Methylated Spirits: *Epigenetic Hypotheses of Psychiatric Disorders*

Stephen M. Stahl, MD, PhD

NEW TREND IN PSYCHOPHARMACOLOGY

Our spirits may be regulated by the methylation of our genes. Methylation, acetylation, and other biochemical processes are the molecular switches for turning genes on and off. There is evidence now that certain behaviors, feelings, and psychiatric symptoms may be modified by turning various genes on or off. If classical genetics is the sequence of DNA that is inherited, then epigenetics is a parallel process determining whether a given gene (ie, a sequence of DNA coding for transcription) is expressed into its RNA or is silenced. Epigenetics is now entering psychiatry with the hypothesis that normal genes as well as risk genes can both contribute to a mental disorder. That is, it has long been hypothesized that when "abnormal" genes with an altered sequence of DNA are inherited as risk genes for a mental illness, these risk genes will make an abnormal gene product in neurons, contributing to inefficient information processing in various brain circuits and creating risk for developing a symptom of a mental illness. Now comes the role of epigenetic actions in mental illnesses. If normal genes make normal gene products but at the wrong time, either being epigenetically expressed in neurons when they should be silenced or epigenetically silenced in neurons when they should be expressed, particularly under the influence of environmental factors and stress, this, too, can contribute to inefficient information processing in brain circuits, increasing the chance of developing symptoms of a psychiatric disorder. Here we describe the role of epigenetics and methylomics (methylating or demethylating upstream genes and downstream molecules) in various psychiatric disorders, emphasizing schizophrenia, and demonstrate whether your spirits can be truly methylated. In a companion article, we describe how psychiatry is on the threshold of new therapeutics that target epigenetic regulation of brain genes via methylomics and aceylation/de-acetylation.

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WHAT IS EPIGENETICS?

Genetics is the DNA code for what a cell can transcribe into specific types of RNA or translate into specific proteins. Epigenetics is a parallel system that determines whether any given gene is actually made into its specific RNA and protein, or if it is instead ignored.[1-3] If the genome is a lexicon of all protein "words," then the epigenome is a "story" resulting from arranging the "words" into a coherent tale. The genomic lexicon of all potential proteins is the same in all of the >200 types of cells in the body of a given individual. Thus, the plot of how a liver cell becomes a liver cell or how a neuron becomes a neuron is the selection of which specific genes are expressed or silenced in the two different cell types. For cells that differentiate into neurons, both genetics and epigenetics seem to play a role in determining whether brain circuits connecting these neurons develop into a compelling narrative, such as learning and memory, or regrettably evolve into a tragedy such as drug abuse, stress reactions, or a psychiatric disorder.

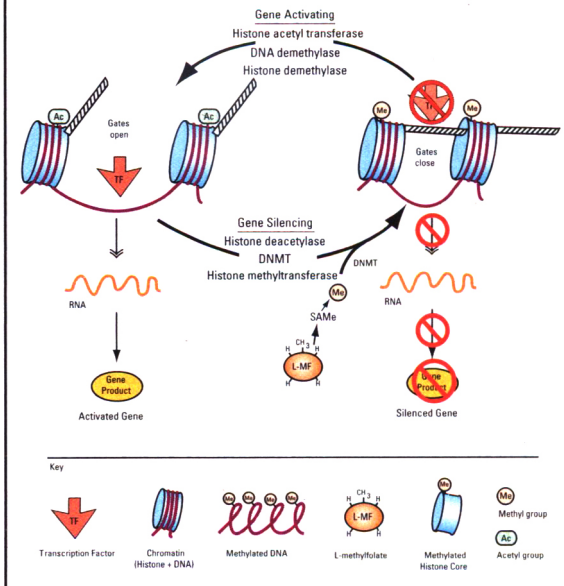
WHAT ARE THE MOLECULAR MECHANISMS OF EPIGENETICS?

Epigenetic mechanisms turn genes on and off by modifying the structure of chromatin in the cell nucleus.[2-4] The character of a cell is fundamentally determined by its chromatin, a substance composed of nucleosomes. Nucleosomes are an octet of proteins called histones around which DNA is wrapped (Figure 1). Epigenetic control over whether a gene is read (ie, expressed) or not read (ie, silenced), is done by modifying the structure of chromatin. Chemical modifications that can do this include not only methylation, but also acetylation, phosphorylation, and others.[2-4] For example, when DNA or histones are methylated, this compacts the chromatin and acts to close off access of molecular transcription factors to the promoter regions of DNA, with the consequence that the gene in this region in silenced (not expressed), so no RNA or protein is manufactured (Figure 1). Silenced DNA means that the molecular features of that gene are not part of a given cell's personality.

Histones are methylated by enzymes called histone methyltransferases and this is reversed by enzymes called histone demethylases (Figure 1). Methylation of histones can silence genes whereas demethylation of histones can activate genes.[2-4] DNA can also be methylated and this, too, silences genes. Demethylation of DNA reverses this. Methylation of DNA is regulated by DNA methyltransferase (DNMT) enzymes and demethylation of DNA by DNA demethylase enzymes (Figure 1). There are many forms of methyltransferase enzymes and they all tag their substrates with methyl groups donated from L-methylfolate via S-adenosyl-methionine (SAMe) (Figure 1).

Methylation of DNA can eventually lead to de-acetylation of histones as well, by activating enzymes called histone de-acetylases (HDACs).[2-4] Deacetylation of histones also has a silencing action on gene expression (Figure 1). Methylation and de-acetylation compress chromatin, as though a molecular gate has been closed, and transcription factors that activate genes can not get access to their promoter regions. Thus, the genes are silenced and not transcribed into RNA or translated into proteins (Figure 1). On the other hand, demethylation and acetylation do just the oppositte; they

FIGURE 1.
Gene activation and silencing



Molecular gates are opened by acetylation and/or demethylation of histones, allowing transcription factors access to genes, thus activating them. Molecular gates are closed by deacetylation and/or methylation provided by the methyl donor SAMe derived from L-methylfolate. This prevents access of transcription factors to genes, thus silencing them.

Ac=acetyl; Me=methyl; DNMT=DNA methyltransferase; TF=transcription factor; SAMe=S-adenosyl-methionine; L-MF=L-methylfolate.

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decompress chromatin as though a molecular gate has been opened, and thus transcription factors can get to the promoter regions of genes and activate them (Figure 1). Activated genes then become part of the molecular personality of a given cell.

MAINTAINING VERSUS CHANGING THE STATUS QUO

Some enzymes try to maintain the status quo of a cell, such as the enzyme DNMT1, which maintains the methylation of specific areas of DNA and keeps various genes quiet for a lifetime.[2-5] For example, this process keeps a liver cell always a liver cell, including when that cell divides into another one. This process also keeps a neuron a neuron, by always silencing a different set of genes. Presumably methylation is maintained at genes that one cell does not need, even though another cell type might.

It used to be thought that once a cell differentiated, the epigenetic pattern of gene activation and gene silencing remained stable for the lifetime of that cell. Now, however, it is hypothesized that there are various circumstances in which epigenetics may change in mature, differentiated cells. For example, in certain cancers, there may be de novo and unwanted activation of diabolical genes to produce cancerous villains as the storyline of certain cell types.[6,7] Cancer therapeutics is vigorously exploring how to selectively silence such evil genes by using heroic epigenetic mechanisms to vanquish cancerous villains, resolve the cellular crisis, and *have only the good cells live happily ever after.*[8]

Similarly in neurobiology, the initial epigenetic pattern of a neuron is indeed set during neurodevelopment to give each neuron its own lifelong "personality."[2-4] However, it now appears that the storyline of some neurons is that they respond to their narrative experiences throughout life with a changing character arc, thus causing de novo alterations in their epigenome. Depending upon what happens to a neuron, such as experiencing child abuse, adult stress, dietary deficiencies, or productive new encounters, it now seems that previously silenced genes can become activated and/or previously active genes can become silenced.[2-4] When this happens, both favorable and unfavorable developments can occur in the character of neurons. Favorable epigenetic mechanisms may be triggered in order for one to learn (eg, spatial memory formation)[4] or to experience the therapeutic actions of psychopharmacologic agents.[3,9] On the other hand, unfavorable epigenetic mechanisms may be triggered in order for one to become addicted to drugs of abuse or to experience various forms of "abnormal learning", such as when one develops fear conditioning, an anxiety disorder, or a chronic pain condition.[4]

How these epigenetic mechanisms arrive at the scene of the crime remains a compelling neurobiological and psychiatric mystery. Nevertheless, a legion of scientific detectives is working these cases and is beginning to show how epigenetic mechanisms are mediators of psychiatric disorders. There is also the possibility that epigenetic mechanisms can be harnessed to treat addictions, extinguish fear, prevent the development of chronic pain states,[4] and maybe even prevent disease progression of psychiatric disorders such as schizophrenia by identifying high risk individuals before the "plot thickens" and the disorder is irreversibly established.

