


# No Time for Lullabies Tracing down Pharmacological Effects & Uses of H1-Antihistamines in Children Younger than 6 Years

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## Abstract

**Objectives.** To provide a qualitative and a quantitative analysis of H1-antihistamines pharmacological uses pattern among children (<6 years old) and to evaluate the parental-related awareness. **Methods.** A cross-sectional study was carried out at 5 retail pharmacies in Jordan over 5 months (October/2019-February/2020). Parents who requested any of H1-antihistamine agent for a child (<6 years) were invited to participate. **Results.** A total of 516 children, most of them were toddlers (1-3) years, received at least 1 H1-antihistamine. More than half of the cases received H1-antihistamine as self-medication (56.3%). Sedating antihistamine agents were the most frequently used among children (<6 years old) (77.9%) among which Chlorpheniramine maleate was the most commonly used agent (62.9%). About half of the children (47.0%) received H1-antihistamine to induce sleep. Whereas, 21.7% and 12.9% received them to manage flu, and allergic rhinitis (AR), respectively. Around 66.6% of the cases were classified as off-label use. Most of the parents (80.5%) were aware of the sedative adverse effects of H1-antihistamines, whereas a fewer number (31.9%) were aware of their cognitive effects. Finally, more than two thirds of parents (79.7%) were unfamiliar with off-label drug use in children. **Conclusion.** Despite the availability of less-sedating H1-antihistamines with a wide safety and efficacy record, the use of sedating H1-antihistamines remains popular in children.

## Keywords

H1-antihistamine, pharmacology, pediatrics, pharmacist, toxicity, off-label, Jordan

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## Introduction

Antihistamines usually refers to H1-receptor antagonists which interfere with H1-Histamine receptors, thereby reducing their activity and allergy severity.<sup>1</sup> H1-antihistamines are marketed for the treatment of allergy-based disease as “first-generation,” the sedating H1-antihistamines, such as chlorpheniramine maleate, promethazine, and dimethindene maleate or “second-generation” (the less-sedating antihistamines) such as cetirizine, levocetirizine, and loratadine.<sup>2,3</sup>

Self-medication among the child population is on the rise,<sup>4</sup> more obviously is the abuse of H1-antihistamines for the sedative effect is becoming more common place today. A study of 13426 patients (median age 8.7 years) revealed that half of the patients were prescribed H1-antihistamines in an off-label basis, mostly due to unlicensed age, creating health risks of toxicity, and failure of treatment.<sup>5</sup>

Many serious side effects of H1-antihistamine abuse especially the first generation “sedating antihistamine” were reported such as cognitive impairment<sup>6</sup> and psychomotor performance.<sup>7</sup> It was reported that students who were treated with sedating H1-antihistamines had poor school performance and learning capacity. In contrast, safety of less-sedating H1-antihistamines has been shown in large randomized clinical trials in adults and children.<sup>8</sup> Therefore, World Health Organization (WHO) launched an Initiative “Better Medicines for Children” with the goal of improving pediatric medicines research,

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**Table 1.** Summary of H1-Antihistamines Under Investigation.

H1-antihistamines	Lower age limit	Availability	Unit price**
Dimethindende maleate	2 years	OTC	2.5
Promethazine	2 years	POM	1.49
Chlorpheniramine maleate	2 years	OTC	1.41
Diphenhydramine	6 years	OTC	7.25
Loratadine	2 years	OTC	4
Desloratadine	12 months	POM	4
Cetirizine	2 years	POM	2.5
Levocetirizine	2 years	POM	5

The table comprises information according to Jordan Food & Drug Administration (JFDA).

Abbreviations: OTC, Over the counter; POM, prescribed-only medication.

\*\*(\$ price is described at the time of publication.

drug use rational and regulation in 2007.<sup>9</sup> On the other side, the U.S. Food and Drug Administration (FDA) and the American Academy of Pediatrics (AAP) released joint statements against the use of cough and cold products containing sedating H1-Antihistamines in children younger than 6 years due to safety concerns in 2008.<sup>10</sup>

The main objectives of this study are to provide a qualitative and a quantitative analysis H1-antihistamine use pattern among children (<6 years) in Jordan and to evaluate parental-related awareness.

