Transdermal Asenapine in Schizophrenia: A Systematic Review

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REVIEW

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Background: Asenapine is a novel antipsychotic that has demonstrated efficacy in controlling psychosis in schizophrenia and mania in bipolar illness. It must be administered as a sublingual formulation because it is nearly completely metabolized in the first pass through the liver. Recently, a transdermal formulation of asenapine has been approved for schizophrenia by the Food and Drug Administration.

Methods: A systematic review of transdermal asenapine was done utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) model.

Discussion: There are several formulations of transdermal asenapine but only Secuado$^\circledR$ has been approved for clinical use. Total bioavailability is 35%. Peak plasma concentration (Cmax) is 4 ng/mL and occurs within 1 hr (Tmax); elimination half-life ($t_{1/2}$) is 24 hrs (range 13.4 to 39.2 h). Asenapine is highly bound (95%) to albumin and α_1-acid glycoprotein. It has a unique receptor profile in which it functions as an antagonist at multiple receptors with affinity that is higher than D_2 (K_i = 1.3) including D_3, D_4, $5HT_{2A}$, $5HT_{2C}$, $5HT_{2B}$, $5HT_7$, $5HT_6$, H_1, and $\alpha2$. This profile suggests that asenapine may be of particular value off label for bipolar depression, anxiety, and aggression. Transdermal asenapine was only tested in one randomized, placebo-controlled study of acute psychosis in schizophrenia. It was superior to placebo at week 6 with nearly one-third of patients experiencing >30% improvement in total PANSS score which translates in a number needed to treat (NNT) of 9.

Keywords: asenapine, schizophrenia, transdermal, topical, antipsychotic

Introduction

Background

Asenapine is a second-generation antipsychotic that was approved in the United States by the Food and Drug Administration (FDA) in August 2009 for the acute treatment of adults with schizophrenia and manic or mixed episodes associated with bipolar I disorder with or without psychotic features.[1] Because of its nearly complete first-pass metabolism when taken orally, asenapine was initially approved as a sublingual formulation – a route that bypassed the first-pass effect. But there are other ways to avoid a devastating first-pass effect.[1]

In October 2019, a transdermal system of delivery for asenapine (brand name Secuado$^\circledR$) was approved for schizophrenia (but was not studied for bipolar disorder) by the FDA.[2] While the active ingredient is still asenapine, the novel route of administration does alter some aspects of how the drug is used. The objective of this article is to summarize the pharmacokinetics, efficacy, and safety of transdermal asenapine in the treatment of schizophrenia.

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Methods
Protocol and Registration
This study utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) model.

Information Sources
Literature was collected from a broad range of databases that include OVID MED, PubMed, PsycInfo, and clinicaltrials.gov.

Search
Search terms that were used include the generic drug name, asenapine, in combination with each of the following keywords: transdermal, topical, transcutaneous, percutaneous, patch, film, liposome, nanoparticle, emulsion, gel, and solution. Reference lists from all relevant literature were hand-searched for clinical trials and patents that fit inclusion criteria. Additionally, the brand name, Secuado®, was used as a key search term. The manufacturer of Secuado, Noven Pharmaceuticals, was also contacted in order to obtain unpublished studies.

Eligibility Criteria and Study Selection
Randomized clinical trials and patents, including unpublished results that have been reviewed by nationally recognized clinical experts (eg, USFDA), were eligible for inclusion. There were no limitations on language or date of publication. Literature was considered applicable if it contained primary data concerning the efficacy, tolerability, and/or pharmacokinetics of ASP administered via transdermal route.

Data Selection Process
Data extraction was performed in duplicate by 2 authors.

Results
Study Selection
After conducting the search process, 51 articles were found. After screening and assessing for eligibility and excluding duplicates, 8 studies were included in this systematic review.

Results of Individual Studies
Table 1 summarizes the most relevant studies examining transdermal asenapine.

Discussion
Chemistry
Asenapine is a tertiary amine belonging to the class dibenzo-oxepino pyrroles; the chemical name is trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7] oxepino [4,5-c] pyrrole (Figure 1). It has a relatively small molecular weight (M = 285.8 g/mol), is lipid soluble (Log P = 4.77), and nonionized with a formal charge (FC) of zero (PubChem CID = 3,036,780 [National Center for Biotechnology Information. PubChem Database. Asenapine, CID=3,036,780, https://pubchem.ncbi.nlm.nih.gov/compound/Asenapine {accessed on Mar. 18, 2020}]). The brand name for approved transdermal asenapine is Secuado®.

