

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 disor-

ders. 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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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 colleagues¹ developed a clinical model of suicidal behavior which suggests that impulsivity makes individuals "more likely to act on suicidal feelings." Similarly, Bryan and Rudd² 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 Suicidology³ 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.

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 colleagues⁶ 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 Premed-

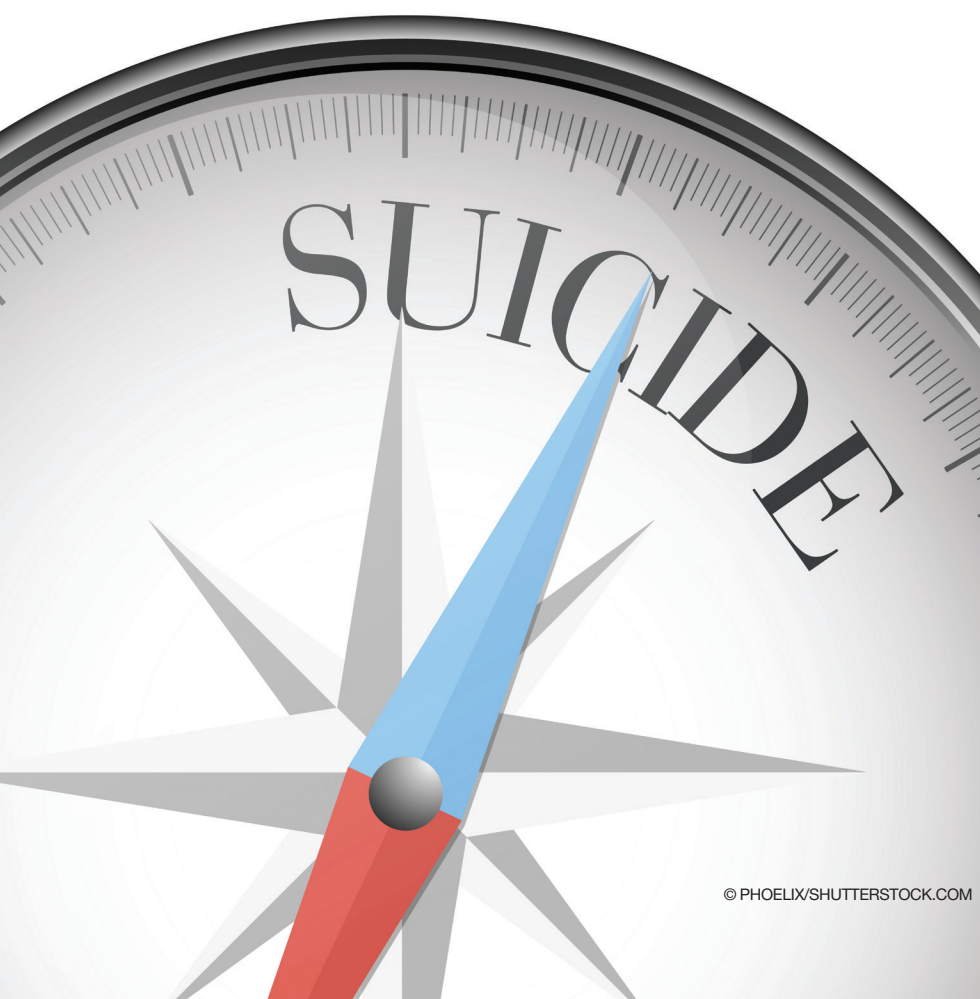
itation (difficulties in foreseeing consequences of actions), poor Perseverance (tendency to give up easily), and Sensation seeking (preference for excitement and stimulation).

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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Suicide Risk

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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 indi-

viduals 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}

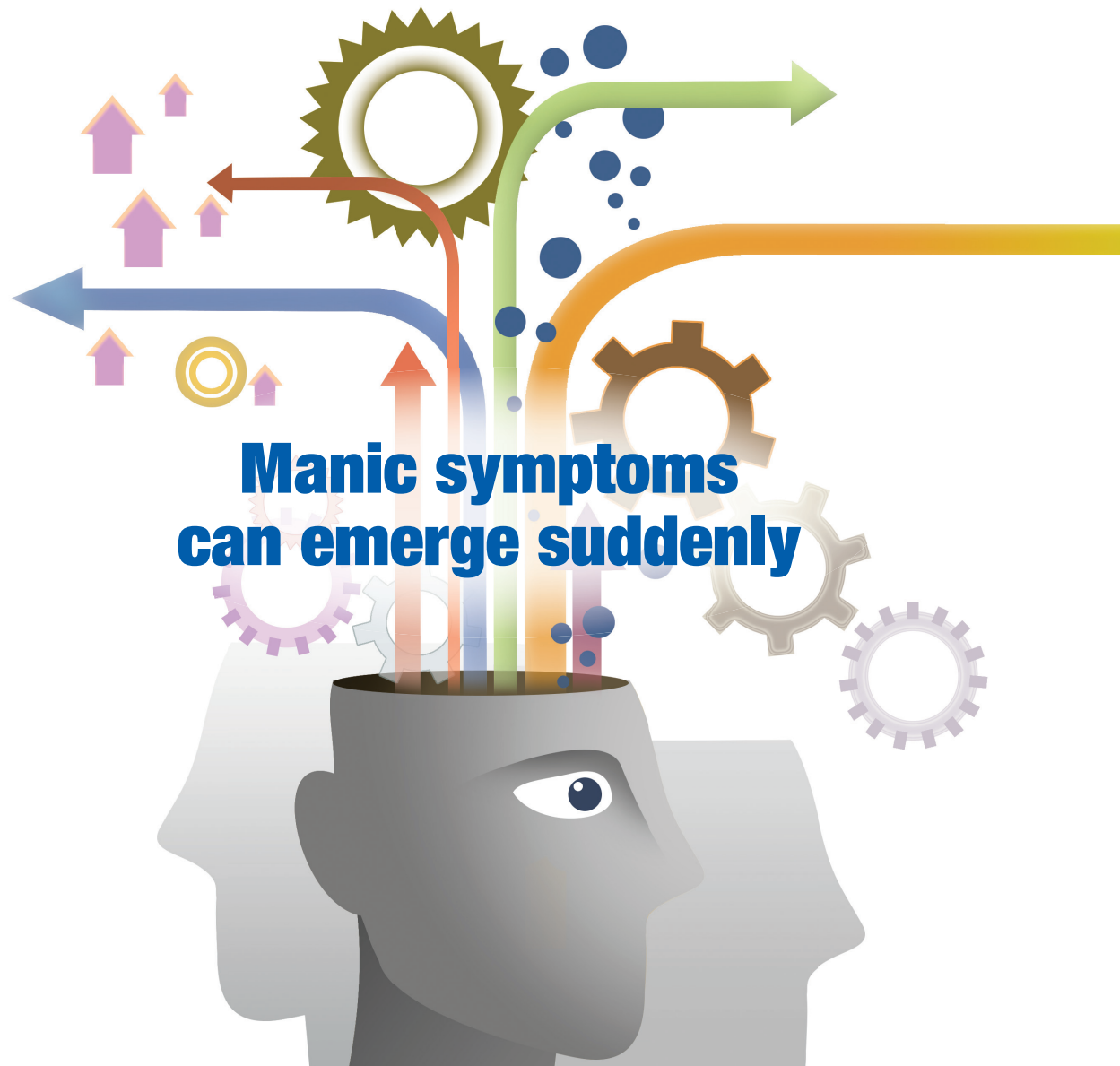
Taken together, studies indicate 2 critical limitations of current knowl-

edge. 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 influenc-

ing 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 colleagues¹² examined the association between measures of impulsivity and measures of suicidal behavior (eg, non-lethal attempts,



Manic symptoms can emerge suddenly

INDICATION AND USAGE

In bipolar I disorder: For the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults as monotherapy or adjunctive therapy with either lithium or valproate.

