A cross the country, the past decade has shown a dramatic increase in patients presenting to hospital emergency departments (EDs) with acute psychiatric crises. Between 2009 and 2015 alone, the number of adult psychiatric cases in EDs rose more than 40%. The number of patients being assessed in EDs for suicidality between 2006 and 2014 jumped a staggering 414%.

CONTINUED ON PAGE 30
SPRAVATO™ (esketamine) CIII Nasal Spray is indicated, in conjunction with an oral antidepressant (AD), for the treatment of treatment-resistant depression (TRD) in adults. SPRAVATO™ is available only through a restricted program under a REMS.

**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 0.2% 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.

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**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.

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

**References:**

1. SPRAVATO™ (Prescribing Information)


**Device as shown does not depict actual position for administration.**
SPRAVATO™ caused cognitive performance decline 40 minutes post-dose. SPRAVATO™, small increases in blood pressure.

or monoamine oxidase inhibitors (MAOIs) [see Drug Interactions (7.2, 7.3)] Closely monitor blood pressure with concomitant use of SPRAVATO™ with psychostimulants.

Closely monitor blood pressure with concomitant use of psychostimulants or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, experiencing symptoms of a hypertensive crisis (e.g., chest pain, shortness of breath) Measure blood pressure around 40 minutes post-dose and subsequently as other cardiovascular and cerebrovascular conditions should be carefully assessed to pressure poses a serious risk (e.g., aneurysmal vascular disease, arteriovenous

SPRAVATO™ is contraindicated in patients for whom an increase in BP or intracranial

SPRAVATO™ causes increases in systolic and/or diastolic 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 dosages. Increases in BP peak approximately 40 minutes after SPRAVATO™ administration and last approximately 4 hours. Approximately 6% to 17% of SPRAVATO™-treated patients experienced an increase of more than 40 mmHg in systolic BP and/or 25 mmHg in diastolic BP in the first 1.5 hours after administration at least once during the first 4 weeks of treatment. A substantial increase in blood pressure could occur after any dose administered even if smaller blood pressure effects were observed with previous administration. 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 intracranial hemorrhage). Before prescribing, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of SPRAVATO™ outweigh its risk. Assess BP prior to administration of SPRAVATO™. In patients whose BP is elevated prior to SPRAVATO™ administration (as a general guide: >140/90 mmHg), a decision to delay SPRAVATO™ therapy should be taken into account to balance the benefit and risk in individual patients. BP should be monitored for at least 2 hours after SPRAVATO™ administration. Measure blood pressure around 40 minutes post-dose and subsequently as clinically warranted until values decline. If BP remains high, promptly seek assistance from practitioners experienced in BP management. Refer patients experiencing symptoms of a hypertensive crisis (e.g., chest pain, shortness of breath) or hypertensive encephalopathy (e.g., sudden severe headache, visual disturbances, seizures, diminished consciousness or focal neurological deficits) immediately for emergency care. Closely monitor blood pressure with concomitant use of SPRAVATO™ with psychostimulants or monoamine oxidase inhibitors (MAOIs) [see Drug Interactions (7.2, 7.3)]. In patients with history of hypertensive encephalopathy, more intensive monitoring, including more frequent blood pressure and symptom assessment, is warranted because these patients are at increased risk for developing encephalopathy with even small increases in blood pressure.

Cognitive Impairment Short-Term Cognitive Impairment: In a study in healthy volunteers, a single dose of SPRAVATO™ caused cognitive performance decline 40 minutes post-dose. SPRAVATO™, treated subjects required a greater effort to complete the cognitive tests at 40 minutes post-dose. Cognitive performance and mental effort were comparable between SPRAVATO™ and placebo at 2 hours post-dose. Sleepiness was comparable after 4 hours post-dose. Long-Term Cognitive Impairment: Long-term cognitive and memory impairment have been observed with repeated ketamine use or abuse. No adverse effects of SPRAVATO™ nasal spray on cognitive functioning were observed in a one-year open-label safety study; however, the long-term cognitive effects of SPRAVATO™ have not been evaluated beyond one year. Impaired Ability to Drive and Operate Machinery: Before SPRAVATO™ administration, instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep. Patients will need to arrange transportation home following treatment with SPRAVATO™. Ulcerative or Interstitial Cystitis: Cases of ulcerative or interstitial cystitis have been reported in individuals with long-term off-label use or misuse/abuse of ketamine. In clinical studies with SPRAVATO™ nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, miction urgency, nocturia, and cystitis) in SPRAVATO™-treated patients than in placebo-treated patients. No cases of esketamine-related interstitial cystitis were observed in any of the studies, which involved treatment for up to a year.

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

Embryo-fetal Toxicity: SPRAVATO™ may cause fetal harm when administered to pregnant women. Advise pregnant women of the potential risk to an infant exposed to SPRAVATO™ 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. The mean esiketamine Cmax and AUC values were higher in elderly patients compared with younger adult patients.

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

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

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

DRUG ABUSE AND DEPENDENCE Controlled Substance: SPRAVATO™ contains esketamine hydrochloride, the (S)-enantiomer of ketamine and a Schedule III controlled substance under the Controlled Substances Act. Abuse: Individuals with a history of drug abuse or dependence may be at greater risk for 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, lathargy, blood pressure increased, vomiting, and feeling drunk.

Please see Brief Summary of full Prescribing Information, including Boxed WARNINGS, on following pages.
**SPRAVATO™** (esketamine) nasal spray, 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:

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

**WARNINGS AND PRECAUTIONS**

**Sedation**

In clinical trials, 49% to 91% 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 of the prolonged sedation, patients must be monitored by a healthcare provider for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting (see Dosage and Administration (2.4) in Full Prescribing Information).

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

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

**Dissociation**

The most common psychological effects of SPRAVATO were dissociative or perceptual changes (including altered sense of time, space and illusions, derealization and depersonalization (61% to 71% of SPRAVATO-treated patients developed dissociative or perceptual changes based on the Clinician Administered Dissociative Symptoms Scale) (see Adverse Reactions). 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 (see Dosage and Administration (2.4) in Full Prescribing Information).

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

**Abuse and Misuse**

**SPRAVATO contains esketamine, a Schedule III controlled substance (CIII), and may be subject to abuse and diversion. Assess each patient’s risk for abuse or misuse prior to prescribing SPRAVATO and monitor all patients receiving SPRAVATO for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy. Contact local state professional licensing board or state-crisis line when esketamine use is associated with significant abuse or diversion of SPRAVATO. Individuals with a history of drug abuse or dependence are at a 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. (see Drug Abuse and Dependence).

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

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

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

**Important requirements of the SPRAVATO REMS include the following:**

- Healthcare settings must be certified in the program and ensure that SPRAVATO is:
  - Only dispensed in healthcare settings and administered to patients who are enrolled in the program.
  - Administered by patients under the direct observation of a healthcare provider and that patients are monitored by a healthcare provider for at least 2 hours after administration of SPRAVATO (see Dosage and Administration (2.4) in Full Prescribing Information).
- Pharmacies must notify the REMS and must only dispense SPRAVATO to healthcare settings that are certified in the program.

Further information, including a list of certified pharmacies is available at www.SPRAVATOREms.com or 1-895-382-6021.

**Suicidal Thoughts and Behaviors in Adolescents and Young Adults**

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 17,000 adult patients and 4,560 pediatric patients (SPRAVATO is not approved in pediatric patients), the incidence of suicidal thoughts and behaviors in patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, and there was an increased risk identified in younger patients in most drug studies used. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD). The drug class differences in the number of cases of suicidal thoughts and behaviors per 1,000 patients treated are 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**

<table>
<thead>
<tr>
<th>Age Range (Years)</th>
<th>Drug/Placebo Difference in Number of Patients with Suicidal Thoughts or Behaviors per 1,000 Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>Increases Compared to Placebo</td>
</tr>
<tr>
<td>18-24</td>
<td>Increases Compared to Placebo</td>
</tr>
<tr>
<td>25-64</td>
<td>25-64</td>
</tr>
<tr>
<td>≥65</td>
<td>≥65</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 17% 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 4 hours of treatment 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). Before prescribing SPRAVATO, patients with other cardiovascular and cerebrovascular conditions should be carefully assessed to determine whether the potential benefits of SPRAVATO outweigh its risks.

**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 the 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/or 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.

**Impaired Schizophrenia or Schizoaffective Disorder**

In a study in healthy volunteers, a single dose of SPRAVATO caused cognitive performance decline 40 minutes post-dose. Compared to placebo-treated subjects, SPRAVATO-treated subjects required a greater effort to complete cognitive tests at 40 minutes post-dose. Cognitive performance as measured by change in the Observer’s Alertness/Sedation scale was comparable between SPRAVATO and placebo at 2 hours post-dose. Sleepiness was comparable after 4 hours post-dose.

**Advice on Reproductive Impairment**

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

**Impaired Ability to Drive and Operate Machinery**

Two placebo-controlled studies were conducted to assess the effects of SPRAVATO on the ability to drive (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 the 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/or 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.

**Uncerebral or Intracerebral Cystitis**

Cases of ureteral or intracerebral cystitis have been reported in individuals with long-term off-label use or misuse/abuse of ketamine. In clinical studies with SPRAVATO nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, mic UIention urgency, nocturia, and cystitis) in SPRAVATO-treated patients than in placebo-treated patients (see Adverse Reactions). No cases of esketamine-related intracranial cystitis were observed in any of the studies, which included treatment for TRD in patients age ≥18 years. Monitor for urinary tract and bladder symptoms during the course of treatment with SPRAVATO, and refer to an appropriate healthcare provider as clinically warranted.

**Embryofetal Toxicity**

Based on published findings from pregnant animals treated with ketamine, the racemic mixture of ketamine and esketamine, 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 who are or may become pregnant to avoid exposure to SPRAVATO, and discuss alternative birth control methods. Women who are or may become pregnant should be counseled about the potential hazards of ketamine use or misuse/abuse of ketamine. In clinical studies with SPRAVATO nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, mic UIention urgency, nocturia, and cystitis) in SPRAVATO-treated patients than in placebo-treated patients (see Adverse Reactions). No cases of esketamine-related intracranial cystitis were observed in any of the studies, which included treatment for TRD in patients age ≥18 years. Monitor for urinary tract and bladder symptoms during the course of treatment with SPRAVATO, and refer to an appropriate healthcare provider as clinically warranted.
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]
- Lacerative 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 compared directly 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 3 long-term studies) and one Phase 2 dose-ranging study. Of all SPRAVATO-treated patients in the completed Phase 3 studies, 47% (30%) received at least 6 months of treatment, and 17% (11%) received at least 12 months of treatment.

Adverse reactions Leading to Discontinuation of Treatment

In short-term studies in adults < 65 years of age (Study 1 pooled with another 4-week study), the proportion of patients who discontinued treatment because of an adverse reaction was 4.6% in patients who received SPRAVATO plus oral AD compared to 1.4% for patients who received placebo nasal spray plus oral AD. For adults ≥ 65 years old, the proportions were 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 3 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%), muscular weakness (0.3%), vertigo (0.2%), hypertension (0.2%), panic attack (0.2%) and sedation (0.2%).

Most Common Adverse Reactions

The most commonly observed adverse reactions in TRD patients treated with SPRAVATO plus oral AD (incidence ≥ 5% and at least twice that of placebo nasal spray plus oral AD) were dissociation, dizziness, anxiety, sedation, vertigo, nausea, vomiting, dizziness, sensation of presence of an object in the head, headache, sleep disturbances, insomnia, nasal dryness, nasal discomfort, tinnitus, and visual disturbances. The most commonly reported adverse reactions in all patients treated with SPRAVATO plus oral AD (at any dose and greater than patients treated with placebo nasal spray plus oral AD) were dissociation (29%), anxiety (13%), nausea (7%), vomiting (7%), vertigo (7%), flushing (7%), and pain (6%).

Table 2: Adverse Reactions Occurring in >2% of TRD 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>Reaction</th>
<th>SPRAVATO + Oral AD (N=206)</th>
<th>Placebo + Oral AD (N=222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia*</td>
<td>6 (2%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>11 (2%)</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 (6%)</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>14 (6%)</td>
</tr>
<tr>
<td>General disorders and administration 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>Sedation</td>
<td>79 (23%)</td>
<td>21 (9%)</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>Depression*</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>Pollakiuria</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>Throat 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>Hyperhidrosis</td>
<td>14 (4%)</td>
<td>5 (2%)</td>
</tr>
</tbody>
</table>

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

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>Reaction</th>
<th>SPRAVATO 56 mg N=72</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td></td>
</tr>
<tr>
<td>Placebo + Oral AD</td>
<td>112</td>
</tr>
<tr>
<td>SPRAVATO + Oral AD</td>
<td>113</td>
</tr>
<tr>
<td><strong>Sedation</strong></td>
<td></td>
</tr>
<tr>
<td>Placebo + Oral AD</td>
<td>61%</td>
</tr>
<tr>
<td>SPRAVATO + Oral AD</td>
<td>69%</td>
</tr>
</tbody>
</table>

Table 4: Incidence of Dizziness (CADSS total score >4 and change >0.5%) in Double-Blind, Randomized, Placebo-Controlled Fixed-Dose Study with Patients ≥65 Years

<table>
<thead>
<tr>
<th>Reaction</th>
<th>SPRAVATO 56 mg N=45</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td></td>
</tr>
<tr>
<td>Placebo + Oral AD</td>
<td>113</td>
</tr>
<tr>
<td>SPRAVATO + Oral AD</td>
<td>116</td>
</tr>
<tr>
<td><strong>Dizziness</strong></td>
<td></td>
</tr>
<tr>
<td>Placebo + Oral AD</td>
<td>5%</td>
</tr>
<tr>
<td>SPRAVATO + Oral AD</td>
<td>12%</td>
</tr>
</tbody>
</table>

Table 5: Adverse Reactions Leading to Discontinuation of Treatment

<table>
<thead>
<tr>
<th>Reaction</th>
<th>SPRAVATO 56 mg N=72</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td></td>
</tr>
<tr>
<td>Placebo + Oral AD</td>
<td>113</td>
</tr>
<tr>
<td>SPRAVATO + Oral AD</td>
<td>114</td>
</tr>
<tr>
<td><strong>Sedation</strong></td>
<td></td>
</tr>
<tr>
<td>Placebo + Oral AD</td>
<td>60%</td>
</tr>
<tr>
<td>SPRAVATO + Oral AD</td>
<td>69%</td>
</tr>
</tbody>
</table>

Table 6: Incidence and Severity of Nausea and Vomiting in Double-Blind, Randomized-Controlled, Fixed-Dose Study

<table>
<thead>
<tr>
<th>Reaction</th>
<th>SPRAVATO 56 mg N=72</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td></td>
</tr>
<tr>
<td>Placebo + Oral AD</td>
<td>112</td>
</tr>
<tr>
<td>SPRAVATO + Oral AD</td>
<td>115</td>
</tr>
<tr>
<td><strong>Sedation</strong></td>
<td></td>
</tr>
<tr>
<td>Placebo + Oral AD</td>
<td>62%</td>
</tr>
<tr>
<td>SPRAVATO + Oral AD</td>
<td>67%</td>
</tr>
</tbody>
</table>

Blood pressure increased includes: blood pressure diastolic increased; blood pressure increased; blood pressure systolic increased; hypertension

Dissociation includes: delusional perception; depersonalization/derealization disorder; derealization; dissociative amnesia; dissociative identity disorder; feeling cold; feeling hot; feeling of body temperature change; hallucination; hallucination, auditory; hallucination, visual; hypersomnia; illusion; ocular dissociation; oral dysesthesia; paranoia; paresthesia oral; pharyngeal paresthesia; photophobia; time perception altered; tenosy; vision blurred; visual impairment

Dizziness includes: dizziness; dizziness exertional; dizziness postural; procedural dizziness

Dysarthria includes: dysarthria; slow speech; speech disorder

Dysnesia includes: dysnesia; hypognesia

Headache includes: headache; sinus headache

Hypoesthesia includes: hypoesthesia; hypoesthesia oral; hypoesthesia teeth; parahypraesthesia

Leptagia includes: fatigue; lethargy

Nasal discomfort includes: nasal crusting; nasal discomfort; nasal dryness; nasal pruritus

Sedation includes: altered state of consciousness; hypnolalia; sedation; somnolence

Tachycardia includes: extrasystole; heart rate increased; tachycardia

Vertigo includes: vertigo; vertigo positional

Sedation

Sedation was evaluated by adverse event reports and using the Modified Observer’s Alertness/ Sedation scale (MOAA/s). In the MOAA/s scale, 5 means “responds readily to name spoken in normal tone” and 0 means “no response after painful tap on zygomaticus.” Any decrease in MOAA/s from pre-dose is considered to indicate presence of sedation, and such a decrease occurred in a higher number of patients on esketamine than placebo during the short-term trials (Table 3). Dose-related increases in the incidence of sedation were observed in a fixed-dose study (see Warnings and Precautions).

Increase in Blood Pressure

The mean placebo-adjusted increases in systolic and diastolic blood pressure (SBP and DBP) over time were about 7 to 9 mmHg in SBP and 4 to 6 mmHg in DBP at 40 minutes post-dose and 2 to 5 mmHg in SBP and 1 to 3 mmHg in DBP at 1.5 hours post-dose in patients receiving SPRAVATO plus oral antihypertensives (Table 5).
neuronal apoptosis in the developing brain of the offspring. There are no data on pregnancy exposures to N-methyl-D-aspartate (NMDA) receptors during the period of peak brain development increases neuronal cell death observed in the brains of their fetuses. This period of brain development translates into the third trimester of human pregnancy and postpartum.

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 1-844-405-8185 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, miscarriage, or other adverse pregnancy outcomes. In published findings from pregnant animals treated with ketamine, the racemic mixture of arketamine and esketamine, SPRAVATO may cause fetal harm when administered to pregnant women (see Data). 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 (see Clinical Considerations). If a woman becomes pregnant while taking treatment 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 peak period of brain development increases neuronal cell death observed in the brains of their fetuses. This period of brain development translates into the third trimester of human pregnancy and postpartum. This window may extend out to approximately 3 years of age in humans. This period of brain development in primates corresponds to periods prior to the third trimester in humans (see Use in Specific Populations). There are no data on pregnancy exposure 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

Disease-Associated Maternal 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. Women who continued antidepressants were more likely to experience a relapse of depression. This is consistent with the recommendation that antidepressants be continued during pregnancy (see Warnings and Precautions).

Animal Data

Based on published data, when female monkeys were treated intravenously with racemic ketamine at anesthetic dose 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 neurotoxicity correlates with long-term cognitive deficits.

Racemic ketamine was administered intrathecally to pregnant rats during the period of organogenesis at doses of 15, 50, and 150 mg/kg/day. Estimated 50% of the exposure to be from esketamine, the NGAEL 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 intravenously gestational day 6 to 18 at doses of 10, 30, and 100 mg/kg/day. The high dose was lowered from 100 to 50 mg/kg after 5 days of dosing due to excessive mortality in the pregnant rabbits. Skeletal malformations 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 the maximum recommended adult intravenous (intravenous ketamine dose). In addition, a dose-dependent delay in the age of attainment of Preyer response reflex was observed in pups at doses during the preweaning period. This sensory/motor development in pups during the preweaning period was without effect on the maximum recommended adult intranasal dose of 15 mg/kg/day which was associated with a plasma exposure (AUC) that was 0.07-times 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 breastfeeding 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.
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Mike Hennessy Sr.
Chairman and Founder, MJH Life Sciences

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We expect 2020 to hold many more exciting stories as well as new features for Psychiatric Times. For instance, keep your eyes out for our upcoming Psychiatric Times video series, which will provide you with additional opportunities to explore these and other hot topics.

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Mike Hennessy Sr.
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Mindfulness

John J. Miller, MD  |  Editor in Chief

I n 1991, at the end of my fourth year of psychiatry residency at the University of Massachusetts (UMass) Medical Center/Worcester I presented a grand rounds, “The Role of Meditation in the Treatment of Psychiatric Disorders,” the conclusion to my research that year on the benefits of mindfulness meditation for anxiety disorders. At that time this was an unusual and unconventional topic for a grand rounds in psychiatry. This was made very clear to me when I presented a version of this lecture at 2 nearby hospitals—both with announcements of my lecture editing out the word “meditation.” At one hospital the announcement was for “The Therapy of Silence: Meditation [should have been Meditated] as a Healing Modality,” and the other replaced the word “meditation” with “meditation” in the title for my initial grand rounds. Today, mindfulness has become a household word, and the psychiatric and psychological literature abound with publications implementing mindfulness as a treatment or self-help tool for everything that ails you.

Resources for how to learn and practice mindfulness abound—books, articles, Apps, workshops, institutional based courses, seminars, weekend retreats, and so much more. The paradox is that mindfulness is not intellectual, and the practice of mindfulness involves surrendering the common mind states of thinking, describing, judging, and assessing to retreat to a state of awareness where raw and egoless observation is present to learn from whatever content enters into our awareness in that moment.

In 1979 Jon Kabat-Zinn, PhD, 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. Dr. Kabat-Zinn provided a foundational definition of mindfulness for the clinical setting: “Paying attention, on purpose, in the present moment, in the service of self-understanding.” In his first book, he provides a detailed manual of the structure and experience of his MBSR clinic, after spending over 10 years developing and optimizing mindfulness for patients at a university medical center. His second book is an easy-to-read map of the many ways mindfulness can be inserted into our busy western lives.

Clinical applications of mindfulness

Over the past 3 decades clinical medicine and psychology have integrated the basic principles of mindfulness into many diverse treatment modalities. These principles are free of any dogma or ritual and serve to empower the individual to practice mindfulness as a lifestyle enhancement that often provides a wide range of benefits—physically, emotionally, interpersonally, and sometimes spiritually. With mindfulness, there is no ultimate accomplishment or mastery, rather a continued strengthening of the mind’s ability to stay attentive in the present moment, and experience it directly, free of the many filters of thought, expectation, desire or aversion that usually intrude, pulling us away from the direct experience. Given

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Mindfulness

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the general nature of the practice of mindfulness, not surprisingly, it has found its way into numerous applications.

These include:

- Mindfulness based stress reduction
- Pain management clinics
- Mindfulness based cognitive behavioral therapy
- Dialectical behavior therapy
- Addiction treatment
- Acceptance and commitment therapy
- Augmentation of individual psychotherapy

Strawberry mindfulness

In our western culture, which values intellectual knowledge and material rewards, the concept of mindfulness is often initially difficult to grasp. Busy schedules, lengthy “to do” lists, and group activities leave little time for self-reflection and inquiry into the nature of our minds. In fact, all of these activities serve to keep us running on automatic pilot, and strength- en behavioral patterns previously learned that create efficiency when automatically enacted. An analogy I often use to explore the question of the potential benefits of practicing mindfulness is to ask which of the following two individuals is truly an expert on the experience of what a strawberry tastes like:

An individual who has studied the science of strawberries to the degree that he or she is considered to be the world’s expert—agriculture, botany, genetics, human taste receptors that send gustatory information that is decoded in the brain, digestion, visual responses to seeing a strawberry, and the author of over 100 books on all aspects of strawberries—but, has NEVER eaten a strawberry?

OR

An individual who is uneducated but has just paid close attention to all of the sensations and experiences of taking a fresh strawberry, looking at it, smelling it, placing it in his or her mouth, observing the taste and texture as he or she bites into it, and mindful of the plethora of the “here and now” strawberry experiences?

The answer is usually self-evident and conjures an image or feeling of the warm juice of a strawberry sloshing around in your mouth. Mindfulness is the practice of experiencing each moment like the strawberry.

Common mindfulness adventure

Briefly speaking, there are two sub-types of meditation: concentration and mindfulness. As a general principle, it is important to become proficient in concentration meditation before expanding into mindfulness. Concentration practice involves choosing an object, like the breath, a phrase, or a word that becomes an anchor for the mind’s attention. The instructions are simple: watch the breath as it moves in and out of the body, choosing a spot to watch it that feels natural (the nose, mouth, lungs or movement of the abdomen). Inevitably, the mind’s attention will be distracted by some thought, feeling, sound, or emotion, and the mind starts to drift down an endless path of mind content. As soon as you are aware of having left the breath, without judging yourself, the task is simply to return to the breath. The same basic steps are followed if you are using a phrase or a word.

Here’s a common example: awareness of the inbreath and the outbreath . . . inbreath and outbreath . . inbreath and outbreath . . you hear a car driving down your street, and your mind drifts to the thought of the car . . . my car . . . my car payment . . . bills to pay . . . do I have enough money saved to buy that new iPhone . . . images of the cool new camera on the iPhone 11 pro . . . wait a minute, I left my breath . . . inbreath and outbreath . . inbreath and outbreath . . inbreath and outbreath . . the muscle in my left calf is starting to cramp up . . . I need to start stretching my muscles again . . . why did I stop stretching regularly . . . should I rejog the gym . . . the last time I was at the gym I saw Tom . . . Tom was a great college roommate . . . college was such a great experience . . . maybe I’ll drive out there and take a walk on campus . . . college is so expensive these days . . . how will I pay for my child’s college tuition in a few years? . . oh yeah, my breath . . . inbreath and outbreath . . inbreath and outbreath . . inbreath and outbreath . . .

This is how much of the time practicing meditation is initially spent, and usually is so frustrating that most people stop meditating long before their attention is strengthened. With perseverance and practice the mind slowly develops the capacity to stay with the breath for extended periods of time. This commonly results in calmness, relaxation, mental clarity as well as an anti-fight or flight phys- iology.

Once the mind’s concentration has stability, that focused awareness can be intentionally refocused on the mind’s activity itself, and this is the beginning of mindfulness. A holding environment of sorts is created whereby impersonal and non-judgmental attention is watching the many mind states that come and go, the only task being to stay present and learn from what is observed with open acceptance. As mindfulness strengthens, the underlying themes and patterns that fill our mind automatically are seen clearer, and it becomes easier to disengage from them, remaining in the present moment with pure mindfulness. Like exercise, continued practice sustains the ability to be mindful, while lack of practice allows a regression to automatic patterns.

The practice of mindfulness

In our role as clinicians, we participate in the practice of medicine because there is always more to learn, and more experience to be gained. Such is the case with mindfulness—it is always patiently waiting for us to resume that selfless non-judgmental awareness of the present moment—with more to learn about the patterns and themes of our own mind, and continued opportunity to choose a different thought or behavior. As 2019 draws to an end, and we soon begin a new decade, the practice of mindfulness is but a breath away, and is a worthy companion.

REFERENCES


Read more from Dr Miller at PsychiatricTimes.com

Depressions Journey From Monoamines to Glutamate

Esketamine (Spravato) is FDA approved as an intranasal spray to combine with a traditional oral antidepressant to treat individuals with severe recalcitrant depression. https://www.psychiatrictimes.com/depression/esketamine-depressions-journey-monoamines-glutamate

Psychiatric Pharmacogenomic Testing: The Evidence Base

Why we are not yet at the point where pharmacogenomic panels of testing numerous genes is either evidence based or actionable for clinical practice. https://www.psychiatrictimes.com/psycho/pharmacology/psychiatric-pharmacogenomic-testing-evidence-base

A Drug’s Journey: From the Pill Bottle to the Toilet

One of the most significant nemeses for the practicing clinician in psychiatry: drug formulations that impose drug dosage and dispensing limitations that quite often result in an unnecessary and burdensome obstacle to our goal of effectively treating patients. https://www.psychiatrictimes.com/psycho/pharmacology/drugs-journey-pill-bottle-toilet
recently received a consultation request from a colleague concerning an autistic male to female transgender adolescent who had started on cross sex hormones. She had also recently revealed her years-long identification as a cat, and this trans-species or “otherkin” identity was of greater distress than the gender dysphoria.

Seemingly unusual and overlapping erotic and psychological identities are nothing new to clinicians specializing in matters of sexuality. I have treated or consulted on cases of teenagers erotically attracted to cross-dressing, children, giantesses, extraterrestrial aliens, decapitation videos, and a fair number of trans-species identifications.

