicuculline. CNS effects include seizures, encephalopathy, tremors, hyperactivity, and excitation.

Penicillins. Piperacillin/tazobactam and ampicillin are the penicillins most likely to contribute to CNS adverse effects. Quinton and colleagues examined the effects of a piperacillin/tazobactam continuous infusion and found symptoms such as decreased level of consciousness, delayed awakening after sedation cessation, myoclonus, seizures, and hallucinations. The onset of piperacillin/tazobactam neurotoxicity is usually within seven days, with renal impairment as a predisposing factor. Ampicillin neurotoxicity is more likely to occur in low-birthweight infants where there is increased permeability of the blood-brain barrier.

Cephalosporins. Cefepime and cefazidime are the most common cephalosporins to cause nonconvulsive status epilepticus, which presents as altered mental status. In critically ill patients, myoclonus and decreased consciousness were the most common symptoms of cepetime-associated neurotoxicity. Renal impairment appears to be the largest risk factor, and discontinuation of the cephalosporin results in resolution of symptoms.

Carbapenems. Carbapenems are associated with seizure activity because of its antagonism of the GABA-A receptor. Risk factors for seizure activity include renal insufficiency, advanced age, history of seizures, and stroke. Ertapenem has been associated with psychosis—patients have presented with delusions and both visual and auditory hallucinations. Neurotoxicity from ertapenem can persist for up to 14 days after discontinuation. Meropenem and ertapenem may also cause delirium.

Metronidazole
Metronidazole is used for protozoal infections and bacterial vaginosis. It is also used for anaerobic coverage in intra-abdominal infections and for toxic megacolon caused by Clostridium difficile. Metronidazole can cause psychosis; it is thought to be a result of inhibition of monoamine oxidase (MAO), a dopamine catabolizing enzyme. Psychosis generally resolves within 14 days of discontinuation. Contributing factors for psychosis include the concurrent use of disulfiram and supratherapeutic metronidazole levels. Cumulative metronidazole exposure is believed to contribute to neurotoxicity (doses 13-228 g). Seizures have been linked to cumulative doses of more than 40 grams. Impaired renal or hepatic function are risk factors for supratherapeutic levels and cumulative exposure, thereby increasing the risk of adverse effects.

Other neurotoxic symptoms associated with metronidazole include peripheral neuropathy, paresthesia, ataxia, and encephalopathy. Slow onset myoclonus is a common feature of metronidazole induced encephalopathy. These adverse effects may be due to metabolites of metronidazole which inhibit the GABA receptor in the vestibular and cerebellar system.

Macrolides
Macrolides, including clarithromycin, azithromycin, and erythromycin, are used to treat respiratory infections, peptic ulcer disease caused by Helicobacter pylori, sexually transmitted diseases, and mycobacterium avium complex. Of the macrolides, clarithromycin has been associated with the most CNS adverse effects. Neurotoxicity associated with clarithromycin can manifest as mania, delirium, acute psychosis, and even hallucinations. It is also one of the most common causative agents of antibiotic, referring to antibiotics that can cause mania. A few case reports of clarithromycin-induced psychiatric manifestations in children describe a different clinical picture with symptoms that range from hypomania and aggression to insomnial and even hypersonmia. Visual hallucinations have been reported in patients taking clarithromycin in the setting of end-stage renal disease. Although rare, there are case reports of azithromycin causing psychosis, delirium, and hallucinations in elderly patients who did not have an underlying psychiatric disorder. It may be that the CNS effects of macrolides are due to GABA-A antagonism because of their ability to produce epileptogenic activity. Other theories include drug interactions and accumulation of clarithromycin’s active metabolite, as macrolides are substrates of CYP3A4 (clarithromycin and erythromycin are also CYP3A4 inhibitors).

Fluoroquinolones
Fluoroquinolones are among the most frequently reported causes of antibiotic-induced neuropsychiatric reactions. Based on a recent study, fluoroquinolones may be more commonly associated with delirium and psychosis than previously thought. Like macrolides, it is suspected that GABA-A antagonism causes proconvulsant activity, leading to adverse CNS effects. Additionally, fluoroquinolones have been reported to affect N-methyl-D-aspartate (NMDA) receptors in vitro, but further studies are needed to fully elucidate its mechanism.

The most common neuropsychiatric-related adverse effects from fluoroquinolones are excitatory effects, including insomnia, dizziness, headache, nervousness, and restlessness, which usually resolve upon discontinuation. Fluoroquinolone antibiotics can also cause more serious reactions. They have a black-box warning for potentially disabling and irreversible adverse effects including CNS events. Seizures and status epilepticus can occur due to GABA-A inhibition. Therefore, fluoroquinolones should be used with caution in patients with a history of epilepsy. Encephalopathy, antiionemia, delirium, hallucinations, and acute psychosis are among the other neurotoxic manifestations associated with fluoroquinolones.

Findings indicate that nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk for neurotoxicity when given concomitantly with fluoroquinolones. A single-center, retrospective study of 631 hospitalized veterans who received a fluoroquinolone for at least 48 hours found that FQ-induced delirium or psychosis was more prevalent in elderly patients and in...
those who were prescribed a first-generation antipsychotic. Caution is advised when prescribing fluoroquinolones in this patient population.

**Oxazolidinones**

Linezolid and tedizolid comprise the oxazolidinone class of antibiotics. These antibiotics are used for vancomycin-resistant *Enterococcus* and methicillin-resistant *Staphylococcus aureus* infections. Skin and skin structure infections and pneumonia are common indications for oxazolidinone antibiotics.

Linezolid exerts its CNS action through MAO inhibition, which is an enzyme responsible for the metabolism of monoamine neurotransmitters (dopamine, norepinephrine and serotonin). Tyramine-rich foods and co-administration with other serotonergic medications may enhance the risk of hypertensive crises and serotonin syndrome. The significance of this interaction, however, has been questioned due to linezolid’s low affinity for MAO and subsequent low degree of MAO inhibition.

There are limited neuropsychiatric data available for tedizolid, however, in vitro testing showed that tedizolid reversibly inhibited MAO enzymes similar to linezolid. Therefore, similar precautions are advised for tedizolid.

Linezolid has also been associated with peripheral and optic neuropathy, with vision loss in adults and children. This adverse reaction appears to primarily occur with extended courses of therapy (ie, longer than 28 days). Peripheral neuropathy appears to be most commonly reported and can be permanent. Optic neuropathy typically improves or completely resolves after discontinuation of linezolid, although it may occasionally be permanent.

The mechanism of neuropathy is thought to be due to inhibition of protein synthesis and subsequent mitochondrial injury, in addition to its ability to penetrate the CNS. Several reviews indicate risk factors for developing linezolid associated-neuropathy are pre-existing neurologic disease, alcohol abuse, diabetes, chemotherapy, and antiviral therapy.

**Nitrofurans**

Nitrofurantoin is used for the treatment and prophylaxis of cystitis. This antibiotic has been associated with peripheral neuropathy. Although the association of nitrofurantoin with peripheral neuropathy is rare, the risk appears to be increased in patients with anemia, renal impairment (CrCl < 60 mL/m), diabetes mellitus, vitamin B deficiency, debilitating disease, or electrolyte imbalance. The onset of neuropathy also appears to be dose and duration independent.

The exact mechanism inciting nitrofurantoin-associated neuropathy is unknown; however, it may be due to axon loss. A literature review found that neuropathy developed primarily in patients who had impaired renal function, noted by uremia. The combination of uremia and serum accumulation of nitrofurantoin could potentially contribute to neuropathy. Caution should be used when using nitrofurantoin in patients with these conditions.

**Sulfonamides**

Sulfamethoxazole-trimethoprim is a sulfonamide antibiotic that works via interference of folic acid synthesis. It has gram negative and positive activity and is approved for the treatment of a variety of infections including skin and skin structure, urinary tract, and some respiratory tract infections.

Psychiatric effects of sulfamethoxazole-trimethoprim have been well described, with reports dating as far back as 1942. Originally, most psychiatric symptoms were associated with use of sulfamethoxazole-trimethoprim for treatment of urinary tract infections. However, immunocompromised patients are at increased risk for acute psychosis. Geriatric patients also appear to be at an increased risk for neuropsychiatric effects, specifically hallucinations and psychosis, which is likely due to increased rates of renal impairment. Other neuropsychiatric effects include neurotoxicity, hallucinations, depression, apathy, nervousness, and other general psychotic symptoms. Sulfonamide antibiotics have the ability to cross the blood-brain barrier, which may account for the development of such effects. A glutathione and tetrahydrobiopterin deficiency has also been postulated. Episodes of aseptic eosinophilic meningitis have additionally been described, possibly due to a type I hypersensitivity reaction.

It appears that a temporal relation-

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**TABLE.** Various neuropsychiatric adverse effects caused by antibiotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>CNS MOA</th>
<th>ADR</th>
<th>Dose type</th>
<th>Crosses BBB</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-lactams</td>
<td>GABA-A antagonist</td>
<td>Seizures, hallucinations, delirium, psychosis</td>
<td>Dose dependent</td>
<td>Yes</td>
<td>Renal failure, advanced age, prolonged alcohol use, chronic benzodiazepine, vigabatrin, tiagabine, and valproic acid derivative use</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Unknown: possible GABA antagonist, inhibition of MAO</td>
<td>Paresthesia, neuropathy, seizures, ataxia, encephalopathy, psychosis</td>
<td>Dose dependent</td>
<td>Yes</td>
<td>Disulfiram use, cumulative exposure, supratherapeutic dosage levels</td>
</tr>
<tr>
<td>Macrolides</td>
<td>GABA-A antagonist</td>
<td>Mania, delirium, acute psychosis, hallucinations</td>
<td>Unclear</td>
<td>Yes</td>
<td>Psychiatric comorbidities, drug interactions</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>GABA-A antagonist; possible NMDA activity</td>
<td>Restlessness, anxiety, insomnia, headache, mania, acute psychosis, delirium, seizures</td>
<td>Dose dependent</td>
<td>Yes; least with levofloxacin</td>
<td>Epilepsy, NSAIDs, theophylline, atypical antipsychotics, antiretrovirals, advanced age, compromised renal/hepatic function</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Inhibition of MAO and protein synthesis (mitochondrial injury); CNS penetration</td>
<td>Peripheral neuropathy, optic neuropathy, serotonin syndrome, encephalopathy, delirium</td>
<td>Duration dependent</td>
<td>Yes</td>
<td>Prolonged therapy, pre-existing neurologic disease, alcohol abuse, diabetes mellitus, chemotherapy, antiviral therapy, concomitant serotonergic medications, consumption of food or beverages with high tyramine content</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Axon loss</td>
<td>Peripheral neuropathy</td>
<td>Duration dependent</td>
<td>Unknown</td>
<td>Anemia, renal impairment (CrCl &lt; 60 mL/m), diabetes mellitus, vitamin B deficiency, debilitating disease, electrolyte imbalance, advanced age</td>
</tr>
<tr>
<td>Sulfamethoxazole-trimethoprim</td>
<td>Glutathione deficiency, tetrahydrobiopterin deficiency, hypersensitivity</td>
<td>Acute psychosis, hallucinations, depression, apathy nervousness, aseptic eosinophilic meningitis</td>
<td>Dose dependent</td>
<td>Yes</td>
<td>Advanced age</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Unknown, blockage of mitochondrial calcium channels, retinal catabolism inhibition, NOS inhibition</td>
<td>Tinnitus, blurred vision, light headedness, dizziness, vertigo and loss of balance, pseudotumor cerebri, suicide</td>
<td>Possibly dose dependent</td>
<td>Increased ADRs in reduced CYP2C19 activity</td>
<td>Yes</td>
</tr>
</tbody>
</table>

MOA=mechanism of action; ADR= adverse drug reaction; BBB=blood brain barrier; CrCl=creatinine clearance.
ship exists, with neuropsychiatric symptoms often developing between 3 to 10 days following initiation of therapy. Effects have been shown to be dose dependent and resolve upon discontinuation of therapy. Reduction in infusion rate or change from intravenous to oral therapy has been shown to decrease the risk of or improve neuropsychiatric effects.

Tetracyclines

Tetracycline antibiotics, including doxycycline and minocycline, are approved for the treatment of respiratory infections, skin and soft tissue infections, and several tick-borne diseases. While there are some reports that tetracycline antibiotics—doxycycline, in particular—may have beneficial neuropsychiatric effects, the majority of the literature regarding tetracyclines does not support this.

Most of the literature regarding neuropsychiatric effects is on minocycline. The effects include vestibular symptoms such as tinnitus, blurred vision, light headedness, dizziness, vertigo, and loss of balance. The mechanism of injury from minocycline was originally thought to be due to changes in liquid volume and ion concentration secondary to its osmotic activity. Female gender and those of advanced age are at an increased risk for the development of these symptoms, probably because of the higher serum concentrations as a result of smaller body size and the lipophilic nature of minocycline.

Other neuropsychiatric adverse effects of tetracyclines vary in severity, with the most serious resulting in suicide. The suspected mechanism of action is suprapharmacologic levels as a result of CYP2C19 mutations. Pseudotumor cerebri is also a rare but serious adverse effect that may be due to decreased cerebrospinal fluid absorption. This is also a noteworthy reaction as related symptoms may be irreversible, despite discontinuation of therapy. Aside from pseudotumor cerebri and suicidality, neuropsychiatric symptoms are generally reversible with discontinuation of tetracycline therapy.

Conclusion

Monitoring, early detection, and discontinuation of the offending agent is essential for antibiotics that have the potential for neuropsychiatric adverse effects. Neuropsychiatric complications may be curtailed if prescribers are aware of the potential psychiatric reactions that exist among the various antibiotics. The Table provides a synopsis of the various neuropsychiatric reactions potentially caused by antibiotics. Depending on the pathogen, however, some antibiotics may be unavoidable. Therefore, early detection of any psychiatric disturbance is essential.

We can avoid repeated exposure to antibiotics that have caused neuropsychiatric events in patients by utilizing the allergy and adverse reaction section of the patient’s medical record. Although this seems redundant, it is often overlooked and not done in practice. Antibiotics have the potential to cause neuropsychiatric adverse events, which can complicate the treatment of infections in patients with other psychiatric conditions.

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11. Sivextro (tedizolid) [prescribing information]. Pfizer Inc; Updated: March 2019.

Gun Violence and Medical Professional Organizations

Continued from page 10

Donation decisions. Nevertheless, professional medical PACs raise their money almost exclusively from their organization’s members.

If the APA PAC and other medical affiliated PACs continue patterns of making political contributions in direct opposition to the APA’s and other affiliated medical organizations’ stated positions on firearm reform, physician members should consider whether they want to continue contributing to these PACs. It is not enough for the APA to take public positions about gun violence and public health. We can talk the talk, but our PAC needs to walk the walk. The gun violence epidemic is undoubtedly our lane. Let’s be the public health leaders America needs.

Dr Gold is Clinical Professor of Psychiatry, Georgetown University, Washington, DC.
Dark Chocolate for Depression

Chris Aiken, MD

Dark chocolate lowers the risk of depression, according to a cross-sectional survey of over 13,000 US adults. The study compared self-reported chocolate consumption with self-reported depressive symptoms, as measured by the Patient Health Questionnaire-9 (PHQ-9). People who ate dark chocolate in the past 24 hours were 70% less likely to report depression.