One of the mechanisms for changing the status quo of epigenomic patterns in a mature cell is via de novo DNA methylation by a type of DNMT enzyme known as DNMT2 or DNMT3.[4] These enzymes target neuronal genes for silencing that were previously active in a mature neuron. Of course, deacetylation of histones near previously active genes would do the same thing, namely silence them, and this is mediated by enzymes called HDACs.[2-4] In reverse, demethylation or acetylation of genes both activate genes that were previously silent. The real question is how does a neuron know which genes among its thousands to silence or activate in response to the environment, including stress, drugs, and diet? How might this go wrong when a psychiatric disorder develops? This part of the story remains a twisted mystery but some very interesting detective work has already been done by various investigators who hope to understand how some neuronal stories evolve into psychiatric tragedies. These investigations may set the stage for rewriting the narrative of various psychiatric disorders by therapeutically altering the epigenetics of key neuronal characters so that the story has a happy ending. That possibility is described in a companion article.[10]

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METHYLOMICS AND THE SCIENCE OF METHYLATED SPIRITS IN PSYCHIATRY

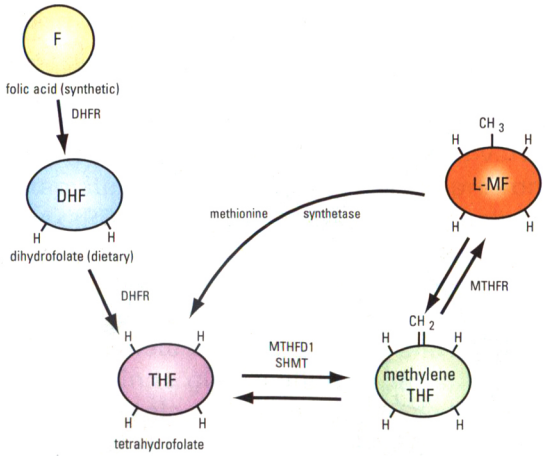
Methylomics is how the body uses methyl groups for various metabolic functions, from maintaining DNA methylation to the synthesis of vital cellular components to the inactivation of various biological substances.[11,12] The body cannot make methyl groups, but gets them from dietary sources, especially by converting folate to L-methylfolate, methionine, and ultimately to SAMe which is the universal methyl donor (Figure 2). Methyl groups are important in the synthesis of nucleic acid bases,[11] which are linked not only to the synthesis of DNA and RNA,[11] but also to the synthesis of biopterin[13] (Figure 3), the critical cofactor required by the enzymes that synthesize the monoamine neurotransmitters dopamine (DA), norepinephrine (NE), and serotonin (5-HT) (Figure 4). Methyl groups are also involved in the synthesis of melatonin and epinephrine, and in the inactivation of DA and NE, the latter by the methyltransferase enzyme known as catechol-o-methyl transferase (COMT) (Figure 5). Thus, methylomics is a critical regulatory process for genetics, epigenetics, and neurotransmitters, and is in a key position to influence our spirits, not only those that occur during normal brain development, but those that represent symptoms of psychiatric disorders.

UPSTREAM VERSUS DOWNSTREAM METHYLOMICS IN PSYCHIATRY

Information flow starts at the genome and can be considered "upstream." Genetic instructions then flow "downstream" into various gene products, small molecules, and cellular functions. Epigenetic molecular mechanisms act upstream and are thought to negotiate how the environment interfaces with genes.[4] For example, epigenetic mechanisms are recruited to drive experience-dependent modifications in cognition and behavior.[4] When these upstream mechanisms go awry in the brain, they are thought to be capable of producing psychiatric symptoms and mental illnesses. Downstream consequences of epigenetic mechanisms include the ability to form new synapses with input of new information, to make enzymes and receptors capable of regulating neurotransmitter levels, and to regulate the availability of methyl groups themselves for use in both upstream and downstream methylomics.[2-4] The efficient operation of these downstream functions is also necessary in order to prevent breakdown of neuronal functioning, and potentially, to prevent psychiatric disorders.

Upstream histone and DNA methylation provide important clues about gene expression in the human brain during normal development and in certain disease states. For example,

FIGURE 2.
Formation of l-methylfolate from folic acid



F=folic acid; DHFR=dihydrofolate reductase; ; DHF=dihydrofolate; L-MF=L-methylfolate; MTHFR=methylene tetrahydrofolate reductase; SHMT=serine hydroxy methyl transferase; MTHFD1=MTHF dehydrogenase.

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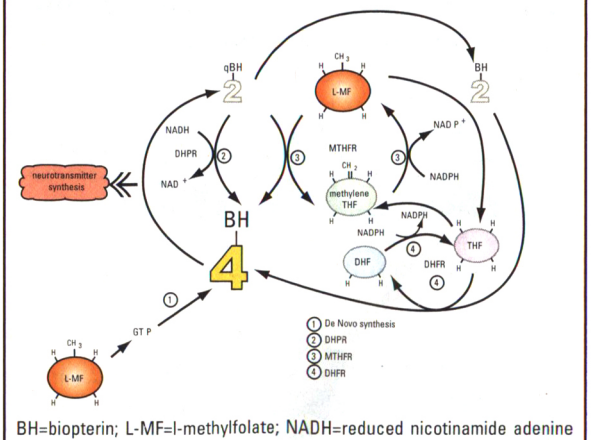
FIGURE 3.
L-Methylfolate regulates biopterin production



BH=biopterin; L-MF=l-methylfolate; NADH=reduced nicotinamide adenine dinucleotide; DHPR=dihydro pteridine reductase; NADP=nicotinamide adenine dinucleotide phosphate; MTHFR=methylene tetrahydrofolate reductase; THF=tetrahydrofolate; DHF=dihydrofolate; DHFR=dihydrofolate reductase; GTP=guanosine triphosphate.

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mutations within genes encoding for various histone methyltransferases are linked to mental retardation (eg, the H3K9 specific histone methyltransferease EHMT1) and to autism (eg, H3K4 specific histone memethylase JARID1C/SMCX).[14] Mutations in the gene for a methylated DNA binding protein (MeCP2) that normally silences genes are linked to the behavioral abnormalies of Rett syndrome.[15] Histone hyper-trimethylation has been described in Huntington's Disease.[15]

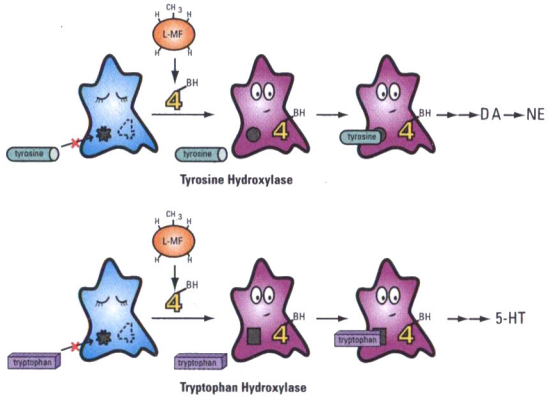
SCHIZOPHRENIA IS A VAST CONSPIRACY

For a long time, studies of identical twins have hinted that epigenetics are in play in schizophrenia. An explanation is needed for why only half of co-twins of schizophrenics also have this illness even though both have inherited all the same genes. A leading hypothesis today is that genes interact epigenetically with the environment, essentially conspiring to cause schizophrenia when some genes are expressed in the affected twin, and yet not to cause schizophrenia in the unaffected twin because some critical risk genes remain silent.[2]

Another hint that such epigenetic mechanisms are involved in schizophrenia is the observation that methionine administration can exacerbate schizophrenia. This used to be attributed to downstream methylomics, namely the hypothetical formation of transmethylated neurotransmitters that were hallucinogenic,[16] but this was never substantiated. Perhaps instead this methyl donor upsets the delicate balance of upstream methylomics, conspiring with epigenetic mechanisms to cause unwanted epigenetic changes and thus exacerbation of schizophrenia. The mechanism of methionine-induced actions in schizophrenia, however, still remains undetermined.

Today, the most active theories about schizophrenia have to do with neurodevelopmental hypotheses due to a confluence of multiple genetic, epigenetic, and environmental factors, each named as potential co-conspirators in schizophrenia.[9] Alterations in slowly developing changes in the normal neurodevelopment of the brain are hypothetically mediated by alterations in the upstream epigenetic regulation of gene expression over time[2-4] and these are linked to the cause of schizophrenia and other psychiatric illnesses.[2-4] For example, the H3K4 specific histone methyl transferase MLL1 is essential for hippocampal synaptic plasticity and might be involved in cortical dysfunction in some cases of schizophrenia.[14] Upstream epigenetic alterations in DNA methylation of some genes or gene promoters, such as those for COMT,[17,18] for various types of glutamate receptors,[9] for glutamic acid decarboxylase (GAD) the enzyme that synthesizes γ-amino butyric acid (GABA),[14,19-22] and for the critical synaptic structural protein reelin, have been described in some,[20-26] but not

FIGURE 4.
Biopterin cofactor for monoamine neurotransmitter synthesis



L-MF=L-methylfolate; BH=biopterin; DA=dopamine; NE=norepinephrine; 5-HT=serotonin.

