dopaminergic transmission in mesolimbic and mesocortical circuits that play a role in assessing and acting on information about potential rewards and risks of volitional behaviors. These disorders can have devastating effects on the lives of patients and their families. Yet they are often insidious and difficult to recognize clinically, only coming to attention as the result of major consequences.

More judicious prescribing of dopamine agonists for PD and greater efforts to educate patients and their families about the risks of impulse control disorders would likely reduce the frequency of these disorders. When these disorders are discovered, their management requires close coordination between psychiatry and neurology. Reducing offending medications as much as possible, treating comorbid psychiatric illness, and using interventions aimed at interrupting dysfunctional reward-seeking behavior are keys to optimal management.

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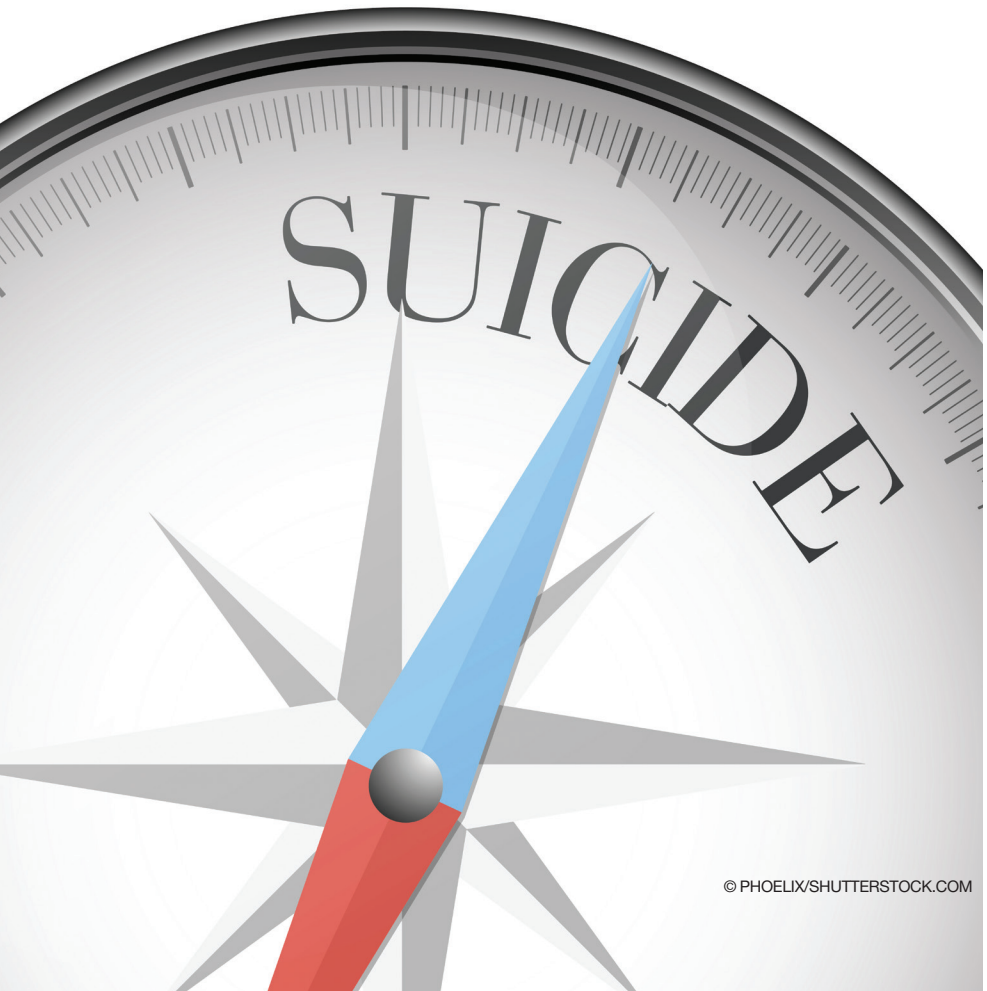
SPECIAL REPORT

Impulsivity and Suicide Risk: Review and Clinical Implications

by E. David Klonsky, PhD and Alexis M. May, MA

Impulsivity, a frequently misunderstood aspect of suicide risk, has long been considered important to the etiology and prediction of suicide. In particular, impulsivity is highlighted for its role in facilitating suicidal actions among those with suicidal ideation. Mann and colleagues[1] developed a clinical model of suicidal behavior which suggests that impulsivity makes individuals "more likely to act on suicidal feelings." Similarly, Bryan and Rudd[2] state that impulsivity "may actually be a more significant indicator of suicide attempt than the presence of a specific suicide plan."

Impulsivity has been adopted as a risk factor or warning sign for suicide. The American Association of Suicidology[3] includes impulsivity as both a chronic and an acute suicide risk factor. Impulsivity is also highlighted by the American Foundation for Suicide Prevention and the Substance Abuse and Mental Health Services Administration.[4,5] However, as discussed below, these widely held perceptions about impulsivity do not appear to be supported by research.



