

Selective Histamine H₁ Antagonism: Novel Hypnotic and Pharmacologic Actions Challenge Classical Notions of Antihistamines

By Stephen M. Stahl, MD, PhD

NEW TREND IN PSYCHOPHARMACOLOGY

Numerous "antihistamines" as well as various psychotropic medications with antihistamine properties are widely utilized to treat insomnia. Over-the-counter sleep aids usually contain an antihistamine and various antidepressants and antipsychotics with antihistamine properties have sedative-hypnotic actions. Although widely used for the treatment of insomnia, many agents that block the histamine H₁ receptor are also widely considered to have therapeutic limitations, including the development of next-day carryover sedation, as well as problems with chronic use, such as the development of tolerance to sedative-hypnotic actions and weight gain. Although these clinical actions are classically attributed to blockade of the H₁ receptor, recent findings with H₁ selective agents and H₁ selective dosing of older agents are challenging these notions and suggest that some of the clinical limitations of current H₁-

blocking agents at their currently utilized doses could be attributable to other properties of these drugs, especially to their simultaneous actions on muscarinic, cholinergic, and adrenergic receptors. Selective H₁ antagonism is emerging as a novel approach to the treatment of insomnia, without tolerance, weight gain, or the need for the restrictive prescription scheduling required of other hypnotics.

INTRODUCTION

The sedating properties of antihistamines and of numerous psychotropic medications with antihistamine properties have long been exploited for the treatment of insomnia.¹ Antihistamines are among the most common hypnotics in use today in over-the-counter (OTC) products for the treatment of insomnia, whereas antidepressants with antihistaminic properties, such as trazodone, and antipsychotics with antihistaminic properties, such as quetiapine, are among the most frequently used prescription agents by psychiatrists and psychopharmacologists for the treatment of insomnia comorbid with various psychiatric disorders.¹

Dr. Stahl is adjunct professor of psychiatry in the Department of Psychiatry at the University of California—San Diego in La Jolla.

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The use of these various multifunctional agents (ie, drugs that bind to numerous neurotransmitter receptors simultaneously) over the years has led to notions about the contribution of histamine H₁ antagonism to the clinical actions of such drugs, but only recently have studies been conducted with selective agents or with older agents at selective doses. In addition, significant advances have been made in understanding the role of histamine as a central neurotransmitter and particularly its role in sleep, wake, and arousal. These events have converged, and there is now a reconceptualization of the mechanism of action of agents with selective H₁ antagonist properties and the role of H₁ antagonism in the hypnotic actions of agents with multiple pharmacologic actions with the promise that truly H₁ selective agents may represent a therapeutic advance in the treatment of insomnia.

This column reviews the neurobiology of sleep, wakefulness, and arousal, and particularly, the role of histamine in these functions. It also reviews the pharmacology of various agents with H₁ antagonist actions that are used to treat insomnia, debunk certain myths that have arisen about the clinical consequences of blocking H₁ receptors, and show what happens when these receptors are selectively blocked in the treatment of insomnia.

PSYCHOPHARMACOLOGY OF AROUSAL: A BALANCING ACT AND A SPECTRUM

The psychopharmacology of arousal balances neurotransmitter systems that drive wakefulness with those that drive sleep.^{1,2} "Wake-promoting" neurotransmitters that drive wakefulness include histamine, acetylcholine (ACh), the monoamines norepinephrine (NE) and serotonin (5-HT), and the peptide orexin, among others.¹⁻¹³ The brain areas from which these neurons project are sometimes called "wake promoters," especially the tuberomammillary nucleus (TMN) of the hypothalamus, from where all histamine neurons in the brain arise and to where various neurotransmitters that control wakefulness converge (Figure 1). Wake-promoting neurotransmitters project widely throughout the brain, and activate the cortex and facilitate arousal.¹⁻¹³

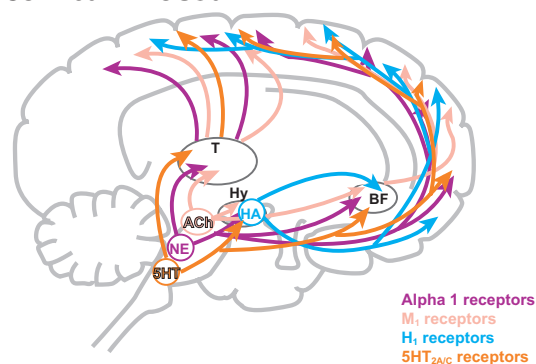
These wake-promoting neurotransmitters are balanced by sleep-promoting neurotransmitters, especially γ -aminobutyric acid (GABA) and also the peptide galanin and others.^{1-3,14} In fact, there is another region of the hypothalamus known as the "sleep promoter," namely the ventrolateral

preoptic area (VLPO).² The VLPO projects inhibitory GABA connections to each of the wake-promoting centers and is another site where wake-promoting neurotransmitters converge (Figure 2).¹⁻¹⁴ The VLPO and GABA act to promote sleep by inhibiting wake-promoting neurotransmitter centers.^{1-3,14} GABA also acts within inhibitory interneurons in the cerebral cortex to inhibit the actions of wake-promoting neurotransmitters there as well.¹

Well-characterized circadian and homeostatic drives regulate the balance between sleep and wakefulness, and thus determine whether the switch is "off" (ie, the sleep-promoting areas and neurotransmitters predominate with GABA tone) or "on" (ie, wake-promoting histamine and other neurotransmitters predominate with activation of wake-promoting neurotransmitter centers as well as the cortex).² There even seem to be degrees of wakefulness, ranging from sleepiness to overstimulation (Figure 3), and these different states along the spectrum of arousal are associated with numerous psychiatric disorders.^{1,3}

For example, insomnia is one of the disorders associated with an abnormality in arousal, hypothetically due to a state of hyperarousal at night (Figure 3).^{1,15} Interestingly, current hypotheses indicate that chronic insomnia may involve hyperarousal, not only at night, so sleep is disrupted, but also in the daytime, so that the patient may not be sleepy during the day and even overly aroused despite the lack of adequate sleep at night.^{1,15} Psychiatric disorders are also hypothetically associated with insomnia due to excessive arousal at night, but, in contrast to chronic insom-

FIGURE 1.
Cortical Arousal



T=thalamus; Hy=hypothalamus; ACh=acetylcholine; HA=histamine; BF=basal forebrain; NE=norepinephrine; 5-HT=serotonin; M=muscarinic; H=histamine.