IMPORTANT SAFETY INFORMATION

WARNING: 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. SAPHRIS is not approved for treatment of patients with dementia-related psychosis.

Contraindications: SAPHRIS is contraindicated in patients with severe hepatic impairment (Child-Pugh C) or known hypersensitivity to SAPHRIS or its formulation components. Reactions have included anaphylaxis and angioedema.

Cerebrovascular Adverse Events, Including Stroke: In clinical trials with antipsychotic drugs, elderly subjects with dementia had a higher incidence of cerebrovascular adverse reactions, including fatalities vs placebo. SAPHRIS is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with antipsychotics, including SAPHRIS. NMS may cause hyperpyrexia, muscle rigidity, altered mental status, irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Management includes immediate discontinuation of antipsychotics and other drugs not essential to concurrent therapy, intensive symptomatic treatment and monitoring, and treatment of any concomitant serious medical problems.

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 Joiner¹³ 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 colleagues¹² 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-

(Please see Suicide Risk, page 16)

An atypical antipsychotic for the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults

SAPHRIS

Helps manage acute manic symptoms

Approved as monotherapy or adjunctive therapy with either lithium or valproate in adults.

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IMPORTANT SAFETY INFORMATION (CONTINUED)

Tardive Dyskinesia (TD): Risk of developing TD (a syndrome of potentially irreversible, involuntary dyskinetic movements) and the likelihood it will become irreversible may increase as the duration of treatment and total cumulative dose of antipsychotic drugs given to the patient increase. The syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribe SAPHRIS in a manner most likely to minimize TD. If signs and symptoms of TD appear, drug discontinuation should be considered.

Metabolic Changes: Atypical antipsychotics have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk:

- **Hyperglycemia and Diabetes Mellitus:** Hyperglycemia, in some cases associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics. Patients with risk factors for diabetes mellitus starting treatment with antipsychotics should undergo fasting blood glucose testing at the beginning of and during treatment. Monitor any patient treated with antipsychotics for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop these symptoms during treatment should undergo fasting blood glucose testing. In some cases, hyperglycemia resolved when the antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the antipsychotic drug.

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

To learn more about SAPHRIS, visit www.SAPHRISHCP.com.

Saphris[®] (asenapine)
sublingual tablets 5 and 10 mg

THE ONE UNDER THE TONGUE™

Suicide Risk

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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 infor-

mation 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

IMPORTANT SAFETY INFORMATION (CONTINUED)

Metabolic Changes (Continued)

- **Dyslipidemia:** Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.
- **Weight Gain:** Increases in weight have been observed with SAPHRIS. Monitor weight regularly in patients on SAPHRIS.

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

Orthostatic Hypotension, Syncope, and Other Hemodynamic Effects: SAPHRIS may induce orthostatic hypotension and syncope. Use SAPHRIS with caution in patients with cardiovascular/cerebrovascular diseases, conditions which predispose to hypotension, and in the elderly. Use SAPHRIS cautiously with other drugs that can induce hypotension, bradycardia, or respiratory or central nervous system depression. Monitor orthostatic vital signs, and consider a dose reduction if hypotension occurs.

Leukopenia, Neutropenia, and Agranulocytosis:

Leukopenia/neutropenia have been reported with antipsychotics, including SAPHRIS. Agranulocytosis (including fatal cases) has been reported with other antipsychotics. Monitor complete blood count in patients with pre-existing low white blood cell count (WBC)/absolute neutrophil count or history of drug-induced leukopenia/neutropenia. Discontinue SAPHRIS at the first sign of a clinically significant decline in WBC and in severely neutropenic patients.

QT Prolongation: In an adult QT study, SAPHRIS was associated with increases in the QTc interval from 2 to 5 msec vs placebo. No SAPHRIS patients had QTc increases of ≥ 60 msec or a QTc of ≥ 500 msec. Avoid SAPHRIS in combination with other drugs known to prolong QTc interval, in patients with congenital prolongation of QT interval or a history of cardiac arrhythmias, and in circumstances that may increase occurrence of torsades de pointes and/or sudden death in association with the use of drugs that prolong QTc interval.

Hyperprolactinemia: Like other drugs that antagonize dopamine D₂ receptors, SAPHRIS can elevate prolactin levels and the elevation can persist during chronic administration. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds.

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

Potential for Cognitive and Motor Impairment: Somnolence was reported with SAPHRIS. Caution patients about performing activities requiring mental alertness (eg, operating hazardous machinery or a motor vehicle).

Body Temperature Regulation: Appropriate care is advised when using SAPHRIS in patients who will experience conditions that increase body temperature, eg, exercising strenuously, extreme heat, concomitant anticholinergics, or dehydration.

Suicide: The possibility of suicide attempt is inherent in psychotic illnesses and bipolar disorder. Close supervision of high-risk patients should accompany drug therapy. Prescriptions should be written for the smallest quantity of tablets to reduce risk of overdose.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotics. Aspiration pneumonia is a common cause of morbidity/mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SAPHRIS should not be used in patients at risk for aspiration pneumonia.

Drug Interactions: Monitor blood pressure and adjust antihypertensive drugs when taken with SAPHRIS. Based on clinical response, SAPHRIS dose reduction may be necessary when used with strong CYP1A2 inhibitors (fluvoxamine). Reduce paroxetine (CYP2D6 substrate and inhibitor) dose by half when taken with SAPHRIS.

Pregnancy: Advise patients to notify their healthcare provider of a known or suspected pregnancy. SAPHRIS may cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Based on animal data, SAPHRIS may cause fetal harm. The National Pregnancy Registry for Atypical Antipsychotics monitors pregnancy outcomes in women exposed to antipsychotics, including SAPHRIS, during pregnancy. For information, contact 1-866-961-2388 or <http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/>.

