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Research Article

A STUDY TO EVALUATE THE EFFECTS OF MULTIPLE ORAL DOSES OF BILASTINE, DESLORATADINE, AND LEVOCETIRIZINE ON PSYCHOMOTOR PERFORMANCE AND SALIVARY FLOW IN PATIENTS WITH CHRONIC URTICARIA ATTENDING DERMATOLOGY OUTPATIENT DEPARTMENT AT A TERTIARY CARE CENTER

IMRAN KHAN[1]*, PADMAJA MEKALA[1], ASIYA BEGUM[2], USHARANI PINGALI[1], SUMEDH GK[1]

[1]Department of Clinical Pharmacology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India. [2]Department of Dermatology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India.
***Corresponding author: Imran Khan; Email: imran.khan1705@gmail.com**

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ABSTRACT

Objectives: Antihistamines are the most used systemically delivered medications for skin conditions that can inhibit cholinergic (muscarinic) receptors and block central H1 receptors leading to effects such as dryness of mouth and sedation, respectively. Bilastine, desloratadine, and levocetirizine are second-generation antihistamines which have variable effects on dryness of mouth and sedation; hence, the objective of this study is to evaluate any differences in these effects in chronic urticaria patients prescribed the above-mentioned antihistamine drugs.

Methods: Subjects with chronic urticaria who were prescribed any of the three antihistamines by the dermatologist were enrolled. Baseline readings of salivary flow by cotton ball method and psychometric performances by digit letter substitution test (DLST), six letter cancellation test (SLCT), card sorting test, and Visual Analog Scale (VAS) for dryness of mouth and sedation measured before administration of prescribed antihistaminic drug and compared with readings taken of the same tests after 7 days of antihistaminic drug administration.

Results: A total of 36 subjects were enrolled median age of 38.5 years (range 18–57 years) and 55% (20/36) were males. Reduction in the mean salivary flow and the psychomotor performance were not significantly different between the three drug groups, although there were reductions in the three groups in the outcome measures salivary flow and psychomotor performance tests including DLST and SLCT when compared to baseline.

Conclusion: The three drugs are similar with respect to their adverse effect profile in terms of causing dryness of mouth and impairment of psychomotor performance.

Keywords: Bilastine, Desloratadine, Levocetirizine, Salivary flow, Psychomotor performance.

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INTRODUCTION

The most popular drugs for skin diseases that are administered systemically are antihistamines. The frequency of itching as a non-specific indicator of skin problems and the broad anti-pruritic effects of antihistamines are the causes of this. H1 antihistamines are often categorized as "first generation" (linked to problematic side effects include atropine-like effects, anti-adrenergic effects, and somnolence) and "second generation" (with fewer or no side effects) [1].

At prescribed dosages, antihistamines block cholinergic (muscarinic) receptors. Dry lips, dry eyes, mydriasis, sinus tachycardia, constipation, urine retention, and memory problems are all symptoms of cholinergic antagonism. Histamine is produced by both mast cells and neurons in the central nervous system (CNS), where it functions as a neurotransmitter and a neurohormone. Its primary function is to keep people awake by inhibiting central H1 receptors, which results in drowsiness [2].

Only a small number of the many techniques that researchers have created to evaluate performance impairment have sufficient evidence to back up their use. The most popular approach is the battery of psychomotor tests, which assess central integration function and sensory-motor coordination. The most common methods for assessing subjective tiredness are Visual Analog Scales (VAS) or drowsiness assessment tools like the stanford sleepiness scale [3]. Psychometric studies have their application in drug development to aid in screening of drug molecules for activity in the CNS and to identify the CNS adverse effects.

Understanding that sensory information is a combination of perceptual configuration and stored or pre-existing stimulus patterns. The execution of digit symbol substitution and cancellation tests serves as a good example of this. A performance test that involves sensory, motor, and central components is the card sorting test (CST) (to examine the frontal lobe function). Several of these tests can be used to assess how medications affect psychomotor performance.

Patients are frequently distressed by dry mouth. Therefore, it is essential to observe how these medications affect salivary flow when evaluating them. There are multiple ways to assess how medications affect salivary flow using unstimulated whole saliva output. Among these, cotton balls or dollery are among the most straightforward techniques that do not require any complex tools or technical know-how. All we need are sterile cotton balls and a delicate balance. Dollery *et al*. describe this approach, which is widely used to assess a drug's anti-sialagogue effects. VASs are the most common tool used to assess subjective dry mouth.