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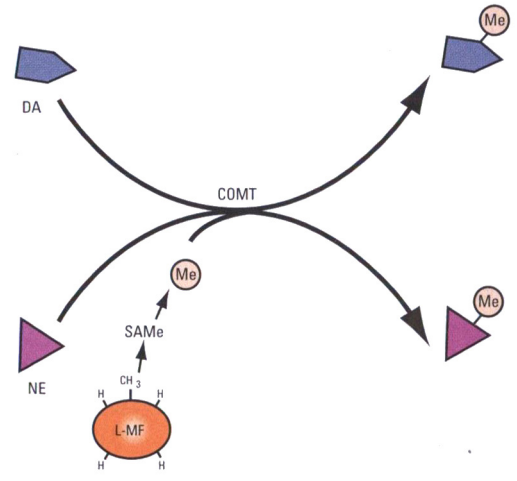
FIGURE 5.
Inactivation of dopamine and norepinephrine by COMT



COMT=Catechol-O-Methyl Transferase; DA=dopamine; Me=methyl; SAMe=S-adenosyl-methionine; L-MF=L-methylfolate.

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all,[27-29] studies of cerebral cortex of patients with psychosis. Whether the abnormalities in methyl marks on DNA that are postulated to be present in psychiatric disorders such as schizophrenia are due to inherited factors, acquired factors, or both, is not yet known but both are suspected.

Modern theories of major mental illnesses do not suggest that genetics is the cause of mental illnesses so much as it is a co-conspirator with epigenetics interfacing with the environment.[3,4,9,30] There appear to be no major mental illnesses due to a single gene mutation, but there do appear to be many mental illnesses linked to the inheritance of multiple simultaneous risk genes.[9] Even this is not enough for most mental illnesses to become manifest as it seems that stress from the environment, probably because it triggers aberrant epigenetic mechanisms, is also required before the brain decompensates and develops a mental disorder.[4,9,30] Thus, mental illness may really be a conspiracy among many genetic, epigenetic, and environmental co-conspirators.

GLUTAMATE AND GABA AS CO-CONSPIRATORS IN SCHIZOPHRENIA

Although there is no "gene for schizophrenia" there are multiple candidates for risk genes, many of which may need to be simultaneously inherited in order for schizophrenia to occur. Several of these genes are thought to be those that express proteins whose functions converge at glutamate synapses.[9,19-26] This observation has led to the hypothesis that the glutamate synapse with N-methyl-d-aspartate (NMDA) glutamate receptors that regulate DA circuits is the scene of the crime for schizophrenia.[9] One notion is that there is abnormal connectivity between GABAergic interneurons and glutamatergic pyramidal neurons, or between various glutamatergic pyramidal neurons in prefrontal cortex (PFC) in schizophrenia due to the diabolical actions of GABA and glutamate co-conspirators at glutamate synapses.[9]

Speaking epigenetically, glutamate receptor genes (for metabotropic GRM 1-7 and ionotropic NMDA, kainite glutamate receptors) undergo dynamic, region, and cell specific changes in expression during the course of normal brain development, accompanied by complementary alterations in methylation (H3K4 di- and trimethylation) at the sites of the corresponding promoters.[14-31] There is also normally progressive upregulation of GABAergic mRNAs during development of human PFC relected by parallel increases in J3K4 methylation at sites of these promoters,[14,32] suggesting H3K4 di- and trimethylation defining actively expressed genes in the normally developing human brain.[14]

Hypothetically, schizophrenia causes inherited and environment- or experience-triggered, disease-related changes in gene expression for glutamate and GABA systems, potentially explained by alterations of H3K4 trimethyation or other histone modifications.[14] A deficit in H3K4me3 marks at the promoter of the GABA synthesis gene GAD (GAD1/GAD67) has been described in the postmortem schizophrenic brain, along with a deficit in GAD1 transcript and increased levels of the repressive marker H3K27me3.[14] Altered methylation of DNA of a more global nature has also been described in schizophrenia.[33,34] Most theories of schizophrenia that involve glutamate and GABA suggest that multiple simultaneous co-conspirators, acting either epigenetically or genetically, must plot together in the conspiracy in order for schizophrenia to occur.[9]

L-METHYLFOLATE AS A CO-CONSPIRATOR IN SCHIZOPHRENIA

Another interesting link of schizophrenia with upstream methylomics is that to the enzyme methylene tetrahydrofolate reductase (MTHFR), the enzyme that synthesizes the methyl donor L-methyl folate[11-13] (Figure 2). MTHFR supplies methyl groups used by upstream and downstream methylomic reactions by synthesizing L-methylfolate from folate precursors derived from the diet[11-13] (Figure 2). Severe MTHFR deficiency, although rare, is associated with psychosis and developmental delay.[35] A more common inherited form of MTHFR, known as the C677T variant and also called the T allele, shows a less profound reduction in enzyme activity but nevertheless causes elevation in homocysteine levels, an indirect indication of L-methylfolate deficiency[36,37] (Figure 6). The T allele of MTHFR may thus be associated with a marginal functional availability of methyl donor groups. Interestingly, homocysteine levels have been reported to be high and folate levels low in patients with schizophrenia. Folate levels correlate with the severity of negative symptoms of schizophrenia.[38-40] Administration of folate or L-methylfolate raise L-methylfolate levels and

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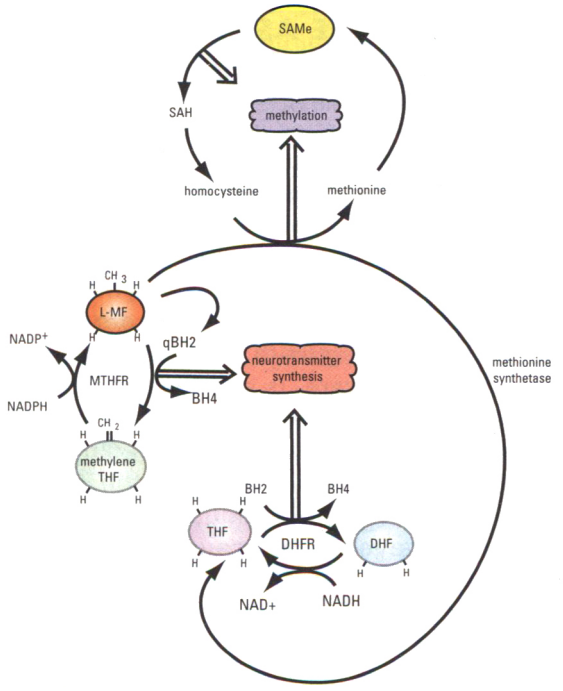
reduce homocysteine levels.[36,37] In schizophrenic patients, folate and L-methylfolate have also been reported to improve positive, negative, and cognitive symptoms.[38-40]

Inheriting the T form of MTHFR increases the risk for schizophrenia[41-48] and especially the risk for executive dysfunction in schizophrenia.[41,47,48] Since inheriting the T allele of this enzyme means significantly reduced enzyme activity of MTHFR as well as reduced availability of methyl donors, this allele could compromise both upstream DNA methylation and downstream metabolic reactions dependent upon methylation. It thereby increases the risk for schizophrenia or cognitive dysfunction in schizophrenia.

Another link of methyl donor deficiency to schizophrenia comes from observations that variants of two additional enzymes regulating synthesis and metabolism of L-methylfolate are both associated with increased risk for schizophrenia.[49] Firstly, the enzyme MTHFD1, which converts tetrahydrofolate (derived from dietary folate) into the direct precursor of L-methylfolate, has a variant with low enzyme activity and thus the deficient formation of L-methylfolate that is associated with increased risk for schizophrenia.[49] Secondly, a variant of methionine synthetase, the enzyme that converts L-methylfolate into methionine is also associated with increased risk for schizophrenia.[49] Thus, there are several mechanisms whereby L-methylfolate can be a co-conspirator in schizophrenia.

FIGURE 6.
Methyl donor metabolism in methylomics



SAMe=S-adenosyl-methionine; SAH=S-adenosyl-homocysteine; L-MF=L-methylfolate; NADP=nicotinamide adenine dinucleotide phosphate; NADPH=reduced NADP; BH=biopterin; THF=tetrahydrofolate; DHFR=dihydrofolate reductase; NADH=reduced nicotinamide adenine dinucleotide.

