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EIM Asenapine Formulary Summary

Executive Summary
Literature Summary

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EIM Asenapine Executive Summary

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Asenapine is a novel atypical antipsychotic with tetracyclic properties that is been approved in Canada for the treatment of schizophrenia, as well for the acute treatment of manic or mixed episodes associated with bipolar disorder type I. Asenapine belongs to the class dibenzo-oxepino pyrroles. While asenapine is still considered an atypical antipsychotic, it is a new chemical entity.

At this point, registration trials for this drug address bipolar disorder type I, mixed disorders, and schizophrenia. The primary patient populations that appear to experience the highest degree of efficacy are bipolar and mixed patients, with a high degree of resolution in terms of the clinical triad of agitation, irritability and anxiety. These symptoms represent important treatment challenges that need to be addressed. It makes sense that asenapine holds promise in mitigating these symptoms due to its receptor profile.

From a socio-economic viewpoint, less than 1% of Canadians use roughly 25% of the mental health hospital beds in Canada, according to a 2012 Statistics Canada summary published by Johansens and Fines. With both empirical evidence and anecdotal observations supporting their claims, these authors concluded, “substantial gaps remain in understanding the impact of mental illness on the use of health care services.”

The percentage of acute care hospital days involving mental comorbidity differs by major disease type. However, disease categories associated with a relatively high percentage of days with a **comorbid mental diagnosis** are metabolic disorders (22.9%), injuries/poisoning (23.6%), and infectious disorders (23.1%). Regardless of disease category, mental co-morbidity is associated with a **substantial increase** in the average length of inpatient hospital stay. Of note, reasons for prolonged stays include complications from metabolic disorders, cardiovascular load, and impairment of cognitive and decision-making processes. (Johansens and Fines. Statistics Canada Statistics Canada, Catalogue no. 82-003-XPE • Health Reports, Vol. 23, no. 4, December 2012 Accessed April 10,2013)

Schizophrenia is a chronic, severe, and disabling mental illness that affects men and women with equal frequency. Usually diagnosed between the ages of 17 and 35 years, the illness tends to appear earlier in men (in their late teens or early twenties) than in women (who often present in their twenties to early thirties). In Canada, the overall incidence in the general population is approximately 0.6%. The causes of schizophrenia are not known. However, some interplay between genetic, biological, environmental, and psychological factors is thought to be involved. In biological models of schizophrenia, genetic (familial) predisposition, infectious agents, allergies, and disturbances in metabolism have all been investigated.

Bipolar disorder can be as devastating as schizophrenia, from a bio-psycho-social perspective. Its incidence varies in the literature, but ranges from 2-7%, depending upon the reference. As with schizophrenia, it tends to present early in life, with men and women approximately equally represented. Patients who have a classic mixed presentation (i.e. the simultaneous presence of both manic and depressive symptoms) are among the most challenging to treat, with conventional therapies currently available running the risk of either over-flattening a patient’s

affect or swinging them into clear mania.

Asenapine belongs to a class of drugs called 'atypical antipsychotics', but it is unique within that class. It is, for example, the first atypical that may be considered a '**smart atypical antipsychotic**', meaning that the molecule been tailored to take advantage of the primary therapeutic advantages of two other drugs already used in clinical practice. So optimized, it has the combined benefits of these two other drugs, with fewer of their side effects. The two drugs upon which asenapine has been chemically based are clozapine and mirtazapine, the former sporting Level 1 evidence documenting efficacy in depression and other depressive disorders, according to CANMAT (www.CANMAT.org); and the latter with Level 1 evidence indicating efficacy in the treatment of psychosis.

In terms of receptor binding and resultant activities, the asenapine molecule exerts effects at several receptors linked to cognition. Advantages of asenapine are that it tends to have a more favourable profile of receptor affinities, in terms of efficacy and side effects, than many other drugs.

With respect to negative outcomes and negative prognostics, activation of histamine [H_1] receptors is strongly associated with sedation and weight gain, and asenapine has a low affinity for this receptor. There is approximately the same impact [albeit, slightly less] with this molecule as there is for quetiapine at the histamine receptor. However, there are marked advantages in favour of asenapine over quetiapine, in terms of cognition, as well as the former's activity at the alpha-receptors, activation of which exerts little direct impact on metabolism. This may be one of the reasons we see less metabolic syndrome in patients prescribed asenapine.

One term often used in the literature to quantify the risks of a given drug is the *number needed to harm* [NNH]. For metabolic syndrome, the NNH for asenapine has been estimated as 34, which means that fewer than 3% of patients on this drug (1/34 = 2.9%) will develop this disorder. This renders asenapine relatively metabolically benign, comparable to drugs like risperidone or paliperidone. For example, weight gain is one of the criteria for metabolic syndrome, and there is roughly a 7% incidence of weight gain with asenapine (NNH = 14), which is clearly far less than the 45% incidence (NNH=2.2) seen with olanzapine or the 60% incidence observed with clozapine (NNH=1.7). Quetiapine is variable in nature and has numbers quoted between 10 and 25% (NNH=4 to 10), depending on the patient population and consequent demographics studied.

From a pharmacoeconomic perspective, Lachaine et al. addressed the treatment of bipolar disorder in Canada, looking at Ministry of Health data and societal costs in yearly cycles over five years. These investigators studied patients with moderately severe bipolar disorder who had been treated with an atypical antipsychotic. They noted that, in the treatment of bipolar disorder, asenapine was a "dominant strategy over olanzapine" from both Ministry of Health and societal perspectives. It would be anticipated from the Ministry of Health perspective that this would be due to the decreased risk of adverse metabolic sequelae seen with asenapine versus olanzapine. Incremental cost utility ratios [ICUR] demonstrated similar quality-adjusted life-year (QALY) profiles in the two antipsychotics. However, per 1000 individuals, there was approximately a $3.85 million reduction in Ministry of Health related costs and a $3.88 million reduction in societal costs over five years with asenapine. Extrapolated to a full decade, again per 1000 individuals, the overall reduction in costs with asenapine versus olanzapine exceeded $15 million. Moreover, an improved QALY ratio was noted for asenapine; though how clinically significant this difference in QALY is, was not formally ascertained.

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EIM Asenapine Literature and Formulary Summary

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1) Conflict(s) of Interest

Dr Joel Lamoure discloses the following lifetime potential conflicts of interest:

- **Research Funding:** Eli Lilly Canada
- **Advisory Boards:** Janssen-Ortho, Pfizer Canada, BMS Canada, Lundbeck Canada, Pfizer Global, Sunovion Canada
- **Speaking Honoraria:** Eli Lilly, Janssen-Ortho, Pfizer, Astra-Zeneca, Shire, Lundbeck Canada, Valeant Canada, Otsuka Canada
- **International Congress Funding:** Pfizer Canada, Lundbeck Canada
- **Medical Writing Consultant:** Medscape, Canadian Journal of CME (STA Communications), Canadian Healthcare Network (Rogers Healthcare)

2) Product Indications and Efficacy

Drug name [generic and brand]: Saphris® (asenapine)
Manufacturer: Merck & Co., Inc.
Dosage forms and strengths: 5 and 10mg ODT (Oral Dissolving SL Tablet)

3) Reason(s) for Review:

3a) Is this a novel class of drug therapy?

Asenapine belongs to an already-established class of drugs called 'atypical antipsychotics', but it is unique within that class. It is, for example, the first atypical that could be considered a '**smart atypical antipsychotic**', meaning that it has been tailored to take advantage of the primary therapeutic advantages of two other drugs already used in clinical practice. So optimized, it has the combined benefits of these two other drugs, with fewer of their side effects. The two drugs upon which asenapine has been chemically based are clozapine and mirtazapine, the former sporting Level 1 evidence documenting its efficacy in depression and other depressive disorders, according to the Canadian Network of Mood and Anxiety Treatments (CANMAT, www.CANMAT.org); and the latter with Level 1 evidence indicating efficacy in the treatment of psychosis.

Asenapine also belongs to a class of drugs called *dibenzo-oxepino pyrroles*. At this time, registration trials have assessed its use in bipolar type I disorder, mixed disorders, and schizophrenia. The primary patient populations that appear to experience the highest degree of efficacy are bipolar and mixed patients, who tend to exhibit highs degree of agitation, irritability and anxiety, all of which fit the medication's receptor profile.

In terms of receptor affinity, the molecule exerts effects at several receptors linked to cognition. As noted below, its affinities for, and activity at, various receptors affords asenapine a favourable profile relative to many other antipsychotic medications. It also, as an orally disintegrating tablet (ODT) preparation, has an advantage relative to the phenomenon called 'cognitive clouding'; from which many bipolar and schizophrenic patients suffer. These mental clouding causes most psychotic patients to self medicate, particular by smoking cigarettes because of the almost immediate cognitive enhancing effects of tobacco in the pre-frontal cortex.

3b) Is this a new indication for a drug in current use?

No new indication for a drug already in use is being proposed. However, there currently is conflicting evidence for patients with mixed bipolar disorder. We could expect certain medications, like olanzapine, to have some degree of effect in mixed patients. Interestingly, however, by the time a patient has three or more mixed state symptoms, asenapine is statistically more effective than olanzapine.