Pharmacokinetics
Asenapine is rapidly metabolized by the liver via direct glucuronidation by uridine-diphosphoglucuronate glucuronosyl transferase 1A4 (UGT1A4) and oxidative metabolism by cytochrome P450 isoenzymes (predominantly CYP 1A2 and to a lesser degree CYP3A4 and CYP2D6).[11–13] First-pass effects exceed 95%, so that bioavailability (F or fraction in general circulation) is < 2% of oral dose.[13,14] Sublingual administration to escape immediate hepatic catabolism and deactivation results in 35% bioavailability in systemic circulation.[13] Peak plasma concentration of sublingual formulation (Cmax) is 4 ng/mL and occurs within 1 hr (Tmax);[11] elimination half-life ($t_{1/2}$) is 24 hrs (range 13.4 to 39.2 h).[14–16] Asenapine is highly bound (95%) to albumin and α_1-acid glycoprotein.[14] Asenapine has weak affinity to the permeability glycoprotein (P-gp), and so would be unlikely to cause an inordinate increase in prolactin like risperidone, paliperidone, and amisulpride.[17]

A transdermal system of delivery could offer several alternatives relative to a dissolvable tablet. In addition to being convenient, painless, non-invasive, and able to bypass first-pass metabolism by the liver, it is also unaffected by food or drink intake surrounding the time of administration.[18,19] While the sublingual route is acknowledged for its rapid absorption and onset, a transdermal system provides a steadier, sustained delivery ($C_{max} \sim$ 1.72 ng/mL), with a controlled release over a longer period of time (Tmax ~16 hrs, $t_{1/2}$ = 30 hrs).[20,21] The peak to trough ratio of sublingual asenapine is the highest among antipsychotics (> 3) because of the rapid initial absorption,[22] but this ratio is only 1:1 for transdermal

Table 1 Summary of the Most Relevant Studies Examining Transdermal Asenapine

Author	Title	Summary	Results
Citrome et al 2019[3]	HP-3070 Asenapine Transdermal System in Adults with Schizophrenia Categorical Response and Clinical Relevance as Assessed in a Phase 3 RCT	Citrome et al 2019 evaluated the efficacy and tolerability of this formulation in a Phase 3, randomized, double-blind, fixed dose, placebo-controlled inpatient study conducted in 59 centers worldwide. The study took place in a period of 6 weeks with a 30 day follow-up including 616 adults with schizophrenia, with a total of 489 participants completing the full length of the trial. Patients were divided evenly among three groups: (1) High dose treatment (7.6mg/24hrs), (2) Low dose treatment (3.8mg/24hrs), and (3) Placebo. The primary endpoint was change from baseline in the sum of all participants' PANSS score to Week 6. CGI-S is another widely used medical instrument that consists of a 7-point scale requiring a clinician to determine the extent of illness severity improvement relative to baseline (7= extremely ill) (Leucht et al 2019). The key secondary endpoint was the change from baseline in sum of CGI-S scores at Week 6. Primary safety outcomes included the overall treatment emergent adverse events (SAEs), deaths, and dermal side-effects.	High dose: PANSS=29.6% responders NNT=10 (95% CI 6–39) CGI=43.3% responders NNT=11 (not significant) Low dose: PANSS=30.8% responders, NNT=9 (95% CI 5–27) CGI=49.8% responders NNT=7 (95% CI 4–16)
Mohr et al 2018[4] Mohr et al 2019[5]	Transdermal therapeutic system containing asenapine and polysiloxane or polyisobutylene. Transdermal therapeutic system containing asenapine and silicone acrylic hybrid polymer.	This in vivo study placed one patch on 4 Goettingen minipigs each (3 drug-containing and 1 placebo) and determined the blood plasma concentrations of ASP [ng/mL] at 4 hour intervals for a total period of 96 hours. The area under the curve was reported for each 24 hour period. Secondary outcome measures included Draize score and histopathological studies to assess skin toxicity.	C_{max} (ng/mL)= 5.0 AUC_{24} (ng*h/mL)= 78.2 AUC_{96} (ng*h/mL)= 262.4 Draize score= 1/1/1/0 C_{max} (ng/mL)= 6.7 AUC_{24} (ng*h/mL)= 100.9 AUC_{96} (ng*h/mL)= 422.8
Mohr et al 2018[6]	Transdermal therapeutic system containing asenapine.	In addition to measuring skin permeability with an identical study design as the experiments described above, an in vivo clinical study was performed in 16 human participants to determine the pharmacokinetics of this formulation. This was a Phase I clinical trial that aimed at comparing the relative bioavailability of two different transdermal patch formulations of ASP against that of sublingual tablets. The study comprised of three periods of several days where participants were administered one of the given treatments: Period 1= 5mg sublingual tablet b.i.d, Period 2= transdermal formulation 1, and Period 3= transdermal formulation 2. Blood plasma concentrations of ASP as well as key metabolites (eg N-desmethyl-ASP and ASP-glucuronide) were measured at specified time points after administration. The key secondary outcome measure was adverse events of each treatment which was quantified by a numerical grading system determined by physicians in the study.	C_{max} (ng/mL)= 4.4–6.8 AUC_{24} (ng*h/mL)= 64.4–109.5 AUC_{96} (ng*h/mL)= 317.9–439.3 Draize score at 84 and 96 h = 1/1/1/0 Patch: C_{max} (ng/mL)= 2.93 ± 1.14 AUC_{48} (ng*h/mL)= 95.06 ± 37.20 AUC_{84} (ng*h/mL)= 152.36 ± 48.81 t_{lag} (h)= 4.27 ± 1.00 Sublingual tablet: C_{max} (ng/mL)= 4.71 ± 1.68 AUC_{84} (ng*h/mL)= 178.44 ± 63.59 t_{lag} (h)= 0.5