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nia, these patients may often have daytime sleepiness due to lack of restorative sleep at night.¹

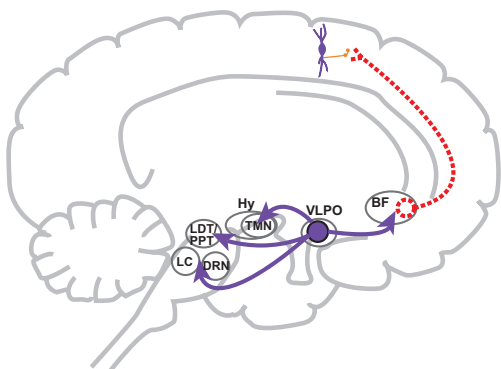
PSYCHOPHARMACOLOGY OF HYPNOTICS: TWO WAYS TO REDUCE THE AROUSAL OF INSOMNIA

As shown in Figures 1–3, the tendency to sleep is determined by a balance of wake- and sleep-promoting systems. Some evidence suggests that hypnotics may act to reduce the excessive arousal that hypothetically occurs at night, especially in young and middle-aged insomniacs, and that causes insomnia in such patients. Hypnotics hypothetically either block the neurotransmitters that drive wakefulness or activate the neurotransmitters that drive sleep (Figure 3).^{1,2,14-16} Thus, the treatment of insomnia is based upon agents that act either by enhancing the inhibitory wake-promoting neurotransmitter GABA or by blocking receptors for wake-promoting neurotransmitters, especially histamine, but also various cholinergic, adrenergic, and serotonergic receptors, often at the same time.^{1,2} Either approach is effective, but can often cause either too little or too much hypnotic action, leading to attempts to optimize hypnotic effects by a number of new approaches.

Hypnotic Agents That Act by Enhancing GABA

The best known and most widely used prescription hypnotics act by enhancing the inhibitory action of GABA.¹ This approach results in inhibition of all neurotransmitters that drive arousal.²

FIGURE 2.
Sleep-promoting GABA system



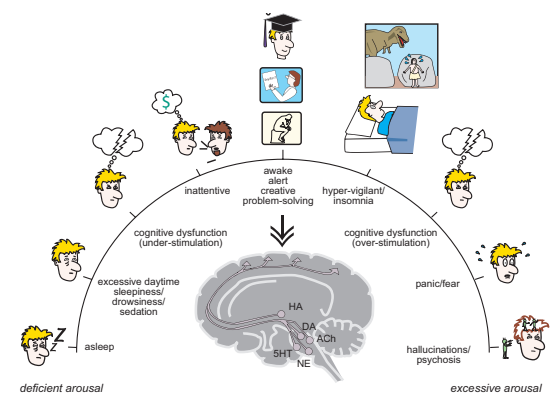
GABA=γ-aminobutyric acid; Hy=hypothalamus; BF=basal forebrain; LDT=laterodorsal tegmental; PPT=pedunculopontine tegmental; TMN=tuberomammillary nucleus; VLPO=ventrolateral preoptic nucleus; LC=locus coeruleus; DRN=dorsal raphe nucleus.

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Originally, this included various barbiturates, later the benzodiazepines, and, more recently, the emphasis has switched to prescribing the related “Z drugs” (eg, zolpidem, zaleplon and S-zopiclone), which, like benzodiazepines, also act as positive allosteric modulators of GABA-A receptors.¹ Although current research is attempting to clarify whether there is a pharmacologic distinction between agents that act at numerous GABA-A receptor subtypes (eg, benzodiazepines and S-zopiclone) versus those that act more selectively (eg, zaleplon and zolpidem), it is clear that these agents as a class are mostly differentiated by their pharmacokinetic properties.¹

That is, at or above a certain critical level of receptor occupancy, patients appear to sleep if administered an agent that acts at a receptor site within the GABA-A complex.¹ However, if half-life exceeds the duration of the sleep period significantly, the compound accumulates and can cause dangerous degrees of daytime sedation both immediately and over time. If the half-life matches or slightly exceeds the duration of the sleep period, the compound may not accumulate, but may have a hangover effect due to residual drug, present at a level high enough to cause daytime sedation and cognitive dysfunction.¹ On the other hand, compounds that are too short acting wear off before morning and have problems maintaining sleep through the night.¹ The ideal is a compound that exceeds the threshold for sleep by the time the onset of sleep is desired, stays

FIGURE 3.
Arousal spectrum of sleep and wakefulness



HA=histamine; DA=dopamine; ACh=acetylcholine; 5-HT=serotonin; NE=norepinephrine.