Physicians (especially psychiatrists) have long had the privilege of hearing patients’ most intimate revelations about their sexual behaviors and inner lives. Doctors since antiquity have dealt with matters of fertility, potency, and sexually transmitted diseases. However, it only has been since the 19th century that Western physicians systematically have studied and classified the broad diversity of human sexuality.

Victorian sexologists lumped all non-heterosexual, extramarital eroticism under the rubric of sexual perversions. In 1886, Richard von Krafft-Ebing’s Psychopathia Sexualis became the bible of paraphilias; he coined many of the terms we still use today, like sadism and masochism. During the 20th century, the list of what is considered perverse has been whittled down significantly. Mid-century sex researchers, like Alfred Kinsey, PhD, demonstrated that what had been considered rare and pathological behavior was actually commonplace: masturbation, homoeroticism, extra-marital affairs, and fetishism.

Cultural politics also revolutionized public sentiment on sexuality. The Civil Rights movement, feminism, and gay pride all contributed to changing attitudes about interracial relationships, women’s sexuality, and gay sex. Far from the time and mindset of Krafft-Ebing, many of those so-called perversions are now considered part of the great variety and color of human mating dances.

Classical psychoanalysis placed sexuality at the center of human psychological development. While Freudian theory was initially criticized for its pansexuality and emphasis on erotic fantasy (particularly in children), the general public has come to expect us shrinks to possess special insight into sexuality. Unfortunately, psychiatric education has failed on this count. Surveys of training directors find that little didactic time is devoted to even traditional matters of reproductive health or women’s sexuality. Instead, psychiatric residents are most likely to learn about sexual adverse effects of medications and strategies for treating them. Training directors are open to having lectures on LBGT sexuality, for example, but cannot find the time in the psychopharmacology cur

CONTINUED ON PAGE 14
Normal Versus Abnormal Sexual Behavior in Adolescents

Yanig Efrati, PhD

Over the past two decades, the internet has allowed instant access to a wide variety of content, including sexual content that portrays a variety of sexual activities such as masturbation, oral sex, vaginal and anal intercourse, and group sex. During the normal sexual developmental phase (usually between the ages of 9 and 16 years), one of the most common sexual activities is consumption of pornography, either intentional or accidental exposure. In the United Kingdom, 55% of adolescents aged 11 to 16 years have seen online pornography at least once, and the vast majority have viewed pornography before the age of 14. In the United States, 20% to 30% of children aged 10 to 12 years have reported some exposure to pornography.

In most cases, consumption of pornography does not promote the development of mental health disorders and reflects a normal exploration of sexuality. However, in 10% to 18% of all adolescents, consumption of pornography reflects compulsive sexual behavior. The disorder is characterized by extensive pornography use and masturbation, use of paid sexual services, risky sexual behaviors, and an intense preoccupation with sex. These behaviors often lead to impaired social or occupational functioning, distress, and negative affect.

How can we identify compulsive sexual behavior among adolescents? And, what are the best practices to treat compulsive sexual behavior?

Normative development

Human beings are sexual and beginning in childhood are capable of sexual responses. Many youngsters report experiencing sexual interest, arousal, and desire before puberty around the age of 10 years, when adrenal glands mature. Adolescence marks the onset of considerable changes in sexual and reproductive maturity that coincide with significant changes in cognitive, emotional, and social functioning.

The progression of sexual events among adolescents follows a fairly consistent sequence: kissing and holding hands, breast and chest fondling, manual genital contact, touching under clothes or without clothes, touching genitals directly, oral sex, and penile-vaginal intercourse. Sometimes these are followed by less common variations, such as anal sex. Although most adolescents show a normal sexual development, some develop compulsive sexual behavior.

Compulsive behavior

ICD-11 includes compulsive sexual behavior as a disorder. This impulse control disorder is characterized by a repetitive and intense preoccupation with sexual fantasies, urges, and behaviors that lead to clinically significant distress or impairment in social and occupational functioning and to other adverse consequences. Moreover, it compulsive sexual behavior often promotes sexual objectification of women and risky sexual behavior.

A recent study showed that consumption of pornography as part of compulsive sexual behavior predict...
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¹Randomized, 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.

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**Important Safety Information**

**WARNING: ABUSE AND DEPENDENCE**

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

Please see Additional Important Safety Information on the following page.

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

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

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

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

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

Psychiatric Adverse Reactions
CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder. CNS stimulants may induce a manic or mixed episode in patients. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression). CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing Adhansia XR. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients, compared to 0% in placebo-treated patients.

Priapism
Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products, in both pediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to 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.

Peripheral Vasculopathy, 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

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(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, 5.2, 5.3)]

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, 5.2, 5.3)]

5.2. Serious Cardiovascular Events

5.2.1. Sudden death, stroke, and myocardial infarction have occurred in adults treated with CNS stimulant treatment at recommended doses. Sudden death has occurred in association with serious cardiovascular abnormalities, other serious heart problems, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmia while taking ADHANSIA XR treatment. Safety data for ADHD stimulants show that patients treated with CNS stimulants can also have increases 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 or tachycardia (mean increase approximately 3 to 6 bpm). 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 [see Drug Interactions (7.7)]

5.3. Blood Pressure and Heart Rate Increases

Further clinical evaluation (e.g., rheumatology referral) may be necessary for patients with history of psychotic illness or mania. If such symptoms occur, consider discontinuing ADHANSIA XR. New Psychotic 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 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 mania symptoms occurred at approximately 0.1% of placebo-treated and 0.05% of methylphenidate-treated patients. Existing Psychiatric CNS stimulants may exacerbate signs of behavior disturbance and thought disorder in patients with a pre-existing psychiatric disorder. Induction of a Manic Episode in Patients with Bipolar Disorder CNS stimulants may induce a mania or mixed episode in patients. 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Pediatric Patients (6 to 17 years) with ADHD Study 4, conducted in pediatric patients 6 to 12 years of age, was comprised of a 6-week open-label dosing optimization phase in which all patients received ADHANSIA XR (n=56), mean dose 48 mg, followed by a 1-week, double-blind controlled phase in which patients were randomized to continue ADHANSIA XR (n=78) or switch to placebo (n=73). During the open-label ADHANSIA XR treatment phase, adverse reactions reported in >5% of patients included decreased appetite (15%), upper abdominal pain (10%), affect lability (8%), nausea (7%), vomiting (5%), 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>
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<tbody>
<tr>
<td>Clinical Impact:</td>
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<tr>
<td>Intervention:</td>
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<tr>
<td>Examples:</td>
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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 1-866-961-2388. Risk Summary Published studies and post-marketing reports on methylphenidate use during pregnancy are insufficient to identify a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the fetus associated with the use of central nervous system (CNS) stimulants during pregnancy. The Safety and effectiveness of ADHANSIA XR in pediatric patients has not been established.

8.2. Lactation Risk Summary Limited published literature, based on breast milk sampling from five mothers, reports that methylphenidate is present in human milk, which resulted in infant doses of 0.06% to 0.7% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.0 to 11.7. There are no reports of adverse effects on the breastfed infant and no effects on milk production. Long-term neurodevelopmental effects on infants from stimulant exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ADHANSIA XR and any potential adverse effects on the breastfed infant. ADHANSIA XR contains methylphenidate, a Schedule II controlled substance. Consider the possibility of multiple drug overdosage. 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 (1-888-827-0618) for information on this product.

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. Abusers of CNS stimulants may chew, snort, inject, or use other unapproved routes of administration which can result in overdose and death [see Overdose (10)]. To reduce the potential for abuse, and to ensure the safe use of ADHANSIA XR, the drug should be prescribed only by practitioners well acquainted with its characteristics, use, and potential for abuse. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants, monitor for signs of abuse while on therapy, and periodically review the patient’s medical record. ADHANSIA XR has not been studied in the patients over the age of 72 years.

10. OVERDOSAGE 10.1. Signs and Symptoms Signs and symptoms of acute methylphenidate overdose, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: nausea, vomiting, diarrhea, restlessness, anxiety, agitation, tremors, hyperreflexia, muscle twitching, convulsion (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hypertension, tachycardia, palpitations, cardiac arrhythmias, hypertension, hypotension, tachypnea, mydriasis, dryness of mucous membranes, and rhabdomyolysis. 10.2. Management of Overdose Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice on the management of overdose with methylphenidate. Provide supportive care, including close medical supervision and monitoring. Treatment should consist of general measures employed in the management of overdose with any drug. Consider the possibility of multiple drug overdosage. 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 (1-888-827-0618) for information on this product.

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U.S. Patent Numbers: 9,974,752 and 10,111,839
This brief summary is based on Adhansia XR Prescribing information, 07/2019
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Adolescents
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misperceptions about the difficulties associated with problematic sexual behavior among clinicians, how to recognize these issues, and/or what factors to target in treatment. When seeking to refer a patient for compulsive sexual behavior, psychiatrists should look for a therapist who specializes in treating sexual disorders.

To date, there are no placebo-controlled studies on any treatment modality for compulsive sexual behavior. Most recommendations are based on case studies and/or on studies using small samples without control groups; the studies mainly comprise adults. The most promising modalities are cognitive behavioral therapy (CBT), cognitive analytic therapy (CAT), and mindfulness.

The aim of CBT is to identify underlying dysfunctional thoughts and utilizing cognitive tasks and behavioral interventions allow patients to avoid the triggers for compulsive sexual behavior. (See Birchard[1] for a detailed review.) It begins by a formulation of therapeutic goals to create a blueprint for the intervention, to prevent therapeutic drift, and to keep the work on target. Diagrammatic explanations of the history and function of a problematic sexual behavior are used to bring order into what would otherwise be chaos and uncertainty. During this phase, factors that cause the patient to turn to their harmful behavior are recognized. Next, using various cognitive techniques these factors are targeted to break the link between them and the harmful behavior. For example, therapist may use the Socratic questioning method to elicit new understandings for the patient, helping them to think about the problematic patterns. The third and final phase is revision, which focuses on change and culminating in an exchange of farewell letters between therapist and patient. CBT and CAT share commonalities; the main difference is the cognitive versus the narrative construction of the problematic behavior (eg, history of relations with parents).

Mindfulness-based therapy focuses attention to thoughts, emotions, and bodily sensations in the present in a nonjudgmental manner. It is often taught through a variety of meditation techniques. Mindfulness may be a meaningful component of successful therapy among patients seeking help for compulsive sexual behavior—open communication about sexuality between parents and children. Communication reduces shame, promotes sexual exploration in a supportive environment, and enables the development of healthy romantic relationships. Healthy sexuality promotes a health society.

Dr. Efrati is Founder and Head of the Israeli Center for Healthy Sexuality, and Assistant Professor, Beit-Beri College, Kfar Saba, Israel. He reports no conflicts of interest concerning the subject matter of this article.

References continuing from page 8

Communication reduces shame, promotes sexual exploration in a supportive environment, and enables the development of healthy romantic relationships.

identities
Continued from page 12

curriculum or the right faculty to teach this important area. A particularly novel challenge for clinicians is the impact of the internet on the lives of adults and children alike. The internet has supported a type of erotic speculation far beyond that of even the 19th century medicalization of sexual perversities (the term erotic speculation was astutely coined by Gayle Rubin, PhD). The internet has allowed individuals who might have felt like they were the only people in the world with a particular sexual (or other) inclination to discover that they are not alone. Furthermore, the internet helps people to nurture their sexual interests with textual and visual erotica as well as emotional support and even compatible partners. Some of these erotic interests may just be creative pleasures that add to the diversity of sexuality. Some, however, may be illegal, cause distress to individuals, be of concern to parents, or become too time consuming.

When people turn to mental health professionals about sexual problems—cyber or otherwise—how comfortable and informed are we? This collection of articles makes a valuable contribution to updating psychiatrists on challenging issues of sexuality. But they are just a launching point to help clinicians feel more at ease in supporting patients in their exploration of the spectrum of sexuality and untangling psychiatric problems from the effects of cultural opprobrium. These are not easy distinctions but require professional wisdom and nonjudgmental curiosity.

Dr. Rosario is an Associate Clinical Professor in the Department of Psychiatry at the UCLA David Geffen School of Medicine, and a child and adolescent psychiatrist with the Los Angeles County Department of Mental Health. He reports no conflicts of interest concerning the subject matter of this Special Report.

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Special Issues in Treating Adolescents With Gender Dysphoria

Anna van der Miesen, MD, Marijn Arnoldussen, MD, and Annelou de Vries, MD, PhD

In recent years, transgender and gender incongruent adolescents have been the focus of media attention, public debate (eg, around the use of preferred pronouns and bathroom use), and, last but not least, best clinical practice. While the term transgender is mostly being used as an umbrella term for all forms of gender diversity, gender dysphoria is the diagnostic term as described in DSM-5.

Adolescents with gender dysphoria experience a marked incongruence between their experienced gender identity and their gender assigned at birth (based on their sexual anatomy) accompanied by distress. Gender identity refers to one’s sense of self as female or male. Increasingly, youth identify with a gender that differs from the traditional dichotomous classification of females and males: non-binary, gender fluid, gender queer etc (For an overview of terminology, see Sidebars). Parallel to the growing public attention, there has been a marked increase in the establishment of specialty gender services around the world and a sharp increase in the number of referred adolescents. Whether this is due to a true increase or increased awareness is not yet established.

The prevalence of a DSM-5 gender dysphoria diagnosis has never been studied in systematic population-based studies in adolescents and only estimates based on referrals to adult gender identity services are available. A meta-analysis found this prevalence to be 4.6 per 100,000.1 Estimates based on adolescent population samples (eg, high schools) provide much higher prevalence rates of self-identification as transgender or gender-incongruent of 3.6% for birth-assigned females and 1.7% for birth-assigned males.2 Another recent observation is the overrepresentation of assigned-females compared with assigned males at birth, which was reversed in earlier years.3

Clinical presentation

Transgender adolescents and their families can present in many different ways. Some adolescents seek help for further gender identity exploration, while others have an already established desire for physical sex characteristics of the experienced gender. Additionally, while some transgender adolescents have shown gender non-conformity since early childhood, other adolescents might experience gender dysphoria during or after the onset of pubertal physical changes.

Some adolescents may have kept their gender incongruence to themselves for a long time. They did not speak out because they feared non-acceptance and rejection. They may have become depressed, socially isolated, and anxious. Other adolescents have been open about their feelings from an early age and may have socially transitioned to their experienced gender role supported by family and peers.

Depression, anxiety and suicidality

Various studies show that transgender adolescents are at a higher risk for mental health problems compared with cisgender peers and thus can present to clinicians with mental health difficulties. Stigma presumably plays an important role in this distress. In 2003, Meyer published his Minority Stress Model, which posits that minorities are often confronted with rejection and discrimination.4 Subsequently, this can lead to fear and negative feelings towards their minority group and themselves.

A study of transgender adolescents showed that poor peer relations were the most important predictor of mental health difficulties.5 Despite decreased stigmatization and growing tolerance, transgender adolescents are still relatively often victims of (cyber) bullying, harassment, and violence. A survey among transgender and gender diverse students from Minnesota showed that approximately 25% to 52% experienced different types of victimization is the past month.6 These negative experiences contribute to the fact that depression and anxiety occur about five times more often in transgender adolescents.7 Another major health concern is the seemingly high number of suicidal ideation in transgender adolescents. A study among American high school students found that the prevalence of suicidal ideation in gender diverse students was nearly twice as high compared with cisgender youth and that both depressive symptoms and school-based victimization were associated with this ideation.7

Although the above numbers are reason for concern, there are also opportunities to change the current situation. Gender diverse adolescents growing up in a supportive and tolerant environment, who trust that their families will profit from some psychiatric support

CASE VIGNETTE

Abigail is a 14-year-old assigned female at birth who at age 11 received a diagnosis of autism spectrum disorder. Abigail loved to play an online game building a virtual character with other people. In this game, Abigail created the male character “Amon.” Over time, Abigail started playing the game for longer periods, often for several hours a day and became socially isolated. When her parents asked about what was going on, Abigail responded that she felt she was a boy. Since the parents thought it was important to examine this further, they went to Abigail’s child and adolescent psychiatrist. After discussing gender with Abigail, the psychiatrist decided to refer her to a gender clinic.

At the clinic, Abigail had several sessions with a psychologist. During the sessions they discussed Abigail’s childhood fixations. The psychologist tried to differentiate whether Abigail’s desire to be a boy was a fixation. Abigail showed insight in these fixations and experienced them as likeable things to do, creating happiness. On the other hand, her gender dysphoric feelings were unlikeable and made Abigail sad instead of happy. After the sessions, treatment with puberty blockers was started to release the distress Abigail experienced around body changes. After social transition and the start of puberty blockers, Abigail took the name Amon and flourished: he had more contact with other adolescents, undertook more activities, and his schoolwork improved.

Psychiatric support

Support should be tailored to the adolescent. Some adolescents need individual explorative psychotherapy, others need treatment for depression or other co-occurring psychiatric conditions. Most adolescents and their families will profit from some sort of support on how to inform friends and relatives, how to present at school, and how to deal with possible stigma. In addition, transgender adolescents who are accepted and supported show better well-being.10 Assessment of adolescents with co-occurring autism (characteristics) might be more complex to understand and additional support might...
be needed when considering medical affirming treatment.

**Affirming treatment**

Medically intervening in a healthy body is a far-reaching option that has proven its usefulness in transgender adults, but has only been studied in a few adolescents. According to what has been named the “Dutch model,” which includes the intervention of puberty suppression without permanent effects, gender affirming care is offered in a step-wise model. Before medical interventions are provided, a comprehensive assessment exploring the nature of the adolescent’s gender identity is performed in a supportive and respectful way. The adolescent is assessed whether a diagnosis of gender dysphoria (according to the DSM-5) or gender incongruence (according to the ICD-11) can be given. Co-existing mental health difficulties like depression, anxiety, risk of self-harm, and suicide as well as autism characteristics that have an impact on diagnosis or treatment should be assessed and a referral for psychotherapy given if it is indicated.

Family and school functioning are also assessed and family or other caretaker support (in case an adolescent lives in out of home care) and caretaker support (in case an adolescent is living with their biological family) are assessed and family or other health professionals collaborate with the adolescent to include their opinion in the informed consent process. It is essential that the adolescent and the family have access to a multidisciplinary care team, in which mental health professionals collaborate with (pediatric) endocrinologists, surgeons, and fertility specialists.

**Controversies and challenges**

Transgender care for adolescents is surrounded by controversies, challenges, and uncertainties. At present, the aforementioned increase in prevalence, the shift in sex ratio, and the presentations of non-binary gender identities are yet to be understood. Long-term outcome studies of early medical interventions still come from a limited number of clinics and include only binary identifying transgender adolescents with prepubertal onset gender incongruence.

Whether puberty blocking at a young age is effective and safe for non-binary and post-puberty onset transgender adolescents is unknown. Long-term physical consequences of puberty blocking on bone density, fertility, duration, and surgical options are uncertain. Various ethical dilemmas arise around the capacity for informed consent of adolescents, parents’ role in treatment, and whether the right for best care for transgender children should include the right for medical transitioning.

**Conclusion**

Some clinicians may be hesitant in their work with transgender adolescents. Transgender adolescents and their families experience barriers to care and specialized providers might not always be available. However, the work with transgender adolescents can be rewarding. Transgender youth can profit enormously by the psychological, emotional, and social support that mental health professionals can give by showing their compassion and understanding.

Dr Miesen is Junior Researcher Adolescent Amsterdam Cohort of Gender Dysphoria (A-ACOG) and Psychiatry Consultant, Center of Expertise on Gender Dysphoria (CEDG); and Dr Arnoldussen is Junior Researcher, A-ACOG and Psychiatry Consultant, CEDG. Dr de Vries is Principal Investigator, A-ACOG, and Lead, Department of Child and Adolescent Psychiatry, CEDG. The authors are all affiliated with Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Child and Adolescent Psychiatry. The authors report no conflicts of interest concerning the subject matter of this article.

**References**


**Terminology Associated With Gender Dysphoria**

- **Gender dysphoria**: Psychological distress due to the incongruence between one’s experienced and assigned gender at birth; the classification used in DSM-5. Not all individuals with gender incongruence experience dysphoria.

- **Gender incongruence**: Individuals whose gender identity and gender assigned at birth do not match; also the classification used in ICD-11. Gender assigned at birth.

- **Birth sex**: Gender assigned to an infant at birth; generally based on observed physical characteristics (eg, genitalia).

- **Gender identity, experienced gender**: the individual’s personal sense of gender.

- **Gender expression**: The outward presentation of gender identity, e.g., clothing

- **Gender role**: A characteristic or social role that is considered “masculine” or “feminine” by a particular culture.

- **Transgender**: Usually used as an umbrella term and refers to the broad spectrum of individuals who identify with a gender other than that associated with their birth sex.

- **Transboy**: A transgender adolescent who identifies as boy/male (typically with a female birth sex).

- **Transgirl**: A transgender adolescent who identifies as girl/female (typically with a male birth sex).

- **Cisgender**: Refers to persons whose experienced gender aligns with birth-assigned gender.

- **Non-binary**: Identification with gender identities outside the female/male binary.

- **Gender variant, gender diversity, gender non-conforming**: Describe the wide range of gender identity identifications outside conventional gender categories.

- **Gender queer**: Gender identities that are not experienced as exclusively male or female.

- **Gender fluid**: Someone who fluctuates between genders.

- **Gender affirming treatment/surgery**: Treatments aimed at supporting an individual’s experienced gender identity. This can relate to psychological support, medical treatment (hormones and/or surgery), and legal aspects of care.
**Fasting Glucose**

<table>
<thead>
<tr>
<th>Treatment Arm Na Patients n (%)</th>
<th>Mean (360 days)</th>
<th>Mean (at least 360 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>11/87 12.6</td>
<td>11/88 12.6</td>
</tr>
<tr>
<td>ABILIFY MAINTENA</td>
<td>3/11 27.3</td>
<td>3/13 29.0</td>
</tr>
</tbody>
</table>

* n = the total number of subjects who had a measurement at baseline and at least one post-baseline result.

**Fasting LDL Cholesterol**

<table>
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<tr>
<th>Treatment Arm Na Patients n (%)</th>
<th>Mean (360 days)</th>
<th>Mean (at least 360 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2/81 2.0</td>
<td>2/83 2.0</td>
</tr>
<tr>
<td>ABILIFY MAINTENA</td>
<td>1/79 1.3</td>
<td>1/77 1.3</td>
</tr>
</tbody>
</table>

* n = the total number of subjects who had a measurement at baseline and at least one post-baseline result.

**Fasting HDL Cholesterol**

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<th>Treatment Arm Na Patients n (%)</th>
<th>Mean (360 days)</th>
<th>Mean (at least 360 days)</th>
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<tr>
<td>Placebo</td>
<td>0/75 0.0</td>
<td>0/75 0.0</td>
</tr>
<tr>
<td>ABILIFY MAINTENA</td>
<td>1/59 1.7</td>
<td>1/63 1.7</td>
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* n = the total number of subjects who had a measurement at baseline and at least one post-baseline result.

**Fasting Triglycerides**

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<th>Mean (360 days)</th>
<th>Mean (at least 360 days)</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>6/110 5.3</td>
<td>6/112 5.3</td>
</tr>
<tr>
<td>ABILIFY MAINTENA</td>
<td>4/78 6.2</td>
<td>4/80 6.2</td>
</tr>
</tbody>
</table>

* n = the total number of subjects who had a measurement at baseline and at least one post-baseline result.

**Blood Pressure**

<table>
<thead>
<tr>
<th>Treatment Arm Na Patients n (%)</th>
<th>Mean (8,578 patient-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>72% 119/74/9</td>
</tr>
<tr>
<td>ABILIFY MAINTENA</td>
<td>72% 119/74/9</td>
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</tbody>
</table>

* n = the total number of subjects who had a measurement at baseline and at least one post-baseline result.

**Weight**

<table>
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<th>Treatment Arm Na Patients n (%)</th>
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**Total Cholesterol**

<table>
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</thead>
<tbody>
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Borderpolar: Patients with Borderline Personality Disorder and Bipolar Disorder

A colleague approached me and said that she was referring a patient to the partial hospital program who had borderpolar. Having not previously heard this term, clarification was sought, and it was explained that the patient had both borderline personality disorder and bipolar disorder. My colleague further explained that this term is frequently used in the psychiatrist chat room she visits as a shorthand for patients with both disorders who are severely ill and have high levels of psychosocial morbidity. A PubMed search on the term borderpolar did not turn up any citations.

Both bipolar disorder and borderline personality disorder (BPD) are significant public health problems. Both disorders are associated with impaired functioning, high utilization of psychiatric services, high rates of substance use disorders, and suicidality. Despite the psychosocial morbidity and risk for premature mortality, both disorders are frequently underdiagnosed. As a result, calls for improved recognition have been voiced for both disorders.1,2

For years there has been debate as to how to conceptualize the relationship between BPD and bipolar disorder. Some experts have suggested that BPD is part of the bipolar spectrum. Review articles have summarized the evidence supporting and opposing the bipolar spectrum hypothesis, with most of the recent reviews concluding that BPD and bipolar disorder are valid and distinct diagnostic entities. And since each disorder suggests different treatment emphases—a focus on pharmacotherapy with possible adjunctive psychotherapy for patients with bipolar disorder versus a focus on psychotherapy with possible adjunctive medication for patients with BPD—making the differential diagnosis is that much more important. Meanwhile, many authors and clinicians have described the diagnostic uncertainty and the challenges in determining if a patient has bipolar disorder or BPD.

The comorbidity: borderpolar

The most frequently researched aspect of the relationship between BPD and bipolar disorder has been the frequency of their co-occurrence. Several reviews report an estimated 20% overlap in diagnostic frequency. That is, approximately 20% of patients with bipolar disorder have comorbid BPD and approximately 20% of patients with BPD have bipolar disorder. Thus, while only a minority, there is a meaningful number of patients with a comorbid diagnosis.

Meanwhile, reviews and commentaries have focused on identifying clinical characteristics that distinguish the two disorders to help with differential diagnosis. This approach implies that the diagnosis is an either/or decision. Framing the discussion as a dichotomous choice underplays the fact that one-fifth of patients have both disorders. The almost exclusive focus on differential diagnosis might discourage clinicians from making both diagnoses when appropriate and can result in overlooking an important comorbidity in patients with the greatest need.

Frias and colleagues reviewed the literature on the clinical impact of one disorder on the other. Overall, they found that there have been far more studies that compared patients who have bipolar disorder with and without BPD than there have been of patients with BPD who do and do not have bipolar disorder. The researchers also noticed that amongst patients with bipolar disorder, those with comorbid BPD reported more mood episodes, an earlier age of onset of bipolar disorder, greater suicidality, greater hostility, and a higher prevalence of substance abuse. Of note, they found little research that examined treatment response, psychosocial functioning, time unemployed, disability payments, or prospectively observed longitudinal course.

The MIDAS project

It has been my clinical experience that patients with both bipolar disorder and BPD (hereafter referred to as borderpolar) are a group at elevated risk for suicide and marked impairment; they also are high utilizers of the most costly levels of care. My colleagues and I recently examined this issue in the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project. We compared psychiatric outpatients with borderpolar to patients with BPD without bipolar disorder and patients with bipolar disorder without BPD. We hypothesized that the borderpolar patients would exhibit significantly more psychosocial morbidity than patients with only one of these disorders.

The Rhode Island MIDAS project represents an integration of research methodology into a community-based outpatient practice affiliated with an academic medical center. Psychiatric outpatients presenting for treatment were evaluated with semi-structured interviews. We compared the demographic, family history, and clinical characteristics of three non-overlapping groups of patients: borderpolar (n = 59), BPD without bipolar disorder (n = 330), and bipolar disorder without BPD (n = 128).