The same effects were not seen with milk chocolate, which suggests that the benefits were not simply due to the pleasures of consuming the food. Indeed, most people consider milk chocolate as the more pleasurable of the two. There is also the possibility that people who strive for a healthy lifestyle are more likely to consume dark chocolate. This treat, after all, has well-publicized health benefits, including prevention of cardiovascular disease, diabetes, and cognitive decline.

To disentangle confounding variables, the researchers controlled for other lifestyle factors, including physical activity, smoking, alcohol, and total sugar and caloric intake; they also controlled for age, sex, marital status, education, income, weight, and presence of chronic medical problems. In the end, the association remained. Once more, those who ate the largest quantities of chocolate had the lowest rates of depression.

In addition, it did not take much dark chocolate to achieve these antidepressive effects. On average, the consumers of dark chocolate ate only 12 grams a day, a little less than half an ounce. The cut-off for dark chocolate was 245% cocoa. In contrast, the optimal dose for physical health is 1 to 2 ounces a day of ≥70% cocoa. Keeping the percentage high and the ounces low maximizes the healthy ingredients while minimizing the calories and sugar.

Chocolate has long been associated with depression. Almost half (45%) of patients report craving chocolate during episodes of depression, and many believe that it relieves feelings of anxiety and irritability. Chocolate cravings are particularly high during atypical depression, winter depression, and premenstrual dysphoria.

However, two previous epidemiologic surveys arrived at the opposite conclusion of the current one, finding that chocolate consumption was associated not with mental health but with depressive symptoms. Those studies did not look specifically at dark chocolate, and they did not control for confounding variables as well as this study.

There are several mechanisms that may explain the putative antidepressant effects of dark chocolate:

1. Flavanols. These brain-protecting nutrients are particularly prominent in dark chocolate. They are also found in red wine, berries, apples, citrus, and green and black teas—all are associated with improvements in mood and cognition. Cocoa is the main source of theobromine, while caffeine is found in many foods.

2. Caffeine and theobromine. These adenosine-agonists have rapid effects on energy and cognition. Caffeine is an analogue of the adenosine receptor, which is an endogenous cannabinoid with anxiolytic and euphoric effects.

3. N-acyltylarnamines. This fatty acid is an analogue of anandamide, an endogenous cannabinoid with anxiolytic and euphoric effects.

4. Phenylethylamine. A natural monoamine that increases the release of norepinephrine, dopamine, and acetylcholine.

Studies of healthy volunteers attest to the mood-enhancing effects of chocolate, which relieve negative moods more effectively than spring water and other active controls. Although intriguing, these results are not definitive enough to foster sweeping recommendations of dark chocolate for depression. Dark chocolate is not without risks. It has been known to cause migraines, insomnia, kidney stones, and dental problems.

What this study does is reveal some of the guilt that accompanies the consumption of chocolate, particularly during depression. Even in the studies of participants with depression where chocolate enhanced mood, guilt was sometimes noted as an adverse effect. Chocolate is one of life’s pleasures, and pleasant feelings help pave the way out of depression. They give rise to altruism, creative problem solving, and social engagement.

Patients with depression are not the only ones who can benefit from those mental shifts. The cognitive benefits of chocolate apply to doctors as well. In the 1990s, a series of studies tested whether the positive mental state induced by chocolate could improve medical problem-solving skills. The researchers asked a group of doctors to make a diagnosis after reading through a folder of clinical data. Half of the doctors were given a small bag of Hershey’s Miniature Chocolates along with the reports and told not to eat them until the diagnostic work was completed. Just the idea of chocolate made a difference; the doctors who received it made more accurate diagnoses.

Dr. Aiken is the Director of the Mood Treatment Center and an Instructor in Clinical Psychiatry at the Wake Forest University School of Medicine. As the Editor in Chief of The Carlat Psychiatry Report, he hosts a weekly podcast with Kellie Newsome on psychiatric practice. He is the coauthor with Jim Phelps, MD, of Bipolar, Not So Much. He does not accept honoraria from pharmaceutical companies.

REFERENCES
Adhansia XR is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older.1

**ARE YOU TREATING YOUR PATIENT’S FULL DAY?**

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

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

**Important Safety Information**

**WARNING: ABUSE AND DEPENDENCE**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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


For more information, visit AdhansiaXR-hcp.com
ADHANSIA XR®
(methylphenidate HCI) extended-release capsules

BRIEF SUMMARY OF PRESCRIBING INFORMATION

FOR complete details, please see the Full Prescribing Information and Medication Guide.

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including ADHANSIA XR, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy. See Warnings and Precautions (4.1), Drug Abuse and Dependence (5.2). [DirecT]

4. CONTRAINDICATIONS

ADHANSIA XR is contraindicated in patients: • With a known hypersensitivity to methylphenidate or other components of ADHANSIA XR. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other methylphenidate products, see Adverse Reactions (5.1). • Receiving concomitant treatment with monoamine oxidase inhibitors (MAOIs), and also within 14 days following discontinuation of treatment with a MAOI, because of the risk of hypertensive crisis [see Drug Interactions (7.1)]. • With active or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression). Existing Psychosis CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder. Induction of a Manic Episode in Patients with Bipolar Disorder. CNS stimulants may induce a mania or mixed episode in patients. Prior to initiating treatment screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression). New Psychiatric or Manic Symptoms CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychiatric illness or mania. If such symptoms occur, consider discontinuing ADHANSIA XR. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients. Existing Psychiatric: CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients. \n
5. WARNINGS AND PRECAUTIONS

5.1. Potential for Abuse and Dependence CNS stimulants, including ADHANSIA XR, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy. See Warnings and Precautions (4.1), Drug Abuse and Dependence (5.2). [DirecT]

5.2. Serious Cardiovascular Events

Sudden death, stroke, and myocardial infarction have occurred in adults treated with CNS stimulant treatment at recommended doses. Sudden death has occurred in patients with known structural cardiac abnormalities, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncopal, or arrhythmia during ADHANSIA XR treatment. Blood Pressure and Heart Rate Increases CNS stimulants cause an increase in blood pressure (mean increase approximately 2 to 4 mm Hg) and heart rate (mean increase approximately 3 to 6 bpm). Individuals may have larger increases. Monitor all pediatric patients (7 to 12 years), and adults for hypertension and tachycardia. \n
5.3. Blood Pressure and Heart Rate Increases

CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, severe heart arrhythmia, coronary artery disease, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncopal, or arrhythmia during ADHANSIA XR treatment. Blood Pressure and Heart Rate Increases CNS stimulants cause an increase in blood pressure (mean increase approximately 2 to 4 mm Hg) and heart rate (mean increase approximately 3 to 6 bpm). Individuals may have larger increases. Monitor all pediatric patients (7 to 12 years), and adults for hypertension and tachycardia. \n
5.4. Psychiatric Adverse Reactions

ADHANSIA XR is contraindicated in patients: • With a known hypersensitivity to methylphenidate or other components of ADHANSIA XR. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other methylphenidate products, see Adverse Reactions (5.1). • Receiving concomitant treatment with monoamine oxidase inhibitors (MAOIs), and also within 14 days following discontinuation of treatment with a MAOI, because of the risk of hypertensive crisis [see Drug Interactions (7.1)]. • With active or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression). Existing Psychiatric: CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder. Induction of a Manic Episode in Patients with Bipolar Disorder. CNS stimulants may induce a mania or mixed episode in patients. Prior to initiating treatment screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression). New Psychiatric or Manic Symptoms CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychiatric illness or mania. If such symptoms occur, consider discontinuing ADHANSIA XR. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients. Existing Psychiatric: CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients. \n
5.5. Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products, in both pediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug. In lab-based data, ADHANSIA XR resulted in an increase in dose. Priapism has also appeared during a period of drug withdrawal [drug holidays or during discontinuation]. Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention. \n
5.6. Peripheral Vascular Effects Including Raynaud’s Phenomenon CNS stimulants, including ADHANSIA XR, used to treat ADHD are associated with peripheral vasospasm, including Raynaud’s phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasospasm, including Raynaud’s phenomenon, have been reported in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients. \n
5.7. Long-Term Suppression of Growth CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Careful follow-up of weight and height in pediatric patients aged 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic pediatric subgroups of newly methylphenidate-treated and non-medication treated pediatric patients over 36 months (to the ages of 10 to 15 years), suggests that consistently medicated pediatric patients (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including ADHANSIA XR. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted. \n
5.8. Allergic-Type Reactions: FD&C Yellow No. 5 ADHANSIA XR 45 mg capsules contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions including bronchial asthma in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity [see Contraindications (4)]. \n
6. ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling: - Known hypersensitivity to methylphenidate or other ingredients of ADHANSIA XR (see Contraindications (4)). - Use in children with sudden unexpected death or myocardial infarction when used concomitantly with monoamine oxidase inhibitors [see Contraindications (4) and Drug Interactions (7.1)]. - Drug dependence (see Boxed Warning, Warnings and Precautions (5.1), and Drug Abuse and Dependence (9.2,9.3)). - Serious cardiovascular reactions [see Warnings and Precautions (5.2)], Blood pressure and heart rate increases [see Warnings and Precautions (5.3)], Psychiatric adverse reactions [see Warnings and Precautions (5.4)], Priapism [see Warnings and Precautions (5.5)], Peripheral vasospasm, including Raynaud’s phenomenon [see Warnings and Precautions (5.6)], - Long-term suppression of growth [see Warnings and Precautions (5.7)], and - Allergic reactions [see FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity [see Contraindications (4)].
Pediatric Patients: (6 to 12 years) with ADHD Study 4, conducted in pediatric patients 6 to 12 years of age, was comprised of a 6-week open-label dose optimization phase in which all patients received ADHANSIA XR (n=56) mean dose 48 mg/day, followed by a 1-week, double-blind controlled phase in which patients were randomized to continue ADHANSIA XR (n=75) or switch to placebo (n=73). During the open-label ADHANSIA XR treatment phase, adverse reactions reported in > 5% of patients included decreased appetite (35%), upper abdominal pain (15%), affect lability (13%), nausea or vomiting (13%), weight decreased (12%), insomnia (10%), irritability (10%), headache (10%), and heart rate increased (10%). Because of the trial design (6-week open-label active treatment phase followed by a 1-week, randomized, double-blind, placebo-controlled withdrawal), the adverse reaction rates described above are lower than expected in clinical practice. No difference occurred in the incidence of adverse reactions between ADHANSIA XR and placebo during the 1-week, double-blind, placebo-controlled treatment phase.

7.1. Clinically Important Drug Interactions Table 3 presents clinically important drug interactions with ADHANSIA XR.

Table 3: Drugs Having Clinically Important Interactions with ADHANSIA XR

<table>
<thead>
<tr>
<th>Monoamine Oxidase Inhibitors (MAOI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Impact</strong></td>
</tr>
<tr>
<td>Concomitant use of MAOIs and CNS stimulants can cause hypertension crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure [see Contraindications] [4].</td>
</tr>
</tbody>
</table>

**Intervention:** Do not administer ADHANSIA XR concomitantly with MAOIs or within 14 days after discontinuing MAOI treatment.

**Examples:** selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, milnacipran, and venlafaxine.

<table>
<thead>
<tr>
<th>Gastric pH Modulators</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Impact</strong></td>
</tr>
<tr>
<td>May change the release, PK profiles and alter the pharmacodynamics of ADHANSIA XR</td>
</tr>
</tbody>
</table>

**Intervention:** Monitor patients for changes in clinical effect and use alternative therapy based on clinical response.

**Examples:** Omeprazole, esomeprazole, pantoprazole, famotidine, sodium bicarbonate.

8. USE IN SPECIFIC POPULATIONS 8.1. Pregnancy: Pregnancy Exposure Registry There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADHANSIA XR during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychostimulants at 1-866-468-2538. Risk Summary Published studies and post-marketing reports on methylphenidate use during pregnancy are insufficient to identify a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the fetus associated with the use of central nervous system (CNS) stimulants during pregnancy. Drug Effects on Breastfeeding Methylphenidate is excreted in breast milk. Breast feeding is not recommended if the mother is taking ADHANSIA XR. The safety and effectiveness of ADHANSIA XR in breastfed infants have not been established. Based on heredity effects, the plasma concentration of methylphenidate in breastfed infants is approximately 36 times the maximum recommended human dose (MRHD) of 85 mg/day given to children on a mg/m² basis. In the study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 7 weeks, starting in the postnatal period (postnatal day 7) and continuing through sexual maturity (postnatal week 10). When these animals were treated as adults (postnatal week 15-16), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 3 times the MRHD of 85 mg/day given to children on a mg/m² basis) or greater, and a deficit in the acquisition of a specific learning task was observed in females exposed to the highest dose (6 times the MRHD given to children on a mg/m² basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (approximately 0.35 times the MRHD given to children on a mg/m² basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

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

9. DRUG ABUSE AND DEPENDENCE 9.1. Controlled Substance ADHANSIA XR contains methylphenidate, a Schedule II controlled substance. 9.2. Abuse CNS stimulants including ADHANSIA XR, other methylphenidate-containing products, and amphetamines have a high potential for abuse. Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Abuse is characterized by impaired control over drug use, continued use despite harm, and craving. Signs and symptoms of CNS stimulant abuse include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, suicidal or homicidal ideation have also been observed. Absences of CNS stimulants may occur in screen, snort, inject, or use other unapproved routes of administration which can result in overdose and death [see Overdose (10)]. To reduce the risk of adverse events, data suggests concurrent administration of an antecedent CNS stimulant, including ADHANSIA XR, can cause vasoconstriction and thereby decrease placental perfusion. No fetal and/or neonatal adverse reactions have been reported with the use of therapeutic doses of methylphenidate during pregnancy; however, premature delivery and low birth weight infants have been reported in amphetamine-dependent mothers. Data Animal Data In embryofetal development studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis. In both species, no adverse effects were observed at doses up to 36 times the maximum recommended human dose (MRHD) of 85 mg/day given to adolescents on a mg/m² basis. In the study conducted in young rats, methylphenidate production. Long-term neurodevelopmental effects on infants from stimulant exposure are unknown.

10. OVERDOSE 10.1. Signs and Symptoms Signs and symptoms of acute methylphenidate overdose, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: nausea, vomiting, diaphoresis, restlessness, anxiety, agitation, tremors, hyperflexia, muscle twitching, convulsion [may be followed by coma], euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hypertension, tachycardia, palpitations, cardiac arrhythmias, hyperthermia, hypotension, tachyphylaxis, mydriasis, dryness of mucous membranes, and rhinolalia. 10.2. Management of Overdose Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice on the management of overdose with methylphenidate. Provide supportive care, including close medical supervision and monitoring. Treatment should consist of general measures employed in the management of overdose with any drug. Consider the possibility of multiple drug overdose. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures. Healthcare professionals can telephone Adlon Therapeutics’ Medical Information Department (1-888-827-0616) for information on this product.