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above this level throughout the sleep period but then rapidly falls to below the level that causes sleep or sedation by morning arousal.¹

Even these properties do not necessarily make for an ideal hypnotic. That is, if the patient has to get up at night, it is often not possible for the wake-promoting systems to escape their inhibition by GABA mechanisms sufficiently for safe functioning, such as driving, or even in some cases, walking to the bathroom without falling. GABA inhibition at a critical level of receptor occupancy provides a profound degree of inhibition of arousal. This state is not necessarily readily reversible if the patient tries to awaken prior to the wearing off of the drug to a level below that degree of receptor occupancy that provokes sleep and deep sedation. Furthermore, long-term administration of benzodiazepines can be associated with tolerance, withdrawal, and rebound insomnia, although the Z drugs, acting at a different but related site, seem to have far fewer of such problems with long-term administration.¹ Nevertheless, all hypnotic drugs acting through a GABA mechanism are currently restricted as scheduled substances under United States law.

Hypnotic Agents That Act by Blocking Wake-Promoting Neurotransmitter Systems

Almost all agents working to block wake promotion have antihistamine properties, including most OTC sleep aids available without a prescription.¹ Although often characterized as "antihistamines," these agents usually have notable simultaneous antimuscarinic actions; many also

act on adrenergic systems, especially as alpha 1 antagonists (Figure 1).¹ As with agents active at GABA-A receptors, there appears to be a critical degree of receptor occupancy of histamine, ACh, and NE receptors, that, when blocked simultaneously will cause daytime sedation, and, when an even higher level of receptor occupancy is reached, will cause nocturnal sleep (Figure 2).^{1-3,16} Of course, there are additional side-effect burdens caused by blockade of muscarinic cholinergic receptors (eg, dry mouth, blurred vision, urinary retention) and by blockade of alpha 1 adrenergic receptors (eg, orthostatic hypotension).¹ Additional actions at dopamine and 5-HT receptors can also contribute both to nocturnal sleep and to mechanism specific side effects, such as daytime sedation, and weight gain.¹ Specific agents that induce sleep by blocking these various wake-promoting neurotransmitter systems are discussed in detail next.

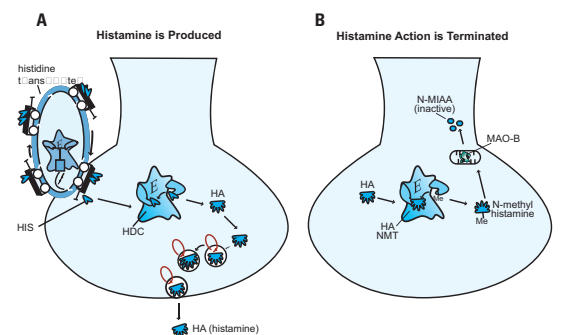
A CLOSER LOOK AT THE PSYCHOPHARMACOLOGY OF HISTAMINE

In order to separate the actions of blocking H₁ receptors from the other actions of drugs with additional effects on other neurotransmitter systems, a closer look at the unique properties of this interesting neurotransmitter system is useful.

Histamine Neurons, Histamine Pathways, and Arousal

As stated earlier and as also illustrated in Figure 1, all the cell bodies for 60,000 or so neu-

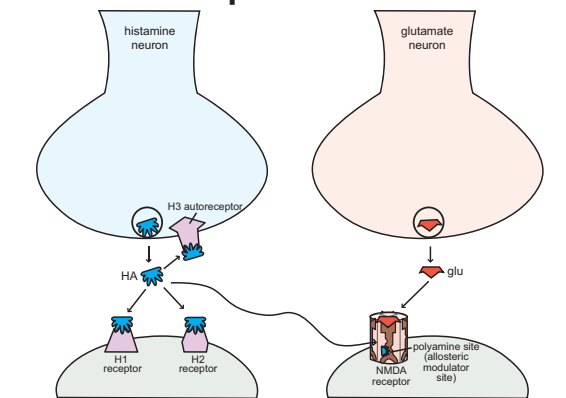
FIGURE 4.
Production and degradation of histamine



N-MIAA=*N*-methyl indole acetic acid; E=enzyme; MAO-B=monoamine oxidase B; HA=histamine; Me=methyl; HIS=histidine; HDC=histidine decarboxylase; NMT=*N*-methyltransferase.

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FIGURE 5.
Histamine receptors