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COMT REGULATION OF DA SIGNALING

The enzyme COMT inactivates the catecholamines DA and NE by a transmethylation reaction that involves the transfer to DA or NE of a methyl group derived directly from SAMe[9] (Figure 5), which is itself synthesized from folate and L-methylfolate via MTHFR[13] (Figure 6). Although COMT is active at all DA and NE synapses, it is much more important for regulating DA levels in brain areas such as PFC that lack a competing inactivation process, namely the DA reuptake pump, or dopamine transporter (DAT) which has only low levels in PFC.[9]

Thus, when COMT enzyme activity is high in PFC, DA levels are low; and vice versa, when COMT enzyme activity is low, DA levels are high in PFC. Since DA profoundly affects the information processing of pyramidal neurons in PFC, it also profoundly influences cognitive functioning.[9,47,48] DA does this by its actions specifically in dorsolateral PFC, not only in normal controls, but also in patients who have cognitive dysfunction associated with a number of disorders including schizophrenia, depression, and attention-deficit/hyperactivity disorder.[9] Thus, the activity of COMT is a key regulator of cognition because it is a key regulator of DA in PFC.

This is in contrast to other brain areas, such as basal ganglia or nucleus accumbens, that have high densities of DAT and where DA levels are therefore regulated far less profoundly by COMT.[9] This is important to understand in order to interpret the importance of COMT regulation in schizophrenia, since the DA hypothesis of schizophrenia suggests that DA levels are overly active in limbic areas such as nucleus accumbens yet hypoactive in cortical areas such as PFC.[9] Thus, changes in COMT activity would be expected to change DA levels much more in PFC than in

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nucleus accumbens and by extension, to regulate cognitive symptoms (thought to be regulated in PFC) much more than positive symptoms (thought to be regulated in nucleus accumbens).

WHEN METHYLOMICS AND DA ACT AS CO-CONSPIRATORS IN SCHIZOPHRENIA: *THE DOUBLE WHAMMY*

The activity of COMT is regulated both by genetics and by epigenetics. Epigenetically, upstream methylation of the COMT promoter decreases the amount of COMT enzyme that is made, and thus reduces COMT activity and raises PFC DA.[17,18,47,48] Interestingly, the amount of methylation that this promoter has is strongly inherited.[47,48] This may affect the efficiency of information processing even in normals. In schizophrenia, deficits are reported in the methylation of the COMT promoter, perhaps caused by or compounded in patients who have the T form of MTHFR, who might therefore have inefficiency in their ability to methylate.[47,48] We begin to see the shape of a conspiracy between methylomics and DA here. Reduced COMT promoter methylation causes increased amounts of COMT to be expressed, and thus increased COMT enzyme activity, lower PFC DA, and reduced efficiency of information processing. Thus, decreased availability of methyl donors due to inheriting decreased MTHFR activity from the T allele could lead epigenetically to increased amount of COMT enzyme being made, and thus reduced DA signaling in PFC.

Downstream, the conspiracy deepens. Decreased availability of methyl donors for use in metabolic reactions due to inheriting this same decreased MTHFR activity via the T allele could lead to reduced synthesis of the biopterin cofactor for DA synthesis via tyrosine hydroxylase[13] (Figures 3 and 4). This reduction of DA would conspire to compound the already reduced DA signaling caused by reduced methylation of the COMT promoter and increased activity of COMT described above. Even though reduced availability of methyl donors might simultaneously decrease the downstream inactivation of DA by COMT, which itself uses methyl donors, this is unlikely to change DA levels since other inactivating mechanisms such as the norepinephrine transporter (NET) and diffusion would take up any slack.

Bottom line: inheriting reduced MTHFR activity via the T allele could conspire with DA to result in a double whammy of reduced DA availability by both an upstream mechanism that increases DA inactivation by increasing COMT activity and by a downstream mechanism that reduces the synthesis of DA via reducing the availability of the biopterin cofactor for tyrosine hydroxylase. Since decreased DA signaling in PFC is linked to executive dysfunction such as problem solving difficulties from deficient working memory in many disorders, including schizophrenia, this may underlie the observations of reduced executive functioning in schizophrenia patients who inherit the T allele of MTHFR.

COMT AS A CO-CONSPIRATOR IN SCHIZOPHRENIA

An additional regulator of COMT activity is not just epigenetic methylation and genetic control of methylation via MTHFR, but also which type of COMT that is inherited, valine or methionine (val or met). The val form of COMT is more stable and has 2–4 times higher enzyme activity. Thus, it has lower PFC DA levels compared to the met form of COMT, which is more labile, has lower enzyme activity, and is less able to inactivate DA in PFC, thus raising DA levels and increasing DA signaling in PFC.[9,27,28,47,48] The val form of COMT, presumably because it is associated with lower DA levels PFC, has been consistently shown to be associated with less efficient activation of PFC brain circuits during tests of memory performance.[9,47,48] However, this does not appear to be specific for schizophrenia and even occurs in normals. Some investigators also suggest that inheriting the val form of COMT may increase either the risk of schizophrenia or at least the risk of cognitive dysfunction in schizophrenia.[9,17,18,43,47,48]

METHYLOMICS AND THE ENVIRONMENT

There are many situations in which the environment can trigger aberrant epigenetic reactions, leading to the activation or silencing of normal genes, but the wrong genes at the wrong time. For example, both good and bad experiences can drive the production of epigenetic methyl "marks" even in adults.[2-4] That is, epigenetic changes in gene transcription seem to underlie long term memories, good and bad.[4] Thus, experimental animals have epigenetic mechanisms linked not only to normal

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hippocampus dependent spatial memory formation but also to associative fear conditioning, a model of anxiety disorders, and to extinction of learned fear, a model of psychotherapeutic recovery from anxiety disorders.[4]

The environment can also influence epigenetics indirectly if it leads to folate, L-methylfolate, and methyl donor deficiencies. In addition to an environment in which there is poor nutritional intake of folate, several other environmental facts can reduce the availability of methyl donors, including smoking, alcohol, many anticonvulsant drugs, and many other medications.[13] Also, if the "environment" of the brain includes the rest of a person's body, various illnesses can reduce the availability of folate and methyl donors, such as pregnancy, gastrointestinal and absorption disorders, and eating disorders. Finally, if the environment during prenatal development includes the uterus, methyl donor deficiencies of the mother could affect embryonic development, methylation, and epigenetics of the unborn child.[50-52] It could be that the MTHFR genotype of the mother is just as important as that of the patient in determining the risk of schizophrenia, but this is rarely determined.

Upstream

The environment can drive epigenetics by altering methyl marks due to regulating the availability of downstream methyl donors used in upstream epigenetic mechanisms. For a cell to preserve its stable characteristics, its upstream maintenance of DNA methylation is vital. The use of methyl groups for maintenance DNA methylation is so important, that it takes precedence over the use of methyl groups downstream for other purposes.[5] In fact, the enzyme DNMT1 seems to act as a sensor for the DNA methylation capacity of a cell.[5] If the downstream availability of methyl groups for upstream DNA methylation goes down, there is a compensatory increase in DMNT1 activity, perhaps due to lack of methylation of its own promoter at its own gene. This increased DNMT1 activity is due to the synthesis of more copies of DNMT1, which theoretically can then more successfully compete for available methyl groups in order to preserve maintenance DNA methylation at the most critical sites in DNA.

On the one hand, this "up regulation" of DNMT1 activity may also lead to unwanted hypermethylation of some other components of DNA, causing unwanted silencing of some normal genes.[23-26] On the other hand, shunting methyl groups towards use by DNMT1 for maintenance DNA methylation may simultaneously starve the cell of the other important uses of methyl groups, including for de novo DNA methylation, histone methylation, nucleic acid synthesis, and neurotransmitter synthesis.[5] This would theoretically lead to unwanted hypomethylation of other components of DNA that could cause abnormal activation of certain genes.

Downstream

Another consequence of methyl donor deficiency, whether due to genetic factors such as MTHFR or to environmental factors such as those that reduce folate levels, is downstream due to the resultant decrease in L-methylfolate levels and increase in the levels of the SAMe metabolite homocysteine (Figure 6). If severe, this condition is sometimes called hyperhomocysteinemia and is caused when SAMe is not replenished due to L-methylfolate deficiency.[40,53] In fact, elevated homocysteine levels can be a sensitive indicator of folate and L-methylfolate deficiency, and are normalized by administering either folate or L-methylfolate.[35-40] Elevated levels of homocysteine are also associated with hypomethylation of certain components of DNA and histones, and theoretically could lead to activating some important genes, thus linking reduction in methyl donor availability with upstream epigenetic methylomics.[49,54] This is thought to occur in some conditions such as uremia,[55] but it is not known whether the same thing happens in psychiatric disorders associated with elevated homocysteine levels such as schizophrenia, although it is suspected.[56] Folate deficiency is well known to cause problems in DNA repair[57] and to activate promoters in cancer cells,[57-61] and presumably would likely have the same consequences in neurons.