## Methods

### Study Population and Data Collection Form

A cross-sectional study was carried out at 5 retail pharmacies in the north of Jordan (Irbid city) over 5 months (October/2019-February/2020). Parents/caregivers who requested any of H1-antihistamine agent listed in Jordan National Drug Formulary for a child (<6 years old) (Table 1) either providing a physician's prescription or as self-medicating were invited to participate. On child level, age, gender, and reason for H1-antihistamine use were recorded. On parent level, semi-structured interviews were conducted to address the safety of H1-antihistamine use in children. Data collection interviews were always performed by registered pharmacists. The study protocol was approved by Institutional Review Board (IRB) (ref. no.779-1-13).

### Statistical Analysis

All responses were collected in Microsoft Excel software (version 14.4.7). Data were analyzed using IBM SPSS Statistics package (version 25, NY, USA). For items assessing: parental-related awareness and students' feedback, responses were expressed as a percentage rounded to 1 decimal point to summarize the results.

**Table 2.** Demographics of Children (<6 years), n=516.

Characteristic	n (%)
Boys	312 (60.4)
Girls	204 (39.5)
Infants (<1 year)	152 (29.4)
Toddlers (1-3 years)	296 (57.3)
Pre-School (4-5 years)	68 (13.1)
H1-Antihistamines dispensing	n (%)
Providing a prescription	225 (44.0)
(Pediatrician, General practitioner)	186 (82.6), 39 (17.3)
Self-medicating	291 (56.3)

## Results

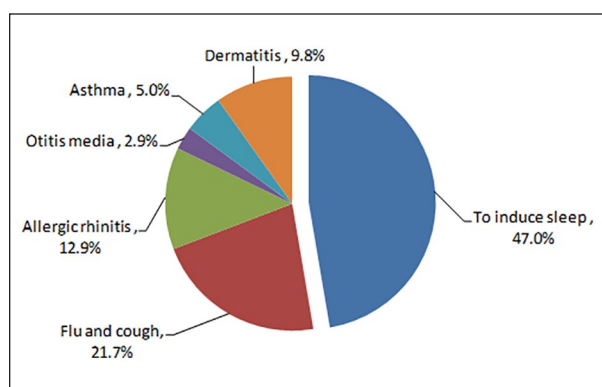
**Demographics and clinical data of children (<6 years).** At total, 516 children received at least one H1- antihistamine agent during the study period. Around 60% of children were boys. Infants (<1 year) formed 29.4% (n=152) of the cases, compared to toddlers (1-3 years) 57.3% (n=296), and Pre-school (4-5 years) 13.1% (n=68). More than half of the cases received H1-antihistamine based on self-medication 56.3% (n=291), while 44.0% (n=225) of the cases, prescriptions were presented either from a pediatrician, 82.6% (n=186) or a general practitioner, 17.3% (n=39) (Table 2).

### Pattern of H1-antihistamines Use in Children (<6 years)

Sedating H1-antihistamine agents was more frequently used among children (<6 years old) (77.9%; n=402) compared to less sedating agents (22.0%; n=114). Chlorpheniramine maleate was the most commonly used (62.9%; n=325), followed by dimethindene maleate (10.0%; n=52) and cetirizine (8.9%; n=46) (Table 3).

**Table 3.** Pattern of H1-Antihistamines Use in Children (<6 years), n= 516.

H1-antihistamine	Infants (<1 year), n (%)	Toddlers (1-3 years), n (%)	Pre-School (4-5 years), n (%)	Total, n (%)
Chlorpheniramine maleate	83 (54.6)	204 (68.9)	38 (55.8)	325 (62.9)
Promethazine	13 (8.5)	7 (2.3)	5 (7.3)	25 (4.8)
Oimethindene maleate	21 (13.8)	22 (7.4)	9 (13.2)	52 (10.0)
Total, n (%)	117 (22.6)	233 (45.1)	52 (10.0)	402 (77.9)
loratadine	9 (5.9)	19 (6.4)	1 (1.4)	29 (5.6)
Oesloratadine	6 (4.8)	10 (3.3)	11 (16.1)	27 (5.2)
Cetirizine	17 (11.1)	25 (8.4)	4 (5.8)	46 (8.9)
Levocetirizine	3 (1.9)	9 (3.0)	0 (0.0)	12 (2.3)
Total, n (%)	152 (29.4)	296 (57.3)	68 (13.1)	114 (22.0)
Total, n (%)	269 (52.1)	529 (97.2)	120 (23.2)	516

**Figure 1.** Reason for H1-antihistamines use among children (<6 years).

### Indication for Antihistamines Use in Children (<6 years)

The most common reason for using H1-antihistamine was to induce sleep (47.0%; n=245), followed by their use to manage flu and cough (21.7%; n=112) and allergic rhinitis (AR) (12.9%; n=67). Other less commonly reported reasons, including dermatitis (9.8%; n=51), asthma (5.0%; n=26), and otitis media (2.9%; n=15) (Figure 1).