(Continued)

Table 1 (Continued).

Author	Title	Summary	Results
Shreya et al 2016[7]	Nano-transfersomal formulations for transdermal delivery of asenapine maleate: in vitro and in vivo performance evaluations.	Tested the ability of artificial liposomes designed to mimic cell vesicles, known as nano-transfersomes, to deliver ASP percutaneously. Chemical enhancers were also screened for their ability to further increase skin permeability to the nano-carrier system. Transfersomes were prepared with soy phosphatidylcholine (SPC) and sodium deoxycholate (SDC) via thin film hydration method and incorporated into a carbopol gel base. The formulation was optimized by testing the effect of sonification amplitude, amount of drug, SPC:SDC ratios on particle size, polydispersity index, zeta potential, and entrapment efficiency of the nano-particle transfersomes. Pharmacokinetic data was determined in two groups of Wistar rats (n= 6): Group 1 receiving a pill formulation administered orally, and Group 2 receiving the optimized transfersome gel formulation. ASP plasma concentrations were measured at various time intervals for 24 hours after drug administration. The nano-carrier transdermal formulation showed significantly different pharmacokinetic parameters compared to oral administration.	Transdermal route: C_{max} (ng/mL)= 426.78 ± 26.16 t_{max} (h)= 2.33 ± 0.82 AUC_∞ (ng*h/mL) = 7517.4 ± 278.86 Oral route: C_{max} (ng/mL)= 368.2 ± 17.78 t_{max} (h)= 1.17 ± 0.41 AUC_∞ (ng*h/mL) = 5764.1 ± 201.95
Solomon, 2010[8]	Transdermal Compositions of Asenapine for the Treatment of Psychiatric Disorders.	In vitro preliminary investigations were conducted using human skin and a Franz cell in order to compare the epidermal permeation between a number of transdermal formulations that include non-film forming spray, gel, patch, cream, spray-on (non-occlusive), and spray-on (occlusive). The gel composition provided the highest maximum permeation level; this was followed by the occlusive spray-on composition, the cream, and fourthly the non-occlusive spray-on formulation. In vivo pharmacokinetic studies were then performed using three pigs in order to study the transdermal absorption of asenapine. A dose of 50 μg of the spray formulation (approx. one spray) was administered to each subject and asenapine concentrations were measured periodically via blood sampling for 24 hours.	Gel: Cumulative amount of permeation (μg/cm2)= 44.5 ± 11.60 T_{max} (minutes)= 10–20
Suzuki et al 2017[9]	n/a	Suzuki et al 2017, 2018 aimed to develop a transdermal patch of ASP that (1) is capable of achieving a therapeutically effective level of plasma concentration of ASP which is higher than ever achieved in previous studies and (2) is capable of sufficiently suppressing the plasma concentration of N-desmethyl ASP (the metabolite responsible for dermal side-effects). This formulation was comprised of a support layer, an ASP adhesive agent layer containing isopropyl palmitate as a transdermal absorption enhancer, and an adhesive base agent. Sodium diacetate was additionally added to the adhesive agent layer in order to further increase the skin permeability of ASP constantly over time. Suzuki et al 2017 applied the patch (area of 8 cm^2) to the upper arm of 18 healthy adult male participants. Blood plasma concentrations of free ASP and N-desmethyl ASP were measured every 4 hours for a period between 2 hours after application and 120 hours. An area under plasma concentration-time curve (AUC_{2-120} [pg*hr/mL]) was calculated for both free ASP and its metabolite, N-desmethyl ASP.	Free asenapine: AUC_{2-120} (pg*h/mL) = 33,981 Asenapine metabolite: AUC_{2-120} (pg*h/mL)= 5,432

(*Continued*)

Table 1 (Continued).