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Correcting misperceptions

The claim that impulsivity facilitates transition from suicidal thoughts to suicide attempts suggests a clear and testable prediction: trait impulsivity should be higher among those who attempt suicide than among those who only consider suicide. However, to the surprise of many, research on the role of impulsivity has routinely failed to support this claim. For example, a 2007 study of young adults by Brezo and colleagues[6] found that attempters scored no higher on the Barratt Impulsiveness Scale than patients with suicidal ideation who had never attempted suicide.

More recently, my colleagues and I examined a military population and found that while both suicide attempters and patients with suicidal ideation scored higher on a measure of impulsivity than those who had never been suicidal, impulsivity scores were equivalent between attempters and patients with suicidal ideation who had never attempted suicide.[7] In other words, impulsivity was moderately elevated in anyone with a history of suicidality (thoughts or behavior), but the study failed to show any further elevation among those who acted on their ideation and progressed to suicide attempts.

On the basis of these surprising findings, we conducted a subsequent analysis using the UPPS Impulsive Behavior Scale. The UPPS developers, Whiteside and Lynam,[8] suggest that impulsivity is a heterogeneous construct. They used a series of factor and psychometric analyses to identify 4 distinct impulsivity-related traits: Urgency (responding rashly to negative emotions), poor Premeditation (difficulties in foreseeing consequences of actions), poor Perseverance (tendency to give up easily), and Sensation seeking (preference for excitement and stimulation).

Using a brief version of the UPPS in a large sample of adolescents and young adults, we found that attempters and individuals with suicidal ideation exhibited equivalent scores on 3 of the dimensions (Urgency, Perseverance, and Sensation seeking) and that attempters scored only very slightly higher on the fourth (Premeditation). Taken together, the findings suggest that suicide attempters and individuals with suicidal ideation exhibit similar levels of trait impulsivity, a pattern that is contrary to clinical beliefs and guidelines.

The studies described above examined impulsivity as a personality trait that could occur at higher or lower levels within an individual. However, there is a second body of research that is also relevant to the role of impulsivity in suicide.

This research examines the impulsive nature of the suicide attempt itself. Many different definitions of attempt impulsivity have been used, including degree of forethought, amount of time between the decision to choose suicide and the actual suicide attempt, time spent contemplating the attempt before making the attempt, presence of a suicide plan, and amount of time spent making a plan, among many others. Given the many ways to define or identify an impulsive attempt, it is not surprising that studies on attempt impulsivity produce widely divergent results.

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For example, the percentage of suicide attempts estimated to be impulsive has ranged from a low of 20% to a high of 85%.[9,10]

Perhaps one of the most surprising findings is that trait impulsivity and attempt impulsivity appear to be unrelated. In other words, among individuals who have made suicide attempts, those who score higher on personality measures of impulsivity are not the ones making the more impulsive suicide attempts. This pattern has been found and reported by 2 separate research teams and thus appears to be true despite its counterintuitive nature.[10,11]

Taken together, studies indicate 2 critical limitations of current knowledge. First, when it comes to characterizing impulsivity in suicide, there is a disconnect between clinical guidelines and research. The way impulsivity is described in lists of suicide risk factors and warning signs is not supported—and is in some cases disputed—by empirical research. Second, the field continues to struggle to understand the role impulsivity plays in influencing the likelihood and nature of suicide attempts, as well as how to best understand suicide and suicide risk.

Understanding impulsivity

Looking at data from 70 studies, Anestis and colleagues[12] examined the association between measures of impulsivity and measures of suicidal behavior (eg, non-lethal attempts,

death by suicide). Across all studies, the relationship between impulsivity and suicidal behavior was modest (Hedges' g = 0.37). However, most of these studies were cross-sectional; current impulsivity was used to predict a history of suicidal behavior. In the studies that explored impulsivity as a predictor of future suicidal behavior, the association was even smaller, barely above 0 (Hedges' g = 0.09). The researchers conclude that the role of impulsivity in suicide is likely to be small and indirect rather than central or causal.

Anestis and colleagues next proposed a model specifying the role of impulsivity in suicide. In particular, the authors noted work by Joiner[13] that suggested that to make a potentially lethal suicide attempt, one must have the capability to make an attempt. Pain and fear of death serve as barriers to making a suicide attempt, and certain kinds of experiences can allow people to habituate to pain and fear of death and overcome these barriers. These experiences are referred to by Joiner as painful and provocative events and can include a variety of experiences and events, such as exposure to violence, nonsuicidal self-injury, and substance use.

Anestis and colleagues[12] theorized that rather than a direct relationship, impulsivity has a distal relationship to suicidal behavior by virtue of increasing one's exposure to painful and provocative events. Indeed, they noted that initial studies have found that painful and provoca-

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tive events mediate the relationship between impulsivity and suicidal behavior. In short, it appears that impulsivity exhibits its small relationship to suicidal behavior because it facilitates a lifestyle in which painful and provocative events are more likely to be experienced.