Adlon Therapeutics L.P.
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Stamford, CT 06901-5431

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U.S. Patent Numbers: 9,794,752 and 10,111,839
This brief summary is based on Adhansia XR Prescribing information, 07/2019

ADLON THERAPEUTICS
Lamotrigine: Its Role in Bipolar Disorder

David N. Osser, MD

Lamotrigine monotherapy has emerged as a possible treatment for bipolar depression. It is not associated with weight gain and is less likely to cause neurocognitive adverse effects and sedation. Most patients tolerate it well. It does carry a risk of dangerous rashes, but the risk is minimized by slow dosage titration and alert monitoring. The incidence of serious rash may also be less than previously reported (in particular, when faster dosage titration was used). The rate now appears to be 0.1% or less.

The evidence supporting lamotrigine usage for acute bipolar depression, however, is mixed. On the positive side, one double-blind, placebo-controlled study of lamotrigine (50 mg/d, 200 mg/d, or placebo) in bipolar I depression (n = 195) showed favorable results.1 At 50 mg, 41% of patients improved; on 200 mg, 51% responded; and 26% improved on placebo. These positive findings about lamotrigine had been countered, however, by four negative studies that are large, industry-supported, double-blind, placebo-controlled clinical trials studying lamotrigine treatment in acutely depressed bipolar I and II patients. None of the four studies found a statistical difference between lamotrigine and placebo. As a result, lamotrigine did not receive Food and Drug Administration approval for acute bipolar depression. A meta-analysis of these five studies, however, found a small benefit with an overall effect size of 0.27.2 In more severely ill patients (Hamilton 24 or more), lamotrigine had a greater separation from placebo (0.47) mostly because placebo effect was lower in this group. Lamotrigine was not better than placebo if the baseline Hamilton was lower than 24 (0.07 effect size). In another approach to predicting response, a small observational study showed better results at lamotrigine blood levels around 4 ng/ml.3 The efficacy of lamotrigine as maintenance therapy is fairly robust. Two large, 18-month studies showed efficacy, enabling lamotrigine to obtain FDA approval for maintenance use.4 It had no efficacy for preventing mania, but at least it did not increase the risk of mania compared with placebo.

Lamotrigine has shown no efficacy in treating acute mania, which makes it less desirable than lithium, quetiapine, or cariprazine in that there will be no coverage for the manic/hypomanic phases. It also has no apparent benefit for suicidal ideation or behaviors. In fact, like all anticonvulsants, it carries a warning about possible increased risk of suicidality. On the other hand, its relatively benign side effect profile might make it a first choice for some patients, especially if the past hypomanias have been mild. Lamotrigine might also be worth considering in women of childbearing potential. The teratogenic risk of lamotrigine is approximately 1% to 4%, the lowest among the antiepileptic medications. A large observational study found an odds ratio compared with controls of 1.3 for orofacial cleft abnormalities.5 If, after carefully weighing the options, lamotrigine is selected for these women, close monitoring of serum level is prudent as dosing and serum concentration dramatically differ depending on the stage of pregnancy.

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References
E-Cigarettes and Substance Use

Heidi Moawad, MD

In 2019, a number of serious health effects including death were reported in association with e-cigarette use, which led the US government to create new restrictions on e-cigarettes. In addition to the health effects already known about e-cigarettes, adults and young people who obtain them through “black market” routes may experience health effects that have not yet been observed or described, especially if these products contain materials that were not present in products that had previously been legal.

E-cigarettes have become commonplace and are used by people of all ages. Some proponents suggest that they could be safer than traditional cigarettes and that they may be used as a means to prevent or replace the smoking of combustible (regular) cigarettes. Some of the current research shows that use of e-cigarettes is associated with a lower incidence of substance abuse disorder (SUD) and tobacco use disorder (TUD). Yet, the use of e-cigarettes may precede cigarette smoking as well as the use of other substances, especially among young people. It is therefore not clear whether e-cigarettes protect against SUD, lead to it, or are a sign of an inherent predisposition to the condition.

The concept of gateway drugs is well established in the area of illegal recreational drugs of abuse. An inherent disposition to SUD could precede or be exacerbated by the use of drugs that are typically considered gateway drugs, such as combustible cigarettes, alcohol, and marijuana. E-cigarettes are also gaining recognition as a potential gateway to smoking cigarettes and using other drugs.

Nicotine and e-cigarettes

E-cigarettes vary in their nicotine content. Not only does the experience of using nicotine e-cigarettes differ from the experience of using non-nicotine e-cigarettes, the subsequent tendency to smoke regular cigarettes may differ depending on whether a person uses nicotine e-cigarettes or non-nicotine e-cigarettes. Among some people, smoking E-cigarettes may predispose a person to marijuana use.

Chadi and colleagues1 examined the relationship between e-cigarettes and subsequent use of marijuana. The researchers found that “odds of marijuana use were higher in youth who had an e-cigarette use history in comparison to those who did not.” They did not distinguish between study participants who used nicotine e-cigarettes and study participants who used non-nicotine e-cigarettes. Given that the study was a large retrospective meta-analysis that included 128,227 participants, it is not easy to draw a conclusion regarding the cause of this link or whether the students were addicted to either substance.

Marijuana is one of the substances commonly used by individuals who suffer from SUD. The role of e-cigarettes prior to the use of marijuana could be related to an inherent tendency to use substances, or it could increase the chances of trying marijuana.

Multi-substance abuse

E-cigarette use is also associated with the use of several substances that are commonly abused among people who have an SUD. In a longitudinal multi-center study, Temple and colleagues surveyed the drug use habits of 662 participants in an ethnically diverse sample to examine a possible association between e-cigarettes and abuse of other substances.

The researchers found that e-cigarette use was closely linked with use of “combustible cigarettes, alcohol, marijuana, cocaine, amphetamines, inhalants, hallucinogens, ecstasy, and misuse of over-the-counter and prescription medications.” They also noted that users of e-cigarettes reported that taste was the primary appealing feature. This suggests a very different motive for using e-cigarettes than the motives that are typically associated with some of the other drugs—most of which are not typically associated with taste. Alcohol, marijuana, and regular combustible cigarettes, all of which have been described as gateway drugs, are, however associated with a distinctive taste, which may also be an appealing factor for some users.

The bottom line

The link between e-cigarettes and numerous drugs that are commonly abused in people who have SUD suggests that e-cigarettes have a stronger effect on users than satisfying their need for the taste, and that they could predispose to use of other drugs.

TAKE HOME POINTS

- E-cigarettes are often the first substance that young people use, and they have been associated with a future risk of multi-substance use.
- Adults or youth who are trying to curb their use of regular combustible cigarettes may begin to use e-cigarettes as a strategy to help reduce smoking.
- Adults and youth who use e-cigarettes along with combustible cigarettes are at a higher risk of SUD than those who use e-cigarettes but do not smoke combustible cigarettes.
- It is worthwhile to discuss warning signs of addiction with patients who use e-cigarettes. At an early stage, patients may be receptive to recognizing, admitting, and addressing the signs of substance abuse disorder before the condition begins.

REFERENCES

Examining the Link Between the Immune System and Schizophrenia

Continued from Cover

The researchers performed the largest systematic analysis of differential blood cell counts in patients with first-episode psychosis and unmedicated schizophrenia. As neutrophil and monocyte counts only partly normalized during antipsychotic treatment, the researchers concluded that increased numbers of innate immune cells may represent a trait marker for psychosis.

They also found that neutrophil counts correlated with positive symptoms at baseline and with antipsychotic treatment, suggesting that these cells may be modulatory of acute disease severity. Uregulated NGAL and MIP-1α supports a potential role of bacterial infections as a triggering factor of psychosis.

The strengths of the study included a large sample size and clinically well-characterized patients. The limitations included the inability to determine the potential precipitants of neutrophil and monocyte activation and absence of brain imaging data.

The bottom line
There is evidence in some patients of a transient inflammatory response during onset of acute psychosis that wanes afterwards and persists in an attenuated form. Antipsychotics may have anti-inflammatory effects. Neutrophil and monocyte counts as well as CRP levels may be useful markers of disease acuity, severity, and treatment response.

Collaborative Care Meets Hospital Medicine
Proactive Consultation-Liaison Psychiatry

Mark A. Oldham, MD, Khushminder Chahal, MD, and Hochang B. Lee, MD

Mental illness accounts for a third of all years lived with disability and is associated with twice the relative risk of all-cause mortality. It also contributes to other leading causes of death such as heart disease, cancer, and cerebrovascular disease. An estimated 8 million deaths are attributable to mental disorders every year, with two-thirds due to comorbid medical illness.

Medical and psychiatric conditions are often interdependent with complex relationships between them. Medical conditions can cause mental illness by way of psychological and/or physiological effects; mental illness may make it difficult to engage in medical care due to barriers to access, poor motivation, functional impairment, and the like; and many medical and psychiatric conditions share common psychosocial determinants (eg, adverse childhood experiences).

CASE VIGNETTE 1

A 56-year-old man with schizophrenia, hyperlipidemia, and hypertension who smokes a pack of cigarettes a day presents to the emergency department (ED) with chest pain. The diagnosis is acute coronary syndrome; he is admitted and scheduled for cardiac catheterization with possible angioplasty. On admission, blood pressure and cholesterol medications are continued. However, the primary team is unaware of his recent increase in risperidone dose from 2 mg qhs to 2 mg bid and starts him on 2 mg qhs. Nicotine replacement is not discussed.

The patient becomes distressed and increasingly paranoid about blood work and cardiac monitoring; he refuses cardiac catheterization for two days, saying, “I’ll think about it and let you know tomorrow.” On hospital day 3, he accuses his nurse of trying to poison him and refuses all medications. Agitated, he demands an against-medical-advice discharge and pushes the nurse, prompting security involvement, physical restraint, and sedation.

The medical team orders a constant companion (ie, sitter) and consults psychiatry. The patient is psychotic when evaluated by the consultation-liaison (C-L) psychiatrist the following day and found to lack capacity to refuse medical care. The patient’s cardiac enzymes normalize with medical treatment instead of cardiac catheterization while the hospital pursues temporary conservatorship. The patient waits another three days until a psychiatric hospital bed becomes available. He is in the psychiatric wing of the hospital for several days when he once again has chest pain at rest, and he is promptly transferred back to a medical wing.

CASE VIGNETTE 2

A 46-year-old woman with chronic PTSD and a general mistrust of authority figures is admitted to the hospital with hematochezia, hypotension, and concern about a lower gastrointestinal bleed. On admission, the patient is identified on chart review by a proactive C-L service because she has a major psychiatric diagnosis and a documented history of psychiatric hospitalization.

During a brief evaluation by a psychiatric social worker the morning of hospital day 2, the patient is hypervigilant and ruminates about an anticipated colonoscopy: the social worker recommends that the primary team order a psychiatric consultation. A C-L psychiatrist sees the patient that day, begins to develop rapport with the patient, and helps to establish basic principles of trauma-informed care. Feeling more comfortable with her treatment team and the outlined plan of care, the patient undergoes colonoscopy without delay or incident; she is referred for mental health aftercare for treatment of PTSD.

CASE DISCUSSION

These two cases contrast how major mental illness might be managed on a hospital medicine unit supported by traditional reactive C-L psychiatry versus by a proactive C-L model (Figure). The first case illustrates difficulties in communication and managing psychiatric illness. Ultimately, the patient’s care was compromised, the providers were exasperated, and the system incurred greater costs. The second case illustrates the potential value of meeting psychiatric needs from the time the patient arrives at the hospital. A multidisciplinary team identified patient-specific concerns and facilitated communication, which resulted in safe and efficient care.

Currently, more than a dozen sites around the country, including academic medical centers (eg, University of Rochester, Yale, University of Pennsylvania, Johns Hopkins, Northwestern) and community hospitals (eg, Sarasota Memorial Hospital), have fully established or pilot proactive C-L psychiatry services.

Care delivery in the general hospital

Psychiatric comorbidity among medicine and surgery inpatients is high, yet roughly half of these conditions go unrecognized. Based on claims data, in 3 hospital patients has a psychiatric diagnosis; however, more than half of the patients admitted for non-psychiatric admission may have a diagnosis of mental illness. ‘SimCo) hospital patients have a mental health concern deserving clinical attention. Patients with active psychiatric conditions undergo more procedures, receive more consultations of any kind, have longer durations of hospital stay, and are more likely to be discharged to a facility rather than home. They are also more likely to leave against medical advice and to have higher utilization of hospital care and other health care resources after discharge.

Although medical complexity may explain a portion of the poorer outcomes observed in patients with psychiatric comorbidity, other factors contribute as well. For example, patients with mental illness may receive substandard medical care because of a provider’s implicit bias or both patient and provider stigma associated with mental illness.

Improved care

Psychiatric comorbidity in the hospital is overlooked by primary teams more than half the time, and only one in five medical inpatients with psychiatric comorbidity is in outpatient mental health treatment at the time of acute hospital care. Psychiatric consultation offers several benefits including enhanced medication and psychosocial interventions. Moreover, patients may be more likely to engage in care after speaking with a psychiatric consultant, especially where psychological issues contribute to care refusal.
TABLE. Distinctions between traditional C-L model and proactive C-L model

<table>
<thead>
<tr>
<th>Service delivery</th>
<th>Personnel</th>
<th>Case identification</th>
<th>Intervention</th>
<th>Primary goals</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional C-L model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactive to consultation</td>
<td>Single discipline</td>
<td>Primary team requests</td>
<td>To consulting service</td>
<td>Answer consultation question</td>
<td>Typically hospital wide</td>
</tr>
<tr>
<td>Proactive C-L model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proactive screening</td>
<td>Multidisciplinary</td>
<td>Record screening; real-time communication with nurses and providers; primary team requests</td>
<td>To consulting service as well as to nursing, social worker, and broader system of care</td>
<td>Facilitate safe, effective care delivery of an entire unit</td>
<td>Embedded in assigned medical units</td>
</tr>
</tbody>
</table>

Psychiatric consultation can lead to shorter duration of hospital stay and consequently to financial savings. This effect may be more pronounced when consultations occur earlier during hospitalization. Consultations also facilitate outpatient mental health referrals, which may include psychiatric admission or discharge to another level of mental health care and might also reduce 30-day readmission rates.5

Team-based proactive C-L psychiatry

Proactive C-L psychiatry provides the benefits of traditional C-L psychiatry while simultaneously enriching the care (Table). At Yale New Haven Hospital, the C-L service conducted a pilot study of embedded care, which led to shorter durations of hospital stay; in this program, a psychiatric disposition, aftercare, and sitter use.

The 11-month pilot was shown to shorten the duration of stay among patients receiving BIT care compared with patients who had received non-BIT psychiatric consultation a year earlier (6.7 days versus 7.3 days). Moreover, the mean duration of stay for all patients was statistically lower than it was the preceding year. Based on the most conservative models, the BIT service is cost-neutral, but when the cost savings attributable to shorter hospital stays and increased revenue from backfill are considered, a net cost-benefit was shown with a return on investment of nearly 2 to 1.6 BIT was also rated favorably by roughly 9 out of 10 nurses.

The first step aims to achieve selective prevention by identifying patients with or at increased risk of active mental health issues that may interfere with medical care.12 A team member reviews the electronic health record (EHR) of each patient newly admitted to specific units, looking for evidence of psychiatric comorbidity.