3c) Is there improved efficacy relative to existing class comparators?

Non-inferiority trials with asenapine, versus what I could conceptualize to be an equipotent dose of olanzapine (15-20mg in most trials), do not demonstrate clinical superiority over current class comparators (olanzapine or, in some studies, haloperidol). However, while there is no proven improved efficacy, the rapid sublingual ODT tablet may enhance efficacy via greater drug adherence/compliance.

3d) Is there improved convenience relative to existing class comparators?

In published studies involving patients with major depressive disorder (MDD, which is where most current data on ODT can be found), long-term non-adherence rates tend to be between 42% and 49%. Persistent non-adherence can progress to clinical deterioration in a patient's mental status attributable to spontaneously missed doses over a sufficient period of time. Alternatively, a pattern of steady decline in medication use may occur following the initiation of treatment

Regardless of its pattern, non-adherence in psychiatric patients has been associated with poorer clinical outcomes, higher costs due to decreased productivity, and increased costs related to managing recurrences. For example, in a neuroimaging study by MacQueen et al., relapse in patients with a mood or affective component to their psychiatric symptoms was strongly associated with subsequent treatment resistance. Perhaps this is due to some sort of serotonin depletion syndrome, hippocampal volume atrophy, changes in the regulation of receptors, or indeed a combination of all three, depending on the patient's co-existing Axis 2 condition. It is important to note that neurobiological changes have been documented related to patient non-adherence. Non-adherence leads to relapses; and patients who have recurrent major depressive episodes experience hippocampal atrophy, based in the work by Dr. Glenda MacQueen et al. This may further entrench the mood component, leading to what Dr. Lamoure at the University of Western Ontario has termed 'osteomyelitis of the mind'.

The acceptability of ODT formulations and patient preferences comparing oral and oro-dispersible tablets for different indications have been investigated. Since psychological status and personality traits influence attitudes and preferences, it is appropriate that evaluations be conducted in patients being treated for major depressive disorder with antidepressant drugs.

Partial adherence is the most frequently encountered type of non-adherence in schizophrenia. In fact, fewer than 25% of individuals with schizophrenia are fully adherent; on average, schizophrenia patients are adherent with their antipsychotics about 58% of the time. In a study of adherence over a four-year period, 37% to 38% of individuals with schizophrenia had issues with adherence in any given year, averaging across all the years, while 60% of individuals had issues with adherence at some point over the four years.

Managing complex medication regimens can be particularly problematic in schizophrenics, as the illness can cause impairment in recognition memory (i.e., being able to identify a present object, item or event as having been previously seen or experienced.)

To date, only olanzapine and risperidone offer an ODT/SL tablet in the schizophrenia/bipolar psychosis market.

References:

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3. Wade AG, Crawford GM, Young D. A survey of patient preferences for a placebo orodispersible tablet [published online ahead of print, March 20, 2012]. *Patient Prefer Adherence.* 2012; 6:201-206. doi:10.2147/PPA.S28283.
4. Leucht S, Heres S. Epidemiology, clinical consequences, and psychosocial treatment of nonadherence in schizophrenia. J Clin Psychiatry 2006; 67 Suppl 5:3-8.
5. Valenstein M, Ganoczy D, McCarthy JF, Myra KH, Lee TA, Blow FC. Antipsychotic adherence over time among patients receiving treatment for schizophrenia: a retrospective review. J Clin Psychiatry 2006; 67(10):1542-1550.
6. Burton SC. Strategies for improving adherence to second-generation antipsychotics in patients with schizophrenia by increasing ease of use. J Psychiatr Pract 2005; 11(6):369-378.

3e) Is there a lower cost than for existing class comparators?

Pricing information with respect to the cost per tablet is not included in this evidence informed review. The reason for this is that evidence reviews should consider all aspects of the patient, among which costs comprise only a small determinant. However, it is well known that there are many generics on the psychosis market that, depending upon the province, can drive costs down to 25% of the innovator's initial pricing. While this is widely recognized as beneficial for provincial payers, two recent studies in Ontario and Quebec have demonstrated a high degree of recidivism and subsequent relapse of symptoms among patients receiving generic formulations. Indeed, if there is an 'osteomyelitic' pattern, or change in receptor pattern and/or neurobiological changes, this creates huge concerns regarding the 'penny-wise, pound-foolish' concept due to readmissions, decreased patient productivity, and reduced ability for the patient to otherwise function in society. One simple case of treatment failure - requiring hospital readmission through an emergency room, seven in-patient days, and a CT scan to rule out space occupying lesions as a cause of readmission -carries a price tag in excess of $12,500 in Ontario. Often, in an EIM review, the costs are non-tangible and will be established longer-term by the organization or provincial or federal body. In this particular review of asenapine, these non-tangible factors that improve functionality as well as quality of life would present themselves as long-term metabolic benefits, improved cognition and enhanced adherence.

This may be reflected as a patient taking a medication that improves cognition, so that they then become more likely to continue taking their medication. Asenapine is provided in a sublingual ODT

tablet that further reinforces adherence. Once the patient achieves adherence, whether primarily or secondarily through improved cognition, longer-term positive outcomes may result.

In schizophrenia and bipolar disorder, there is a negative affective component and burden of illness that both the patient and society bear. From a patient perspective, this is associated with declines in work, relationships, schooling, and integration into the general societal pool. From a neurobiological perspective, when a patient becomes less adherent, or stops taking medications entirely, hippocampal atrophy may result. This atrophy may not be quantifiable in dollars and cents, but in patient outcomes. In 2003, MacQueen et al. demonstrated that, once a patient has five depressive episodes in their lifetime, the statistical probability of the patient achieving a satisfactory level of functioning is approximately 1%, secondary to relapses in the mood component of the disorder. This leads to progressively increasing rates of relapse and readmission, and a subsequently magnified burden on society.

Within the past decade, a paper was published looking at aggressive upfront doses of risperidone, averaging 4 mg per day, decreasing the average length of in-hospital stay by three days. Data from Europe over the fall of 2012 indicate that asenapine use also is associated with decreased average lengths of hospital stay, in line with initial papers looking at rapid management and control of symptoms with risperidone. This study comes to light again as there may be a 'signaling' picture associated with asenapine, and thereby some positive predictive value in the first 48 hours of use: if a patient is an early responder to asenapine, he or she will tend to continue to have a robust response and may be continued on this drug. From an administration perspective, however, there is also the predictive value of a negative response to asenapine. This signal may not be evident with all drugs, such that many patients remain on a given medication, when in fact clinicians may be clinically 'flogging a dead horse' as the receptors of interest are not acted upon by the drug being used. This leads to longer lengths of stay and resultant higher costs. With asenapine, we seem to see a strong predictive signal. If the drug fails to generate any minimal positive effect within the first 48-72 hours, switching to a different antipsychotic is indicated. This 'rapid response assessment', as I term it, is of tremendous value to the country, the health care organization, and especially the patient and staff. In addition, such an early warning of ineffectiveness prevents further damage to the neurobiological structure from acute attacks, an effect that has not yet been fully quantified.

With respect to a hospital budget, short-term allocation impact, the manufacturer of asenapine in their hospital formulary binder has produced a worksheet to determine the impact to costs, from a dollars and cents perspective, if asenapine is added to the formulary. These cost calculators are in both Excel and worksheet format, and for both schizophrenia and bipolar type I disorder patients. What is needed is knowledge about the typical hospital stay, in days, for any given facility. Of note, patients at acute versus chronic psychiatric facilities generally have different average lengths of stay. This will help to determine costs per patient. That cost per patient may then be extrapolated to the number of patients who may end up using asenapine over a given period of time.

Dosages that are employed within the hospital calculator are:

Schizophrenia: 5 mg sublingual bid.

Bipolar type I: Scenario A - 5 mg sublingual bid.
Scenario B - 10 mg sublingual bid.

At the time of this writing, the cost of asenapine per unit is $1.43 per tablet irrespective of the number of milligrams per tablet. Keeping in line with ODT formulations, please note that the tablets are very hygroscopic and, as such, are not meant to be split for the purpose of unit dose packaging or split in advance of administration.

Reference:

Macqueen G, Campbell S, McEwen B, *et al:* Course of Illness, Hippocampal Function, and Hippocampal Volume in Major Depression. PNAS 2003; 100(3):1387–1392.

Rouleau B, Lavoie L, Leblanc J, Moretti S, Collin C, Watson J. Reporting of adverse drug reactions by community pharmacists: a qualitative study in Quebec. Canadian Drug Information Association 2010 Meeting. Poster Presentation.

Lamoure J, Stovel J., Milovanovic D., Huynh T., Reporting of Adverse Drug Reactions by Community Pharmacists in Ontario. (Poster). Presented at Canadian Pharmacists Association 99th Annual Conference Montreal, Quebec, Canada. May 30,2011

3f) Fewer side effects/better safety profile:

To better appreciate the safety profile of asenapine versus standard atypical agents, an understanding of receptor affinities is needed.