The results showed that significantly more patients with borderpolar had diagnoses of three or more Axis I disorders than patients with bipolar disorder. Borderpolar patients also reported significantly more PTSD, obsessive-compulsive disorder (OCD), substance use disorder, and somatoform disorder compared with the patients with bipolar disorder. Similarly, patients with borderpolar reported significantly more OCD than patients with BPD.

In terms of risk factors, the MIDAS study found that borderpolar patients had the most psychopathology in their first-degree relatives. Compared with patients with bipolar disorder, the morbid risk for depression, bipolar disorder, PTSD, specific phobia, drug and alcohol use disorders was significantly higher in the

Mark Zimmerman, MD

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The following adverse reactions have been identified during post-approval use of oral aripiprazole or ABILIFY MAINTENA:

### Adverse Reactions

#### Psychiatric Disorders:
- Agitation
- Akathisia
- Anxiety
- Depression
- Distress
- Frustration
- Hostility
- Irritability
- Lack of judgment
- Lack of motivation
- Lack of self-control
- Mood swings
- Nervousness
- Preoccupation
- Self-harm
- Self-injury
- Suicidal ideation
- Urgency
- Withdrawal

#### Endocrine Disorders:
- Gynecomastia
- Increased prolactin
- Priapism

#### Gastrointestinal Disorders:
- Dry mouth
- Dysphagia
- Nausea
- Vomiting

#### Hematological Disorders:
- Anemia
- Neutropenia

#### Hypersensitivity Reactions:
- Hypersensitivity reactions
- Infusion site reactions
- Rash

#### Immune System Disorders:
- Anaphylactic reaction
- Anaphylaxis
- Exfoliative dermatitis
- Erythematous rash
- Rash

#### Injury, Poisoning, and Procedural Complications:
- Cardiopulmonary arrest
- Cardiorespiratory arrest
- Complications of procedure
- Death
- Dorsal column myelotomy
- Hemorrhage
- Hypothyroidism
- Neuritis

#### Musculoskeletal and Connective Tissue Disorders:
- Arthralgia
- Back pain
- Muscle cramps
- Myalgia
- Myopathy
- Nerve compression

#### Neurological Disorders:
- Abnormal movement
- Ataxia
- Bruxism
- Hypertonia
- Hypotonia
- Myoclonus
- Nystagmus
- Paresthesia
- Scapulohumeral rhythm disorder
- Sedation
- Sleep disorder
- Tremor
- Toothache

#### Ocular Disorders:
- Blurred vision
- Cataract
- Conjunctivitis
- Dry eye
- Night vision disturbance
- Photophobia

#### Respiratory, Thoracic and Mediastinal Disorders:
- Dyspnea
- Paroxysms
- Pruritus

#### Skin and Appendage Disorders:
- Acne
- Vesicles

#### Vascular Disorders:
- Hypertension
- Hypotension

### Adverse Reactions Reported in Clinical Trials with Oral Aripiprazole:

#### Cardiovascular Disorders:
- Hypertension
- Hypotension

#### Gastrointestinal Disorders:
- Abdominal pain
- Diarrhea
- Vomiting

#### General Disorders and Administration Site Conditions:
- Injection site pain

#### Hematological and Lymphatic System Disorders:
- Anemia
- Thrombocytopenia

#### Immune System Disorders:
- Hypersensitivity reactions

#### Metabolic and Nutritional Disorders:
- Hyperglycemia

#### Musculoskeletal and Connective Tissue Disorders:
- Joint pain

#### Nervous System Disorders:
- Cerebellar ataxia
- Gait disturbance
- Seizure

#### Respiratory, Thoracic, and Mediastinal Disorders:
- Dyspnea

#### Skin and Appendage Disorders:
- Exfoliative dermatitis
- Erythematous rash
- Nails
- Skin discoloration

### Adverse Reactions Associated with Specific Concomitant Drug Use

#### CYP2D6 Poor Metabolizers:
- Aripiprazole may be more potent in CYP2D6 poor metabolizers

#### Drug-Drug Interactions:

#### CYP2D6 Inhibitors
- High doses of aripiprazole may be more potent in patients taking CYP2D6 inhibitors

#### CYP2D6 Inducers
- The concomitant use of oral aripiprazole and CYP2D6 inducers may be less potent

### Precautions for Patient Counseling

#### Hypersensitivity Reactions
- Be aware of the risk of hypersensitivity reactions

#### Injection Site Reactions
- Injection site reactions may occur

#### Sedation
- Sedation may occur

#### Seizures
- Seizures may occur

#### Overdosage
- Overdosage may occur

#### Management of Overdosage
- Management of overdose may be required

### Additional Information

#### Adverse Reactions
- Adverse reactions may occur

#### Precautions for Patient Counseling
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### Drug Interactions

#### CYP2D6 Inhibitors
- Monitor for increased sedation and other adverse events

#### CYP2D6 Inducers
- Monitor for decreased sedation and other adverse events

#### Concomitant Use of ABILIFY MAINTENA
- Concomitant use of ABILIFY MAINTENA with other medications may be required

### General Considerations

#### Administration Site Reactions
- Injection site reactions may occur

#### Sedation
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#### Overdosage
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borderpolar patients. Compared with patients with BPD, borderpolar patients had significantly higher morbidity risks for bipolar disorder, PTSD, and drug and alcohol use disorder. Furthermore, psychosocial morbidity was greatest in the borderpolar patients. Compared with bipolar disorder patients, the borderpolar patients reported more episodes of depression, more anger, suicidal ideation, history of suicide attempts, childhood trauma, chronic and persistent unemployment, impaired social functioning, and psychiatric hospitalizations. These patients were also more likely to receive disability payments and they exhibited significantly more psychosocial morbidity than the patients with BPD. The borderpolar patients reported more episodes of depression, childhood trauma, chronic and persistent unemployment, history of suicide attempts, and psychiatric hospitalizations.

The results from the MIDAS project indicate that patients with both bipolar disorder and BPD are more severely ill than patients with only one of these disorders. While clinicians might seek diagnostic parsimony and diagnose only one disorder, it is important that they not overlook the potential presence of the other disorder.

Looking forward
During the past decade, significant effort has been put forth to improve the recognition of bipolar disorder in depressed patients. Several screening scales for bipolar disorder have been developed, and they have been extensively researched. Similarly, peer reviewed journals have published review articles and commentaries about the importance of recognizing bipolar disorder in patients presenting for treatment of depression. Much less has been written about the importance of improving the recognition of BPD. Just as it is important for clinicians to include questions to screen for a history of manic or hypomanic episodes in their evaluation of depressed patients, it is important to screen for the presence of BPD in patients with mood disorders.

To date, practically no research has examined potential treatments for patients with both diagnoses. There are only a small number of open-label trials of medication, one controlled medication trial, and no controlled psychotherapy trials of patients with both disorders.

While the literature has clearly demonstrated that bipolar disorder and BPD are distinct disorders, the importance of diagnosing both disorders when comorbid has gotten lost in the dialogue. It is our hope that by giving this group of severely ill patients a unique name—borderpolar—the recognition of this comorbidity will increase. And, as such, there will be increased efforts to identify the most effective treatment approaches.

Concluding thoughts
The ongoing debate as to whether BPD belongs on the bipolar spectrum, which has generated a robust empirical data base establishing that these are distinct diagnostic entities, has sidetracked researchers and clinicians from recognizing the importance of diagnosing both disorders when both are present. Patients with comorbid bipolar disorder and BPD (ie, borderpolar) represent a group with severe psychosocial morbidity who are often unemployed, suicidal, and utilize more costly forms of health care services. Efforts to identify effective approaches towards treating these patients have been minimal and are needed.

Dr. Zimmerman is Professor of Psychiatry and Human Behavior at The Warren Alpert Medical School of Brown University and Director, Partial Hospital Program and Adult Outpatient Psychiatry at Lifespan. He presented “Borderpolar: Diagnosis and Treatment of Patients With Bipolar Disorder and Borderline Personality Disorder” at the 2019 Psych Congress in San Diego, CA.

REFERENCES
Paraphilias
From Diagnosis to Treatment

Brian Holoyda, MD, MPH, MBA

Paraphilias are defined by the presence of atypical sexual interests and may be considered disordered if they are distressing to the individual or harmful to oneself or others. Treatment options are limited and must include a thorough informed consent procedure.

Significance for Practicing Psychiatrists

Paraphilias are defined by the presence of atypical sexual interests and may be considered disordered if they are distressing to the individual or harmful to oneself or others. Treatment options are limited and must include a thorough informed consent procedure.

- DSM-5 distinguishes between paraphilias and paraphilic disorders.
- Recommended biological treatment options include SSRIs and antiandrogen medications.
- Treatment should be more aggressive based on the risk posed by the individual.

Diagnostic Considerations

Individuals with atypical sexual interests or problematic sexual behaviors rarely present to the general psychiatrist for evaluation and treatment. Stigma or fear of embarrassment may deter some individuals, whereas legitimate concerns regarding the legal consequences of disclosure of sexual fantasies or behaviors to a mandated reporter may prevent others. These individuals may not be aware of treatment options for problematic sexual behaviors, or their sexual thoughts and behaviors may be ego-syntonic, so they do not see a need to change. Occasionally a patient may reveal atypical sexual interests in the context of a long-term relationship with a provider, for example during psychodynamic psychotherapy.

Psychiatrists practicing psychotherapy commonly learn about patients’ sexual fantasies and behaviors, which may be typical or atypical. In such cases it may be important for the psychiatrist to determine if a patient’s sexual interest is evidence of a paraphilia, paraphilic disorder, another psychiatric disorder, or something more benign, such as sexual experimentation. It is also necessary to assess if the sexual interest causes the individual any impairment, emotional distress, or risk of harm and if it requires any intervention.

Even when patients voluntarily present for psychiatric care related to atypical sexual interests, concerns about stigma, shame, and embarrassment may prevent them from fully sharing their sexual history and the breadth and extent of the sexual behavior, which can make diagnosis and treatment problematic. Early research on paraphilic interests demonstrated that most individuals with paraphilic interests have more than one atypical sexual interest and many have more than five, a phenomenon referred to as “cross-over.”

Furthermore, an incomplete understanding of the breadth of a patient’s atypical sexual interests precludes effective treatment planning. Table 2 lists strategies to overcome patients’ hesitancy to describe their history of sexual behaviors. One method to improve a patient’s comfort with disclosure is to provide a detailed self-report questionnaire prior to the initial psychosexual evaluation. Patients may find it easier to complete such an assessment in the privacy of their own home, rather than in a physician’s office. The clinical interview can then focus on specific areas in which the patient has responded affirmatively to the questionnaire.

As is often the case, collateral sources of information may also be helpful. Prior relationship and/or sexual partners may be able to elaborate on a patient’s sexual behaviors. Collateral documentation sources including prior treatment records and police reports may also be useful. Police reports can document sexual offending behaviors associated with a patient’s paraphilic interest and may signal a greater need for treatment.

Specific tests are not needed to make a diagnosis of a paraphilic disorder. When there is concern for inaccurate reporting of fantasies and

Table 1. DSM-5 specified paraphilic disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Atypical sexual interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voyeuristic disorder</td>
<td>Observing an unsuspecting person who is naked, disrobing, or engaging in sexual activity</td>
</tr>
<tr>
<td>Exhibitionistic disorder</td>
<td>Exposure of one’s genitals to an unsuspecting person</td>
</tr>
<tr>
<td>Frotteuristic disorder</td>
<td>Touching or rubbing against a nonconsenting person</td>
</tr>
<tr>
<td>Sexual masochism disorder</td>
<td>Being humiliated, beaten, bound, or otherwise made to suffer</td>
</tr>
<tr>
<td>Sexual sadism disorder</td>
<td>Physical or psychological suffering of another person</td>
</tr>
<tr>
<td>Pedophilic disorder</td>
<td>Prepubescent children</td>
</tr>
<tr>
<td>Fetishistic disorder</td>
<td>Nonliving objects or nongenital body parts</td>
</tr>
<tr>
<td>Transvestic disorder</td>
<td>Cross-dressing</td>
</tr>
</tbody>
</table>
arousal patterns, however, psycho-physiologic assessments may assist to clarify whether a paraphilic interest is present. Visual reaction time (VRT) and penile plethysmography (PPG) are two types of psychophysiological assessment. They are typically available only in forensic contexts or specialized sexual disorders clinics.

VRT describes the relative amount of time that an individual observes an image. People typically spend more time looking at images that are sexually appealing to them. Computer programs can assess VRT by displaying images of male and female adults and children on a computer screen and having a patient click through the images and rate his self-reported interest in them. Increased VRT for prepubescent images may signal the presence of a pedophilic interest. PPG, on the other hand, measures the change in penile circumference or volume in response to potentially arousing auditory or visual stimuli. PPG is also used to assess for pedophilic interest, but it can also be used to identify the presence of sexual response to other stimuli, such as sadistic themes, animals, etc.

**Treatment options and risk stratification**

There are limited treatment options for paraphilic disorders. Although not all individuals with paraphilic disorders are sexual offenders, much of the literature used to guide treatment in patients with paraphilic disorders derives from studies of sexual offenders. Sexual offender treatment programs typically utilize various forms of psychotherapy, though there is little evidence that such approaches are helpful at reducing recidivism. A 2012 Cochrane review failed to demonstrate a reduction in sexual offense recidivism from psychological interventions in sexual offenders. Similarly, a recent large-scale study of a sexual offender therapy-based intervention delivered to over 15 thousand prisoners in the UK found that treated men had an increased risk of recidivism compared to untreated men.

Mild paraphilias and sub-diagnostic atypical sexual interests and fantasies may be managed with psychotherapies such as cognitive-behavioral therapy. For paraphilic disorders, however, medications should be a mainstay of treatment. Table 3 summarizes the different classes of medications used to treat paraphilic disorders, as well as their mechanisms of action and beneficial effects on paraphilic disorders. SSRIs frequently cause sexual dysfunction in patients treated for other conditions such as depression and anxiety. Such impairment may be desirable in patients with paraphilic disorders, so SSRIs can be used to induce dysfunction in libido, arousal, and orgasm.

Antiangrogen medications, including synthetic steroidal analogs like medroxyprogesterone acetate and gonadotropin releasing hormone analogs like leuprorelin, reduce testosterone levels by different mechanisms with the goal of decreasing sex drive and eliminating paraphilic fantasies and urges. They have the added benefit of injectable, long-acting formulations that can improve patient adherence to the treatment regimen. Data regarding the effectiveness of these treatments are limited. Studies tend to have small sample sizes composed primarily of sexual offenders, only some of whom have paraphilic disorders. In addition, the primary endpoint for most studies is sexual offense recidivism, as opposed to subjective improvement in paraphilic symptoms and related distress. A 2015 Cochrane review of pharmacologic interventions for individuals who sexually offended or are at risk of offending evaluated the evidence for each medication category. The researchers did not identify any studies that used SSRIs or gonadotropin releasing hormone (GnRH) analogs; only six studies that used synthetic steroidal analogs were found. The overall evidence was found to be poor. In their 2010 guidelines for the biological treatment of paraphilias, the World Federation of Societies of Biological Psychiatry (WFSBP) was able to provide recommendations on the three categories of medication with only level C evidence, or “minimal research-based evidence to support the recommendation.” Despite the lack of evidence, the WFSBP published practical guidelines to assist clinicians in making rational treatment decisions for paraphilic disorders. The guidelines indicate that treatment should be more rigorous and based on the severity of risk of harm posed by an individual’s paraphilia or paraphilic disorder. Table 4 briefly describes the levels of treatment needed and recommended treatments per the WFSBP. Escalating severity of the paraphilic disorder and risk for violence indicate the need for antiandrogen treatment, including a combination of a GnRH analog and synthetic steroidal analog for the most severe cases. The general psychiatrist should exercise caution, however, as formulating estimates of sexual violence risk is outside the realm of general psychiatric and even most forensic psychiatric practice. If a clinician encounters a patient and has concern for sexual offending due to a paraphilic disorder, consultation with or referral to a forensically trained sexual disorders specialist is warranted.

**Informed consent**

Informed consent is an essential element of any clinical encounter, but it is particularly relevant to consider when working with patients with paraphilic disorders. Although discussing SSRIs and their associated risks with patients may be second nature to practicing psychiatrists, antiandrogen medications may be less familiar. Psychiatrists treating patients with antiandrogen agents should be aware of the various adverse effects and educate patients accordingly. Medroxyprogesterone acetate, for example, commonly causes weight gain and headache and is also associated with the development of gallstones, thromboembolism, hot flashes, insomnia, and other distressing symptoms. GnRH analogs tend to be better tolerated than the synthetic steroids, but can cause hot flashes, headache, and nausea.

Another relevant issue in providing informed consent to a patient with a paraphilia or paraphilic disorder is mandated reporting. Clinicians

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**Table 3. Medication treatments for paraphilic disorders**

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Mechanism of action</th>
<th>Effect on paraphilic disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs (eg, fluoxetine, sertraline)</td>
<td>Inhibition of serotonin reuptake via SERT; enhanced activation of 5HT2 receptor</td>
<td>Impaired libido, arousal, and orgasm; reduction in obsessive paraphilic fantasies and urges and compulsive paraphilic sexual behaviors; management of comorbid anxiety and depressive symptoms/disorders</td>
</tr>
<tr>
<td>Synthetic steroidal analogs (eg, MPA)</td>
<td>Increased hepatic catabolism of testosterone; suppression of hypothalamic-pituitary-gonadal axis; increased testosterone protein binding; decreased cellular uptake of androgens</td>
<td>Suppression of sex drive; reduction of intensity and frequency of sexual urges</td>
</tr>
<tr>
<td>GnRH analogs (eg, leuprorelin)</td>
<td>Suppression of physiologic, pulsatile release of luteinizing hormone (hormone responsible for stimulating testes to produce testosterone)</td>
<td>Reduction of paraphilic fantasies and behaviors</td>
</tr>
</tbody>
</table>

SERT, serotonin transporter; MPA, medroxyprogesterone acetate; GnRH, gonadotropin releasing hormone.
LGBTQ Mental Health: What Every Clinician Needs to Know

Albina Veltman, MD, and Tara La Rose, MSW, PhD, RSW

SIGNIFICANCE FOR PRACTICING PSYCHIATRISTS

This article highlights key concepts that every mental health clinician should be aware of when working with individuals who identify as LGBTQ:

- An overview of mental health disparities affecting LGBTQ-identified people
- A brief review of terminology related to LGBTQ identities
- Resources for becoming an ally and creating LGBTQ-positive health care spaces

Dual alienation

The concept of “dual alienation” is the idea that individuals who belong to more than one marginalized group are doubly marginalized. Individuals with mental health issues who identify as LGBTQ belong to at least two traditionally marginalized groups. If they also happen to belong to other marginalized groups because of their race, ability, socioeconomic status, or any other factor, the marginalization they experience is cumulative and much more complex.

Increased risk

Moreover, individuals who identify as members of sexual and gender minorities experience increased risk for some mental health issues. For example, LGB-identified individuals have a 2 to 6 times higher lifetime risk of suicide and/or depression than the general population. Among trans-identified individuals, the statistics on suicidality are staggering, with 77% of respondents in one Canadian study reporting that at some time in their lives they had seriously considered suicide and 43% reporting they had made at least one suicide attempt. In a large study of people who identify as gender variant (6450 participants), 41% reported attempting suicide at some point in their lives.

This increased risk for various mental health conditions in this population is mostly a result of discrimination, marginalization, and homophobia, biphobia and/or transphobia, rather than something inherent to having an LGBTQ identity. LGBTQ-identified individuals experience increased vulnerability to mental health issues due to a variety of factors, including bullying, violence, discrimination, heterosexism/cisgenderism, homophobia, biphobia and/or transphobia, and potentially, the loss of support and rejection by friends and family. As an example of the potential detrimental effects of rejection by family, in a large study of LGB-identified youth, those who came from highly rejecting families were more than 8 times as likely to have attempted suicide than LGB peers who reported no or low levels of family rejection.

Treatment approaches

While there are some unique mental health risks and concerns among LGBTQ-identified individuals, it should be emphasized that LGBTQ people also have many of the same concerns as the general population. Mental health clinicians should be mindful of taking a holistic, patient-centered approach by treating each patient as a whole, unique individual, rather than a collection of risk factors.

Another important issue to remember is that while LGBTQ populations are often combined as a single entity for research and/or clinical purposes, each of these identities represents a distinct population with their own specific health needs. The experiences of LGBTQ individuals are not uniform and are shaped by intersectional identities and factors such as race, ethnicity, socioeconomic status, geographical location, disability, religion, and age.

Education and training

In most health care education programs, there is a lack of training on LGBTQ-related issues. In a study of over 150 medical schools in North America, the median number of hours of education dedicated to LGBTQ-related issues was only 5 hours and more than half of all medical schools reported zero hours of clinical training in LGBTQ health. This lack of education on LGBTQ-related issues has a negative effect on patient care for this population and contributes to the barriers faced by LGBTQ individuals in accessing high quality, culturally safe, and appropriate mental health care.

Some clinicians adopt a neutral position on the issue of patients’ sexual orientation and gender identity, believing that these issues do not or should not affect their treatment in any way. However, neutrality can equate to dismissiveness in that this stance does not take into account an important part of a person’s identity and life experiences (ie, does not incorporate an understanding of homophobia, biphobia and/or transphobia as well as other experiences of marginalization).

Access and quality of care

To improve access to and quality of mental health care for individuals who identify as LGBTQ, it is important for clinicians to become allies to this marginalized community. Table 1 describes some tips on how to support LGBTQ communities. Creating a positive space in health care settings requires more than simply placing a rainbow sticker on the clinic office door; it requires multiple layers of action that demonstrate to LGBTQ patients that their identity and concerns are important and normalized as part of the diversity that

Table 1. How to be an ally

- Reflect on your own reactions and feelings
- Examine your own language use
- Speak up when you see discrimination, insensitivity, and gaps in knowledge action
- Advocate for policy changes that are LGBTQ-affirmative
- Include gender identity, gender expression and sexual orientation in a zero-tolerance discrimination policy at your organization
- Come out as an ally!

Table 2. Suggestions for creating a positive space of safety and acceptance

- Use inclusive language in interviews and intake forms
- Reflect back the language used by your patient, including using preferred name and pronouns
- Do not make any assumptions about patient’s sexual orientation or gender identity
- Display posters, pamphlets, and/or signs that are inclusive of LGBTQ people and issues
- Offer gender-inclusive bathrooms
- Post a non-discrimination policy that includes sexual orientation, gender identity, and gender expression
- Accept and celebrate diversity
SPECIAL REPORT

Glossary of LGBTQ-Related Terms

**Ally:** A person who supports and advocates for members of a community other than his or her own, reaching across differences to achieve mutual goals.

**Bisexual:** A person who is attracted to and may form emotional, romantic, and/or sexual relationships with both men and women, although not usually equally or simultaneously.

**Cisgender:** A person who conforms to gender and/or sex-based expectations of society (also referred to as gender normative).

**Cisgenderism:** Assuming that everyone is cisgender, therefore marginalizing people who identify as transgender. Believing cisgender people are superior, holding people to traditional expectations based on gender, and/or excluding people who do not conform to traditional gender expectations.

**Disorders/differences of sex development (DSD):** Congenital conditions in which development of chromosomal, gonadal, or anatomic sexual organs are atypical.

**Gay:** A person whose primary sexual orientation is to members of the same sex. Gay can refer to men and women, although many women prefer the term lesbian.

**Gender-confirming surgeries:** Surgical procedures by which a person’s physical appearance and function of existing sexual characteristics are altered to resemble that of the sex to which they are transitioning.

**Gender expression:** The way in which a person expresses gender identity through clothing, behavior, posture, mannerisms, patterns of speech, activities, and more.

**Gender identity:** Internal and psychological sense of oneself as male, female, both, or neither.

**Gender nonconforming:** A person who does not conform to society’s expectations of gender expression based on the gender binary or expectations of masculinity and femininity.

**Heterosexual:** A primary sexual orientation towards members of the other sex (also referred to as straight).

**Heterosexism:** The assumption that everyone is or should be heterosexual and that heterosexuality is inherently superior to and preferable to all other sexual orientations.

**Heterosexual privilege:** Benefits derived automatically by being (or being perceived as) heterosexual that are denied to people who identify as having non-heterosexual orientations.

**Homosexual:** A primary sexual orientation towards members of the same sex or gender. As this term is historically associated with a medical model of homosexuality, most people prefer to self-identify as gay, lesbian, or queer.

**Homophobia:** The irrational fear or hatred of, aversion to, and discrimination against people who identify as gay, lesbian, or queer.

**Internalized homophobia:** The experience of guilt, shame or self-hatred in reaction to one’s feelings of attraction for a person of the same sex or gender as a result of societal homophobia and heterosexism.

**Intersex:** A condition in which sex-related chromosomes, gonads, or anatomy do not develop in a way that is typically male or female. Intersex is an umbrella term that includes many different conditions (ie, disorders and/or differences of sex development).

**Lesbian:** A woman whose primary sexual orientation is to other women.

**Non-binary:** A spectrum of gender identities that are not exclusively masculine or feminine. Non-binary people may identify as being multi-gender, having no gender, moving between genders, or having a fluctuating/liquid gender identity, being third gender or other-gender (genderqueer is an earlier term with a similar meaning to non-binary).

**Queer:** In contemporary usage, queer is an inclusive, unifying, socio-political and self-affirming umbrella term encompassing a broad range of sexual and gender expression, including people who identify as gay, lesbian, bisexual, transgender, intersex, genderqueer or any other non-heterosexual sexuality or nonconforming gender identity. Queer is a reclaimed term, which was previously seen as derogatory, but many people (though not all people) within the LGBTQ community are comfortable using this term to describe themselves.

**Questioning:** A self-identification sometimes used by people who are exploring their sexual orientation and/or gender identity.

**Sexual orientation:** An inherent or immutable enduring emotional, romantic, or sexual attraction to people of the same gender, different gender, or more than one gender.

**Transgender or trans:** Someone whose gender identity or expression differs from conventional expectations of masculinity or femininity. Often used as an umbrella term that includes people who identify as cross-dressers, transsexuals, two-spirit, intersex, and genderqueer.

**Transition:** A complicated, multi-step process that can take years as transgender people align their anatomy and/or their gender expression with their gender identity.

**Transphobia:** Irrational fear or hatred of, aversion to, and discrimination against people who identify as transgender.

**Two-spirit:** A term used by some North American indigenous cultures to describe people in their communities whose nature is comprised of both male and female spirits. People who identify as two-spirit may also identify as gay, lesbian, bisexual, transgender, intersex, or have multiple gender identities.

Adapted from Veltman and Chaimowitz.1

Table 2 offers suggestions on how to create an LGBTQ-positive space in health care settings. There are many resources available for mental health clinicians to educate themselves about LGBTQ-related issues. A variety of useful online resources related to LGBTQ health are provided in Table 3.

Dr Veltman is Associate Professor, Department of Psychiatry and Behavioural Neurosciences, McMaster University; Psychiatrist, Hamilton Assertive Community Treatment Team, Dual Diagnosis Team, and LGBTQ Mental Health Clinic, St. Joseph’s Healthcare, Hamilton, ON, Canada. Dr La Rose is Assistant Professor, School of Social Work, McMaster University, Hamilton, ON.

The authors report no conflicts of interest concerning the subject matter of this article.