Team-based proactive C-L vis-à-vis traditional C-L

How does team-based proactive C-L differ from traditional C-L? Team-based proactive C-L differs in three ways that derive from modern advances in outpatient mental health care: it proactively identifies patients who might benefit from psychiatric care, employs a collaborative approach, and delivers care using a multidisciplinary team. The first of these seeks to prevent a cascade effect of medical and psychosocial complications that can accumulate in patients with psychiatric disorders.7 The second incorporates insights gleaned from outpatient models of integrated mental health care (eg, as in the IMPACT trial). The third draws on the value of the medical teamwork approach.8

How does proactive C-L psychiatry identify mental health needs? Rather than providing universal consultation as in some earlier models, which yields a high false-negative rate, proactive C-L psychiatry uses a multi-step process.10

The first step aims to achieve selective prevention by identifying patients with or at increased risk of active mental health issues that may interfere with medical care.12 A team member reviews the electronic health record (EHR) of each patient newly admitted to specific units, looking for evidence of psychiatric comorbidity.

Two chart-review approaches have been implemented to date. The original strategy is to have a mental health provider (eg, psychiatric nurse practitioner, clinical social worker) review the History & Physical, Problem List, and home Medications sections, supplemented by a review of notes pertaining to prior mental health care. A recently developed strategy involves an automated EHR reporting tool to

FIGURE. Traditional C-L Psychiatry versus Proactive C-L Psychiatry
Needlepoint Sampler

Richard M. Berlin, MD

I did my best

—Emma Hull 1793

I imagine Emma on a winter night, an eight-year-old curled fireside in a wing chair, proving her skill with weeping willows fashioned from a rhythm of XOXOs, gold diamonds suspended like stars in the corners, an alphabet without J, abandoned at q, sutured with blood red silk.

Hung now in my child’s room, the mottled linen square hides all signs of Emma’s struggle as she aimed her needle’s sharp intent with all the backbone a soul can summon.

For years I believed she stopped before Z from boredom or springtime, but now I imagine her bedridden, fallen from her horse, threading hours until recovery, inspiring me after my own daughter’s Shanghai crash, one vertebrae crushed, spinal cord spared, flat on her back in Ruijin Hospital waiting for titanium rods and screws, her surgeon and I reviewing the MRI when he makes a pledge: I will do my best to take good care of your daughter, words that make me dizzy, ecstatic, comforted by a strange harmony with Emma’s assertion, suddenly trusting him in my bones, how he understood the A B C’s of hope and taught me to make his promise to every patient, enduring as diamonds sewn into cloth, simple enough for a child to grasp.

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Screen large numbers of patients across a health care system. The result of either strategy is the creation of a clinical analytics team. The second step aims to achieve the indicated prevention: a team member, drawing upon their mental health expertise, screens patients on the list by discussing each patient with the patient’s nurse and with the primary care team to identify active mental health concerns. The C-L team social worker also may briefly evaluate patients in person to supplement this process.

One of the following outcomes is chosen for each patient: no change in care is recommended; curbside advice to the primary team is provided without consultation; or full psychiatric consultation is requested. The C-L team member then writes a brief screening note for each patient reviewed and documents that the patient was screened, why the screen occurred (i.e., what in the chart prompted the screen), and what the result of the screen was, including any care recommendations.

Who is on a proactive C-L team?

The core members of the team are a C-L psychiatrist, a psychiatric nurse practitioner, and a clinical social worker. The psychiatrist is the team leader who oversees clinical care, provides consultations and, as often required in certain jurisdictions and by hospital policies, performs capacity assessments and completes medicolegal forms (e.g., involuntary psychiatric commitment). The psychiatric nurse practitioner is the primary care worker who serves as the primary contact for primary teams, triages inquiries and new consultations, performs consultations, and assists with chart reviews and screens. The psychiatric social worker—ideally one with experience in acute psychiatric settings such as inpatient psychiatry or a psychiatric emergency department—is the team coordinator and collaborates with the medical social worker and care management, commonly sees patients with the psychiatrist or psychiatric nurse practitioner, arranges psychiatric aftercare, and performs chart reviews and screens.

How is proactive C-L psychiatry integrated with medicine?

The overarching element of integration with this model is that it fosters personal relationships between floor staff and C-L team members.

The team-based multidisciplinary nature of this model allows for unique collaboration with corresponding providers on the medical unit: physician to physician, nurse practitioner to advanced practice providers and nursing staff, and social worker to social worker and care manager. This kind of multi-level interdisciplinary collaboration overcomes many systemic, referent, and patient-specific barriers to accessing psychiatric care.

Looking to the future

More than a dozen US hospitals have adopted a proactive C-L model. Over the past several years, interest in piloting this model across the country has been growing across the US. We are routinely solicited for information about the model and are increasingly working with institutions who have laid the preliminary groundwork and developed business plans in preparation for launching a proactive C-L program.

Questions remain about several aspects of potential value offered by this model of care, including reduction in cost of sitters, staff turnover, and 30-day readmission rates. Likewise, we need to understand the scope of potential benefits related to patient experience and outcomes, staff satisfaction, unit-based teamwork, work-life quality of care providers, and the culture shift that embraces the interconnectedness of medical and mental health.

The ongoing HOME study in the UK is a randomized hospital-based trial currently looking at the efficacy of proactive C-L psychiatry among older adult inpatients. Similar trials in the US are needed to determine if the benefits of this approach extend to younger patients. The preliminary groundwork and development of business plans in preparation for launching a proactive C-L program in the UK is a randomized hospital-based trial currently looking at the efficacy of proactive C-L psychiatry among older adult inpatients.

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The influenza virus itself was not selective in its victims, belying notions of gender, class, and racial superiority. ... Anyone might become ill, anyone might provide comfort. Nancy K Bristow

Infectious outbreaks have shaped the psyche of humanity for times immemorial. Epidemics and pandemics propagate fear and erratic behavior and, long after they are over, remain entrenched within the global psyche, often in the form of folk tale and literary or historical accounts. Naturally, logically, and unsurprisingly, the larger the scale of an outbreak, the larger the impact and magnitude of its sequelae. The black plague pandemic, starting in 1345, claimed up to 100 million lives and is still the topic of lively speculation and research to this day; the influenza pandemic of 1918 still receives attention. The Table summarizes major historical outbreaks, with estimated lives affected.

In recent years, media attention has shaped outbreak coverage in various ways, heightening alarm while serving as a useful tool for encouraging precautions and prevention. However, pandemic spread of infectious diseases has also been a cause of concern because of increased air travel and an overall increase in global connectedness. Smaller outbreaks receive much media coverage as infectious diseases thought to be eradicated resurface, but also in light of crowded or unsanitary conditions. Outbreaks of mumps, measles, and polio have been noted in various communities (such as jails, detention centers, daycare centers). Large numbers of refugees, victims of global strife, often have limited access to medical care, and have been found to lack required levels of sero-prevalence needed for herd immunity for vaccine-preventable infections.

Outbreak, epidemic, and pandemic are all terms that are coming back into the human lexicon after decades of complacency about the protections of modern medicine. An “outbreak” is a sudden increase in a condition, or disease cluster—infectious or otherwise. An “epidemic” is defined as a widespread occurrence of an infectious or non-infectious disease in a community at a particular time; whereas a “pandemic” is an epidemic that crosses country and continent boundaries.

The effect of outbreaks on mental illness can be loosely conceptualized as:
- Potentially affecting existing illnesses;
- Precipitating new-onset mental symptoms in children or adults, possibly related to the interplay of immunity and mental illness; and
- Causing distress in the caretakers of affected individuals (Figure).

Alternatively, the psychiatrist can consider the effects in terms of acute versus chronic issues.

Outbreaks as precipitating risk factors for mental illness
Regardless of exposure, the stress of media news and fear of injury or death can contribute to a mental breakdown, whether mood-related or psychotic. This is not, however, a well-studied area. Small studies from the Ebola outbreak in Sierra Leone and from the H1N1 outbreak in 2009 indicated an increase in depression, anxiety, and somatoform presentations. In the acute phase, the onset of an outbreak can understandably instill fear in most individuals. This fear and concern can be amplified by pre-existing anxiety and depressive disorders. Personal reactions may differ, although increased rumination about the possibility of acquiring an illness or having already acquired an illness can profoundly modify behavior and socialization.

The effect of outbreaks on psychosis has not been studied fully, but worsening paranoia and the incorporation of outbreak-related facts into delusional thinking is highly likely; resulting delusional parasitosis is a possible logical extension of this event chain. Patients with mental illness have a higher rate of cutaneous/skin disorders at baseline and intensifying media coverage can exacerbate concern about dermatological manifestations. Severe anxiety can also precipitate a relapse into substance abuse in highly susceptible individuals as the stress level increases.

Furthermore, for patients struggling with depression or anxiety who are also parents, the effects can be deepened as concerns of protecting children arise. Psychiatrists may sometimes have to allay guilt feelings of parents worried about having caused their children’s illness, or not done enough to prevent it.

In youths, adult behavior may set the tone for coping skills, but the existence of certain personality characteristics or symptoms shape response to crisis. In rare cases, mental issues can be protective—children with social phobia have been found to have delayed onset of measles, mumps, and rubella, presumably because of their reluctance to socialize.

Lastly, anxiety and a feeling of helpless can encourage the adoption of unproven methods and remedies that can be harmful or outright toxic. A solid therapeutic rapport between the patient and the psychiatrist can go a long way in managing those fears and reducing associated unhealthy behaviors.

Bidirectional effect of mental illness and immunity
As our understanding of the interaction between immunity and mental symptoms grows, it is obvious that worsening mental symptoms (eg, depression) can render a person more susceptible to certain physical ailments. This is supported by studies showing lower IgG titers of measles in individuals with major depressive disorders and diminished response to herpes zoster vaccination in elderly persons with depression. Yet, psychoneuroimmunology findings do not consistently apply to children and adolescents, and at least one study has found that adolescents with depression exhibited an enhanced response to the influenza vaccine. Thus, more studies are needed in this area.

Conversely, some infections can...
cause longstanding sequelae. Some are relatively well characterized, such as post-measles subacute sclerosing panencephalitis (SSPE), which occurs 7 to 10 years after a measles illness and present swih neuropsychiatric symptoms. Although SSPE-related mortality decreased with increased measles vaccine use, it is currently experiencing a resurgence.

Similarly, maternal infectious processes are related to mental pro occurs in offspring. Following close to two million Swedish-born people for more than 40 years, Al-Haddad and colleagues found an increased rate of autism and depression following severe maternal infections.

Other after-effects of infections are less well understood. It is possible that the stress caused by infections distorts the relationship between the immune system and the CNS, triggering or consolidating a depressive process. Additionally, receiving the flu vaccine can worsen depressive symptoms in individuals with pre-existing depression or those pre-disposed to depression.

Stigma
Stigma and shaming are closely intertwined with the nature of an outbreak. As recent pandemics have illustrated, humanity still has the benefits of preventive interventions, stigma can also extend to groups who are vaccinated versus those who are not. As communicable diseases re-surge, the potential for a new group of target individuals that can be discriminated against also emerges, especially if lasting skin effects linger.

Anti-stigma measures can target a wide range of conditions, from HIV to mental illness to diseases with visible skin markings, and education is the most widely used measure. In the area of epidemics, psychiatry can have a pivotal role in promoting inclusiveness and anti-discriminatory practice, as well as helping patients deal with micro-aggressions and resulting mental symptoms.

Proactive approaches to understanding and managing outbreaks
In past decades, many infectious outbreaks have alarmed the public. The reasons for these vary from reduced immunity and under-vaccination to the emergence of new viral strains (as in the case of influenza). Salmonella outbreaks clusters are fairly common, but typically do not cause wide-ranging alarm beyond involved communities. Pertussis outbreaks occur in highly vaccinated communities when there is divergence between strains used in vaccines and those prevalent in the population.

The role of psychiatry varies depending on the etiology of the crisis and the magnitude of the impact on the individual and surrounding circumstances, such as a raging epidemic. The prospect theory of behavior is well established. Prospect theory has been used to provide an operationalized framework for various health-related behaviors including management of chronic diseases as well as to distinguish attitudes in clinical versus non-clinical decisions. Moreover, prospect theory can be helpful in framing the health care message underlying informed consents. In a study of women with children, Abyhankar and colleagues found that the intent to get the measles, mumps, and rubella (MMR) vaccine for one’s child varied on whether the women were exposed to a loss-framed versus a gain-framed message, with variations in perceptions of vaccine efficacy.

A careful risk benefit analysis is needed for any community affected by outbreaks of infectious disease, and ongoing monitoring is essential. Perspective and accumulated experience can shape decision-making. For example, with a case of influenza virus, the choice of oseltamivir is a public health decision that benefits communities and saves lives. However, oseltamivir is associated with an increased odds ratio of adverse neuropsychiatric adverse effects including confusion, hallucinations, psychosis, anxiety, depression, mania, sleeping disorder, aggression, suicidal ideation, encephalitis, ataxia, and vertigo. Acute and long-term neuropsychiatric symptoms with untreated influenza illness can further complicate matters.

From an individual perspective, choosing to use a medication with known potential adverse effects may very well be subject to an emotional component congruent with prospect theory and subject to risk-taking paradigms. Decisions would conceivably change depending on the level of stress of the individual and surrounding circumstances, such as a raging epidemic.

Lessons learned and the role of psychiatry
The last few pandemics have yielded valuable lessons in terms of global responses. In a review of efforts since 1952, the World Health Organization noted that surveillance networks were instrumental in monitoring and mitigating the spread of influenza viruses. It is hoped that similar organizational effort can target other re-emerging communicable diseases. Organized resources are crucial in terms of detection and marshalling quick local and community-wide responses, combined

TABLE. Summary of memorable epidemics/pandemics

<table>
<thead>
<tr>
<th>Pandemics</th>
<th>Period in history</th>
<th>Estimated number of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black plague</td>
<td>1346-1350</td>
<td>25 million people*</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1981-present</td>
<td>529,113, with more than 940,000 cases reported</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>WHO estimates that 1.3 million people die every year from this disease</td>
<td></td>
</tr>
<tr>
<td>Smallpox</td>
<td>1633; 1790s; 1949*</td>
<td>Approximately 1.5 million</td>
</tr>
<tr>
<td>Cholera</td>
<td>Of the 3 million cases every year 100,000 to 120,000 result in death</td>
<td></td>
</tr>
<tr>
<td>SARS</td>
<td>2003</td>
<td>774</td>
</tr>
<tr>
<td>Malaria</td>
<td>&gt;200 million people infected; approximately 600,000 deaths every year</td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>This virus has been responsible for 3 pandemics, including the H1 Spanish flu, the H1N1 swine flu, and the H5N1 avian (bird) flu</td>
<td></td>
</tr>
<tr>
<td>Avian (bird) flu</td>
<td>2003</td>
<td>&gt;700 cases reported</td>
</tr>
<tr>
<td>H1N1</td>
<td>2009</td>
<td>274,304 hospitalizations and 12,469 deaths</td>
</tr>
<tr>
<td>Ebola</td>
<td>1976; 2014-2015</td>
<td>20,000</td>
</tr>
</tbody>
</table>

*One-third of Europe’s population.
*Most recent case in the US.
*Influenza virus A(H1N1) pandemic began in April 2009 and was declared over in September 2010; in the US, 609 cases were confirmed.