If, contrary to commonly held clinical beliefs, impulsivity is not a strong or central predictor of suicide or suicide risk, what may be a more accurate, more useful alternative model?

The ideation-to-action framework

The often cited risk factors for suicide, such as impulsivity as well as depression, hopelessness, and most mental disorders, are indeed greater among suicidal populations, but they distinguish poorly between those who attempt suicide and those who consider but never attempt suicide.[14] In other words, once an individual is known to have suicidal ideation, assessing his or her depression, hopelessness, psychiatric diagnosis, and impulsivity offers little to no information about the risk of acting on that ideation and making a suicide attempt. This distinction is critical because most individuals with suicidal ideation do not go on to attempt suicide.

This pattern of findings, replicated in numerous studies by numerous investigators, led to the ideation-to-action framework. From this perspective, predictors and explanations

for suicide should be classified as to how they address (a) the risk of suicide ideation, (b) the risk of suicide attempts among those with suicidal ideation, or (c) both. For example, depression, hopelessness, impulsivity, and most psychiatric disorders appear to be best characterized as predictors of suicidal ideation.[15-17]

In contrast, fearlessness and reduced pain sensitivity appear to specifically characterize suicide attempters, but not patients with suicidal ideation.[18] Other risk factors, such as nonsuicidal self-injury, appear to confer risk of both suicidal ideation and attempts.[19] Thus, conceptual and clinical models guided by an ideation-to-action framework can greatly improve models of suicide risk as well as efforts to understand and prevent suicide.

A new model of suicide and suicide risk

A new theory of suicide positioned within the ideation-to-action framework is the 3-step theory (3ST). The 3ST makes 3 central claims, all of which are consistent with existing evidence that is supported by recent findings.[20]

First, the combination of pain and hopelessness is what brings about suicidal ideation. The nature of pain is intentionally not specified. Any type of pain that makes daily life aversive, regardless of its source, can be implicated in suicidal ideation. When efforts to engage with life are paired with emotional, psychological, or physical pain, the individual is behaviorally conditioned to want

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to avoid engaging with life, which, in turn, decreases the desire to live. Furthermore, if the experience of pain is accompanied by hopelessness (over the idea that the pain will never improve), suicidal thinking begins. However, if there is hope that one's situation can improve, then one will continue to engage with life. It is the confluence of pain and hopelessness that leads to suicidal thoughts.

Indeed, pain and hopelessness are the two primary motivations for suicide.[21] More to the point, recent research suggests that it is the *combination* of pain and hopelessness that matters. Specifically, suicidal ideation was negligible in those low on both pain and hopelessness and was negligible in those either high on pain or high on hopelessness; in contrast, suicidal ideation was elevated only in the subgroup high on both pain and hopelessness.[20]

Second, the 3ST suggests that connectedness prevents suicidal ideation from escalating in those at risk (ie, those experiencing both pain and hopelessness). In other words, if connectedness to life—to loved ones, to a valued role, or to any sense of meaning or purpose—exceeds the pain, suicidal ideation will remain at modest levels. However, if pain exceeds the connectedness to or investment in life, suicidal ideation becomes strong and active. Recent findings support this notion: connectedness was found to be a significant buffer against suicidal ideation only in those with pain and hopeless-

ness; in everyone else, connectedness is negligibly related to suicidal ideation.[20]

Finally, the 3ST states that strong suicidal ideation leads to a suicide attempt if, and only if, one has the capacity to make an attempt. Three specific categories of variables contribute to suicide capacity: dispositional, acquired, and practical. Recent research has found that each of these 3 variables predicts suicide attempt history, even when controlling for past and current suicidal ideation.[20]

Dispositional variables are driven largely by genetics, such as pain sensitivity. For example, someone born with low pain sensitivity will have a higher capacity to carry out a suicide attempt. Indeed, more recent work from Smith and colleagues[22] indicates that capability for suicide may be largely genetic. Acquired variables are experiences associated with pain, injury, fear, and death, and they can lead over time to a higher capacity for a suicide attempt.[13] Practical variables are concrete factors that make a suicide attempt easier. These factors include access to, knowledge of, comfort with, and practice with lethal means. There are countless ways for someone to increase practical capacity. Each of these 3 factors—dispositional, acquired, practical—contribute to the capacity for attempted suicide, and an individual with strong suicidal ideation will only make a suicide attempt if and when he has the capacity to do so.