REFERENCES

5. Haas AP, Eliason M, Miyas VM, et al. Suicide and suicide risk in lesbian, gay, bisexual, and transgender
Table 3. Useful Online Resources Regarding LGBTQQ health

<table>
<thead>
<tr>
<th>Health care professional organizations devoted to LGBTQQ health</th>
</tr>
</thead>
<tbody>
<tr>
<td>• World Professional Association for Transgender Health: <a href="http://www.wpath.org">http://www.wpath.org</a></td>
</tr>
<tr>
<td>• Gay and Lesbian Medical Association: <a href="http://www.glama.org">http://www.glama.org</a></td>
</tr>
<tr>
<td>• Association of Gay and Lesbian Psychiatrists: <a href="https://www.aglp.org/">https://www.aglp.org/</a></td>
</tr>
</tbody>
</table>

Standards of care for transgender individuals

- TransCare BC: Primary Care Toolkit http://www.phsa.ca/transgender/Documents/Primary%20Care%20Toolkit.pdf

Suicide prevention in LGBTQ communities

- The Trevor Project: www.thetrevorproject.org
- It Gets Better Project: www.itgetsbetter.org

Other useful websites

- 2 Spirited People of the First Nations: www.2spirits.com
- Accord Alliance: www.accordalliance.org/
- The Fenway Institute: www.fenwayhealth.org
- LGBT Mental Health Curriculum: www.aglp.org/gap/
- TransPulse Project: www.transpulse.ca
- Queer Queering and Questioning Project: www.youtube.com/watch?v=IiL5-aMaQQ42

Table 4. Brief overview of WFSBP paraphilia/paraphilic disorder treatment algorithm

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Paraphilias that do not affect conventional sexual activity</td>
<td>Psychotherapy (eg, CBT)</td>
</tr>
<tr>
<td>2</td>
<td>Mild cases of hands-off paraphilic disorders with low risk of sexual violence</td>
<td>SSRI</td>
</tr>
<tr>
<td>3</td>
<td>Hands-on paraphilic disorders with fondling but without penetration; paraphilic sexual fantasies without sexual sadism</td>
<td>SSRI with low-dose antianxiety</td>
</tr>
<tr>
<td>4</td>
<td>Moderate and high risk of sexual violence without sexual sadism</td>
<td>Full dosage synthetic steroidal analog</td>
</tr>
<tr>
<td>5</td>
<td>High risk of sexual violence and severe paraphilic disorders</td>
<td>Long-acting GnRH analog</td>
</tr>
<tr>
<td>6</td>
<td>Catastrophic cases</td>
<td>GnRH analog with synthetic steroidal analog; may consider SSRI</td>
</tr>
</tbody>
</table>

Paraphilias

Continued from page 20

should be aware of what specific behaviors or crimes require reporting in their jurisdiction, as they can vary state by state.15 For example, some states mandate reporting of the use of child pornography, whereas others do not. The limits of confidentiality should be fully discussed with patients prior to initiation of treatment.

Conclusion

Paraphilic disorders are rarely encountered in general psychiatric practice and pose numerous challenges for the treating clinician. Patients may be hesitant to seek or engage in treatment for atypical sexual interests, there is limited evidence by which to guide treatment decisions and medication selection; and the use of hormone-altering agents can have severe adverse effects that require patient education and careful informed consent procedures prior to implementation.

For difficult or high-risk cases, consultation with or referral to a sexual disorders specialist is essential. Despite these concerns, both patients and society at large can benefit from the effective management of paraphilic disorders. Treatment can curb patients’ unwanted, distressing sexual urges and fantasies and reduce the risk of harmful sexual behavior. Psychiatrists should therefore be aware of this class of disorders, feel comfortable conducting a complete sexual behaviors history, and be able to discuss treatment options, even if the patient ultimately receives care elsewhere.

Dr Holodya is Forensic Psychiatrist and Chair, Sexual Offenders Committee, American Academy of Psychiatry and the Law, Sacramento, CA. He reports no conflicts of interest concerning the subject matter of this article.

REFERENCES

Sexing: The Technological Evolution of the Sexual Revolution

Swathi Krishna, MD

Many times, as psychiatrists, in a psychosocial assessment we inquire about an individual’s sexual behavior and social behavior. But, as the social habits of our patients change, are we keeping current of the changes we need to make to identify problems that may lead to psychiatric sequelae in the future? Specifically, what is the impact of online sexual behavior and associated factors that have become so prevalent in our current society.

Over the course of human history, there have always been periods of evolution and transformation of existing thought processes in the social, political, and cultural climate. Moreover, personal, artistic, and sexual expression has also evolved over time. From “free love,” to the Play-Boy era, to the women’s sexual liberation movement there have been many examples of paradigm shifts in adult sexual expression. As with most social shifts, some of these changes have brought unforeseen and unintended consequences and, ultimately, the need for society to address these consequences and associated risks.

The advent of sexing

The rise of the Internet and smartphones has created a proliferation of “sexting” between adults and, even more concerning, youths. The term sexting is used generally to encompass a wide variety of digital activities: sending, receiving, or forwarding sexually explicit messages, photographs, or images. Although mobile phones are the most common vehicle for sexting, the term can also apply to sending sexually explicit messages through any digital media such as email, instant messaging, and social media sites.

Sexting is somewhat of a natural marriage of previous forms of sexual expression and modern day technology. It was once treated as deviant behavior but was not thought to be widespread. But, as we have learned over the past few years, it is actually a widely prevalent phenomenon and is often rapidly replacing more traditional forms of sexual expression and sexual communication. In this regard, mental health professionals should be addressing this behavior as a natural expression of normative sexual behavior between consenting adults.

However, we must also be aware of the potential of sexting to cause catastrophic consequences in vulnerable populations susceptible to victimization such as women, minors, and persons with mental health issues. That is why psychiatrists need to be informed of the practice of sexting and how to talk to patients openly about these behaviors to mitigate psychosocial consequences and psychological risks.

Sexual sharing

Sexting is becoming a more acceptable and widely used form of sexual communication within the adult population. One study from 2016 included 58045 single adults from the aged 21 to 75 years.1 Findings from this study by Garcia and colleagues indicate that 21% of participants reported sending and 28% reported receiving sexually explicit text messages. One concerning fact is that 22.9% of those who received a sext shared it with others and some of this sharing was without the permission of the original sender. Almost 3 out of 4 people reported discomfort with unauthorized sharing of sext beyond the intended recipient.

These statistics raise an important point that we should be talking to patients about: the unintended consequences of individuals sharing sexts without permission. The ease of transmission and ability to rapidly disseminate this type of personal and sensitive information on the Internet without permission increases the risk of victimization and psychological consequences that individuals involved in sexting may have not considered.

The adults in this study reported concern about the potential consequences of sexting on their social lives, careers, and psychosocial well-being, which shows the presence of a more mature thought process. But what about the individuals who may not have the biological or psychological ability to engage in this mature process and, therefore, unintentionally open themselves up to significant emotional, social, and psychological risks with sexting behaviors?

Increased risk for youths

The most vulnerable populations are minors. The prevalence of sexting among youths is generally unknown, reported estimates vary widely from 1.3% to 60%. What complicates the issue is that different teenage populations often have individualized definitions of what sexting is. In a 2012 study of teens, after being asked generally if they had engaged in sexting, when specifically asked if they had sent a naked photo of themselves, the rates were much lower.2 This might mean that they considered sending sexually explicit material such as Snapchat videos, Instagram posts, or sexual “memes,” as sexting instead of naked photos of themselves.

In a study by Temple and colleagues,3 teenagers were specifically asked about texting nude photos of themselves or others; however, not all current studies have controlled for that distinction. Therefore, we cannot know the exact prevalence of teenage sexual messaging. This is an important factor that highlights the importance of asking specific questions about messaging behaviors of young patients.

Furthermore, a distinction has to be made between the texting that occurs within a sexual relationship between teens versus the sexting of nude pictures. One study showed that young adults were using more text messaging in emerging sexual relationships.4 Cautionary tales

Under federal law, any sexually explicit images of minors under age 18 are considered child pornography, even if the minors created the images themselves. Many minors are not aware of the legal and social ramifications of sexting. And, even more concerning, the unintended social and psychological consequences that can occur secondary to sexting behavior such as humiliation, bullying, and the effect on their future.

These social and psychological consequences can often lead to depression, anxiety, social isolation, a negative self-image, and even suicidal thoughts and self-harm behaviors. With all of these factors, why do the rates of sexting among youths continue to rise? Part of the problem is that teens use sexually explicit words and posts on social media to promote themselves. Many of the celebrity role models that youths are looking up to these days are part of the “selfie effect” and often these pictures can be quite provocative for attention.

Additionally, with the competition for number of “likes” develops into a form of positive reinforcement that fuels the motivation to post more often and further test limits. Youth that engage in sexting can have more difficulties detecting and regulating their own emotion, which can result in depression and anxiety as well as low self-esteem, anger, loneliness, and attention seeking.

In a 2014 study of college students, more than half reported sexting as minors.5 About one-third reported sending pictures, others endorsed sending sexually explicit text messages or social media messages. More than half (61%) of the students who reported sexting as minors said they were not aware that sending a sexually explicit text could be considered child pornography under federal law; 59% said that had they known it was a prosecutable offense it “would have or probably would have deterred their behavior.” This highlights an opportunity for discussion points with adolescents regarding the potential consequences of sexting behaviors. Another point is that only 2% reported telling a teacher or adult about a sext they received, this also highlights the need for more open communication about risky online behavior in youth between parents, providers, and responsible adults.

The largest meta-analysis to date focused on sexting behavior in youths.6 It included 39 studies with a total of 111,380 participants between the ages of 11 and 17 (mean age 15.2). It showed that sexting prevalence in this age group has increased over time and increases with age. Mean prevalence for sending a sext was 14.8% and prevalence for receiving a sext was 27.4%. This shows that a smaller percentage of people send sexts than receive them, which suggests that a few people are engaging in the behavior but the sexts are being sent to larger groups of people with or without their knowledge. About 1 in 10 individuals in the analysis reported forwarding a sext without consent and just 8% of individuals reported that their own sext had been
Sexting practices: Talking points for adults

- Do you often share personal information online?
- Do you regularly use social media? How often do you share personal information?
- How do you feel about sexting? Have you ever sent or received sexts?
- Did you ever send a sexually explicit photograph of yourself to anyone?
- If you did, do you realize that whoever you sent it to can send it to others without your consent?
- How would you feel if you sent someone a sext, and they shared it without your permission?
- What do you think can happen if unintended people receive images/sexts about you?
- Do you know if anyone has sent a sext about you without your permission?
- Has anyone ever tried to force you to share sexts?
- Has anyone ever threatened to send sexual material about you if you didn’t comply with their demands?

Sexting practices: Talking points for children and their parents

- Has anyone ever asked you to send naked pictures of yourself over the phone?
- Have you ever sent, received, or posted naked or inappropriate photos or words about yourself or someone else?
- Has anyone ever used inappropriate pictures or words to bully you?
- Since you are a minor do you know that sending sexual pictures of yourself or of any other minor is illegal? What do you think that means?
- What would happen if your siblings, coaches, and/or teachers saw those photos? How would that make you feel?
- Why do you think other people post sexual photos of themselves online? What do you think about that?
- Can you give me an example of someone famous who posts sexual posts online? How do you feel about that?

forwarded without consent. There was no significant difference between boys and girls in sending or receiving sexts. This study shows the upwards trend of sexting within youth populations and identifies many points to initiate discussion with young patients about their own sexting practices and the associated risks.

Sexting behaviors also show a correlation with other risky behaviors that parents and psychiatrists should be aware of. The study by Temple and colleagues shows a significant association between sexting behaviors and having multiple sex partners. It also shows that the use of alcohol and drugs before sex was higher among those who sent, received, or asked for a sext.

Another consequence of the normalization of this type of sexual content among youth is that it may contribute to a normalized culture of sexual violence and exploitation. According to a UK article, sexting is linked to generalized physical and sexual harassment as well as bullying of girls in secondary school. The article also highlights the devastation and the sexual and emotional exploitation that the girls felt by having their private information sent out without their permission. At least one girl died by suicide after sexually explicit material was distributed about her. By not addressing the risk for sexual violence and exploitation as an extreme consequence of sexting behavior, we may be leaving our youths in a vulnerable position.

Theory of developmental vulnerability

The developmental vulnerability theory posits that early victimization results in vulnerabilities, disinhibiting influences, and conditioning of experiences that manifest over time to create propensities for sexual and non-sexual violence. Sexting can be a form of early victimization and increase the threshold for permissible sexual behavior. It lowers the threshold for recognizing one’s own sexual exploitation or the exploitation of others.

Yoder and colleagues looked at 200 adjudicated male youths aged 13 to 19 years in the juvenile justice system: 65.5% had engaged at least once in a sexting experience and the number rose to 73.5% when age was increased to 20 years. Study data show a correlation between exposure to violence or adversity in childhood and an emotionally disinhibiting state that allowed for more risky behaviors. This study also shows a statistically significant relationship between sexting between friends/acquaintances and dating violence.

Another major significance of all of these findings is the high risk of sexual victimization that can occur with sexting. One NY Times article reported that more than half of adolescents studied had dated someone who tried to monitor or control them using digital content by threatening to spread rumors, post embarrassing or hurtful messages, or making physical threats. About one-third experienced sexual coercion via digital means, they had been pressured to have sex, received unwanted sexual images, were urged to send sexual images, or had their nude photos sent to others without permission.

Conclusion

A thorough psychosocial assessment and social history should include details of online activity of all patients and should address risks associated with any risky online behavior. Provide information to parents of adolescents on how to ask about and talk directly about online risks with their children—statistics show that most adolescents are aware of sexting practices among peers at school.

Psychiatrists should provide direct education to their patients about social, legal, and psychological consequences and risks of sexting. Remind patients that their sensitive information can easily be disseminated without their consent or knowledge. Most important is to approach the patient without judgment and provide open, safe communication about sexting practices.

Dr. Krishna is the recent Chief Resident, Emory University Child and Adolescent Psychiatry Fellowship Program, Atlanta, GA. She graduated in 2019 and is currently working in private practice in Atlanta, GA. She reports no conflicts on interest concerning the subject matter of this article.

REFERENCES
Illuminate Life Processes by Taking a Sexual History

Stephen B. Levine, MD

E very person possesses a complexity called sexuality that slowly manifest itself in variable ways from childhood to old age. Sexuality’s two major elements are sexual identity and sexual function, each of which has several components (Table 1). The components evolve predictably over the life cycle, but also may abruptly change in response to personal, interpersonal, mental and physical difficulties, and cultural forces. The most central component is sexual desire, a complexity that represents the energy/motivation to socially express one’s gender identity, orientation, and intention as well as the force that shapes around desire, and penetration experiences.

All of the components of sexuality except orientation are used to organize DSM-5 sexual dysfunction and sexual identity diagnoses. A working knowledge of all the components guides the sexual history. DSM-5 sexual diagnoses do not capture the actual sexual dramas of patients’ lives; they only characterize the seemingly negative outcomes of life processes.

As these processes become illuminated by the sexual history, a wide array of influential adversities become apparent. These include medical and psychiatric disorders, infidelity, infertile, preoccupation with commercial sex, childhood abuse and neglect, attachment problems, sexual identity struggles, sexual victimization, marital discord, divorce, grief, medication effects, ignorance, and the like. Sexual life is disrupted by many of the same forces that compromise mental health.

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In discussing a patient’s sexual life, consider the following important cautions.

1. Do not consider sexual life separate from what you already understand about biopsychosocial processes during the life cycle. Because we experience our own sexuality as an intensely private subjective matter, we assume that patients do as well. We may not realize that they consider the psychiatrist as more knowledgeable than they are about this frequently problematic realm. They may welcome our inquiries and our attempts to understand and assist them. Clinical sexual expertise grows by the doctor’s interest and emerging personal comfort rather than the accumulation of esoteric knowledge.

2. Do not assume the process of taking a sexual history is a difficult personal process. Ask the patients if they have any sexual concerns that they would like to discuss. When they answer “yes” or when they spontaneously mention a sexual topic, invite them to tell you more: “Please say more about that” or “Tell me what you think it is important for me to know about that.” This shows the patient that you are interested and want to be helpful.

3. Do not make this a matter of gender. While many men and women may prefer to discuss their concerns with a professional of the same gender, others prefer the opposite. Regardless of their preference, the patient’s discomfort quickly dissipates when the psychiatrist asks illuminating questions.

Concepts that foster competence
There is no such thing as a complete sexual history. The clinician’s responses follow from the patient’s concern: a 16-year-old who wants to change her social presentation; a 40-year-old who confesses his lifelong premature ejaculation; a 53-year-old woman who has new dyspareunia; a 24-year-old who has never had an orgasm; a 67-year-old gay man with faltering potency; a couple who has not had any sex for three years after the wife’s infidelity; a man caught in a sting operation for watching child pornography; a man in the midst of an affair with little desire for his wife, etc. All of these scenarios would elicit very different history taking.

The sexual history evolves. Clinicians should not burden themselves with the idea that each problem should generate a long list of items that must be covered during that session. Patients expect to have the conversation continue and will provide additional relevant information when the clinician mentions the previous sexual concern.

After the first session, the patient is either impressed or unimpressed with the doctor’s interest. It is not difficult to engage the patient in the topic during the next session. When the concern is the highly prevalent selective serotonin reuptake inhibitors-induced dysfunction, the patient will expect the doctor to follow up on any suggestions.

Of course, there are specific things that we want to know in each situation, but these questions naturally occur to clinicians after the patients tell their stories. If not, it is useful to consult a relevant article, readily found via PubMed by topic, or a book to augment the doctor’s knowledge of the patient’s concern. There are numerous comprehensive texts covering the broad range of sexual concerns, problems, and diagnoses.

Is the problem lifelong or acquired? This distinction guides the search for the causal factors in symptom production (Table 2). Without considering this fundamental distinction, the clinician’s work tends to be unfocused, inefficient, and confusing to both parties. Premature ejaculation and women’s anorgasmia typically tend to be lifelong, whereas erectile inconstancy and women’s desire/erosion problems tend to be acquired.

When problems are acquired, we zero in on what was occurring before the symptom appeared. We want to know if an acquired problem is specific to one partner or is true in all circumstances. Lifelong problems invite a focus on the patient’s family processes, relationship with parents, siblings, and...
experiences of abuse and neglect. We are interested in the patient’s sense of what historically has influenced the pattern. When “I don’t know” is the response, it is fine to say, “These patterns have multiple influences, but I presume you have considered certain ideas. Can you share them with me?”

Try to formulate the likely pathway to the problem. Understanding the pathways to these problems is often necessary to improving patients’ lives. Psychiatrists can intervene with a phosphodiesterase-5 inhibitor, fibabaner, bremelanotide, and an SSRI to address erectile dysfunction, sexual interest/ arousal disorder, and premature ejaculation. These prosexual prescriptions are best provided after careful listening and questioning, which is essential in establishing a trusting therapeutic alliance.

The understanding of pathogenesis can become more complete with each session as we learn more about the patient’s experiences, capacities, and thinking. Such understanding that derive from learning about the person’s sexual struggles does not mean that every psychiatric patient requires a sexual history. But do not be shocked when a patient brings up the topic in the context of a nonsexual problem.

Confronting our rationalizations

When sexuality is relevant to understanding the patient’s problem, some psychiatrists deflect the topic with comments such as “I am not a sexual specialist;” “We don’t have time for that subject;” or “Share that with your psychotherapist.” Such rejecting responses often indicate one or more of the following private concerns of the psychiatrist. “My personal sexual life is problematic. What do I have to offer patients if I can’t solve my own sexual issues?”

The more you know about the universality of sexual concerns, the frequency of sexual problems, and the prevalence of DSM-5 sexual diagnoses, the better you will feel about taking a sexual history. Our difficulties can generate interest as well as empathy. A doctor can feel addicted to pornography, not have sex with her husband, have difficulty ejaculating, or have dyspareunia—yet still be helpful to patients. Helping others exposes you to considerations that can illuminate an avenue of your own concerns.

“I do not know enough about the subject to help.” Often the clinician knows more than they originally thought and can readily acquire more knowledge. Few psychiatrists have in-depth knowledge of all disorders (eg, depression, anxiety, psychosis), and yet we calmly provide care.

“I am afraid of what I may feel while hearing about sexual fantasies and behavior.” Transient arousal, envy, attraction, and disgust may indeed occur during a session. These brief feelings are not disclosed to the patient; however, they are often not discussed with the supervisor either. Each of these fears affects have a different personal meaning that needs to be considered. Envy, for example, teaches the psychiatrist what they might like to personally experience, while disgust informs the doctor what they considers abnormal. No psychiatrist can possibly experience the full range of human sexual behaviors; we should expect a private affective response. These transient internal experiences are stimuli for our professional growth.

“My values preclude my dealing with sexual minority patients in any depth.” The subtle privilege of being a psychiatrist is the opportunity for life-long learning. In-depth patient experience is a powerful source of learning. Your personal values, whatever their sources, create a priori negative judgments that you fear will become evident to the patient. Getting to know the actual person who has a variation in gender identity, orientation, or intention is the best way to overcome such prejudice.

Each new sexual minority patient can be your personal continuing medical education course, if only you allow yourself to be with the patient over time. At one point or another, every psychiatrist wants to run away from patients whose behavior is socially offensive, but it is a developmental task for clinicians to grow comfortable separating themselves from the differing lives of patients and to counter our morally censorious impulses to live up to our time-honored professionalism.

Sexual language

The power of these four rationalizations help psychiatry residents, fellows, and practicing psychiatrists to avoid inquiring or responding to sexual issues and creates a hesitation to use words involving sexuality. In basic seminars, I invite the group to speak a series of sexual words out loud: penis, vagina, clitoris, scrotum, breast, labia minora, labia majora, and nipple. This produces mirth. Then: menstruation, sexual intercourse, ejaculation, orgasm, cummings, anal intercourse, and fellatio. I usually notice some people are skipping some words. It is initially difficult for both patients and doctors to transfer one’s private sexual language into professional language. Then I ask them to repeat words that some patients will use: blow job, eating her, going down, dick, snatch. I end the desensitization by asking the group to call out as many words as possible for the penis and then the breast. This short anxiety-provoking icebreaker precedes a presentation about the sexual history.

Conclusion

The sexual history is undertaken under a variety of circumstances; for instance, the patient’s sexual complaint, report of an individual’s or a couple’s relationship disappointment, a general review of psychiatric symptoms, a joke told to the doctor, a casual “by the way” remark, medication nonadherence, or a lack of mention of this vital aspect of life. Any professional delay of the sexual inquiry should be temporary. Sexual life is not just about sexual identity and sexual behavior. Sex serves other functions such as the illumination of the relational self, the ability to love, the ability to remain lovable, and the ability to manage one’s emotional life.

REFERENCES


2. Levine SB. Rosen SB, Althof SE. Eds. Handbook of Clinical Sexuality for Mental Health Professionals. In March 2005, he and two colleagues received a lifetime achievement Masters and Johnson’s Award from the Society for Sex Therapy and Research. He reports no conflicts of interest concerning the subject matter of this article.

Talking With Your Patient

Cautions

Do not make sexual life separate from what you already understand about biopsychosocial processes.

Do not make sexual history-taking a difficult process.

Do not make this a matter of gender.

Fostering competence

Know that there is no such thing as a complete sexual history.

Know that the sexual history evolves.

Classify the problem as lifelong or acquired in your mind at the first session.

Continue to formulate the pathway to the patient’s problem at each session.
VETERANS AND SUICIDE: THE LAST STRAW

» Lawrence H. Climo, MD

When I saw the statistic, the number of American veterans who suicide daily, I was shocked. (It’s approximately 20 each day.) When I read about ongoing efforts to assess, prevent, and treat potential suicides I was impressed. But when I looked at the root causes I was disappointed. All the causes listed were essentially stressors, symptoms of medical disorders, potential predictors of suicide like moral injury, psychic bruising, and guilt. None gave me what I was looking for, that final trigger, that last straw that made them do it. I had hoped someone might have identified one. I wasn’t surprised, then, when I encountered

INDICATIONS AND USAGE

INVEGA SUSTENNA® (paliperidone palmitate) is indicated for the treatment of:

- Schizophrenia in adults [see Clinical Studies (14.1) in Full Prescribing Information]
- Schizoaffective disorder in adults as monotherapy and as an adjunct to mood stabilizers or antidepressants [see Clinical Studies (14.2) in Full Prescribing Information]

CONTRAINdications

INVEGA SUSTENNA® should be contraindicated in patients with a known hypersensitivity to either paliperidone or risperidone, or to any of the excipients in the INVEGA SUSTENNA® formulation. Hypersensitivity reactions, including anaphylaxis and angioedema, have been reported in patients treated with risperidone and in patients treated with paliperidone. Paliperidone palmitate is conjugated to paliperidone, which is a metabolite of risperidone.

WARNINGS AND PRECAUTIONS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 2.3 times the risk of death in placebo-treated patients. Over the course of a typical 10-week control trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

Although the cause of death was varied, most of the deaths appeared to be cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia). In nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to other aspects of the treatment of elderly patients with dementia-related psychosis [see Boxed Warning and Warnings and Precautions]

Neuroleptic Malignant Syndrome

A neuroleptic malignant syndrome complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs, including paliperidone. Paliperidone palmitate extended-release injectable suspension for intramuscular use may cause symptoms of the syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of Torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) lidocaine; (2) haloperidol; (3) other antipsychotics (e.g., chlorpromazine, thioridazine); antibiotics (e.g., tetracycline, aminoglycosides, or any other class of medications known to prolong the QTc interval; it should be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

The diagnostic evaluation of patients with this syndrome is complicated. In patients with a chronic illness that is known to respond to antipsychotic drugs. In some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients.

QT Prolongation

Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class IA (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antarrhythmic medications, antipsychotic medications [e.g., chlorpromazine, thioridazine], antibiotics (e.g., tetracycline, aminoglycosides), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

The effects of oral paliperidone on the QT interval were evaluated in a double-blind, active-controlled (placebo 400 mg single dose), multicenter QT study in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 8-week, fixed-dose efficacy trials in adults with schizophrenia.

In the QT study (n=141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted increase from baseline in QTcLD of 13.2 msec (90% CI: 6.8; 19.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate release (Cmax,steadystate = 113 ng/mL) was more than 2-fold the exposure observed with the maximum recommended 328 mg dose of INVEGA SUSTENNA® administered in the oral formulation (peak plasma concentration = 50 ng/mL). In this study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which Cmax,steadystate = 35 mg/mL, showed an increased placebo-subtracted QTcLD of 8.8 msec (90% CI: 3.6; 13.0), on day 2 at 1.5 hours post-dose.

In the three fixed-dose efficacy studies of oral paliperidone extended release formulation of paliperidone, for which Cmax,steadystate = 35 mg/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 4.6; 9.0), on day 2 at 1.5 hours post-dose. The effects of oral paliperidone on the QT interval were evaluated in a double-blind, active-controlled (placebo 400 mg single dose), multicenter QT study in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 8-week, fixed-dose efficacy trials in adults with schizophrenia.

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this caveat: “Knowing the reason behind a suicide is difficult or impossible, even for family members who knew the victim best.” Clearly I’d have to pursue this alone.

What follows—my understanding and conclusions about at least one last straw for at least some veteran suicides—has been drawn from published war accounts and memoirs and my own clinical experience. It is not based on academic research.

That said . . .

Sense of one’s self: So fragile, so crucial (a prisoner’s story)

It’s evening. An agitated street criminal behind bars is explaining to the on-call psychiatrist why he needs to be transferred to a psychiatric hospital for his safety. He’s suicidal. He describes how, earlier, on the way to chow, several prisoners had taunted him with cruel insults and he was unable to respond. His taunters were out of reach. When he returned to his cell he was beside himself with rage at that humiliation and the frustration of not being able to get back, get even. It was in this mental state that he began thinking of killing himself and then couldn’t stop. Why kill himself? “I had to kill someone.” he explained. His story was deemed threshold-credible, his reasoning bizarre, but his desperation genuine. His transfer to the psychiatric hospital was approved.

Invega Sustenna® (paliperidone palmitate)

extended-release injectable suspension, for intramuscular use

treated with atypical antipsychotics. These cases were, for the most part, seen in post-marketing clinical use and epidemiologic studies, not in clinical trials. Hypoglycemia and diabetes have been reported in trial subjects treated with INVEGA SUSTENNA®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiologic studies suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics.