EFFECT ON CARETAKERS

Table continues on next page...
Infectious Burden and Alzheimer Disease: Is There a Link?

A

lzheim
er disease (AD) is a common chronic neurodegenerative disease that primarily affects people aged 65 or older. According to a report by the Alzheimer Association, about 5.8 million individuals of all ages are suffering from AD in the US alone. About 3.5 million women and 2.3 million men have AD.

Disproportionate number of women

New findings from prospective studies were presented at the 2019 Alzheimer’s Association International Conference (AAIC) in Los Angeles. Discussions about gender influences on the prevalence and development of AD were particularly relevant.

KEY FACTORS that play vital roles in the understanding of AD’s progression include:

1. Non-employed women have a more rapid memory decline compared with women who continue to engage in their careers.

2. The verbal memory of healthy women, as well as that of female patients with AD, surpassed that of healthy men. Women appear to have a comparative verbal advantage that may enable them to compensate more effectively in the early stages of AD.

3. A critical feature of AD is neurofibrillary tangles, which are intracellularly formed by tau protein. Women with mild cognitive impairment had a denser distribution and higher burden of tau. The findings suggest that female brains may have a stronger connection with abnormal tau protein.

4. Using genome sequencing, 11 genes have been found that are related to gender; immune gene (CD16) in women and the mucoelipin gene (MCOLN3) in men appear to be risk factors for AD.

Risk factors for AD include infectious pathogens that can initiate a cascade of chronic neuroinflammatory processes in elderly people. AD can be aggravated by infections of different origin, which implies that it is necessary to accurately diagnose and provide appropriate treatment based on the impact of an infectious burden on disease progression.

The key role of neuroinflammation in AD pathogenesis

Over the past three decades, scientists around the world have been studying the causes of AD. In recent years, various hypotheses have been advanced that propose various mechanisms of pathogenesis and risk factors that are correlated with the disease. The most frequently discussed hypothesis is the amyloid-β-hypothesis. It is based on two pathological key aspects in the brains of patients with AD: the neurofibrillary tangles formed with tau-protein inside cells and insoluble clumps of amyloid-β (Aβ) peptide or so-called senile plaques formed outside cells.

Recent research reveals that Aβ oligomers have antimicrobial properties and, therefore, can be involved in the production and deposition of Aβ that may be indicative of infectious agents. Three primary contributors have been found in the pathogenesis of AD: neuroinflammatory processes, oxidative stress, and vascular factors.

As illustrated in the Figure, cumulative infections (bacterial and viral origin), amyloid-β (Aβ) deposits, and an increase in abnormal tau protein lead to a neuroinflammatory process in CNS. Aβ fibrils aggregate into clumps and thereby disrupt the signal transmissions between neurons. Concurrently, neurofibrillary tangles consisting of misfolded tau protein cause the degradation of nerve cells. When resident immune cells such as microglia, macrophages, lymphocytes, and astrocytes are activated, they release pro-inflammatory cytokines (IL-1β, IL-6, IL-18, TNF-α, IFN-γ). This and other inflammatory agents can contribute to additional amounts of Aβ. As a result of sustained inflammatory insults, a detrimental effect on neurons and the loss of neuronal communication occurs.

The blood-brain barrier can be damaged as a result of oxidative stress caused by microglia and reactive oxygen species. Furthermore, vascular risk factors are known to decline cognitive functions (cerebral hypoperfusion, cerebrovascular lesions, etc) and in combination with an amyloid-related oxygen species peptide lead to oxidative stress. Chronic inflammation may contribute to neurodegeneration and cognitive disorders and it may impair clearance of damaged neuronal proteins in the aged brain.

Pathogens that contribute to the accumulation of infectious burden

Results published in 2015 in the European Journal of Neurology confirmed a link between infectious burden and AD. Findings suggest that infectious burdens are risk factors pre-onset and responsible for faster progression post-onset. Antibody titers of cytomegalovirus herpes simplex virus type 1 (HSV-1) (B burgdorferi, C pneumonia, and H pylori) were assessed using the ELISA serological test in patients with AD and a control group. In all cases, the infectious burden was positively associated with AD. Individuals who had higher infectious burdens and, consequently, increased serum Aβ levels were more affected with respect to cognitive deficits.

Bacteria, viruses, fungi, and, occasionally, protozoa are able to cross through the blood-brain barrier and in turn cause chronic illnesses. Various types of spirochetes (eg, B burgdorferi) and obligate intracellular bacteria (C pneumoniae) are among the most frequently invasive infectious entities that can generate persistent infection in the brain. In turn, this finding suggests that these pathogens could enhance the Aβ deposition in AD and trigger peripheral inflammation. Moreover, there is a suggestion that B burgdorferi causes intracellular inflammation in brain tissues, which leads to neurodegenerative and cognitive changes in people with neuroborreliosissanAD.Hpylori—specific IgG antibody in serum is thought to be a marker for AD. However, further research is needed to detect the availability of these antibodies in the brain.

Viral burden of herpes simplex virus (HSV), human herpesvirus (HHV), and the hepatitis C virus (HCV) is commonly associated with AD by apolipoprotein E-ε4 (APOE-ε4). The accumulation of senile amyloid plaques

SIGNIFICANCE FOR PRACTICING PSYCHIATRISTS

It is crucial for practicing psychiatrists to consider that Alzheimer disease can be aggravated by infections of different origin. This implies that it is necessary to accurately diagnose and provide the appropriate treatment based on the impact of an infectious burden on disease progression.
and tau-protein is a significant risk in people with AD due to the combination with APOE-e4. One of the biomarkers of HSV reactivation detected by ELISA showed a significant link between the presence of anti-HSV-1 IgG, anti-HSV-1 IgM antibodies, and AD. According to data from the Center for Disease Control and Prevention, one in three people aged 60 or over suffer from HHV. For this reason, shingles indicate a risk for future AD.

There are limited studies to explain the mechanisms that underly HCV infection and dementia.

**TWO HYPOTHESES have been advanced:**

1. The virus causes the systemic inflammation and thereby contributes to indirect neurotoxicity;
2. The virus is able to disintegrate brain tissues through a direct cumulative neurotoxic effect.

**Pharmacotherapy**

There is no consensus on the key mechanisms that can trigger a cascade of AD-causing processes. Furthermore, there is no agreement on how to implement specific, strategic pharmacotherapy. It is estimated that there were about 146 failed attempts to develop a potential drug for AD treatment between the period of 1998 and 2017. A possible contributing factor to these failures is a focus on a single target approach: the amyloid-β hypothesis. At present there are no treatments to stop and/or delay underlying disease progression. Current prevalent therapies help to mask the symptoms, but they do not solve the underlying root cause(s).

A fundamental premise for effective treatment is to diagnose AD at the earliest feasible stage. The main symptoms are characterized by cognitive declines across a wide range of abilities: hippocampus-dependent spatial memory, visuospatialagnosia, constructional apraxia, and language and writing problems. Mental status testing, neuropsychological examination to assess patients’ thinking ability, and genetic testing (eg, to detect the presence of APOE-e4 in serum) should be performed. Subsequent tests used to complement identification of AD include MRI, CT, and PET scans.

The following agents are FDA-approved medications to treat cognitive impairments: cholinesterase inhibitors (donepezil, rivastigmine, galantamine); N-methyl-D-aspartate receptor (NMDA)-antagonists (memantine); and the combination of memantine and donepezil (Namzaric). Donepezil and other cholinesterase inhibitors elevate acetylcholine in the brain. Increased activation of cholinergic receptors on microglia contribute to decreased release of cytokines.

Glutamate may contribute to AD symptoms because of the over-activation of NMDA-receptors, which leads to neurotoxicity. Memantine blocks NMDA-receptors and inhibits glutamate excitatory neurotransmission.

The effectiveness of these drugs is dependent on individual tolerance. Namzaric, memantine, and donepezil can be prescribed at all stages of AD. Rivastigmine and galantamine are approved to treat mild and moderate conditions. These drugs have common adverse effects, including nausea, vomiting, muscle cramps, headache, and dizziness.

Use of antiviral and anti-inflammatory drugs is off-label for AD. Nevertheless, this kind of treatment supported by evidence-based research may slow the progression of dementia.

Recent findings have shown that not only microtubule-associated protein tau but also amyloid plaques were associated with HSV1 DNA replication. This suggests that HSV-1 promotes the accumulation of toxic Aβ clumps which induces AD-related pathology. Several antiviral drugs could be used for treating AD but only for APOE-e4-carriers. Acyclovir passes through the blood-brain barrier and inhibits viral DNA replication, thereby reducing hyperphosphorylation of p-tau. The decrease in Aβ deposits reduces levels of HSV1, which minimizes the viral transmission in the brain. Acyclovir has few adverse effects; however, it should be used with caution given its potential for renal failure.

Valtrex (valacyclovir) has shown positive initial results in new indication trials for AD. Compared with placebo, valacyclovir resulted in a decrease in Aβ formation and a smaller increase in 18F-MK-6240 binding to cerebral tau protein. Furthermore, valacyclovir was shown to be effective and safe, which indicates a potential benefit for the future treatment of patients with AD.

So far, no antimicrobial treatment has been developed for AD. However, it was found that elderly patients with AD frequently have an inflammatory state of gut mucosa because of age-related changes in their gut microbiome (eg, decrease in bacterial diversity). In turn, chronic systemic inflammation promote neuroinflammation as result of blood-brain barrier impairment by proinflammatory mediators and bacterial metabolic products.

A team at the University of Chicago utilized a long-term antibiotic mix on experimental rodents. The results show a decrease in the growth of amyloid plaques and the activation of microglia. Although, the use of antibiotics for AD may not make sense, the fact of a possible association between gut bacteria and CNS has clinical benefits for further development of new drugs in patients with AD.

Anti-inflammatory drugs also have a role in AD therapy. Nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of AD. It is believed that NSAIDs selectively inhibit the isoforms of COX-2 and attenuate prostaglandin synthesis. Even though results showed that the risk of Alzheimer dementia was reduced, a wide range of NSAIDs are not therapeutically effective because they require long-term treatment.

Natural immunomodulatory drugs are a possible means to prevent the onset of neurodegeneration. There is a need for development of new drugs in patients with AD.
sizable evidence that resveratrol possesses an anti-inflammatory effect combined with dietary supplementation. Lipo polysaccharide was used as an inducer of neuroinflammation in response to peripheral infection.20 Moreover, AD is an infectious disease caused by spirochetes, which form biofilms in the skin that in turn initiate the innate immune response. The innate immune system is a first responder—the toll-like receptor 2 generates nuclear factor (NF)-κB and TNF-α, which will likely try to kill the spirochetes in the biofilm, but it cannot penetrate the “slime.”21 NF-κB is also responsible for the generation of amyloid-β, which is antimicrobial and cannot penetrate the biofilm either. Consequently, the accumulation of Aβ leads to the destruction of the cerebral neocortex.

Preventive measures

It is significant to note that preventive measures are needed to avoid the risk of premature viral infection in AD patients. There are six pillars of AD care during the Ebola virus disease outbreak in Sierra Leone.21


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CONFERENCE REPORTER

Presenters at Psych Congress Share Clinical Tips, New Research

Heidi Anne Duerr, MPH

From addressing borderline personality disorder to preventing drug-drug interactions and more, Psych Congress faculty shared useful diagnostic and treatment information. The featured speakers, which included *Psychiatric Times*’ Editorial Board members Philip Resnick, MD, and Thomas Kosten, MD, discussed hot issues in psychiatry during the four-day conference.

Several sessions addressed the complexities of treating patients as well as new potential treatment options. For instance, Marlene Freeman, MD, Director of Clinical Services in the Perinatal and Reproductive Psychiatry Program at Massachusetts General Hospital, shared tips and insights for treating women of reproductive potential. One important point she impressed on attendees is balancing the risk of psychopharmacological agents with the risk associated with an untreated mental disorder. For instance, untreated antenatal depression is associated with the risk of low birth weight, prematurity, small gestational age, and neonatal behavioral differences (eg, irritability and decreased activity). Yet recent findings indicate the absolute risk of selective serotonin reuptake inhibitor exposure in pregnancy is small. Similarly, case-control studies have shown inconsistent data regarding teratogenic risk of SSRIs. Thus, for moderate-to-severe depression, Freeman suggested clinicians discuss the risks and benefits of antidepressants with mothers and, when warranted, use the lowest effective dose. She also emphasized that non-medications alternatives, such as psychotherapy, should be maximized.

On the opposite side of the spectrum, Rick Doblin, PhD, founder and executive director of the Multidisciplinary Association for Psychedelic Studies (MAPS), shared insights in using methylenedioxy-methamphetamine (MDMA) to treat posttraumatic Stress Disorder. Although MDMA has received a bad rap as an illicit party drug (eg, Molly, Ecstasy), Doblin explained its pharmacology could be utilized in patients who do not respond fully to psychotherapy alone. According to Doblin, MDMA increases the release of serotonin, nor-epinephrine, and dopamine and it enhances the release of oxytocin, prolactin, vasopressin, and cortisol.

Brain imaging studies have shown that the positive effects of MDMA can counter the negative neurological effects of PTSD.

MAPS concluded its Phase 2 trial of MDMA-assisted psychotherapy with positive results. They found that 56% of patients no longer met criteria for PTSD following the treatment, compared with 23% in the placebo group. Plus, the number grew over time for the MDMA group, with 68% no longer meeting criteria at 12-month follow-up. Building on this success, MAPS has initiated Phase 3 studies, with the hope of obtaining FDA approval for the treatment at the conclusion of these studies.

On the attention-deficit/hyperactivity disorder front, Timothy Wilens, MD, Chief of the Division of Child and Adolescent Psychiatry and Associate Professor of Psychiatry at Harvard Medical School in Boston, discussed newer medications and those in development to treat children and adolescents. New formulations have come out in recent years that allow easier treatment, including dissolving and chewable pills.

Now, the focus is on new pharmacological approaches to treating ADHD. Wilens noted a few drugs that are recently approved or in the later stages of study. For instance, dasotraline, which is a novel dual-acting dopamine and norepinephrine reuptake inhibitor, is in the registration phase with the FDA. Centanafadine, a triamine reuptake inhibitor that works with dopamine, serotonin, and norepinephrine, is in Phase 3 trials. Molindrone (SPN-810) is being studied to address impulsive aggressive behavior associated with ADHD; it is in Phase 3 trials. Another norepinephrine reuptake inhibitor, known as SPN-812, is in Phase 3 randomized control trials for ADHD in adolescents. Wilens also reported that the norepinephrine reuptake inhibitor mazindol, which was previously approved by the FDA for the treatment of obesity, had positive results in Phase 2 studies.

The editors at *Psychiatric Times* invited speakers to share highlights of their sessions with readers. The diverse faculty and topics underscore the wide variety of issues facing psychiatrists and their patients. As always, *Psychiatric Times* strives to keep our valued readers up-to-date with practical clinical information and guidance to help you in your practices and patients. In doing so, we welcome your feedback.