Adverse Reactions: In adult clinical trials with SAPHRIS (5 and 10 mg BID) vs placebo, commonly observed adverse reactions ($\geq 5\%$ and at least twice the rate of placebo) were:

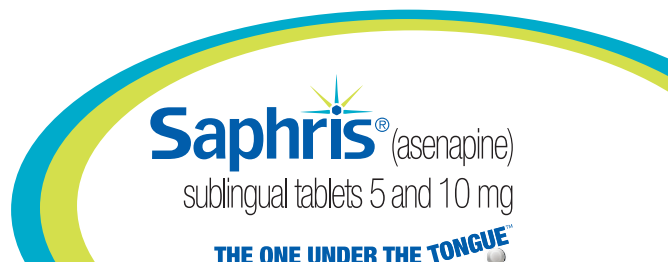
- Bipolar I (monotherapy): somnolence (24% vs 6%), dizziness (11% vs 3%), extrapyramidal symptoms other than akathisia (7% vs 2%), and increased weight (5% vs $<1\%$)
- Bipolar I (adjunctive): somnolence (22% vs 10%) and oral hypoesthesia (5% vs 0%)

Postmarketing Experience: Application site reactions, primarily sublingual, have been reported (eg, oral ulcers, blisters, peeling/sloughing, and inflammation). Choking has been reported, sometimes associated with oropharyngeal muscular dysfunction or hypoesthesia.

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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 spe-

cifically 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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SAPHRIS® (asenapine) sublingual tablets

Brief Summary of full Prescribing Information
Initial U.S. Approval: 2009

WARNING: 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. SAPHRIS® (asenapine) is not approved for the treatment of patients with dementia-related psychosis (see Warnings and Precautions).

INDICATIONS AND USAGE: SAPHRIS is indicated for: Schizophrenia; Acute treatment of manic or mixed episodes associated with Bipolar I disorder as monotherapy or adjunctive treatment to lithium or valproate [see Clinical Studies in the full Prescribing Information].

CONTRAINDICATIONS: SAPHRIS is contraindicated in patients with: Severe hepatic impairment (Child-Pugh C) [see Specific Populations, Clinical Pharmacology in the full Prescribing Information]; A history of hypersensitivity reactions to asenapine. Reactions have included anaphylaxis and angioedema [see Warnings and Precautions and Adverse Reactions, and Patient Counseling Information in the full Prescribing Information].