### Off-Label Use of Antihistamines in Children (<6 years)

Of the 615 recorded cases, 66.6% (n=344) were classified as off-label use, mostly by unlicensed indication (51.1%; n=176), followed by unlicensed age (43.8%; n=151) and unlicensed dose/frequency (4.9%; n=17) (Figure 2).

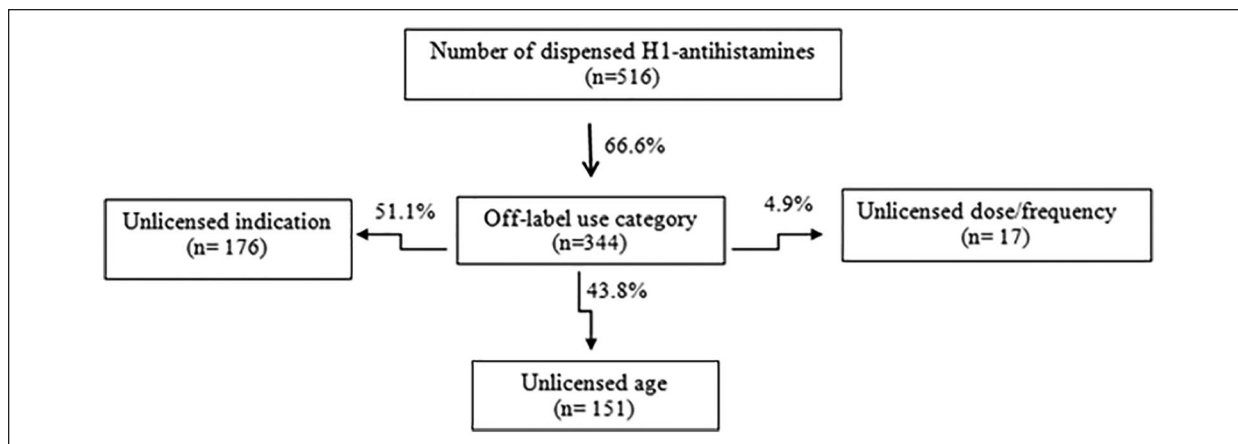
### Parental-Related Awareness

When parents (n=607), the majority of whom had at least a bachelor's degree, were asked about H1-antihistamines use among children, most of them (80.5%; n=489) were aware of the sedative adverse effects of H1-antihistamines, whereas a fewer number (31.9%; n=194) were aware of their cognitive effects. Moreover, 71.8% (n=438) were not aware of the signs of H1-antihistamines overdose. Finally, more than two thirds of parents (79.7%; n=484) were unfamiliar with off-label drug use in children (Figure 3).

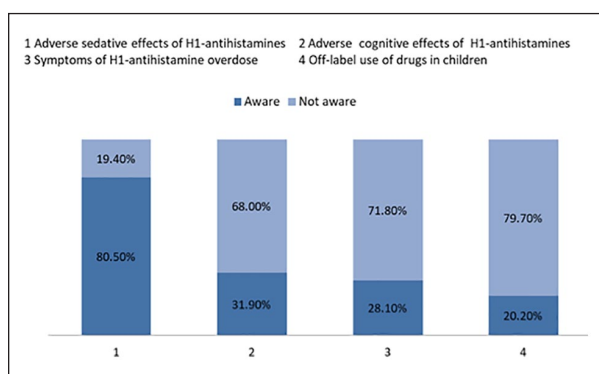
### Discussion

Due to a wide margin of safety, and high efficacy, less-sedating H1-histamines are recommended as the mainstay treatment for allergic rhinitis, urticarial, and atopic dermatitis in adults and children.<sup>11</sup> It was notable that the use of sedating H1-histamines was more dominant among children (<6 years old) than the less-sedating H1-anthistamines, specifically was Chlorpheniramine maleate. Chlorpheniramine maleate is a synthetic alkylamine derivative, licensed for symptomatic relief of allergy symptoms in case of hay fever, urticaria, and other allergic conditions.<sup>11</sup> Sedation, drowsiness, fatigue, and decreased concentration were reported at therapeutic dosages.<sup>12</sup> Due to the lack of safety of Chlorampheniramine, it is not recommended in newborns or infants. Children, especially those younger than 6 years old may experience paradoxical hyperexcitability. The exact mechanism is not completely understood; it was suggested that it might be related to differences in the number and functional nature of brain histamine receptors.<sup>13</sup>