If you would like to learn more about these and other topics from Psych Congress, or have suggestions for future meeting or topic coverage, please let us know via email PTEditor@mmhgroup.com.

ANXIETY AND STRESS DISORDERS

OCD

A Common Psychiatric Disorder With a Constellation of Solutions

Jon E. Grant, JD, MD, MPH

Obsessive-compulsive disorder (OCD) is a common psychiatric disorder that affects approximately 2% of the world’s population. Without treatment, OCD often results in significant disability, increased rates of suicide, and the chance of remission is quite low. With appropriate treatment, however, patients report substantially higher rates of symptom response and/or remission.

Only approximately one-third of patients with OCD receive appropriate pharmacotherapy, and less than 10% receive evidence-based psychotherapy. First-line therapies include exposure and response prevention (ERP) (which uses repeated and prolonged exposures to fear-eliciting stimuli plus abstinence from compulsive behaviors), and serotonin reuptake inhibitors (ie, clomipramine or SSRIs such as fluoxetine or sertraline).

When these medications are ineffective or only partially effective, a range of augmentation options (with varying degrees of supporting evidence) may be used (these include adding other serotonergic agents, antipsychotics, or glutamate modulators).

Beyond the above stated clinical approach, the actual treatment of OCD presents some unique issues clinicians should be aware of. This brief report highlights just a few of the clinical hurdles that OCD may present.

For example, 60% to 85% of patients report a considerable reduction in symptoms with ERP and improvement is often maintained for up to 5 years. The problem is that many people cannot find trained ERP therapists. Thus, the most effective treatment option for OCD is sometimes unavailable to them.

Another hurdle for many people with OCD is that the illness itself may prevent them from seeing their clinician or being compliant with treatment. Obsessions may make it impossible for the person to leave their home (eg,
Arshya Vahabzadeh, MD

Digital Psychiatry: Augmenting the Future of Mental Health Practice

Digital psychiatry has come a long way over the past five years. There has been an explosion of research and commercial interest, accompanied by much excitement and hope. The Food and Drug Administration and many other organizations have published guidelines and developed programs to foster development of responsible and safe mental health-related technologies.

Despite the enthusiasm, the impact on day-to-day clinical practice has been limited. In 2013, I realized that psychiatry would be one of the most fertile fields to benefit from emerging technologies, prompting my transition from traditional psychiatry to working on artificial intelligence and augmented reality.

With that said, digital psychiatry has considerable potential to change future clinical practice and to augment the work of clinicians and researchers. One area of impact will be the typical outpatient office visit. We continue to rely on subjective patient reporting, often relying on recollection of symptoms and functioning over many weeks. This reporting is combined with our ability only to assess the patient during that appointment in the clinic, a snapshot of one moment in time. But now we have technologies, like smartphones, whose sensors can help us to monitor our patient’s mood and behaviors during the 99% of the time that they are not in our clinics. This longitudinal assessment can provide for more objective and quantitative patient data.

Research has already made headway into “digital phenotyping,” a process whereby a smartphone (or smart device) collects data about how a user interacts with it and how users engage with the world around them. For example, background data are collected as individuals go about their normal lives (ie, passive data), such as call/message logs, the GPS movements of users, or their typing characteristics on the screen keyboard. Data can also be collected when the user is explicitly asked to perform a task like filling out a mood diary or a memory test (ie, active data).

There is also a digital means of measuring almost every component of the mental state exam (MSE). This cornerstone of clinical practice remains subjective and non-quantitative, and technology may allow for a more quantitative and objective way of assessing an MSE. Consider speech as a component of any good MSE. Research has shown that conditions such as psychosis or depression can be evaluated through digital analysis of speech production that looks at components such as phonation, resonance, pitch, and language patterns. The task of taking enormous amounts of data and making it meaningful is no easy feat and, arguably, one of the most difficult. Yet, we may find that through technologies like machine learning, we can uncover digital signatures that might help the subtyping of heterogeneous clinical conditions or allow for models to help predict relapse or treatment response. These advances could help us to understand our patients in a data-driven way that would have advantages through the expert-driven frameworks of psychiatric illness (eg, DSM-5) and brain functioning (eg, Research Domain Criteria [RDoC]). Benefits include a more reliable and accurate assessment compared with DSM-5, and the ability to incorporate it into clinical practice (ie, RDoC).

BROADLY, WE ARE SEEING DIGITAL PSYCHIATRY AT WORK IN THREE KEY AREAS:

1. Technologies that can help improve current services and treatment;
2. Technologies that can become the treatment; and
3. Technologies that can have far-reaching effects in terms of prevention and research.

Telepsychiatry is an example of a technology whose clinical use will mature over the short term. The growth in telepsychiatry has been fueled by increased legislative support, broader reimbursement, decreased equipment cost, increased patient and provider acceptance, as well as a way to address the shortage of psychiatrists that many communities face. Many clinicians run a series of telepsychiatry clinics every month.

While connecting patients to psychiatrists via technology is not a new, a range of chatbot digital therapists have also been created to provide cognitive behavioral therapy (CBT). One commercially available chatbot has been shown to reduce depression symptoms when used as the intervention in a controlled research trial.

Secondly, mental health apps on smartphones and other devices have already gained FDA approval. For example, there are two apps that help provide CBT to patients who are in substance use disorder treatment (RESSET and RESSET-0 as well as Pear Therapeutics). These apps also record various patient symptoms and provide a dashboard so that clinicians can review their patients’ program and monitor symptoms like cravings.

There are also efforts to enhance adherence through both software and hardware. One company has created a version of aripiprazole that contains a tiny sensor. Gastric fluids activate this sensor, resulting in a signal that is sent to a patch worn on the skin and transmitted to a smartphone app. The patient and their clinical team can then monitor when and what dose of this medication has been taken. Another company uses a smartphone camera and artificial intelligence to analyze how a patient attempts to take the medication orally. Through the camera, the software can accurately identify the patient, the medication, and whether the medication was genuinely ingested.

We should probably not forget virtual and augmented reality, technologies that have been around for several decades but have advanced dramatically over the last few years. There is a wealth of evidence that these technologies can treat a range of psychiatric disorders, with anxiety disorders and posttraumatic stress disorder being most prominent. Yet while these technologies were developed long before smartphones and speech-analyzing home smart devices (like Alexa), they have failed to become ubiquitous in society or to have the same degree of ecological validity. Relatively few individuals have expertise or access to virtual and augmented reality technologies, and that is despite these technologies becoming far more affordable.

My work has focused on the use of augmented reality and affective computing in a range of smart devices. These devices, such as smartglasses, use machine-learning to assess and improve emotional and behavioral functioning in students with autism. They have been validated through a series of study researches and commercialized in the consumer and educational space.

Finally, there is also hope that technology can become the main treatment option for some symptoms. A range of companies have developed evidence-based digital CBT platforms to target insomnia. Other companies have created games that they feel can work just as well as stimulants for attention-deficit/hyperactivity disorder, but these are still in the FDA review process.

Many other advances, such as the use of big data in medical records as well as social media, are far too numerous to discuss here.

WHAT IS IMPORTANT, HOWEVER, IS THAT WE KNOW WHAT QUESTIONS TO ASK WHEN A TECHNOLOGY IS PRESENTED TO US. FOR EXAMPLE:

1. Does it work? And who does it work for?
2. Under what circumstances can or should it be used?
3. What are the negative effects, and when do we expect to see them?
4. Who has access to the user data, and how is it safely guarded?
5. Is it a viable product, usable by real people, and with enough demand?
6. Is it affordable and who will pay for it?
7. Does it have other features, such as FDA approval?

Dr. Vahabzadeh is on the faculty at Massachusetts General Hospital, Innovation Officer at the Massachusetts General Hospital Psychiatry Academy, and the Chief Medical Officer of BrainPower LLC, Cambridge, MA. He has served on the MIT Solve Brain Leadership Group and on the faculty at Harvard Medical School. Dr. Vahabzadeh spoke at the 2019 Psych Congress in San Diego, CA, where he presented “Future Psychiatry: A Technological and Neuroscientific Convergence.”

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Patients on opioids for chronic pain management have complications that respond best to discontinuation and consideration of alternative pharmacotherapies, often in combination with behavioral interventions. This overview addresses two medications for analgesia of chronic benign pain, both of which also have substance abuse risks—cannabinoids and ketamine.

Cannabinoids
Cannabinoids are associated with complications in terms of their use, potential for abuse, and administration. Without concurrent opioids, cannabinoids’ efficacy as an analgesic is poor; and 10% of people who use tetrahydrocannabinol (THC) become addicted to it. Moreover, the cannabinoids, particularly cannabidiol (CBD), can potentiate the efficacy of and reduce tolerance to, opioids. This brief overview focuses on CBD, because data and legal regulation have been rapidly progressing for its potential role in chronic pain management both within psychiatric and primary care settings. Furthermore, all 50 states have laws legalizing CBD with varying degrees of restrictions, and many people obtain CBD online without a medical cannabis license or physician prescription.

Although we do not know the most effective therapeutic dose of CBD for pain, we can compare analgesic effects using the number of patients needed to treat (NNT) for a clinically significant therapeutic effect. Tricyclic antidepressants and opioids have lowest NNT for treating neuropathic pain (2.6 and 2.1, respectively). This means that for every single patient showing a therapeutic response to each of these agents, we need to treat 2.6 patients and 2.1 patients for tricyclics and opioids, respectively. Perhaps more simply, one of every two patients treated with opioids will have satisfactory analgesia from chronic neuropathic pain. In comparison, an oral CBD spray was found to have an NNT of 5.0, which is comparable to many routine agents used in treating neuropathic pain, including selective serotonin reuptake inhibitors (NNT = 5.0) and gabapentin (NNT = 6.4). It is also important to look at the negative aspects of treatment. A meta-analysis of 18 double-blind, randomized controlled trials on CBD efficacy analyzed the harms associated with CBD. They found that the number needed to harm (NNH) with CBD, which ideally would be high, was instead relatively low. For CBD, the NNH ranged from 5 to 8 patients, while other analgesics have NNH values above 20. Specific adverse events contributing to the poor value for NNH included impaired motor function (NNH = 5), altered perception (NNH = 7), and altered cognitive function (NNH = 8). Thus, assessing the efficacy of CBD must be balanced against the potential for harm in the management of neuropathic pain.

The CBD oral solution Epidiolex® is available in the US for management of refractory epilepsy, but it has been used off label for chronic pain conditions. GW Pharmaceuticals also produce nabiximols, which is a marijuana extract currently approved in the United Kingdom to treat neuropathic pain, pain due to spasticity, overactive bladder, and other symptoms associated with multiple sclerosis. GW Pharmaceuticals is currently planning Phase 3 trials for nabiximols in the United States. Thus, these medications are likely to become available in FDA-approved formulations at doses that have potential analgesic efficacy in the not too distant future.

Ketamine
The role of ketamine for chronic pain is more complex, including the setting for delivery. However, ketamine use for chronic pain could be adopted within the specialized psychiatry settings that the new REMS (Risk Evaluation and Mitigation Strategies) programs are mandating for esketamine to treat depression. Ketamine might best be considered among the antidepressants that have consistently shown efficacy for chronic pain in conditions such as peripheral neuropathy, diabetic neuropathy, phantom limb pain, and patients with depression and pain. The relative efficacy of antidepressants based on NNT follows the efficacy of opioids, which has an NNT of 2.1, as previously noted. In comparison, the NNT for similar opioid alternatives are: 3.6 for tricyclic antidepressants; 6.4 for SNRIs; 7.2 for gabapentin; and 7.7 for pregabalin. However, the onset of full efficacy for opioids is rapid (and usually only a few minutes after oral ingestion), while these other medications typically take 6 to 8 weeks for full efficacy as analgesics.

In contrast to the slow onset for these antidepressant and related agents, ketamine for chronic pain has shown surprisingly quick and long-lasting results. Ketamine has obvious acute analgesic efficacy, and sustained infusions of ketamine over one to 100 hours have produced sustained analgesia for months after these single treatments. One study showed substantially reduced chronic neuropathic pain after 30 minutes of ketamine infusion at 0.5 mg/kg, but, in some patients, this relief lasted only several hours. A second set of studies using 100-hour infusions of ketamine at 20 to 30 mg/hour or 4-hour daily infusions for 10 days relieved pain for 3 months, but relief started declining by 4 to 6 weeks after the acute treatments. Overall, these ketamine studies showed large effect sizes in the first week following treatment (1.2, P≤0.001), but by week 4, the effect sizes dropped to 0.4 (although they remained statistically significant at P = 0.04). Unfortunately, these reports are 5 to 10 years old, and more recent reports are not available. Similarly, there are no studies using the newly available intranasal formulation of esketamine, which would make the administration easier than the previous intravenous studies.

Some important caveats for ketamine:

- There was no improvement in functionality with analgesia from ketamine.
- Cognition and memory impairment may be persistent with longer duration or more frequent administration; and no long-term data exist.
- Ketamine has negative inotropic effects on the heart and can produce elevated liver functions with repeated dosing.
- Less serious adverse effects include drowsiness and dizziness during repeated treatment (about one-quarter of patients reported these symptoms).
- Dissociation and abuse are potential psychiatric complications from even a single administration of ketamine.

Concluding thoughts
Chronic pain continues to be a hot button issue, and psychiatrists need to be aware of non-opioid options, especially for their patients with substance use histories. Both ketamine and CBD are on the horizon as new treatments for chronic pain. Since both have risks for inducing substance use disorders, their use needs to be considered cautiously.

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REFERENCES
Eulogies and Bedtime Stories
Reflections on My State Mental Hospital Service

» Lawrence H. Climo, M.D.

I was trained in psychoanalytic psychotherapy but found myself working as a staff psychiatrist on a locked unit of a state mental hospital. Talk therapy was not practiced here, so I had to learn about my patients—all chronically and seriously mentally ill long-term residents—by reading their records. Of course, that is not the same thing as getting to know them. And I wanted them to get to know me, I wanted them to feel safe with me and to accept me, a stranger, as their doctor. So I came up with this idea. What better way to show them who I am than by showing them who they are in my eyes?

From time to time during quiet moments and in public spaces, I would stand with the occasional patient and, in the course of conversation, casually re-tell their story as I understood it. I did this in terms not of their illness and its progression and the treatments and their effects, but in terms of their ordeal and strengths. The retelling was not about accounting for their disorganized and psychotic thinking or their obvious inadequacies and failures, but rather about their grit and endurance in the face of such trauma and adversity. I commented on the stamina called for by those who were surviving it. I acknowledged the effort it must take for them to endure the disorganization of thoughts and isolation as well as the fear driven by voices. I was hoping in this acknowledgment of their humanity and their battered integrity that was buried deep in the chaos of their lives—and by giving that chaos names—to demonstrate my respect for them and, through this, earn their trust.

I quickly gained confidence in this strategy, a confidence earned not by my patient’s rapt attention to my words but by the rapt attention of the inevitable cluster of patients who would discretely gather within earshot to eavesdrop and listen to these stories. I was confident that it was not the wonder and satisfaction of it. After all, for a child who has never been to a zoo, let alone absorb and process so many sights, movements, smells, and noise, it is not just the animals that make up this accomplishment. It is the surviving the loss of the familiar and holding course while encountering the exciting unknown.