A wide range of studies performed on healthy volunteers as well as patients to see the CNS and anticholinergic effects have shown that both the first and second-generation antihistamines are known to cause psychomotor impairment and dryness of mouth; however, second-generation antihistamines have lesser CNS and anticholinergic effects when compared to first-generation antihistamines.

In contrast to first-generation antihistamines, second-generation antihistamines have a different ionic charge and are more lipophobic.

They also consist of bigger molecules than the agents of the previous generation. It seems that the combination of all three of these factors is what significantly more challenging for these compounds to get across the blood–brain barrier. This is not to imply that they do not do it at all; second-generation agents can enter the brain, but they can only do it much less often [4]. According to Yanai *et al.*'s [5] research, second-generation agents had a significantly lower occupancy rate than their first-generation predecessors, taking up just 20% of the brain's H1-receptor sites. Moreover, it has been demonstrated that brain-receptor occupancy correlates with the severity of cognitive impairment.

There are a smaller number of studies comparing the CNS and anticholinergic effects within the second-generation antihistamines. The aim of this study is to compare the peripheral and central profile of bilastine, desloratadine, and levocetirizine to determine any differences between the drugs in the extent of their CNS and anticholinergic effects.

METHODS

The study was done after approval from the Institutional Ethics Committee and obtaining informed consent from the subjects in the Department of Clinical Pharmacology and Therapeutics and the Outpatient Department of Dermatology.

Sample size of 36 subjects is based on the requirement of participants for pilot study of 12 subjects per group. Subjects aged 18–60 years attending the dermatology outpatient department diagnosed with chronic urticaria and who were prescribed any of the antihistaminic drugs (levocetrizine, bilastine, or desloratidine) as a standard of care by the dermatologist and willing to comply with the study procedures were included in the study after explaining the study procedures and obtaining written informed consent.

All the eligible subjects were assigned to either of the three arms based on dermatologists' prescription of antihistamine, i.e., levocetirizine, desloratadine, or bilastine group and were asked to visit department of clinical pharmacology for study procedures for assessment of baseline salivary flow by cotton ball method and baseline psychomotor performance by digit letter substitution test (DLST), six letter cancellation test (SLCT) and CST, subjective awareness of dryness of mouth and level of sedation was assessed using VAS for dryness of mouth and level of sedation, respectively. After the procedures, the subjects were instructed to take the antihistamine as prescribed by the dermatologist and were instructed to visit the department after 7 days.

Follow-up assessment

Subjects were scheduled for a follow-up assessment after the initial 7-day period of antihistamine administration. During the follow-up visit, the same psychomotor performance tests (DLST, SLCT, and CST) were repeated to evaluate any changes.

Adverse effects monitoring

Throughout the study, subjects were monitored for any adverse effects related to the antihistamine medications.

Data analysis

Collected data from the study procedures were analyzed to assess the impact of different antihistamines on salivary flow, psychomotor performance, and subjective symptoms. Statistical analysis was conducted to determine any significant differences between the three antihistamine groups.

Measurement of salivary flow

The subjects were asked to rinse the mouth with clean water for 2–3 times and were seated comfortably with eyes open and head tilted slightly forward. After a rest for 5 min to minimize the orofacial movements, four unweighted cotton balls were placed, one in each buccal pouch on either side, below the tongue. They were left for 2 min to collect the residual saliva and discarded. A second set was similarly placed for 60 s, removed and placed in plastic cover, and weighed. Again, a third set was placed in the same position as before for the same period. The difference between the initial and final weight of cotton balls was recorded. An average of the 2 readings was taken to calculate the salivary flow in gram/minute [6].

Performance of DLST

The subjects were given DLST sheet. The working sheet consists of 144 target digits placed in 9 rows and 16 columns. Care was taken that the same digit does not appear consequently in any row or column. This is one of the most widely used tests measuring attention response speed, central integration, and visuomotor coordination. It is also a useful indicator of drug-induced changes in sensory processing performance [7].

Performance of SLCT

This test is used to assess the attention. This test uses a response sheet containing six letter targets that are distributed among pseudorandom letters. The six key letter targets are printed on top of the sheet. Subjects were asked to work through the sheet and cross the target letters that they found in 90 s. The number of correct cancellations for the target letters was noted. This test was repeated 3 times and the average of the number of correct cancellations for the target letters was calculated [8-10].