Asenapine is active at most serotonin receptors, including antagonism at the $5HT_6$ and $5HT_7$ receptors. There is also a strong affinity for most of the dopaminergic receptors, as well as moderate impacts and affinities at the adrenergic as well as histamine and adrenergic receptors. Compared to other antipsychotics, there is appreciably less affinity at the muscarinic receptor bundle (negligible with asenapine), though it is as potent as quetiapine at H_1 receptors [though less at H_2 than quetiapine]. In addition to its lack of affinity for muscarinic receptors, it appears to have little to no affinity for beta-, H_3, or $5HT_3$ receptors.

This selective receptor affinity profile may lead to fewer adverse effects, as well as enhanced beneficial properties.

References:

1. Shahid M, Walker GB, Zorn SH, Wong EHF. Asenapine: a novel psychopharmacologic agent with a unique human receptor signature. J Psychopharmacol 2009; 23: 65–73.
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3. Jardemark K, Marcus MM, Shahid M, Svensson TH. Effects of asenapine on prefrontal N-methyl-D-aspartate receptor-mediated transmission: involvement of dopamine D1 receptors. Synapse 2010; 64 (11): 870–874.
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Patients with mental illnesses like schizophrenia and bipolar disorder have an increased prevalence of metabolic syndrome and all its components, including risk factors for cardiovascular disease and type 2 diabetes. Although the prevalence of obesity and other risk factors like hyperglycemia are increasing in the general population, patients with major mental illnesses are more likely to be overweight or obese; to have hyperglycemia, dyslipidemia and/or hypertension; and to be cigarette smokers; and they have substantially higher mortality rates than an age-matched general population. Persons with major mental disorders lose an estimated 25 to 30 years of potential life versus the general population, primarily due to premature cardiovascular mortality. The causes of increased cardiometabolic risk in this population include non-disease

related factors such as poverty and reduced access to medical care, as well as adverse metabolic side effects associated with psychotropic medications like antipsychotics. Individual antipsychotic medications are associated with well-defined risks of weight gain, as well as related risks for adverse changes in glucose and lipid metabolism. Based upon the medical risk profile of persons with major mental illnesses, and the evidence that certain medications can contribute to increased risk, screening and regular monitoring of metabolic parameters like weight (body mass index), waist circumference, plasma glucose and lipids, and blood pressure are recommended to manage risk in this population. Treatment decisions should incorporate information about medical risk factors in general and cardiometabolic risk in particular. In addition to implications relevant to individual clinicians, disparate capacities to meet healthcare needs for persons with mental illness versus the general population have become an important public policy concern, prompting recent recommendations from the National Association of State Mental Health Program Directors and the Institute of Medicine (IOM).

Abdominal obesity and related increases in insulin resistance are important factors that contribute to excess morbidity and mortality. Obesity can lead to insulin resistance or reduced tissue sensitivity to insulin's actions, which in turn is associated with the development of other cardiovascular disease risk factors, including dyslipidemia, prothrombotic and proinflammatory states, and diabetes. The association between increasing body mass index (BMI) and cardiovascular risk and mortality is well established. Central adiposity (i.e., visceral abdominal adiposity) is particularly associated with insulin resistance and the increased risk of type 2 diabetes and cardiovascular disease.

References:

Casey DE, Haupt DW, Newcomer JW, et al. Antipsychotic-induced weight gain and metabolic abnormalities: implications for increased mortality in patients with schizophrenia. *J Clin Psychiatry.* 2004; 65(suppl 7): 4-18.

Newcomer, J. W. (2007). Metabolic Syndrome and Mental Illness-Page 4. *Am J Manag Care*, *13*, S170-S177.American Heart Association. Metabolic syndrome.

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Grundy SM. Obesity, metabolic syndrome, and coronary atherosclerosis. *Circulation.* 2002;105:2696- 2698.

Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. *N Engl J Med.* 1999;341:427-434.

Banerji MA, Lebowitz J, Chaiken RL, et al. Relationship of visceral adipose tissue and glucose disposal is independent of sex in black NIDDM subjects. *Am J Physiol.* 1997;273(2 Pt 1):E425-E432.

Advancing the treatment of people with mental illness: a call to action in the management of metabolic issues. *J Clin Psychiatry.* 2005;66(6):790-798

What is Metabolic Syndrome?

At least three criteria are required for an individual patient to meet the definition of metabolic syndrome (see Table 1).

Table 1: Criteria for metabolic syndrome.

Factor	Measurement
1) Obesity	
Waist circumference	
Males	>102cm (>40in)
Females	>88cm (>35in)
2) Dyslipidaemia	
Triglycerides	≥1.7 mmol/L
HDL cholesterol	
Males	<1.0 mmol/L
Females	<1.2 mmol/L
3) Hypertension	≥130/85 mmHg
4) Fasting glucose	≥5.5 mmol/L

Reference: Newcomer JW. Metabolic syndrome and mental illness. *Am J Manag Care*. 2007;13(suppl 7):S170-S7.

4) What are the proposed indications and patient groups for the therapeutic use of the reviewed medication?

The following patients are considered for treatment:

Patients with schizophrenia
Patients with bipolar type 1 disorder
Patients with mixed bipolar disorder

Although substance use disorder and post-traumatic stress disorder (PTSD) have not been reflected in clinical trial populations, it might be reasonable to include such patients for future trials and treatment based upon receptor affinities.

5) Identify any drugs and/or interventions that the reviewed medication could replace.

What may be suggested is the delisting(s) of medications at high risk for inducing metabolic syndrome with CHRONIC use (olanzapine), or changing their access status to provide clinical documentation if they are used preferentially, due to the high rate of mortality associated with adverse cardiovascular and metabolic outcomes. At this point, although asenapine demonstrates efficacy within a 72hr window and may identify early responders vs non-responders, there is no indication for acute treatment of mania or medical emergencies involving psychosis in schizophrenia.

6) Outline the therapeutic benefit(s) of the reviewed medication:

a) Initial evidence-based primary clinical research papers used in registration trials for the reviewed medication. If no Level One evidence (DBRCT) is available, attach and include additional discussion about the use of this drug in the absence of such evidence.

Asenapine, like all drugs, is a molecule that forms a complex by binding to various receptors, so as to serve a given biological purpose. There are a variety of ways by which this binding may occur. Related to this, one must remember that each such drug has both an association constant (Ki) and a disassociation constant (Kd). It is generally accepted that it is usually non-reversible binding that provides the pharmacological activity of medication. Binding may occur through Van der Waal forces, hydrogen bonds, or ionic bonding.

When this binding occurs, there is attachment of the drug to the receptor/receptor protein, the process of which induces or inhibits release of a given neurotransmitter from vesicles. Inhibition or induction, activation or inhibition of neurotransmitters may occur directly or via a cascade. Binding affinity is quantified using the term Ki. In general, the lower the Ki value, the higher the degree of affinity is for a particular molecule/drug at a particular receptor.

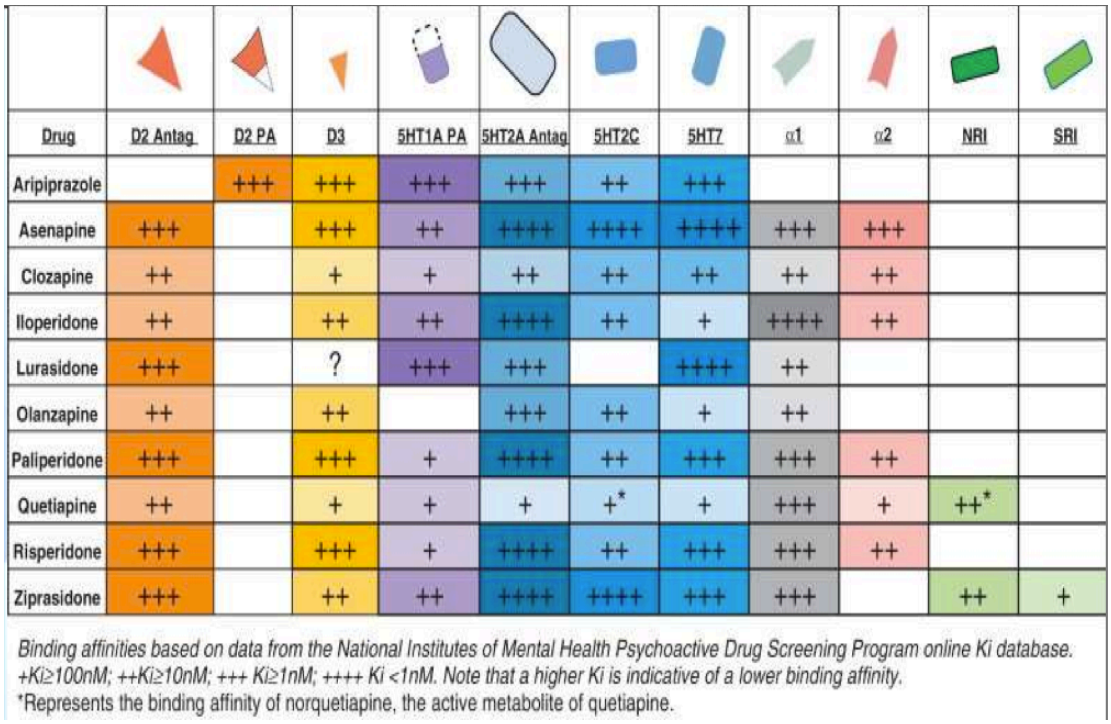
Overview of receptors and affinities:

The list of neurotransmitters under scrutiny is long, but special attention has been given to dopamine, serotonin, and glutamate. The different subtypes are summarized in the following table:

Neurotransmitter	Role in the Body
Acetylcholine	A neurotransmitter used by spinal cord neurons to control muscles and, via numerous neurons in the brain, to regulate memory. In most instances, acetylcholine is excitatory.
Dopamine	The neurotransmitter that produces feelings of pleasure when released by the brain reward system. Dopamine has multiple functions depending on where in the brain it acts. It is usually inhibitory.
GABA (Gamma-aminobutyric acid	The major inhibitory neurotransmitter in the brain.
Glutamate	The most common excitatory neurotransmitter in the brain.
Glycine	A neurotransmitter used mainly by neurons in the spinal cord. It probably always acts as an inhibitory neurotransmitter.
Norepinephrine	Norepinephrine acts as both a neurotransmitter and hormone. In the peripheral nervous system, it is part of the 'fight-or-flight' response. In the brain, it acts as a neurotransmitter regulating normal brain processes. Norepinephrine usually is excitatory, but it is inhibitory in a few brain areas.
Serotonin	A neurotransmitter involved in many functions, including mood, appetite, and sensory perception. In the spinal cord, serotonin is inhibitory within pain pathways.

Reference: NIH Publication No. 00-4871

A list of specific Ki values may be found in the *National Institutes of Health* (NIH) *Psychoactive Drug Screening Program* (PDSP) Ki database.



Drug	D2 Antag	D2 PA	D3	5HT1A PA	5HT2A Antag	5HT2C	5HT7	α1	α2	NRI	SRI
Aripiprazole		+++	+++	+++	+++	++	+++				
Asenapine	+++		+++	++	++++	++++	++++	+++	+++		
Clozapine	++		+	+	++	++	++	++	++		
Iloperidone	++		++	++	++++	++	+	++++	++		
Lurasidone	+++		?	+++	+++		++++	++			
Olanzapine	++		++		+++	++	+	++			
Paliperidone	+++		+++	+	++++	++	+++	+++	++		
Quetiapine	++		+	+	+	+*	+	+++	+	++*	
Risperidone	+++		+++	+	++++	++	+++	+++	++		
Ziprasidone	+++		++	++	++++	++++	+++	+++		++	+

Binding affinities based on data from the National Institutes of Mental Health Psychoactive Drug Screening Program online Ki database. +Ki≥100nM; ++Ki≥10nM; +++ Ki≥1nM; ++++ Ki <1nM. Note that a higher Ki is indicative of a lower binding affinity.
*Represents the binding affinity of norquetiapine, the active metabolite of quetiapine.

The symbols have been taken from the references and the affinities denoted by the plus symbols. The more the plus symbols, the higher the degree of affinity of that particular medication.

Asenapine exhibits high affinities for serotonin 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5 HT_{2C}, 5-HT_5, 5-HT_6, and 5-HT_7 receptors (Ki = 2.5, 4.0, 0.06, 0.16, 0.03, 1.6, 0.25, and 0.13 nM, respectively), dopamine D_2, D_3, D_4, and D_1 receptors (Ki = 1.3, 0.42, 1.1, and 1.4 nM, respectively), and alpha$_1$ and alpha$_2$-adrenergic receptors (Ki = 1.2 and 1.2 nM, respectively). It displays a lower affinity for histamine H_1 receptors (Ki = 1.0 nM), and a moderate affinity for H_2 receptors (Ki = 6.2 nM). In *in-vitro* assays, asenapine acts as an antagonist at these receptors. Asenapine has no appreciable affinity for muscarinic cholinergic receptors (e.g., Ki value = 8128 nM for M_1).

The lower a drug's Ki value at a given receptor, the higher its affinity and *vice versa*. Serotonin and dopamine are inhibitory neurotransmitters. The receptor $5HT_{7a}$ has possible roles in circadian rhythms, sleep, mood, thermoregulation, learning and memory, and endocrine regulation, though much about this neurotransmitter receptor remains unknown. Secondary to its roles in cognition, we would expect this receptor to be involved in schizophrenia and other neuropsychiatric disorders. As we increase serotonin levels, there is a corresponding decrease in dopamine levels.

The $5HT_{1a}$ receptor inhibits cortical parameters in neurons, and regulates hormone release, both of which have a possible role in the treatment of depression and anxiety, as well as the enhancement of patient cognition.

Finally, the $5HT_{2c}$ receptor is involved in the regulation of dopamine and norepinephrine release. It may be hypothesized that there is a possible role in obesity and determining mood. Obesity may occur secondary to decreased dopamine levels, in turn secondary to increases in serotonin. The clinical implications of this is that, as dopamine levels fall, patients look to other forms of satiety

and, as such, may increase the amount of food they ingest. Intriguingly, the $5HT_{2c}$ receptor also may play a role in cognition.

Activation of histamine [H_1] receptors is strongly associated with sedation and weight gain. Asenapine has a low affinity for this receptor, an affinity that is even slightly lower than that of quetiapine. There is marked differentiation in favour of asenapine over quetiapine for cognition, however, as well as activity at alpha-receptors, the latter of which exert little direct impact on metabolism. This may be one of the reasons metabolic syndrome is less common in patients on asenapine. Although some data indicate an NNH for asenapine of 34, in reality that number is probably less. It may be postulated, based upon receptor affinities, that the real NNH for asenapine, as a cause of metabolic syndrome in the treatment of chronic schizophrenia, is approximately 20 (meaning that roughly one in twenty, or 5% of patients will experience this complication). This positions asenapine in a metabolically positive light relative to many atypical antipsychotic drugs, and rendering it comparable to risperidone and paliperidone.

When the alpha-1 receptor is antagonized, postural hypotension and initial sedation result, while antagonizing the alpha-2 receptor has an antidepressant effect. High affinities for these receptors are associated with corresponding adverse and beneficial effects.

Asenapine exerts no appreciable effects on muscarinic receptors. As such, we would not expect, nor do we see, adverse effects associated with antagonism of this receptor. Adverse effects that occur with such antagonism include but are not limited to constipation, blurred vision, dry mouth, sedation and cognitive dysfunction. These adverse effects are intolerable to many patients. However, muscarinic antagonism does protect against extrapyramidal side effects.

As asenapine has high affinities for so many receptors ($5\text{-}HT_{1A}$, $5\text{-}HT_{1B}$, $5\text{-}HT_{2A}$, $5\text{-}HT_{2B}$, $5\ HT_{2C}$, $5\text{-}HT_5$, $5\text{-}HT_6$, $5\text{-}HT_{7,}$ D_3, D_4, D_1 and $alpha_1$ and $alpha_2$-adrenergic receptors$_{)}$ we would expect potential impacts on glutamine, impacts on dopamine, regulation of hormones, improvement in patients' depression and anxiety and, most importantly, enhanced cognition.

Cognitive symptoms may act through $5HT_{1A}$ antagonism, as well as antagonism of the $5HT_{2c}$, $5HT_7$ and 7a subtype receptors, which may make asenapine more effective for schizophrenia and bipolar type I disorder.

Not only does asenapine improve the negative symptoms of schizophrenia, which together are clinically similar to depression, it thus may improve cognitive symptoms through the receptor affinities as noted above. Patients with schizophrenia often turn to forms of self-medication to enhance their cognition. Most commonly, this involves cigarette smoking, as smoking immediately stimulates the pre-frontal cortex. If we are able to achieve the same cognitive stimulation with medication while also improving other signs and symptoms of schizophrenia, this may decrease the incidence of long-term concurrent medical conditions, including those induced by chronic cigarette use.

The D_2 receptor is involved in the mediation of positive and negative symptoms of psychosis. Inhibition of the D_2 receptor helps to decrease the positive symptoms of schizophrenia, which most commonly present as hallucinations and delusions. Unfortunately, potent inhibition of the D_2 receptors induces extrapyramidal side effects. This may explain some of the movement-related adverse effects caused by asenapine. The D_3 receptors have only recently been explored, in terms of tonic regulation of the mesolimbic dopamine pathway. This allows for the regulation of GABA, a neurotransmitter in the nucleus accumbens, which is part of the pleasure reward system of the brain. Therefore, if we have a drug that has a high affinity for and impact upon the D_3 receptor, we may see a role in mediating reward. As well, D3 receptors are involved in

acetylcholine release within the frontal cortex. D2 receptors seem to play a very important role in both the nucleus accumbens and prefrontal cortex.