Patients with an established diagnosis of diabetes mellitus who are starting treatment with atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continued monitoring of anti-diabetic treatment despite discontinuation of the suspect drug.

Posed data from the four placebo-controlled (one 9-week and three 13-week), fixed-dose studies in subjects with schizophrenia are presented in Table 1.

Table 1: Change in Fasting Glucose from Four Placebo-Controlled, 9- to 13-Week, Fixed-Dose Studies in Subjects with Schizophrenia

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<tr>
<th>Placebo</th>
<th>39 mg</th>
<th>78 mg</th>
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<tr>
<td>Mean change from baseline (mg/dL)</td>
<td>n=207</td>
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Some Glucose Changes from Baseline and Placebo in Subjects with Schizophrenia

Placebo | 39 mg | 78 mg | 156 mg | 234 mg | 234 mg | 234 mg |
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Table 1: Change in Fasting Glucose from Four Placebo-Controlled, 9- to 13-Week, Fixed-Dose Studies in Subjects with Schizophrenia

Cholesterol Change from baseline (mg/dL) | n=207 | n=90 | n=224 | n=110 | n=226 | n=115 |
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Table 2: Change in Fasting Glucose from Four Placebo-Controlled, 9- to 13-Week, Fixed-Dose Studies in Subjects with Schizophrenia (continued)

LDL Change from baseline (mg/dL) | n=207 | n=90 | n=224 | n=110 | n=226 | n=115 |
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Table 3: Change in Fasting Lipids from Long-term Open-label Pharmacokinetic and Safety Study in Subjects with Schizophrenia

Table 2: Change in Fasting Lipids from Four Placebo-Controlled, 9- to 13-Week, Fixed-Dose Studies in Subjects with Schizophrenia

Cholesterol Change from baseline (mg/dL) | n=207 | n=90 | n=224 | n=110 | n=226 | n=115 |
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<td>Placebo</td>
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<tr>
<td>78 mg</td>
<td>-0.5</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>156 mg</td>
<td>-0.5</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>234 mg</td>
<td>-0.5</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

Table 3: Change in Fasting Lipids from Long-term Open-label Pharmacokinetic and Safety Study in Subjects with Schizophrenia

LDL Change from baseline (mg/dL) | n=207 | n=90 | n=224 | n=110 | n=226 | n=115 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.5</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>39 mg</td>
<td>-0.5</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>78 mg</td>
<td>-0.5</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>156 mg</td>
<td>-0.5</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>234 mg</td>
<td>-0.5</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

Table 4: Change in Fasting Lipids from an Open-Label and Double-Blind Period of a Long-term Study in Subjects with Schizophrenic Disorder

LDL Change from baseline (mg/dL) | n=207 | n=90 | n=224 | n=110 | n=226 | n=115 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.5</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>39 mg</td>
<td>-0.5</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>78 mg</td>
<td>-0.5</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>156 mg</td>
<td>-0.5</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>234 mg</td>
<td>-0.5</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

Table 4: Change in Fasting Lipids from an Open-Label and Double-Blind Period of a Long-term Study in Subjects with Schizophrenic Disorder

LDL Change from baseline (mg/dL) | n=207 | n=90 | n=224 | n=110 | n=226 | n=115 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.5</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>39 mg</td>
<td>-0.5</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>78 mg</td>
<td>-0.5</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>156 mg</td>
<td>-0.5</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>234 mg</td>
<td>-0.5</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
</tbody>
</table>
INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

Table 5: Mean Change in Body Weight (kg) and the Proportion of Subjects with ≥ 7% Gain in Body Weight from Four Placebo-Controlled, 5 to 13-Week, Fixed-Dose Studies in Subjects with Schizophrenia

<table>
<thead>
<tr>
<th>Dose</th>
<th>Mean Change (SD) in Body Weight (kg)</th>
<th>Proportion of Subjects with ≥ 7% Gain in Body Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.4 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>39 mg</td>
<td>0.2 (2.0)</td>
<td>2</td>
</tr>
<tr>
<td>78 mg</td>
<td>0.7 (2.6)</td>
<td>6</td>
</tr>
<tr>
<td>156 mg</td>
<td>1.3 (3.8)</td>
<td>13</td>
</tr>
<tr>
<td>234 mg</td>
<td>1.6 (5.0)</td>
<td>25</td>
</tr>
</tbody>
</table>

INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinoma, pharyngeal and pancreatic adenocarcinoma) was observed in the rhesus rhesus monkey carcinogenesis studies conducted in mice and rats (see Nonclinical Toxicology (13.1) in Full Prescribing Information). Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is not limited to be conclusive.

Paliperidone data from two long-term, double-blind, placebo-controlled studies with INVEGA SUSTENNA® are presented below; one study was in a population of patients with schizophrenia; the second study was in patients with schizoaffective disorder.

SCHIZOPHRENIA

In a long-term maintenance trial of INVEGA SUSTENNA® in schizophrenia patients (Study PSY-001), see Clinical Studies (14.1), elevations of prolactin to the above reference range (>18 ng/mL in males and >30 ng/mL in females) relative to open-label baseline at any time during the double-blind phase were noted in a higher percentage of the patients in the INVEGA SUSTENNA® group than those in the placebo group in males (18.1% vs. 8.3%) and in females (30.5% vs. 42.5%). During the double-blind phase, 4 females (4.2%) in the INVEGA SUSTENNA® group experienced potentially prolactin-related adverse reactions (amenorrhea N=2; galactorrhea N=1; menorrhagia irregular N=1). One male (0.9%) in the INVEGA SUSTENNA® group experienced erectile dysfunction and 1 male (0.9%) in placebo group experienced gynecomastia.

Prior to the double-blind phase (during the 32-week open-label phase of the long-term maintenance trial), the mean (SD) serum prolactin values at baseline were 14.2 (22.2) ng/mL in males (N=480) and 35.1 (39.6) ng/mL in females (N=365). At the end of the open-label phase, mean (SD) prolactin values were 24.7 (21.1) ng/mL in males (N=405) and 19.3 (18.1) ng/mL in females (N=350). During the open-label phase, prolactin values in the range of 40-60 ng/mL in males and females were recorded in 49.2% and 47.7% of males and females, respectively. The incidence of prolactin elevations (above the reference range relative to baseline, and a higher proportion of prolactin-related adverse reactions temporally related to antipsychotic agents, compared to males (5.3% vs. 1.8%). Amenoa (2.5%) in females and no single potentially prolactin-related adverse reaction in males were observed with a rate greater than 2%.

Schizoaffective Disorder

In a long-term maintenance trial of INVEGA SUSTENNA® in patients with schizophrenia (Study C50004) see Clinical Studies (14.2), elevations of prolactin to the above reference range (>13.3 ng/mL in males and >27.2 ng/mL in females) relative to open-label baseline at any time during the 15-month double-blind phase were noted in a higher percentage of patients in the INVEGA SUSTENNA® group than those in the placebo group in males (55.6% vs. 23.2%) and in females (44.2% vs. 29.5%). During the 15-month double-blind phase, 11 females (13.5%) in the INVEGA SUSTENNA® group had potentially prolactin-related adverse reactions (hyperprolactinemia N=3; blood prolactin increased N=4; libido decreased N=1; amenorrhea N=2; galactorrhea N=3; while 6 females (6.5%) in the placebo group had 8 potentially prolactin-related adverse reactions (hyperprolactinemia N=2; blood prolactin increased N=1; amenorrhea N=2; galactorrhea N=1). Six males (7.1%) in the INVEGA SUSTENNA® group experienced 9 potentially prolactin-related adverse reactions (hyperprolactinemia N=4; libido decreased N=1; erectile dysfunction N=1), while 1 male (1.2%) in the placebo group experienced adverse reaction (blood prolactin increased).

Prior to the 15-month double-blind phase (during the 32-week open-label phase of the long-term maintenance trial), the mean (SD) serum prolactin values at baseline were 14.8 (14.8) ng/mL in males (N=482) and 39.1 (44.6) in females (N=363). At the end of the open-label phase, mean (SD) prolactin values were 32.8 (17.2) ng/mL in males (N=279) and 72.4 (48.5) in females (N=239). During the open-label phase, 48.8% of females and 0.3% of males experienced elevations of prolactin above the reference range relative to baseline, and a higher proportion of females experienced potentially prolactin-related adverse reactions compared to males (10.5% vs. 9.0%). Amenoa (5.8%) and galactorrhea (2.8%) in females and libido decrease (2.8%) and erectile dysfunction (2.5%) in males were observed with a rate greater than 2%.

Potential for Cognitive and Motor Impairment

Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA SUSTENNA® (see Adverse Reactions). Antipsychotics, including INVEGA SUSTENNA®, have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.

Seizures

In the four fixed-dose double-blind placebo-controlled studies in subjects with schizophrenia, <1% (1/1200) of subjects treated with INVEGA SUSTENNA® experienced seizures. One pregnant woman, one who was widely known to be obnoxious and provocative in his behavior and universally disliked, is assaulted and beaten up by his tent-mates. Several of his ribs are broken, and he needs a medical evacuation in the morning by chopper to Brooke Army Medical Center.

Because this restorative urge to get-even is so universal, normal-
tive, and class-neutral, it’s arguably an instinctive reflex.

Wartime: So many assaults to set, so many ways to get even (a traumatized combat soldier’s story)

Not all the participants in the My Lai massacre became thugs. Some were, themselves, traumatized. Private Paul Meadlo refused Lt Calley’s order to murder the 60 or so Vietnamese men he’d gathered together under Calley’s order and who were now squatting together in a group. Calley, who ordered this mission in unmistakable frustration over his inability to stop Viet Cong attacks that had successfully and repeatedly killed his men before disappearing among the civilians in the area, insisted and became angry when Meadlo demurred. This was to be Calley’s retaliation, killing an entire village of men, women, and children. He gave Meadlo a direct order to shoot those villagers. Private Meadlo reluctantly attempted to obey but quickly broke down. In tears he handed his weapon to another trooper who continued the shooting.

Returning home most townspeople supported Meadlo’s participation in that crime. “Things like that happen in war,” one World War II and Korean War veteran assured him. “They always have and they always will.” “One has to obey one’s officer,” others said. His mother, however, understood. He was a good boy, she recalled with anger.
“He fought for his country and look what they done (sic) to him. Made him a murderer!”

All soldiers go through basic training during which one’s conscience, one’s better nature with its foundational ethics and values, become superceded by orders and a chain of command. Problems inevitably come when orders from above clash with principles from within and rules of engagement don’t help and you have to make your own decision. Which will you honor, order or principles? Which, by default, will you dishonor?

The story of that massacre at My Lai was only the tip of an iceberg.

The parts of that iceberg below-the-surface, the parts not talked about albeit impossible to forget and impacting many, involve not just fear but guilt. If those parts could speak you’d hear, “I shouldn’t have done that. I could have tried harder.” “I should have stayed.” “I could have prevented that.”

Such words of regret and remorse are clear indications of guilt.

Seeds of guilt are everywhere in the military during wartime. It doesn’t matter whether they were sown in the interest of showing off, bonding with buddies, or managing anxiety. Crimes are crimes, and guilt has its own agenda, the restoration of a balance—that-has-no-name. The upside? In the military, relief and reassurance are always

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**INVEGA SUSTENNA®** (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

**Table 6: Incidences of Adverse Reactions ≥2% or More of INVEGA SUSTENNA® Treated Patients (and Greater Than Placebo) with Schizophrenia in Four Fixed-Dose, Double-Blind, Placebo-Controlled Trials (continued)**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Placebo</th>
<th>INVEGA SUSTENNA® 234/39 mg (N=312)</th>
<th>INVEGA SUSTENNA® 234/156 mg (N=163)</th>
<th>INVEGA SUSTENNA® 78 mg (N=223)</th>
<th>INVEGA SUSTENNA® 234/234 mg (N=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agitation</td>
<td>11</td>
<td>15</td>
<td>12</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Anxiety</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Nightmares</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Percentages are rounded to whole numbers. Table includes adverse reactions that were reported in ≥2% or more of patients in any of the INVEGA SUSTENNA® dose groups and which occurred at greater incidence than in the placebo group.

- Placebo group is pooled from all studies included and excludes all donated or gluteal injection depending on study design.
- Initial delirium injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks those dose groups (78 mg, 234 mg and 156 mg) are from studies involving gluteal injection. (See Clinical Studies (14.1) in Full Prescribing Information).

Adverse reactions for which the INVEGA SUSTENNA® incidence was equal or less than placebo are not listed in the table, but included the following: dyspnea, psychotic disorder, schizophrenia, and tremor. The following terms were combined: somnolence/exsanguination, development/brachial pain, abdominal discomfort/abdominal pain/rectal pain/sore abdominal pain/dysphagia/discontinuation, and tachycardia/tinnitus/tachycardia/heart rate increased. All injection site reaction-related adverse reactions were collapsed and are grouped under “Injection site reactions.”

Other Adverse Reactions Observed During the Clinical Trial Evaluation of INVEGA SUSTENNA®

The following list does not include reactions: 1) already listed in previous tables or elsewhere in labeling, for which a drug cause was remote, 3) which were so general as to be uninformative, or 4) which were not considered to have significant clinical implications.

- **Cardiac disorders:** atrioventricular block first degree, bradycardia, bundle branch block, conduction disturbances, postheparin capillary leak syndrome, thyrotoxicosis
- **Ear and labyrinth disorders:** vertigo
- **Eye disorders:** eye movement disorder, eye rolling, oculogyric crisis, vision blurred
- **Gastrointestinal disorders:** constipation, dysphagia, flatulence, salivary Nausea
- **Hypersensitivity:** urticaria
- **Metabolism and nutrition disorders:** decreased appetite, hyperinsulinemia, increased appetite
- **Musculoskeletal and connective tissue disorders:** arthralgia, joint stiffness, muscle rhabdomyolysis, muscle spasm, muscle tightness, muscle twitching, nuchal rigidity
- **Psychiatric disorders:** insomnia, libido decreased, restlessess
- **Reproductive system and breast disorders:** amenorrhea, breast discharge, breast enlargement/breast swelling, breast tenderness/breast pain, ejaculation disorder, erectile dysfunction, galactorrhea, gynecomastia, menstrual disorder, menstruation delayed, menstruation irregular, psychic sexual dysfunction
- **Respiratory, thoracic and mediastinal disorders:** nasal congestion
- **Skin and subcutaneous tissue disorders:** drug eruption, pruritus, pruritus generalisatus, rash, urticaaria

**DERMATOLOGIC DISORDER DIFFERENCES**

An examination of population subgroups in the double-blind placebo-controlled trials did not reveal any evidence of differences in safety on the basis of age, gender, or race alone; however, there were few subjects 65 years of age or older.

**Adverse Events by System Organ Class**

**INVEGA SUSTENNA®** (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

**Table 7: Extrapyramidal Symptoms (EPS) Assessed by Incidence of Rating Scales and Use of Anticholinergic Medication – Schizophrenia Studies in Adults**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>INVEGA SUSTENNA® 234/39 mg</th>
<th>INVEGA SUSTENNA® 234/156 mg</th>
<th>INVEGA SUSTENNA® 78 mg</th>
<th>INVEGA SUSTENNA® 234/234 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Scale</strong></td>
<td>Placebo</td>
<td>(N=262)</td>
<td>234/39 mg (N=223)</td>
<td>234/156 mg (N=223)</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>9</td>
<td>12</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Akathisia</td>
<td>5</td>
<td>7</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Use of Anticholinergic Medications</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

For Parkinsonism, percent of subjects with Simpson-Angus Total score ≥ 3 at endpoint (Total score defined as total sum of item scores divided by the number of items).

- **For Akathisia, percent of subjects with Barnes Akathisia Rating Scale global score ≥ 2 at endpoint**.
- **For Dyskinesia, percent of subjects with a score ≥ 3 on any of the first 7 items or a score ≥ 2 on two or more of any of the first 7 items of the Abnormal Involuntary Movement Scale at endpoint**.
- Per cent of subjects who received anticholinergic medications to treat EPS.

**Table 8: Extrapyramidal Symptoms (EPS)-Related Events by MedDRA Preferred Term – Schizophrenia Studies in Adults**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>INVEGA SUSTENNA® 234/39 mg</th>
<th>INVEGA SUSTENNA® 234/156 mg</th>
<th>INVEGA SUSTENNA® 78 mg</th>
<th>INVEGA SUSTENNA® 234/234 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Percentage of Subjects</strong></td>
<td>Placebo</td>
<td>(N=262)</td>
<td>234/39 mg (N=223)</td>
<td>234/156 mg (N=223)</td>
</tr>
<tr>
<td><strong>EPS Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Hypokinesia</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Tremor</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Dystonia</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Re-entry: The returning veteran’s predicament

While veterans are mustered out of the military none are mustered back into civilian life. The latter has traditionally been a patchwork of as-needed processes. The Navajo Nation is the one exception I’m aware of, although I suspect all the Indian Nations are exceptions. The Diné (Navaho) spiritual leaders have traditionally stood ready to provide cleansing, blessing, and soul healing ceremonies to men and women returning from war. They have always understood that a balance must be restored to the returning warrior.

How do the rest of us address that imbalance—that has-no-name, those wounds to our self-respect, self-worth, and self-confidence? How do we explain our scars of guilt, especially those that don’t become evident right away? Or explain why returning to the battlefront and our comrades there is a good idea? No wonder so many vets coming home find it impossible to return to what and who they were. Their better nature has been in lock-down for so long its surfacing now is not only inconvenient and a burden, it’s...
of self-affirmation, redemption, and finally peace. “I deserve to die,” you’ll write in your note, your final statement, to make clear that you know what you’re doing and have yourself under control. You have last restored a balance. Your Self—is—at last—getting even.

REFERENCES
Disability and the Concept of Return to Work

Barbara Long, MD, PhD, Christopher Flinton, MD, Andrew O. Brown, MD, Sean Sassano-Higgins, MD, and David “Daven” E. Morrison, MD, for the Committee on Work and Organizations, GAP

This article discusses the return to work plan as a solution to the clinical and systemic problems arising from psychiatric disability. The systems that govern administration of “disability” benefits should be guided by:

1. Truth and resolution. The treating psychiatrist is relieved of the fear that he or she acknowledges the truth, ie, the presence of (or potential for) preserved work capacity, his or her patient will suffer.

2. Work-reward relationship. The patient is supported for engaging in behaviors that are reasonably expected to culminate in restoration of the work-reward relationship and a healthy patient- psychiatrist-workplace system.

Among many problems inherent in the American disability system is the medicalization of work stress and its inappropriate conversion into psychiatric diagnoses, which implies impaired or loss of ability to function. This “medicalization” decouples the normal work-reward dynamic in a way that reinforces disability-seeking behaviors. Potential solutions to problems of disability require a multisystemic approach. In the psychiatrist’s office, solutions include the paradigm of “truth and resolution”; in practice, the recoupling of work and reward as a goal, and support for disability reform (eg, the use of standardized functional assessments) but with careful consideration of its possible consequences.

Psychiatrists’ challenges to disability claims

There are challenges to the psychiatrist’s support of a patient’s claim for disability. While it seems obvious that a psychiatrist simply wants to diagnose accurately and make appropriate recommendations, the situation around disability is wrought with pitfalls and is quite complicated. The addition of an economic, potentially income-providing relationship forever changes the treatment dynamic. Supporting a disability claim could mean both administrative (in the form of documents initially justifying, then recertifying the claim) and legal (requiring other documentation and testimony related to the assessment) liabilities. Withholding support for disability benefits could lead to anger, violence, medical board complaints, negative online reviews, or litigation on the part of the patient. The psychiatrist might also feel burdened with significant counter-transference guilt.

A solution to this is “truth and resolution.” These best practices allow psychiatrists to conduct patient care in such a way that they can acknowledge the objective reality of return to work. It includes recognizing the pitfalls of misdiagnosis as well as potential excessive physical, emotional, and financial expense to the patient, the employer, family members, and medical specialists and administrators. These expenses can include unnecessary workups, treatment referrals, and cost to systems as benefits are paid and work production is lost, and the beginning of a process that can result in lifetime disability for a patient. “Truth and resolution” as a treatment approach ensures that providers “first do no harm.” Importantly, it requires training in occupational assessment, which has been a noted weakness among psychiatrists. This training would include review of the difference between impairment and disability, discerning patient job requirements in interviews, consideration of somatic symptom disorders, and curricula that addresses the implications of a patient’s engagement with a disability system and prognostic factors affecting a return-to-work.

The work-reward relationship

The idea of promoting patient behaviors oriented toward restoring the work-reward relationship is an intuitive one which has been investigated in studies of disability and return-to-work across several medical specialties. Some approaches have focused on workplace accommodations. A 1998 review found that patients offered modified work after a workplace injury were about two times more likely to return-to-work than those who were not.1 A 2005 systematic review found that the duration of disability for patients with musculoskeletal and other pain conditions was reduced by offers of work accommodations and communications between medical providers and employers.2

Other approaches to the return-to-work have considered stress and perception of support at work. A 2002 literature review found that a “non-supportive work environment” was associated with disability or retirement for cancer survivors.3 A later study found that “perceived employer discrimination” led to lower return-to-work rates for breast cancer survivors.4 Conversely, a 1998 prospective cohort study found that strong social support was a feature of patients who returned to work after lower extremity fractures.5 This suggests that interventions aiming to encourage actual or perceived support in the workplace could improve chances of a patient’s return.

Investigators have researched therapy when high work stress is identified. In a small Dutch study, patients with adjustment disorders were more likely to return to work and return to work earlier if they were treated with an activating, stress awareness training much like stress-inoculation training.6 Psychiatrists in return-to-work and disability scenarios have also have some limits. Dasinger and colleagues found that a physician’s proactive communication consisting of understanding, questions, and recommendations about the patient’s work and workplace was associated with patients’ return to work within the first 30 days of disability for low back pain. Moreover, a physician’s explicit recommendation for returning to work was associated with a nearly 60% increase in return-to-work rates in patients with more than 30 days of disability. Unfortunately, these effects disappear in the first case and nearly lose statistical significance in the latter case when workers report “high job strain” in the workplace.

Changes in assessment

In addition to changes in clinical approaches between doctor, patient, and employer, government systems have attempted systemic changes in assessments in attempts to reform disability systems. In this process, however, significant consideration must be paid to repercussions of changes made to vital disability benefit systems. In recent years, the United Kingdom has adopted a new functional assessment tool, the Work Capability Assessment (WCA). This tool has been used not only to assess new disability claims, but also to reassess more objectively over 1 million claims who had already been granted disability benefits.

Recently published research reveals that the WCA reassessment process was associated with increases in behavioral health symptoms, antidepressant prescribing, and completed suicides.7 To date, other nations conducting similar disability system reform (eg, the Netherlands, Australia) have not reported such trends. Still, the far-reaching social impact of such programs must be considered before the implementation of systemic disability reform.

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Managing Agitation Associated With Dementia

Marc Agronin, MD

Every clinician who works with individuals who have dementia—what we now refer to as major neurocognitive disorders—encounters states of agitation that can worsen function, pose safety concerns, and increase caregiver stress. It can be both confusing and frustrating to understand and manage these behaviors, but there are several approaches that can make all the difference.

Agitation has been defined by the International Psychogeriatric Association as involving excessive motor activity or verbal or physical aggression that causes emotional distress and excess disability for the affected person, and impairs relationships, social functioning, and activities of daily living. These behaviors are commonly part of a larger constellation of behavioral and psychological symptoms that are associated with all major forms of dementia, including mania, depression, anxiety, apathy, and psychosis. Agitation has many medical, medication-related, psychiatric, psychological, and environmental causes—but underlying all of them is a damaged and vulnerable brain that is less able to properly regulate affect and respond to challenges in an organized manner. Specifically, agitation has been associated with damage to key brain nuclei that regulate cholinergic and serotonergic pathways.

A thorough medical and psychiatric evaluation as well as a review of the circumstances before, during, and after periods of agitation may reveal both enduring causes, such as an underlying depression or the use of a stimulating medication, and transient triggers such as boredom, hunger, or a noxious stimulus in the environment. The DICE algorithm developed by Kales and colleagues is an excellent tool for clinicians as it guides them to describe the behaviors in detail, investigate potential causes, create a team approach to implement various treatments, and then to evaluate the relative success of the interventions.

Management of agitation involves three basic approaches. The first is to identify and address potential causes. The second is to implement behavioral approaches, ranging from increased therapeutic activities (eg, art or music therapy) to redirecting and refocusing the person to more positive activities, especially ones that meet the basic function of the agitation in the first place. The third approach involves the use of psychotropic medications that are targeted towards underlying factors such as anxiety or psychosis, or primarily aimed at reducing agitation by calming brain activity. Benzodiazepines and trazodone are often used emergently but can cause sedation and increase the risk of falling. Antidepressants are being studied since their modulation of serotonergic activity is aimed at reducing impulsivity and aggression. Anticonvulsants have been used to inhibit brain activity causing agitation, but with limited scientific support.

Antipsychotic medications have been widely studied, and while there is a fair amount of evidence suggesting modest benefit for agitation, there are also significant safety concerns, including the black box warnings for an increased risk of death. With any pharmacologic approach, the goal is to use the least amount of medication for the shortest time possible. Finally, there are several approaches that can be used to inhibit brain activity including the black box warnings for an increased risk of death. With any pharmacologic approach, the goal is to use the least amount of medication for the shortest time possible. Finally, there are several approaches that can be used to inhibit brain activity causing agitation, but with limited scientific support.

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Agitation has been associated with damage to key brain nuclei that regulate cholinergic and serotonergic pathways.
RESEARCH UPDATE

Maternal Infection During Pregnancy: Increased Risk of Psychosis in Offspring

Brian Miller, MD, PhD, MPH

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aternal viral infection during pregnancy is a risk factor for schizophrenia.1 But there has been relatively less research on the association between maternal bacterial infection during pregnancy and psychosis risk. Maternal infections may include forms of sexually transmitted disease (STD), some viral respiratory and bacterial infections, toxoplasmosis. One study found that maternal bacterial infection was associated with a two-fold increase in schizophrenia risk.2 Findings from another study suggested an association between pyelonephritis and risk of psychosis.3 Moreover, gestational immune disruption may disproportionately affect males with regards to psychosis risk.4

Lee and colleagues5 investigated the association between maternal bacterial infections during pregnancy and psychosis risk, including potential moderating effects of sex and parental history of psychiatric illness. They considered 16,188 live births enrolled between 1959 and 1966 at the Boston and Providence sites of the Collaborative Perinatal project, currently known as the New England Family Study. Parents and offspring (who are now in their 50s) with psychotic disorders were identified.

A total of 15,421 participants were included in the final analytic sample. Data on infectious disease exposures were collected at regular prenatal visits. The primary exposure variable was any bacterial infection during pregnancy. If women had multiple infections, they were counted only once. Infections affecting more than one major organ system were defined as multisystemic (eg, sepsis), and those affecting one system were defined as localized (eg, vaginitis).

Cohort members with psychosis were identified at ages 32 to 39 years through a systematic follow-up. Affected parents and offspring were identified via record linkage, direct interview, and subject self-report. After systematic follow-up and structured clinical interviews, 116 adult offspring were found to have a nonorganic psychotic disorder (n = 52 schizophrenia or schizoaffective disorder, depressed type; and n = 53 schizoaffective disorder, bipolar type, or mood disorder with psychotic features; n = 11 delusional disorder, brief psychotic disorder, or psychotic disorder not otherwise specified).

The researchers included maternal race, study site, maternal education, parental socioeconomic index, year and season of birth, parental psychiatric history, and maternal viral infection during pregnancy as covariates. Logistic regression was used to estimate the odds of psychosis for maternal exposure to bacterial infection during pregnancy, adjusting for these covariates. The authors also examined effect modification by offspring sex and parental mental illness. They also performed sensitivity analyses considering only confirmed bacterial infection (by antibiotic treatment and/or physician diagnosis).

