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Ignacio Ansotegui, Jean Bousquet, Giorgio Walter Canonica, P Demoly, Rene Maximiliano Gómez, et al.. Why fexofenadine is considered as a truly non-sedating antihistamine with no brain penetration: a systematic review. *Current Medical Research and Opinion*, 2024, 40 (8), pp.1297-1309. 10.1080/03007995.2024.2378172 . hal-04920792

**HAL Id: hal-04920792**

**<https://hal.science/hal-04920792v1>**

Submitted on 30 Jan 2025

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To link to this article: <https://doi.org/10.1080/03007995.2024.2378172>



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Published online: 19 Jul 2024.



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## Why fexofenadine is considered as a truly non-sedating antihistamine with no brain penetration: a systematic review

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### ABSTRACT

**Objective:** Fexofenadine is a second-generation inverse agonist of H<sub>1</sub>-receptor of histamine which is highly selective with proven efficacy in relieving symptoms associated with allergic conditions. It has an additional benefit of not penetrating the blood–brain barrier and therefore do not induce sedation and not impair the cognitive function/psychomotor performance. This review aimed at providing evidence based on available controlled studies to reinforce the non-sedative property of fexofenadine for treating patients with allergic rhinitis and urticaria.

**Methods:** We performed an electronic literature search using keywords such as fexofenadine, drowsiness, somnolence, sedation, fatigue, cognitive, impairment, psychomotor, driving performances, sleep, rapid eye movement, alertness, clinical study, *in vitro* study, *in vivo* study, and pharmacodynamics in the Embase search engine. The review included randomized controlled trials, review articles, systematic reviews, and meta-analyses, together with post-marketing analysis conducted in healthy subjects and patients with allergy and were focused on comparing the antihistaminic potential or safety of fexofenadine with other antihistamines or placebo.

**Results:** Positron emission tomography (PET) and proportional impairment ratio (PIR) data along with other objective tests from various studies confirmed the non-sedative property of fexofenadine. Results of brain H<sub>1</sub>-receptor occupancy (H<sub>1</sub>RO) obtained from PET showed no H<sub>1</sub>RO by fexofenadine, the receptor which is known to cause sedation of H<sub>1</sub> antihistamines. Most studies calculating PIR value as 0 showed fexofenadine to be a non-impairing oral antihistamine regardless of dose. Clinical trials in adults and children showed fexofenadine to be well tolerated without sedative effect or impairment of cognitive/psychomotor function even at higher than recommended doses.

**Conclusion:** Published literature based on various parameters and clinical trials conducted for evaluating the effect of fexofenadine on sedation and central nervous system shows fexofenadine is both clinically effective and non-sedating.

### ARTICLE HISTORY

Received 13 March 2024  
Revised 27 June 2024  
Accepted 5 July 2024

### KEYWORDS

Fexofenadine; antihistamines; sedation; drowsiness; non-drowsy; clinical trials; allergy

## Introduction

In allergic reactions, histamine and other preformed proinflammatory mediators are released following mast cell degranulation. Histamine and its receptors have a pivotal role in the allergic disease pathogenesis. For allergic conditions, oral antihistamines have been considered as an effective and first-line treatment option for decades. The anti-allergic role of antihistamines has been attributed, to their ability to serve as competitive antagonists on H<sub>1</sub>-receptors, thereby preventing the circulating

histamine to bind. However, most antihistamines, as is the case with fexofenadine, also act as inverse agonists. H<sub>1</sub> receptors have constitutive activity, and in their natural state are in equilibrium between their active and inactive conformations, even in the absence of histamine or other agonists. Fexofenadine binds to these receptors at different sites within the H<sub>1</sub> receptors than histamine does, and stabilizes them in their inactive form<sup>1</sup>.

Oral antihistamines have been grouped into first and second generation on the basis of their pharmacological characteristics (selectivity, affinity, PK/PD, whether or not

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they are active metabolites of the parent molecules, etc.), and not only on the basis of the adverse events associated with them<sup>2</sup>. First-generation antihistamines include molecules, such as diphenhydramine, promethazine, chlorpheniramine, and hydroxyzine, and second-generation molecules include loratadine, desloratadine, cetirizine, levocetirizine, bilastine, mizolastine, rupatadine, and fexofenadine<sup>1,2</sup>.

Although first-generation antihistamines are efficient in decreasing various symptoms of allergic conditions, the lack of specificity for H<sub>1</sub>-receptor and their tendency of crossing the blood–brain barrier (BBB) can cause detrimental adverse effects. The BBB consists of non-fenestrated capillaries with tight endothelial junctions, pericytes, and astrocytes that prevent harmful substances from reaching the brain. Furthermore, first-generation antihistamines affect the central nervous system (CNS) by blocking the neurotransmitter effect of endogenous histamine<sup>3</sup>, leading to various adverse events, including sedation, drowsiness, and psychomotor impairment<sup>4</sup>. In addition, the anticholinergic activity of these antihistamines can lead to dryness of mouth, dryness of eyes, constipation and urine retention, and, most concerning, can, even at the prescribed doses, lead to accidental toxicity and death in children<sup>5</sup>. Many studies have shown that due to their tendency to interfere with histamine-mediated neurotransmission at CNS, first-generation antihistamines potentially lead to sedation, drowsiness, and fatigue eventually leading to impaired cognitive function, memory, and psychomotor performance. They alter the circadian sleep/wake cycle, and it has been well established that these drugs can cause daytime somnolence, impairment of concentration and decreased mental acuity. Somnolence frequency has been reported from 40% after use of chlorpheniramine or brompheniramine and 80% after hydroxyzine<sup>6</sup>. First-generation antihistamines cause increased latency to the onset of rapid eye movement (REM) sleep during the night and reduced the duration of REM. The residual effect of first-generation antihistamines is carried to even the next morning activities, which has manifestations that include reduced vigilance, working memory, and sensory motor performance<sup>7</sup>. The sedative effect of antihistamines can be fatal while driving or operating any machine because both these tasks require high level of alertness<sup>8</sup>. In addition to first generation antihistamines being used for allergic rhinitis, they are also sometimes recommended for non-allergic rhinitis to reduce the anterior and posterior rhinorrhea noted with this condition and benefited from the anticholinergic effects of first generation antihistamines<sup>5</sup>.

To provide alternatives to CNS depressant/sedative adverse effects of first-generation antihistamines while maintaining similar efficacy, second-generation oral antihistamines were developed. The advances of second-generation antihistamines helped to overcome the adverse consequences of first-generation antihistamines, as they are highly selective to H<sub>1</sub>-receptors, provide low brain permeability, and generally have a longer duration of action. Second-generation antihistamines were developed to bind to peripheral H<sub>1</sub>-receptors, and these do not bind to central cholinergic or H<sub>1</sub>-receptors; therefore, they do not cause the same degree of sedation<sup>8</sup>. Unlike first-generation antihistamines, second-generation antihistamines

are amphiphilic in nature due to the introduction of hydrophilic groups in their chemical structure. Therefore, these always have positive or negative charge and reduced movement across the lipid-containing BBB<sup>9,10</sup>.

Studies have demonstrated that second-generation antihistamines are preferable due to their favorable therapeutic ratio with a relatively low incidence of sedation<sup>3,11</sup>. One of the major factors for no/modest sedative potential of second-generation antihistamines is the P-glycoprotein. This protein is expressed in the BBB and acts as an efflux pump that reduces the concentration of H<sub>1</sub>-antihistamines in the brain. This reduces the effect of drug on the CNS, resulting in less sedative effect. P-glycoproteins are present apically on the epithelium. The transmembrane domain of P-glycoprotein binds the drug molecule/substrate and the nucleotide-binding domain binds to and hydrolyze the ATP for generating energy to efflux the drug<sup>12</sup>.

It is clear that P-glycoprotein is crucial in minimizing the sedative effects of second-generation H<sub>1</sub>-antihistamines. Nonetheless, additional elements might influence their modestly or non-sedating characteristics, such as individual variability in blood-brain barrier permeability, differences in metabolism, Cytochrome P450 enzymes, enantiomers, molecular weight, and pKa of the individual drug. All these factors may contribute to the modestly or non-sedating properties of the second-generation antihistamines<sup>12</sup>.

### **Fexofenadine**

Fexofenadine is a second-generation potent, selective, non-sedating inverse agonist of the H<sub>1</sub>-receptor. It has demonstrated significant efficacy in relieving clinical symptoms and in improving quality of life (QoL) of patients who suffer from allergic rhinitis (AR), chronic spontaneous urticaria, and other allergic conditions. Fexofenadine, as mentioned previously, is an inverse agonist of H<sub>1</sub>-receptor. Fexofenadine binds to the inactive form of the receptor, which occurs with active form in equilibrium. The inactive form of the receptor is stabilized, and equilibrium is shifted towards the inactive form, which further reduces the number of active receptors for binding of the endogenous histamine. Fexofenadine can also down-regulate the constitutive activity of the receptor, even if histamine is not present<sup>13</sup>.

Fexofenadine has been used for treating AR and urticaria for more than 26 years<sup>12,14</sup>. It has high selectivity towards peripheral H<sub>1</sub>-receptors and is a substrate molecule for P-glycoprotein. It does not penetrate BBB, due to its affinity towards P-glycoprotein, thereby minimizing the drug effects on the CNS and resulting in decreased sedation<sup>15</sup>.