D_1-like inhibition blocks cocaine-induced euphoria. As we commonly see substance abuse in schizophrenic patients, achieving such blockade could be of clinical benefit and certainly warrants future investigation. The D_2 receptor is a G protein-coupled protein that inhibits adenylyl cyclase activity. This mediates the physiological functions of dopamine, ranging from voluntary movements and reward through hormonal regulation. If we have a medication that antagonizes the D_2 receptor, such as asenapine, we would expect no effect on basal activity in the D_2 receptor-linked G protein messenger system, but chronic antagonism of D2 receptors could actually up-regulate the receptors. However, there is mediation of the positive and negative symptoms of psychosis, as noted above. We tend to see psychotic, anti-manic, and extrapyramidal side effects in these patients. Thus, based upon the receptor affinities and resultant Ki values of asenapine, it is not surprising that we are able to control the symptoms of both schizophrenia and bipolar type I disorder, the latter of which commonly presents in a manic phase. We know that efficacy treating positive symptoms is potentially associated with the exacerbation of negative symptoms. Asenapine in schizophrenia is used to treat schizophrenia by reducing D_2 hyperactivity and positive symptoms. This also reduces dopamine activity to an extent that is normally insufficient to induce extrapyramidal symptoms. Again, this may explain why asenapine is associated with a lower risk of extrapyramidal side effects than typical antipsychotics like haloperidol.

The D_3 receptor, when antagonized, is a useful target when treating the negative and cognitive symptoms of schizophrenia and substance abuse disorders. As we can start to see, there is a robust impact on cognition using asenapine on dopamine and highly targeted serotonin receptors [like the $5HT_{1C}$ and $5HT_7$ receptors].

Blocking the $5HT_1$ receptor has antidepressant, anxiolytic and anti-aggressive effects. The $5HT_{1a}$ receptor, in and of itself, is a dopamine accelerator. When we impart agonistic effects on $5HT_{1a}$ receptors, this improves negative, cognitive, and affective symptoms. This actually serves as a bit of a dopamine brake, reducing the risk of extrapyramidal side effects and hyperprolactinemia.

The $5H2_{1a}$ receptor can be made to serve as this dopamine brake. Antagonizing this receptor stimulates dopamine release in certain brain areas, thereby lessening negative, cognitive and affective symptoms. Antagonism of this receptor also reduces extrapyramidal side effects and hyperprolactinemia, while increasing slow wave sleep and potentially enhancing mood. Meanwhile, antagonism of the $5HT_{2a}$ receptor improves negative, cognitive and affective symptoms while simultaneously reducing the risk of extrapyramidal side effects and elevated prolactin levels.

As asenapine also acts on the $5HT_{2c}$ receptor, it is prudent to address its impact on this receptor. This particular receptor is the one that regulates dopamine release. Activity of this receptor may reduce dopaminergic transmission and, as such, also can improve the positive symptoms of schizophrenia. On the other hand, this could worsen cognition and cause extrapyramidal side effects. This being said, asenapine is an antagonist at this receptor, which reduces depression and improves cognition by dis-inhibiting dopamine and norepinephrine release in the prefrontal cortex. As stated above, this is very similar to what we would expect in patients while smoking, a form of self-medication that is used by 80% of schizophrenics to enhance cognition. Smoking enhances cognition of the prefrontal cortex within about seven seconds.

The $5HT_7$ and $5HT_{7a}$ receptor subtypes also have possible roles mediating depressive disorders through cognition. As well, they may do so by regulating circadian rhythms, sleep,

thermoregulation, and learning and memory. Endocrine regulation also may occur through this particular receptor.

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Accessed February 23, 2013

Lamoure J. Psychopharmacology "Boot Camp" Essentials Study Guide Review: 304 pages ISBN 9781300958154

THERAPEUTIC BENEFITS: EMERGENCY ROOM

Based on the specific K_i neurotransmitter effects of asenapine, specifically the effects on D_2, D_3, partial 5-HT_{1A} agonist, plus $5HT_6$ and $_7$ may decrease anxiety, agitation and irritability, it was hypothesized that asenapine would exert benefits on these urgent or emergency situations. Pratts et al demonstrated (Published 10 March 2014) with a total of 120 subjects (60 each to sublingual asenapine (10mg) or placebo) efficacy at controlling these symptoms, with the measurement being the Positive And Negative Syndrome Scale-Excited Component (PANSS-EC) . The PANSS-EC addresses excitement, hostility, tension, uncooperativeness and poor impulse control. The mean baseline PANSS-EC scores for the asenapine-treated and placebo-treated subjects were 19.4 ± 0.66 and 20.1 ± 0.61 respectively. Mean PANSS-EC scores at endpoint based an last observation carried forward (LOCF) was 7.4 ± 0.65 for the asenapine-treated subjects and 14.7 ± 0.98 for the placebo-treated subjects. The reduction in the asenapine treatment arm was statistically significant from the placebo arm, with a number needed to treat (NNT) of 3.

Time to result in reduction of the PANSS-EC Score:

Number Achieving ≥ 40% Reduction in PANSS-EC Score

	Asenapine (N=60)	Placebo (N=60)	NNT (95% CI)
15 minutes, n (%)	14 (23.3%)	8 (13.3%)	9 (ns)
30 minutes, n (%)	31 (51.6%)	13 (21.6%)	3 (2-6)
60 minutes, n (%)	46 (76.6%)	19 (31.6%)	3 (2-4)
90 minutes, n (%)	47 (78.3%)	20 (33.3%)	3 (2-4)
120 minutes, n (%)	47 (78.3%)	21 (35%)	3 (2-4)

Reference:

Pratts, M., Citrome, L., Grant, W., Leso, L., & Opler, L. A. (2014). A single-dose, randomized, double-blind, placebo-controlled trial of sublingual asenapine for acute agitation. *Acta psychiatrica Scandinavica*.

PSYCHIATRIC CONDITIONS:

Bipolar Disorder:

Asenapine has been studied as mono-therapy for bipolar disorder type 1 (BP-I). For registration trials, it typically is deemed appropriate to assess non-inferiority against an accepted comparator rather than superiority to placebo.

In the initial phase, as with all registration trials, superiority versus placebo was assessed. This study had three arms, with patients randomized to generate sample sizes in a ratio of 2:1:2. These arms were analyzed both to identify superiority of asenapine versus placebo. The respective treatments were: (1) asenapine 10 mg orally BID on day #1, with either 10 or 5 mg orally bid to follow; (2) placebo; and (3) olanzapine 15 mg orally daily on day #1, with doses fluctuating from 5 to 20 mg orally daily afterwards. Doses were determined on a case-by-case basis at the discretion of the clinician, based upon patient responses.

To assess further for the non-inferiority of asenapine versus olanzapine, the two arms receiving active treatment were continued, still in a double-blinded fashion. As such, whether patients were receiving asenapine or olanzapine continued to be unknown. This extension trial lasted nine weeks.

A further double-blind extension trials was conducted, the goal of which was to assess drug safety over a 40-week period (total treatment period of 52 weeks for patients starting in the 3-week acute trial and remaining through to the end of the two extension trials). Patients continued within the treatment groups to which they already had been assigned.

McIntyre et al. in Bipolar Disorders 2009 have presented results of the studies. To assess baseline levels of mania, the Young Mania Rating Scale (YMRS) was used. Baseline YMRS scores at the start of the acute trials were 29.0 for controls assigned to placebo [N=103]; 28.3 for subjects assigned to receive asenapine [N = 189]; and 28.6 for those allocated to receive olanzapine [N = 188], indicating a similar baseline level of mania in the three treatment groups.

In this 3-week study, a placebo effect was noted in the placebo arm, exhibited as a mean decrease in the YMRS score of 5.5 at the time of 21-day assessment. Over the same time period, those on asenapine experienced a reduction of approximately 11.5, while those on olanzapine exhibited a mean reduction in YMRS score of just over 12.0. Statistical analysis identified a statistically significant difference between both active interventions and placebo. However, testing for non-inferiority, there was no statistical difference [$p < 0.01$] between asenapine and olanzapine.

In the control of mania itself, McIntyre et al (2009) noted that asenapine was efficacious for the treatment of acute mania and was non-inferior to olanzapine, both within the 3-week trial itself, as well as up to 84 days out.

While the acute trials assessed patients in manic or mixed states, there was *post hoc* analysis to determine if there had been any effect of any treatment on depressive symptoms, quantified using the *Montgomery-Asberg Depression Rating Scale (*MADRS). Patients with a MADRS score >20 at baseline were roughly equally-distributed across the three treatment arms, with only slightly less than 50% of all patients exhibiting this debilitating level of depression. However, by the end of three weeks, the proportion of patients with a MADRS >20 had significantly improved in the asenapine arm versus either olanzapine or placebo. Those on asenapine had a mean 13.5-point reduction in their MADRS score, versus a 10.2-point reduction in those on olanzapine ($p <0.05$). Asenapine generated greater score reductions than placebo, with olanzapine not differing from placebo on baseline MADRAS scores. However, it is of clinical interest that the asenapine arm also had decreased their MADRS score by approximately 11.5 points by as early as day #7, again superior to placebo. This raises the

question: could this medication improve not only mania, but also depressive symptoms in bipolar disorder patients?