The researchers identified 399 (3%) multisystemic and 3191 (21%) localized infections during pregnancy. Localized infections included vaginitis, urinary tract infections, pneumonia, syphilis, gonorrhea, and maternal infection (OR = 2.6; 95% CI, 1.6-4.2), whereas there was no difference in females (OR = 1.0; 95% CI, 0.5-1.9). The pattern of findings was similar when considering localized bacterial infections. Additionally, in sensitivity analysis, the association remained significant and with slightly greater magnitude. By contrast, the association was not moderated by parental mental illness.

The authors concluded that maternal bacterial infection during pregnancy was significantly associated with the development of schizophrenia and related psychoses among offspring, with stronger effects for multisystemic than localized infections, and in males. Findings underscore the potential role of maternal bacterial infections during pregnancy in the etiology of psychosis.

The strength of the study is the systematically collected prospective data in this birth cohort. The authors noted potential misclassification of exposure and interactions between infection and other non-biological factors (eg, socioeconomic status) as study limitations.

The bottom line

Maternal bacterial infections during pregnancy are associated with risk of psychosis in the offspring, which is moderated by the severity of infection and gender. Future, larger samples are needed to address components of the potential etiologic pathway regarding this connection, including gestational timing of exposure and sex-specific transmission. Replicated findings would underscore the need for public health and clinical effects to reduce psychosis risk by preventing and managing bacterial infection in pregnant women.

Dr Miller is Associate Professor of Psychiatry, Department of Psychiatry and Health Behavior, Augusta University, Augusta, Georgia. He is the Schizophrenia Section Editor for Psychiatric Times. The author reports that he receives research support from Augusta University, the National Institute of Mental Health, the Brain and Behavior Research Foundation, and the Stanley Medical Research Institute.

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According to the Federal Emergency Medical Treatment and Active Labor Act (EMTALA), patients with acute psychiatric conditions that make them either a danger to themselves or a danger to others are considered to have emergency medical conditions (EMCs). Because EMCs are legally equivalent to serious physical ailments, they must be evaluated in emergency departments and cannot be discharged until they are stable and safe, with no further emergency danger.

Although high-acuity psychiatric crises qualify as medical emergencies, the general emergency department might not be the best location to care for these patients. With the close quarters of the typical ED, its strange lights and sounds, with busy uniformed personnel rushing about, this environment might be disruptive or even worsen symptoms for those suffering from paranoia, despondency, or anxiety. An alternate, hospital-level emergency setting for crisis patients would be preferable. In response, many health systems and communities nationwide have created high-acuity capable psychiatric emergency programs.

Hospital-level psychiatric emergency programs go by different names, including Psychiatric Emergency Services (PESs), Comprehensive Psychiatric Emergency Programs (CPEPs), Clinical Decision Units (CDUs), and more recently, Emergency Psychiatry Assessment, Treatment, and Healing units (EmPATH unit). Along with different names, sites might even consider themselves to be a community location rather than part of a general hospital, but all could be considered to provide an EMTALA-compliant, hospital-level equivalent site that can work with most patients regardless acuity of their symptoms. These programs can be part of a general hospital campus, or on the license of a general hospital but located away from the main hospital, or on free-standing psychiatric campuses. They differ in size, scope of services, and environment.

Most programs share the same general philosophy for prompt intervention and targeted, compassionate care: “The Six Goals of Emergency Psychiatry” (also known as “Zeller’s Six Goals”)

1. Exclude medical etiologies of symptoms and ensure medical stability
2. Rapidly stabilize the acute crisis
3. Avoid coercion
4. Treat in the least restrictive setting
5. Form a therapeutic alliance
6. Formulate an appropriate disposition and aftercare plan.

Different approaches on how to fulfill these goals has led to various models of emergency psychiatric care facilities, but while no two sites are exactly alike, some basic categories have become evident.

This article is the second in a three-part series on hospital-level psychiatric emergency programs. The first described the differences between hospital-based psychiatric EDs and community crisis centers. This article highlights several different operating models of hospital-level crisis care and their impressive outcomes.

Psychiatric Emergency Services or Comprehensive Psychiatric Emergency Programs

Most commonly, a PES (also known as CPEP in some locations) is a distinct hospital operation solely dedicated to managing and treating psychiatric emergencies. Most can accept patients around the clock, either directly from the field via police or ambulance; other times individuals self-present. Some units also may have mobile crisis teams onsite as well as bridge clinics to ensure quick follow-up appointments for discharged patients.

These programs are often affiliated with major academic hospitals or government health systems and work closely with a nearby medical emergency department. It is not unusual for psychiatry residents to provide much of the direct care under the supervision of attending psychiatrists. While numerous variations exist, many programs have individual rooms for patients, similar to an inpatient psychiatric ward, but will attempt to limit stays to less than 24 or 48 hours.

PES programs are considered emergency outpatient programs. They are staffed by psychiatric physicians, advanced providers, nurses, and therapists. Use of physical restraints and injected medication can occur, but they typically occur at lower rates than a medical ED.

In sharing his experiences, Shalilinder Singh, MD, Medical Director of the Psychiatric Emergency Room at Metropolitan Hospital in New York City, said: “The Psych ER here provides a vital service to an underserved and often overlooked patient population.”

“As an emergency psychiatrist, I bear witness on a daily basis to gross disparities in access to care for patients who desperately need treatment,” noted Suzanne Bird, MD, who leads the Acute Psychiatric Service in the Emergency Department of Massachusetts General Hospital in Boston. “Being an effective and ethical emergency psychiatrist requires relentless advocacy on behalf of the vulnerable populations we serve.”

Regional dedicated psychiatric emergency programs

While many PES programs are part of a single hospital and have a defined local catchment area of patients, some are designed to be the center of a hub-and-spoke, large district system, a model known as a Regional Dedicated Psychiatric Emergency Program. The prevailing design for these programs is of a stand-alone psychiatric campus, including inpatient beds onsite along with the emergency psychiatric unit. It may feature other onsite programs as well, such as outpatient clinics, drop-in counseling, and partial hospitalization.

Such facilities will accept all emergency psychiatric patients from a widespread geographic area, both directly from the field. They also will receive transfers from a number of area EDs. These centers are somewhat analogous to the relationship between a major trauma center and smaller local hospitals: they are the higher-level-of-care ED that accepts patients with psychiatric emergencies from other hospitals. Successful regional dedicated programs are in operation in California and Arizona, and at the Unity Center in Portland, Oregon.

Margaret Balfour, MD, PhD, speaks very positively about the Crisis Response Center in Tucson, Arizona, a stand-alone regional psychiatric program that sees more than 1250 adults and children every month, stabilizing over two-thirds without needing inpatient admissions, and alleviating local ER psychiatric patient boarding. “There are a lot of crisis facilities that don’t take the most acute patients—the highly agitation or violent,” she said. “We want them at our facility, instead of an ED or jail, because we believe that with our staff’s expertise and physical space, we have a much better chance of de-escalating persons in crisis and getting them the treatment they need. It sometimes seems like it’s easier to get into heaven than a psychiatric facility. We try not to put up barriers and instead instill a culture of figure out how to say yes rather than look for reasons to say no.”

Tarak Trivedi, MD, MS, an Emergency Medicine physician at University of California, Los Angeles, published a study in the past year showing that of over 22,000 direct ambulance transfers to a regional psychiatric ED rather than the traditional destination of medical EDs, only 0.3% required later transport to a medical ED. “Use of regional, stand-alone, psychiatric emergency services are a safe, efficient, and patient-centered approach to managing patients in psychiatric crisis,” he reported.

EmPATH units

Although proven effective, not every community has the patient volume, funding, personnel, or academic support to operate an expensive 24/7 PES model. Due to recent innovation, distinct hospital-level psychiatric emergency program can still be made available. This scalable solution, known as the EmPATH unit, is now being implemented at sites across North America.

An EmPATH unit is a discrete, independently run program with its own staff, which operates in concert with the ED and under the same hospital license. Because patients are referred only after a medical screening exam in the general ED, a licensed psychiatric provider may not need to be on-site at all times. An on-demand telepsychiatrist can evaluate patients and commence treatment promptly in a cost-effective way, which can result in quick relief of patient distress.

In the most common EmPATH unit model, patients are initially evaluated in a medical ED to rule out or stabilize emergency medical conditions, and then immediately moved to the more therapeutic EmPATH setting.

EmPATH units contain a layout where prompt medical intervention and supervision combine with the best features of community wellness and recovery programs. Individuals are treated concurrently in a large common milieu room, where staff are always interspersed with patients for constant and safe observation and reassurance. Rather than being assigned to a fixed bed, patients choose their own sleeper chairs or recliners, where they can sit up to participate in activities, group or individual therapy, or fold flat to nap. Unlike the necessarily confining arrangement of a typical ED, this design allows individuals to relax, feel...
comfortable, and move about freely. Easily accessible stations allow patients to get food, drink, or linens without requiring staff involvement or permission. An overall focus on avoiding coercion and causes of frustration has resulted in dramatically lower incidence of physical restraints, aggression, and assaults than more traditional units or EDs, even with a highly acute patient population under involuntary evaluation for dangerousness to self and/or others.7

Now operating in two dozen sites around the nation, the EmPATH unit model contributes significantly to the reduction of ED overcrowding and throughput times by providing prompt transfer to an appropriate psychiatric level of care. Sites typically report 75% or higher avoidance of psychiatric hospitalizations in patients who would have been admitted in more standard ED systems.

EmPATH units are presently working on any scale from eight to 48 chairs; in urban places like Los Angeles or rural settings like Lafayette, Indiana; in academic hospitals or at small community facilities. And given the open floor plan, they can often be created by remodeling an underutilized large room such as a former storage space or shuttered clinic with reasonable conversion costs.

As the Chair of Psychiatry at the Billings Clinic in Montana, Eric Arzubi, MD, led the creation of an EmPATH Unit in April 2018, which today accepts both adults and children, and has led to a substantial reduction in area psychiatric ED boarding and inpatient utilization.

“A well-designed, well-managed EmPATH unit creates value for multiple stakeholders and, most importantly, it improves patient care,” he explained. “At a time when there is a perceived shortage of psychiatric hospital beds, a local EmPATH unit reduces the demand for such beds, allowing the health care system to make more effective use of that precious resource.”

He added, “Public and private payers should be jumping all over this model of care. We found that, due to a lower total hospitalization rate and a decreased 30-day readmission rate, insurers likely saved more than 20% on psychiatric inpatient hospitalization costs. This, in my mind, is among the most powerful examples of value-based care in medicine.”

Taylor Ford, MSW, LISW, is the Assistant Clinical Director of the EmPATH unit which opened in October 2018 at the University of Iowa Hospitals and Clinics. Their 12-chair program has led to a nearly 80% reduction in ED boarding hours, and they have yet to have their first episode of implementing physical restraints, despite a very high-acuity population. “This allows for a more thorough psychiatric evaluation, in which we can work more closely with the individual to develop a safe and supportive plan in a comfortable setting that puts the patient’s needs above all else,” she said. “I can’t tell you how many patients have personally told me that this is the best care they’ve ever received in a psychiatric setting, and that’s exactly what we’re here for.”

**Conclusion**

As hospital-based psychiatric emergency programs around the country demonstrate the ability to minimize ED boarding, provide cost-savings, and improve patient outcomes and clinician satisfaction, the challenge will be to keep these models of psychiatric care self-supporting.

In the next and final article in this series, we will review reimbursement issues that psychiatric EDs face and provide strategies to overcome them.

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CONVERSATIONS IN CRITICAL PSYCHIATRY

S. Nassir Ghaemi, MD, MPH: Beyond Pragmatism in Psychiatry

**Awais Aftab, MD**

The aim of Conversations in Critical Psychiatry is to engage prominent individuals within and outside psychiatry who have made meaningful critiques of psychiatry and have offered constructive alternative perspectives to the current status quo.

I first got exposed to Dr Ghaemi’s ideas about 7 years ago through his critical commentaries on DSM in Psychiatric Times. I subsequently discovered his wealth of writings on philosophical frameworks in psychiatry as well as how these conceptual issues have “real world” implications when it comes to the understanding, classification, and treatment of mood disorders.

A common refrain in Dr Ghaemi’s work has been that psychiatry has lost its way by pursuing a pragmatic, atheoretical framework of understanding mental illness (i.e., progress requires going beyond pragmatism in search of truth). Over the years I have found his ideas to be highly thought provoking and engaging and his opinions have been instrumental in shaping my own views on psychiatry. Dr Ghaemi exemplifies the spirit of a maverick thinker and wields his nuanced understanding of history, philosophy, and research methodology to challenge conceptual errors rampant in the field.

**DR GHAEMI:** I wouldn’t say that characterization is correct. “Depression,” if by that term is meant “melancholia” in older usage, was seen as severe and episodic and common in Kraepelin’s work. The prognosis was not good in the sense that it was recurrent: each episode improved, but then recurred, and suicide was frequent. Neurasthenia reflected what was later termed neurotic depression. It was chronic and rampant in late 19th century America. I think American psychiatry simply is ignorant of the history of mental illnesses.

**DR AFTAB:** You have long crusaded against antidepressant use in bipolar disorder, arguing that these drugs lack efficacy and hinder recovery in patients with bipolar disorder. I think psychiatry’s official position has slowly shifted in that direction (at least for bipolar I), but antidepressants still remain widely prescribed for bipolar disorder, and it is common to hear clinicians say, “I know what the research says but antidepressants are clearly helping my bipolar patients.” What explains this persistent notion of anecdotal efficacy in clinical practice?

**DR GHAEMI:** Clinicians often base their opinions on their experience, not realizing that—as the old saying goes—half of what they see is false; they just don’t know which half. The same reasoning was the basis for the medical profession’s wide acceptance for two millennia of the four-humor theory and of bleeding.

**DR AFTAB:** In On Depression, you’ve argued that sometimes depression is a medical disease but often it is not. You write: “It has become de rigueur to state that depression is a disease. I would say the opposite: most depression is not a disease. The part of it that is recurrent and episodic, or due to a specific medical cause, is disease. But the part that is not episodic, that is chronic and admitted with anxiety, becomes indistinguishable from personality.”

From your perspective, what do you mean when you call something a “disease”? In cases when depression is not a disease, should it be considered a “disorder”?

**DR GHAEMI:** The word “disorder” is meaningless. It is purposefully vague, introduced by DSM-III for every one of its 292 diagnoses in an attempt to be atheoretical about the causes or nature of those diagnoses. DSM-III leaders in 1980 wanted to reject psychoanalytic interpretations, and they did not want to commit to biological causes (diseases), so they replaced the earlier term “reaction” with the purposefully vague term “disorder.”

**DR AFTAB:** Disorder means nothing and everything: anyone can interpret it as they like. That kind of anarchic eclecticism is exactly what DSM-III intended, and psychiatry has inherited for 40 years. The term disease refers to a biological cause of a physical illness. Sometimes depressive states have such causation, as in manic-depressive disease; sometimes they do not. The term “major depressive disorder” vaguely combines many different depressive presentations, and thus, as a whole, means nothing scientifically.

What many clinicians don’t understand is the importance of controversy, bias, that all their experience is confounded by the influence of other factors that they cannot know or control, foremost among these being natural history of recovery in an episodic illness. Each bipolar depressive episode resolves naturally, usually within months. Randomized placebo-controlled data show that antidepressants and placebo produce notable and equal improvement. Placebo is a stand-in for that natural history. Instead of giving nature the credit, as the randomized clinical trials prove, clinicians credit the drugs: a classic mistake of the unscientific practice of medicine.

**DR AFTAB:** Even outside of bipolar disorder, you are not a huge fan of antidepressants. Recently when the Cipriani and colleagues’ meta-analysis was published, you wrote an editorial for Medscape commenting on how the results actually confirm what previous studies have shown, that over-all the benefit from antide-pressants (over and above placebo) falls short of clinically meaningful. It is hard to imagine a group of medications whose efficacy has been as closely scrutinized as that of antidepressants, and yet despite the largest meta-analysis ever conducted, doubts about efficacy remain. Why is this issue so controversial and divisive?

**DR GHAEMI:** The studies are replicated and clear: the effect size of benefit with antidepressants overall in MDD...
is small, and short of the cut-off for clinically meaningful benefit. On the other hand, the natural history of depressive episodes is that they resolve and so clinicians see improvement. They don’t realize that the benefit occurs almost equally with non-drug intervention (placebo). At root, the problem is an unwillingness to accept the verdict of science, as opposed to one’s wishes or beliefs.

The psychiatric profession appears to identify its medical legitimacy with the claimed efficacy of its drugs. There’s no reason to claim this equivalence. In fact, we hurt our legitimacy with the public and with our medical colleagues, when we cling to our treatments excessively. This process is no different now with drugs than it was half a century ago in American psychiatry with psychoanalytic extremism. The basic psychiatric attitude is the same, even though the treatments are different.

We need to change our basic philosophy and accept a self-critical attitude that submits to scientific judgment, with humanistic sensitivity. This basic philosophy is as old as Hippocrates, and reflects being a good doctor, period. It’s the right way to defend our medical and scientific legitimacy.

DR AFTAB: The long-term efficacy data for antidepressants in MDD are even weaker. What is your approach to antidepressant maintenance treatment in practice?

DR GAEMI: Antidepressants have modest short-term symptomatic benefit acutely, like aspirin for fever. They do not prevent depressive episodes in a definitive manner (ie, they are not disease-modifying). In my practice, I prefer to use them for the short-term, but routinely not long-term.

Other agents, especially lithium and possibly lamotrigine, have better evidence for depressive episodes, ie, have long-term disease-modifying effects. Antidepressants are analogous, in my view, to steroids in conditions such as multiple sclerosis: useful in an acute episode, but not preventive. Agents like lithium are disease-modifying, less relevant for active symptoms but indispensable for the underlying disease itself.

DR AFTAB: Given your clinical and research experience, what are your thoughts on the various approaches to new ideas such as mixed syndromes in depression?

DR GAEMI: The views here are strictly my own. There are five major players in these debates: clinicians, academicians, the insurance industry, the FDA, and the pharmaceutical industry. Clinicians, the insurance industry, and the pharmaceutical industry are motivated by the profit motive, at least in part. The FDA is not so motivated but is affected by political influences (ie, the pharmaceutical lobby’s influence on Congress).

Academia’s motivations are complex—they believe what they want to believe with little outside influence. Such academic freedom is good and bad, since one is free to continue to believe untruths, instead of seeking the truth. With new ideas such as mixed states, the groups that are closest to economic influences seem to be the most pragmatic. This utilitarian attitude can be harmful, but it also is flexible, and open to new ideas.

In contrast, academia is often a major obstacle because there is no disease (but how can we demonstrate that one construct is more valid than another? Has our notion of validity made any progress since Robin and Guze’ presented their criteria in 1970?

DR GAEMI: This is a common claim in defense of the theory that underlies DSM-III through DSM-5. It’s a self-prophesying folly: unscientific diagnostic constructs are used to claim that no definitive scientific validation can be made of them. In medicine, only psychiatry engages in this kind of epistemological solipsism. The brain can succumb to diseases, and these diseases can have psychological symptoms. Our job is to identify those diseases, not to create rationalizations why we shouldn’t search for them.

Robins and Guze had good perception: since we had no clear pathological basis for any psychiatric disorder, we could use five lines of evidence (symptoms, course, genetics, biological markers, treatment), which, if they pointed in the same direction, would support the validity of a disease. This is the same rationale as Kraepelin’s emphasis on course of illness, not symptoms, as the basis of diagnosis. It’s also consistent with traditional medical science: symptoms vary among all medical illnesses, but combination with course and laboratory markers validates diagnosis.

There are many medical conditions in which no clear external cause or pathology is known, including seizure disorders, migraine, ulcerative colitis, rheumatoid arthritis. In psychiatry, this approach proved very successful with the carefully defined clinical syndrome of general paresis of the insane, which was later found to correlate with the identification of treponema pallidum. Many DSM advocates claim that things are different now; current diseases are harder to define. Maybe so, maybe not. But we’ll never know if we keep using socially constructed DSM definitions, as opposed to making an effort to find the truth.

DR AFTAB: If Robert Spitzer had never created DSM-III, do you think the field of psychiatry would be in a better or a worse place today? In other words, do you see the legacy of DSM as largely beneficial or harmful?

DR GAEMI: I have no doubt psychiatry would have been better off without DSM-III and, more importantly, DSM-IV and DSM-5. The dictionary of a common language became a fundamental Bible that we all have to believe and buy. Psychiatry has been frozen in 1980, hence the absence of progress since that time is no surprise. DSM’s legacy has been largely harmful.

DR AFTAB: Thank you!
An Overview of Atypical Antipsychotics for Bipolar Depression

Chris Aiken, MD

For most patients, bipolar is a disorder of depression. It’s here that they spend the majority of their days, so an atypical antipsychotic that has benefits in depression is usually the best choice.

The atypical antipsychotics are complex drugs. No two have the same profile, and the line between their receptor profile and clinical effects is a hard one to follow. Only four are FDA-approved in bipolar depression: cariprazine (Vraylar®), lurasidone (Latuda®), olanzapine-fluoxetine combination (Symbyax®), and quetiapine (Seroquel®). The Table provides dosage ranges for the four atypical antipsychotics that are FDA-approved for bipolar depression. Most of the other atypical antipsychotics have been tried but failed to show efficacy in bipolar depression, including a few that work statistically speaking, OFC may be the most effective therapy for acute bipolar depression, with a number needed to treat (NNT) of 2 compared with 5 to 11 for other FDA-approved atypical antipsychotics.

Olanzapine does not treat depression on its own so it requires the fluoxetine component to work. This is a potential drawback because fluoxetine may worsen manic or mixed symptoms. The prescription can be written as a single combo pill, which helps some patients save on their copays, or as the two medications, which is cheaper for patients who pay full price for the medicine. Weight gain and metabolic adverse effects are also significant risks with this medicine, but they can be ameliorated somewhat with metformin. This anti-diabetic agent has the best preventative effects for weight gain on atypical antipsychotics, and it works better when started earlier (500-1000 mg/d with food).

Although most meta-analyses rank OFC at the top of the efficacy list in bipolar depression, the story is different in unipolar depression, where its efficacy usually ranks near the bottom among atypical antipsychotic augmentation agents.

Quetiapine (Seroquel) is FDA-approved for both manic and depressed episodes in bipolar disorder. Moreover, it may improve sleep quality and comorbid anxiety. Quetiapine has favorable rates of akathisia and extrapyramidal effects. However, quetiapine’s adverse effects, particularly sedation and hypotension, are a common cause of discontinuation and emergency department visits. Weight gain and metabolic effects are significant long-term problems. Furthermore, despite early hopes, patients on quetiapine are at risk for tardive dyskinesia.

Both the extended release (XR) and instant release (IR) versions of quetiapine are FDA-approved for bipolar depression. For reasons that have more to do with its patent than its pharmacology, only the XR is approved in unipolar depression. Quetiapine IR can be dosed all-at-night, and this strategy usually results in less daytime fatigue than the XR version. Hypotension, however, is lessened with the smoother peaks of quetiapine XR, particularly in doses higher than 300 mg.

Conclusion
None of the atypical antipsychotics stands out as the best choice for bipolar depression. Both of the generic options are low on tolerability, but OFC is the most likely to work and quetiapine has additional benefits in sleep and anxiety. Cariprazine and lurasidone are better tolerated overall, unless the problem is akathisia or out-of-pocket expense.

REFERENCES

Table. Atypical antipsychotic dosage ranges for bipolar depression

<table>
<thead>
<tr>
<th>Atypical antipsychotic</th>
<th>Indication</th>
<th>Dosage per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cariprazine (Vraylar)</td>
<td>Depression</td>
<td>1.5 mg/d</td>
</tr>
<tr>
<td></td>
<td>Mania/mixed</td>
<td>3 mg/d</td>
</tr>
<tr>
<td>Lurasidone (Latuda)</td>
<td>Depression</td>
<td>20-120 mg/d with &gt; 340 kcal meal; 40-80 mg range is typical</td>
</tr>
<tr>
<td></td>
<td>Mixed (off-label)</td>
<td>Varies with intensity of mixed features</td>
</tr>
<tr>
<td>Olanzapine-fluoxetine combo (Symbyax)</td>
<td>Depression</td>
<td>6/25-12/50 mg/d; mean 7.4/39.3 mg/d</td>
</tr>
<tr>
<td>Olanzapine monotherapy</td>
<td>Mania/mixed</td>
<td>5-20 mg/d (mean 10-15 mg/d)</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>Depression</td>
<td>300 mg/d</td>
</tr>
<tr>
<td></td>
<td>Mania/mixed</td>
<td>400-800 mg/d</td>
</tr>
</tbody>
</table>
PAIN MANAGEMENT
When Medications Affect More Than the Patient: Opioids and Family Members

Steven A. King, MD, MS

When physicians prescribe medications, usually the only thing we need to consider is how the drugs will affect the person for whom we are prescribing. We make choices based on the problems for which they are being prescribed and the risks and benefits based on the overall health of the patients. We rarely have to give much consideration to what, if any, impact the medications may have on the medical status of the patients’ families.

However, three new studies highlight how important it is that when physicians prescribe opioids there can be significant and even potentially fatal consequences for the family members of those for whom they are being prescribed.

The first study examined opioid overdoses among family members of people prescribed opioids using data supplied by a commercial insurance provider that provided information on both the patients and family members.1 The findings indicate that although opioid overdoses by the family members of those prescribed opioids were relatively infrequent, they occurred at almost three times the rate as for members of families where no one was prescribed an opioid. Furthermore, the risk of family member overdoses correlated with the dosage of the prescribed opioids. The risk of overdoses was present across all age groups from children to adults and prescription of long acting/extended release opioids and fentany patches increased the risk for overdoses.

Certainly one might expect that the availability of opioids in a household would increase the risk of someone other than the patient taking the medications and overdosing.

The authors note that the overdoses in children are quite probably accidental while those in adolescents and adults are more likely to be the result of intentionally taking the opioids. However, in either case they acknowledge that health care professionals need to make patients aware that they need to closely monitor the opioids prescribed for them and do their best to prevent family members using them to prevent misuse and potentially life threatening overdoses from occurring.

A second study examined the association between opioids prescribed for parents and the risk of suicide attempts by their children aged 10 to 19 years.2 It, too, found that while suicide attempts by children of parents who were prescribed opioids were relatively rare, they occurred at more than two times the rate for children whose parents were not prescribed opioids.

The authors of the study noted that other factors such histories of substance use disorder, depression, or suicide attempts by the parents or substance use disorder or depression in the children who overdosed did not fully explain the results.

It is also worth noting that the study found that the greatest risk for suicide attempts among children were those where one or both parents were taking a prescribed opioid and a medication for insomnia, either a benzodiazepine or a “Z drug,” although over two times as many were using a benzodiazepine rather than a Z drug.

The researchers did not have an explanation for their results apart from the potential accessi-
family members and when the prescriptions were discontinued, the family members had to seek their own prescriptions in order to continue their use.

Certainly considering the large numbers of patients in the US who have opioid prescriptions for chronic pain and in light of current recommendations that in most of these cases opioids are not appropriate, doctors may feel they are under increased pressure to stop prescribing these medications. It is possible that family members subsequent seeking of opioid prescriptions may be a growing problem and something clinicians need to be aware of.

The last two studies highlight concerns physicians should have about the over prescription of benzodiazepines, a topic that has unfortunately taken a backseat to the opioid epidemic. Another new study notes the important role that both benzodiazepines and opioids can play in mortality and ongoing opioid use following surgery and opioids can play in mortality and ongoing opioid use following surgery. The study examined the use of opioids and benzodiazepines during the 6 months prior to surgery and found that patients who had been prescribed both medications had a greater 30 day mortality rate and long-term risk of mortality. Use of opioids, benzodiazepines, or both prior to surgery all were associated with persistent opioid use following it. 43% of preoperative opioid users and 23% of benzodiazepine users were persistent opioid users while 65% of those who used both medications became persistent users of opioids. This was in contrast to only 12% of patients who took neither opioids nor benzodiazepines preoperatively who became persistent opioid users.