The additional clinical benefit to not inducing sedation is that concentration, memory, or performance are not affected. This review aimed at providing clinical evidence based on well-conducted controlled studies assessing the fexofenadine safety and lack of sedating effects.

### **Methods**

Embase search engine was used to perform an electronic literature search. The following keywords were used for the search:

fexofenadine, drowsiness, somnolence, sedation, fatigue, cognitive, impairment, psychomotor, driving performances, sleep, REM, alertness, clinical study, *in vitro* study, *in vivo* study, pharmacodynamics, objective tests, safety, H<sub>1</sub>-receptors, central nervous system (CNS), and antihistamines. Randomized controlled trials (RCTs), review articles, and post-marketing analysis conducted in healthy subjects and patients with allergy which focused on comparing the antihistaminic potential or safety of fexofenadine with other antihistamines or placebo were selected.

### Measuring sedation

Most of the population taking antihistamines is ambulant; therefore, there is a need to evaluate the cognitive and psychomotor effect of these drugs using standardized methodology and psychometric tests. Proportional impairment ratio (PIR) is a method, which has been adapted from the one used in pharmacovigilance, to predict if a certain antihistamine has associated cognitive or psychomotor impairment effect<sup>16</sup>. If the antihistamine is found to be associated with these adverse effects, it provides the extent of that impairment in comparison with the effects of other antihistamines. The greater PIR indicates greater cognitive and psychomotor impairment<sup>17</sup>. Various studies based on PIR values have shown that fexofenadine does not cause impairment<sup>17,18</sup>.

While evaluating the effect of antihistamines on BBB and further on CNS, various terms, such as somnolence/fatigue and sedation, are used for assessment/reporting. It is important to understand the differences between these terminologies. The frequency and level of daytime dysfunction and impairment determines the severity of abnormal somnolence. The International Classification of Sleep Disorders-2 defined excessive sleep as a "State, subjectively reported by the patient, in which he or she experiences difficulty maintaining alertness and wakefulness, followed by rapid entrance into sleep when sedentary"<sup>19</sup>. Sedation has also been distinguished as impairment and drowsiness. Any interference with patient's ability to perform tasks is referred to as cognitive impairment and measured by objective tests. It

might happen that drowsiness can limit performance, but there could be situation where it may not impact performance<sup>20</sup>. The most undesirable scenario would be impairment without any signs of drowsiness, as it would then be difficult for the patient to detect or recognize their impairment without any subjective clues. Various objective tests have been designed to measure sedation. Sedation scoring must be objective because the assumption regarding the depth of sedation may not provide accurate or consistent measurement. Table 1 indicates various sedation scales that have been used in clinical practice for defining the level of sedation; they vary according to need and local practice<sup>24</sup>.

There are various other parameters to measure the effect of antihistamines on CNS. The critical flicker fusion (CFF) threshold evaluates the level of CNS arousal and the capacity to process information. It specifically measures the ability to distinguish between discrete units of sensory information. Choice reaction time (CRT) is used for measuring the drug-induced modification in psychomotor speed. In compensatory tracking task (CTT), a moving arrow is tracked on a visual display unit for measuring the sensorimotor function. The brake reaction time (BRT) test evaluates cognitive and psychomotor functions in relation to driving, such as attentional efficiency<sup>24</sup>.

## Results

### Brain H<sub>1</sub>-receptor occupancy

The assessment of whether the drug molecule crosses the BBB and affects the CNS needs to be determined by rigorous objective assessment along with non-subjective pharmacological evidence. The lipophilic nature of a drug molecule indicates whether it can cross the BBB and reach cerebral H<sub>1</sub>-receptors. Psychometric tests are developed for evaluating the effect of a drug on CNS or positron emission tomography (PET) can help to objectively measure the penetration of the drug molecule into the CNS<sup>2</sup>. In PET, brain H<sub>1</sub> receptor occupancy (H<sub>1</sub>RO) is measured as an index of sedative potential using a radioactive tracer <sup>11</sup>C-doxepin that investigates the

**Table 1.** Sedation scales.

Scale	Description	Merits/demerits
Ramsay Scale <sup>21</sup>	1) Three levels of "awake" states (score 1–3) 2) Three levels of "asleep" states (score 4–6)	1) Lacks detailed descriptors for a clear discrimination between sedation levels 2) Different levels are not mutually exclusive <sup>22</sup>
Sedation-Agitation Scale <sup>23</sup>	1) Scores from +3 (agitated) to –3 (unarousable) 2) Optimum sedation would aim for a score of 0 (calm and cooperative)	1) Excellent inter-rater reliability 2) Validated against other common sedation scales <sup>24</sup>
Motor Activity Assessment Scale <sup>25</sup>	1) Seven categories to describe the level of sedation 2) Each category based on observed levels of motor activity ranging from 0 (unresponsive) to 6 (dangerously agitated)	NA
Richmond Agitation-Sedation Scale <sup>26</sup>	1) Scores patients on a 10-point scale from +4 (combative) to –5 (unarousable) 2) Zero denoting the level of optimum sedation	1) Easy and quick to use 2) Validated in medical and surgical patients, both with and without mechanical ventilation or sedation
Adaptation to the Intensive Care Environment Scale <sup>27</sup>	1) Most comprehensive assessment scale 2) Provides assessment across domains of consciousness (awakeness and comprehension) and tolerance (calmness, ventilator synchrony, and face relaxation)	1) Relatively more complex and might be difficult to use in everyday ICU clinical practice

ICU, intensive care unit.

distribution of the cerebral H<sub>1</sub>-receptors and blocking effect of antihistamines<sup>9</sup>. "Consensus Group of New Generation of Antihistamines (CONGA)," an expert meeting sponsored by the British Society for Allergy and Clinical Immunology, also confirmed the use of H<sub>1</sub>RO as an index for measuring the non-sedative property of antihistamines<sup>28</sup>. A classification of first- and second-generation antihistamines based on the level of H<sub>1</sub>RO after a single oral administration of antihistamine was given by Yanai and colleagues<sup>10</sup> that classified antihistamine as non-sedating [ $<20\%$  occupancy], less sedating [ $20\text{--}50\%$  occupancy], and sedating [ $>50\%$  occupancy]. Based on the results of various studies conducted, fexofenadine was included in the non-sedating group<sup>10,29</sup>.

A double-blind, placebo-controlled study used three different criteria for comparing the sedative potential of fexofenadine and cetirizine in 20 healthy Japanese patients at the baseline and after the administration of 120-mg fexofenadine or 20-mg cetirizine (the double of recommended daily dose), with hydroxyzine 30 mg as a positive/active control. Results showed fexofenadine (120 mg) H<sub>1</sub>RO as minimal ( $-0.1\%$ ), whereas for cetirizine 20 mg, it was found to be moderately high (26.0%) suggesting that fexofenadine was non-impairing and non-sedating<sup>11</sup>. Psychomotor test results showed no significant difference between fexofenadine and placebo. On the contrary, 20 mg cetirizine was not found to fulfill the criterion for a non-sedative antihistamine as it showed significant difference from placebo in few measures for subjective sleepiness and cognitive impairment. Cetirizine 20 mg was not found to have been significantly different from active control. Both H<sub>1</sub>RO and psychometric tests along with subjective sleepiness showed that 120-mg fexofenadine can be distinguished from cetirizine 20 mg.

Another study evaluated H<sub>1</sub>RO of levocetirizine, a second-generation antihistamine, in comparison with fexofenadine as a negative active control. Negative mean cortical H<sub>1</sub>RO after 60-mg fexofenadine administration indicated no H<sub>1</sub>RO at all, which was in concordance with the results of the previous study<sup>9</sup>. Levocetirizine also did not bind significantly to brain H<sub>1</sub>ROs, neither it induced any significant sedation. Table 2 elucidates the studies on PET showing the lack of H<sub>1</sub>-receptors in the brain occupancy with fexofenadine compared to placebo. Figure 1 represents the H<sub>1</sub>RO value of antihistamines based on the published literature. It could be seen that among published studies, fexofenadine has the lowest H<sub>1</sub>RO value<sup>9,11,32–36</sup>.

### Proportional impairment ratios

PIR, which is based on subjective feeling and objective performance, is another index of measuring sedation due to H<sub>1</sub> antihistamines. It has been used for ranking many first- and second-generation antihistamines. PIR compares the extent to which a particular compound causes disruption compared to other antihistamines<sup>18</sup>.

The formula to calculate the PIR of an antihistamine is:

$$\text{PIR} = a/a + b \text{ divided by } c/c + d$$

	Impairment	No impairment
A specific AH	<i>a</i>	<i>b</i>
All other AHs on the database	<i>c</i>	<i>d</i>

*a*: Number of tests showing "impairment" with the named antihistamine.

*b*: Number of tests showing "no impairment" with the named antihistamine.

*c*: Number of tests showing "impairment" with all other antihistamines.

*d*: Number of tests showing "no impairment" with all other antihistamines.