While not addressed further in the study, this question of asenapine's effectiveness treating depression in bipolar patients is an area worth addressing. Clinical experience suggests that bipolar patients spend approximately 75% of their time in a euthymic or depressive state, and only 25% as hypomanic or manic. To date, according to Cipriani et al., the only comparator that addresses depression so early in the course of treatment of bipolar disorder is S-citalopram. The rapid responsiveness of depressive symptoms to asenapine observed in these post-hoc analyses is both extremely enticing and not all that unexpected, based upon serotonin receptor affinities. In fact, given its receptor affinity profile and increased effects on patient cognition, subtype analysis of asenapine's effect on depression would be of particular interest among patients within the bipolar sphere who present with a mixed disorder, who often have a high degree of anxiety, agitation and irritability.

The premise of impact on the depressive symptoms warrants even further consideration in light of evidence presented in a poster (not peer reviewed) at the Scandinavian College of Neuropsychopharmacology (SCNP) Annual Conference held in Denmark in the spring of 2012, where a combination of asenapine and escitalopram was shown to be more effective treating depressive symptoms than mono-therapy with either agent. Based upon what could be defined as depression remission rates [post hoc, MADRS ≥ 20 scoring at baseline], this would corroborate the above observation that by day #21, approximately 70% of patients administered asenapine whose baseline MADRS score was in the depressive range [N= 45] achieved remission. This contrasts against the 35% of placebo patients who achieved remission within 21 days, a percentage consistent with other examples of placebo effect. Even taking into account this sizeable placebo effect, double the percentage of patients on asenapine who were in a bipolar depressed phase improved, which was a statistically significant difference.

In the 9-week, two-arm phase extension trial – a mono-therapy, non-inferiority study comparing asenapine and olanzapine - patients either received asenapine 5 or 10 mg twice daily [N=173) or olanzapine 5 to 20 mg once daily [N=221). Over the nine weeks, asenapine significantly improved depressive symptoms in patients with mixed episodes. Recall that there had been a decrease in mean MADRS scores in both active treatment arms and the placebo arm during the phase 1 study (see above), but that only patients on asenapine experienced a decline that was statistically different than placebo. This beneficial effect of asenapine on depressive symptoms carried through the next nine weeks in the blinded non-inferiority trial. From an observational perspective, this appears to signify some long-term efficacy of asenapine as an antidepressant, in addition to its anti-manic effects in patients with bipolar or mixed disorder. Comparing olanzapine and asenapine, the reduction in YMRS score was deemed non-inferior in nature, indicating no superiority of olanzapine over asenapine treating manic symptoms. Overall, the YMRS reduction in the olanzapine group was 20 points versus just over 22 points in those administered asenapine.

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Schizophrenia:

Schizophrenia is a chronic mental disorder that is characterized by three broad categories of symptoms: positive, negative, and cognitive. *Positive symptoms* are symptoms that do not occur in healthy individuals, like hallucinations, delusions, disordered thinking, and various movement disorders. *Negative symptoms* are disruptions to normal emotions and behaviours; they include a flat affect, lack of pleasure in daily activities, the inability to initiate or continue planned activities, and rarely speaking. Finally, the *cognitive symptoms* of schizophrenia include the inability to understand information and use it to make decisions, problems focusing and paying attention, and difficulties using information immediately after learning it.

The Potkin review of 2007 was the first randomized clinical trial (RCT) involving asenapine to assess changes in both positive and negative schizophrenia symptoms, measuring them via the published and scientifically validated *positive and negative symptoms scale* (PANSS). In this 6-week study, there were three treatment arms: placebo [n=60), risperidone (n=56), and asenapine (n=58). Baseline characteristics of the three sample groups were similar; the only difference being that the risperidone arm had a slightly lower prevalence of negative symptoms. The active treatment dosages employed in this study were asenapine 5 mg orally twice daily and risperidone 3 mg orally twice daily. It is of note that the risperidone doses used were the highest recommended for standard clinical practice, as daily doses over 6 mg are associated with an increased rate of extrapyramidal side effects with no significant increase in the control of schizophrenic symptomatology. In fact, the dose response curve is flat with daily doses higher than 6 mg. Asenapine in their conclusion was stated to be effective for negative symptoms and "may provide a new option for control of negative symptoms".

Primary analyses should be discussed first: change from baseline on PANSS total score

At the final 6-week endpoint, mean negative symptom score changes from baseline included a reduction of 3.2 in the asenapine arm, versus 1.05 on risperidone and 0.6 on placebo; the reduction for asenapine but not risperidone was statistically greater than for placebo. Integrating the results of the previously mentioned bipolar disorder studies, these new findings should come as no surprise, as negative symptoms are often associated not just with dopamine but also serotonin, and the affinity of asenapine for serotonin receptors is much greater than that of risperidone.

Looking at the PANSS positive symptom score, an overall reduction of 2.0 was identified in the placebo arm, consistent with placebo effects observed in most schizophrenic studies. Meanwhile, reductions exceeded 5.0 both on asenapine and risperidone, though these two agents were not statistically different from each other.

In another study, Kane et al. looked at the efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients suffering from acute exacerbations of schizophrenia. These

results were published in the Journal of Clinical Psychopharmacology in April 2010. In this double-blinded, six-week RCT, 458 patients with acute schizophrenia were randomized to receive (1) haloperidol 4 mg orally bid; (2) asenapine 5 mg orally bid; (3) asenapine 10 mg orally bid; or (4) placebo. On both the positive and negative symptom subscales, all three active treatments were superior to placebo. Asenapine performed better in the negative subscale of the PANSS vs. placebo.

Finally, Kane recently presented the results of a study involving schizophrenia patients in whom improvements in the Calgary Depression Scale were statistically greater for asenapine over six weeks than for either haloperidol or placebo; haloperidol, in fact, was no better than placebo.

Kane et al. then conducted another trial to compare asenapine and placebo in the prevention of schizophrenia relapses after long-term treatment. Relapses are exceedingly common in schizophrenia, due both to the underlying nature of the illness and poor treatment adherence secondary to, among other issues, poor patient insight and adverse drug effects. They assessed the long-term efficacy of asenapine at preventing schizophrenia relapse in a 26-week double-blind, placebo-controlled trial that followed 26 weeks of open-label treatment in stable schizophrenia patients (DSM-IV-TR criteria) who had been cross-titrated from previous medication to sublingual asenapine and had remained stable over the entire 26 weeks of open-label treatment. The study's primary outcome measures were the positive and negative syndrome scale [PANSS] and the clinical global impressions-severity of illness scale [CGI-S].

Of 700 enrolled patients treated with open-label asenapine, 386 entered the double-blind phase to randomly receive either asenapine 10 mg twice daily (n = 194) or placebo (n = 192). Of these, 207 completed the study: 135 of the 194 patients assigned to receive asenapine (70%) verses only 72 of the 192 patients given placebo (38%). Asenapine out-performed placebo in multiple outcomes, including longer times to relapse/impending relapse and to discontinuation for any reason (both $p < 0.00$); and a lower incidence of relapse/impending relapse (12.1% vs. 47.4%, $p < 0.0001$). During the double-blind phase, incidence rates for serious adverse events (AEs) were 3.1% and 9.9% for asenapine and placebo, respectively; and corresponding rates of extrapyramidal symptom-related AEs were 3.1% and 4.7%. The most frequently reported AEs with asenapine and placebo were anxiety (8.2%; 10.9%), weight gain (6.7%; 3.6%), and insomnia (6.2%; 13.5%). The incidence of clinically significant weight gain (≥ 7% increase from double-blind baseline) was 3.7% with asenapine and 0.5% with placebo.

From a placebo perspective, that 62% of placebo-treated patients either were non-adherent or dropped out over the 26 weeks (six months) is in line with commonly quoted literature that indicates that up to 80% of schizophrenia patients will either become grossly non-adherent or totally stop their active medication entirely within one year of treatment initiation.

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6b) Is there a systematic review or health technology assessment comparing the reviewed drug to the current standard of care? If no systematic reviews exist, place the reviewed medication in the context of other possible therapies.

In 2007, the Canadian Agency for Drugs and Technologies and Health (CADTH) sought to optimize medications for the treatment of schizophrenia. This agency looked at and ultimately advocated for mono-therapy for patients receiving pharmacotherapy. They primarily looked at outcomes and costs. Factors they assessed that might affect the cost of treatment including the probability of drug discontinuation [e.g., from lack of efficacy], probability of relapse, time to relapse, and the cost itself of the atypical antipsychotic. They did not look at cognition, as this was not on the differential list of issues in 2007.

Clinical consequences, blended with the probabilities of adverse events [extrapyramidal side effects and diabetes], were utilized to construct a decision-tree model that estimated the mean overall 12-month, per-patient cost of initiating a particular treatment. In addition, the investigators looked at the concept of switching drugs, as well as the progression from first to second to third line therapies, for patients who fail to respond or tolerate a given treatment in any stage.

Several issues that were not considered included cognition [as noted above], long-term implications of diabetes and other metabolic concerns, and patient function. Optimal doses also might not have been addressed. A final major limitation of their analysis was that only 12 months of treatment was considered. This may explain why risperidone and olanzapine fared best among all of the agents. Looking at receptor affinities and the impact and burden of disease, we would consider differently, given that risperidone and olanzapine have been compared to asenapine in non-inferiority analyses and neither was found to be superior.