THE TRIPLE WHAMMY: *WHEN METHYLOMICS CONSPIRE*

Methylomic mechanisms are candidate co-conspirators that are also hypothetically involved in schizophrenia, potentially participating in both upstream and downstream mechanisms. As discussed, some risk genes for aberrant methylomics may be inherited as potential co-conspirators along with glutamate

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and GABA risk genes; furthermore, the environment could trigger aberrant epigenetic mechanisms due to methyl donor deficiency caused by metabolic, dietary, concomitant drugs, concomitant illnesses, and other environmental stressors. This could add to the stress that the environment places on glutamate, GABA, and inherited epigenetic risk genes.

The interaction of the risk genes for COMT and MTHFR is an example of how methylomic risk factors can conspire to make cognitive functioning worse in schizophrenia.[43,47,48] Discussed above are the specific risk genes, the val allele of COMT and the T allele of MTHFR. If a person has the T allele of MTHFR, this on its own renders a double whammy to DA signaling: the T allele has the potential to reduce DA signaling both because it can increase DA inactivation by increasing COMT activity via reduced methylation of the COMT promoter, and because it can reduce DA synthesis by reducing tyrosine hydroxylase activity via decreasing the levels of biopterin. Now, if this same person inherited the gene for the highly active val form of COMT, this val COMT enzyme could conspire with the T form of the MTHFR to deliver a third blow to DA signaling: the val form of COMT causes high enzyme activity in each copy of the enzyme, whereas the T form of MTHFR could reduce methylation of the COMT promoter and cause synthesis of more copies of the enzyme. Both conspire to drive down DA levels due to excessive inactivation of DA by COMT.[47,48] Furthermore, the T form of MTHFR could further conspire to reduce DA by reducing its synthesis in the first place by making methyl donors unavailable for optimal synthesis of biopterin downstream, thus reducing the DA synthetic enzyme tyrosine hydroxylase's activity.[47,48] A triple whammy!

Indeed, it has been shown that the val form of COMT interacts with the T form of MTHFR in schizophrenia to compromise executive function on cognitive tests and to disrupt functional activation of prefrontal circuits on brain imaging.[47,48] Maybe COMT val forms of the enzyme are not robust enough in themselves to increase the risk for schizophrenia but when they conspire with the T form of MTHFR, they can amplify the risk of that gene. One can image that inheriting several abnormal genes regulating glutamate or GABA might have a similar interaction, but this has not yet been proven.

CONCLUSION

Both inherited risk genes as well as abnormalities in epigenetic regulation of normal genes have been implicated in the pathophysiology of many psychiatric disorders. Methylomics, the regulation of gene expression and silencing by methylating DNA and histones, is a key epigenetic mechanism. A conspiracy of multiple risk genes with a stressful environment that triggers epigenetic changes in the expression of normal genes is a current leading hypothesis for schizophrenia and most major mental illnesses. ***CNS***

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A first-line treatment option

With the recommended starting dose —

NEW SAPHRIS® delivers effective symptom control with safety and tolerability[1]

SAPHRIS® is an atypical antipsychotic agent indicated for:

- **Acute treatment of schizophrenia in adults**
- **Acute treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults**

We have a lot to look forward to

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 2.6% in the placebo group
- Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature
- SAPHRIS® is not approved for the treatment of patients with dementia-related psychosis

NEW Saphris® (asenapine)
sublingual tablets 5 and 10 mg
Treat for today and tomorrow

Please see accompanying brief summary of full Prescribing Information, including Boxed Warning.

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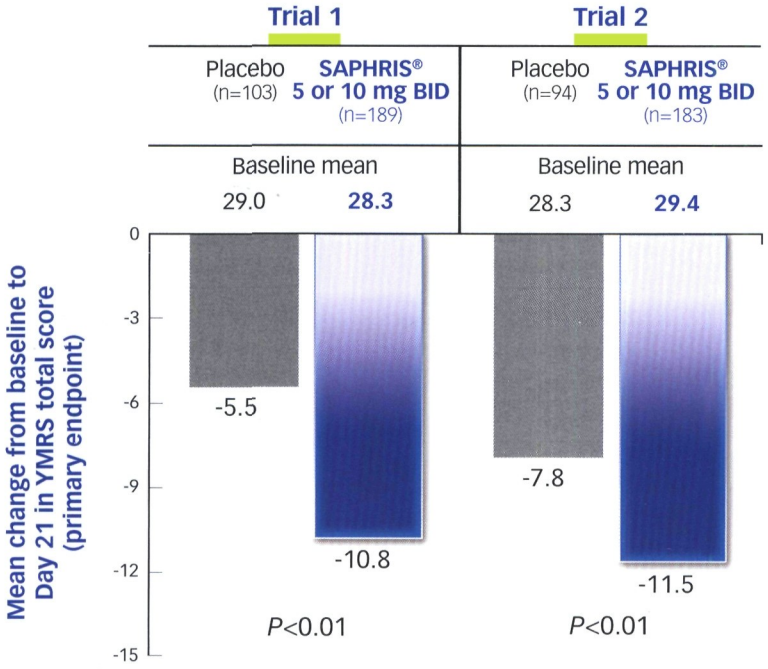
With the recommended starting dose
Effective symptom control in acute mania…

In 2 similarly designed, 3-week, multicenter, randomized, double-blind, placebo-controlled trials in adults receiving SAPHRIS® 5 or 10 mg twice daily (BID)

SAPHRIS® demonstrated significant improvement in Young Mania Rating Scale (YMRS) total score at endpoint[1]



Recommended starting dose for manic or mixed episodes associated with bipolar I disorder[a]

10 mg BID AM PM

90% of the patients studied were maintained at the 10-mg BID dose[b]

[a] The dose can be decreased to 5 mg BID if there are adverse effects.

[b] On the second and subsequent days of the trials, the dose could be lowered to 5 mg twice daily, based on tolerability, but less than 10% of patients had their dose reduced. The safety of doses above 10 mg twice daily has not been evaluated in clinical trials.

Indication

- SAPHRIS® is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults
- The physician who elects to use SAPHRIS® for extended periods for either schizophrenia or bipolar I disorder should periodically reevaluate the long-term risks and benefits of the drug for the individual patient

Cerebrovascular Adverse Events

- 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

Neuroleptic Malignant Syndrome (NMS)

- NMS, a potentially fatal symptom complex, has been reported with administration of antipsychotic drugs, including SAPHRIS®
- NMS can 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 should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems

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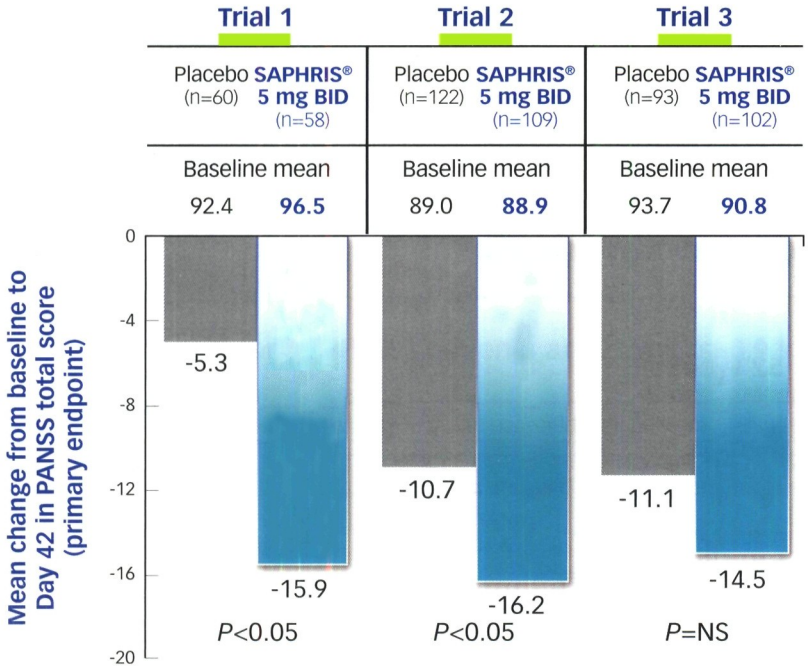
and schizophrenia

In 2 short-term (6-week), multicenter, randomized, double-blind, placebo-controlled trials in adults

SAPHRIS® demonstrated significant improvement in Positive and Negative Syndrome Scale (PANSS) total score at endpoint[1]



In Trial 3, SAPHRIS® could not be statistically distinguished from placebo

Recommended starting dose for schizophrenia

5 mg BID AM PM

In acute treatment, the recommended starting dose is also the target dose[c]

[c] In controlled trials, there was no suggestion of added benefit with the higher dose, but there was a clear increase in certain adverse reactions. The safety of doses above 10 mg twice daily has not been evaluated in clinical studies.