An extensive review conducted by McDonald et al.<sup>17</sup> collated the results of H<sub>1</sub>-receptor antagonist studies for evaluating the magnitude of impairment produced by a particular antihistamine by calculating PIR for each of the drug molecules. Among PIR values calculated based on the objective tests, only one test showed impairment for fexofenadine compared to 92 tests showing no impairment. PIR value based on 26 subjective tests was 0 for fexofenadine even at high dose of 360 mg. The significance of that one test result was discounted suggesting fexofenadine as impairment free<sup>17</sup>. A recent systematic review based on their interpretations ranked fexofenadine as the antihistamine causing least psychomotor impairment compared to other antihistamines present in the Japan market. In this study, Isomura et al. calculated PIRs together with 95% confidence intervals (CIs), as an index of reliability for antihistamines available to compare them for their intrinsic capacity of causing impairment<sup>18</sup>. A total of 45 studies were included in the calculation of new PIR, and the PIR was calculated separately for objective and subjective tests. It was found that 65 objective test results showed no impairment caused by fexofenadine. For fexofenadine, doses between 60, 80, 120, 180, 240, and 360 mg did not show any impairment in objective tests, and PIR values were calculated as 0 at all doses.

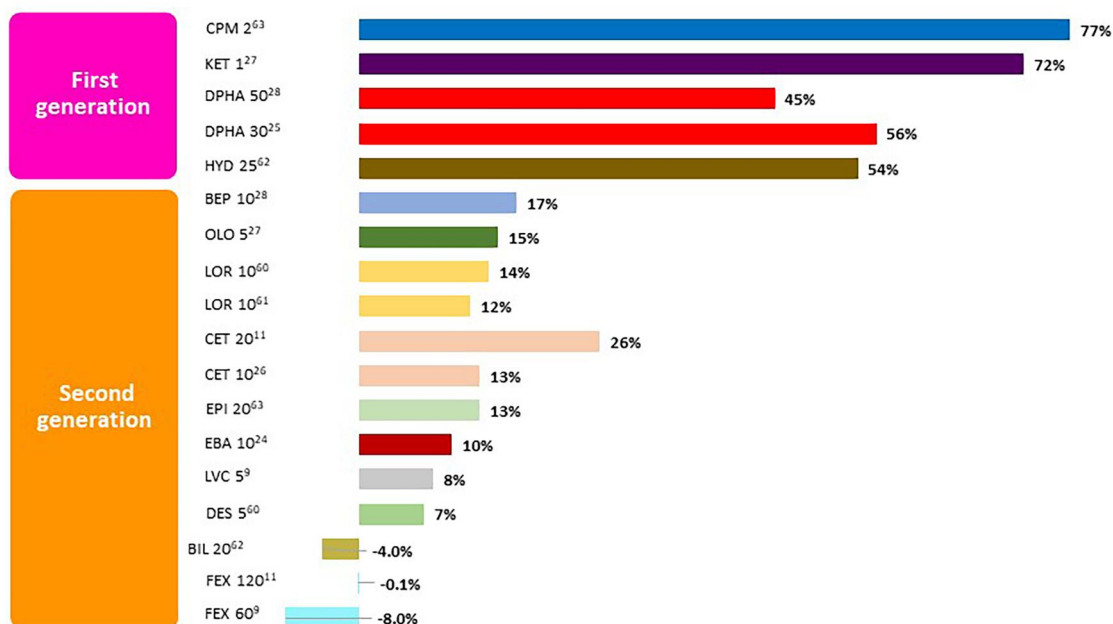
### Clinical studies assessing CNS safety of fexofenadine

In addition, various human studies have been conducted to ascertain if fexofenadine induces any sedation. In a

**Table 2.** Studies indicating the nature of fexofenadine based on PET.

Reference	Findings
Hindmarch et al. 2002 <sup>30</sup>	1) Fexofenadine does not bind to the H <sub>1</sub> -receptor and can be differentiated from other antihistamines.
Hindmarch 2004 <sup>31</sup>	2) Supraclinical doses of fexofenadine were found to be non-impairing. 1) Fexofenadine was identified as a class 1 drug, which is the safest option for CNS impairment and non-sedating and non-impairing even at supraclinical doses.
Tashiro et al. 2004 <sup>11</sup>	1) Fexofenadine is non-sedating and non-impairing as assessed by PET. 2) Histamine H <sub>1</sub> -receptor occupancy in the brain was negligible with fexofenadine but moderately high with cetirizine.
Hiraoka et al. 2015 <sup>9</sup>	Negative mean cortical H <sub>1</sub> RO following fexofenadine 60 mg administration indicated no H <sub>1</sub> -receptor occupancy by fexofenadine in concordance with the results of a previous study.

CNS, central nervous system; H<sub>1</sub>RO, H<sub>1</sub>-receptor brain occupancy; PET, positron emission tomography; PIR, proportional impairment ratio.

ORAL ANTI-HISTAMINES: BRAIN H<sub>1</sub> RECEPTOR OCCUPANCY (H<sub>1</sub>RO %)

CPM, chlorpheniramine; KET, ketotifen; DPHA, diphenhydramine; HYD, hydroxyzine; BEP, bepotastine; OLO, olopatadine; LOR, loratadine; CET, cetirizine; EBA, ebastine; LVC, levocetirizine; DES, desloratadine; BIL, bilastine;

Figure 1. Oral anti-histamines: brain H<sub>1</sub> receptor occupancy (H<sub>1</sub>RO %).

randomized, double-blind, crossover study that included 18 healthy male participants, it was observed that fexofenadine HCl 180 mg alone and with alcohol (0.3 g/kg body weight or -0.43 to 0.50 g/L blood-alcohol concentration) did not show any significant effect on driving related objective measures, along with psychomotor and cognitive function. At any point of the study, results of fexofenadine group were comparable with placebo for most of the objective or subjective tests. On the contrary, hydroxyzine (50 mg), the positive internal control, either alone or taken with alcohol, showed CNS impairment considered as notable as observed in CFF, recognition reaction time, and total reaction time tests compared to both placebo and fexofenadine ( $p < 0.05$ ). Additionally, hydroxyzine showed a significant impact on mean reaction time compared to placebo and fexofenadine ( $p < 0.001$ ). Subjective observations were in line with the objective findings. Subjects treated with hydroxyzine (alone and with alcohol) showed significant impairment in comparison to placebo when assessed based on a sedation factor comprising "less energetic," "more tired," and "more drowsy" than usual. However, study reported no significant or discernible effect in fexofenadine treated subjects. A significant tiredness was reported by subjects treated with hydroxyzine than with alcohol alone<sup>37</sup>.

Among various cognitive function disruptions caused by antihistamines, they could also affect the sleep architecture. A single site, randomized, double-blind, three-way, crossover study compared the effects of a single dose of chlorpheniramine (6 mg), fexofenadine (120 mg), and placebo in 18 healthy Japanese volunteers on the night sleep pattern and on cognitive function and psychomotor performance on the

next day. The study observed a trend towards an increased latency to sleep onset and REM sleep and a reduced duration of REM sleep ( $p \leq 0.01$ ) with chlorpheniramine ( $p \leq 0.05$  for both) compared to placebo; this trend was not observed with fexofenadine. Next morning, there was a decrement in performance with chlorpheniramine, but not with fexofenadine. Data of this study suggested that a single nocturnal dose of fexofenadine was advantageous over first-generation antihistamine chlorpheniramine. Fexofenadine did not cause any disruption in the nighttime sleep and caused no detrimental effects on cognitive performance the following day<sup>38</sup>. Inami et al.<sup>39</sup> conducted a placebo-controlled, double-blind, four-way, crossover study in healthy volunteers who received single doses of 5 mg levocetirizine, 60 mg fexofenadine, 50 mg diphenhydramine, and placebo at a minimum interval of 6 days. To compare the driving performance between these four drugs, simple brake reaction time, choice brake reaction time task (CBRT), a lateral tracking (LT) task, and a multiple task (a mixture of CBRT and LT task) were used. The study also evaluated subjective sense of sedation. Subjects in the fexofenadine-treated group did not show any impairment of psychomotor performance. Car-driving test parameters were not significantly affected, after administering 5 mg levocetirizine. In addition, subjects receiving diphenhydramine significantly impaired the LT compared to placebo<sup>39</sup>.

The cognitive effect of fexofenadine 180 mg was compared with placebo and cetirizine 10 mg in healthy naval flight personnel. Aviation-related cognitive skills were evaluated at both ambient conditions of atmosphere and normobaric hypoxic conditions using Aeromedical Vigilance Test (AVT). A visual analog scale (VAS) was used for self-assessing

drowsiness by the participants. The effect of fexofenadine on cognitive skills important for pilots was found to be comparable to placebo as evaluated by AVT errors. In contrast, cetirizine impaired cognition and could affect the piloting ability. However, no increase in drowsiness was observed in fexofenadine and cetirizine groups compared with placebo<sup>40</sup>.

A study involving 24 healthy volunteers used a randomized, double-blind, placebo-controlled, six-way, crossover design to investigate the effects of fexofenadine at doses of 80, 120, and 180 mg. The study found no significant differences in CFF, CRT, and subjective sedation assessment using line analog rating scales for sedation (LARS) between the fexofenadine-treated group and the placebo group. Additionally, participants did not show any subjective or objective impacts on psychomotor performance, after the administration of fexofenadine at all three tested doses<sup>8</sup>.

A randomized, double-blind, crossover study examined the single doses of second-generation antihistamines, fexofenadine (120 mg), and olopatadine (10 mg) for their acute effects on the cognitive and psychomotor performance. The study included 11 healthy Japanese volunteers and compared the effects of fexofenadine and olopatadine with placebo and d-chlorpheniramine (4 mg) on both objective and subjective assessments. No disruption in psychomotor dysfunction was observed when fexofenadine was administered at its regular daily dose. Additionally, the results indicated that fexofenadine had a distinct profile compared to olopatadine, as olopatadine affected behavioral activity. Overall data suggest that fexofenadine is potentially more suitable for individuals who need to maintain mental alertness during tasks or activities<sup>41</sup>.