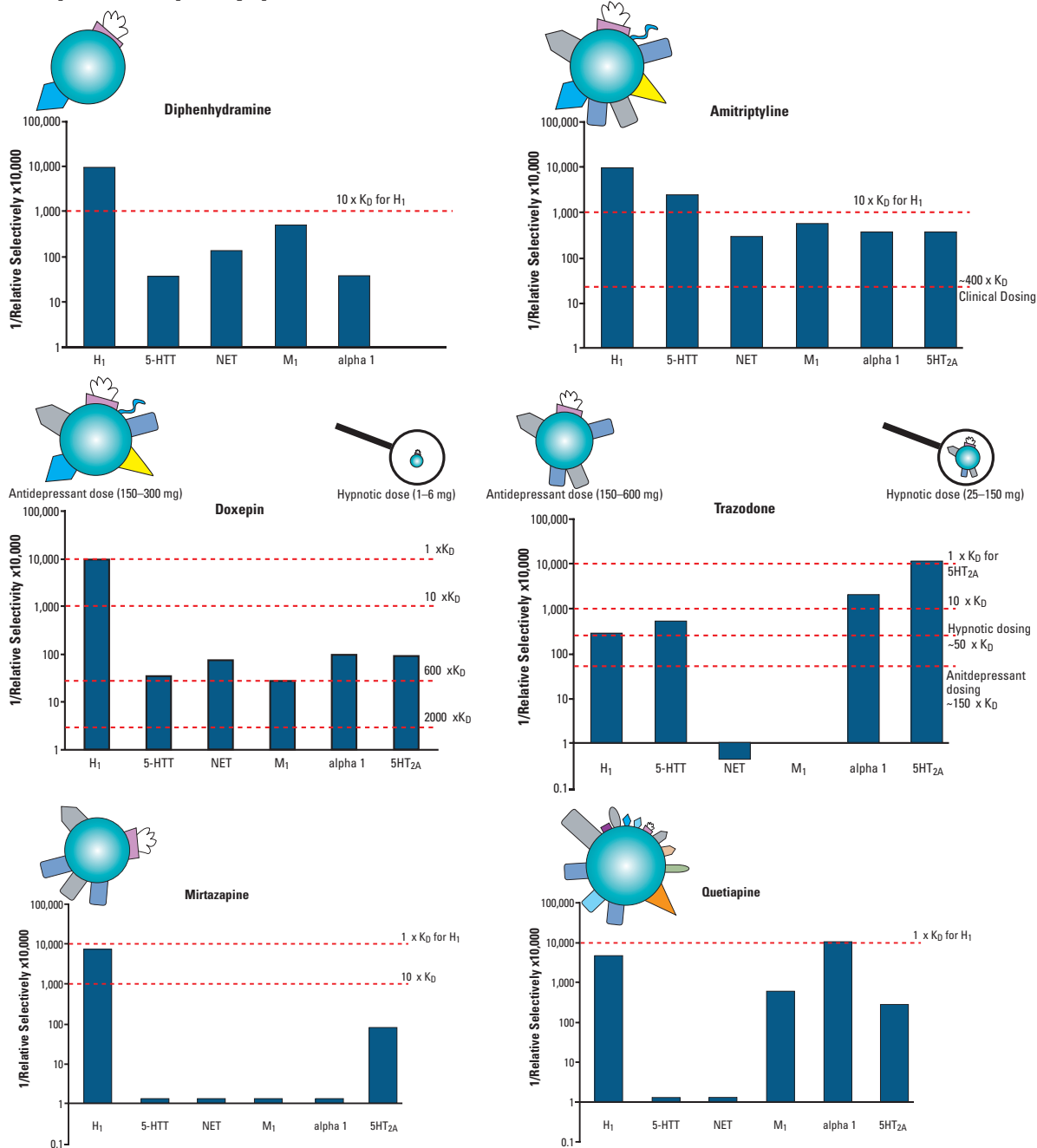
H=histamine; glu=glutamate; HA=histamine; NMDA=*N*-methyl-D-aspartate.

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rons that utilize histamine as neurotransmitter are located in the hypothalamic TMN.^{2,3,5} These neurons may also use a number of co-transmitters, such as various peptides. Ascending

pathways importantly innervate the cortex and thalamus to regulate arousal and learning^{1-3,5,17,18}; they also innervate cholinergic neurons in the basal forebrain, which indirectly can regulate

FIGURE 6.
Receptor occupancy profile of various medications



K_D=equilibrium dissociation constant; H=histamine; 5-HTT=serotonin transporter; NET=norepinephrine transporter; M=muscarinic.

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arousal and memory.^{1,17,18} Ascending histaminergic neurons innervate limbic structures, such as the hippocampus, nucleus accumbens, and amygdala, where they may moderate various behaviors.¹⁻⁵ Descending pathways innervate important brainstem structures, such as the various monoamine neurotransmitter centers, where they regulate neuronal activity and neurotransmitter release from these other systems.¹⁻⁵

Synthesis and Metabolism of Histamine

Histamine is synthesized from the amino acid histidine, which is taken up into histamine neurons and converted to histamine by the enzyme histidine decarboxylase (Figure 4A).^{1,5,19,20} After synthesis, histamine is transported into synaptic vesicles for storage by vesicular monoamine transporter 2 (VMAT2), the same transporter that pumps monoamines into their storage vesicles.^{1,5,19,20}

Histamine's action is terminated largely in glial cells by two enzymes working in sequence: histamine-*N*-methyltransferase, which converts histamine to *N*-methylhistamine, and monoamine oxidase B, which converts *N*-methylhistamine into *N*-methyl indole acetic acid, an inactive substance (Figure 4B).^{1,5,19,20} Additional enzymes, such as diamine oxidase, can also terminate histamine action outside of the brain. Note that there is no apparent presynaptic reuptake pump for histamine.^{1,5} Thus, histamine is likely to diffuse widely away from its synapse once it is released, just like dopamine does in prefrontal cortex, where few dopamine reuptake pumps exist.

Histamine Receptors

There are a number of histamine receptors (Figure 5).^{1,5,19-21} The postsynaptic H₁ receptor is perhaps best known because it is the target of "antihistamines" (ie, H₁ antagonists). When his-

tamine itself binds to H₁ receptors, it activates a G-protein-linked second messenger system that activates phosphatidylinositol and the transcription factor cFOS, resulting in wakefulness, normal alertness, and pro-cognitive actions.^{1,5,19-21}

H₂ receptors, best known for their actions in gastric acid secretion and the target of some anti-ulcer drugs, also exist in the brain (Figure 5). These postsynaptic receptors also activate a G-protein-linked second messenger system with cyclic adenosine monophosphate, phosphokinase A, and the gene product cyclic adenosine monophosphate response element binding.^{1,5,19-21} The function of H₂ receptors in the brain is still being clarified, but some data suggest that H₂ receptor antagonists increase slow-wave sleep.²²

A third histamine receptor is present in the brain, namely the H₃ receptor (Figure 5). Synaptic histamine H₃ receptors are presynaptic and function as autoreceptors. That is, when histamine binds to these receptors, it turns off further release of histamine.^{1,5,19-21} These receptors are also presynaptic on non-histaminergic nerve endings (heteroreceptors) and when activated can inhibit release of neurotransmitters, such as NE.