Indication

- SAPHRIS® is indicated for the acute treatment of schizophrenia in adults
- The physician who elects to use SAPHRIS® for extended periods for either schizophrenia or bipolar I disorder should periodically reevaluate the long-term risks and benefits of the drug for the individual patient

Leukopenia, Neutropenia, and Agranulocytosis

- In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including SAPHRIS®
- Patients with a preexisting low white blood cell count (WBC) or a history of leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy, and SAPHRIS® should be discontinued at the first sign of a decline in WBC in the absence of other causative factors

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NEW SAPHRIS®
Selected safety information — Glucose

Warnings and Precautions

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 who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of and 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 also undergo fasting blood glucose testing
- In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the antipsychotic drug

Laboratory test abnormalities: Glucose in a long-term trial (at the end of 52 weeks)[1]

- Results from a multicenter, randomized, double-blind, active-controlled, flexible-dose study of 908 adults with schizophrenia or schizoaffective disorder. SAPHRIS® patients received 5 or 10 mg BID
- Patients taking SAPHRIS® 5 or 10 mg BID experienced a mean increase from baseline in glucose of 2.4 mg/dL

Laboratory test abnormalities: Glucose in short-term trials

- Short-term bipolar mania trials were 3 weeks in duration, and short-term schizophrenia trials were 6 weeks in duration

Percent of patients with fasting glucose elevations ≥126 mg/dL (at endpoint)

	Bipolar mania	Schizophrenia
SAPHRIS®	4.9%	7.4%
Placebo	2.2%	6%

SAPHRIS® 5 or 10 mg BID
SAPHRIS® 5 mg BID

Mean change from baseline in fasting serum glucose (mg/dL)

	Bipolar mania	Schizophrenia
SAPHRIS®	-0.6	+3.2
Placebo	-0.6	-1.6

SAPHRIS® 5 or 10 mg BID
SAPHRIS® 5 mg BID

Please see accompanying brief summary of full Prescribing Information, including Boxed Warning.

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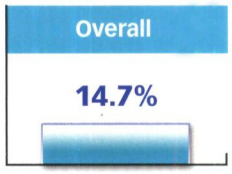
Selected safety information—Weight gain

Warnings and Precautions

Weight gain in a long-term trial (at the end of 52 weeks)

- Results from a multicenter, randomized, double-blind, active-controlled, flexible-dose study of 908 adults with schizophrenia or schizoaffective disorder. SAPHRIS® patients received 5 or 10 mg BID

Percent of patients with a ≥7% increase in body weight



By BMI category at baseline	Low BMI (<23) n=295	Medium BMI (23-27) n=290	High BMI (>27) n=302
	22%	13%	9%

Mean weight gain for SAPHRIS® patients at 52 weeks: 0.9 kg

Mean weight change from baseline by BMI

By BMI category at baseline	Low BMI (<23) n=295	Medium BMI (23-27) n=290	High BMI (>27) n=302
	1.7 kg	1.0 kg	0 kg

Weight gain in short-term trials

- Short-term bipolar mania trials were 3 weeks in duration, and short-term schizophrenia trials were 6 weeks in duration

Percent of patients with ≥7% increase in body weight

	Bipolar mania	Schizophrenia
SAPHRIS®	5.8%	4.9%
Placebo	0.5%	2.0%

SAPHRIS® 5 or 10 mg BID
SAPHRIS® 5 mg BID

In short-term bipolar mania and schizophrenia trials, there were differences in mean weight gain between SAPHRIS® and placebo groups

	Bipolar mania	Schizophrenia
SAPHRIS®	+1.3 kg	+1.1 kg
Placebo	+0.2 kg	+0.1 kg

SAPHRIS® 5 or 10 mg BID
SAPHRIS® 5 mg BID

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NEW SAPHRIS®
Additional important safety information

Warnings and Precautions

Hyperprolactinemia

- Like other drugs that antagonize dopamine D_2 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

Tardive Dyskinesia (TD)

- The risk of developing TD and the potential for it to become irreversible may increase as the duration of treatment and the total cumulative dose increase
- However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribing *should be consistent with the need to minimize TD*
- If signs and symptoms appear, discontinuation should be considered

QT Prolongation

- 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 experience a QTc of ≥500 msec
- SAPHRIS® should be avoided 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 the occurrence of torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval

Dysphagia

- Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. 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

Body Temperature Regulation

- Appropriate care is advised when prescribing SAPHRIS® for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, eg, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration

Orthostatic Hypotension, Syncope, and Other Hemodynamic Effects

- SAPHRIS® may induce orthostatic hypotension and syncope
- SAPHRIS® should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, conditions which would predispose them to hypotension, and 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
- Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if *hypotension occurs*

Potential for Cognitive and Motor Impairment

- Somnolence was reported in patients treated with SAPHRIS®
- 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

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 for SAPHRIS® should be written for the smallest quantity of tablets in order to reduce the risk of overdose

Please see accompanying brief summary of full Prescribing Information, including Boxed Warning.

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Additional important safety information

Warnings and Precautions

Hepatic Impairment

- SAPHRIS® is not recommended in patients with severe hepatic impairment

Drug Interactions

- The risks of using SAPHRIS® in combination with other drugs have not been extensively evaluated. Given the primary CNS effects of SAPHRIS®, caution should be used when it is taken in combination with other centrally acting drugs or alcohol
- Coadministration of SAPHRIS® with strong CYP1A2 inhibitors (fluvoxamine) or compounds which are both CYP2D6 substrates and inhibitors (paroxetine) should be done with caution

Seizures

- SAPHRIS® should be used cautiously in patients with a history of seizures or with conditions that lower seizure threshold (eg, Alzheimer's dementia)

Commonly observed adverse reactions (≥5% and at least twice that for placebo)

Short-term bipolar trials[a]

	Placebo	SAPHRIS® 5 or 10 mg BID
Somnolence	6%	24%
Dizziness	3%	11%
EPS other than akathisia	2%	7%
Weight increased	<1%	5%

[a]Short-term bipolar mania trials were 3 weeks in duration.

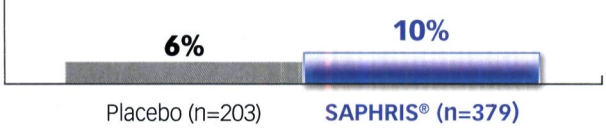
Short-term schizophrenia trials[b]

	Placebo	SAPHRIS® 5 or 10 mg BID
Akathisia	3%	6%
Oral hypoesthesia (numbing of the tongue)	1%	5%
Somnolence	7%	13%

[b]Short-term schizophrenia trials were 6 weeks in duration.

Rates of discontinuation due to adverse events

Short-term bipolar trials[c]

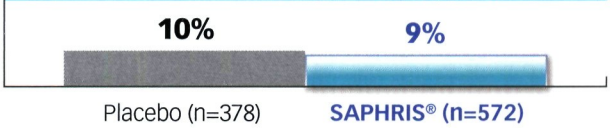


Placebo (n=203) SAPHRIS® (n=379)

[c]Short-term bipolar mania trials were 3 weeks in duration.

- The most common and likely drug-related adverse reactions associated with discontinuation in subjects treated with SAPHRIS® (rate of at least 1% and at least twice the placebo rate) were anxiety (1.1%) and oral hypoesthesia (1.1%)

Short-term schizophrenia trials[d]



Placebo (n=378) SAPHRIS® (n=572)

[d]Short-term schizophrenia trials were 6 weeks in duration.

- There were no drug-related adverse reactions associated with discontinuation in subjects treated with SAPHRIS® at the rate of at least 1% and at least twice the placebo rate

NEW Saphris® (asenapine)
sublingual tablets 5 and 10 mg
Treat for today and tomorrow

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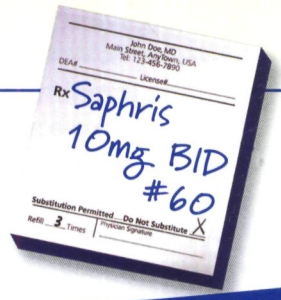
NEW SAPHRIS delivers

A starting dose with proven efficacy

In manic or mixed episodes associated with bipolar disorder:

- Significant improvement in YMRS total score
- Significant improvement in the CGI-BP Severity of Illness score (mania)
- The recommended starting dose of SAPHRIS® is 10 mg sublingually twice daily



In the acute treatment of schizophrenia:

- Significant improvement in PANSS total score
- The recommended starting and target dose of SAPHRIS® is 5 mg sublingually twice daily

A first-line treatment option

With documented safety and tolerability

For more information, please visit our Web site at www.SAPHRIS.com

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 2.6% in the placebo group**
- **Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature**
- **SAPHRIS® is not approved for the treatment of patients with dementia-related psychosis**

Reference: 1. Data on file, Schering Corporation.