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 (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled 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 causes of death were varied, most of the deaths appeared to be either 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 some characteristic(s) of the patients is not clear. SAPHRIS is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning and Warnings and Precautions]. Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis - In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. SAPHRIS is not approved for the treatment of patients with dementia-related psychosis [see also Boxed Warning and Warnings and Precautions]. Neuroleptic Malignant Syndrome - A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SAPHRIS. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. It is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Tardive Dyskinesia - A syndrome of potentially irreversible, involuntary, dyskinetic movements can develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause Tardive Dyskinesia (TD) is unknown. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, SAPHRIS should be prescribed in a manner that is most likely to minimize the occurrence of TD. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of TD appear in a patient on SAPHRIS, drug discontinuation should be considered. However, some patients may require treatment with SAPHRIS despite the presence of the syndrome. Metabolic Changes - Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile. Hyperglycemia and Diabetes Mellitus - Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. 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 reactions is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on 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 continuation of anti-diabetic treatment despite discontinuation of the antipsychotic drug. *Adult Patients:* Pooled data from the short-term placebo-controlled schizophrenia and bipolar mania trials are presented in Table 1. Table 1 in the full Prescribing Information displays the Changes in Fasting Glucose found in Adult Patients in schizophrenia and bipolar mania trials. Changes in the Schizophrenia trial (6-weeks) are displayed in 4 subgroups: Placebo; SAPHRIS 5 mg twice daily; SAPHRIS 10 mg twice daily; and SAPHRIS 5 or 10 mg twice daily[§]. The Mean Change from Baseline in Fasting Glucose at Endpoint, in mg/dL (N*) for these subgroups is: -0.2 (232); 3.8 (158); 1.1 (153); 3.2 (377). The proportion of patients with Normal to High (<100 to \geq 126 mg/dL) shifts from Baseline to Endpoint (n/N*) are: 4.1% (7/170); 4.5% (5/111); 4.5% (5/111); 5.0% (13/262). The proportion of patients with Borderline to High (\geq 100 and <126 to \geq 126 mg/dL) shifts from Baseline to Endpoint (n/N*) are: 5.9% (3/51); 6.8% (3/44); 6.3% (2/32); 10.5% (10/95). Changes in the Bipolar trial (3-weeks) are displayed in 2 subgroups: Placebo; and SAPHRIS 5 or 10 mg twice daily[§]. The Mean Change from Baseline in Fasting Glucose at Endpoint, in mg/dL (N*) for these subgroups is: -0.6 (89); -0.6 (156). The proportion of patients with Normal to High (<100 to \geq 126 mg/dL) shifts from Baseline to Endpoint (n/N*) are: 3.3% (2/61); 2.7% (3/111). The proportion of patients with Borderline to High (\geq 100 and <126 to \geq 126 mg/dL) shifts from Baseline to Endpoint (n/N*) are: 0.0% (0/23); 11.4% (4/35). N* = Number of patients who had assessments at both Baseline and Endpoint. N** = Number of patients at risk at Baseline with assessments at both Baseline and Endpoint. [§]Includes patients treated with flexible dose of SAPHRIS 5 or 10 mg twice daily (N=90). [¶]SAPHRIS 5 mg or 10 mg twice daily with flexible dosing. In a 52-week, double-blind, comparator-controlled trial that included primarily patients with schizophrenia, the mean increase from baseline of fasting glucose was 2.4 mg/dL. *Pediatric Patients:* Data from the short-term, placebo-controlled trial in pediatric patients with bipolar I disorder are shown in Table 2. Table 2 in the full Prescribing Information displays the Changes in Fasting Glucose found in Pediatric Subjects in a 3-week Bipolar I Disorder trial. Changes are displayed in four subgroups: Placebo; SAPHRIS 2.5 mg twice daily; SAPHRIS 5 mg twice daily; and SAPHRIS 10 mg twice daily. The Mean Change from Baseline in Fasting Glucose at Endpoint, in mg/dL (N*) for these subgroups is: -2.24 (56); 1.43 (51); -0.45 (57); 0.34 (52). The proportion of subjects with Normal to High (>45 and <100 to \geq 126 mg/dL) shifts from Baseline to Endpoint (n/N*) are: 0% (0/56); 0% (0/51); 1.8% (1/57); and 0% (0/52). N* = Number of subjects who had assessments at both Baseline and Endpoint. **Dyslipidemia** - Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. *Adult Patients:* Pooled data from the short-term, placebo-controlled schizophrenia and bipolar mania trials are presented in Table 3. Table 3 in the full Prescribing Information displays the Changes in Lipids found in Adult Patients in schizophrenia and bipolar mania trials. Changes in the Schizophrenia trial (6-weeks) are displayed in 4 subgroups: Placebo; SAPHRIS 5 mg twice daily; SAPHRIS 10 mg twice daily; and SAPHRIS 5 or 10 mg twice daily[§]. The Mean Change from Baseline (in mg/dL) for these subgroups is: Total cholesterol (N*): -2.2 (351); -2.4 (258); 3.3 (199); 0.4 (539). LDL (N*): 0.1 (285); -0.2 (195); 1.3 (465). HDL (N*): 0.5 (290); 0.4 (199); 1.0 (199); 0.5 (480). Fasting triglycerides (N*): -7.6 (233); -1.9 (159); 0.1 (154); 3.8 (380). The proportion of patients with Total cholesterol Normal to High (<200 to \geq 240 mg/dL) shifts from Baseline to Endpoint (n/N*): 1.3% (3/225); 0.6% (1/161); 2.2% (3/134); 1.7% (6/343). The proportion of patients with LDL Normal to High (<100 to \geq 160 mg/dL) shifts from Baseline to Endpoint (n/N*): 1.7% (2/117); 0.0% (0/80); 1.2% (1/86); 1.0% (2/196). The proportion of patients with HDL Normal to Low (\geq 40 to <40 mg/dL) shifts from Baseline to Endpoint (n/N*): 10.7% (21/196); 13.3% (18/135); 14.7% (20/136); 14.0% (45/322). The proportion of patients with Fasting triglycerides Normal to High (<150 to \geq 200 mg/dL) shifts from Baseline to Endpoint (n/N*): 2.4% (4/167); 7.0% (8/115); 8.3% (9/108); 7.7% (20/260). Changes in the Bipolar trial (3-weeks) are displayed in 2 subgroups: Placebo; and SAPHRIS 5 or 10 mg twice daily[§]. The Mean Change from Baseline (in mg/dL) for these subgroups is: Total cholesterol (N*): -1.5 (163); 1.1 (322). LDL (N*): 1.9 (158); 1.6 (304). HDL (N*): 0.0 (163); 0.9 (322). Fasting triglycerides (N*): -17.9 (129); -3.5 (237). The proportion of patients with Total cholesterol Normal to High (<200 to \geq 240 mg/dL) shifts from Baseline to Endpoint (n/N*): 1.1% (1/95); 2.5% (5/204). The proportion of patients with LDL Normal to High (<100 to \geq 160 mg/dL) shifts from Baseline to Endpoint (n/N*): 1.9% (1/53); 0.0% (0/141). The proportion of patients with HDL Normal to Low (\geq 40 to <40 mg/dL) shifts from Baseline to Endpoint (n/N*): 7.4% (9/122); 8.7% (21/242). The proportion of patients with Fasting triglycerides Normal to High (<150 to \geq 200 mg/dL) shifts from Baseline to Endpoint (n/N*): 5.1% (4/78); 7.4% (11/148). N* = Number of subjects who had assessments at both Baseline and Endpoint. [§]Includes subjects treated with flexible dose of SAPHRIS 5 or 10 mg twice daily (N=90). [¶]SAPHRIS 5 mg or 10 mg twice daily with flexible dosing. In short-term schizophrenia trials, the proportion of patients with total cholesterol elevations \geq 240 mg/dL (at Endpoint) was 8.3% for SAPHRIS-treated patients versus 7% for placebo-treated patients. The proportion of patients with elevations in triglycerides \geq 200 mg/dL (at Endpoint) was 13.2% for SAPHRIS-treated patients versus 10.5% for placebo-treated patients. In short-term, placebo-controlled bipolar mania trials, the proportion of patients with total cholesterol elevations \geq 240 mg/dL (at Endpoint) was 8.7% for SAPHRIS-treated patients versus 8.6% for placebo-treated patients. The proportion of patients with elevations in triglycerides \geq 200 mg/dL (at Endpoint) was 15.2% for SAPHRIS-treated patients versus 11.4% for placebo-treated patients. In a 52-week, double-blind, comparator-controlled trial that included primarily patients with schizophrenia, the mean decrease from baseline of total cholesterol was 6 mg/dL and the mean decrease from baseline of fasting triglycerides was 9.8 mg/dL. *Pediatric Patients:* Data from the short-term, placebo-controlled bipolar mania trial are presented in Table 4. Table 4 in the full Prescribing Information displays the Changes in Fasting Lipids found in Pediatric Subjects in a 3-week Bipolar I Disorder trial. Changes are displayed in four subgroups: Placebo; SAPHRIS 2.5 mg twice daily; SAPHRIS 5 mg twice daily; and SAPHRIS 10 mg twice daily. The Mean Change from Baseline (in mg/dL) for these subgroups is: Total fasting cholesterol (N*): -2.3 (57); 3.7 (50); 7.2 (57); 9.3 (52). Fasting LDL (N*): -2.5 (57); -0.2 (50); 3.0 (57); 4.9 (51). Fasting HDL (N*): 1.6 (57); 2.3 (50); 1.5 (57); 1.7 (52). Fasting triglycerides (N*): -6.6 (57); 8.7 (50); 13.4 (57); 14.7 (52). The proportion of subjects with Total fasting cholesterol Normal to High (<170 to \geq 200 mg/dL) shifts from Baseline to Endpoint (n/N*): 1.8% (1/57); 0% (0/50); 1.8% (1/57); 0% (0/52). The proportion of subjects with Fasting LDL Normal to High (<110 to \geq 130 mg/dL) shifts from Baseline to Endpoint (n/N*): 1.8% (1/57); 2.0% (1/50); 1.8% (1/57); 0% (0/51). The proportion of subjects with Fasting HDL Normal to Low (\geq 40 to <40 mg/dL) shifts from Baseline to Endpoint (n/N*): 3.5% (2/57); 6.0% (3/50); 3.5% (2/57); 9.6% (5/52). The proportion of subjects with Fasting triglycerides Normal to High (<150 to \geq 200 mg/dL) shifts from Baseline to Endpoint (n/N*): 0% (0/57); 4.0% (2/50); 3.5% (2/57); 1.9% (1/52). N* = Number of patients who had assessments at both Baseline and Endpoint. **Weight Gain** - Increases in weight have been observed in pre-marketing clinical trials with SAPHRIS. Patients receiving SAPHRIS should receive regular monitoring of weight [see Patient Counseling Information in the full Prescribing Information]. *Adult Patients:* Pooled data on mean changes in body weight and the proportion of subjects meeting a weight gain criterion of \geq 7% of body weight from the short-term, placebo-controlled schizophrenia and bipolar mania trials are presented in Table 5. Table 5 in the full Prescribing Information displays the Change in Body Weight found in Adult Patients in schizophrenia and bipolar mania trials. Changes in the Schizophrenia trial (6-weeks) are displayed in 4 subgroups: Placebo; SAPHRIS 5 mg twice daily; SAPHRIS 10 mg twice daily; and SAPHRIS 5 or 10 mg twice daily[§]. The Change from Baseline (in kg) for these subgroups is (N*): 0.0 (348); 1.0 (251); 0.9 (200); 1.1 (532). The

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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 hopelessness.