Looking ahead, one would consider perhaps comparing risperidone and asenapine in terms of both the positive and negative symptoms of schizophrenia. If indeed, as CADTH evidence demonstrates, risperidone is a preferred agent for schizophrenia, then when extending treatment beyond 12 months, asenapine might be indicated as well. This would be for the following reasons, as well as longer-term projections: a better metabolic profile, an improved cognitive profile, and no differences on non-inferiority analysis, all on a background of a superior negative symptom profile among schizophrenia patients.

Overall, twice-daily steady-state pharmacokinetics for asenapine are similar to single-dose pharmacokinetics. Following an initial, more rapid distribution phase, the mean terminal half-life is approximately 24 hrs. As such, steady state is attained within 3.3 days, given that 90% of steady state is achieved in 3.33 half-lives.

Asenapine is eliminated primarily through direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 isoenzymes (CYP1A2 and, to a lesser extent, CYP3A4 and CYP2D6). Asenapine, in fact, is a weak inhibitor of CYP2D6. Population pharmacokinetic analysis has indicated that cigarette smoking, which induces CYP1A2, has no effect on the clearance of asenapine, an important consideration given the high prevalence of tobacco use among

psychiatric patient populations. For example, in one cross-over study in which 24 healthy male subjects (who were smokers) were administered a single 5 mg sublingual dose, concomitant smoking had no effect on the pharmacokinetics of asenapine. Despite this, a higher dose may be indicated for those whose daily smoking habit involves more than seven tobacco cigarettes or one or more marijuana cigarettes. Meanwhile, the consumption of food immediately prior to sublingual administration of asenapine decreases serum levels by 20%; while consumption of food within four hours decreases levels by about 10%. These effects are presumed to be due to increased hepatic blood flow.

Weber and McCormack did a full review of asenapine in their article in CNS Drugs in 2009, plus Citrome et al did a review of the literature to date that same year. The overall conclusions were similar, although it was noted in Citrome that the bulk of literature lie funded by Merck, the manufacturer of asenapine. The summaries of the 2 reviews are as follows:

1) Asenapine is a novel pharmacological structure in the antipsychotic class, with affinities to dopamine, norepinephrine, serotonin and histamine

2) Asenapine is superior to placebo in bipolar mania

3) Asenapine is superior to placebo in schizophrenia and schizoaffective disorders where persistent, dominant negative symptoms prevail

4) Asenapine is non-inferior to olanzapine for bipolar mania and schizophrenia

5) Sublingual asenapine has poor bioavailability

6) Asenapine has a better metabolic profile than olanzapine

7) Discontinuations due to adverse effects were similar to olanzapine (6% vs 7%)

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Lamoure J. Psychopharmacology "Boot Camp" Essentials Study Guide Review: 304 pages ISBN 9781300958154

7) For which types of patients would the reviewed medication be utilized?

The main disorders for which asenapine would be used are

- Bipolar disorder type 1 (Mania)
- Mixed bipolar disorder
- Schizophrenia

8) What are the common side effects and serious toxicities of the reviewed medication and anticipated incidence rates?

Citrome et al best summarized asenapine in 2009 by stating “Although there is no evidence for asenapine’s efficacy to be superior to currently available agents, asenapine’s favorable weight and metabolic profile are of clinical interest”

Overall, looking at the initial registration trial on bipolar mania that spanned 52 weeks, several common adverse events stand out. The most common side effects, which occurred in at least 5% of patients, were over-sedation, hyper-somnolence, dizziness, depression and increased weight. Perhaps the most concerning of these, in terms of its long-term impact on patient health, is weight gain. Weight increased in just 0.6% of those in the placebo arm; meanwhile, weight gain was recorded in 17.0% and 7.2% of those on olanzapine and asenapine, respectively. This fits in with olanzapine and asenapine’s receptor affinity profiles for histamine receptors. That there was a 7% increase over patient ideal body weights is of special concern. These numbers are probably more reflective of truth than those from the 8 to 12 week registration trial, given that they extend over a 52-week period.

The 7.2% incidence of weight gain, though of concern, still positions asenapine with a lower incidence of weight gain than olanzapine, quetiapine or clozapine. However, this incidence remains appreciably higher than for ziprasidone and lurasidone, and slightly higher than for risperidone and paliperidone. It is reasonable to expect at that this 7.2% incidence might rise even higher with long-term treatment beyond one year, though likely to not more than 10%. Schoemaker et al identified at one year, in patients with schizophrenia or schizoaffective disorder, that that Mean weight gain incidence was 0.9 kg with asenapine vs. 4.2 kg with olanzapine. These numbers are lower than seen by McIntyre et al, for both agents.

As stated earlier, activation of histamine [H_1] receptors may cause both over-sedation and weight gain. Asenapine has a low affinity for this receptor, an affinity slightly lower than that of quetiapine. Asenapine is superior to quetiapine in terms of enhancing cognition, however. It also, because of its actions at alpha-receptors, affects metabolism to a lesser degree. Again, this may be one of the reasons metabolic syndrome is less common with asenapine. With an NNH of 34, asenapine is relatively metabolically benign, comparable to risperidone or paliperidone. The 7% incidence of weight gain with asenapine is clearly far less than the 45% incidence (NNH=2.2) seen with olanzapine or the 60% incidence with clozapine (NNH=1.7). Quetiapine is variable in nature and has numbers quoted between 10 and 25% (NNH=4 to 10) depending on the patient population and demographics studied.

In schizophrenia trials performed by Kane et al., treatment-related adverse events were noted in 44% of patients receiving asenapine 5 mg orally twice daily versus 41% in the placebo arm. Higher doses of asenapine were associated with a 52% rate of treatment-related adverse events, compared to 57% in those allocated to take haloperidol 8 mg per day. The most common adverse events were extrapyramidal in nature, with 5% more patients receiving low-dose asenapine experiencing extrapyramidal side effects than those administered placebo. For haloperidol, 24% more patients had

EPS-related movement disorders over placebo. Eight percent of patients receiving high-dose asenapine (10 mg PO bid.) experienced EPS.

In the Kane, Mackle, Snow-Adami et al. trial, the incidence of serious adverse events was 3.1% with asenapine versus 9.1% with placebo. The incidence of extrapyramidal side effects was 3.1 versus 4.7%, respectively. The most common adverse events noted were anxiety, increased weight (greater than 7% increase in ideal body weight, IBW] and insomnia. In this trial, however, clinically significant weight gain was noted just 3.7% with asenapine versus 7.0% elsewhere. For some reason, weight gain appears to be less of a risk in patients being treated for schizophrenia than bipolar disorder. Any links to areas of the brain impacted by these two diseases and treatments or aspects relating to cognition would be purely conjecture.

The oral disintegration tablet (ODT) sublingual formulation of asenapine has been associated with oral hypoesthesia at an incidence of 4%, and dysgeusia at a 3% incidence.

QTc has emerged as a large factor in antipsychotics in the past decade. As such, review of this cardiovascular adverse effect is essential. Chapel et al in 2009 addressed this issue, and at the Cmax for asenapine, the mean change on the QTc interval was predicted to be less than 5msec. This is less than the International Conference on Harmonization's QTc threshold for clinical concern. Of note though, the 95% confidence interval was as high as 7.5 msec increase, placing asenapine in a small patient subset at a low degree of additive concern for QTc prolongation.

Prolactin is in a similar vein with antipsychotics, given the effects on dopamine by these agents. In pooled data from six-week initial trials, prolactin levels decreased 6.5 ng/dL with asenapine, versus a mean 2.8 ng/DL increase with haloperidol 8mg per day. In comparison, risperidone 6 mg per day increased prolactin levels by 39.5 ng/dL, and those taking placebo exhibited a mean reduction in prolactin levels of 10.7 ng/dL.

Asenapine was well tolerated over 1 year of treatment, causing less weight gain than olanzapine but more frequent extrapyramidal symptoms in a study by Schoemaker et al, with only 6% of asenapine patients discontinuing medications secondary to adverse events. This study was a double blind 1-year trial of asenapine in patients with schizophrenia or schizoaffective disorder, in a 3:1 ratio of asenapine: olanzapine.

From an overall perspective, addressing the patient monograph, serious adverse events that occurred in at least 5% of patients receiving asenapine were somnolence, akathisia, and oral hypoesthesia. Further adverse events were as listed below:

Extrapyramidal syndrome (EPS)-related events: (excluding akathisia)

7% with placebo; 9% with 5mg bid asenapine; 12% with 10mg bid

Akathisia: 3% placebo; 4% with 5mg bid asenapine; 11% with 10mg bid

Parkinsonism and akathisia: dose-related, with 5mg bid rate similar to placebo

Short-term registration trials:

Elevated FPG: 7.4% with asenapine; 6% placebo

Elevated cholesterol: 8.3% with asenapine; 7% with placebo

Elevated triglycerides: 13.2% with asenapine; 10.5% with placebo

Orthostatic hypotension < 2%

Dizziness: 4% placebo; 7% asenapine (not dose related)

QTc interval: Increases in QTc interval ranging from 2 to 5 msec, comparable to placebo

> This drug should be avoided in patients with a history of cardiac arrhythmias or congenitally prolonged QTc

Prolactin levels: not statistically different than with placebo

Discontinuation rates: 9% asenapine; 10% with placebo

Oral hypoesthesia (numbing of the tongue): 5% asenapine; 1% placebo

Serious allergic reactions reported: anaphylaxis; angioedema; difficulty breathing; swelling of the face, tongue or throat; light-headedness. Post-marketing surveillance via FDA identified 52 cases of life-threatening allergic reactions

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9) Identify cost impacts (both positive and negative) in non-drug areas. Indicate how the reviewed medication impacts non-drug costs.