It is no wonder that small children listen attentively to bedtime stories—confirmed by their correcting reader mistakes—as a parent walks them through their day in the safety and comfort of their bed or just reads to them. They beg for that bedtime story. It is not to avoid sleep, it is to be prepared for sleep. By recalling how you mastered a first-of-its-kind experience, faced it and were thrilled by it, or by re-visiting it vicariously through that rabbit or bear in the story or by re-visiting it vicariously through that rabbit or bear in the story who is going through their uncannily similar adventures, you render the chaos and novelty of life’s surprises, faced it and were thrilled by it, or by re-visiting it vicariously through that rabbit or bear in the story who is going through their uncannily similar adventures, you render the chaos and novelty of life’s surprises. The world makes sense. It is safe and there is a place in it for you. That is the real story. Then, they relax, and sleep comes. (Same for adults.) It was with this in mind that in the years that followed, it became my practice to take a moment to ask patients suffering severe and chronic mental illness this question: “If someone were to write a book about your life, living with your illness, and all you have seen and suffered and survived, what might be a good title for that book?” Their answers were always rich with poignant honesty. For that moment we were both on the same page. We were people together, trying to make sense of what is going on and what went on, both around us and inside of us. And they were reminded that they were not alien, evil, or crazy, and that things that confuse, frighten, and hurt have names. After all, don’t we all spend our lives trying to make sense of the world and our place in it, too?

Those asylums, our state hospitals, have long since closed and their staffs and patients have moved on. I like to think of those personal stories that I retold as eulogies, in-as-much as they were genuine hero stories. I would also like to think, for those suffering people who may have enjoyed a momentary peace, that the peace-of-mind was portable. I would like to think that, in the days (even years) that followed, at the end of the day, lying in bed in the dark, they might have re-told themselves their story as I told it and experienced again a peace-of-mind moment.

Dr. Climo is the author of Psychiatrist on the Road: Encounters in Healing and Healthcare, an account of his Locum Tenens experience.
Who Knew? The Implications of One Environmental Policy for Mental Health

Benson Ku, MD

The Clean Air Act (CAA) turned 55 years old last year. Like me, most millennials and Gen Xers have had little idea what this legislation has meant for us, even though it may have given us each almost a year of productive life. Passed on December 17, 1963, and amended in 1970 and 1990, CAA was a milestone statute—the first federal law regulating air pollutants and demanding reductions in particulate matter, photochemical oxidants like ozone, carbon monoxide, sulfur oxides, nitrogen oxides, and lead. Over the last five decades, lead in the air has dropped 99%, nitrogen dioxide has dropped more than 60%, sulfur dioxide has dropped more than 90%, and ozone has dropped more than 30%.1 Even in the 28 years that I have been alive, the PM2.5 particulate air pollution that doubles our risk for dementia and causes developmental disorders has decreased 40% from previous levels. I was not alive in the 1950s when the skies of New York City and London were yellow with smog that burned the eyes or when the headlines blasted the bad news of deaths in the Donora disaster in Pennsylvania in 1948.2 Yet, the cleaner air in the US that was motivated by those environmental disasters probably had direct impacts on my mental health as well as that of everyone I know. Since the CAA 1970 Amendment that required lower emissions of lead, children’s blood lead levels in the US have continuously declined. Levels of lead found in human blood decreased more than 80% from 1976 to 1999 in American children aged one to five years, from 17.1 μg/dL to 2.0 μg/dL on average.3

Toxic accumulation of lead results in long-term neurodevelopmental and behavioral problems, including decreases in IQ scores, developmental delays, learning disabilities, antisocial behavior, and reduced educational attainment. Blood lead levels above 10 μg/dL in children, which were much more prevalent before CAA, have been reliably associated with cognitive impairment and behavioral problems such as attention deficit hyperactivity disorder. The impact of CAA on reducing lead emissions can be estimated to have prevented 10.4 million lost IQ points in children from 1970 to 1990. That’s about 15 million IQ points in my lifetime—about 0.14 IQ points for every child born since I was born.

During the same time frame, Americans worked 17 million more days than they would have if they had been sick from bad air. That may represent upwards of 200 productive days for me personally, and I may have also saved myself a trip or two to the Emergency Department for asthma exacerbations that I did not have.

Despite the great and continuing successes of CAA, however, there is reason for concern. In recent years, the greenhouse gas emissions (GHGs) that form much of the air pollution and are the main driver of climate change have begun to rise again, after five decades of steady decrease. In 2018, America’s carbon dioxide emissions rose by 3.4%, the biggest increase in 8 years, as Trump began to roll back EPA protections put in place by Obama to curb this trend.4 Ozone is on the rise. Four in ten Americans still live in places with unhealthy air despite study after study reinforcing that air pollution is doubling the incidence of autism, dementia, and other neuropsychiatric disorders.5 In fact, in late August 2019, the Trump Administration proposed a roll back on the regulation of methane, a GHG that has been shown to be 25 times more powerful than carbon dioxide in trapping heat in the atmosphere.

Air pollution traps heat and raises global temperatures and worsens extreme weather. These conditions disrupt the climate and are leading to a growing number of mental health symptoms and crises. Growing evidence has demonstrated the impact of rising temperature on suicidality. Helama and colleagues6 reported a positive correlation between temperatures and suicide rates in Finland using historical records from 1751 to 1990, when a national suicide prevention program was put into place. A 2016 study of 29 European countries over a 13-year period showed that climatic variables were consistently a better predictor of suicides than socioeconomic factors.7 A more recent study found that as temperatures climbed over the course of decades in the US and Mexico, suicide rates also increased by 0.7% and 2.1%, respectively, for every 1°C increase in monthly average temperature.8 This study estimated that if temperatures continue to go up, climate change will cause a total of 21,770 excess suicides by 2050 in the US and Mexico.

I learned all this while working on a chapter for a forthcoming book to be published by American Psychiatric Association Publishing with help from my chapter editor Elizabeth Haase, MD, and lead editor Michael T. Compton, MD, MPH. It has changed me. I now understand how much difference one good law can make, and I plan to do my part in psychiatric advocacy to make sure we have many such supports for our mental health working for us in our government.

Dr Ku is a Psychiatry Resident, Emory University School of Medicine, Atlanta, GA. He reports no conflicts of interest concerning the subject matter of this article.

REFERENCES
The Misplaced Media Focus on Jeffrey Epstein’s Death

Ronald W. Pies, MD

The death of Jeffrey Epstein—apparently not definitively a suicide—received wall-to-wall coverage in the media for understandable reasons. Epstein—a wealthy financier and convicted sex offender who had been charged with sex trafficking of minors—was clearly a high-profile lightening rod, whose lurid history provoked intense reactions. Furthermore, the unanswered questions surrounding his death kindled wild speculation and baseless conspiracy theories. In short, Epstein’s story was media catnip. Unfortunately, lost in all the sensational coverage of this one man was the systemic mistreatment of people with serious mental illness in the criminal justice system.

According to the Bureau of Justice Statistics, suicide has been the leading cause of death in US jails every year since 2000. In 2013, a third (34%) of jail inmate deaths were attributable to suicide. The suicide rate increased 14%, from 40 suicides per 100,000 jail inmates in 2012 to 46 per 100,000 in 2013. Rates hit a high of 50 deaths for every 100,000 inmates in 2014, the latest year for which the government has released data. Not unexpectedly, men are more likely to die by suicide than women in jail settings, as in the general population.

Suicide rates in jails are generally higher than those in prisons, an effect often attributed to “the shock of confinement” experienced by those in jail—many of whom have never been in serious legal trouble before. According to corrections expert Steve J. Martin,1 being jailed for the first time “…over-takes your being, in the sense that normalcy is gone.” Also, as the Marshall Project has noted, by the time someone arrives in prison, a prisoner’s suicidal tendencies have had a longer time to emerge, and—at least in some cases—to be recognized.2

This last point sheds light on the real scandal within the US penal system. As Jane Wiseman and Stephen Goldsmith have put it, “Today, after decades of deinstitutionalization of all but the most critically ill patients from state mental hospitals, America’s jails are the central address for the mentally ill.”3 Indeed, as Wiseman and Goldsmith note, there are 10 times more people with mental illness in the criminal justice system than are being treated in psychiatric hospitals.

The story gets worse. A joint investigation by The Associated Press (AP) and the University of Maryland’s Capital News Service (CNS) found that “…scores of jail inmates have been sued or investigated in recent years for allegedly refusing inmates medication, ignoring their cries for help, failing to monitor them despite warnings they might harm themselves, or imposing such harsh conditions that the sick got sicker.”4

The AP/CNS investigation also found that in about a third of cases where jail inmates attempted suicide or took their lives, they did so after staff allegedly failed to provide prescription medicines used to manage mental illness. We do not yet know the outcome of these lawsuits, but there is good reason to believe that better assessment and treatment of incarcerated people with mental illness would reduce suicide rates in this population.

In fairness to jail officials, it should be noted that they are dealing with a situation not of their making. As Jonathan Thompson, head of the National Sheriffs’ Association, put it, “We’re not the nation’s psychologists … We have decided that, as a society, let’s just warehouse the mentally ill in a jail … which is neither equipped for, trained to handle, or able to be the most efficient and effective at solving the problem.”5

Those of us in psychiatry who have lost patients to suicide—and sadly, I include myself—know well that suicide risk determinations are complex and harrowing, and sometimes reach the wrong conclusion, despite a thorough assessment. Meanwhile, the much larger issue of why so many people with serious mental illness wind up in jail or prison—and often receive inadequate assessment and treatment there—will loom before us, long after the media have lost interest in Jeffrey Epstein.

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

REFERENCES

OCD Constellations

Continued from page 33

contamination obsessions make the person feel that leaving the home will result in bringing contaminants back into the home or being infected by something deadly.

In some cases, this may necessitate house calls on the part of the clinician. The obsessions may also include taking medication and, therefore, the very thing that could help them is avoided. In these instances, clinicians may need to be flexible as well as patient in their approach.

Furthermore, the content of the obsessions in OCD may confuse clinicians and lead to incorrect diagnoses, such as when someone has sexual obsessions and they are misdiagnosed as having a paraphilia. Initially, the patients may not be forthcoming because of shame and embarrassment and clinicians should take their time in eliciting all possible information concerning the sexual thoughts.

Because the SSRIs are often needed in higher doses than used for depression, clinicians may have concerns when treating OCD comorbid with other disorders such as bipolar disorder. The concern of switching someone into mania from the high doses of SSRIs may be counter-balanced by first starting an antiepileptic and then slowly titrating the SSRI to the needed dose.

Finally, in very rare cases of OCD that are refractory to all standard treatment approaches, neurosurgical interventions may be considered. Because these have been written about in the popular press, patients often inquire about them. It is important to first assess that the person has tried a true trial of quality ERP as well as multiple medication trials (ie, appropriate doses for the appropriate trial periods). In those instances where these have been attempted and an ethical board has reviewed the case independent of the clinician, then neurosurgery may be appropriate.

OCD, like other psychiatric disorders, has evidence-based treatments but there are often clinical aspects that complicate an easy implementation of those treatments. Clinicians treating OCD should be prepared for some of these potential hurdles and have ways of addressing them.

Dr. Grant is Professor of Psychiatry and Behavioral Neuroscience at the University of Chicago. He was a speaker at the 2019 Psych Congress in San Diego, CA, where he presented “Top 5 Complex Patients With OCD.”

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ADDITIONAL READING
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1. McKay D, Abramowitz JS, Steven Taylor S, Eds. Turning Failure Into Success: Strategies for Overcoming Treatment Resistant OCD. Diego, CA, where he presented “Top 5 Complex Patients With OCD.”
on-suicidal self-injury (NSSI), or the deliberate act of self-inflicted damage to one’s body without suicidal intent, is a maladaptive and potentially habitual behavior that often serves to relieve strong negative feelings. NSSI typically emerges in adolescence. The average prevalence of NSSI behavior in adolescents is 18%, while 7% of adolescents potentially qualify for the diagnosis of NSSI disorder as proposed in the DSM-5.1,2 NSSI is associated with multiple psychiatric disorders including depression, anxiety, substance use, eating disorders, personality disorders, and developmental disorders; it can also occur in the absence of any psychiatric disorder.

MARY

“Mary” is a 15-year-old high school student with no previous psychiatric history who was brought to the emergency department (ED) by her parents because of self-inflicted lacerations on her arms. During the assessment, Mary revealed to the physician that she had been cutting herself one to two times a week for several months. In the past year, Mary had experienced episodes of intense sadness and anxiety. She had learned about self-cutting through social media outlets; she also said her peers were using this strategy to manage stress. Mary reported that cutting served to numb her feelings and described it as “the only thing that helps.” Mary reported that about 8 months ago, she had thoughts of wanting to die and took 5 pills from the medicine cabinet; the next morning she woke up feeling fine and told no one about this incident until now. She denied any current suicide attempts, but reported occasionally wishing that she had not been born.

While suicidal behavior and NSSI are separate phenomena, they commonly co-occur. In fact, NSSI is a strong predictor for suicide attempts. Therefore, effective treatment of NSSI represents an avenue for preventing suicide, the second leading cause of death among adolescents. Previous empirical treatment reviews that have summarized behavioral and pharmacological interventions for NSSI have largely focused on adults. Since ado-

TREATMENT GOALS

The goal of this activity is to provide an understanding of the treatment modalities for the management of nonsuicidal self-injury (NSSI) in adolescents.

LEARNING OBJECTIVES

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

• Describe the evidence-based behavioral interventions that are used in the management of NSSI.
• Appreciate the current status of knowledge on somatic treatments for NSSI behavior; and
• Discuss the recommendations for future research on treatment development.

TARGET AUDIENCE

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

CREDIT INFORMATION

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

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Rana Elmaghraby, MD, has no disclosures to report.

Ozra Nobari, MD, has no disclosures to report.

Kathryn R. Cullen, MD, reports that she has received research support in the form of a grant from the American College of Cardiology Foundation and the National Center for Complementary and Integrative Health.

Kaz Nelson, MD (content reviewer), reports that she has received research support in the form of a grant from the American Board of Psychiatry and Neurology; she has received honoraria for writing a chapter on medications for personality disorders, and she receives royalties from Oxford University Press.

Applicable Psychiatric Times staff and CME Outfitters staff have no disclosures to report.

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adolescents. The addition of CBT reduced NSSI frequency in these adults with chronic suicidal behavior. DBT is a CBT-based intervention that was originally designed for suicide attempts and NSSI. Study results show that DBT is helpful in reducing NSSI in adolescents and college students. Furthermore, randomized controlled trials comprising adolescents and college students have confirmed efficacy of DBT in reducing NSSI and suicide attempts in youth.

Mentalization-based treatment (MBT) promotes the understanding of mental states underlying behavior for self and others. A recent RCT reported that MBT was more effective in reducing NSSI in adolescents with NSSI compared with treatment as usual.

Findings from preliminary research suggest that therapy involving the expressive arts, such as voice movement therapy, may have some promise for reducing NSSI in youth, but these approaches remain understudied.