Performance of CST

This is an excellent performance task since it includes sensory and motor and central components [9]. Subjects were asked to sort out 52 cards depending on their design. The time taken to sort was noted in seconds as well as the number of correctly sorted and wrongly sorted cards. The readings were taken 3 times, and the average was calculated in seconds and the average of the number of cards sorted was also calculated.

Subjective feeling of dryness of mouth and level of drowsiness

VAS for recording subjective feeling of dryness of mouth and level of drowsiness were measured with VAS scale for dryness of mouth and sedation after the completion of salivary flow test and psychomotor performance tests, respectively.

RESULTS

A total of 36 chronic urticaria patients were recruited and as per the prescribed antihistamine, bilastine, desloratadine, and lsevocetirizine were grouped into three groups, namely bilastine group, desloratadine group, and levocetirizine group, respectively. Fig. 1 shows the participant flow in the study. Demographic characteristics of the participants are described in Table 1.

Baseline measures of salivary flow and psychomotor performance were comparable in the three groups. The baseline values of the outcome parameters are depicted in Table 2.

End-of-study measurements of salivary flow show no significant changes between the groups; however, when compared to baseline, the end-of-study measurements were reduced with 4.2% reduction in bilastine group, 6.12% reduction in desloratadine group, and 6.38% reduction in the levocetirizine group. Changes in the VAS for dryness of mouth were also not significant. Outcomes in salivary flow and VAS for dryness of mouth are depicted in Fig. 2.

Measures of psychomotor performance

DLST

Between-group comparison reveals no significant difference, however, within-group comparison from baseline to end of study shows a significant reduction in the mean number of correct attempts from baseline to end of study with 5.29%, 9.66%, and 10.31% reductions in bilastine group, desloratadine group, and levocetirizine group, respectively.