A placebo-controlled, double-blind, crossover study, compared the clinical efficacy of a first-generation antihistamine, promethazine, and second-generation antihistamines, fexofenadine and olopatadine, based on their potential as peripheral inhibitors of histamine-induced wheal and flare in 24 healthy volunteers. Their sedative effects on the CNS were tested using a battery of psychometric tests. Fexofenadine did not have any significant effect on any of the psychomotor tests. These tests included CFF, CRT, compensatory tracking, rapid visual information processing, and a line analog rating scale for subjective evaluation of sedation. Wrist actigraphy showed no effect of fexofenadine on the behavioral activity. Fexofenadine and olopatadine showed significantly different inhibitory effects from those of the placebo on wheals and similar on flares<sup>42</sup>. A significant reduction in the wheal-and-flare responses induced by histamine was observed at single therapeutic dosages of all the antihistamines.

A randomized, double-blind, placebo-controlled, three-way, crossover study focused on additive effects that use of cellular phones could have on driving performance in antihistamine-taking individuals showed, no significant difference in Brake Reaction Time (BRT) with fexofenadine compared to placebo in four different tested conditions: while only driving, completing simple and complex calculations while driving, and conversing on a cellular phone while driving (Table 3), of course it is not recommended to use phone when driving<sup>43</sup>.

The danger related to the use of cellular phone while driving has been well documented, and these studies showed that with increasing cellular phone use, there was a drastic increase in car accidents<sup>52-55</sup>. Therefore, although this study supports the non-sedative potential of fexofenadine, but above data strongly give a message for not using mobile phones while driving.

In a double-blind, randomized, crossover study conducted by Gupta et al.<sup>44</sup>, involving 10 healthy adult volunteers, fexofenadine at doses of 120 mg did not show any significant differences compared to placebo in both subjective and objective tests. These measures included simple reaction time, multiple-choice reaction time task, critical flicker fusion frequency threshold, Stanford Sleepiness Scale, digit cancellation task, digit symbol substitution task, and mental arithmetic tests. Fexofenadine 120 mg did not cause any impairment in psychomotor function and did not differ from placebo in any test used<sup>44</sup>.

The effect of fexofenadine on modulation of daytime sleepiness or performance was studied in a placebo-controlled, double-blind trial with a six-way crossover design with six healthy volunteers. Fexofenadine did not cause any changes in the performance or sleepiness at any of the doses used (120, 180, and 240 mg) at any time compared to placebo<sup>45</sup>.

The Test of Variables of Attention (TOVA) is a continuous performance test that is used for measuring the speed and accuracy of attentional processing. TOVA was used to evaluate the effect of 180 mg fexofenadine and 50 mg diphenhydramine on the cognitive performance of 42 participants. This study also ascertained whether TOVA was sensitive enough to differentiate between the effects of first- and second-generation antihistamines on cognitive performance. Fexofenadine did not show any significant effect of TOVA measures of performance as well as no self-reported drowsiness compared to placebo<sup>46</sup>. Increased response time ( $p=0.0230$ ) and more omission errors ( $p=0.0398$ ) were observed in participants administered with diphenhydramine and this drug also led to increased drowsiness VAS ratings ( $p=0.0065$ ) compared to placebo. More commission errors were observed in participants treated with diphenhydramine than fexofenadine ( $p=0.0354$ ).

Genetic variations might affect the drug responses<sup>56</sup>. A randomized, crossover, double-blind study was performed in 24 Japanese volunteers with a hypothesis that genetic variations might attenuate the lack of effect of fexofenadine on CNS. Participants received single doses of 60-mg and 120 mg fexofenadine, 25 mg promethazine, and placebo, with a washout period of 6 days between treatments. Fexofenadine did not differ significantly from placebo in any of the objective measures, including CFF, CRT, and CTT. No negative cognitive or psychomotor effects were observed in any of the tests conducted with both the doses of fexofenadine in Japanese participants. Promethazine 25 mg showed noticeable sedative effects from 2 h after it was administered in the participants, and significant disruption of CFF, CRT, and CTT performance continued the whole test day. After 4 h of dosing, profound impairment was generally observed<sup>47</sup>.



Table 3. List of studies with fexofenadine assessing sedation and CNS function.

Study reference	Test drug	Comparator	Design	Objective	Findings
Ridout et al. 2003 <sup>37</sup>	Fexofenadine 180 mg	Placebo, all alone and with alcohol	Randomized, double-blind, placebo-controlled, six-way, crossover study	To measure acute effects of fexofenadine 180 mg, with and without a "social" dose of alcohol	Fexofenadine 180 mg: No disruptive effects on objective measures related to car driving/ aspects of psychomotor and cognitive function, even in combination with alcohol
Boyle et al. 2006 <sup>38</sup>	Fexofenadine 120 mg and chlorpheniramine 6 mg	Placebo	Randomized, single-site, double-blind, three-way, crossover study	To evaluate the acute effects of two histamine H1-receptor antagonists on: 1) nocturnal sleep architecture 2) Next day cognitive function and psychomotor performance	1) One nocturnal dose of fexofenadine advantageous over first-generation antihistamine chlorpheniramine 2) Free from disruption of nighttime sleep and detrimental effects on cognitive performance next day
Inami et al. 2016 <sup>39</sup>	Levocetirizine 5 mg	Fexofenadine (60 mg), diphenhydramine (50 mg), and placebo	Double-blind, placebo-controlled, four-way, crossover study	To evaluate the effects of levocetirizine 5 mg and fexofenadine 60 mg on car-driving performance	1) No significant differences between subjects administered fexofenadine and placebo 2) No impairment of psychomotor performance in subjects performing simulated car-driving tasks
Hindmarch et al. 1999 <sup>8</sup>	Fexofenadine (80, 120, and 180 mg) and loratadine (10 mg)	Promethazine (30 mg, as positive internal control) and placebo	Randomized, double-blind, placebo-controlled, six-way, crossover study	To evaluate disruptive effects of fexofenadine in a dose range of 80–180 mg on psychomotor and cognitive function if any	3) Car-driving test parameters not significantly affected with levocetirizine 5 mg 4) Subjects receiving diphenhydramine significantly impaired the LT compared to placebo
Vacciano et al. 2008 <sup>40</sup>	Fexofenadine	Placebo (passive control) and cetirizine (active control)	Randomized, double-blind, single-center, three period, crossover study	To evaluate cognitive effects of fexofenadine in healthy naval flight personnel	No subjective or objective effects on psychomotor performance with fexofenadine
Hindmarch et al. 2002 <sup>30</sup>	Fexofenadine (360 mg)	Placebo and promethazine (30 mg)	Randomized, double-blind, placebo-controlled, three-way, crossover study	To evaluate the acute effect of fexofenadine (360 mg) on various aspects of cognitive and psychomotor functions	Fexofenadine comparable to placebo in affecting cognitive skills important for piloting an aircraft
Kamei et al. 2003 <sup>41</sup>	Fexofenadine, (120 mg daily) and olopatadine (10 mg daily)	Placebo and d-chlorpheniramine, 4 mg: half daily dose	Randomized, double-blind, placebo-controlled, crossover study	To evaluate the effects of fexofenadine and olopatadine on psychomotor and cognitive function in Japanese healthy volunteers	No subjective or objective effects on psychomotor performance after fexofenadine administration 1) No sedative effects of fexofenadine on psychomotor performance
Kamei et al. 2012 <sup>42</sup>	Fexofenadine (60 mg), olopatadine (5 mg), and promethazine (25 mg); daily dose	Placebo	Randomized, double-blind, placebo-controlled, crossover study	To evaluate the sedative effect of test drugs on CNS	2) CNS profile of fexofenadine was different from olopatadine No cognitive or psychomotor impairment by fexofenadine
Tashiro et al. 2005 <sup>43</sup>	Fexofenadine (120 mg)	Hydroxyzine HCl (30 mg) and placebo	Randomized, double-blind, placebo-controlled, three-way, crossover study	To evaluate: 1) Sedative effect of antihistamine on driving performance Whether cellular phone operation while driving would compound the impairing effect	Hydroxyzine-treated subjects were significantly more sedated with slower brake reaction time compared with subjects administered fexofenadine or placebo in all test conditions
Gupta et al. 2004 <sup>44</sup>	Fexofenadine	Cetirizine, diphenhydramine, and placebo	Randomized double-blind, crossover study	To evaluate the effect of fexofenadine on psychomotor performance and comparison with cetirizine	1) No impairment effect of fexofenadine on psychomotor function 2) Cetirizine was mildly sedating without impairment of objective psychometric tests
Nicholson et al. 2000 <sup>45</sup>	Fexofenadine (120, 180, and 240 mg)	Promethazine (active control) and placebo	Double-blind, six-way, crossover study	To assess the effects of fexofenadine at various doses on digit symbol substitution, tracking, and vigilance tasks, and on objective and subjective sleepiness in healthy volunteers	No changes in performance or sleepiness at any dose of fexofenadine at any time compared with placebo
Mansfield et al. 2003 <sup>46</sup>		Placebo		To evaluate the effect of fexofenadine on cognitive performance using TOVA	

(continued)

Table 3. Continued.