Author	Title	Summary	Results
Suzuki et al 2018[10]	n/a	Suzuki et al 2018 used a similar study design and patch formulation to determine data on pharmacokinetics and efficacy. Primary efficacy endpoints used were dopamine D_2 receptor occupancy and total PANSS score. Pharmacokinetic parameters were calculated by measuring blood plasma concentrations of free ASP and N-dimethyl ASP every 4 hours over a period of 120 hours after applying a single patch (N= 40 adult human participants, M= 20, F= 20). D_2 receptor occupancy was determined by administering a single patch containing a dose of 4.5mg/10cm^2, 9.0mg/20cm^2, or 18.0mg/40cm^2 on healthy adult participants (N= 5) for seven days (new patch applied each day). Position emission topography (PET) scan data was used to quantify receptor occupancy in the caudate and putamen. Lastly, Suzuki et al 2018 determined clinical efficacy by administering a single patch (dose level of 9.0mg/20cm^2 or 18.0mg/40cm^2) daily for 6 weeks in 204 patients diagnosed with schizophrenia. The PANSS total score was obtained at baseline and Day 42 of the study. According to this data, a statistically significant difference in PANSS score was found for this formulation of transdermal ASP.	Free asenapine: C_{max} (ng/mL)= 2.02–2.46 t_{max} (h)= 16 AUC_∞ (ng*h/mL) = 63.2–73.2 Asenapine metabolite: C_{max} (ng/mL)= 20% or less of C_{max} of free asenapine AUC_∞ (ng*h/mL) = 22% or less of AUC_∞ of free asenapine D_2 occupancy caudate 4.5 mg dose: 45.5% 9.0 mg dose: 57.1% 18 mg dose: 55.2% D_2 occupancy putamen 4.5 mg dose: 37.5% 9.0 mg dose: 51.6% 18 mg dose: 51.1% PANSS score was reported to be statically significant in both 9 mg (p<0.001) and 18mg (p= 0.006) groups at the 6 week endpoint.

asenapine.[23] Application of the patch to the abdomen, upper back, arms, or hips are all acceptable. The location of the patch should be varied with subsequent applications.
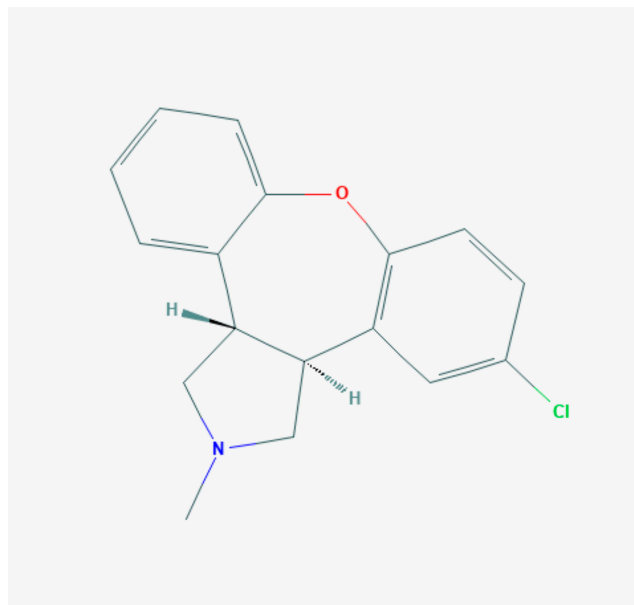

Figure 1 The chemical structure of asenapine. (image courtesy PubChem).

Placement over broken skin should be avoided. It is important to note that heat can double the absorption rate from the patch to a T_{max} of approximately 8 hrs.[21] This maybe an issue in winter if patients use a heated blanket, but is not an issue with environmental heat (eg, on a hot summer day).