There is a fourth type of histamine receptor, H₄, but these are not known to occur in the brain.^{1,5,19-21} Finally, histamine also acts at glutamate receptors (Figure 5).^{1,5,19-21} Interestingly, when histamine diffuses away from its synapse to a glutamate synapse containing *N*-methyl-

TABLE 1.
Myths About the Clinical Actions of "Antihistamines"

Myth 1: Antihistamines block H₁ receptors, so this is the cause of all their clinical actions

Myth 2: Blocking H₁ receptors at night will cause daytime sedation as well as nighttime hypnotic actions, and these effects will wear off over time.

Myth 3: H₁ receptor blockade causes weight gain

H=histamine.

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TABLE 2.
Adverse Effects of Lower Doses of Doxepin (25–50 mg)

Side Effect	DXP (n=24)		Placebo (n=23)	
	n	%	n	%
Dry mouth	17	70.8	12	52.2
Headache	6	25.0	8	34.8
Increased appetite	5	20.8	4	17.4
Hypotonia	4	16.7	5	21.7
Dizziness	5	20.8	2	8.7
Nervousness	3	12.5	4	17.4
Abnormal dreams	2	8.3	3	13.0
Somnolence	4	16.7	1	4.3
Increased weight	2	8.3	0	0.0

DXP=doxepin.

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D-aspartate (NMDA) receptors, it can act at an allosteric modulatory site called the polyamine site, to alter the actions of glutamate at NMDA receptors. The role of histamine and function of this action are not well clarified.

MYTHS ABOUT ANTIHISTAMINES: DOES SELECTIVE H₁ ANTAGONISM DIFFER FROM NONSELECTIVE H₁ ANTAGONISM?

Several longstanding notions about the clinical consequences of blocking H₁ receptors with "antihistamines" have arisen over time and stem from the use of agents that are actually not very selective for the H₁ receptor. Studies of selective H₁ antagonists as well as H₁ selective, very low doses of older drugs are leading to several surprises, as some of these clinical ideas are turning out to be myths (Table 1). Here, three such myths are discussed and it is shown how several new concepts are emerging for what are the real clinical consequences of selective H₁ antagonism.

Myth 1: Antihistamines Block H₁ Receptors, So This is the Cause of All of Their Clinical Actions

Antihistamines have a long and illustrious past in psychopharmacology. Until recently, essentially all antihistamines have really been multifunctional drugs with multiple simultane-

ous receptor actions at the clinically used doses. For example, the first effective treatments of schizophrenia discovered in the 1950s were "antihistamines," such as chlorpromazine.¹ It was later determined that chlorpromazine and other conventional antipsychotics worked in schizophrenia by blocking D₂ receptors and not by blocking H₁ receptors.¹

The first antidepressants were also "antihistamines," such as the tricyclic compounds amitriptyline and doxepin (Figure 6).¹ Later, it was determined that the tricyclic antidepressants (TCAs) work as antidepressants by blocking the transporters for 5-HT and for NE, but not by blocking H₁ receptors.¹ Nevertheless, the ability to improve sleep and cause daytime sedation has long been attributed to the H₁ antagonist properties of certain antipsychotics and antidepressants.^{1,5,16,19-21}

Amitriptyline and doxepin have H₁ antagonism as their most potent pharmacologic property, but both are dosed far beyond the range necessary to block H₁ receptors, in order to recruit the blockade of 5-HT and NE reuptake (Figure 6).^{1,23,24} For many TCAs, there is about a 10-fold higher potency for H₁ receptors than for monoamine transporters (amitriptyline in Figure 6).^{23,24} However, for doxepin, there is >2 orders magnitude potency separation between antidepressant actions and H₁ antagonism (doxepin in Figure 6).^{23,24}

TABLE 3.
Adverse Effects of Very Low Dose Doxepin 1, 3, and 6 mg/day^{39,42}

	5-Week Adult			3-Month Elderly		
	PBO	DXP 3 mg	DXP 6 mg	PBO	DXP 1 mg	DXP 3 mg
Overall	27%	35%	32%	52%	40%	38%
CNS	14%	12%	12%	20%	8%	11%
Headache	10%	5%	0%	14%	3%	6%
Somnolence/sedation	5%	9%	8%	5%	5%	3%
Dizziness	1%	0%	0%	2%	0%	2%
Memory Impairment	0%	0%	0%	1%	0%	0%
Gastrointestinal	4%	4%	8%	12%	5%	6%
Respiratory	3%	1%	1%	6%	3%	5%
Psychiatric	1%	1%	3%	1%	1%	2%
Other Events of Interest						
Dry mouth	0%	0%	0%	2%	1%	2%
Increased appetite	0%	0%	0%	0%	1%	0%

PBO=placebo; DXP=doxepin; CNS=central nervous system.

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Two other examples of "antihistamines" often utilized for treating insomnia, which also not only have very high potency H₁ antagonism, but also other multifunctional properties to which their antidepressant or antipsychotic properties are linked, include the antidepressant mirtazapine and the antipsychotic quetiapine (Figure 6).^{1,23-26} Trazodone is another multifunctional drug, but its highest potency receptor action is as an antagonist for 5-HT_{2A} receptors; nevertheless, trazodone does not have hypnotic properties unless the dose is increased to recruit the blockade of H₁ receptors and does not have antidepressant properties unless the dose is further increased to recruit the blockade of the 5-HT transporter (Figure 6).^{1,23,24,27}

Diphenhydramine (Benadryl) is often considered to be the prototypical "antihistamine." This, too, is a multifunctional agent with notable muscarinic cholinergic-blocking properties at the same doses where H₁ receptors are blocked (Figure 6).¹ The same is true for doxylamine, an antihistamine that is often used, as is diphenhydramine, in OTC sleep remedies. Thus, these prototypical "antihistamines" are not merely antihistamines. In fact, antidepressants and antipsychotics used as sedative-hypnotics are also not merely antihistamines. The question is: Which properties of these agents can be attributed to H₁ antagonist action and which properties to their other pharmacologic actions?