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trials of another drug and may not reflect the rates observed in practice. ***Adult Patients with Schizophrenia:*** The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of three 6-week fixed-dose trials and one 6-week flexible-dose trial) in which sublingual SAPHRIS was administered in doses ranging from 5 to 10 mg twice daily. *Adverse Reactions Associated with Discontinuation of Treatment:* A total of 9% of SAPHRIS-treated patients and 10% of placebo-treated patients discontinued due to adverse reactions. There were no drug-related adverse reactions associated with discontinuation in patients treated with SAPHRIS at the rate of at least 1% and at least twice the placebo rate. *Adverse Reactions Occurring at an Incidence of 2% or More in SAPHRIS-Treated Patients with Schizophrenia:* Adverse reactions associated with the use of SAPHRIS (incidence of 2% or greater, rounded to the nearest percent, and SAPHRIS incidence greater than placebo) that occurred during acute therapy (up to 6-weeks in patients with schizophrenia) are shown in **Table 8**. Table 8 in the full Prescribing Information lists Adverse Reactions Reported in 2% or More of Adult Patients in Any SAPHRIS Dose Group and Which Occurred at Greater Incidence Than in the Placebo Group in 6-week Schizophrenia Trials. Values shown are in parentheses as Placebo [N=378]; SAPHRIS 5 mg twice daily [N=274]; SAPHRIS 10 mg twice daily [N=208]; ALL SAPHRIS§ 5 mg or 10 mg twice daily [N=572]: Gastrointestinal disorders: Constipation (6%; 7%; 4%; 5%); Dry mouth (1%; 3%; 1%; 2%); Oral hypoesthesia (1%; 6%; 7%; 5%); Salivary hypersecretion (0%; <1%; 4%; 2%); Stomach discomfort (1%; <1%; 3%; 2%); Vomiting (5%; 4%; 7%; 5%); General disorders: Fatigue (3%; 4%; 3%; 3%); Irritability (<1%; 2%; 1%; 2%); Investigations: Increased weight (<1%; 2%; 2%; 3%); Metabolism disorders: Increased appetite (<1%; 3%; 0%; 2%); Nervous system disorders: Akathisia* (3%; 4%; 11%; 6%); Dizziness (4%; 7%; 3%; 5%); Extrapyramidal symptoms (excluding akathisia)† (7%; 9%; 12%; 10%); Somnolence‡ (7%; 15%; 13%; 13%); Psychiatric disorders: Insomnia (13%; 16%; 15%; 15%); Vascular disorders: Hypertension (2%; 2%; 3%; 2%). *Akathisia includes: akathisia and hyperkinesia. †Extrapyramidal symptoms included dystonia, oculogyration, dyskinesia, tardive dyskinesia, muscle rigidity, parkinsonism, tremor, and extrapyramidal disorder (excluding akathisia). ‡Somnolence includes the following events: somnolence, sedation, and hypersomnia. §Also includes the Flexible-dose trial (N=90). *Dose-Related Adverse Reactions:* In the short term schizophrenia trials the incidence of akathisia appeared to be dose-related (see Table 8). ***Monotherapy in Adult Patients with Bipolar Mania:*** The following findings are based on the short-term placebo-controlled trials for bipolar mania (a pool of two 3-week flexible-dose trials) in which sublingual SAPHRIS was administered in doses of 5 mg or 10 mg twice daily. *Adverse Reactions Associated with Discontinuation of Treatment:* Approximately 10% (38/379) of SAPHRIS-treated patients in short-term, placebo-controlled trials discontinued treatment due to an adverse reaction, compared with about 6% (12/203) on placebo. The most common adverse reactions associated with discontinuation in patients treated with SAPHRIS (rates at least 1% and at least twice the placebo rate) were anxiety (1.1%) and oral hypoesthesia (1.1%) compared to placebo (0%). *Adverse Reactions Occurring at an Incidence of 2% or More Among SAPHRIS-Treated (Monotherapy) patients with Bipolar I Disorder:* Adverse reactions associated with the use of SAPHRIS (incidence of 2% or greater, rounded to the nearest percent, and SAPHRIS incidence greater than placebo) that occurred during acute monotherapy (up to 3-weeks in patients with bipolar mania) are shown in **Table 9**. Table 9 in the full Prescribing Information lists Adverse Reactions Reported in 2% or More of Adult Patients in Any SAPHRIS Dose Group and Which Occurred at Greater Incidence Than in the Placebo Group in 3-week Bipolar Mania Trials. Values shown are in parentheses as Placebo [N=203]; SAPHRIS 5 or 10 mg twice daily* [N=379]: Gastrointestinal disorders: Dry mouth (1%; 3%); Dyspepsia (2%; 4%); Oral hypoesthesia (<1%; 4%); Toothache (2%; 3%); General disorders: Fatigue (2%; 4%); Investigations: Increased weight (<1%; 5%); Metabolism disorders: Increased appetite (1%; 4%); Musculoskeletal and connective tissue disorders: Arthralgia (1%; 3%); Pain in extremity (<1%; 2%); Nervous system disorders: Akathisia (2%; 4%); Dizziness (3%; 11%); Dysgeusia (<1%; 3%); Headache (11%; 12%); Other extrapyramidal symptoms (excluding akathisia)† (2%; 7%); Somnolence‡ (6%; 24%); Psychiatric disorders: Anxiety (2%; 4%); Depression (1%; 2%); Insomnia (5%; 6%). *SAPHRIS 5 mg to 10 mg twice daily with flexible dosing. †Extrapyramidal symptoms included: dystonia, blepharospasm, torticollis, dyskinesia, tardive dyskinesia, muscle rigidity, parkinsonism, gait disturbance, masked facies, and tremor (excluding akathisia). ‡Somnolence includes the following events: somnolence, sedation, and hypersomnia. ***Monotherapy in Pediatric Patients with Bipolar Mania:*** The following findings are based on a 3-week, placebo-controlled trial for bipolar mania in which SAPHRIS was administered at doses of 2.5 mg, 5 mg, or 10 mg twice daily. *Adverse Reactions Leading to Discontinuation of Treatment:* A total of 6.7% (7/104) of patients treated with SAPHRIS 2.5 mg twice daily, 5.1% (5/99) of patients treated with SAPHRIS 5 mg twice daily, and 5.1% (5/99) of patients treated with SAPHRIS 10 mg twice daily discontinued treatment due to adverse reactions compared to 4% (4/101) on placebo. The most common adverse reactions that led to discontinuation in pediatric patients treated with SAPHRIS (rates at least 2% in any SAPHRIS arm and at least twice the placebo rate) were somnolence (3% in the 2.5 mg twice daily group, 1% in the 5 mg twice daily group, and 2% in the 10 mg twice daily group), abdominal pain (2% in the 10 mg twice daily group), and nausea (2% in the 10 mg twice daily group). No placebo-treated patients dropped out for these events. *Adverse Reactions Occurring with SAPHRIS at an Incidence of 2% or More in SAPHRIS-treated Bipolar Patients:* Adverse reactions associated with the use of SAPHRIS (incidence of ≥2% in any SAPHRIS dose group and greater than placebo) that occurred during acute therapy are shown in **Table 10**. Table 10 in the full Prescribing Information lists Adverse Reactions Reported in 2% or More of Pediatric Patients (Ages 10 to 17 Years) in Any SAPHRIS Dose Group and Which Occurred at Greater Incidence Than in the Placebo Group in a 3-Week Bipolar Mania Trial. Values shown are in parentheses as Placebo [N=101]; SAPHRIS 2.5 mg twice daily [N=104]; SAPHRIS 5 mg twice daily [N=99]; SAPHRIS 10 mg twice daily [N=99]; All SAPHRIS 2.5, 5, and 10 mg [N=302]: Cardiac Disorders: Tachycardia[1] (0%; 3%; 0%; 1%; 1%); Gastrointestinal Disorders: Oral paraesthesia[2] (4%; 25%; 25%; 30%; 27%); Nausea (3%; 6%; 6%; 6%; 6%); Vomiting (3%; 4%; 4%; 4%; 4%); Abdominal pain[3] (7%; 9%; 3%; 5%; 6%); Glossodynia (0%; 0%; 2%; 0%; 1%); General Disorders and Administrative Site Disorders: Fatigue[4] (5%; 4%; 8%; 14%; 9%); Irritability (1%; 1%; 1%; 2%; 1%); Injury, Poisoning, and Procedural Complications: Muscle strain (0%; 0%; 0%; 2%; 1%); Investigations: Increased weight (0%; 6%; 2%; 2%; 3%); Hyperinsulinemia[5] (0%; 1%; 3%; 1%; 2%); ALT increased (0%; 0%; 0%; 2%; 1%); AST increased (0%; 0%; 0%; 2%; 1%); Metabolism and Nutrition Disorders: Increased appetite (2%; 10%; 9%; 6%; 8%); Dehydration (1%; 0%; 2%; 0%; 1%); Musculoskeletal and Connective Tissue Disorders: Myalgia (0%; 0%; 2%; 1%; 1%); Nervous System Disorders: Somnolence[6] (12%; 46%; 53%; 49%; 49%); Headache (6%; 8%; 11%; 9%; 9%); Dizziness (3%; 6%; 10%; 5%; 7%); Dysgeusia (2%; 4%; 5%; 9%; 6%); Akathisia (0%; 2%; 2%; 1%; 2%); Parkinsonism (0%; 1%; 0%; 2%; 1%); Psychiatric Disorders: Insomnia (3%; 3%; 4%; 3%; 3%); Suicidal ideation (1%; 4%; 1%; 3%; 3%); Anger (0%; 0%; 0%; 2%; 1%); Reproductive System and Breast Disorders: Dysmenorrhea (1%; 0%; 2%; 0%; 1%); Respiratory, Thoracic, and Mediastinal Disorders: Oropharyngeal pain (2%; 0%; 3%; 1%; 1%); Nasal congestion (1%; 0%; 2%; 0%; 1%); Dyspnea (0%; 0%; 2%; 0%; 1%); Skin and Subcutaneous Tissue Disorders: Rash (1%; 0%; 1%; 2%; 1%). [1]Includes the preferred terms tachycardia and heart rate increased. [2]Includes the preferred terms oral hypoesthesia, oral paresthesia, and oral dysesthesia. [3]Includes the preferred terms abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort. [4]Includes the preferred terms fatigue and lethargy. [5]Includes the preferred terms hyperinsulinemia and blood insulin increased. [6]Includes the preferred terms somnolence, sedation, and