Despite the fact that there has been little literature to support the co-prescription of opioids and benzodiazepine and much to recommend against it, it still continues to occur not infrequently. How hard it has been to change the habits of doctors who are doing the coprescribing is demonstrated by another new study.

This study examined the impact of the 2016 Centers for Disease Control and Prevention guideline on the use of opioids for chronic pain, which strongly advised against the co-prescription of these with benzodiazepines. A small but statistically significant decrease in the rates of co-prescription was seen in the two years following the release of the guideline among patients using opioids for extended periods. However, there was no change in what the researchers described as “intensity of co-prescription” measured by the number of days both medications were prescribed concurrently. Curiously, although the study found that there was a reduction in co-prescription for patients with Medicare Advantage no reduction was seen among patients with commercial insurance.

One other interesting finding of the study was that in most cases the same physician prescribed both the opioids and benzodiazepines, which suggests that the problem was not due to lack of coordination between physicians where different ones were prescribing each medication.

None of the findings of any of these studies indicate that physicians should cease to prescribe either opioids or benzodiazepines to patients who truly require them. They do, however, highlight the many issues associated with their use that they may not need to consider when prescribing other medications but do with these two classes.

**Aripiprazole for Bipolar Disorder**

In bipolar depression, the situation is a little more complicated, but in short, aripiprazole has not been found to be effective. Two large manufacturer-sponsored trials failed to show any difference from placebo after eight weeks of treatment. It is not FDA-approved for bipolar depression. What is confusing for clinicians is that aripiprazole is well-known for its antidepressant effect. The proposed mechanism is that at lower doses there could be less akathisia and it might have kept working on the depression over the full eight weeks.

This is possible and deserves study. However, in the one maintenance study of aripiprazole in bipolar disorder (which resulted in FDA-approval as a maintenance agent in bipolar disorder), there was significant benefit for reducing manic episodes over six months compared with placebo, but no efficacy in preventing depressions or mixed states with depressive symptoms.

Other antipsychotics used as monotherapy have been found effective for bipolar depression. These include quetiapine, lurasidone, and cariprazine (all FDA-approved). Lamotrigine and lithium have efficacy and FDA-approval as maintenance treatments in bipolar depression. Thus, for many patients with bipolar depressions, these five medications would be preferred over aripiprazole.

**REFERENCES**


**Do you have opinions about issues raised in any of the articles in this issue? Write to us at PTeditor@MMHGroup.com or post your comments on our website.**

**Mood Disorders**

**Aripiprazole for Bipolar Disorder Continued from Cover**

**REFERENCES**

INDICATION

ZULRESSO™ (brevanalone) CIV is indicated for the treatment of postpartum depression (PPD) in adults.

Select IMPORTANT SAFETY INFORMATION for ZULRESSO

WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS

Patients treated with ZULRESSO are at risk of excessive sedation or sudden loss of consciousness during administration. Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their children. Because of these risks, ZULRESSO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS.

Please see Full Important Safety Information and Brief Summary of Full Prescribing Information, including Boxed Warning, on adjacent pages.
The primary endpoint was the mean change from baseline in depressive symptoms as measured by the HAM-D total score at the end of the infusion if there are signs or symptoms of excessive sedation. After symptoms resolve, the infusion may be resumed at the same or lower dose as clinically appropriate. Immediately stop the infusion if pulse oximetry reveals hypoxia. After hypoxia, the infusion should not be resumed.

Concomitant use of opioids, antidepressants, or other CNS depressants such as benzodiazepines or alcohol may increase the likelihood or severity of adverse reactions related to sedation. Patients must be accompanied during interactions with their child(ren) while receiving the infusion because of the potential for excessive sedation and sudden loss of consciousness. Patients should be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving, after infusion until any sedative effects of ZULRESSO have dissipated.
ZULRESSO, the FIRST AND ONLY FDA-approved treatment indicated for postpartum depression.


RAPID AND SIGNIFICANT IMPROVEMENT OF DEPRESSIVE SYMPTOMS IN 2.5† DAYS²

**Study 1**

62.3% reduction in mean HAM-D total score at Hour 60 with ZULRESSO 90 mcg/kg/hour (n=41)† vs 49.0% with placebo (n=43; P=0.0252)†

In a group of 38 patients in Study 1, a ZULRESSO titration to a target dose of 60 mcg/kg/hour was also superior to placebo in improvement of depressive symptoms.

The recommended dosage of ZULRESSO is 90 mcg/kg/hour.

HAM-D=Hamilton Depression Rating Scale.

**Study 2**

64.6% reduction in mean HAM-D total score at Hour 60 with ZULRESSO 90 mcg/kg/hour (n=51)† vs 53.3% with placebo (n=53; P=0.0160)†

*2.5 days=Hour 60.
†Intention to treat population.
‡Statistically significant after multiplicity adjustments.

Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness, ZULRESSO is available only through a restricted program called the ZULRESSO REMS.

Warnings and precautions for ZULRESSO include:

- Risk of excessive sedation, risk of sudden loss of consciousness, and suicidal thoughts and behaviors.

Most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush.

Use in specific populations:

- Pregnancy: May cause fetal harm
- Avoid use in patients with end stage renal disease (ESRD)

Select IMPORTANT SAFETY INFORMATION

ZULRESSO Risk Evaluation and Mitigation Strategy (REMS):

Notable requirements of the ZULRESSO REMS include:

- Healthcare facilities must enroll in the program and ensure that ZULRESSO is only administered to patients who are enrolled in the ZULRESSO REMS
- Pharmacies must be certified with the program and must only dispense ZULRESSO to healthcare facilities who are certified in the ZULRESSO REMS
- Patients must be enrolled in the ZULRESSO REMS prior to administration of ZULRESSO
- Wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies

Further information, including a list of certified healthcare facilities, is available at www.zulressorems.com or call 1-844-472-4379

For more information about ZULRESSO treatment and access, visit ZulressoHCP.com

Please see Full Important Safety Information and Brief Summary of Full Prescribing Information, including Boxed Warning, on the following pages.

References:
INDICATION
ZULRESSO™ (brexanolone) CIV is indicated for the treatment of postpartum depression (PPD) in adults.

IMPORTANT SAFETY INFORMATION for ZULRESSO

WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS
Patients treated with ZULRESSO are at risk of excessive sedation or sudden loss of consciousness during administration.

Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren).

Because of these risks, ZULRESSO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS.

WARNINGS AND PRECAUTIONS
Excessive Sedation and Sudden Loss of Consciousness: In clinical studies, 5% of ZULRESSO-treated patients compared to 0% of placebo-treated patients experienced sedation and somnolence that required dose interruption or reduction. Loss of consciousness or altered state of consciousness was reported in 4% of ZULRESSO-treated patients compared with 0% of placebo-treated patients.

During the infusion, monitor patients for sedative effects every 2 hours during planned, non-sleep periods. Immediately stop the infusion if there are signs or symptoms of excessive sedation. After symptoms resolve, the infusion may be resumed at the same or lower dose as clinically appropriate. Immediately stop the infusion if pulse oximetry reveals hypoxia. After hypoxia, the infusion should not be resumed.

Concomitant use of opioids, antidepressants, or other CNS depressants such as benzodiazepines or alcohol may increase the likelihood or severity of adverse reactions related to sedation. Patients must be accompanied during interactions with their child(ren) while receiving the infusion because of the potential for excessive sedation and sudden loss of consciousness.

Patients should be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving, after infusion until any sedative effects of ZULRESSO have dissipated.

ZULRESSO Risk Evaluation and Mitigation Strategy (REMS):
ZULRESSO is available only through a restricted program under a REMS called the ZULRESSO REMS because excessive sedation or sudden loss of consciousness can result in serious harm.

Notable requirements of the ZULRESSO REMS include:
- Healthcare facilities must enroll in the program and ensure that ZULRESSO is only administered to patients who are enrolled in the ZULRESSO REMS
- Pharmacies must be certified with the program and must only dispense ZULRESSO to healthcare facilities who are certified in the ZULRESSO REMS
- Patients must be enrolled in the ZULRESSO REMS prior to administration of ZULRESSO
- Wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies

Further information, including a list of certified healthcare facilities, is available at www.zulressorems.com or call 1-844-472-4379.

SUICIDAL THOUGHTS AND BEHAVIORS
In pooled analyses of placebo-controlled trials of chronically administered antidepressant drugs (SSRIs and other antidepressant classes) that include approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD).

ZULRESSO does not directly affect monoaminergic systems. Because of this and the comparatively low number of exposures to ZULRESSO, the risk of developing suicidal thoughts and behaviors with ZULRESSO is unknown. If depression becomes worse or patients experience emergent suicidal thoughts and behaviors, consider changing the therapeutic regimen, including discontinuing ZULRESSO.

ADVERSE REACTIONS
The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush.

USE IN SPECIFIC POPULATIONS
- Pregnancy: Based on findings from animal studies of other drugs that enhance GABAergic inhibition, ZULRESSO may cause fetal harm.

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

- Lactation: Brexanolone is transferred to breastmilk in nursing mothers. There are no data on the effects of ZULRESSO on a breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ZULRESSO and any potential adverse effects on the breastfed child from ZULRESSO or from the underlying maternal condition.

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

- Renal Impairment: No dosage adjustment is recommended in patients with mild, moderate, or severe renal impairment. Avoid use of ZULRESSO in patients with end stage renal disease (ESRD).

CONTROLLED SUBSTANCE
ZULRESSO contains brexanolone, a Schedule IV controlled substance under the Controlled Substances Act.

To report SUSPECTED ADVERSE REACTIONS, contact Sage Therapeutics, Inc. at 1-844-4-SAGERX (1-844-472-4379) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

For more information about ZULRESSO treatment and access, visit ZulressoHCP.com

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Please see Brief Summary of Full Prescribing Information, including Boxed Warning, on the following pages.
ZULRESSO™ (brexanolone) injection \( \text{Rx only} \)

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

(For complete details, please see Full Prescribing Information, including Boxed Warning, and Medication Guide.)

**WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS**

- Patients are at risk of excessive sedation or sudden loss of consciousness during administration of ZULRESSO.
- Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their children.
- Because of these risks, ZULRESSO is available only through a restricted program called the ZULRESSO REMS.

1 **INDICATIONS AND USAGE:** ZULRESSO™ is indicated for the treatment of postpartum depression (PPD) in adults.

2 **DOSE AND ADMINISTRATION**

A healthcare provider must be available on site to continuously monitor the patient, and intervene as necessary, for the duration of the infusion. Administered as a continuous intravenous infusion over 60 hours (2.5 days) as follows:

- 0 to 4 hours: Initiate with a dosage of 30 mcg/kg/hour
- 4 to 24 hours: Increase dosage to 60 mcg/kg/hour
- 24 to 52 hours: Increase dosage to 90 mcg/kg/hour (alternatively consider a dosage of 60 mcg/kg/hour for those who do not tolerate 90 mcg/kg/hour)
- 52 to 56 hours: Decrease dosage to 60 mcg/kg/hour
- 56 to 60 hours: Decrease dosage to 30 mcg/kg/hour

Dilution required prior to administration.

4 **CONTRAINDICATIONS:** None.

5 **WARNINGS AND PRECAUTIONS**

5.1 Excessive Sedation and Sudden Loss of Consciousness

In clinical studies, ZULRESSO caused sedation and somnolence that required dose interruption or reduction in some patients during the infusion (5% of ZULRESSO-treated patients compared to 0% of placebo-treated patients). Some patients were also reported to have loss of consciousness or altered state of consciousness during the ZULRESSO infusion (4% of the ZULRESSO-treated patients compared with 0% of the placebo-treated patients).

Time to full recovery from loss or altered state of consciousness, after dose interruption, ranged from 15 to 60 minutes. A healthy 55-year-old man participating in a cardiac repolarization study experienced severe somnolence and a 1-minute episode of apnea while receiving twice the maximum recommended dosage of ZULRESSO (180 mcg/kg/hour). All patients with loss of or altered state of consciousness recovered with dose interruption.

There was no clear association between loss or alteration of consciousness and pattern or timing of dose. Not all patients who experienced a loss or alteration of consciousness reported sedation or somnolence before the episode. During the infusion, monitor patients for sedative effects every 2 hours during planned, non sleep periods. Immediately stop the infusion if there are signs or symptoms of excessive sedation.

After symptoms resolve, the infusion may be resumed at the same or lower dose as clinically appropriate. Immediately stop the infusion if pulse oximetry reveals hypoxia. After hypoxia, the infusion should not be resumed. Patients should be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving after infusion until any sedative effects of ZULRESSO have dissipated. Patients must be accompanied during interactions with their children while receiving the infusion because of the potential for excessive sedation and sudden loss of consciousness. Concomitant use of opioids, sedating antidepressants, or other CNS depressants such as benzodiazepines or alcohol may increase the likelihood or severity of adverse reactions related to sedation.

Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness, ZULRESSO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS.

5.2 ZULRESSO Risk Evaluation and Mitigation Strategy (REMS) ZULRESSO is available only through a restricted program under a REMS called the ZULRESSO REMS because excessive sedation or sudden loss of consciousness can result in serious harm. Notable requirements of the ZULRESSO REMS include:

- Healthcare facilities must enroll in the program and ensure that ZULRESSO is only administered to patients who are enrolled in the ZULRESSO REMS
- Pharmacies must be certified with the program and must only dispense ZULRESSO to healthcare facilities who are certified in the ZULRESSO REMS
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Further information, including a list of certified healthcare facilities, is available at www.zulressorem.com or call 1-844-472-4379.

5.3 Suicidal Thoughts and Behavior

In pooled analyses of placebo-controlled trials of chronically administered antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 12 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD). The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

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

<table>
<thead>
<tr>
<th>Age Range (years)</th>
<th>Drug-Placebo Difference in Number of Patients with Suicidal Thoughts or Behaviors per 1000 Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increases Compared to Placebo</td>
</tr>
<tr>
<td>-18</td>
<td>14 additional patients</td>
</tr>
<tr>
<td>18-24</td>
<td>5 additional patients</td>
</tr>
<tr>
<td></td>
<td>Decreases Compared to Placebo</td>
</tr>
<tr>
<td>25-64</td>
<td>1 fewer patient</td>
</tr>
</tbody>
</table>

**6 ADVERSE REACTIONS**

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

- Excessive Sedation and Sudden Loss of Consciousness

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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.

The data described below reflect exposure to ZULRESSO in 140 patients with postpartum depression (PPD). A titration to a target dosage of 90 mcg/kg/hour was evaluated in 102 patients and a titration to a target dose of 60 mcg/kg/hour was evaluated in 38 patients. Patients were then followed for 4 weeks.

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush (Table 2).

Adverse Reactions Leading to Discontinuation, Dosage Interruption, or Dosage Reduction

In the pooled placebo-controlled studies, the incidence of patients who discontinued due to any adverse reaction was 2% of ZULRESSO-treated patients compared to 1% of placebo-treated patients. The adverse reactions leading to treatment discontinuation in ZULRESSO-treated patients were sedation-related (loss of consciousness, vertigo, syncope, and presyncope) or infusion site pain.

In the pooled placebo-controlled studies, the incidence of patients who had an interruption or reduction of the dosage due to any adverse reaction was 7% of ZULRESSO-treated patients compared to 3% of placebo-treated patients. The adverse reactions leading to dose reduction or interruption in ZULRESSO-treated patients were sedation-related (loss of consciousness, syncope, somnolence, dizziness, fatigue), infusion site events, changes in blood pressure, or medication error due to infusion pump malfunction. Three ZULRESSO-treated patients who had a dosage interruption because of loss of consciousness did not resume the infusion.

Table 2 presents the adverse reactions that occurred in ZULRESSO-treated PPD patients at a rate of at least 2% and at a higher rate than in the placebo-treated patients during the 60 hour treatment period.

Table 2: Adverse Reactions in Placebo-Controlled Studies in Patients with PPD Reported in ≥ 2% of ZULRESSO-Treated Patients and Greater than Placebo-Treated Patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo (n=107)</th>
<th>Maximum dosage 60 mcg/kg/hour (n=38)</th>
<th>Maximum dosage 90 mcg/kg/hour (Recommended dosage) (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Disorders</td>
<td>-</td>
<td>3%</td>
<td>-</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>-</td>
<td>4%</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1%</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>-</td>
<td>-</td>
<td>2%</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>-</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dizziness, presyncope, vertigo</td>
<td>7%</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>-</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Sedation, somnolence</td>
<td>6%</td>
<td>21%</td>
<td>13%</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>Flushing, hot flush</td>
<td>-</td>
<td>5%</td>
<td>2%</td>
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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure.

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

Risk Summary

Based on findings from animal studies of other drugs that enhance GABAergic inhibition, ZULRESSO may cause fetal harm. There are no available data on ZULRESSO use in pregnant women to determine a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, malformations were not seen in rats or rabbits at plasma levels up to 5 and 6 times the maximum recommended human dose (MRHD), respectively. Developmental toxicities were seen in the fetuses of rats and rabbits at 5 and 3 times the plasma levels at the MRHD, respectively. Reproductive toxicities were seen in rats at 3 times the plasma levels at the MRHD. These effects were not seen in rats and rabbits at 2 and 1.2 times the plasma levels at the MRHD. Brexanolone administered to pregnant rats during pregnancy and lactation resulted in lower pup survival at doses which were associated with ≥2 times the plasma levels at the MRHD and a neurobehavioral deficit in female offspring at 5 times the plasma levels at the MRHD. These effects were not seen at 0.8 times and 2 times the plasma levels at the MRHD, respectively.

In published animal studies, administration of other drugs that enhance GABAergic inhibition to neonatal rats caused widespread apoptotic neurodegeneration in the developing brain. The window of vulnerability to these changes in rats (postnatal day 0-14) corresponds to the period of brain development that takes place during the third trimester of pregnancy in humans.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have 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.

Data

Animal Data

In pregnant rats and rabbits, no malformations were seen when brexanolone was given during the period of organogenesis at continuous intravenous doses up to 60 and 30 mcg/kg/day, respectively. These doses were associated with maternal plasma levels 5 and 6 times the plasma levels at the MRHD of 90 mcg/kg/hour, in rats and rabbits, respectively. In rats, a decrease in fetal body weights was seen at 60 mcg/kg/day (5 times the plasma level at the MRHD). In rabbits, increased numbers of late resorptions and a decrease in fetal body weights were seen at doses equal to and greater than 15 mcg/kg/day (3 times the plasma levels at the MRHD) with fewer live fetuses and a higher post-implantation loss seen at 30 mcg/kg/day (6 times the plasma levels at the MRHD) in the presence of maternal toxicity (decreased food consumption and decreased body weight gain and/or body weight loss). Effects in rats and rabbits were not seen at 2 and 1.2 times the plasma levels at the MRHD, respectively.

When brexanolone was administered to pregnant rats by continuous intravenous administration at 30 and 60 mcg/kg/day (2 and 5 times plasma levels at the MRHD, respectively) during the period of organogenesis and throughout pregnancy and lactation, increased numbers of dead pups and fewer live pups at birth were seen. This effect was not seen at 0.8 times the plasma levels at the MRHD. Increased pup viability between postnatal day 0 and 4 in the presence of maternal toxicity (decreased body weight gain and food consumption during lactation) was seen at 5 times the plasma levels at the MRHD. These effects were not seen at 2 times the plasma levels at the MRHD. A neurobehavioral deficit, characterized by slower habituation in the maximal startle response in the auditory startle test, was seen in female offspring of dams dosed at 5 times the plasma levels at the MRHD. This effect was not seen at 2 times the plasma levels at the MRHD.

8.2 Lactation

Risk Summary

Available data from a lactation study in 12 women indicate that brexanolone is transferred to breastmilk in nursing mothers. However, the relative infant dose (RID) is low, 1% to 2% of the maternal weight-adjusted dosage. Also, as ZULRESSO has low oral bioavailability (~5%) in adults, infant exposure is expected to be low. There were no reports of effects of ZULRESSO on milk production. There are no data on the effects of ZULRESSO on a breastfed infant. Available data on the use of ZULRESSO during lactation do not suggest a significant risk of adverse reactions to breastfed infants from exposure to ZULRESSO. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZULRESSO and any potential adverse effects on the breastfed child from ZULRESSO or from the underlying maternal condition.

Data

A study was conducted in twelve healthy adult lactating women treated with intravenous ZULRESSO according to the recommended 60-hour dosing regimen (maximum dosage was 90 mcg/kg/hour). Concentrations of ZULRESSO in breast milk were at low levels (~10 ng/ml) in ~95% of women by 36 hours after the end of the infusion of ZULRESSO. The calculated maximum relative infant dose for ZULRESSO during the infusion was 1% to 2%.
**Book Review**

**The Rabbit Effect**

Reviewed by Sarah Helland, MD

Can kindness help determine who gets sick and who stays healthy? It is a question Dr Kelli Harding answers in her inaugural book, *The Rabbit Effect*, when she invites us to take a leap of faith into the world of self-help by following the story of a white rabbit, just as Alice and Neo did before us. Her book is an illuminating exploration of a new vision of the practice of medicine and health that demonstrates what our lives could be like if we targeted our “hidden factors of health.”

The story begins in 1978 with Dr Robert Nerem and his lab of researchers who as a group performed a study on rabbits in order to establish the relationship between a high-fat diet and heart health. Instead of the expected now long-proven result, his discovery that kindness can cause rabbits to be healthier was a potentially much larger paradigm shift. In his study, Dr Nerem analyzed the number of fatty deposits in the small blood vessels of a group of New Zealand White rabbits after they were fed a diet high in fat. The team expected that the rabbits would have fatty deposits in their small blood vessels that were commensurate with their high cholesterol levels, but instead the unexpected result was that a significant number of the rabbits did not. After much examination, the team discovered that the group of rabbits with far healthier blood vessels was under the care of an especially kind post-doctoral student who treated the animals with love and patience when handling them. A second similar study focusing on the type of care the rabbits received was done, which confirmed that kind treatment can in fact lead to healthier rabbits.

Dr Harding uses the study described above to introduce the more profound ideas that both rabbits and people thrive in community, that health is bolstered by “love, connection and purpose,” and that kind treatment in general can modify health on a molecular, individual, interpersonal, and global level. Unfortunately, many people have few opportunities for positive interaction, and suffer preventable health consequences that cannot be reversed by our limited biomedical model of practice. To illustrate the effects of kindness or the lack thereof, she leads the reader down the path of her career through her education and practice of medicine, all the while providing concrete examples using stories drawn from interactions she has with her own patients as well as providing the hard, scientific evidence needed to back up her hypothesis.

In each chapter she focuses on the different categories of family, work, relationships, community, neighborhood, and passions, which she defines as the “hidden factors of health.” The chapters start with various far-ranging problems or barriers to health and happiness she identifies within each category such as chronic loneliness, mental illness, isolation, adverse childhood events, and clinician bias, to name a few. But the chapters are also replete with a variety of easily adopted solutions that include participation in everything from the “No One Eats Alone Program,” which is implemented in middle schools across the country on certain days when no child is allowed to eat alone in order to combat social isolation and promote a sense of belonging in school-aged children, to the “Happy Café Network,” which includes a group of cafés designated by sticker where one can go to meet other like-minded individuals in a safe space in order to build new friendships. More locally she highlights the “Thrive NYC” program, which trains laypeople to educate their communities about mental health in order to combat stigma and administer mental health first aid. At the end of each chapter there is a list of simple activities to peruse for those with truly limited free time. Her overarching goal is to provide tools to empower individual to create a healthier, more meaningful life by building a variety of satisfying relationships with others in their community.

This book is well worth reading whether you are a doctor or just interested in a self-help book whose creative solutions seem both plausible and achievable. For my doctor colleagues, I give this book a glowing recommendation as Dr Harding not only courageously critiques the current medical establishment, but also provides inspiration and a needed reminder that we as doctors, and specifically psychiatrists, have lots of power in our relationships with patients and when we treat them with care and support we may be the only ones who do so. She believes that our acts of kindness in the treatment room will not only ripple out through the actions of our patients but will also provide us with greater satisfaction in our own professional and personal lives. We can choose to spread joy and Dr Harding gives us many ways to do so.

**Not Guilty**

Richard M. Berlin, MD

Our daughter’s first day of Med School ten years ago, computer charged, a career choice nourished by frozen yogurt she inhaled in the hospital café, her too-sick-for-school days spent watching videos from a call room bed, our spooky trips to the sub-basement morgue, dinners that orbited depression, dialysis, dengue fever, and death, our complaints about administrators and managed care, moments she witnessed the weight of a doctor’s responsibility when we left the table to answer a suffering patient’s call.

We never told her, “Become a doctor,” but today at 5 pm we hear her last sign out from training, a married mother who absorbed her parents the way bodies soak up sugar and salt, relieved to know she witnessed the arc and ache of our lives in Medicine and judged us “Not guilty” of crimes we committed in the name of healing.

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

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**Publisher:** Atria Books
**August 27, 2019**

**272 pages**

$18.98 (hardcover)
$12.99 (e-book)
Earth provides enough to satisfy every man’s needs, but not every man’s greed. – Mahatma Gandhi

My epiphany came a dozen or so years ago, soon after my third grandchild was born. I was sent to the corner grocery for some supplies. As I was checking out, the clerk asked: “Paper or plastic?” Usually, my answer came quickly, but not this time. I froze. Finally, I muttered “neither,” grabbed the items, and left, shaken.

Later that day, I wondered what had happened? What was the right answer? Did my professional work as a community psychiatrist have anything to do with this community interaction?

The answer to plastic or paper was easy to find out. Bring your bag was obviously the best for the environment. But the relevance of psychiatry was unclear. Other than immediately following a natural disaster, psychiatrists tend not to think about our natural environment much. Sure, I had heard a little about global warming and climate change, but we psychiatrists and organized psychiatry did not seem concerned at that time, even if human behavior was the main causative factor.

Yet, if this experience had something to do with my grandchildren’s future, I needed to keep looking. I learned from the other mental health disciplines such as psychology, which were already trying to help. Slowly, but surely, other psychiatrists and psychiatry joined in. I founded the informal Psychiatrists for Environment Action & Knowledge (PEAK), which later morphed into the Climate Psychiatry Alliance (CPA). We now know that the climate and many other environmental problems are indeed of psychiatric relevance.

About a generation ago, there was a call for psychiatrists and organized psychiatry to pay attention to how our ecology affected health and mental health. We even prayed for it at the American Psychiatric Association (APA) Annual Meeting in 1985 when the psychiatrist and minister E. Mansell Pattison offered a prayer to open the meeting.

This focus on ecology followed a obvious focus on the subject by the American Psychiatric Association in the late 1970s. During that time, the APA established a Task Force to examine what we knew about the relationship of the environment to mental health and illness, using the term “ecopsychiatry.” Interest then waned and several decades passed when nothing much happened. About 10 years ago, spurred by societal attention to climate change, ecology got the attention of psychiatry once again.

A model for our times
Our traditional model for psychiatry and general medicine is the bio-psycho-social one. However, this model has had its limitations. It has not prevented psychiatry from becoming dominated by biology, as in the criticized bio-bio-bio revision of the model.1 Nor has it included such aspects as the spiritual, which would go beyond the psychological to beliefs of meaning that cannot be (yet) verified by science.

Occasionally, there is confusion about whether to use the term ecology or environment. Ecology is generally broader, referring to the relationships of organisms, including humans, to the environment in which we live. That is why I use the term ecology (eco), as in ecopsychiatry and the recommendation to have a bio-psycho-social-eco model of medicine.