In order to answer this question, Figure 6 suggests that it would be possible to turn some multifunctional drugs at high doses into H₁ selective drugs at very low doses. However, until recently,

this had never been tried. Such an approach would require using a dose between 10 and 100 times lower than the usual clinical doses, and none of these agents has dosage forms in this range available for clinical use. Recent studies are beginning to look at such very low doses, especially for the TCA doxepin and for the active S-enantiomer of mirtazapine. Other drugs with potent actions at H₁ receptors, such as HY10275 and others, are also in testing as novel hypnotics. Most of what is currently known about the clinical actions of H₁ selective antagonists derives from numerous studies of doxepin at very low doses, so those studies will be reviewed here.

Very Low Dose Doxepin

For a TCA usually categorized as a "dirty drug," it can seem at first counter-intuitive that doxepin is actually quite selective for H₁ receptors. Because of its wide separation of binding potency at H₁ receptors compared to that at other receptors (Figure 6),^{1,23} doxepin is now used in trace doses as a selective ligand for labeling H₁ sites both in vitro^{28,29} and with human positron emission tomography scans in vivo.³⁰⁻³⁴ Receptor binding estimates also suggest that a few milligrams of oral doxepin would be sufficient to block a substantial number of H₁ sites and thus to act effectively as a hypnotic.³⁵ Higher doses would theoretically only recruit additional receptors once the H₁ receptor is saturated

TABLE 4.
Doxepin: Summary of Next-Day Residual Effects^{39,42}

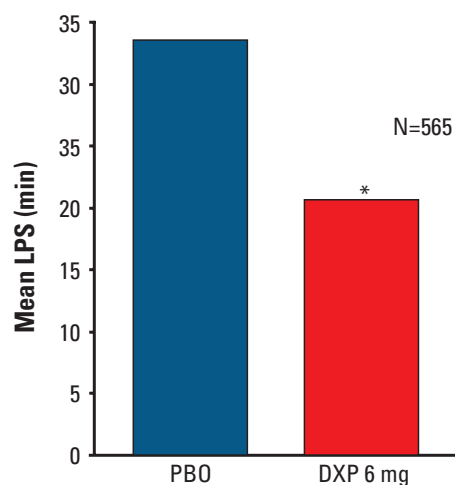
		PBO	DXP 1 mg	DXP 3 mg
Night 1	DSST Score	47.8	49.2	46.5
3-month elderly trial	SCT Score	93.6	94.9	89.2
	VAS Score	59.0	59.3	61.5
Night 1	DSST Score	61.8	59.3	59.7
4-week adult trial	SCT Score	117.8	114.2	117.8
	VAS Score	57.1	56.6	51.4

* Lower score=more sedation on all three parameters; plotting of VAS is inverted for consistency with DSST and SCT results.

PBO=placebo; DXP=doxepin; DSST=Digit-Symbol Substitution Test; SCT=Short Category Test; VAS=Visual Analog Scale.

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FIGURE 7.
Doxepin: reduction in latency to persistent sleep—transient insomnia trial³⁸



* $P < .0001$.

LPS=latency to persistent sleep; min=minutes; PBO=placebo; DXP=doxepin.

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(Figure 6),²³ with possible additional effects, but not necessarily more therapeutic effects for insomnia. In fact, the efficacy of very low dose doxepin for insomnia in selective H₁ antagonist doses has been confirmed in several clinical trials: namely, doxepin 1, 3, and 6 mg/day is effective for sleep onset (Figure 7)^{36-39,42} and sleep maintenance (Figure 8)^{36-39,42} in treating insomnia. This is much different from the use of doxepin for the treatment of depression, where exponentially higher doses are known to be necessary (Figure 6).¹⁻³

Summary

So-called antihistamines and other psychotropic drugs with antihistamine properties do not block H₁ receptors selectively at doses used in clinical practice. However, selective blockade of H₁ receptors can be attained by highly potent H₁ antagonists at very low doses. H₁ antagonist actions can be linked to efficacy for the treatment of insomnia, but not efficacy for treatment of psychosis or depression. It is now reasonable to ask: Can H₁ antagonist actions be linked to the side effects of drugs with antihistamine properties?

Myth 2: Blocking H₁ Receptors at Night Will Cause Daytime Sedation as well as Nighttime Hypnotic Actions, and These Effects Will Wear Off Over Time

There is evidence that antihistamines given in multifunctional doses of drugs that generate next-day residual drug levels capable of blocking significant numbers of H₁ receptors can cause next-day sedation (Table 2), with these effects appearing to wear off over time (Figure 9).^{40,41} Furthermore,

chronic treatment with these agents at these doses can show loss of hypnotic efficacy and rebound insomnia after sudden discontinuation from chronic treatment (Figure 10).⁴¹

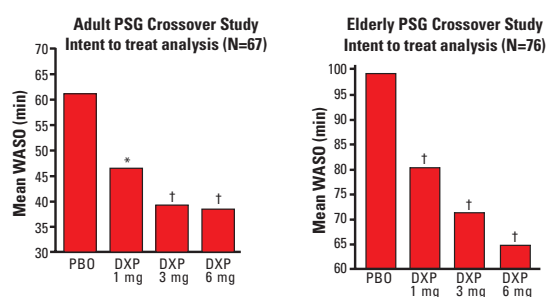
However, selective blockade of H₁ receptors at night by very low doses of doxepin is not associated with daytime sedation, either by self report (Table 3)^{39,42} or by cognitive testing (Table 4).^{39,42} Selective H₁ blockade is also not associated with loss of hypnotic efficacy (Figures 11 and 12)^{39,42} or with rebound insomnia (Figure 13).⁴²