Pharmacodynamics

Asenapine is a novel second-generation antipsychotic with a unique receptor profile (Table 2) that has been approved in its sublingual formulation for treatment of people with schizophrenia and bipolar disorder.[24–27] Its exact mechanism of action in schizophrenia and bipolar disorder is unknown, but it has a unique human receptor signature, with binding affinity and receptor profiles that differ considerably from other antipsychotic drugs. It has antagonist activity for the D_3, D_4, $5HT_{2A}$, $5HT_{2C}$, $5HT_{2B}$, $5HT_7$, and $5HT_6$, histamine type 1 (H_1), and alpha adrenergic type 2 ($\alpha2$)-receptors, all at higher affinity than to the dopamine type 2 (D_2) receptor (Table 2).[28,29] It has negligible partial agonist activity at the serotonin (5HT) type 1A ($5HT_{1A}$) receptor (with intrinsic activity of approximately 25%[30]),

Table 2 The Inhibitory Constant of Asenapine and Potential Neurotransmitters

Receptor	K_i (nM)	Comment
Dopamine		
D_3	**0.42**	
D_4	**1.1**	
D_{2A} (long form)	**1.3**	
D_{2B} (short form)	**1.4**	
Serotonin		
$5HT_{2C}$	**0.03**	
$5HT_{2A}$	**0.07**	
$5HT_7$	**0.11**	
$5HT_{2B}$	**0.18**	
$5HT_6$	**0.25**	
$5HT_{5A}$	**1.6**	
$5HT_{1A}$	2.5	Partial agonist with 25% intrinsic activity[30]
$5HT_{1B}$	2.7	
Norepinephrine		
α_{2B}	**0.33**	
$\alpha_{\alpha A}$	**1.2**	
α_{2A}	**1.2**	
α_{2C}	**1.2**	
Histamine		
H_1	**1.0**	
H_2	6.2	
Acetylcholine		
M_1	8128	Essentially no activity at this receptor

Notes: Since dosing is based on circa 70% D2 receptor occupancy, and Ki above 2.0 [not bolded] means that there is no meaningful activity at that receptor at clinically relevant doses; unless otherwise noted, the activity of asenapine is inhibitory.[28,29]

so that it is a functional antagonist at $5HT_{1A}$. Affinity, or attractiveness of the drug to neurotransmitter receptor, is measured by the inhibitory constant (K_i). K_i values represent the concentration of the drug that is required to displace the intrinsic neurotransmitter off of the receptor. Dosing strategies for schizophrenia, for either sublingual or transdermal administration, aim to achieve roughly 75% D_2 receptor occupancy.[31] Consequently, any receptors with a K_i value that are higher than the K_i for D_2 (ie, lower affinity), will not be occupied sufficiently to mediate any measurable effects in routine clinical care; for asenapine at a typical dose of 5 mg twice daily (BID), any receptor with $K_i \geq 2.0$ would fall into that category (eg, $5HT_{1A}$ and $5HT_{1B}$). However, those receptors may be adequately occupied at 10 mg BID.

The widespread antagonism of postsynaptic serotonin, along with the relatively higher D_4 versus D_2 affinity[32] may mediate the observed benefit of asenapine in agitation and aggression in severely ill patients, and affective instability in borderline personality disorder.[33–36] Similarly, blockade of $5HT_7$ has been associated with antidepressant action in animal models[37,38] and this is believed to mediate the antidepressant effect of lurasidone in bipolar depression.[39] Consequently, it is not surprising that sublingual asenapine has also demonstrated antidepressant efficacy in bipolar depression.[40] Transdermal asenapine has only been examined in schizophrenia.

Transdermal Technology

The stratum corneum (ie, outermost layer of skin) is a difficult barrier for drugs to penetrate. It is composed of 10–15 layers of epidermal cells that are tightly packed with keratin and is lipid-rich to exclude unwanted toxins and prevent unnecessary water loss.[41] Various methods, both physical and chemical, have been employed on transdermal drug delivery systems in order to augment permeation through the skin. Applying a voltage gradient (ie, iontophoresis), ultrasound waves (ie, sonophoresis), and skin ablation via heat, lasers, or microneedles (ie, electropermeabilization) are all physical modes that can be used to enhance percutaneous drug delivery. Chemical enhancers act on the stratum corneum by either increasing partitioning of the tightly packed cell layer or increasing the diffusion ability of the drug. Examples of chemical penetration enhancers include polyalcohols, pyrrolidones, fatty acids, alkanes, surfactants, terpenes, and others.[7,42-44]. Each one of these strategies is associated with its own potential adverse reactions, but all such consequences are quite local in scope.