proportion of patients with a $\geq 7\%$ increase in Body Weight: 1.6%; 4.4%; 4.8%; 4.9%. Changes in the Bipolar trial (3-weeks) are displayed in 2 subgroups: Placebo; and SAPHRIS 5 or 10 mg twice daily. The Change from Baseline (in kg) for these subgroups is (N): 0.2 (171); 1.3 (336). The proportion of patients with a $\geq 7\%$ increase in body weight: 0.5%; 5.8%. N = Number of subjects who had assessments at both Baseline and Endpoint. *Includes subjects treated with flexible dose of SAPHRIS 5 or 10 mg twice daily (N=90). †SAPHRIS 5 mg or 10 mg twice daily with flexible dosing. **Adult Patients:** In a 52-week, double-blind, comparator-controlled adult trial that included primarily patients with schizophrenia, the mean weight gain from baseline was 0.9 kg. The proportion of patients with a $\geq 7\%$ increase in body weight (at Endpoint) was 14.7%. Table 5 provides the mean weight change from baseline and the proportion of patients with a weight gain of $\geq 7\%$ categorized by Body Mass Index (BMI) at baseline. Table 6 in the full Prescribing Information displays the Weight Change Results Categorized by BMI at Baseline: Comparator-Controlled 52-Week Study in Adults with Schizophrenia. Results are displayed in 3 SAPHRIS groups: BMI <23 [N=295]; BMI 23–27 [N=290]; BMI >27 [N=302]. Mean change from Baseline (in kg): 1.7; 1.1; 0. The percentage of patients with a $\geq 7\%$ increase in body weight: 22%; 13%; 9%. **Pediatric Patients:** Data on mean changes in body weight and the proportion of pediatric patients meeting a weight gain criterion of $\geq 7\%$ of body weight from the short-term, placebo-controlled bipolar mania trial are presented in Table 7. To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]), which normalize for the natural growth of pediatric patients by comparisons to age- and sex-matched population standards. The distance of a z-score from 0 represents the distance of a percentile from the median, measured in standard deviations (SD). After adjusting for age and sex, the mean change from baseline to endpoint in weight z-score for SAPHRIS 2.5 mg, 5 mg, and 10 mg twice daily, was 0.11, 0.08 and 0.09 SD versus 0.02 SD for placebo, respectively. When treating pediatric patients, weight gain should be monitored and assessed against that expected for normal growth. Table 7 in the full Prescribing Information displays the Change in Body Weight found in Pediatric Subjects in a 3-week Bipolar I Disorder trial. Changes are displayed in four subgroups: Placebo; SAPHRIS 2.5 mg twice daily; SAPHRIS 5 mg twice daily; and SAPHRIS 10 mg twice daily. The Change from Baseline (in kg) for these subgroups is (N): 0.5 (89); 1.7 (92); 1.6 (90); 1.4 (87). The proportion of subjects with a $\geq 7\%$ increase in body weight: 1.1%; 12.0%; 8.9%; 8.0%. N = Number of subjects who had assessments at both Baseline and Endpoint. **Hypersensitivity Reactions - Hypersensitivity reactions** have been observed in patients treated with SAPHRIS. In several cases, these reactions occurred after the first dose. These hypersensitivity reactions included: anaphylaxis, angioedema, hypotension, tachycardia, swollen tongue, dyspnea, wheezing and rash. **Orthostatic Hypotension, Syncope, and Other Hemodynamic Effects -** SAPHRIS may induce orthostatic hypotension and syncope in some patients, especially early in treatment, because of its α_1 -adrenergic antagonist activity. In short-term schizophrenia adult trials, syncope was reported in 0.2% (1/572) of patients treated with therapeutic doses (5 mg or 10 mg twice daily) of SAPHRIS, compared to 0.3% (1/378) of patients treated with placebo. In short-term bipolar mania adult trials, syncope was reported in 0.3% (1/379) of patients treated with therapeutic doses (5 mg or 10 mg twice daily) of SAPHRIS, compared to 0% (0/203) of patients treated with placebo. During adult pre-marketing clinical trials with SAPHRIS, including long-term trials without comparison to placebo, syncope was reported in 0.6% (11/1953) of patients treated with SAPHRIS. In a 3-week, bipolar mania pediatric trial, syncope was reported in 1% (1/104) of patients treated with SAPHRIS 2.5 mg twice daily, 1% (1/99) of patients treated with SAPHRIS 5 mg twice daily, and 0% (0/99) for patients treated with SAPHRIS 10 mg twice daily compared to 0% (0/101) for patients treated with placebo. Patients should be instructed about non-pharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). SAPHRIS should be used with caution in (1) patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications); and (2) in the elderly. SAPHRIS should be used cautiously when treating patients who receive treatment with other drugs that can induce hypotension, bradycardia, respiratory or central nervous system depression [see Drug Interactions (7.1)]. Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs. **Leukopenia, Neutropenia, and Agranulocytosis -** In clinical trial and postmarketing experience, leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including SAPHRIS. Agranulocytosis (including fatal cases) has been reported with other agents in the class. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and history of drug induced leukopenia/neutropenia. In patients with a pre-existing low WBC/ANC or drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of SAPHRIS at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue SAPHRIS in patients with severe neutropenia (absolute neutrophil count <1000/mm³) and follow their WBC until recovery. **QT Prolongation -** The effects of SAPHRIS on the QT/QTc interval were evaluated in a dedicated adult QT study. This trial involved SAPHRIS doses of 5 mg, 10 mg, 15 mg, and 20 mg twice daily, and placebo, and was conducted in 151 clinically stable patients with schizophrenia, with electrocardiographic assessments throughout the dosing interval at baseline and steady state. At these doses, SAPHRIS was associated with increases in QTc interval ranging from 2 to 5 msec compared to placebo. No patients treated with SAPHRIS experienced QTc increases ≥ 60 msec from baseline measurements, nor did any patient experience a QTc of ≥ 500 msec. Electrocardiogram (ECG) measurements were taken at various time points during the SAPHRIS clinical trial program (5 mg or 10 mg twice daily doses). Post-baseline QT prolongations exceeding 500 msec were reported at comparable rates for SAPHRIS and placebo in these short-term trials. There were no reports of Torsade de Pointes or any other adverse reactions associated with delayed ventricular repolarization. The use of SAPHRIS should be avoided in combination with other drugs known to prolong QTc including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and antibiotics (e.g., gatifloxacin, moxifloxacin). SAPHRIS should also be avoided in patients with a history of cardiac arrhythmias and in other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including bradycardia; hypokalemia or hypomagnesemia; and presence of congenital prolongation of the QT interval. **Hyperprolactinemia -** Like other drugs that antagonize dopamine D₂ receptors, SAPHRIS can elevate prolactin levels, and the elevation can persist during chronic administration. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects. In SAPHRIS adult clinical trials, the incidences of adverse events related to abnormal prolactin levels were 0.4% versus 0% for placebo. In a 3-week, bipolar mania pediatric trial, the incidence of adverse events related to abnormal prolactin levels were 0% in the SAPHRIS 2.5 mg twice daily treatment group, 2% in the SAPHRIS 5 mg twice daily treatment group, and 1% in the SAPHRIS 10 mg twice daily treatment group versus to 1% for patients treated with placebo [see Adverse Reactions]. 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. 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 too limited to be conclusive. **Seizures -** Seizures were reported in 0% and 0.3% (0/572, 1/379) of adult patients treated with doses of 5 mg and 10 mg twice daily of SAPHRIS, respectively, compared to 0% (0/503, 0/203) of patients treated with placebo in short-term schizophrenia and bipolar mania trials, respectively. During adult pre-marketing clinical trials with SAPHRIS, including long-term trials without comparison to placebo, seizures were reported in 0.3% (5/1953) of patients treated with SAPHRIS. There were no reports of seizures in pediatric patients treated with SAPHRIS in a 3-week-term, bipolar mania trial. As with other antipsychotic drugs, SAPHRIS should be used with caution in patients with a history of seizures or with conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older. **Potential for Cognitive and Motor Impairment -** Somnolence was reported in patients treated with SAPHRIS. It was usually transient with the highest incidence reported during the first week of treatment. In short-term, fixed-dose, placebo-controlled schizophrenia adult trials, somnolence was reported in 15% (41/274) of patients on SAPHRIS 5 mg twice daily and in 13% (26/208) of patients on SAPHRIS 10 mg twice daily compared to 7% (26/378) of placebo patients. In short-term, placebo-controlled bipolar mania adult trials of therapeutic doses (5–10 mg twice daily), somnolence was reported in 24% (90/379) of patients on SAPHRIS compared to 6% (13/203) of placebo patients. During adult pre-marketing clinical trials with SAPHRIS, including long-term trials without comparison to placebo, somnolence was reported in 18% (358/1953) of patients treated with SAPHRIS. Somnolence (including sedation) led to discontinuation in 0.6% (12/1953) of patients in short-term, placebo-controlled trials. In a 3-week, placebo-controlled, bipolar I pediatric trial, the incidence of somnolence (including sedation and hypersomnia) for placebo, SAPHRIS 2.5 mg twice daily, 5 mg twice daily, and 10 mg twice daily, was 12% (12/101), 46% (48/104), 53% (52/99), and 49% (49/99), respectively. Somnolence led to discontinuation in 0%, 3%, 1%, and 2% of patients treated with placebo, and SAPHRIS 2.5 mg twice daily, 5 mg twice daily, and 10 mg twice daily, respectively. 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 SAPHRIS therapy does not affect them adversely. **Body Temperature Regulation -** Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. In the short-term placebo-controlled trials for both schizophrenia and acute bipolar disorder, the incidence of adverse reactions suggestive of body temperature increases was low ($\leq 1\%$) and comparable to placebo (0%). During clinical trials with SAPHRIS, including long-term trials without comparison to placebo, the incidence of adverse reactions suggestive of body temperature increases (pyrexia and feeling hot) was $\leq 1\%$. Appropriate care is advised when prescribing SAPHRIS for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration. **Suicide -** The possibility of a suicide attempt is inherent in psychotic illnesses and bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for SAPHRIS should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. **Dysphagia -** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Dysphagia was reported in 0.2% and 0% (1/572, 0/379) of patients treated with therapeutic doses (5–10 mg twice daily) of SAPHRIS as compared to 0% (0/378, 0/203) of patients treated with placebo in short-term schizophrenia and bipolar mania adult trials, respectively. During adult pre-marketing clinical trials with SAPHRIS, including long-term trials without comparison to placebo, dysphagia was reported in 0.1% (2/1953) of patients treated with SAPHRIS. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SAPHRIS is not indicated for the treatment of dementia-related psychosis, and should not be used in patients at risk for aspiration pneumonia [see also Warnings and Precautions]. **Use in Patients with Concomitant Illness -** Clinical experience with SAPHRIS in patients with certain concomitant systemic illnesses is limited [see Clinical Pharmacology in the full Prescribing Information]. SAPHRIS has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from pre-marketing clinical trials. Because of the risk of orthostatic hypotension with SAPHRIS, caution should be observed in cardiac patients [see Warnings and Precautions].