Climate change
Climate change, or climate instability, or climate crisis—whichever term is used—has recently had the most extensive coverage because of its detrimental effects on our ecology. Like all the major ecological threats to our mental health, there is a two-way street between humans and the environment in a kind of ongoing feedback loop. Indeed, in the Torah, there were two different genesis stories that predated the development of different groups of people: one in which humans were shepherds of the environment in a kind of ongoing feedback loop. In the Torah, there were two different genesis stories that predated the development of different groups of people: one in which humans were masters of the environment for their own use, the other in which humans were shepherds of the environment.

Climate change is somewhat unique in that its major effects will be seen in the future—when our children or their children come of age. This is particularly difficult for our minds to appreciate and address, given our evolutionary tendency to pay attention to immediate dangers and problems. Nevertheless, there are already concrete repercussions (e.g., stronger and more frequent storms, more droughts and wildfires).

Given our understanding of how patients recognize and respond to chronic mental illness, we should have a particular expertise in helping people respond to real or perceived threats of climate change. Such patients can deny that such problems exist and prioritize other problems first. We can help our patients understand that optimism is essential to avoid feeling helpless in the face of environmental threat.

Pollution
The environmental problem that is perhaps the most similar to climate change is air pollution. However, air pollution has different causes and brain repercussions, and it has the potential to be redressed more quickly. Despite federal clean air standards, risk continues. Air pollution has been found to be toxic to the brain. An increased prevalence of psychiatric symptoms was seen in adolescents exposed to nitrogen dioxide and nitrogen oxides released by diesel vehicles.2 Prenatal and infant exposure to pesticides increases the risk of autism spectrum disorders.3 Moreover, air pollution may be responsible for brain diseases such as autism in children and dementia in older adults.4

Toxins. Toxic causes of mental illness are often overlooked. The consequences of the unprecedented number of substances that have been released into the atmosphere are not
yet fully understood. However, the potential toxicity to the brain from heavy metals, pesticides, plasticizers, and other compounds is likely to be the underlying factor responsible for cognitive dysfunction, memory disturbance, and subtle alterations in mood and/or behavior. For example, higher than normal levels of lead have been linked to brain damage.1

Noise pollution. Probably the most studied urban variable on health is noise. The ear picks up the sound wave and transmits it to the temporal lobe for interpretation, and the brain determines whether that sound is unwanted, unpleasant, or disturbing. Noise can trigger a strong stress response. Loud noise has been linked to an increased prevalence depression and anxiety.6

Chronic noise can impair a child’s development, including the acquisition of cognition and language skills.3 When the noise causes hearing damage and job loss, a secondary outcome is often depressive and/or traumatic symptoms. Psychiatrists know how important it is to have soundproof offices; however, people in general seem to have an ambivalent attitude toward noise.

Clinical implications

The health and mental health consequences of these environmental changes are becoming clearer. Given that the adverse effects of environmental change threaten our basic psychological needs of safety and security, how could that be otherwise? Moreover, once we realize our own role in these environmental changes, some guilt, conscious or unconscious, is inevitable.

All these adverse environmental effects may show up in the clinician’s office. Patients can run the gamut from being apathetic to being overactive to environmental change. Those who are apathetic are a particular challenge and require a sensitive clinical response. The ecologically astute clinician will look for denial of risk, a mindfulness and cognitive behavioral therapy to help patients accept adverse events and to stay engaged in activities that give their life meaning. At both individual and community levels, transformational resilience can be supported by the clinician. At the societal level, psychiatrists can help bridge the conflicts between conflicting points of view on climate change.

Getting out into nature can help concentration and decrease anxiety. Taking time to be in gardens is often calming and refreshing. Biophilia, that is, the love of nature and living things, seems to be part of human nature. Similarly, hortophilia, the desire to interact with and tend to nature, also seems to be ingrained in us. When outdoor exposure is particularly difficult, being able to look outside into nature or bringing nature inside with plants and flowers can be helpful. When the clinician’s office decor reflects an appreciation for nature, it can be both soothing and provide a model for the patients.

Conclusions

Taken together, the environmental factors in addition to climate change—air pollution, toxins, noise—seem to have detrimental psychological repercussions. Although the climate is receiving the most attention right now in psychiatry and society, that is only one of the harmful environmental processes impairing health and mental health. There is overlapping brain damage from environmental poisons, including agricultural pesticides that become ingrained in our food, microscopic particles of carbon and other pollutants in the air, and lead in the water.

Humans have played an essential role in these harmful developments. Virtually all the major categories of mental disorders, including ADHD, MDD, and anxiety disorders as well as psychotic conditions, seem to have an associated increase in prevalence. New syndromes are being described and named, such as ecological grief and eco-anxiety. The environment, like genetics, involves conjoined and complex networks of many interacting elements that influence mental processes that can lead to mental disorders.

We can hope that we are moving beyond the time when psychiatrist leaders thought that environmental risks were irrelevant to the everyday practice of patient care. The everyday ongoing relevance of environmental changes must change our conception of disaster. Instead of focusing on acute disasters, we must pay attention to slowly developing disasters, ranging from a nuclear disaster to global warming. Indeed, by now, paying attention to our ecology is an ethical priority.

Ecology consists of the relationship of humans and the environment. At least in the US, virtually all major ecological problems are human made by for-profit corporations, primarily by fossil fuel industries. With the international relationships between psychiatrists around the world, we have the potential to work together globally to improve the environments in which we live. The World Psychiatric Association is the logical organization to help coordinate such a challenge.

Dr Moffic is retired from clinical work and his tenured professorship at the Medical College of Wisconsin in 2019, but he continues to write, his latest book is Combating Physician Burnout: A Guide for Psychiatrists. He is on the editorial board of Psychiatric Times.

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Antipsychotics for Bipolar Continued from page 34

A g e is the greatest risk factor for memory loss and dementia, defined as a cognitive decline that interferes with independent functioning. By age 45, the objective memory performance of average individuals is lower than it was during their twenties, but for most, these mental slips are minimal and do not progress.

For those with a family history of Alzheimer disease (AD), these age-related memory complaints cause considerable anxiety: patients worry that their normal aging symptoms are the initial indication of a progressive cognitive impairment that they have observed in their relatives.

Differential diagnosis and assessment
AD is the most common cause of dementia. It has a gradual onset and progression and leads to abnormal protein deposits—amyloid plaques and tau tangles—that accumulate in the brain regions that control thinking and memory. However, many other conditions can cause dementia, such as depression, adverse effects of medications, thyroid imbalances, and other medical illnesses. Treating these underlying medical conditions may cure a reversible dementia or lead to partial symptom improvement.

Other irreversible neurodegenerative diseases that cause dementia include Lewy body disease, vascular dementia, and frontotemporal degeneration. Even if there is no cure for the underlying cause of a dementia, treatments are available that stabilize symptoms and help people remain healthier longer.

A clinical assessment of cognitive issues includes a search for risk factors, such as smoking history, lack of sleep, prior head trauma, or history of untreated high blood pressure or high cholesterol. A detailed inventory of the patient’s medications is essential. Many prescription and over-the-counter drugs for allergies (diphenhydramine) or sleep (eg, Sominex, which also contains diphenhydramine) can impair cognition. Sedating medicines, narcotic agents, histamine H2-receptor antagonists (eg, famotidine, cimetidine) for gastrointestinal problems, cardiac medications such as digoxin and beta-blockers, corticosteroids, NSAIDs (eg, naproxen, ibuprofen), and antibiotics are all among the list of medicines that may contribute to symptoms.

A mental status assessment will help determine the patient’s degree of cognitive impairment, as well as the presence of depression or anxiety that can worsen memory. A brief evaluation of cognitive abilities will determine degree of cognitive impairment, and neuropsychological cognitive testing may be ordered to detail these deficits through neuropsychological testing.

A physical and neurological examination and screening blood tests for thyroid, metabolic, and other possible abnormalities are recommended to uncover medical causes of confusion. To ensure that a tumor, stroke, or other brain abnormality is not present, a computed tomography (CT) or magnetic resonance imaging (MRI) scan is performed.

Treatments for Alzheimer dementia
For patients with a diagnosis of Alzheimer dementia, symptomatic medications temporarily stabilize symptoms but do not cure the disease. These medicines help patients remain at a higher functional level longer than if they did not take the medicine and may benefit patients with other forms of dementia such as Lewy body disease and vascular dementia.

Patients are often started on a cholinergic medicine, such as donepezil or a rivastigmine patch (if patients have adverse effects from the former). Cholinergic medicines are thought to exert their effects by increasing availability of acetylcholine, which is important for normal cognitive functioning.

Once the patient is stabilized on one of these cholinergic drugs, the clinician often adds a second symptomatic medication, the N-methyl-D-aspartate (NMDA) receptor antagonist memantine. We know that combining a cholinergic drug with memantine leads to a better outcome than using either type of medication alone. In addition to helping with cognitive symptoms of dementia, these symptomatic medicines have been shown to delay the emergence of agitation and other behavioral symptoms associated with dementia.

It is important for clinicians to manage patient and family expectations about medication benefits. One strategy is to explain that if the patient tolerates the drug, then that patient will do significantly better than without the medication after a year, but some patients do experience temporary improvement. However, if there is an expectation of definite improvement and it does not emerge, patients and family members may become discouraged and prematurely discontinue the medicine. It is also helpful to inform patients and families that symptoms eventually progress. However, remaining on the medicine when that occurs will lead to a slower rate of cognitive decline than discontinuing the medication.

Other interventions for dementia
Recent research has shown that a healthy lifestyle can protect brain health as people age. A healthy brain lifestyle includes regular physical activity, balanced nutrition, stress management, and mental stimulation.

Healthy lifestyle programs that seem most effective include three elements: educating patients about the association between daily habits and brain health; setting reasonable goals that are not too daunting; and providing feedback of initial success to motivate participants.

Many families express interest in volunteering for research protocols involving new dementia interventions. Usually patients can remain on their symptomatic treatments while participating in research.

A variety of interventions are currently being tested, including new medications, vaccines, supplements, antibody blood infusions, nasal insulin spray (diabetes increases dementia risk), and focused ultrasound waves targeting the brain’s hippocampal memory center in attempts to activate these neural circuits. Most of the clinical trials are testing disease-modifying treatments, which would lead to an enduring change in the clinical progression of AD by interfering with the underlying pathophysiological mechanisms of the disease.

Dr Small is Pantow-Sokolou Professor on Aging, Professor of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA; Director of the UCLA Longevity Center; and Director, Geriatric Psychiatry Division at Semel Institute for Neuroscience and Human Behavior, Los Angeles. At the 2019 Psych Congress in San Diego, CA, Dr Small presented, “Age-Related Cognitive Decline: Clinical Applications of New Research.”

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<th>OCD: A Common Psychiatric Disorder With a Constellation of Solutions</th>
<th>Digital Psychiatry</th>
<th>Innovative Non-Opioids for Chronic Pain: Ketamine and Cannabidiol</th>
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<tr>
<td>Jon E. Grant, JD, MD, MPH</td>
<td>Arshya Vahabzadeh, MD</td>
<td>Thomas R. Kosten, MD</td>
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ACTIVITY GOAL
The goal of this activity is to provide an understanding of problematic pornography use and how it relates to compulsive sexual behavior disorder.

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

• Discuss the classification of and diagnostic criteria for compulsive sexual behavior disorder;
• Define the potential risk factors for problematic pornography use;
• Identify the proposed psychological and neurological mechanisms involved in problematic pornography use;
• Recognize the dichotomy of problematic behavior and moral incongruence.

TARGET AUDIENCE
This continuing 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.

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Matthias Brand, PhD, reports that he has received grants (to University of Duisburg-Essen) from the German Research Foundation (DFG), the German Federal Ministry for Research and Education, the German Federal Ministry for Health, and the European Union; he has performed grant reviews for several agencies; he has edited journal sections and articles; he has given academic lectures in clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts.

Gretchen R. Blycker, LMHC, has no disclosures to report.

Mark N. Potenza, MD, PhD, reports that he receives support from NIH (R01 DA039136, R01 DA042911, R01 DA026437, R03 DA045289, R21 DA042911, and P51 DA064271), the Connecticut Department of Mental Health and Addiction Services, the Connecticut Council on Problem Gambling, and the National Center for Responsible Gaming; he has consulted for and advised Rivermend Health, Game Day Data, Addiction Policy Forum, and Opiant Therapeutics; he received research support from the Mohegan Sun Casino and the National Center for Responsible Gaming; he has consulted for or advised legal and gambling entities on issues related to impulse control and addictive behaviors; provided clinical care related to impulse control and addictive behaviors; performed grant reviews; edited journal sections; has academic lectures in grand rounds; CME events and other clinical/scientific venues; and he has generated books or chapters for publishers of mental health texts.

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Based on extant data, problematic pornography use may be considered a behavioral addiction. A more detailed discussion of classification and diagnostic procedures can be found in a recent systematic review of literature related to problematic pornography use.1 Prevalence estimates for CSBD have not been systematically evaluated, but may be roughly between 5% and 12%, with males being twice as likely to experience features of CSBD or related phenomena. Prevalence estimates are currently imprecise because different scales have been used across studies; moreover, most studies do not distinguish problematic pornography use from other (hyper) sexual behaviors. However, one national sample showed “clinically relevant levels of distress and/or impairment associated with difficulty controlling sexual feelings, urges, and behaviors” in 8.6% of individuals (10.3% of men and 7.0% of women).2 In another report sexual impulsivity was acknowledged by 14.7% of individuals (18.9% of men and 10.9% of women).3 These data suggest that a large proportion of US adults are experiencing clinically relevant features of CSBD.

Problematic internet pornography use can also be a concern in individuals with normal/average socio-sexual behaviors, which means that these individuals have a specific problem in controlling their internet pornography consumption, but not hypersexual behaviors in other domains. It is therefore important to define whether problems related to pornography are only one component of CSBD that may co-exist with compulsive sexual behaviors offline (eg, frequent sexual intercourse with multiple partners, going to prostitutes, anonymous sexual contacts). When making treatment decisions, it is important to consider potentially addictive aspects of the behavior, such as experiencing gratification and cravings (eg, responses to triggers or pornography-related stimuli) as well as impaired control of pornography consumption despite adverse consequences.

### Risk factors
Specific socio-demographic variables may represent risk factors for problematic pornography use, with males more likely to be affected. Co-occurring depression, anxiety, and substance-use disorders exist in individuals with problematic pornography use. Another factor that has been linked to problematic pornography use is hypersexuality, which may include high general sexual excitability and high trait sexual motivation.4 These and other potential risk factors are summarized in Table 2 (for a systematic review of risk factors, please see Wéry and Billieux.5)

### Psychological and neurobiological mechanisms
The psychological and neurobiological mechanisms underlying problematic pornography use show similarities with substance-use disorders as well as gambling and gaming disorders. The mechanisms have been summarized in the updated theoretical Interaction of Person-Affect-Cognition-Execution (I-PACE) model of addictive behaviors.6 Cue-reactivity and craving in combination with reduced inhibitory control, implicit cognitions (eg, approach tendencies), and gratification are linked to pornography use. Furthermore, compensatory mechanisms over time may undermine problematic pornography use and other internet-use behaviors. Neuroscientific studies suggest the involvement of addiction-related brain circuits, including the ventral striatum and other parts of fronto-striatal loops, in the development and maintenance of problematic pornography use.7

### Table 1. Comparison of ICD-11 criteria for CSBD, gaming disorder, and the criteria for gaming disorder adopted to pornography-use disorder

<table>
<thead>
<tr>
<th>Criteria for CSBD</th>
<th>Criteria for gaming disorder</th>
<th>Potential criteria for pornography-use disordera</th>
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<tr>
<td>Persistent pattern of failure to control intense, repetitive sexual impulses or urges resulting in repetitive sexual behavior</td>
<td>Impaired control over gaming (eg, onset, frequency, intensity, duration, termination, context)</td>
<td>Impaired control over pornography use (eg, onset, frequency, intensity, duration, termination, context)</td>
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<tr>
<td>Symptoms may include repetitive sexual activities becoming a central focus of the person’s life to the point of neglecting health and personal care or other interests, activities, and responsibilities</td>
<td>Increasing priority given to gaming to the extent that gaming takes precedence over other life interests and daily activities</td>
<td>Increasing priority given to pornography to the extent that pornography use takes precedence over other life interests and daily activities</td>
</tr>
<tr>
<td>Numerous unsuccessful efforts to significantly reduce repetitive sexual behavior; continued repetitive sexual behavior despite adverse consequences or deriving little or no satisfaction from it</td>
<td>Continuation or escalation of gaming despite the occurrence of negative consequences</td>
<td>Continuation or escalation of pornography use despite the occurrence of negative consequences</td>
</tr>
<tr>
<td>Behavior causes marked distress or significant impairment in personal, family, social, educational, occupational, or other important areas of functioning</td>
<td>Behavior pattern is of sufficient severity to result in significant impairment in personal, family, social, educational, occupational, or other important areas of functioning</td>
<td>Behavior pattern is of sufficient severity to result in significant impairment in personal, family, social, educational, occupational, or other important areas of functioning</td>
</tr>
</tbody>
</table>

*aAdapted from criteria for gaming disorder.

### Table 2. Potential risk factors for developing problematic pornography use

<table>
<thead>
<tr>
<th>Characteristic/domain</th>
<th>Motivation/specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motives for using pornography</td>
<td>Stress reduction, emotion regulation, compensating for experiencing unfulfilled sexual fantasies in real life</td>
</tr>
<tr>
<td>Past negative life events or trauma</td>
<td>Past sexual abuse, PTSD</td>
</tr>
<tr>
<td>Attachment style</td>
<td>Insecure attachment style, attachment anxiety, attachment avoidance</td>
</tr>
<tr>
<td>Sexual excitability</td>
<td>High trait sexual motivation, high sexual arousal in response to pornographic stimuli, positive implicit cognitions about pornography</td>
</tr>
</tbody>
</table>

A role for moral incongruence
Problems related to pornography use may involve feelings of moral incongruence related to pornography and may not represent excessive or real addictive use.8 Moral incongruence may be defined as feelings or thoughts related to specific behaviors (eg, using pornography) that are in opposition to one’s core set of beliefs or values. Questions remain whether the processes underlying problematic pornography use as an addictive behavior and problems related to pornography use due to moral incongruence are alike or different.9 ICD-11, however, states in the criteria for CSBD that “distress that is entirely related to moral judgments and disapproval about sexual impulses, urges, or behaviors is not sufficient to meet this [CSBD] requirement.”

For clinical practice, it is important to consider both pornography-related problems in the contexts of compulsive or addictive use and moral incongruence. In working with patients, psychiatrists should examine explicitly patterns of pornography use, diminished control over pornography use,
and, importantly, distress and impairment related to pornography use in considering addictive use and moral incongruence.

**Treatment approaches**

In treating individuals with problematic pornography use and CSBD, case reports and proof-of-concept studies suggest the efficacy of pharmacological interventions. Drugs targeting dopamine, norepinephrine, serotonin, and opioidergic systems have shown efficacy to varying degrees. An open-label case report indicates that cognitive-behavioral therapy may help reduce pornography consumption. However, in this setting of reduced consumption craving increased, which decreased with 50 mg naltrexone administration daily.10

Data from an open-label case series of 20 mg paroxetine daily show that paroxetine treatment was associated with reductions in pornography consumption and anxiety.11 However, new problematic sexual concerns emerged relating to paying for sex or engaging in extra-marital affairs.

Assessing for multiple possible outlets for CSBD is important in treating individuals with problematic pornography use. Furthermore, randomized placebo-controlled clinical trials are needed to demonstrate potential short- and long-term efficacies and tolerabilities of pharmacological interventions, given that many studies of problematic pornography use have methodological limitations.12 Currently there are no medications with an approved Food and Drug Administration indication for CSBD.

Psychotherapeutic options warrant consideration. Cognitive-behavioral therapy and mindfulness-based interventions, perhaps accompanied by acceptance and commitment therapy, may be effective in reducing pornography use and increasing quality of life.13,14 Systematic studies are scarce, and clinicians should consider treatment motivations and individual goals of those seeking treatment for problematic pornography use. Among male pornography viewers, approximate-ly one in seven has reported interest in seeking treatment for pornography use, and those interest-ed in treatment reported more pornography use and hypersexuality.15

These findings are in line with those indicating that slightly more than 80% of men in treatment for hypersexuality have reported problems with pornography use.16 Specific situations or emotion-al states have been reported to link to perceived difficulties in controlling pornography use (eg, when using the internet and experiencing stress or negative mood states), and decreased self-efficacy in these situations has been linked to pornography use frequency and hypersexuality; as such, they may represent treatment targets in therapy.17 Other treatment options include online forums: NoFap and Reboot Nation were founded to help young males quit pornography viewing, with some men experiencing erectile dysfunction, which they attributed to altered sexual arousal altered resulting from use of pornography.

Systematic studies on the efficacies of prevention and treatment efforts for problematic pornography use are an important topic for future research and practice. Refererral to therapists who focus on sexual and relational health may be indicated. Several programs (eg, the American Association of Sexuality Educators, Counselors [AASECT], International Institute for Trauma and Addiction Professionals [IITAP], and Society for the Advancement of Sexual Health [SASH]) provide training and certification for therapists who treat individuals with CSBD and other sexual and relational concerns. However, before making referrals, psychiatrists and other clinicians should identify concerns that are often not disclosed without direct questioning because of shame, guilt, or ambivalence.

**Clinical implications and tips**

Given the high comorbidity of problematic pornography use with depression, anxiety, and other psychological disorders and given that some people feel ashamed of their pornography use, clinicians might overlook problems related to pornography use if they do not ask specific questions. To elicit information from patients, begin by acknowledging the interconnected nature of physical, mental, and sexual health. Since there are individual differences and variability in sexual orientation and expression as well as gender identity and expression, sexual health comprises multiple expressions. The following are some tips for beginning the conversation.

1. **Ask patients about any potential barriers to healthy sexual expression or experiences as well as potential excessive and risky behaviors, including pornography use.**

2. **Ask patients about impairment related to pornography use, understanding that such impairment may be in relational, occupational, educational, or other domains. In order not to over-pathologize behaviors, it is important to assess functional impairment in everyday life related to pornography use (see ICD-11 criteria for CSBD and those for other disorders such as gaming disorder). The diagnosis is justified only if the pattern of sexual behaviors including pornography use results in significant impairment in personal, family, social, educational, occupational, or other important areas of functioning.**

3. **Examine symptom severity of problematic pornography use including impairment, poor control, preoccupation, and continued use despite negative consequences instead of only asking for time and frequency of pornography use. Given that behavioral addictions are not defined by the objective amount of time spent with the behavior, it is important to consider the symptoms and distress and impairment, including those listed in ICD-11 criteria for CSBD.**

4. **Examine potential conflicts between pornography use and moral values. Explore individuals’ personal perspectives and beliefs regarding what promotes their sexual health and support them in a process of their own harm assessment. It is important to distinguish between distress resulting from a conflict between pornography use and moral values and functional impairment due to addictive use of pornography, although these factors are not mutually exclusive.**

5. **Examine individual goals and treatment motivation. Treatment goals may be different (eg, abstinence or reducing the behavior, gaining better control over the behavior, increasing acceptance of the [reduced] behavior). Consider these goals to provide individualized care and optimal treatment.**

**CASE VIGNETTE**

“Dr Jones” has a 26-year history of problematic pornography use, paying for sex during times of stress as well as untreated compulsive sexual behaviors that damaged trust, led to sexual disconnection, and contributed to a divorce.

In his 30s, Dr Jones sought treatment twice to address his concerns of problematic pornography use, about which he started to feel guilty and wondered whether it was interfering with situational sexual functioning during dyadic sex with his first wife. He met with therapists who minimized his distress and normalized his pornography use. Without his concerns being addressed, the negative consequences became more severe over the next three years. At age 37 he was compelled to enter into couples therapy with his first wife. However, once again, his compulsive sexual behaviors were not addressed. The treatment represented another missed opportunity for a therapeutic behavioral intervention to address some of the underlying compulsive sexual behaviors that were contributing to the barriers to his sexual and emotional health.

By not identifying and addressing the problems, his treatment providers may have unwittingly enabled his growing denial of compulsive sexual behaviors. He did not take responsibility for his contributions to the sexual problems in the marriage for which he initially blamed his wife. At age 38, he was divorced; he remarried at age 42 to his current wife.

During this current marriage, he continued past patterns of behaviors that directed his sexual energy and attention to secret pornography use despite a commitment to himself and to his wife to stop. Because it was no longer as pleasurable or stimulating as it had been in the past, his use of pornography escalated to continually more extreme sexually explicit content. He engaged in risky sexual behaviors that included viewing pornography during work hours and sexting with a staff member at work, which crossed professional boundaries and resulted in a sexual misconduct violation.

At age 47, after the sexual misconduct violation and the relational and professional consequences he experienced from his compulsive sexual behaviors, Dr Jones entered mindfulness-based treatment for CSBD. He has engaged in this treatment for 1.5 years. The treatment plan included mindfulness-based therapy weekly meetings, attending weekly 12-step Sex and Love Addicts Anonymous (SLAA) meetings, building a relationship with a sponsor, and installing Internet accountability software to his digital devices for one year.

Early in therapy, he created a working abstinence list that included identifying and detailing specific problematic behaviors with a comprehensive plan for avoidance of or non-engagement in the identified behaviors. Through self-awareness and mindfulness-based therapy, he integrated healthy boundary-promoting behaviors including a mindful and compassionate practice that helped him manage the mental and physical effects of stress. He practiced...
health, communication, honesty, and transparency with his wife and family and emotional vulnerability with trusted people. He utilized materials from a mindfulness-based relapse prevention program that included listening to Stop, Observe, Breath, Expand, Respond (SOBER)—breathing and urge-surfing guided meditations.18 

Mindful inquiries were also utilized during treatment, which expanded the connection and integration of his mind, body, and emotions.19 Early in treatment when learning to be present while mindfully observing his inner experiences in the moment, he noted that “The thoughts and intense feelings change and go away.” He integrated this practice and habit of being present during his experiences of intense feelings, urges, and cravings, and this strengthened his tolerance of uncomfortable states without acting out to escape them. He also proactively developed healthy ways to manage stress. Through mindful inquiries, he became aware of the part of himself that felt sad about letting go of the anticipation of engaging in the exhilarating pornography use and other compulsive sexual behaviors that were a part of his escape from stress. He realized that his coping habits of seeking intense excitement were short-term experiences that created more problems and led to growing feelings of shame. Letting go of compulsive sexual behaviors felt less like deprivation or loss when he identified how many healthy pleasures he had been integrating into his life during recovery. He shared his new insights: “I notice my thoughts seeking to blame others. I see how this enables my feeling powerless and how this leads to feeling resentment.” This awareness allowed him to practice curiosity about this pattern in relational dynamics, and he was able to make positive changes that benefitted him and many of his personal and professional relationships.

Practicing mindful management of sexual desire and expression and exploring practices that contributed to health, balance, and boundaries helped him to change his patterns of seeking to engage in risky or problematic sexual behaviors when he experienced stress or frustration. In addition to reducing problematic and harmful behaviors, he engaged in a process of integrating healthy practices that provided tools to help promote mental and sexual wellness. Throughout the course of treatment, he experienced more emotional stability, which led to avoiding problematic use of pornography for short-term pleasure at the cost of long-term harm. He is now able to manage healthy boundaries personally and professionally, and he continues on a shared path of exploration of mindful sexual connection with his wife.

Table 3 explores examples of the connections between ICD-11 criteria for CSBD and the Case Vignette.

Conclusion
Theoretical considerations and empirical evidence suggest that the psychological and neurobiological mechanisms involved in addictive disorders may apply to problematic pornography use. Systematic studies that address potential treatment strategies are a main area for future research. In addition, dissecting further the potential overlap and differentiation between problematic pornographic use that may or may not co-exist with other forms of CSBD, and other types of dysfunctional use of the internet for sexual purposes (e.g., sexting, excessive use of dating apps, Instagram with sexual content) should be addressed in future studies. Such research could provide support for evidence-based prevention and treatment of problematic pornography use.

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