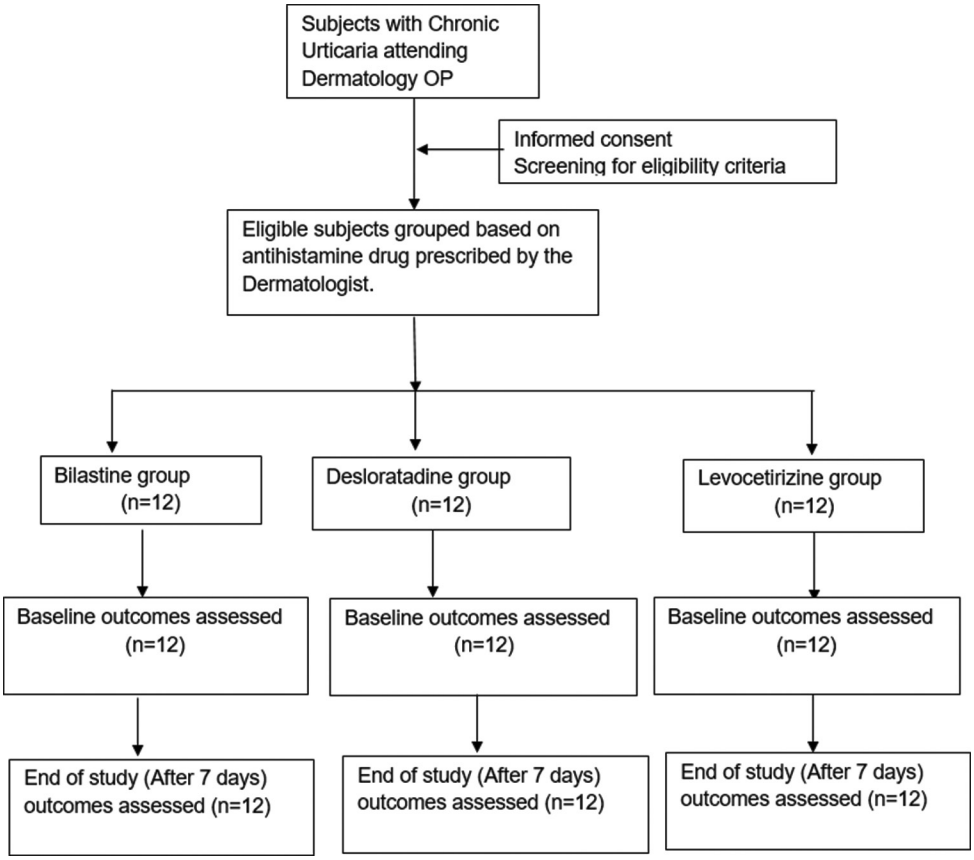

Fig. 1: Participant flow diagram

Table 1: Demographic characteristics of the participants

S. No.	Characteristic	Bilastine group (n=12)	Desloratadine group (n=12)	Levocetirizine group (n=12)	p-value
1	Age (mean±SD)	35.5±10.7	41.4±11.35	35.7±10.2	0.36
2	Gender (M: F)	5:7	9:3	6:6	0.23
3	BMI (mean±SD)	25.3±3.9	26.8±3.3	25.3±3.6	0.15
4	Comorbidities (%)				
	Diabetes	2 (16)	1 (8.3)	2 (16)	-
	HTN	0 (0)	1 (8.3)	0 (0)	-
	DM±HTN	1 (8.3)	1 (8.3)	1 (8.3)	-
	Psoriasis	1 (8.3)	0 (0)	0 (0)	-
	Hypothyroidism	1 (8.3)	1 (8.3)	1 (8.3)	-

SD: Standard deviation, BMI: Body mass index, DM: Diabetes mellitus, HTN: Hypertension

Table 2: Baseline outcome measures

S. No.	Baseline outcome measure	Bilastine group (n=12)	Desloratadine group (n=12)	Levocetirizine group (n=12)	p value*
1	Salivary flow (mean±SD)	0.46±0.08	0.49±0.19	0.47±0.13	0.927
2	Correct substitutions in DLST (mean±SD)	47.9±8.7	48.6±12.4	44.02±14.3	0.601
3	Correct cancellations in SLCT (mean±SD)	36.4±6.6	34.6±3.1	35.8±4.5	0.684
4	Card sorting time in seconds (mean±SD)	126.7±14.8	127.3±25.6	130.9±13	0.838
5	VAS for dryness of mouth in mm (mean±SD)	26.9±9.7	28.7±11.4	30.25±9.7	0.735
6	VAS for sedation in mm (mean±SD)	29.9±12.1	29.42±13.2	22.6±7.3	0.226

*One-way ANOVA test. DLST: Digit letter substitution test, SLCT: Six letter cancellation test, VAS: Visual Analog Scale, SD: Standard deviation, ANOVA: Analysis of variance

SLCT

Between-group comparison reveals no significant difference, however within group from baseline to end-of-study comparison shows a significant reduction in the mean number of correct attempts from baseline to end of study with 6%, 6.8%, and 9.97% reductions in bilastine group, desloratadine group, and levocetirizine group, respectively.

CST

Between-group comparison and within-group comparison reveals no significant differences in card sorting times.

VAS for sedation

Between-group comparison and within group reveal no significant differences in the readings of subjective drowsiness as measured by VAS.

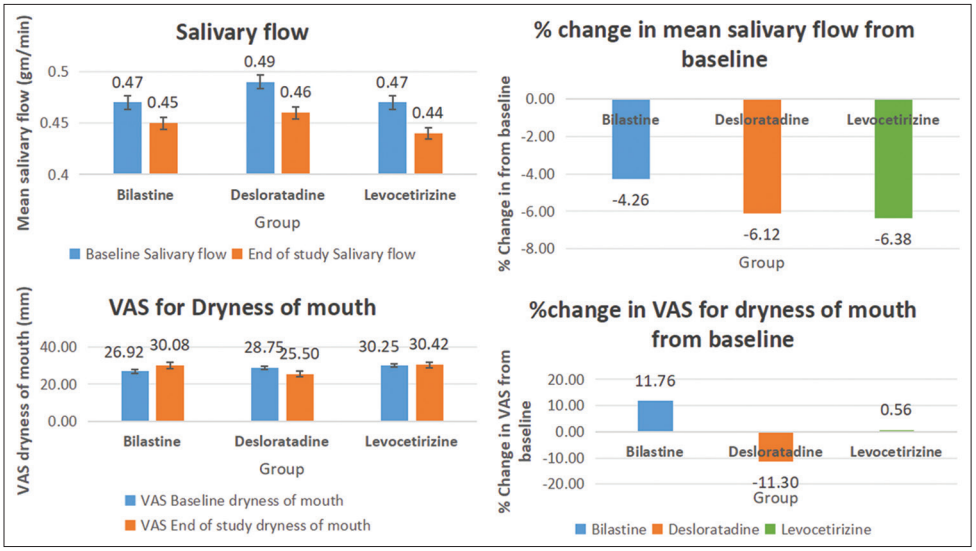

Fig. 2: Effect on salivary flow measured by cotton ball method and subjective dryness of mouth measured by Visual Analog Scale for dryness of mouth