hypersomnia. *Dose-Related Adverse Reactions:* In the short term pediatric bipolar trials the incidence of fatigue appeared to be dose-related (see **Table 10**). ***Adjunctive Therapy in Adult Patients with Bipolar Mania:*** The following findings are based on a 12 week placebo-controlled trial (with a 3 week efficacy endpoint) in adult patients with bipolar mania in which sublingual SAPHRIS was administered in doses of 5 mg or 10 mg twice daily as adjunctive therapy with lithium or valproate. *Adverse Reactions Associated with Discontinuation of Treatment:* Approximately 16% (25/158) of SAPHRIS-treated patients discontinued treatment due to an adverse reaction, compared with about 11% (18/166) on placebo. The most common adverse reactions associated with discontinuation in subjects treated with SAPHRIS (rates at least 1% and at least twice the placebo rate) were depression (2.5%), suicidal ideation (2.5%), bipolar I disorder (1.9%), insomnia (1.9%) and depressive symptoms (1.3%). *Adverse Reactions Occurring at an Incidence of 2% or More Among SAPHRIS-Treated (Adjunctive) Bipolar Patients:* Adverse reactions associated with the use of SAPHRIS (incidence of 2% or greater, rounded to the nearest percent, and SAPHRIS incidence greater than placebo) that occurred during acute adjunctive therapy at 3 weeks, a time when most of the patients were still participating in the trial, are shown in **Table 11**. Table 11 in the full Prescribing Information lists Adverse Reactions Reported in 2% or More of Adult Patients In Any SAPHRIS-Dose Group and Which Occurred at Greater Incidence Than in the Placebo Group at 3 Weeks in Adjunctive Bipolar Mania Trials. Values shown are in parentheses as Placebo [N=166]; SAPHRIS 5 or 10 mg twice daily* [N=158]: Gastrointestinal disorders: Dyspepsia (2%; 3%); Oral hypoesthesia (0%; 5%); General disorders: Fatigue (2%; 4%); Edema peripheral (<1%; 3%); Investigations: Increased weight (0%; 3%); Nervous system disorders: Dizziness (2%; 4%); Other extrapyramidal symptoms (excluding akathisia)† (5%; 6%); Somnolence‡ (10%; 22%); Psychiatric disorders: Insomnia (8%; 10%); Vascular disorders: Hypertension (<1%; 3%). *SAPHRIS 5 mg to 10 mg twice daily with flexible dosing. †Extrapyramidal symptoms included: dystonia, parkinsonism, oculogyration, and tremor (excluding akathisia). ‡Somnolence includes the following events: somnolence and sedation. ***Dystonia:*** Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups *[see Use in Specific Populations, and Dosage and Administration and Clinical Pharmacology in the full Prescribing Information]*. ***Extrapyramidal Symptoms:*** In the short-term, placebo-controlled schizophrenia and bipolar mania adult trials, data was objectively collected on the Simpson Angus Rating Scale for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (for akathisia) and the Assessments of Involuntary Movement Scales (for dyskinesias). The mean change from baseline for the all-SAPHRIS 5 mg or 10 mg twice daily treated group was comparable to placebo in each of the rating scale scores. In the short-term, placebo-controlled schizophrenia adult trials, the incidence of reported EPS-related events, excluding events related to akathisia, for SAPHRIS-treated patients was 10% versus 7% for placebo; and the incidence of akathisia-related events for SAPHRIS-treated patients was 6% versus 3% for placebo. In short-term placebo-controlled bipolar mania adult trials, the incidence of EPS-related events, excluding events related to akathisia, for SAPHRIS-treated patients was 7% versus 2% for placebo; and the incidence of akathisia-related events for SAPHRIS-treated patients was 4% versus 2% for placebo. In a 3-week, placebo-controlled pediatric trial with bipolar I disorder, the incidences of EPS-related events, excluding events related to akathisia, were 4%, 3%, and 5% for patients treated with SAPHRIS 2.5 mg, 5 mg, and 10 mg twice daily, respectively, as compared to 3% for placebo-treated patients. EPS-related events include: bradykinesia, dyskinesia, dystonia, oromandibular dystonia, muscle contractions involuntary, muscle twitching, musculoskeletal stiffness, parkinsonism, protrusion tongue, resting tremor, and tremor. For events of akathisia, incidences were 2%, 2%, and 1% for patients treated with SAPHRIS 2.5 mg, 5 mg, and 10 mg twice daily, respectively, as compared to 0% for placebo-treated patients. ***Other Findings:*** Oral hypoesthesia and/or oral