Please see accompanying brief summary of full Prescribing Information, including Boxed Warning.

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NEW Saphris® (asenapine)
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SAPHRIS®
(asenapine) sublingual tablets

BRIEF SUMMARY (For full Prescribing Information, see package insert.)

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. 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® (asenapine) is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

1.1 Schizophrenia

SAPHRIS is indicated for the acute treatment of schizophrenia in adults *[see Clinical Studies (14.1)]*. The physician who elects to use SAPHRIS for extended periods in schizophrenia should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient *[see Dosage and Administration (2.1)]*.

1.2 Bipolar Disorder

SAPHRIS is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults *[see Clinical Studies (14.2)]*. If SAPHRIS is used for extended periods in bipolar disorder, the physician should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient *[see Dosage and Administration (2.2)]*.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 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 the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

5.2 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 (5.1)]*.

5.3 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.

5.4 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.

5.5 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. In clinical trials of SAPHRIS, the occurrence of any adverse reaction related to glucose metabolism was less than 1% in both the SAPHRIS and placebo treatment groups. 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, which did not include SAPHRIS, suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics included in these studies.

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.

5.6 Weight Gain

In short-term schizophrenia and bipolar mania trials, there were differences in mean weight gain between SAPHRIS-treated and placebo-treated patients. In short-term, placebo-controlled schizophrenia trials, the mean weight gain was 1.1 kg for SAPHRIS-treated patients compared to 0.1 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 4.9% for SAPHRIS-treated patients versus 2% for placebo-treated patients. In short-term, placebo-controlled bipolar mania trials, the mean weight gain for SAPHRIS-treated patients was 1.3 kg compared to 0.2 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 5.8% for SAPHRIS-treated patients versus 0.5% for placebo-treated patients.

In a 52-week, double-blind, comparator-controlled trial of patients with schizophrenia or schizoaffective disorder, the mean weight gain from baseline was 0.9 kg. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 14.7%. **Table 1** provides the mean weight change from baseline and the proportion of patients with a weight gain of ≥7% categorized by Body Mass Index (BMI) at baseline:

TABLE 1: Weight Change Results Categorized by BMI at Baseline: Comparator-Controlled 52-Week Study in Schizophrenia

	BMI < 23 SAPHRIS N=295	BMI 23 - ≤ 27 SAPHRIS N=290	BMI > 27 SAPHRIS N=302
Mean change from Baseline (kg)	1.7	1	0
% with ≥ 7% increase in body weight	22%	13%	9%

5.7 Orthostatic Hypotension, Syncope, and Other Hemodynamic Effects

SAPHRIS may induce orthostatic hypotension and syncope in some patients, especially early in treatment, because of its α1-adrenergic antagonist activity. In short-term schizophrenia 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 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 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.

Four normal volunteers in clinical pharmacology studies treated with either intravenous, oral, or sublingual SAPHRIS experienced hypotension, bradycardia, and sinus pauses. These spontaneously resolved in 3 cases, but the fourth subject received external cardiac massage. The risk of this sequence of hypotension, bradycardia, and sinus pause might be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs.

Patients should be instructed about nonpharmacologic 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)]*. Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs.

5.8 Leukopenia, Neutropenia, and Agranulocytosis

In clinical trial and postmarketing experience, events of leukopenia/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

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(WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and SAPHRIS should be discontinued at the first sign of decline in WBC in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm^3) should discontinue SAPHRIS and have their WBC followed until recovery.

5.9 QT Prolongation

The effects of SAPHRIS on the QT/QTc interval were evaluated in a dedicated 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.

5.10 Hyperprolactinemia

Like other drugs that antagonize dopamine D_2 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 clinical trials, the incidences of adverse events related to abnormal prolactin levels were 0.4% versus 0% for placebo *[see Adverse Reactions (6.2)]*.

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.

5.11 Seizures

Seizures were reported in 0% and 0.3% (0/572, 1/379) of 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 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. 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, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

5.12 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 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 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 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.

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.

5.13 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 (≤1%) and comparable to placebo. 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 ≤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.

5.14 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.

5.15 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 trials, respectively. During 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 (5.1)]*.

5.16 Use in Patients with Concomitant Illness

Clinical experience with SAPHRIS in patients with certain concomitant systemic illnesses is limited *[see Clinical Pharmacology (12.3)]*.

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 premarketing clinical trials. Because of the risk of orthostatic hypotension with SAPHRIS, caution should be observed in cardiac patients *[see Warnings and Precautions (5.6)]*.

6 ADVERSE REACTIONS

The most common adverse reactions (≥5% and at least twice the rate on placebo) in schizophrenia were akathisia, oral hypoesthesia, and somnolence.

The most common adverse reactions (≥5% and at least twice the rate on placebo) in bipolar disorder were somnolence, dizziness, extrapyramidal symptoms other than akathisia, and weight increased.

The information below is derived from a clinical trial database for SAPHRIS consisting of over 3350 patients and/or normal subjects exposed to one or more sublingual doses of SAPHRIS. Of these subjects, 1953 (1480 in schizophrenia and 473 in acute bipolar mania) were patients who participated in multiple-dose effectiveness trials of therapeutic doses (5 or 10 mg twice daily, with a total experience of approximately 611 patient-years). A total of 486 SAPHRIS-treated patients were treated for at least 24 weeks and 293 SAPHRIS-treated patients had at least 52 weeks of exposure.

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. The figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatment, uses, and investigators. The cited figures, however, do provide the prescriber with some basis for estimating the relative contribution of drug and nondrug factors to the adverse reaction incidence in the population studied.

6.2 Clinical Studies Experience

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 subjects and 10% of placebo subjects discontinued due to adverse reactions. There were no drug-related adverse reactions associated with discontinuation in subjects 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 Schizophrenic 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 therapy (up to 6-weeks in patients with schizophrenia) are shown in **Table 2**.

TABLE 2: Adverse Reactions Reported in 2% or More of Subjects in one of the SAPHRIS Dose Groups and Which Occurred at Greater Incidence Than in the Placebo group in 6-Week Schizophrenia Trials

System Organ Class / Preferred Term	Placebo N=378	SAPHRIS 5 mg twice daily N=274	SAPHRIS 10 mg twice daily N=208	All SAPHRIS[§] 5 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				
Weight increased	<1%	2%	2%	3%
Metabolism disorders				
Increased appetite	<1%	3%	0%	2%
Nervous system disorders				
Akathisia*	3%	4%	11%	6%
Dizziness	4%	7%	3%	5%
Extrapyramidal symptoms (excluding akathisia)†	7%	9%	12%	10%
Somnolence‡	7%	15%	13%	13%
Psychiatric disorders				
Insomnia	13%	16%	15%	15%
Vascular disorders				
Hypertension	2%	2%	3%	2%

* Akathisia includes: akathisia and hyperkinesia.

† Extrapyramidal symptoms included dystonia, oculogyration, dyskinesia, tardive dyskinesia, muscle rigidity, parkinsonism, tremor, and extrapyramidal disorder (excluding akathisia).

‡ Somnolence includes the following events: somnolence, sedation, and hypersomnia.

§ Also includes the Flexible-dose trial (N=90).

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Dose-Related Adverse Reactions: Of all the adverse reactions listed in **Table 2**, the only apparent dose-related adverse reaction was akathisia.

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 subjects 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 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 therapy (up to 3-weeks in patients with bipolar mania) are shown in **Table 3**.

TABLE 3: Adverse Reactions Reported in 2% or More of Subjects in one of the SAPHRIS Dose Groups and Which Occurred at Greater Incidence Than in the Placebo Group in 3-Week Bipolar Mania Trials

System Organ Class / Preferred Term	Placebo N=203	SAPHRIS 5 or 10 mg twice daily* N=379
Gastrointestinal disorders		
Dry mouth	1%	3%
Dyspepsia	2%	4%
Oral hypoesthesia	<1%	4%
Toothache	2%	3%
General disorders		
Fatigue	2%	4%
Investigations		
Weight increased	<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 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.

Dystonia: *Antipsychotic Class Effect:* 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.

Extrapyramidal Symptoms: In the short-term, placebo-controlled schizophrenia and bipolar mania 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 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 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.

Laboratory Test Abnormalities: *Glucose:* The effects on fasting serum glucose levels in the short-term schizophrenia and bipolar mania trials revealed no clinically relevant mean changes *[see also Warnings and Precautions (5.5)]*. In the short-term placebo-controlled schizophrenia trials, the mean increase in fasting glucose levels for SAPHRIS-treated patients was 3.2 mg/dL compared to a decrease of 1.6 mg/dL for placebo-treated patients. The proportion of patients with fasting glucose elevations ≥126 mg/dL (at Endpoint), was 7.4% for SAPHRIS-treated patients versus 6% for placebo-treated patients. In the short-term, placebo-controlled bipolar mania trials, the mean decreases in fasting glucose levels for both SAPHRIS-treated and placebo-treated patients were 0.6 mg/dL. The proportion of patients with fasting glucose elevations ≥126 mg/dL (at Endpoint), was 4.9% for SAPHRIS-treated patients versus 2.2% for placebo-treated patients.