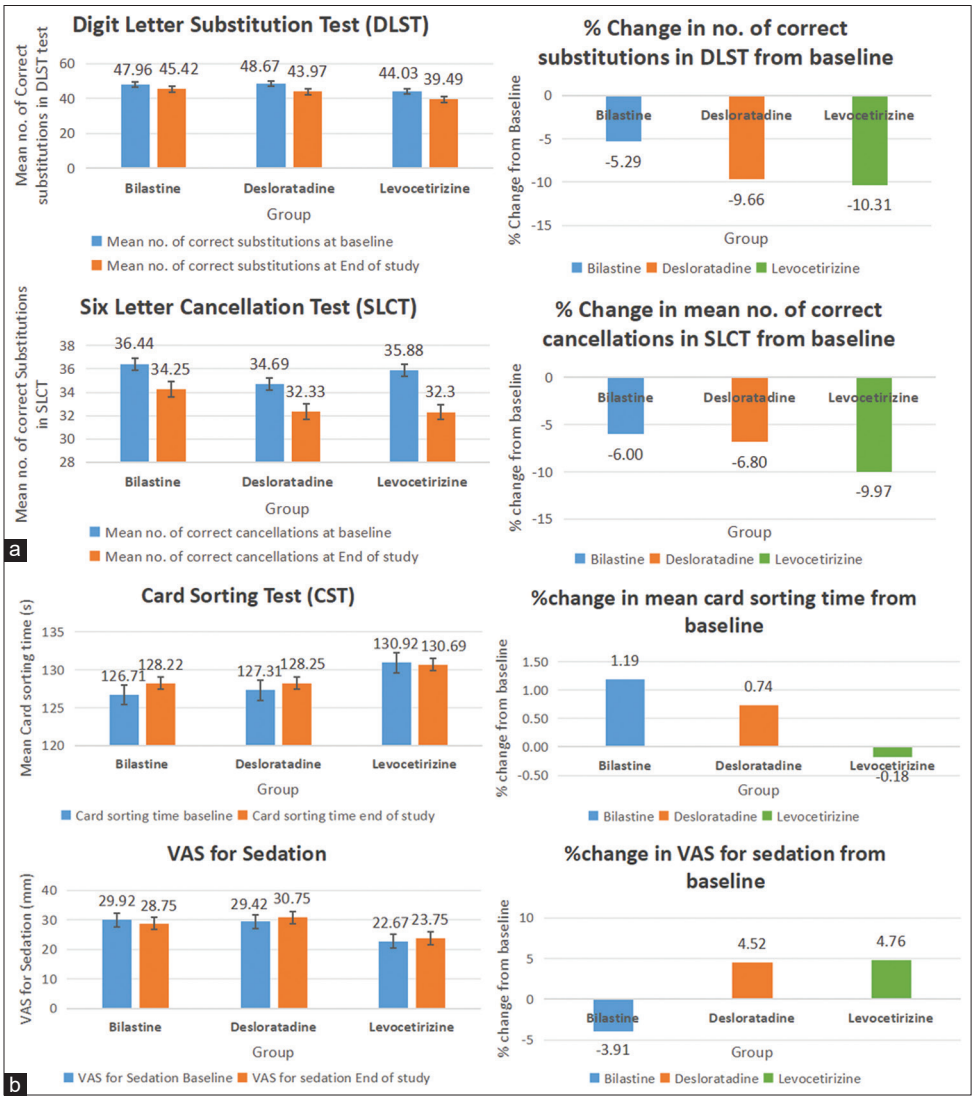

Fig. 3: (a and b) Effect on psychomotor performance measured by digit letter substitution test, six letter cancellation test and card sorting test and subjective sedation measured by Visual Analog Scale for sedation