In summary, the efficacy of several behavioral interventions for addressing NSSI in youth have been explored and tested to date. At present, DBT has the strongest evidence base as a well-established, empirically supported treatment for reducing both NSSI and suicide attempts in adolescents.

### Behavioral Interventions

#### Dialectical Behavioral Therapy (DBT)

DBT is a CBT-based intervention that was originally designed for adults with chronic suicidal behavior. DBT includes individual and group components and teaches skills including distress tolerance, emotion regulation, mindfulness, and interpersonal effectiveness. A robust literature supports the use of DBT in adults with self-harm behaviors (both suicide attempts and NSSI). Study results show that DBT is helpful in reducing NSSI in adolescents and college students.

Furthermore, randomized controlled trials comprising adolescents and college students have confirmed efficacy of DBT in reducing NSSI and suicide attempts in youth.

Mentalization-based treatment (MBT) promotes the understanding of mental states underlying behavior for self and others. A recent RCT reported that MBT was more effective in reducing NSSI in adolescents with NSSI compared with treatment as usual.

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In summary, the efficacy of several behavioral interventions for addressing NSSI in youth have been explored and tested to date. At present, DBT has the strongest evidence base as a well-established, empirically supported treatment for reducing both NSSI and suicide attempts in adolescents.

### Somatic Treatments: Pharmacological and Neuromodulation Approaches

There are currently no somatic treatments that have approval from the Food and Drug Administration for the specific treatment of NSSI. Therefore, in the following paragraphs, all discussion of potential effects on NSSI behavior by somatic treatments refers to off-label use of these agents.

Antidepressants are commonly used in the treatment of adolescents with NSSI because this behavior often occurs in the context of depression and anxiety symptoms. However, no studies have formally tested if antidepressants reduce NSSI frequency in adolescents. Moreover, combination treatment using SSRIs and CBT has not been shown to help with NSSI. One case report noted improvement in NSSI behavior with fluoxetine treatment in an adolescent with intellectual disability in whom a trial of naltrexone had previously failed. Despite their common use in neurotypical adolescents with NSSI, there is currently limited evidence to support antidepressant medication efficacy for reducing NSSI specifically.

Opioid antagonists have been investigated as an intervention for NSSI, with the idea of blocking endogenous opioids generated by and reinforcing the behavior. To date, research has focused primarily on adult patients with developmental disorders. However, there are some reports of opioid antagonist use in adolescents with neurodevelopmental disorders. One case series reported that treatment with naltrexone was associated with reduced NSSI behaviors in 3 of 6 male adolescents with profound intellectual disability.

Two single-subject, placebo-controlled, crossover-design studies added to the evidence that opiate blockade may be useful for decreasing NSSI in youth with

#### Table

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<td><strong>Psychotherapy approaches</strong></td>
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<td><strong>CBT</strong></td>
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<tr>
<td>Brent et al.3</td>
<td>Depressed adolescents aged 12-18 yrs with non-response to SSRIs</td>
<td>334</td>
<td>RCT</td>
<td>SSRI &lt; SSRI + CBT; venlafaxine, venlafaxine + CBT (12 wks)</td>
<td>No significant difference between groups in incidence of NSSI during the study</td>
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<tr>
<td>Goodyear et al.4</td>
<td>Depressed adolescents aged 12-18 yrs with nonresponse to brief psychosocial intervention</td>
<td>208</td>
<td>RCT</td>
<td>SSRI vs CBT + SSRI</td>
<td>Decreased frequency by more than 50% (no significant difference between groups)</td>
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<td><strong>DBT</strong></td>
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<td>Goldstein et al.4</td>
<td>Adolescents aged 14-18 years with bipolar disorder</td>
<td>10</td>
<td>Open-label trial</td>
<td>DBT with individual and family skills training; 24 wks followed by continuation (tapering frequency to 1 yr)</td>
<td>4 adolescents reported NSSI history at intake; no adolescents reported NSSI at final assessment</td>
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<tr>
<td>Mehlum et al.6,9</td>
<td>Adolescents aged 12-18 yrs with self-harm behavior</td>
<td>77</td>
<td>RCT</td>
<td>DBT-A (shortened form) vs EUC (19 wks)</td>
<td>Greater decrease in NSSI frequency in DBT-A group vs EUC; DBT-A group remained superior to EUC in decreased incidence of NSSI at 1 yr</td>
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<tr>
<td>McCauley et al.3</td>
<td>Adolescents aged 13-18 yrs with a history of suicide attempt</td>
<td>173</td>
<td>RCT</td>
<td>DBT vs IGST (6 mos)</td>
<td>50% in DBT group vs 40% in ISGT group; no NSSI at 6 mos</td>
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<tr>
<td>Pistorello et al.10</td>
<td>College students aged 18-25 yrs with baseline suicidal thoughts, history of ≥ 1 NSSI episode or suicide attempt and ≥ 3 BPD criteria</td>
<td>63</td>
<td>RCT</td>
<td>DBT vs OTAU (7-12 mos)</td>
<td>Similar incidence of NSSI during the trial; mean NSSI count was lower for DBT than for OTAU</td>
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<td><strong>MBT</strong></td>
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<td>Rossouw and Fongay11</td>
<td>Adolescents aged 14-17 years with depression and self-harm</td>
<td>80</td>
<td>RCT</td>
<td>MBT-A vs TAU</td>
<td>56% of adolescents in MBT-A were self-harming at 12 mos vs 86% in TAU group</td>
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</tbody>
</table>
developmental disabilities. However, there have been no studies in the past two decades on opioid antagonists in adolescents or neurotypical adolescents with NSSI. Lithium is a mainstay for treating bipolar disorder and is known for its anti-suicide effect in patients with unipolar depression. However, to date no studies have investigated the role of lithium in treating NSSI in adolescents.

In addition to their use for treating psychotic disorders, atypical antipsychotics have been prescribed off-label with increasing frequency to children and adolescents to address non-psychotic problems. Some studies indicate utility of these medications in reducing NSSI in youth. A placebo-controlled RCT that examined adolescents and adults (mean age=22 years) with borderline personality disorder found that aripiprazole treatment was associated with fewer NSSI episodes than placebo. A retrospective chart review found that ziprasidone treatment was associated with lower NSSI frequency in 16 female adolescents. In two case studies (consisting of 3 non-psychotic adolescents), clozapine treatment was associated with a reduction in NSSI behaviors. However, the adverse effects of atypical antipsychotics limit their

Table Continued: Selected clinical trials evaluating treatments for adolescents with NSSI

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<th>Reference</th>
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<td><strong>Medication and nutritional supplements</strong></td>
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<td><strong>SSRIs</strong></td>
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<tr>
<td>Bass and Beltis.</td>
<td>Young male aged 17 yrs with intellectual disability and NSSI with nonresponse to naltrexone</td>
<td>1</td>
<td>Case report</td>
<td>40-mg fluoxetine (2 yrs)</td>
<td>45% - 55% reduction in NSSI frequency over 2 yrs</td>
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<td><strong>Opiate antagonists</strong></td>
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<td>Kars et al.</td>
<td>Inpatients aged 15-31 years with intellectual disability and NSSI</td>
<td>6</td>
<td>Double-blind placebo-controlled crossover study</td>
<td>Naltrexone daily vs placebo (3 wks each phase)</td>
<td>2 patients showed a significant reduction in NSSI and a third showed a partial reduction</td>
</tr>
<tr>
<td>Walters et al.</td>
<td>Adolescent aged 14 yrs with autism, intellectual disability, and severe NSSI</td>
<td>1</td>
<td>Single-subject double-blind placebo-controlled</td>
<td>Naltrexone vs placebo (21 days, 2 phases of each)</td>
<td>NSSI episodes were markedly reduced during active drug phases (1st and 3rd) and during the second placebo phase (4th)</td>
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<tr>
<td>Bernstein et al.</td>
<td>18-year-old with intellectual disability and severe NSSI</td>
<td>1</td>
<td>Single-subject double-blind placebo-controlled</td>
<td>Trial 1: naloxone 0.5 mg - 1 mg every 30 min over 6 h vs placebo; trial 2: naltrexone 12.5 mg daily vs placebo; each phase 15 days</td>
<td>Naloxone was associated with a 50% decrease in NSSI frequency; naltrexone was associated with a 33% decrease in NSSI frequency</td>
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<tr>
<td>Cullen et al.</td>
<td>Adolescents aged 13-21 yrs with NSSI</td>
<td>35</td>
<td>Open-label</td>
<td>N-acetylcysteine (titrated, 3600 mg/d for 8 wks)</td>
<td>Significant decrease in NSSI episode frequency at 8 wks</td>
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<td><strong>Neuromodulation</strong></td>
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<td>Nixon et al.</td>
<td>Adolescent inpatients with depression and NSSI (1/wk for past 6 mos)</td>
<td>9</td>
<td>Open-label</td>
<td>Auricular acupuncture (3 treatments over 3 wks)</td>
<td>NSSI decreased in frequency by more than 50%</td>
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<td><strong>Expressive arts</strong></td>
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<tr>
<td>Martin et al.</td>
<td>Young women aged 16-25 yrs</td>
<td>19</td>
<td>Open-label</td>
<td>Voice movement therapy; 10 weekly group therapy sessions, 1 booster session</td>
<td>Nonsignificant trend for reduction in NSSI frequency</td>
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<td><strong>Antipsychotic medications</strong></td>
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<tr>
<td>Nickel et al.</td>
<td>Adolescents and young adults aged ≥ 16 yrs (mean age 22 yrs) with BPD</td>
<td>52</td>
<td>Double-blind, placebo-controlled trial</td>
<td>Aripiprazole 15 mg/d for 8 wks</td>
<td>2/26 patients in the aripiprazole group and 7/26 in the placebo group exhibited NSSI during 8 wks of treatment</td>
</tr>
<tr>
<td>Libal et al.</td>
<td>Girls aged 13-17 yrs</td>
<td>16</td>
<td>Retrospective chart review</td>
<td>8 patients received ziprasidone 40-80 mg; 8 patients received a different neuroleptic; varying treatment duration; 14 patients also received other medications</td>
<td>47.3% reduction in NSSI frequency in aripiprazole group; 17.8% decrease in NSSI frequency in other group</td>
</tr>
<tr>
<td>Kumar et al.</td>
<td>Girls aged 11 and 15 years</td>
<td>2</td>
<td>Case series</td>
<td>Clozapine</td>
<td>Clozapine reduced self-injurious behaviors in both girls</td>
</tr>
<tr>
<td>Argent et al.</td>
<td>Young woman aged 17 years with borderline personality disorder</td>
<td>1</td>
<td>Case report</td>
<td>Clozapine</td>
<td>Reduction of self-harm was noted; most remained in the context of suicidal thoughts</td>
</tr>
</tbody>
</table>

CBT, cognitive behavioral therapy; DBT, dialectical behavioral therapy; EUC, enhanced usual care; ISGT, individual and group supportive therapy; BPD, borderline personality disorder; OTAU, optimized treatment as usual; TAU, treatment as usual; MBT, mentalization-based therapy.
broad use for treating NSSI in adolescents.

Given the wide-spread problem of NSSI in adolescents, interventions that are safe and broadly accessible are needed. Off-label use of N-acetylcysteine (NAC), an inexpensive and widely-available nutritional supplement, has shown treatment potential in multiple psychiatric disorders.\(^2\) NAC is a precursor in the formation of glutathione (GSH), the primary antioxidant in the brain, which suggests its potential to confer neuroprotection. NAC also modulates glutamate and dopamine receptors that play a role in motivation and reward, therefore it has relevance in the treatment of habitual behaviors.

An 8-week open-label study showed that an oral NAC was associated with reduced frequency of NSSI, decreased depressive symptoms, and global psychopathology.\(^3\) However, there are no results from placebo-controlled RCTs for NAC in adolescents with NSSI.

Neuromodulation approaches such as electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) may have a role in the treatment of self-harm behaviors. ECT is known to have an important anti-suicide effect, and case reports have suggested its ability to reduce aggression and self-mutilation in adolescents with autism spectrum disorders and intellectual disabilities.\(^4\) There is no research on non-invasive neuromodulation such as TMS for the treatment of NSSI; this may represent an important avenue for future research.

Auricular acupuncture involves stimulation of acupuncture points on the external surface of the ears. Nine adolescents on an inpatient unit with depression and NSSI were administered auricular acupuncture bilaterally at five ear sites for five days per week for three weeks.\(^5\) The treatment was well tolerated, and a reduction in NSSI and internalization of anger was seen.

### CASE VIGNETTE (CONT’D)

In the ED, Mary’s injuries were treated with topical ointment. The emergency physician disclosed the past suicide attempt to Mary’s parents and engaged the family in a detailed safety plan (eg, removal of access to sharps in the home, locking up home medications). Mary was discharged to home with referrals to an adolescent DBT program and to a child psychiatrist for further assessment of depression and anxiety.

### Conclusion

NSSI is a highly prevalent problem in youth and represents an important risk factor for later suicide attempts. Early and effective treatment is therefore critical for suicide prevention. Because of ongoing neurodevelopment during adolescence, this represents an especially important time for effective intervention, as these developmental processes likely:

- **Play a role in disease vulnerability;**
- **Contribute to how adolescents respond to different interventions; and**
- **Enhance brain plasticity, potentially allowing maximal impact from interventions.**

While some evidence is available to support interventions for adolescents with NSSI, the field stands in need of significant advancement in multiple areas.

The next steps in treatment development for adolescents with NSSI (both behavioral and pharmacological approaches) should incorporate:

- **Larger samples and rigorous, unbiased study designs with improvement of NSSI symptoms as the primary outcome;**
- **An experimental medicine approach to identify not only whether a treatment works but also how it works, providing the basis for optimization based on biological effects; and**
- **A personalized medicine approach, to discover for whom each treatment is most suitable based on factors such as demographic, clinical and biological characteristics, patient preferences, and available community resources.**

Meanwhile, as the field awaits new research to provide improved, evidence-based intervention options, how to treat adolescents in our offices who present with NSSI?

Information should be drawn from the patient, the family, and the available literature to select the best treatment path. While currently DBT has the strongest evidence as an intervention for NSSI in adolescents, research on other psychotherapies (both individual and family) and somatic (eg, medication, nutritional supplements, neuromodulation) interventions are emerging. Comorbid psychiatric conditions must be assessed and treated, and psychosocial issues, including family dynamics, must be addressed. Healthy connections with supportive networks (eg, family, friends, teachers, coaches, etc.) can play a key role in restoring and maintaining the health and safety of children and adolescents. The final ingredients that a clinician can offer when caring for youth with NSSI include instilling hope, modeling resilience to setbacks, and maintaining the goal of full remission and restoration of healthy brain and behavioral development.

### REFERENCES


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- **Residency Training Program Director – Ocean Medical Center, (Brick, NJ)**

- **Pediatric Psychiatry Collaborative**

- **Consultation Liaison Psychiatrists:**
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  - Ranitan Bay Medical Center (Perth Amboy, NJ)
  - Ocean Medical Center (Brick, NJ)

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  - Hackensack University Medical Center (Hackensack, NJ)

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

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Psychiatry Residency Training Program Director

Ocean Medical Center, Brick, New Jersey

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dr. Sheldon benjamin, Physician Recruiter
jessica.saintelus@umassmemorial.org
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