Several groups have been working to develop transdermal administration of asenapine. Secuado® is simply the first on the American market. It was developed by Noven Pharmaceuticals based in Miami, Florida, a subsidiary of the Japanese Hisamitsu Pharmaceutical Company. Hisamitsu specializes in transdermal technology. Worldwide there are two antipsychotics available in transdermal formulation: blonanserin for schizophrenia in Japan,[45,46] and asenapine for schizophrenia in the United States.

The patch technology for Secuado® is outlined in a series of patents, eg,[9,10] The patch (area of 8 cm^2) uses reservoir-technology comprised of a support layer, an asenapine plus adhesive agent layer containing isopropyl palmitate as a transdermal absorption enhancer, and an

adhesive base agent.[9,10] Sodium diacetate was added to the adhesive layer in order to further increase the skin permeability to asenapine constantly over time.

Sonobe et al[47] filed a patent describing different adhesive layer formulations that decreased drug degradation, improved drug release, or increased adhesion even when moisture was applied. It was found that by using a rubber-based adhesive agent, the skin permeability of asenapine could be enhanced; while at the same time, this novel system decreased adhesive forces. The given patent describes a series of studies using hairless mice to confront this problem. The findings suggest that a patch formulation comprising free-asenapine, a rubber-based adhesive agent, and a maleic acid alkali salt was able to effectively penetrate mouse skin while still retaining adhesive capabilities.

A group from Germany led by Mohr has filed at least three patents.[4–6] They also use a reservoir-type patch (area of 10 cm^2) consisting of a backing layer, an asenapine-containing matrix layer (asenapine + silicone polymer [polysiloxones/polyisobutylenes] + tocopherol [stabilizer] + polyvinylpyrrolidone [crystallization inhibitor]), and optionally an additional skin contact layer,[4,5] or an acrylic adhesive layer.[6] This system was tested in animals (Goettingen minipigs[4]) and humans.[5] They actually performed Phase I trials demonstrating the adequacy of asenapine drug levels with their system.[6]

Solomon[8] studied a variety of transdermal routes in pigs (sprays, aerosols, patches, films, gels, creams, ointments, lotions, and foams) with the spray method showing the shortest Tmax (10–20 min), in vivo; this is comparable to the Tmax of sublingual asenapine. Additional in vitro experiments showed the gel formulation to have the highest maximum permeation.

A group in India used Asenapine maleate and combined chemical and nanocarriers (transfersomes) to improve transdermal absorption. This method of increased bioavailability with a physical process resulted in transdermal bioavailability the exceeded oral bioavailability.[7] It is not clear how this method compares with what is already on the market.

Transdermal Asenapine Dosing

Secuado®, the transdermal formulation of asenapine, is designed as a patch that is applied every 24 hrs on the torso. The recommended dosing is 3.8 mg/24 hrs patch once daily; based on efficacy and tolerability, the dose may be increased as clinically indicated to 5.7 mg/24 hrs or 7.6 mg/24 hrs after 1 week at a lower dose.[21] The transdermal asenapine patch of 3.8 mg/24 contains a total of 6.4 mg of asenapine and is equivalent to a sublingual asenapine dose of 5 mg BID. The 7.6 mg/24 hrs patch contains 12.8 mg of asenapine and is equivalent to 10 mg BID.[21]

Oral hypoesthesia and bitter taste are among the most frequently reported side-effects associated with sublingual asenapine and can contribute to patient noncompliance.[48] However, skin irritation is a common adverse reaction of topical administration (14–15%),[21] and could also lead to patient discomfort and noncompliance. Sublingual versus transdermal route of administration does not affect the volume of distribution of asenapine (V_d = ~20 to 25 L/kg), which is relatively large due to its extensive extravascular spread.

Clinical Studies: Efficacy

There was one Phase 3, randomized, double-blind, fixed-dose, placebo-controlled inpatient study that evaluated the efficacy and tolerability of transdermal asenapine in acutely ill subjects with schizophrenia.[3] It enrolled 616 adults with schizophrenia in 59 centers in the United States, Russia, Bulgaria, Serbia, and Ukraine. A total of 489 participants completed the trial.[3] Subjects were treated for 6 weeks with high-dose asenapine patch (7.6mg/24hrs; equivalent to 10mg BID of the sublingual formulation), low-dose asenapine patch (3.8mg/24hrs; equivalent to 5mg BID of the sublingual formulation) or placebo. All subjects had two patches placed daily (either active or placebo) to maintain the blind.[23] Additionally, subjects were seen 30 days after study termination. The efficacy outcomes measured include the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impressions-Severity (CGI-S) rating scales. PANSS is a 30 item scale used to quantify the severity of positive symptoms, negative symptoms, and general psychopathy in subjects with schizophrenia.[49–51] The primary endpoint changed from baseline in the sum of all participants' PANSS score to Week 6.