ADVERSE REACTIONS: The following adverse reactions are discussed in more detail in other sections of the labeling: **Use in Elderly Patients with Dementia-Related Psychosis [see Boxed Warning and Warnings and Precautions]; Neuroleptic Malignant Syndrome [see Warnings and Precautions]; Tardive Dyskinesia [see Warnings and Precautions]; Metabolic Changes [see Warnings and Precautions]; Hypersensitivity Reactions [see Contraindications, Warnings and Precautions and Patient Counseling Information in the full Prescribing Information]; Application site reactions including oral ulcers, blisters, peeling/sloughing and inflammation [see Adverse Reactions]; Orthostatic Hypotension, Syncope, and other Hemodynamic Effects [see Warnings and Precautions]; Leukopenia, Neutropenia, and Agranulocytosis [see Warnings and Precautions]; QT Interval Prolongation [see Warnings and Precautions]; Hyperprolactinemia [see Warnings and Precautions]; Seizures [see Warnings and Precautions]; Potential for Cognitive and Motor Impairment [see Warnings and Precautions]; Body Temperature Regulation [see Warnings and Precautions]; Suicide [see Warnings and Precautions]; Dysphagia [see Warnings and Precautions]; Use in Patients with Concomitant Illness [see Warnings and Precautions]. The most common adverse reactions ($\geq 5\%$ and at least twice the rate of placebo) reported with acute treatment in adults with schizophrenia were akathisia, oral hypoesthesia, and somnolence. The safety profile of SAPHRIS in the maintenance treatment of schizophrenia in adults was similar to that seen with acute treatment. The most common adverse reactions ($\geq 5\%$ and at least twice the rate of placebo) reported with acute monotherapy treatment of manic or mixed episodes associated with bipolar I disorder in adults were somnolence, dizziness, extrapyramidal symptoms other than akathisia, and increased weight and during the adjunctive therapy trial in bipolar I disorder in adults were somnolence and oral hypoesthesia. The adult information below is derived from a clinical trial database for SAPHRIS consisting of over 4565 patients and/or healthy subjects exposed to one or more sublingual doses of SAPHRIS. A total of 1314 SAPHRIS-treated patients were treated for at least 24 weeks and 785 SAPHRIS-treated patients had at least 52 weeks of exposure at therapeutic doses. In a 3-week monotherapy trial, the most common adverse reactions ($\geq 5\%$ and at least twice the rate of placebo) reported in pediatric patients with bipolar I disorder treated with SAPHRIS were somnolence, dizziness, dysgeusia, oral paresthesia, nausea, increased appetite, fatigue, and increased weight. No new major safety findings were reported from a 50-week, open-label, uncontrolled safety trial. A total of 651 pediatric patients were treated with SAPHRIS. Of these patients, 352 pediatric patients were treated with SAPHRIS for at least 180 days and 58 pediatric patients treated with SAPHRIS had at least 1 year of exposure. The safety of SAPHRIS was evaluated in 403 pediatric patients with bipolar I disorder who participated in a 3-week, placebo-controlled, double-blind trial, of whom 302 patients received SAPHRIS at fixed doses ranging from 2.5 mg to 10 mg twice daily. The stated frequencies of adverse reactions represent the proportion of individuals who experienced a treatment-emergent adverse event of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Clinical Trials Experience -** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical**