Study reference	Test drug	Comparator	Design	Objective	Findings
Ridout and Hindmarch 2003 <sup>47</sup>	Fexofenadine (180 mg) and diphenhydramine (50 mg) Fexofenadine (60 and 120 mg) and promethazine (25 mg)	Placebo	Randomized, double-blind, placebo-controlled, crossover study Randomized, double-blind, crossover study	To: 1) Compare pharmacodynamics of fexofenadine and promethazine with placebo in Japanese volunteers 2) Assess whether genetic variations might attenuate lack of CNS effects of fexofenadine, diphenhydramine, alcohol, and placebo on driving performance	No significant effect of fexofenadine 180 mg on the TOVA measures of performance or on self-reported drowsiness compared to placebo No negative cognitive or psychomotor effects of fexofenadine 60 and 120 mg in Japanese volunteers  1) Similar performance by drivers when treated with fexofenadine or placebo 2) After alcohol use, overall performance was disturbed 3) After diphenhydramine, driving performance was poorest 1) Both doses of fexofenadine were non-sedative 2) Combined incidences of drowsiness were 9% with cetirizine and 4% with placebo ( $P = 0.07$ ) or fexofenadine ( $P = 0.02$ ) Fexofenadine was safe and non-sedative at all doses
Weiler et al. 2000 <sup>20</sup>	Fexofenadine (60 mg), diphenhydramine (50 mg), and alcohol (approximately 0.1% blood alcohol concentration)	Placebo	Randomized, double-blind, double-dummy, four-treatment, four-period, crossover study, including 40 licensed drivers with seasonal allergic rhinitis	To compare the effects of fexofenadine, diphenhydramine, alcohol, and placebo on driving performance	
Howarth et al. 1999 <sup>48</sup>	Fexofenadine (120 or 180 mg once daily) and cetirizine (10 mg once daily) (active control)	Placebo	Double-blind, parallel-group, placebo-controlled trial	To compare efficacy and safety of fexofenadine (120 and 180 mg once daily) and cetirizine (10 mg once daily) in the treatment of SAR	
Bernstein et al. 1997 <sup>49</sup>	Fexofenadine (60, 120, and 240 mg bid doses)	Placebo	Multicenter, 14-day, placebo-controlled, double-blind trial, including ragweed SAR patients	To assess the efficacy and safety of fexofenadine in the treatment of ragweed SAR	
Tanner et al. 1999 <sup>50</sup>	Fexofenadine		Pooled analysis of two multicenter, placebo-controlled, double-blind, randomized studies	To assess safety and efficacy of fexofenadine in a subset of children suffering from seasonal allergic rhinitis	Significant reductions in classroom time missed and overall classroom impairment compared with placebo at Week 1 ( $P \leq 0.05$ )
Meltzer et al. 2004 <sup>51</sup>	Included studies evaluated fexofenadine HCl 30 mg bid; two studies used fexofenadine at 15 and 60 mg bid		Pooled data from three, randomized, double-blind, placebo-controlled, parallel-group, 2-week trials in children (6–11 years) with SAR	To assess safety and efficacy of fexofenadine in children suffering from seasonal allergic rhinitis	1) Dose of fexofenadine up to 60 mg bid was found to be safe and non-sedating 2) No drowsiness reported

CNS, central nervous system; LT, lateral tracking; SAR, seasonal allergic rhinitis; TOVA, Test of Variables of Attention.

A systematic review and meta-analysis included various first- and second-generation antihistamines used worldwide for evaluating the effects and safety of fexofenadine. A total of 51 RCTs of 14,551 participants comparing the adverse events and sedative and cognitive functions impairment caused by antihistamines or placebo for healthy individuals and allergic patients were included in the study. In comparison with placebo, fexofenadine was found to produce the most significant antihistaminic potential. The sedative effect and the cognitive/psychomotor impairment of fexofenadine were found to be similar to that of placebo and were recommended for safety-related workers<sup>57</sup>.

Since fexofenadine has proven efficacy in seasonal allergic rhinitis (SAR)<sup>48,49,58</sup> cedar pollinosis, and other allergic conditions, various studies including patients with these ailments also supported the non-sedative nature and safety of fexofenadine. In a randomized, double-blind, double-dummy, four-treatment, four-period, crossover trial, effects of fexofenadine, diphenhydramine, alcohol, and placebo was assessed on the driving performance of 40 licensed drivers with SAR. Coherence and the capability of the drivers to match the changing speed of a vehicle followed by them was measured as the primary endpoint. Drowsiness along with other measures of driving such as keeping vehicle within the lane and

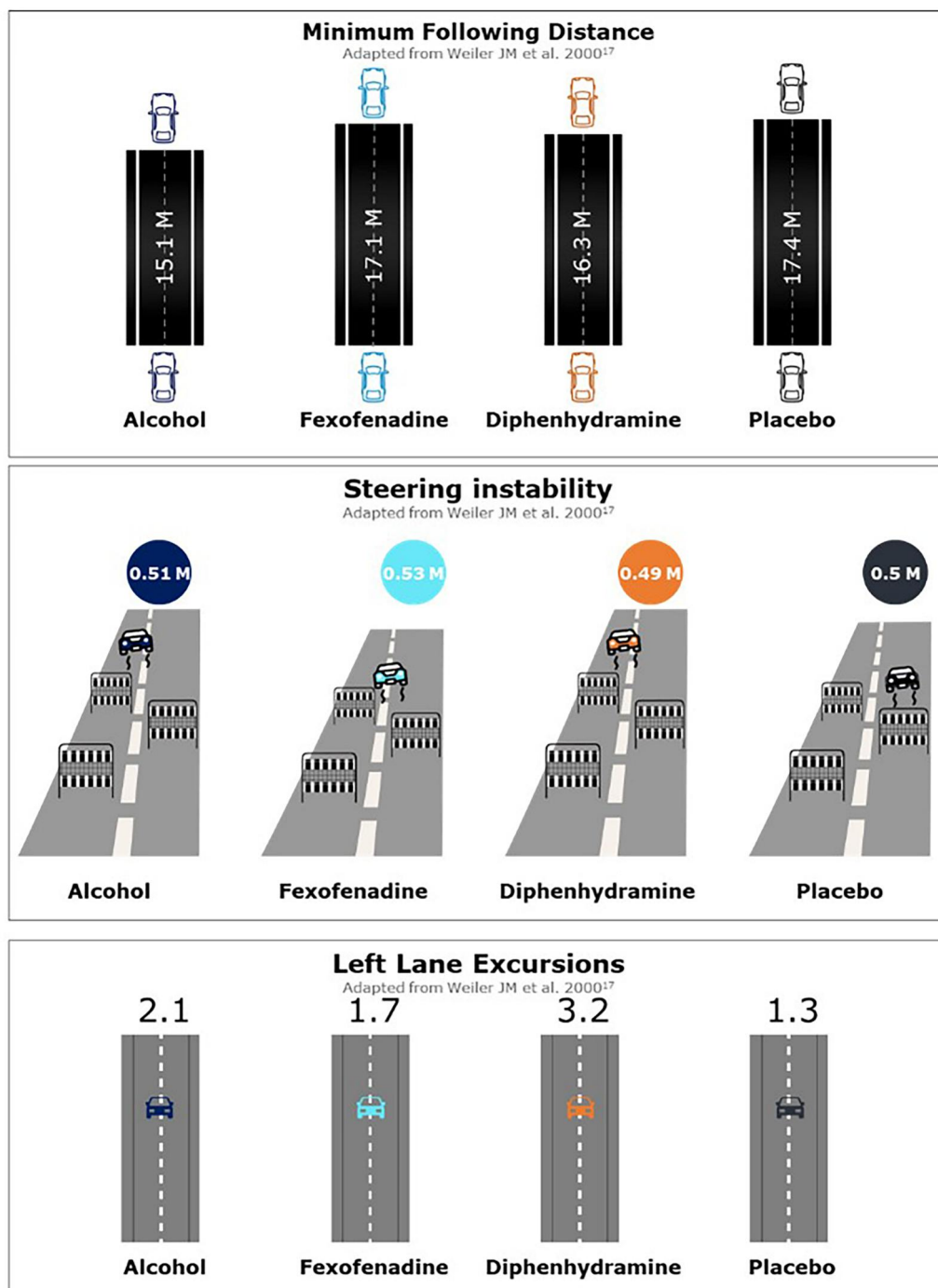


Figure 2. Driving performance measures: Alcohol vs Fexofenadine vs Diphenhydramine vs Placebo.

response required for a vehicle that suddenly blocked the lane ahead were recorded as secondary endpoints. Participants in the alcohol or fexofenadine group had better coherence than those in the diphenhydramine group. Lane-keeping (crossing the center line and steering instability) was impaired in the alcohol and diphenhydramine groups compared to the fexofenadine group. Similar performance was observed in participants treated with fexofenadine or placebo, suggesting that fexofenadine does not cause performance impairment while driving<sup>20</sup>. Figure 2 summarizes some evidence showing the non-sedative property of fexofenadine based on the driving performance test.