Both low dose and high-dose transdermal asenapine separate significantly from placebo at week two.[52] That persists until the study end at week 6 (Figure 2).[23,52] Nearly one-third of asenapine-treated patients responded (ie, experienced > 30% improvement in total PANSS score by week 6) (Figure 3).[53] This is comparable to changes seen with sublingual asenapine in schizophrenia.[26,27] This translates in a number needed to treat (NNT) of 9 for low-dose transdermal asenapine and 10 for high-dose
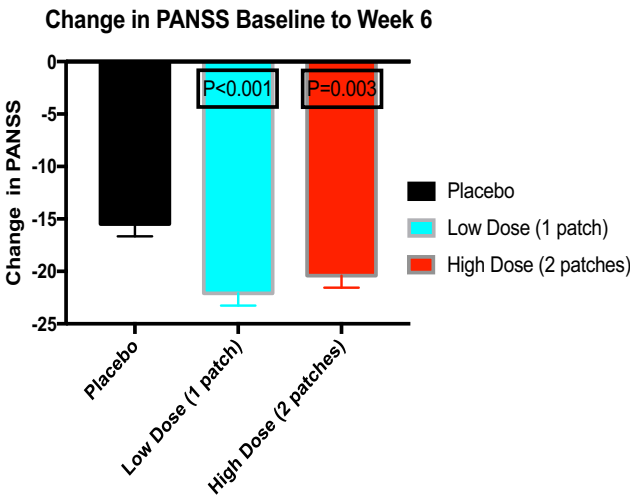
Change in PANSS Baseline to Week 6

Figure 2 Change in PANSS score in subjects with acute schizophrenia and baseline score of 97.4 (placebo), 97.0 (low dose), and 95.6 (high dose). Data From Citrome et al's study.[53]
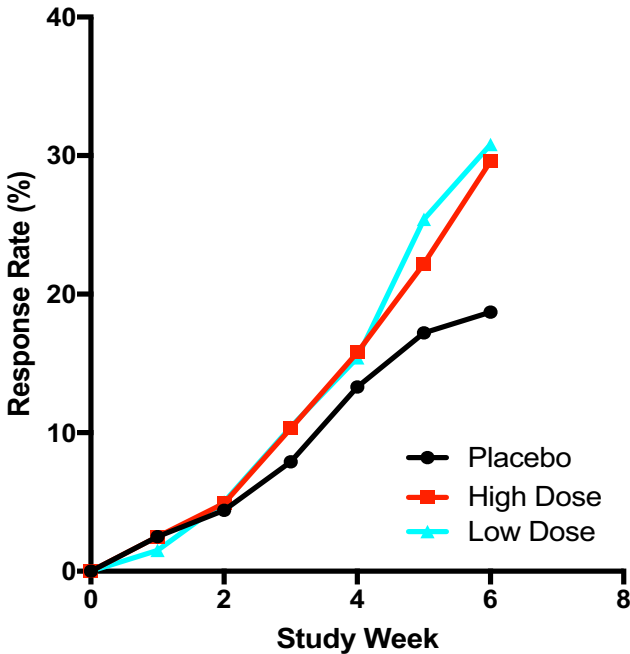

Figure 3 Response rates over time in in subjects with acute schizophrenia treated with low-dose transdermal asenapine (3.8 mg/24 hours), high-dose transdermal asenapine (7.6 mg/24 hours), and placebo. Only week 6 is significantly higher than placebo for both doses (P < 0.05). Data from Citrome et al's study.[3]

transdermal asenapine.[53] This is comparable to an NNT for acute psychosis in schizophrenia with sublingual asenapine (administered at 5 mg BID).[54]

The key secondary endpoint was the change from baseline in the sum of Clinical Global Impression – Severity (CGI-S) scores at Week 6.[55] All groups were equally severe at baseline (CGI mean = 4.9). Placebo treated patients experienced the smallest improvement by week 6 (4.0 ± SD 1.01),

but both the low-dose (3.6 ± 0.93) and high-dose (3.7 ± 0.96) groups experienced significantly more improvement (−0.8, −1.2, and −1.1, respectively, P < 0.001 vs placebo).[23,52]

While sublingual asenapine has been studied and approved for acute mania in bipolar illness,[24,25] transdermal asenapine has not been examined in this patient population group.