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 colleagues²² indi-

cates 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%, 3%); 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, blepharospasm, 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 Trial. Values shown are in parentheses as Placebo [N=203]; SAPHRIS 5 mg 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† (0%, 3%, 0%, 1%, 1%); Gastrointestinal Disorders: Oral paraesthesia‡ (4%, 25%, 25%, 30%, 27%); Nausea (3%, 6%, 6%, 6%); Vomiting (3%, 4%, 4%, 4%, 4%); Abdominal pain‡ (7%, 9%, 3%, 5%, 6%); Glossodynia (0%, 0%, 2%, 0%, 1%); General Disorders and Administrative Site Disorders: Fatigue§ (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¶ (0%, 1%, 3%, 1%); 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‡ (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%). †Includes the preferred terms tachycardia and heart rate increased. ‡Includes the preferred terms oral hypoesthesia, oral paresthesia, and oral dysesthesia. §Includes the preferred terms abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort. ¶Includes the preferred terms fatigue and lethargy. ††Includes the preferred terms hyperinsulinemia and blood insulin increased. †††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 end-point) 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 (1.3%), 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 mg or 10 mg twice daily* [N=158]. **Gastrointestinal disorders:** Dyspepsia (2%, 3%); Oral hypoesthesia (0%, 5%); General disorders: Fatigue (4%, 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 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 focus-

ing 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.

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on pharmacologic or other grounds. Reactions already listed for either adults or pediatric patients in other parts of *Adverse Reactions*, or those considered in *Contraindications*, *Warnings and Precautions* or *Overdosage* are not included. Reactions are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (frequent) (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); those occurring in 1/1000 to 1/10000 patients (infrequent); and those occurring in fewer than 1/10000 patients (rare). *Blood and lymphatic disorders*: infrequent: anemia; rare: thrombocytopenia; *Cardiac disorders*: infrequent: temporary bundle branch block; *Eye disorders*: infrequent: accommodation disorder; *Gastrointestinal disorders*: infrequent: swollen tongue; *General disorders*: rare: idiosyncratic drug reaction; *Investigations*: infrequent: hyponatremia; *Nervous system disorders*: infrequent: dysarthria. Following is a list of MedDRA terms not already listed either for adults or pediatric patients in other parts of *Adverse Reactions*, or those considered in *Contraindications*, *Warnings and Precautions* or *Overdosage* that reflect adverse reactions reported by pediatric patients (Ages 10 to 17 years) treated with sublingual SAPHRIS at doses of 2.5 mg, 5 mg, or 10 mg twice daily during any phase of a trial within the database of pediatric patients. *Eye disorders*: infrequent: diplopia, vision blurred; *Gastrointestinal disorders*: infrequent: gastroesophageal reflux disease; *Injury, Poisoning, and Procedural Complications*: infrequent: fall; *Skin and subcutaneous tissue disorders*: infrequent: photosensitivity reaction; *Renal and urinary disorders*: infrequent: enuresis. **Postmarketing Experience** - The following adverse reactions have been identified during post-approval use of SAPHRIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure. In many cases, the occurrence of these adverse reactions led to discontinuation of therapy. Application site reactions, primarily in the sublingual area, have been reported. These application site reactions included oral ulcers, blisters, peeling/sloughing, and inflammation. Choking has been reported by patients, some of whom may have also experienced oropharyngeal muscular dysfunction or hypoesthesia.

DRUG INTERACTIONS: Drugs Having Clinically Important Drug Interactions with SAPHRIS - Table 12 in the full Prescribing Information lists the Clinically Important Drug Interactions with SAPHRIS by the Concomitant Drug Name or Drug Class: Antihypertensive Drugs - Clinical Rationale: Because of its α_1 -adrenergic antagonism with potential for inducing hypotension, SAPHRIS may enhance the effects of certain antihypertensive agents [see *Warnings and Precautions*]. Clinical Recommendation: Monitor blood pressure and adjust dosage of antihypertensive drug accordingly. Strong CYP1A2 Inhibitors (e.g., fluvoxamine) - Clinical Rationale: SAPHRIS is metabolized by CYP1A2. Marginal increase of asenapine exposure was observed when SAPHRIS is used with fluvoxamine at 25 mg administered twice daily [see *Clinical Pharmacology in the full Prescribing Information*]. However, the tested fluvoxamine dose was suboptimal. Full therapeutic dose of fluvoxamine is expected to cause a greater increase in asenapine exposure. Clinical Recommendation: Dosage reduction for SAPHRIS based on clinical response may be necessary. CYP2D6 substrates and inhibitors (e.g., paroxetine) - Clinical Rationale: SAPHRIS may enhance the inhibitory effects of paroxetine on its own metabolism. Concomitant use of paroxetine with SAPHRIS increased the paroxetine exposure by 2-fold as compared to use paroxetine alone [see *Clinical Pharmacology in the full Prescribing Information*]. Clinical Recommendation: Reduce paroxetine dose by half when paroxetine is used in combination with SAPHRIS. **Drugs Having No Clinically Important Interactions with SAPHRIS** - No dosage adjustment of SAPHRIS is necessary when administered concomitantly with paroxetine (see Table 12 in Drug Interactions for paroxetine dosage adjustment), imipramine, cimetidine, valproate, lithium, or a CYP3A4 inducer (e.g., carbamazepine, phenytoin, rifampin). In addition, valproic acid and lithium pre-dose serum concentrations collected from an adjunctive therapy study were comparable between asenapine-treated patients and placebo-treated patients indicating a lack of effect of asenapine on valproic and lithium plasma levels.

USE IN SPECIFIC POPULATIONS: Pregnancy - Pregnancy Exposure Registry - There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to SAPHRIS during pregnancy. For more information contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit <http://www.nationalpregnancyregistry.org/>. **Risk Summary** - Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. Studies have not been conducted with SAPHRIS in pregnant women. There are no available human data informing the drug-associated risk. The background risk of major birth defects and miscarriage for the indicated populations are unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies. No teratogenicity was observed in animal reproduction studies with intravenous administration of asenapine to rats and rabbits during organogenesis at doses 0.7 and 0.4 times, respectively, the maximum recommended human dose (MRHD) of 10 mg sublingually twice daily. In a pre- and post-natal study in rats, intravenous administration of asenapine at doses up to 0.7 times the MRHD produced increases in post-implantation loss and early pup deaths, and decreases in subsequent pup survival and weight gain [see *Data*]. Advise pregnant women of the potential risk to a fetus. **Clinical Considerations: Fetal/Neonatal Adverse Reactions** - Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. **Data - Animal Data** - In animal studies, asenapine increased post-implantation loss and decreased pup weight and survival at doses similar to or less than recommended clinical doses. In these studies there was no increase in the incidence of structural abnormalities caused by asenapine. Asenapine was not teratogenic in reproduction studies in rats and rabbits at intravenous doses up to 1.5 mg/kg in rats and 0.44 mg/kg in rabbits administered during organogenesis. These doses are 0.7 and 0.4 times, respectively, the maximum recommended human dose (MRHD) of 10 mg twice daily given sublingually on a mg/m² basis. Plasma levels of asenapine were measured in the rabbit study, and the area under the curve (AUC) at the highest dose tested was 2 times that in humans receiving the MRHD. In a study in which rats were treated from day 6 of gestation through day 21 postpartum with intravenous doses of asenapine of 0.3, 0.9, and 1.5 mg/kg/day (0.15, 0.4, and 0.7 times the MRHD of 10 mg twice daily given sublingually on a mg/m² basis), increases in post-implantation loss and early pup deaths were seen at all doses, and decreases in subsequent pup survival and weight gain were seen at the two higher doses. A cross-fostering study indicated that the decreases in pup survival were largely due to prenatal drug effects. Increases in post-implantation loss and decreases in pup weight and survival were also seen when pregnant rats were dosed orally with asenapine. **Lactation - Risk Summary** - Lactation studies have not been conducted to assess the presence of asenapine in human milk, the effects of asenapine on the breastfed infant, or the effects of asenapine on milk production. Asenapine is excreted in rat milk. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for SAPHRIS and any potential adverse effects on the breastfed infant from SAPHRIS or from the underlying maternal condition. **Pediatric Use** - Safety and efficacy of SAPHRIS in pediatric patients below the age of 10 years of age have not been evaluated. **Bipolar I Disorder** - The safety and efficacy of SAPHRIS as monotherapy in the treatment of bipolar I disorder were established in a 3-week, placebo-controlled, double-blind trial of 403 pediatric patients 10 to 17 years of age, of whom 302 patients received SAPHRIS at fixed doses ranging