Table 3: End-of-study outcome measures

S. No.	End-of-study outcome measures	Bilastine group (n=12)	Desloratadine group (n=12)	Levocetirizine group (n=12)	p-value*
1	Salivary flow (mean±SD)	0.45±0.13	0.45±0.19	0.44±0.18	0.979
2	Correct substitutions in DLST (mean±SD)	45.4±9.3	43.9±11.8	39.42±13.8	0.451
3	Correct cancellations in SLCT (mean±SD)	34.2±9.1	32.3±4.5	32.9±6.3	0.699
4	Card Sorting Time in seconds (mean±SD)	128.2±18.7	128.2±19.5	130.6±17.5	0.933
5	VAS for dryness of mouth in mm (mean±SD)	30±9.1	25.5±10	30.4±12.2	0.452
6	VAS for sedation in mm (mean±SD)	28.7±12	30.7±9.4	23.7±12.3	0.311

*One-way ANOVA test. DLST: Digit letter substitution test, SLCT: Six letter cancellation test, VAS: Visual Analog Scale, SD: Standard deviation, ANOVA: Analysis of variance

Table 4: Within-group comparison of study outcomes

Difference in End of study to Baseline measures	Bilastine group (n=12)	Desloratadine group (n=12)	Levocetirizine group (n=12)
Salivary flow	−0.02	−0.03	−0.03
DLST	−2.5*	−4.7*	−4.6*
SLCT	−2.2*	−2.4*	−3.5*
CST	1.51	0.94	−0.23
VAS dryness of mouth	3.1	−3.25	0.17
VAS sedation	−1.17	1.33	1.08

*p<0.05 (Paired *t*-test). DLST: Digit letter substitution test, SLCT: Six letter cancellation test, CST: Card sorting test, VAS: Visual Analog Scale

Changes in the outcomes for psychomotor performance and VAS for sedation are depicted in Fig. 3. Between-group comparisons for the end-of-study outcomes are represented in Table 3 and within-group comparisons from baseline to end of study are represented in Table 4.

Tolerability

All the three drugs were well tolerated by all the participants. None of the participants experienced serious adverse effects necessitating discontinuation of treatment.

DISCUSSION

The primary aim of this research was to delve into the potential discrepancies among the three treatments – Bilastine, Desloratadine, and Levocetirizine – concerning their likelihood to induce dryness of the mouth and impede psychomotor performance. The findings of our study did not reveal any significant variations across the three groups in terms of causing dryness of the mouth and impacting psychomotor performance. Nevertheless, it was observed that the salivary flow in all three groups experienced a reduction by the conclusion of the study in comparison to the initial baseline values, although this decrease was not deemed statistically significant. Moreover, the differences in the outcomes of psychomotor tests did not display any significant variances among the three groups. However, a noteworthy decline in the performance of tests such as DLST and SLCT was noted from the baseline measurements to the end of the study period. The alterations in the VASs utilized to evaluate the subjective feelings of dryness of the mouth and drowsiness did not demonstrate any statistical significance either between the groups at the conclusion of the study or within each group when comparing the final measurements to the baseline values. In essence, while the study did not yield substantial differences in the effects of the three treatments on dryness of the mouth and psychomotor performance, it did uncover certain nuanced changes in salivary flow and specific test performances.

Limitations of the study

- Acknowledge the need for larger sample sizes to detect subtle differences in outcomes
- Address any confounding variables that may have influenced the study results
- Consider additional measures to assess psychomotor performance beyond the DLST, SLCT, and CST tests.

CONCLUSION

The findings of this study shed light on the comparable adverse effect profiles of the second-generation antihistamines bilastine, desloratadine, and levocetirizine. While examining both peripheral effects like salivary flow and central effects such as impairment of psychomotor performance, no significant differences were observed among these three drugs. It is evident that these medications exhibit similar tendencies in causing dryness of the mouth and drowsiness in individuals. This information is crucial for healthcare professionals when considering the selection of antihistamines for patients, as it emphasizes the need to weigh the risks and benefits of each drug based on their adverse effect profiles. Further research could delve deeper into the underlying mechanisms that contribute to these common side effects, potentially leading to improved drug development and patient care in the future.

FUNDING

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CONFLICTS OF INTEREST

Authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTION

All the authors have contributed to designing, planning, conducting the study, and manuscript writing.

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