Clinical Studies: Safety

Transdermal asenapine was generally well-tolerated. Some treatment-emergent adverse events (TEAEs) were experienced by nearly half of all subjects (51.5%, 53.9%, and 55.4% of placebo-, low-dose-, and high-dose-treated subjects, respectively).[52] Those occurring at a rate of at least 5% are presented in Table 3.[52] Serious adverse events were rare (1.9%, 1.5%, and 1.0% in placebo-, low-dose-, and high-dose-treated subjects, respectively), as were discontinuations due to adverse events (6.8%, 4.9%, and 7.8% of placebo-, low-dose-, and high-dose-treated subjects, respectively).[52] Approximately a sixth of patients developed some kind of mild to moderate skin reaction at the patch site (14.2% high-dose; 15.2% low-dose; 4.4% placebo; see Table 3), but < 0.5% of patients stopped the study due to a skin reaction. No information is available regarding the effect on skin with long-term exposure.

Table 3 Treatment-Emergent Adverse Effects (TEAE) That Occurred in the Phase 3 Trial of Transdermal Asenapine at a Rate of 5% of More in Subjects Receiving at Least One Dose

TEAE	High-Dose [n (%)] (Total n =204)	Low-Dose [n (%)] (Total n=204)	Placebo [n (%)] (Total n=206)
Headache	19 (9.3)	18 (8.8)	13 (6.3)
Extrapyramidal disorder	19 (9.3)	13 (6.4)	3 (1.5)
Akathisia	9 (4.4)	8 (3.9)	5 (2.4)
Insomnia	14 (6.9)	15 (7.4)	23 (11.2)
Anxiety	11 (5.4)	10 (4.9)	13 (6.3)
Application site erythema	20 (9.8)	19 (9.3)	3 (1.5)
Application site pruritus	8 (3.9)	10 (4.9)	4 (1.9)
Application site irritation	0 (0.0)	4 (2.0)	1 (0.5)
Constipation	9 (4.4)	11 (5.4)	9 (4.4)
Weight increased	12 (5.9)	8 (3.9)	4 (1.9)

Note: Application site reactions are included even though they occurred at a rate lower than 5%.[52]

There were no human deaths in the development program.[23]

Weight gain occurred in roughly 5% of patients receiving transdermal asenapine over the 6 weeks of the study (Table 3). There is no long-term exposure data with transdermal asenapine, but long-term safety studies with sublingual asenapine demonstrate weight gain.[56] In a naturalistic, post-marketing study of 20 patients with different diagnoses receiving sublingual asenapine for an average of 7.6 months, patients gained an average weight of 0.32 kg/month (0.7 lbs/month).[57]

In general, safety considerations with transdermal asenapine are the same as with sublingual asenapine. Asenapine is metabolized predominantly by direct glucuronidation, so there is little drug–drug interaction. However, it is also broken down by CYPs 1A2, 3A4, and 2D6 and so can have variations in level in response to enzyme inducers or inhibitors, or to smoking. Similarly, same considerations as sublingual asenapine regarding physical illness, such as severe liver disease or kidney disease need to be kept in mind. It is perhaps wise to avoid transdermal asenapine in the presence of significant skin disease."

Summary

Asenapine is a unique second-generation antipsychotic that is nearly completely destroyed in the first pass through the liver, so that dosing strategies must bypass the gut. A sublingual formulation has been available. Recently, a topical transdermal formulation has been approved in the United States for schizophrenia. Doing the transdermal formulation results in plasma levels and receptor occupancy that are equivalent to the sublingual formulation. Clinical response in terms of efficacy and adverse consequences to transdermal asenapine is also comparable to sublingual asenapine. The dermal route avoids some of the problematic issues with sublingual administration (complex instruction, bitter taste, and potential for mouth ulcers[58]), but replaces them with the potential for topical reactions (Table 3). What might be considered advantages of a specific formulation for a specific patient may be disadvantages for another patient. Nonetheless, this is the only topical antipsychotic available in the United States and offers patients and clinicians with an additional option to maximize patient adherence and satisfaction.

Disclosure

Dr Rif S El-Mallakh reports personal fees from Alkermes, Indivior, Intra-Cellular Therapeutics, Janssen, Lundbeck, Otsuka, Sunovion, and Teva, outside the submitted work. The authors report no other conflicts of interest in this work.

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