You would anticipate that, as the risk of metabolic syndrome is decreased, there would be less monitoring required. As such, non-drug costs may be mitigated both in the short-term and long-term. Such costs can have an impact on a patient's quality and quantity of life. If we can decrease the incidence of increased fasting plasma glucose and the dysregulation of lipids, we would expect fewer long-term complications. In the short-term, we would observe less use of anti-diabetic agents [metformin, glyburide etc.] and their potential adverse effects. Monitoring requirements also would be lessened, resulting in lower costs, both for glucose test strips and other equipment.

In the long-term, we would expect to see a decrease in the microvascular and microvascular complications of diabetes. These include neuropathies and various cardiovascular concerns.

To address concerns relating to microvascular complications, improving lipid control would be of great benefit. If we were able to increase high-density lipoproteins, decrease low-density lipoproteins and decrease very low-density lipoproteins through diet and exercise, we would expect to see improved cardiovascular outcomes. This may be achieved in two ways using more metabolically neutral medications. First and foremost, there would be fewer initial cardiovascular concerns. In addition, there would be the benefits of not needing additional medications, like the statins [HMG-coenzyme inhibitors]. These medications, in and of themselves, are associated with numerous potential side effects. These potentially include neuropsychiatric side effects at higher doses, as well as an increased risk of rhabdomyolysis. It is intriguing that rhabdomyolysis is also seen with overdoses of atypical anti-psychotics. Thus, patients who require higher doses of these medications may have their risk of rhabdomyolysis further augmented by statin medications prescribed to control high lipid levels. As well, some of these drugs are substrates of the CYP3A4 isozyme, which increases the risk of drug-drug interactions.

10) What relevant economic evaluations of the reviewed medication might be necessary, relative to alternatives?

Asenapine is a novel atypical antipsychotic with tetracyclic properties that is been approved in Canada for the treatment of schizophrenia, as well for the acute treatment of manic or mixed episodes associated with bipolar disorder type I, as listed. Schizophrenia is a chronic, severe, and disabling mental illness. It affects men and women with equal frequency. Schizophrenia is usually diagnosed between the ages of 17 and 35 years. The illness tends to appear earlier in men (in their late teens or early twenties) than in women (who generally present in their twenties to early thirties. In Canada, the overall incidence in the general population is about 0.6%. The causes of schizophrenia are not known. However, some interplay between genetic, biological, environmental, and psychological factors are thought to be involved in biological models of schizophrenia, genetic (familial) predisposition, infectious agents, allergies, and disturbances in metabolism have all been investigated. Schizophrenia is known to run in families. Thus, the risk of illness in an identical twin of a person with schizophrenia is 40-50%.

A child of a parent suffering from schizophrenia has a 10% chance of developing the illness. One of the major challenges with treatment using antipsychotics as that, despite being somewhat effective at alleviating schizophrenia symptoms, they are perceived to be palliative in nature and limited in efficacy. There is evidence that patients who are diagnosed and treated at an earlier stage of the disease typically experience better outcomes.

Since schizophrenia typically presents during that stage of life when people are starting a career, attending post secondary education, or starting a family, it stands to reason that decreasing psychotic symptoms, both positive and negative, might result in major long-term beneficial outcomes. Risk factors for a poor initial response to early intervention in the first year are: male gender, obstetrical complications, more severe symptomatology, and the development of adverse effects from medications (e.g., EPS or parkinsonian symptoms).

Another quality of life issue that impacts schizophrenia is that of substance abuse/chemical dependency. It is important that, as we read through this section, we also consider that chemical dependency largely reflects behaviors more than the substance itself. Proof of this is the tremendous diversity of addictions, with which the 'substance of choice' may be a drug, alcohol, pornography, the internet, gambling, shopping, or sex, to name but a few. What is most important from the patient's perspective is the reduction in the quality and quality of their life across the period of use. All of these addictive behaviours place strain on the Canadian healthcare system.

Pulling all these factors together, two papers have looked at the cost effectiveness of asenapine in the treatment of both bipolar disorder type I and schizophrenia within the Canadian system. The lead author in both of these papers was Dr. J. Lachine.

In one study, Lachine et al. assessed the treatment of bipolar disorder in Canada by analyzing both Ministry of Health data and societal costs over a five-year time period, looking at yearly cycles. These investigators looked at patients with moderate severity bipolar disease who had been treated with an atypical antipsychotic. What they noted was that asenapine was a "dominant strategy over olanzapine" from both Ministry of Health and societal perspectives. It would be anticipated, from a Ministry of Health perspective, that this would be due to the decreased adverse metabolic impact of asenapine versus olanzapine. Incremental cost utility ratio [ICUR] analysis demonstrated similar quality adjusted life years (QALY) with the two antipsychotics. However, per 1000 individuals treated, asenapine was associated with an approximately $3.85 million reduction in Ministry of Health perspective costs and a $3.88 million reduction in societal-perspective costs over five years. Across a 10-year time horizon per 1000 individuals, the overall reduction of costs with asenapine versus olanzapine totaled $14 million. In addition, asenapine use was associated with an improved quality adjusted life year ratio, though how clinically significant this difference is, was never formally assessed.

Looking at the cost-effectiveness of asenapine in the treatment of schizophrenia in Canada, using a similar model to that described above, the authors looked at patients with moderately severe schizophrenia treated with an atypical antipsychotic at approximately 40 years of age. In this study, the investigators were concerned with the incidence and costs associated with long-term metabolic complications, diabetes, hypertension, coronary heart disease, stroke, fatal cardiovascular outcomes, and suicide. As for bipolar disease, quality adjusted life years improved for both asenapine and olanzapine. However, per 1000 individuals over five years, the former drug was associated with Ministry of Health cost savings of $6.25 million and societal cost savings of $6.28 million, together amounting to more than $12.5 million. This would extrapolate to $25 million per 1000 patients over a decade.

Hence, for both moderate-severity bipolar type I disorder and moderate-severity schizophrenia, major cost savings are achieved utilizing asenapine, with no loss of efficacy.

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11) Are there any special administration guidelines that may be required for this medication? (E.g., route of administration, qualifications of administering individuals, monitoring and need for further education)

At this time, asenapine is an oral preparation with no special administration requirements required, or special training necessary for allied health staff. The only point of concern is that the Canadian product, which is an ODT tablet, is not flavored, vs. the United States, which is black cherry flavor.

Drinking water within 10 minutes of sublingual administration may decrease the preparation's bioavailability. Bioavailability is 35% when taken sublingually and if eater or food is ingested 10 minutes later. This number reduced to < 1% if ingested (swallowed). However, the percentage reduction in the bioavailability has been observed following water administration at 2 and 5 minutes, as some patients may not wait the 10 minutes. At 2 minutes, approximately 80% of the 35% total bioavailable is available for effect, with the number rising to almost 90% of the 35% available/absorbed at 5 minutes.

10 minutes water/ food free post dose: appx 35% of the dose is bioavailable
5 minutes water/ food free post dose: appx 88% of the 35% of the dose is bioavailable= appx 30.8%
2 minutes water/ food free post dose: appx 78% of the 35% of the dose is bioavailable= appx 27.3%

However, maximum absolute bioavailability of asenapine is achieved within 10 minutes following administration, but this demonstrates that there may be some fluctuation and efficacy if patient or clinician preference so indicates.

Proposed Medication Administration Record (MAR) Note:

" For SL use only. Do not chew, crush or swallow tablet. Avoid food or water within 10 minutes."

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12) What follow-up/evaluations using educational and/or research mechanisms could be utilized to assess the reviewed medication's utilization and benefits relative to comparators?

It is suggested that prospective metabolic screening be utilized on all patients across all therapies. Given the hypothetical odds of adverse metabolic effects of slightly less than 10% with asenapine versus 45% with olanzapine and 60% with clozapine, this may help to optimize treatments according to risk, to identify early adverse metabolic effects and perhaps change medications, and thereby to reduce the long-term complications associated with metabolic disorder.

A review could be undertaken to determine how the use of asenapine might affect quality-adjusted life-years, metabolic effects, metabolic screening, and the use of outpatient resources to determine the stability of patients.

Inpatient lengths of stay and, perhaps more importantly, re-admissions could be studied at six months or a year, and at both two and five years to determine adherence to, and efficacy of asenapine.

All re-admissions to hospital, irrespective of the cause, should be considered, as cardiovascular and metabolic side effects of medication might precipitate admissions to medicine versus psychiatry units. One test of efficacy may be readmissions to a psychiatric or emergency unit; but another must include longer-term admissions to medicine or cardiovascular services within the health region.

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