Thus, clinical doses of so-called antihistamines and other psychotropic drugs with antihistamine properties seem to hit the brain's arousal system with the "triple whammy" of saturation of H₁ receptors at night, saturation of H₁ receptors in the daytime, and blockade of multiple additional arousal systems night and day by nonselective high doses.³⁵ This may lead not only to hypnotic actions, but also to daytime sedation and adaptive changes in the arousal system, such that tolerance and rebound occur. However, when selective saturation of H₁ receptors occurs predominantly at night, only long-term efficacy for treating insomnia is apparent.

Myth 3: H₁ Receptor Blockade Causes Weight Gain

Certainly, psychotropic drugs with antihistaminic properties can cause weight gain with chronic use (Table 2).^{1,43} However, chronic treatment with very low dose doxepin for 4 or 12 weeks was not associated with either appetite

FIGURE 8.
Doxepin: significantly improves wake after sleep onset^{36,37}

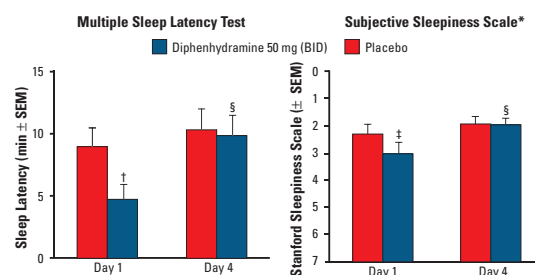


* $P < .01$.
† $P < .0001$.

PSG=polysomnography; WASO=wake after sleep onset; PBO=placebo; DXP=doxepin.

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FIGURE 9.
Diphenhydramine: tolerance to daytime sedative effects⁴⁰



* Plotting of SSS is inverted for consistency with MSLT results.

† $P < .05$ vs placebo.

‡ $P < .001$ Day 1 vs Day 4.

§ $P = .001$ vs placebo.

SSS=Subjective Sleepiness Scale; MSLT=Multiple Sleep Latency Test.

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increase or weight gain in studies of insomnia (Table 3, Figure 14).^{39,42} Thus, it does not appear that H₁ antagonism on its own is sufficient for causing weight gain, and that administration of H₁ selective doses of antihistamines may be surprisingly weight neutral.

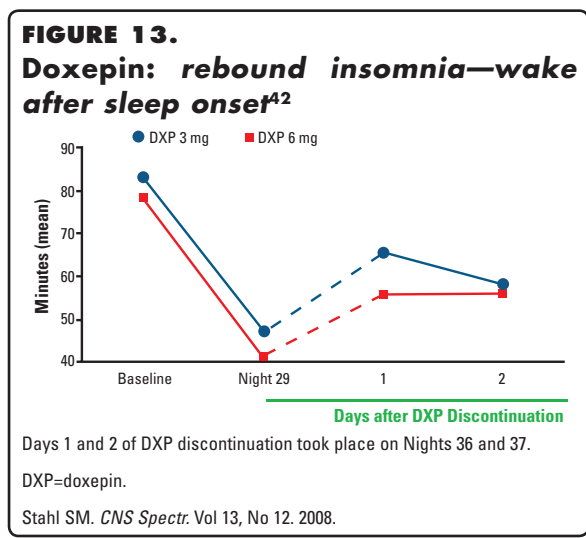
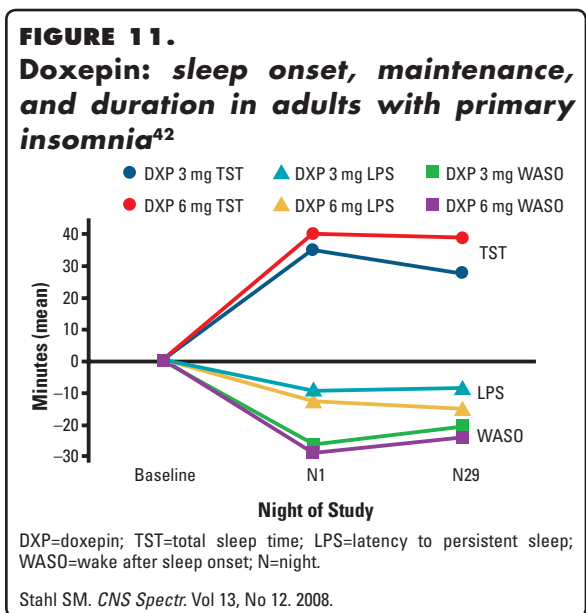
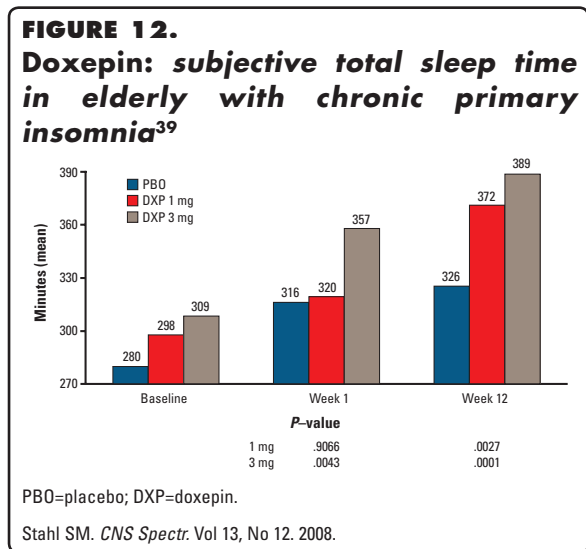
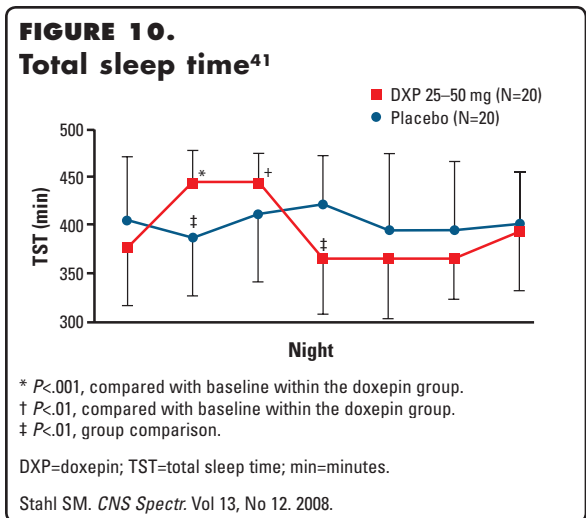
Selective H₁ Antagonism Versus Artificial Hibernation and Lobotomie Pharmacologique: an Emerging Therapeutic Option for Insomnia