In a 52-week, double-blind, comparator-controlled trial of patients with schizophrenia and schizoaffective disorder, the mean increase from baseline of fasting glucose was 2.4 mg/dL.

Lipids: The effects on total cholesterol and fasting triglycerides in the short-term schizophrenia and bipolar mania trials revealed no clinically relevant mean changes. In short-term, placebo-controlled schizophrenia trials, the mean increase in total cholesterol levels for SAPHRIS-treated patients was 0.4 mg/dL compared to a decrease of 3.6 mg/dL for placebo-treated patients. The proportion of patients with total cholesterol elevations ≥240 mg/dL (at Endpoint) was 8.3% for SAPHRIS-treated patients versus 7% for placebo-treated patients. In short-term, placebo-controlled bipolar mania trials, the mean increase in total cholesterol levels for SAPHRIS-treated patients was 1.1 mg/dL compared to a decrease of 1.5 mg/dL in placebo-treated patients. The proportion of patients with total cholesterol elevations ≥240 mg/dL (at Endpoint) was 8.7% for SAPHRIS-treated patients versus 8.6% for placebo-treated patients. In short-term, placebo-controlled schizophrenia trials, the mean increase in triglyceride levels for SAPHRIS-treated patients was 3.8 mg/dL compared to a decrease of 13.5 mg/dL for placebo-treated patients. The proportion of patients with elevations in triglycerides ≥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 mean decrease in triglyceride levels for SAPHRIS-treated patients was 3.5 mg/dL versus 17.9 mg/dL for placebo-treated subjects. The proportion of patients with elevations in triglycerides ≥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 of patients with schizophrenia and schizoaffective disorder, 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.

Transaminases: Transient elevations in serum transaminases (primarily ALT) in the short-term schizophrenia and bipolar mania trials were more common in treated patients but mean changes were not clinically relevant. In short-term, placebo-controlled schizophrenia 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 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. No cases of more severe liver injury were seen.

In a 52-week, double-blind, comparator-controlled trial of patients with schizophrenia and schizoaffective disorder, the mean increase from baseline of ALT was 1.7 units/L.

Prolactin: The effects on prolactin levels in the short-term schizophrenia and bipolar mania trials revealed no clinically relevant changes in mean change in baseline. In short-term, placebo-controlled 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 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 trial of patients with schizophrenia and schizoaffective disorder, the mean decrease in prolactin from baseline for SAPHRIS-treated patients was 26.9 ng/mL.

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 on pharmacologic or other grounds. Reactions already listed in other parts of *Adverse Reactions (6)*, or those considered in *Warnings and Precautions (5)* or *Overdosage (10)* are not included. Although the reactions reported occurred during treatment with SAPHRIS, they were not necessarily caused by it. 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 (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); those occurring in 1/100 to 1/1000 patients; and those occurring in fewer than 1/1000 patients.

Blood and lymphatic disorders: <1/1000 patients: thrombocytopenia; *≥1/1000 patients and <1/100 patients:* anemia

Cardiac disorders: ≥1/1000 patients and <1/100 patients: tachycardia, temporary bundle branch block

Eye disorders: ≥1/1000 patients and <1/100 patients: accommodation disorder

Gastrointestinal disorders: ≥1/1000 patients and <1/100 patients: oral paraesthesia, glossodynia, swollen tongue

General disorders: <1/1000 patients: idiosyncratic drug reaction

Investigations: ≥1/1000 patients and <1/100 patients: hyponatremia

Nervous system disorders: ≥1/1000 patients and <1/100 patients: dysarthria

7 DRUG INTERACTIONS

The risks of using SAPHRIS in combination with other drugs have not been extensively evaluated. Given the primary CNS effects of SAPHRIS, caution should be used when it is taken in combination with other centrally-acting drugs or alcohol.

Because of its α1-adrenergic antagonism with potential for inducing hypotension, SAPHRIS may enhance the effects of certain antihypertensive agents.

7.1 Potential for Other Drugs to Affect SAPHRIS

Asenapine is cleared primarily through direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450isoenzymes (predominantly CYP1A2). The potential effects of inhibitors of several of these enzyme pathways on asenapine clearance were studied.

TABLE 4: Summary of Effect of Coadministered Drugs on Exposure to Asenapine in Healthy Volunteers

Coadministered drug (Postulated effect on CYP450/UGT)	Dose schedules		Effect on asenapine pharmacokinetics		Recommendation
	Coadministered drug	Asenapine	C_{max}	$AUC_{0-\infty}$	
Fluvoxamine (CYP1A2 inhibitor)	25 mg twice daily for 8 days	5 mg Single Dose	+13%	+29%	Coadminister with caution*

*The full therapeutic dose of fluvoxamine would be expected to cause a greater increase in asenapine plasma concentrations. AUC: Area under the curve.

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TABLE 4: Summary of Effect of Coadministered Drugs on Exposure to Asenapine in Healthy Volunteers *(cont)*

Coadministered drug (Postulated effect on CYP450/UGT)	Dose schedules		Effect on asenapine pharmacokinetics		Recommendation
	Coadministered drug	Asenapine	C_{max}	$AUC_{0-\infty}$	
Paroxetine (CYP2D6 inhibitor)	20 mg once daily for 9 days	5 mg Single Dose	–13%	–9%	No SAPHRIS dose adjustment required *[see Drug Interactions (7.2)]*
Imipramine (CYP1A2/2C19/3A4 inhibitor)	75 mg Single Dose	5 mg Single Dose	+17%	+10%	No SAPHRIS dose adjustment required
Cimetidine (CYP3A4/2D6/1A2 inhibitor)	800 mg twice daily for 8 days	5 mg Single Dose	–13%	+1%	No SAPHRIS dose adjustment required
Carbamazepine (CYP3A4 inducer)	400 mg twice daily for 15 days	5 mg Single Dose	–16%	–16%	No SAPHRIS dose adjustment required
Valproate (UGT1A4 inhibitor)	500 mg twice daily for 9 days	5 mg Single Dose	2%	–1%	No SAPHRIS dose adjustment required

*The full therapeutic dose of fluvoxamine would be expected to cause a greater increase in asenapine plasma concentrations. AUC: Area under the curve.

7.2 Potential for SAPHRIS to Affect Other Drugs

Coadministration with CYP2D6 Substrates: *In vitro* studies indicate that asenapine weakly inhibits CYP2D6.

Following coadministration of dextromethorphan and SAPHRIS in healthy subjects, the ratio of dextrorphan/dextromethorphan (DX/DM) as a marker of CYP2D6 activity was measured. Indicative of CYP2D6 inhibition, treatment with SAPHRIS 5 mg twice daily decreased the DX/DM ratio to 0.43. In the same study, treatment with paroxetine 20 mg daily decreased the DX/DM ratio to 0.032. In a separate study, coadministration of a single 75-mg dose of imipramine with a single 5-mg dose of SAPHRIS did not affect the plasma concentrations of the metabolite desipramine (a CYP2D6 substrate). Thus, *in vivo*, SAPHRIS appears to be at most a weak inhibitor of CYP2D6. Coadministration of a single 20-mg dose of paroxetine (a CYP2D6 substrate and inhibitor) during treatment with 5 mg SAPHRIS twice daily in 15 healthy male subjects resulted in an almost 2-fold increase in paroxetine exposure. Asenapine may enhance the inhibitory effects of paroxetine on its own metabolism.

SAPHRIS should be coadministered cautiously with drugs that are both substrates and inhibitors for CYP2D6.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies of SAPHRIS in pregnant women. 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. SAPHRIS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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. 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/m^2 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/m^2 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.

8.2 Labor and Delivery

The effect of SAPHRIS on labor and delivery in humans is unknown.

8.3 Nursing Mothers

Asenapine is excreted in milk of rats during lactation. It is not known whether asenapine or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SAPHRIS is administered to a nursing woman. It is recommended that women receiving SAPHRIS should not breast feed.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 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 premarketing 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.

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]*.

8.6 Renal Impairment

The exposure of asenapine following a single dose of 5 mg was similar among subjects with varying degrees of renal impairment and subjects with normal renal function *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

In subjects with severe hepatic impairment who were treated with a single dose of SAPHRIS 5 mg, asenapine exposures (on average), were 7-fold higher than the exposures observed in subjects with normal hepatic function. Thus, SAPHRIS is not recommended in patients with severe hepatic impairment (Child-Pugh C) *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Human Experience: In premarketing 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.

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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