from 2.5 mg to 10 mg twice daily [see *Adverse Reactions*, and *Dosage and Administration*, *Clinical Pharmacology*, and *Clinical Studies in the full Prescribing Information*]. In a Phase 1 study, pediatric patients aged 10 to 17 years appeared to be more sensitive to dystonia with initial dosing with asenapine when the recommended dose escalation schedule was not followed. No new major safety findings were reported from a 50-week, open-label, uncontrolled safety trial in pediatric patients with bipolar disorder treated with SAPHRIS monotherapy. The safety and efficacy of SAPHRIS as adjunctive therapy in the treatment of bipolar I disorder have not been established in the pediatric population. In general, the pharmacokinetics of asenapine in pediatric patients (10 to 17 years) and adults are similar [see *Clinical Pharmacology in the full Prescribing Information*]. **Schizophrenia** - Efficacy of SAPHRIS was not demonstrated in an 8-week, placebo-controlled, double-blind trial, in 306 adolescent patients aged 12 to 17 years with schizophrenia at doses of 2.5 and 5 mg twice daily. The most common adverse reactions (proportion of patients equal or greater than 5% and at least twice placebo) reported were somnolence, akathisia, dizziness, and oral hypoesthesia or paresthesia. The proportion of patients with an equal or greater than 7% increase in body weight at endpoint compared to baseline for placebo, SAPHRIS 2.5 mg twice daily, and SAPHRIS 5 mg twice daily was 3%, 10%, and 10%, respectively. The clinically relevant adverse reactions identified in the pediatric schizophrenia trial were generally similar to those observed in the pediatric bipolar and adult bipolar and schizophrenia trials. No new major safety findings were reported from a 26-week, open-label, uncontrolled safety trial in pediatric patients with schizophrenia treated with SAPHRIS monotherapy. **Juvenile Animal Data** - Subcutaneous administration of asenapine to juvenile rats for 56 days from day 14 of age to day 69 of age at 0.4, 1.2, and 3.2 mg/kg/day (0.2, 0.6 and 1.5 times the maximum recommended human dose of 10 mg twice daily given sublingually on a mg/m² basis) resulted in significant reduction in body weight gain in animals of both sexes at all dose levels from the start of dosing until weaning. Body weight gain remained reduced in males to the end of treatment, however, recovery was observed once treatment ended. Neurobehavioral assessment indicated increased motor activity in animals at all dose levels following the completion of treatment, with the evidence of recovery in males. There was no recovery after the end of treatment in female activity pattern as late as day 30 following the completion of treatment (last retesting). Therefore, a No Observed Adverse Effect Level (NOAEL) for the juvenile animal toxicity of asenapine could not be determined. There were no treatment-related effects on the startle response, learning/memory, organ weights, microscopic evaluations of the brain and, reproductive performance (except for minimally reduced conception rate and fertility index in males and females administered 1.2 and 3.2 mg/kg/day). **Geriatric Use** - Clinical studies of SAPHRIS in the treatment of schizophrenia and bipolar mania did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Of the approximately 2250 patients in pre-marketing clinical studies of SAPHRIS, 1.1% (25) were 65 years of age or over. Multiple factors that might increase the pharmacodynamic response to SAPHRIS, causing poorer tolerance or orthostasis, could be present in elderly patients, and these patients should be monitored carefully. Based on a pharmacokinetic study in elderly patients, dosage adjustments are not recommended based on age alone [see *Clinical Pharmacology in the full Prescribing Information*]. Elderly patients with dementia-related psychosis treated with SAPHRIS are at an increased risk of death compared to placebo. SAPHRIS is not approved for the treatment of patients with dementia-related psychosis [see *Boxed Warning*]. **Renal Impairment** - No dosage adjustment for SAPHRIS is required on the basis of a patient's renal function (mild to severe renal impairment, glomerular filtration rate between 15 and 90 mL/minute). The exposure of asenapine was similar among subjects with varying degrees of renal impairment and subjects with normal renal function [see *Clinical Pharmacology in the full Prescribing Information*]. The effect of renal function on the excretion of other metabolites and the effect of dialysis on the pharmacokinetics of asenapine has not been studied. **Hepatic Impairment** - SAPHRIS is contraindicated in patients with severe hepatic impairment (Child-Pugh C) because asenapine exposure is 7-fold higher in subjects with severe hepatic impairment than the exposure observed in subjects with normal hepatic function. No dosage adjustment for SAPHRIS is required in patients with mild to moderate hepatic impairment (Child-Pugh A and B) because asenapine exposure is similar to that in subjects with normal hepatic function [see *Contraindications and Clinical Pharmacology in the full Prescribing Information*]. **Other Specific Populations** - No dosage adjustment for SAPHRIS is required on the basis of a patient's sex, race (Caucasian and Japanese), or smoking status [see *CLINICAL PHARMACOLOGY in the full Prescribing Information*].

OVERDOSAGE: Human Experience - In adult pre-marketing clinical studies involving more than 3350 patients and/or healthy subjects, accidental or intentional acute overdosage of SAPHRIS was identified in 3 patients. Among these few reported cases of overdose, the highest estimated ingestion of SAPHRIS was 400 mg. Reported adverse reactions at the highest dosage included agitation and confusion. **Management of Overdosage**: There is no specific antidote to SAPHRIS. The possibility of multiple drug involvement should be considered. An electrocardiogram should be obtained and management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Consult with a Certified Poison Control Center for up-to-date guidance and advice on the management of overdose (1-800-222-1222.) Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of SAPHRIS-induced alpha blockade). In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

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Please also see full Prescribing Information at www.SAPHRIS.com.

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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 irresist-

times meticulously, often report that they had to surrender to overwhelming urges.

Neurobiology and experience

Over 30 years ago, Linnoila and colleagues³ 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 cingulate 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