Current sedative hypnotics essentially shut down the arousal system, either by enhancing GABA action to inhibit all arousal systems (Figures 2 and 3), or by blocking multiple arousal

systems simultaneously with sedative hypnotic doses of multifunctional drugs that have antihistaminic, antimuscarinic, antiadrenergic, and/or antiserotonergic effects (Figures 1 and 3). Both of these approaches can create powerful sedative-hypnotic actions, but the pharmacologic state induced may be more like “artificial hibernation” for conventional hypnotics acting on GABA systems or “lobotomie pharmacologique” for multifunctional antipsychotics than natural sleep.^{44,45}

CONCLUSION

What is the difference between selective H₁ blockade and a more widespread shut-down of the arousal system caused by current hypnotics? Early studies reviewed here indicate that



blocking a substantial number of H₁ receptors at night may also be sufficient to block the excessive arousal thought to be the cause of chronic insomnia, yet not cause next-day sedation (Tables 3 and 4). H₁ selective antagonism at night does not directly interfere with the other arousal neurotransmitter systems (Figure 1) and may explain the apparent lack of daytime sedation with very low doses of doxepin.

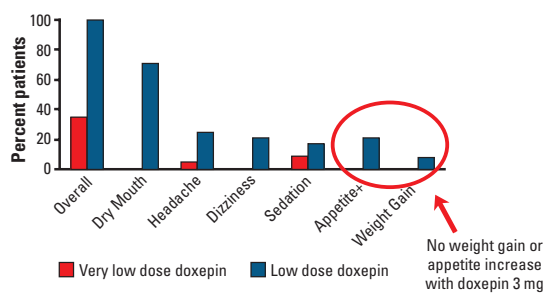
One explanation for the lack of daytime sedation with H₁ selective dosing at night could be that H₁ selective antagonism does not directly block the activation of other arousal systems in the morning, such as NE, ACh, 5-HT, and orexin. Also, histamine release, normally reduced at night, not only increases in the daytime but may become more active during the middle and the end of the night. Animal models have also clearly documented histamine “spikes” during the transition period to rapid eye movement. Since H₁ antagonists do not interfere with histamine release in the synapse, where high concentrations of neurotransmitters occur following physiological release,^{46,47} there is the possibility of successful competition of histamine itself with any residual H₁ antagonist for postsynaptic H₁ receptors. Therefore, the patient is awake and not sedated in the daytime.

Furthermore, these observations suggest an interesting prediction from the selective actions of H₁ antagonists. That is, unlike drugs that enhance GABA inhibition or block multiple arousal systems, selective blockade of histamine does not appear to globally suppress arousability, thus potentially allowing patients to wake up as needed throughout the night without feeling “drugged.” Whereas it is difficult to be aroused from a state of drug-induced

“artificial hibernation” until such drugs wear off, selective antagonism of only the histamine system might become reversible if the patient needs to wake up. This might be a particular advantage for some populations, such as the elderly, who not only have increasing problems with sleep maintenance as they age but may often need to get up at night without the risk of sustaining a fall. Further research is necessary to investigate this potential advantage of selective H₁ antagonism.

Nonselective saturation of H₁ receptors night and day but not selective saturation of H₁ receptors at night can cause daytime sedation, and this can wear off with time, with tolerance developing to hypnotic effects and rebound insomnia occurring. The differences between selective and nonselective H₁ blockade may be due not only to the recruitment of additional neurotransmitter receptors blocked by nonselective agents (Figure 6),^{1,23} but also to the continuous saturation of H₁ receptors during the day as well as at night by the high doses usually administered. An explanation for the surprising lack of tolerance, rebound, or weight gain by H₁ selective antagonism may be that blocking H₁ receptors at night, when they are normally receiving reduced histamine input anyway,¹⁻³ may create a state that is analogous to normal functioning of the histamine arousal system. Keeping H₁ receptors below the level of complete saturation during the day may explain the lack of tolerance, rebound, and weight gain, because substantial blockade of H₁ actions in the daytime is not normal, and when it occurs may cause arousal systems and the body to adapt, thus creating unwanted long-term side effects. Selective H₁ antagonism does appear to be emerging as an interesting new therapeutic option for insomnia, with some potential advantages compared to current hypnotics. **CNS**

FIGURE 14.
Comparing side-effect profiles of low (25–50 mg) and very low dose (3 mg) doxepin^{41,42}



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