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Efficacy and safety of fexofenadine in children with allergic rhinitis

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Allergic rhinitis is the most common undiagnosed chronic condition in children and negatively affects sleep, school performance and leisure activities. Intranasal corticosteroids and oral antihistamines are first-line treatments. The first generation of oral antihistamines is often used in children due to the cheaper costs, despite the high frequency of adverse events, like overall cognitive and psychomotor effects, which could increase the allergic rhinitis burden. A recent review by Meltzer et al. highlighted that second-generation antihistamines are effective and well tolerated in children with allergic rhinitis and are rated superior to first-generation antihistamines.

Allergic rhinitis (AR) has a prevalence of up to 40% in children, although it frequently goes unrecognized, and its prevalence appears to increase further. Additionally, untreated AR predisposes children to asthma and other chronic conditions [1]. Moderate to severe AR symptoms such as increased sneezing, mucus secretion, nasal itch and congestion, often accompanied by ocular symptoms can be troublesome by negatively affecting sleep, school performance, leisure activities and increasing absenteeism [2].

Intranasal corticosteroids and oral antihistamines are first-line pharmacological treatments of AR, with the latter often preferred in children based on ease of administration [2]. First-generation antihistamines are effective against many AR symptoms but because of poor selectivity for H_1 histamine receptors and penetration through the blood-brain-barrier (BBB) exhibit sedative, cardiovascular and/or anti-cholinergic side effects [3]. Particularly in children with AR, this often results in daytime fatigue, irritability, tiredness, inattention, reduced short-term memory and behavioral problems, significantly affecting learning and social activities. They are even not recommended to be administrated in the evening due to the hangover effect the following morning [4] as highlighted by Meltzer et al. in a recent review comparing the efficacy and safety of first and second-generation antihistamines in children with AR [5].

In the brain, histamine regulates sleep/wake behavior through binding to four distinct G protein-coupled histamine (H) receptors. Thus, histamine receptors blockers (antihistamines) used to treat AR symptoms may produce somnolence. Accordingly, excessive sleepiness is often an unwanted side effect of antihistamines [6], overall, from the first generation [5]. Fexofenadine is a second-generation non-sedating highly selective H_1-receptor antagonist, which does not cross the BBB, therefore cannot bind to H_1-receptors in the central nervous system [7]. The recommended doses of fexofenadine have demonstrated efficacy and safety in different clinical trials [5]. Moreover, it relieved ocular symptoms of allergic conjunctivitis that occur concomitantly with AR and mitigated the adverse impact of AR on quality of life.

The pharmacodynamic and pharmacokinetic profiles of fexofenadine translate into an absence of sedative effects and a lack of impaired concentration, memory, or performance across the approved dosage range (**Tab. 1**). Additionally, fexofenadine is not associated with any objective or subjective performance, or cognitive/academic impairments. Regarding drug-drug interactions, the coadministration of erythromycin or ketoconazole with fexofenadine results in increases in fexofenadine plasma concentrations; however, these increases remain within the safety margins provided by the wide therapeutic window of fexofenadine without any effects on the QT interval [8]. Moreover, fexofenadine has no dose-related effect on the corrected QT (QTc) interval with cardiovascular safety well established in children and adult patients even when used at higher than recommended doses. Overall, fexofenadine is well tolerated and displayed a good safety profile in children with AR, aged 6 months to 11 years and over.

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Tab. 1. Side effects of first- and second-generation antihistamines. Adapted with permission from [5].

	Antihistamines Class	
	First-generation	**Second-generation**
Central nervous system	Agitation, confusion, dystonia, dyskinesia, hallucinations, headache impairment in coordination, learning, memory, psychomotor and sensorimotor functions, and sedation	Variable (such as sedation with cetirizine) Minimal or no side effects with fexofenadine
Cardiovascular system	Dose-dependent sinus tachycardia, reflex tachycardia, atrial refractory period prolongation and supraventricular arrhythmias	No side effects
Toxic high dose	Severe CNS and cardiac side effects, may lead to death unless treated	No severe side effects or deaths reported

An international non-interventional study including 4581 children aged 2–12 years found that fexofenadine was associated with greater treatment satisfaction with respect to efficacy, tolerability and impact on sleep and school performance as compared to most other antihistamines [9].

In conclusion, the second-generation antihistamine fexofenadine combines effectiveness in the treatment of AR including concomitant ocular symptoms and with superior tolerability and safety as compared to first-generation compounds and does not display sedating effects.

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