Two doses of fexofenadine HCl (120 and 180 mg once a day) were compared with cetirizine (10 mg once a day) for the treatment of SAR in patients (12–65 years old) in a multicenter, double-blind, parallel-group, placebo-controlled trial. Both doses of fexofenadine were found to be better than placebo in reducing SAR symptoms. The combined incidences of drowsiness or fatigue were similar to placebo (4%) and less than that of cetirizine (9%)<sup>48</sup>.

A 14-day, multicenter, double-blind, placebo-controlled trial including 517 patients who were suffering from moderate to severe ragweed SAR was conducted for evaluating the safety and efficacy along with dose–response relationship of fexofenadine HCl at doses 60, 120, and 240 mg bid. No sedative effect was observed in patients with these doses of fexofenadine<sup>49</sup>.

Mann et al.<sup>58</sup> investigated the frequency of sedative events reported for four second-generation drugs: loratadine, cetirizine, fexofenadine, and acrivastine, using post-marketing surveillance studies. Data were obtained for a total of 43,363 patients. After adjusting odd ratios for age and sex, the rate of sedation was calculated to be 0.63 (95% CI: 0.36–1.11;  $p = 0.1$ ) for fexofenadine; 2.79 (1.69–4.58;  $p < 0.0001$ ) for acrivastine, and 3.53 for loratadine. Overall, this study suggested fexofenadine is more appropriate for individuals with job requirement of critical safety<sup>58</sup>.

A pooled analysis was conducted by Tanner et al.<sup>50</sup> for two multicenter, placebo-controlled, double-blind, randomized studies to assess the effect of fexofenadine on QoL in 1498 patients suffering from SAR. One study including a subset of school-aged children showed significant reductions in missed classroom time and overall classroom impairment with fexofenadine compared with placebo at Week 1 ( $p \leq 0.05$ ); patients on fexofenadine also showed significant reductions in the impairment of work, overall performance impairment, along with reduced impairment of daily activities than placebo recipients<sup>50</sup>.

Pooled data from three, randomized, double-blind, placebo-controlled, parallel-group, 2-week trials in children (6–11 years) with SAR were taken to assess the safety of fexofenadine in children. It was found that fexofenadine HCl at doses of 15, 30, and 60 mg bid was safe and non-sedating and its dose of 30 mg bid could effectively reduce all symptoms of SAR in children<sup>51</sup>.

Supraclinical dosage of fexofenadine (360 mg) was assessed in a 3-way, crossover, double-blind study wherein various aspects of cognitive and psychomotor impairment

were compared between fexofenadine, placebo, and promethazine was used as positive internal control. Fifteen healthy volunteers received fexofenadine 360 mg, promethazine 30 mg, and placebo. CFF, CRT, and CTT tests were done for objective assessment and LARS for subjective assessment. Fexofenadine showed similar results for all the objective and subjective tests as placebo for up to 7 h of drug administration. On the contrary, all the measures assessed were impaired significantly in the group treated with promethazine, confirming the test battery sensitivity for sedation. Findings of this study clearly showed that fexofenadine was non-sedative even at three times the usual SAR dose (off-label dosage) and double the dose which is recommended for chronic idiopathic urticaria<sup>30</sup>.

In view of the evidence that fexofenadine is non-sedative, an expert consensus in the United States of America recommended to the National Aeronautics and Space Administration (NASA) that pilots can use fexofenadine, if necessary<sup>59</sup>. All the clinical studies discussed so far have been summarized in Table 3.

## Conclusion

H1-antihistamines are essential for managing allergic conditions such as SAR, PAR, and urticaria. Antihistamines are basically classified as first-generation and second-generation antihistamines. First-generation antihistamines are known for their sedative side effects, including drowsiness, impaired cognitive functions and psychomotor performance, and fatigue. Due to these drawbacks, second-generation antihistamines were developed as a less sedative alternative. However, not all second-generation antihistamines are free from sedative effects, making it important to choose those that do not impair cognitive function. Fexofenadine is a non-sedating, second-generation antihistamine that selectively inhibits peripheral H1-receptors and does not penetrate the BBB, due to its affinity for P-glycoprotein. P-glycoprotein, expressed in the BBB functions as an efflux pump and helps minimize its impact on the CNS, thereby reducing sedation. One of the indices used to classify antihistamines into non-sedating, less sedating, and sedating groups is H<sub>1</sub>RO. Results from studies that calculated subjective and objective PIR values for fexofenadine showed it as impairment free.

Studies including CFF, CRT, CTT, and BRT conducted in healthy individuals using these parameters have shown the non-sedative potential of fexofenadine. Further, observation based on results from various clinical studies also showed that fexofenadine is one of the best options among available antihistamines in terms of non-sedating properties. The studies conducted for evaluating the efficacy and sedative property of fexofenadine in children found that fexofenadine could not only improve the disease condition but also had a subsequent effect on QoL. It did not display sedative properties in children even at higher doses (higher doses are off-label). Moreover, it was also not found to be associated with impairment in any cognitive/academic performance or objective/subjective performance. Fexofenadine was also

found not to increase sleep latencies or affect the next day activities in individuals taking it.

Overall published data indicates that among all available oral antihistamines, fexofenadine is the only drug that does not cause impairment of cognitive and psychomotor function as demonstrated in controlled clinical studies.

## Transparency

### Declaration of funding

This work was funded by Sanofi.

### Declaration of financial/other relationships

**IJA** received personal fees from Abbott, Bayer, Bial, Eurodrug, Faes Farma, Gebro, Menarini, MSD, Organon, Roxall, and Sanofi. **JB** reported personal fees from Cipla, Menarini, Mylan, Novartis, Purina, Sanofi-Aventis, Teva, and Uriach; a shareholder in KYomed INNOV and MASK-air-SAS. **PD** received grants from Viatrix, AstraZeneca, Thermo Fischer Scientific, and GSK; consulting fees from ALK, Viatrix, Stallergènes Greer, Thermo Fischer Scientific, and Menarini; payment for honoraria for lecture from Zambon; support for attending meetings from ALK and Stallergènes Greer. **RMG** received honoraria for lectures from Sanofi, Opella, GSK, and AbbVie; leadership or fiduciary role in Catholic University of Salta, Argentinean Association of Allergy/Clinical Immunology, Argentina, and World Allergy Organization. **EOM** received consulting fees from Church and Dwight, Hikma, and Sanofi; honoraria from Optinose, Regeneron, Glenmark, and Merck; support for attending meetings from Optinose and Hikma; participated in data monitoring board for Gossamer Bio and Bristol Myers Squibb. **MM-A** is an employee of Sanofi and may hold shares or stock options in the company. **RMN** received consulting fees from Sanofi and Lyra; payment for honoraria for lectures from Regeneron. **NRF** received payment for honoraria for lectures from AbbVie, Novartis, AstraZeneca, Sanofi, Chiesi, and Viatrix; support for attending meetings from AstraZeneca; participated in an advisory board for Glenmark and Sanofi. **GKS** received honoraria from ALK, AstraZeneca, Britannia Pharmaceuticals, Capnia, Church & Dwight, Circassia, Grupo Uriach, GSK, Meda/Mylan/Viatrix, Merck, MSD, Noucor, Ono Pharmaceuticals, Oxford Therapeutics, Sanofi-Aventis, Stallergenes, UCB; travel funding from ALK, Bayer, GSK, Meda; scientific editor for Rhinology Section, Frontiers in Allergy and vice president and lead for Allergic Rhinitis, EUFORJA journals. **GWC** did not have any conflict of interest for the present work.

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

### Author contributions

All authors were involved in the conception of the work and critically revising the manuscript, and take full accountability for the work, for all content, and editorial decisions. All authors approved the final version to be published.

### Acknowledgements

Pragya Misra, PhD, and Sambasiva Kolati, M.S. Pharm from Sanofi provided medical writing and editorial support for this manuscript, respectively.

## References

- [1] Meltzer EO, Rosario NA, Van Bever H, et al. Fexofenadine: review of safety, efficacy and unmet needs in children with allergic