paresthesia may occur directly after administration of SAPHRIS and usually resolves within 1 hour. ***Laboratory Test Abnormalities:*** *Transaminases:* Transient elevations in serum transaminases (primarily ALT) in the short-term schizophrenia and bipolar mania adult trials were more common in treated patients. In short-term, placebo-controlled schizophrenia adult trials, the mean increase in transaminase levels for SAPHRIS-treated patients was 1.6 units/L compared to a decrease of 0.4 units/L for placebo-treated patients. The proportion of patients with transaminase elevations ≥3 times ULN (at Endpoint) was 0.9% for SAPHRIS-treated patients versus 1.3% for placebo-treated patients. In short-term, placebo-controlled bipolar adult mania trials, the mean increase in transaminase levels for SAPHRIS-treated patients was 8.9 units/L compared to a decrease of 4.9 units/L in placebo-treated patients. The proportion of patients with transaminase elevations ≥3 times upper limit of normal (ULN) (at Endpoint) was 2.5% for SAPHRIS-treated patients versus 0.6% for placebo-treated patients. In a 52-week, double-blind, comparator-controlled trial that included primarily adult patients with schizophrenia, the mean increase from baseline of ALT was 1.7 units/L. In a 3-week, placebo-controlled pediatric trial with bipolar I disorder, transient elevations in serum transaminases (primarily ALT) were more common in treated patients. The proportion of pediatric patients with ALT elevations ≥3 times upper limit of normal (ULN) was 2.4% for patients treated with SAPHRIS 10 mg twice daily versus none for the other SAPHRIS dose groups and placebo-treated patients. *Prolactin:* In short-term, placebo-controlled adult schizophrenia trials, the mean decreases in prolactin levels were 6.5 ng/mL for SAPHRIS-treated patients compared to 10.7 ng/mL for placebo-treated patients. The proportion of patients with prolactin elevations ≥4 times ULN (at Endpoint) were 2.6% for SAPHRIS-treated patients versus 0.6% for placebo-treated patients. In short-term, placebo-controlled bipolar mania adult trials, the mean increase in prolactin levels was 4.9 ng/mL for SAPHRIS-treated patients compared to a decrease of 0.2 ng/mL for placebo-treated patients. The proportion of patients with prolactin elevations ≥4 times ULN (at Endpoint) were 2.3% for SAPHRIS-treated patients versus 0.7% for placebo-treated patients. In a long-term (52-week), double-blind, comparator-controlled adult trial that included primarily patients with schizophrenia, the mean decrease in prolactin from baseline for SAPHRIS-treated patients was 26.9 ng/mL. In a 3-week, placebo-controlled pediatric trial with bipolar I disorder, the mean increases (at Endpoint) in prolactin levels were 3.2 ng/mL for patients treated with SAPHRIS 2.5 mg twice daily, 2.1 ng/mL for patients treated with SAPHRIS 5 mg twice daily, and 6.4 ng/mL for patients treated with SAPHRIS 10 mg twice daily compared to an increase of 2.5 ng/mL for placebo-treated patients. There were no reports of prolactin elevations ≥4 times ULN (at Endpoint) for patients treated with SAPHRIS or placebo. Galactorrhea or dysmenorrhea were reported in 0% of patients treated with SAPHRIS 2.5 mg twice daily, 2% of patients treated with SAPHRIS 5 mg twice daily, and 1% of patients treated with SAPHRIS 10 mg twice daily compared to 1% of placebo-treated patients. There were no reports of gynecomastia in this trial. *Creatine Kinase (CK):* The proportion of adult patients with CK elevations >3 times ULN at any time were 6.4% and 11.1% for patients treated with SAPHRIS 5 mg twice daily and 10 mg twice daily, respectively, as compared to 6.7% for placebo-treated patients in short-term, fixed-dose trials in schizophrenia and bipolar mania. The clinical relevance of this finding is unknown. The proportion of patients with CK elevations ≥3 times ULN during a 3-week trial in pediatric bipolar I disorder at any time were 1%, 0%, and 1% for patients treated with SAPHRIS 2.5 mg, 5 mg, and 10 mg twice daily, respectively, versus 3% for placebo-treated patients. ***Other Adverse Reactions Observed During the Premarketing Evaluation of SAPHRIS:*** Following is a list of MedDRA terms that reflect adverse reactions reported by patients treated with sublingual SAPHRIS at multiple doses of ≥5 mg twice daily during any phase of a trial within the database of adult patients. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related