The US FDA released recommendations to avoid empirical treatment of flu in children with products containing sedating H1-antihistamines.<sup>14</sup> In the recent



**Figure 2.** Off-labels of H1-antihistamines use among children (<6 years).



**Figure 3.** Parental-related awareness (n = 607).

Educational level: Primary school diploma, n = 13 (2.4%). High school diploma, n = 28 (4.6%). Bachelor's, n = 495 (81.5%). Professional degree beyond a bachelor's, n = 71 (11.6%).

study, 21.9% of the study children were received H1-antihistamine for flu and cough. The anticholinergic adverse effects of sedating H1-antihistamines, which include dry mucus membranes, might seem to improve nasal congestion.<sup>15</sup> However, critical analysis of well-designed studies shows a lack of evidence for their use in children with common cold and cough; the use of sedating H1-antihistamines did not shorten the average duration of illness or improve common cold symptoms.<sup>16</sup>

Less sedating H1-antihistamines have not been shown to be useful in the absence of allergy.<sup>17</sup> The AAP recommend the use of antiviral drugs to treat confirmed or suspected influenza in children, optimally within the first 2 days of illness.<sup>10</sup> Additionally, current guidelines recommend the use of less sedating H1-antihistamines in case of AR, especially in children due to the low risk of adverse effects.<sup>18</sup>

Surprisingly, 47% of the study children received H1-histamines to induce sleep, with no other complaints. The Consumer Healthcare Products Association (CHPA) advised manufacturers to add warnings, “Do not use to make a child sleepy.”<sup>19</sup> Sedated children are often unable to communicate, and there is a tendency of dose titration to achieve what it seems to be a desirable pharmacological effect for parents and caregivers. Cases of fetal intoxication by sedating H1-antihistamines given in babies bottles were previously reported.<sup>20,21</sup> Depending on developmental status and age, a normal sleep requirement is 14 to 15 hours for an infant, 12 to 14 hours for a toddler (1 to 5 years), and 9 to 11 hours for school-aged children (6 to 12 years).<sup>22</sup> Insomnia in an otherwise healthy child is typically caused by behavioral problems which varies depending on a child's age, such as the absence of parents for infants, or nocturnal fears for toddlers.<sup>23</sup> Behavioral interventions, such as setting a regular bedtime or avoiding certain foods and drinks is preferable before starting pharmacological management.<sup>23</sup>

The term “Off-label” use indicates that a drug is being used on unlicensed FDA's basis, in the United States approximately 75% of prescription drugs are not labeled for use in infants and children.<sup>24</sup> These results are in agreement with previous reports which revealed that higher rates of off-label prescribing were reported in neonates compared to pediatrics.<sup>25,26</sup>

All H1-antihistamines formulations under investigation are considered to be remarkably cheap and some are available over-the counter (OTC). A recent FDA report revealed that 86% in a sample of 1000 parents would use an OTC medication prior to or instead of consulting a pediatrician.<sup>27</sup> Studies showed that customers, who ask for over-the counter products assume having enough knowledge about these products, and do not feel the

need to engage with pharmacy staff. Our results revealed that approximately 80% of were not familiar with the term “off-label” drugs use in children. It is important to enhance public education about serious consequences of aberrant drug use behaviors.<sup>28,29</sup> Any decision about off-label prescription has to be based on true child’s needs and interests.<sup>30,31</sup> This study has some limitations including the snapshot nature of the cross-sectional design. Further cohorts are required to generalize the study outcomes

## Conclusion

Despite the availability of less-sedating H1-antihistamines with a wide safety and efficacy record, the use of sedating H1-antihistamines remains popular in children. Physicians, pharmacists and regulatory agencies are all responsible for enforcing implementation of clinical recommendations, when selecting H1-antihistamines for children.

## Author Contributions

AY contributed to conception and design; contributed to interpretation; drafted the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. MN contributed to acquisition; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. LM contributed to analysis; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

## Declaration of Conflicting Interests

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