- rhinitis. *Allergy Asthma Clin Immunol.* 2021;17(1):113. doi: [10.1186/s13223-021-00614-6](https://doi.org/10.1186/s13223-021-00614-6).
- [2] Kawauchi H, Yanai K, Wang DY, et al. Antihistamines for allergic rhinitis treatment from the viewpoint of non-sedative properties. *Int J Mol Sci.* 2019;20(1):213.
- [3] Juniper EF, Ståhl E, Doty RL, et al. Clinical outcomes and adverse effect monitoring in allergic rhinitis. *J Allergy Clin Immunol.* 2005; 115(3 Suppl 1):390–413. doi: [10.1016/j.jaci.2004.12.014](https://doi.org/10.1016/j.jaci.2004.12.014).
- [4] Conboy-Ellis K. Management of seasonal allergic rhinitis: comparative efficacy of the newer-generation prescription antihistamines. *J Am Acad Nurse Pract.* 2005;17(8):295–301. doi: [10.1111/j.1745-7599.2005.0050.x](https://doi.org/10.1111/j.1745-7599.2005.0050.x).
- [5] Baena-Cagnani CE. Safety and tolerability of treatments for allergic rhinitis in children. *Drug Saf.* 2004;27(12):883–898. doi: [10.2165/00002018-200427120-00005](https://doi.org/10.2165/00002018-200427120-00005).
- [6] Druce HM, Thoden WR, Mure P, et al. Brompheniramine, loratadine, and placebo in allergic rhinitis: a placebo-controlled comparative clinical trial. *J Clin Pharmacol.* 1998;38(4):382–389. doi: [10.1002/j.1552-4604.1998.tb04439.x](https://doi.org/10.1002/j.1552-4604.1998.tb04439.x).
- [7] Church MK, Maurer M, Simons FER, et al. Risk of first-generation H(1)-antihistamines: a GA(2)LEN position paper. *Allergy.* 2010; 65(4):459–466. doi: [10.1111/j.1398-9995.2009.02325.x](https://doi.org/10.1111/j.1398-9995.2009.02325.x).
- [8] Hindmarch I, Shamsi Z, Stanley N, et al. A double-blind, placebo-controlled investigation of the effects of fexofenadine, loratadine and promethazine on cognitive and psychomotor function. *Br J Clin Pharmacol.* 1999;48(2):200–206. doi: [10.1046/j.1365-2125.1999.00993.x](https://doi.org/10.1046/j.1365-2125.1999.00993.x).
- [9] Hiraoka K, Tashiro M, Grobosch T, et al. Brain histamine H1 receptor occupancy measured by PET after oral administration of levocetirizine, a non-sedating antihistamine. *Expert Opin Drug Saf.* 2015;14(2):199–206. doi: [10.1517/14740338.2015.989831](https://doi.org/10.1517/14740338.2015.989831).
- [10] Yanai K, Zhang D, Tashiro M, et al. Positron emission tomography evaluation of sedative properties of antihistamines. *Expert Opin Drug Saf.* 2011;10(4):613–622. doi: [10.1517/14740338.2011.562889](https://doi.org/10.1517/14740338.2011.562889).
- [11] Tashiro M, Sakurada Y, Iwabuchi K, et al. Central effects of fexofenadine and cetirizine: measurement of psychomotor performance, subjective sleepiness, and brain histamine H1-receptor occupancy using 11C-doxepin positron emission tomography. *J Clin Pharmacol.* 2004;44(8):890–900. doi: [10.1177/0091270004267590](https://doi.org/10.1177/0091270004267590).
- [12] Hu Y, Sieck DE, Hsu WH. Why are second-generation H1-antihistamines minimally sedating? *Eur J Pharmacol.* 2015;765:100–106. doi: [10.1016/j.ejphar.2015.08.016](https://doi.org/10.1016/j.ejphar.2015.08.016).
- [13] Smith SM, Gums JG. Fexofenadine: biochemical, pharmacokinetic and pharmacodynamic properties and its unique role in allergic disorders. *Expert Opin Drug Metab Toxicol.* 2009;5(7):813–822. doi: [10.1517/17425250903044967](https://doi.org/10.1517/17425250903044967).
- [14] Simpson K, Jarvis B. Fexofenadine: a review of its use in the management of seasonal allergic rhinitis and chronic idiopathic urticaria. *Drugs.* 2000;59(2):301–321. doi: [10.2165/00003495-200059020-00020](https://doi.org/10.2165/00003495-200059020-00020).
- [15] Simons FE, Simons KJ. Histamine and H1-antihistamines: celebrating a century of progress. *J Allergy Clin Immunol.* 2011;128(6): 1139–1150 e4. doi: [10.1016/j.jaci.2011.09.005](https://doi.org/10.1016/j.jaci.2011.09.005).
- [16] Shamsi Z, Hindmarch I. Sedation and antihistamines: a review of inter-drug differences using proportional impairment ratios. *Hum Psychopharmacol Clin Exp.* 2000;15(5):S3–S30. doi: [10.1002/1099-1077\(200010\)15:1+<::AID-HUP247>3.0.CO;2-S](https://doi.org/10.1002/1099-1077(200010)15:1+<::AID-HUP247>3.0.CO;2-S).
- [17] McDonald K, Trick L, Boyle J. Sedation and antihistamines: an update. Review of inter-drug differences using proportional impairment ratios. *Hum Psychopharmacol.* 2008;23(7):555–570. doi: [10.1002/hup.962](https://doi.org/10.1002/hup.962).
- [18] Isomura T, Kono T, Hindmarch I, et al. Central nervous system effects of the second-generation antihistamines marketed in Japan—review of inter-drug differences using the proportional impairment ratio (PIR). *PLoS One.* 2014;9(12):e114336. doi: [10.1371/journal.pone.0114336](https://doi.org/10.1371/journal.pone.0114336).
- [19] McWhirter D, Bae C, Budur K. The assessment, diagnosis, and treatment of excessive sleepiness: practical considerations for the psychiatrist. *Psychiatry (Edgmont).* 2007;4(9):26–35.
- [20] Weiler JM, Bloomfield JR, Woodworth GG, et al. Effects of fexofenadine, diphenhydramine, and alcohol on driving performance. *A*