Suicide Risk

Continued from page 19

One reason the 3ST is useful is that it suggests clear clinical implications. To reduce suicide risk, clinicians can reduce pain, increase hope, foster connection, and/or decrease capacity. Although these domains require more study and validation, they may be a useful way to conceptualize how a specific set of interventions with a particular patient can target and impact suicide risk.

Conclusion

Contrary to commonly held beliefs, a large body of research suggests that impulsivity is *not* a strong predictor or cause of suicidal behavior. Instead, trait impulsivity appears to be a modest and distal predictor of suicide; however, large, prospective studies that could best address this issue are still needed.

Future studies guided by the ideation-to-action framework may be able to specifically test the degree to which the impulsivity-suicidality relationship is explained by impulsivity's impact on the pain and hopelessness that cause ideation and/or on suicide capacity. Instead of focusing on impulsivity, it may be fruitful to focus on domains that have been consistently shown to predict and motivate suicidal ideation and suicide attempts, including pain and hopelessness (especially in combination), connectedness, and suicide capacity. Interventions for suicide risk may be most effective when one or more of these domains is improved.

Impulse Control, Impulsivity, and Violence: Clinical Implications

by Sean Z. Kaliski, MB, BCh, PhD

At some point in their life, most people are likely to have acted on impulses or reacted to provocations. This is accepted normal human behavior. However, in some cases it is pathological and some individuals behave this way habitually—as part of a pattern of behaviors that may have begun sometime in their youth. Although there are protean manifestations of these behaviors, ranging from suicidal gestures, substance abuse, risk taking, and antisocial behaviors, a subset of individuals are also aggressive and violent.

The terms "impulsivity" and "disorders of impulse control" have customarily been used interchangeably. Yet there have been contrasting definitions in the literature. "Impulsivity" has been defined as a decreased sensitivity to negative consequences, rapid unplanned reactions to stimuli (without adequate processing of information), and lack of regard for long-term consequences. "Disorders of impulse control" have been characterized as repeated failures to resist an impulse or perform an act that is harmful, with a preceding subjective sense of increasing tension (or arousal) and an experience of pleasure or gratification, ie, catharsis, while committing the act.[1,2] In both cases, the consequences of the acting out are usually deleterious, with subsequent feelings of regret or guilt.

No studies have directly compared individuals whose impulsivity only takes the form of acting precipitously to stimuli with those who act solely because of impelling urges. In practice, there are many who possess an admixture of both aspects, such as those with borderline personality disorder who repeatedly act out their urges and can also respond explosively to stimuli. In DSM-5, an important criterion for borderline personality disorder is impulsivity, which also encompasses risk-taking activities that are exemplars of poor impulse control, such as excessive spending, promiscuity, and reckless driving. Individuals with intermittent explosive disorder, a "pure" impulse control disorder, exhibit "impulsive (or anger-based) aggressive outbursts" in response to minor provocations or stressors. Whatever the distinctions, individuals with these disorders all have in common a deficit in inhibiting damaging behavior.

In clinical practice, it may actually be difficult to differentiate between compulsions, addictions, and irresistible impulses. Almost all self-damaging behaviors, especially if they occur in the context of a psychiatric disorder, can be reframed as impulse disorders, such is the looseness of the definitions. Commonly, individuals who habitually cannot control their aggressive impulses also have other impulse control disorders, such as gambling and alcohol and substance abuse.

"You clearly know about his toxic personality."

Forensic psychiatrists and the courts have long grappled with the difficult distinction between "impulses that cannot be resisted" and "impulses that are not resisted"—namely the "irresistible impulse" defense. In the former, there is the possibility that the person has an inherent biological propensity to act violently and therefore ought to be excused; the latter implies that the loss of control was voluntary and consequently not excusable. This applies mostly when someone responds violently following provocation. But impulses can also build up over an extended period until they demand urgent expression. Even serial killers who plan their homicides, sometimes meticulously, often report that they had to surrender to overwhelming urges.

Neurobiology and experience

Over 30 years ago, Linnoila and colleagues[3] found that impulsive violent offenders had significantly lower cerebrospinal fluid (CSF) concentrations of the major metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA). Their findings have been convincingly validated.[4,5]

Serotonin is an important inhibitory neurotransmitter, especially in the amygdala, anterior cingulated cortex, and dorsal-lateral prefrontal and orbitofrontal cortices. Reduced or dysregulated serotonin activity is associated with impulsivity and aggression. The possible mechanism may be the disruption of circuits between the amygdala and the medial prefrontal cortex, which results in amygdala hyperactivity and reduced prefrontal inhibition.[6] Impulsive aggression presumably occurs consequent to ongoing arousal (from the amygdala) that primes negative urgency—the tendency to respond impulsively and aggressively to provocations or perceptions of threat.

Individuals who have the X-linked allele that codes for low-functioning monoamine oxidase A (MAOA-L), the most important enzyme for the metabolism of central serotonin, tend to display enhanced activation in subcortical limbic areas (especially the amygdala) and reduced prefrontal inhibition. This allele has now acquired the moniker "warrior gene" because of its consistent association with impulsive aggressive behavior.

Individuals who have the s/s allele for the serotonin transporter promoter gene also tend to exhibit patterns of impulsive violence, probably because of the reduced presynaptic reuptake of serotonin. It may seem paradoxical that low-functioning versions of *MAOA* and serotonin promoter genes are associated with impulsive aggression because these genes lead to increased levels of serotonin. The most likely mechanism is that increased levels of serotonin occupy serotonin 1A and serotonin 1B autoreceptors that "switch" the presynaptic neuron off and functionally cause a serotonin deficiency.[5]

(Please see Violence, page 22)

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