- randomized, placebo-controlled trial in the Iowa driving simulator. *Ann Intern Med.* 2000;132(5):354–363. doi: [10.7326/0003-4819-132-5-200003070-00004](https://doi.org/10.7326/0003-4819-132-5-200003070-00004).
- [21] Ramsay MA, Savege TM, Simpson BR, et al. Controlled sedation with alphaxalone-alphadolone. *Br Med J.* 1974;2(5920):656–659. doi: [10.1136/bmj.2.5920.656](https://doi.org/10.1136/bmj.2.5920.656).
- [22] Hansen-Flaschen J, Cowen J, Polomano RC. Beyond the Ramsay scale: need for a validated measure of sedating drug efficacy in the intensive care unit. *Crit Care Med.* 1994;22(5):732–733.
- [23] Riker RR, Fraser GL, Cox PM. Continuous infusion of haloperidol controls agitation in critically ill patients. *Crit Care Med.* 1994;22(3):433–440. doi: [10.1097/00003246-199403000-00013](https://doi.org/10.1097/00003246-199403000-00013).
- [24] Waldmann C. Using and understanding sedation scoring systems. *JICS.* 2010;11:15–16.
- [25] Devlin JW, Boleski G, Mlynarek M, et al. Motor Activity Assessment Scale: a valid and reliable sedation scale for use with mechanically ventilated patients in an adult surgical intensive care unit. *Crit Care Med.* 1999;27(7):1271–1275. doi: [10.1097/00003246-199907000-00008](https://doi.org/10.1097/00003246-199907000-00008).
- [26] Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med.* 2002;166(10):1338–1344. doi: [10.1164/rccm.2107138](https://doi.org/10.1164/rccm.2107138).
- [27] De Jonghe B, Cook D, Griffith L, et al. Adaptation to the Intensive Care Environment (ATICE): development and validation of a new sedation assessment instrument. *Crit Care Med.* 2003;31(9):2344–2354. doi: [10.1097/01.CCM.0000084850.16444.94](https://doi.org/10.1097/01.CCM.0000084850.16444.94).
- [28] Holgate ST, Canonica GW, Simons FER, et al. Consensus Group on New-Generation Antihistamines (CONGA): present status and recommendations. *Clin Exp Allergy.* 2003;33(9):1305–1324. doi: [10.1046/j.1365-2222.2003.01769.x](https://doi.org/10.1046/j.1365-2222.2003.01769.x).
- [29] Yanai K, Yoshikawa T, Yanai A, et al. The clinical pharmacology of non-sedating antihistamines. *Pharmacol Ther.* 2017;178:148–156. doi: [10.1016/j.pharmthera.2017.04.004](https://doi.org/10.1016/j.pharmthera.2017.04.004).
- [30] Hindmarch I, Shamsi Z, Kimber S. An evaluation of the effects of high-dose fexofenadine on the central nervous system: a double-blind, placebo-controlled study in healthy volunteers. *Clin Exp Allergy.* 2002;32(1):133–139. doi: [10.1046/j.0022-0477.2001.01245.x](https://doi.org/10.1046/j.0022-0477.2001.01245.x).
- [31] Hindmarch I. Comparing the safety consequences of newer antihistamines. *Adv Stud Med.* 2004;4(7):S501–S507.
- [32] Tagawa M, Kano M, Okamura N, et al. Neuroimaging of histamine H1-receptor occupancy in human brain by positron emission tomography (PET): a comparative study of ebastine, a second-generation antihistamine, and (+)-chlorpheniramine, a classical antihistamine. *Br J Clin Pharmacol.* 2001;52(5):501–509. doi: [10.1046/j.1365-2125.2001.01471.x](https://doi.org/10.1046/j.1365-2125.2001.01471.x).
- [33] Tashiro M, Duan X, Kato M, et al. Brain histamine H1 receptor occupancy of orally administered antihistamines, bepotastine and diphenhydramine, measured by PET with <sup>11</sup>C-doxepin. *Br J Clin Pharmacol.* 2008;65(6):811–821. doi: [10.1111/j.1365-2125.2008.03143.x](https://doi.org/10.1111/j.1365-2125.2008.03143.x).
- [34] Tashiro M, Kato M, Miyake M, et al. Dose dependency of brain histamine H(1) receptor occupancy following oral administration of cetirizine hydrochloride measured using PET with [<sup>11</sup>C]doxepin. *Hum Psychopharmacol.* 2009;24(7):540–548. doi: [10.1002/hup.1051](https://doi.org/10.1002/hup.1051).
- [35] Tashiro M, Mochizuki H, Sakurada Y, et al. Brain histamine H receptor occupancy of orally administered antihistamines measured by positron emission tomography with (<sup>11</sup>C)-doxepin in a placebo-controlled crossover study design in healthy subjects: a comparison of olopatadine and ketotifen. *Br J Clin Pharmacol.* 2006;61(1):16–26. doi: [10.1111/j.1365-2125.2005.02514.x](https://doi.org/10.1111/j.1365-2125.2005.02514.x).
- [36] Zhang D, Tashiro M, Shibuya K, et al. Next-day residual sedative effect after nighttime administration of an over-the-counter antihistamine sleep aid, diphenhydramine, measured by positron emission tomography. *J Clin Psychopharmacol.* 2010;30(6):694–701. doi: [10.1097/jcp.0b013e3181fa8526](https://doi.org/10.1097/jcp.0b013e3181fa8526).
- [37] Ridout F, Shamsi Z, Meadows R, et al. A single-center, randomized, double-blind, placebo-controlled, crossover investigation of the effects of fexofenadine hydrochloride 180 mg alone and with alcohol, with hydroxyzine hydrochloride 50 mg as a positive internal control, on aspects of cognitive and psychomotor function related to driving a car. *Clin Ther.* 2003;25(5):1518–1538. doi: [10.1016/s0149-2918\(03\)80137-6](https://doi.org/10.1016/s0149-2918(03)80137-6).
- [38] Boyle J, Eriksson M, Stanley N, et al. Allergy medication in Japanese volunteers: treatment effect of single doses on nocturnal sleep architecture and next day residual effects. *Curr Med Res Opin.* 2006;22(7):1343–1351. doi: [10.1185/030079906X112660](https://doi.org/10.1185/030079906X112660).
- [39] Inami A, Matsuda R, Grobosch T, et al. A simulated car-driving study on the effects of acute administration of levocetirizine, fexofenadine, and diphenhydramine in healthy Japanese volunteers. *Hum Psychopharmacol.* 2016;31(3):167–177. doi: [10.1002/hup.2524](https://doi.org/10.1002/hup.2524).
- [40] Vacchiano C, Moore J, Rice GM, et al. Fexofenadine effects on cognitive performance in aviators at ground level and simulated altitude. *Aviat Space Environ Med.* 2008;79(8):754–760. doi: [10.3357/asem.2212.2008](https://doi.org/10.3357/asem.2212.2008).
- [41] Kamei H, Noda Y, Ishikawa K, et al. Comparative study of acute effects of single doses of fexofenadine, olopatadine, d-chlorpheniramine and placebo on psychomotor function in healthy volunteers. *Hum Psychopharmacol.* 2003;18(8):611–618. doi: [10.1002/hup.538](https://doi.org/10.1002/hup.538).
- [42] Kamei H, Isaji A, Noda Y, et al. Effects of single therapeutic doses of promethazine, fexofenadine and olopatadine on psychomotor function and histamine-induced wheal- and flare-responses: a randomized double-blind, placebo-controlled study in healthy volunteers. *Arch Dermatol Res.* 2012;304(4):263–272. doi: [10.1007/s00403-011-1192-2](https://doi.org/10.1007/s00403-011-1192-2).
- [43] Tashiro M, Horikawa E, Mochizuki H, et al. Effects of fexofenadine and hydroxyzine on brake reaction time during car-driving with cellular phone use. *Hum Psychopharmacol.* 2005;20(7):501–509. doi: [10.1002/hup.713](https://doi.org/10.1002/hup.713).
- [44] Gupta S, Kapoor B, Gillani Z, et al. Effects of fexofenadine, cetirizine and diphenhydramine on psychomotor performance in adult healthy volunteer. *JK Sci.* 2004;6(4):201–205.
- [45] Nicholson AN, Stone BM, Turner C, et al. Antihistamines and air-crew: usefulness of fexofenadine. *Aviat Space Environ Med.* 2000;71(1):2–6.
- [46] Mansfield L, Mendoza C, Flores J, et al. Effects of fexofenadine, diphenhydramine, and placebo on performance of the test of variables of attention (TOVA). *Ann Allergy Asthma Immunol.* 2003;90(5):554–559. doi: [10.1016/S1081-1206\(10\)61850-9](https://doi.org/10.1016/S1081-1206(10)61850-9).
- [47] Ridout F, Hindmarch I. The effects of acute doses of fexofenadine, promethazine, and placebo on cognitive and psychomotor function in healthy Japanese volunteers. *Ann Allergy Asthma Immunol.* 2003;90(4):404–410. doi: [10.1016/S1081-1206\(10\)61824-8](https://doi.org/10.1016/S1081-1206(10)61824-8).
- [48] Howarth PH, Stern MA, Roi L, et al. Double-blind, placebo-controlled study comparing the efficacy and safety of fexofenadine hydrochloride (120 and 180 mg once daily) and cetirizine in seasonal allergic rhinitis. *J Allergy Clin Immunol.* 1999;104(5):927–933. doi: [10.1016/s0091-6749\(99\)70070-9](https://doi.org/10.1016/s0091-6749(99)70070-9).
- [49] Bernstein DI, Schoenwetter WF, Nathan RA, et al. Efficacy and safety of fexofenadine hydrochloride for treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol.* 1997;79(5):443–448. doi: [10.1016/S1081-1206\(10\)63041-4](https://doi.org/10.1016/S1081-1206(10)63041-4).
- [50] Tanner LA, Reilly M, Meltzer EO, et al. Effect of fexofenadine HCl on quality of life and work, classroom, and daily activity impairment in patients with seasonal allergic rhinitis. *Am J Managed Care.* 1999;5:S235–S247.
- [51] Meltzer EO, Scheinmann P, Rosado Pinto JE, et al. Safety and efficacy of oral fexofenadine in children with seasonal allergic rhinitis—a pooled analysis of three studies. *Pediatr Allergy Immunol.* 2004;15(3):253–260. doi: [10.1111/j.1399-3038.2004.00167.x](https://doi.org/10.1111/j.1399-3038.2004.00167.x).
- [52] De Jong MJ. Cellular telephone use while driving: growing awareness of the danger. *J Emerg Nurs.* 2003;29(6):578–581. doi: [10.1016/s0099-1767\(03\)00353-2](https://doi.org/10.1016/s0099-1767(03)00353-2).
- [53] Stutts J, Feaganes J, Rodgman E, et al. The causes and consequences of distraction in everyday driving. *Annu Proc Assoc Adv Automot Med.* 2003;47:235–251.
- [54] Johnson MB, Voas RB, Lacey JH, et al. Living dangerously: driver distraction at high speed. *Traffic Inj Prev.* 2004;5(1):1–7. doi: [10.1080/15389580490269047](https://doi.org/10.1080/15389580490269047).

- [55] Lesch MF, Hancock PA. Driving performance during concurrent cell-phone use: are drivers aware of their performance decrements? *Accid Anal Prev.* 2004;36(3):471–480. doi: [10.1016/S0001-4575\(03\)00042-3](https://doi.org/10.1016/S0001-4575(03)00042-3).
- [56] Urban TJ. Race, ethnicity, ancestry, and pharmacogenetics. *Mt Sinai J Med.* 2010;77(2):133–139. doi: [10.1002/msj.20168](https://doi.org/10.1002/msj.20168).
- [57] Huang CZ, Jiang ZH, Wang J, et al. Antihistamine effects and safety of fexofenadine: a systematic review and Meta-analysis of randomized controlled trials. *BMC Pharmacol Toxicol.* 2019;20(1):72. doi: [10.1186/s40360-019-0363-1](https://doi.org/10.1186/s40360-019-0363-1).
- [58] Mann RD, Pearce GL, Dunn N, et al. Sedation with “non-sedating” antihistamines: four prescription-event monitoring studies in general practice. *BMJ.* 2000;320(7243):1184–1186. doi: [10.1136/bmj.320.7243.1184](https://doi.org/10.1136/bmj.320.7243.1184).
- [59] DuBuske L. Pharmacokinetics/pharmacodynamics and psychomotor performance aspects of antihistamine therapies. *Clin Appl Immunol Rev.* 2001;1(5):277–289. doi: [10.1016/S1529-1049\(01\)00032-0](https://doi.org/10.1016/S1529-1049(01)00032-0).
- [60] Nakamura T, Hiraoka K, Harada R, et al. Brain histamine H1 receptor occupancy after oral administration of desloratadine and loratadine. *Pharmacol Res Perspect.* 2019;7(4):e00499. doi: [10.1002/prp2.499](https://doi.org/10.1002/prp2.499).
- [61] Kubo N, Senda M, Ohsumi Y, et al. Brain histamine H1 receptor occupancy of loratadine measured by positron emission tomography: comparison of H1 receptor occupancy and proportional impairment ratio. *Hum Psychopharmacol.* 2011;26(2):133–139. doi: [10.1002/hup.1184](https://doi.org/10.1002/hup.1184).
- [62] Farré M, Pérez-Mañá C, Papaseit E, et al. Bilastine vs. hydroxyzine: occupation of brain histamine H1 -receptors evaluated by positron emission tomography in healthy volunteers. *Br J Clin Pharmacol.* 2014;78(5):970–980. doi: [10.1111/bcp.12421](https://doi.org/10.1111/bcp.12421).
- [63] Yanai K, Ryu JH, Watanabe T, et al. Positron emission tomographic study of central histamine H1-receptor occupancy in human subjects treated with epinastine, a second-generation antihistamine. *Methods Find Exp Clin Pharmacol.* 1995;17 Suppl C:64–69.