Original Article

Old versus new antihistamines: Effects on cognition and psychomotor functions

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Abstract

Context: Antihistamines (AHs) are the most widely long-term therapeutic option to manage allergic diseases. This research aimed to study the effects of long-term administration of AHs: on cognitive (memory, mood, attention, sleep and executive function) and psychomotor performance. **Materials and Methods:** This prospective, observational study for a total duration of 30 months was carried out at the Dermatology OPD in adult patients with dermatological condition who were newly prescribed either chlorpheniramine (4 mg, BD), levocetirizine (10 mg, OD), fexofenadine (180 mg, OD) or bepotastine (10 mg, BD) for at least 28 days as per inclusion and exclusion criteria after taking written informed consent. A detailed history of the patients, memory (using PGI memory scale) and psychomotor functions, Brief Mood Introspection Scale and Epworth Sleepiness Scale were assessed at baseline, 1 week and 4 weeks. Data obtained were analysed using paired sample *t*-test and one-way ANOVA followed by post hoc analysis (*P*-value <0.05 statistically significant). **Results:** A total of 22 in chlorpheniramine group, 23 in levocetirizine group, 20 in fexofenadine group and 18 in bepotastine group were analysed. Chlorpheniramine and levocetirizine had deteriorating effects on cognitive and psychomotor performance, whereas fexofenadine and bepotastine showed positive effect on various cognitive and psychometric tasks. The study results showed chlorpheniramine and levocetirizine to be having sedative effects, whereas fexofenadine was nonsedating. In bepotastine group, no effect on sleep was observed. No significant difference in mood scores was observed in between chlorpheniramine, levocetirizine and fexofenadine groups. In bepotastine group, arousal calm and positive tired scores increased at 4 week as compared to baseline. **Conclusion:** Patients with dermatological illnesses can be prescribed fexofenedine and bepotastine, as compared to chlorpheniramine and levocetirizine, and their cognitive and psychological functions should be evaluated periodically with suitable tests.

Keywords: Bepotastine, cognation, chlorpheniramine, levocetirizine, fexofenadine, psychomotor function

Introduction

Antihistamines (AHs) are a class of drugs used by physicians, in general, and dermatologists for long term for disorders like chronic urticaria, psoriasis, tinea infections and atopic dermatitis.[1,2] AHs that cross the blood–brain barrier and bind to H_1-receptors (H1Rs) in the brain suppress central nervous system (CNS) arousal and disrupt circadian sleep–wake rhythmicity, thus impairing both cognitive function and psychomotor performance.[3]

However, data currently available are mainly through the studies conducted to assess the acute (hours–1 day) or subchronic (3–5 days) effects of AHs that too on healthy volunteers.[4] Chronic effects of AHs have not been studied so far and the data cannot be extrapolated. This study investigated the effects of long-term administration of AHs: chlorpheniramine, levocetirizine, fexofenadine and bepotastine on cognitive (memory, mood, attention, sleep and executive

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function) and psychomotor performance in patients suffering from various dermatological conditions.

Materials and Method

Participants: This prospective, observational study for a total duration of 30 months was carried out at the Dermatology OPD in patients who were newly prescribed either chlorpheniramine (4 mg, BD), levocetirizine (10 mg, OD), fexofenadine (180 mg, OD), or bepotastine (10 mg, BD) for at least 28 days. A sample size of 30 in each group was calculated considering power of study as 95%, level of significance 0.5%, and considering the loss to follow-up. Patients in the age group of 18–65 years, having education at least up to fifth standard of schooling, who could read or write in either Gujarati, English or Hindi and who gave written informed consent were included. Patients having history of any disease known to cause cognitive and psychomotor impairment; or who were on treatment with drugs known to cause cognitive and psychomotor impairment; or those who had a history of alcoholism, tobacco use, or smoking; or who had taken AH in past 1month were excluded from the study.

Methodology: After approval from the Institutional Ethics Committee, patients who satisfied the enrolment criteria were included and randomised into one of the four groups using computer-generated table by the clinician. A detailed history of the patients and patients' memory was assessed using PGI memory scale,[5] and for psychomotor functions, several tests were used, namely, digit-letter substitution, six-letter cancellation, hand steadiness, critical flicker fusion and choice reaction time test.[6] Brief Mood Introspection Scale[7] (BMIS) and Epworth Sleepiness Scale[8] were used to assess mood and sleep, respectively. All observations were recorded at baseline, 1 week and 4 weeks. Safety of the drugs was also studied, and causality,[9,10] preventability[11] and severity[12] assessment was done for the ADRs if any. All the scales used as study tools were translated to the appropriate vernacular languages by a qualified translator.

Data analysis: Data obtained were entered in Microsoft Excel version 2007, and statistical analysis was done using IBM SPSS version 25. Paired sample *t*-test and one-way ANOVA followed by post hoc analysis were used for data analysis. *P* value less than 0.05 was considered to be statistically significant.

Results

The present study evaluated 123 patients out of which three patients were excluded from the study after screening and 37 patients were lost to follow-up. So a total of 83 patients were included for final analysis of which 22 were in chlorpheniramine group, 23 in levocetirizine group, 20 in fexofenadine group and 18 in bepotastine group. The mean age of the patients was 35.03 ± 11.334 years (Mean ± SD). The mean age of patients in all four groups was comparable at baseline. The most common clinical conditions observed in the study were tinea cruris followed by eczema, tinea corporis and scabies. Concomitant medications prescribed included oral anti-fungal agents, vaseline, topical steroids, oral vitamins/minerals, topical antifungal agents, oral antiparasitic agents, topical antiparasitic agents, topical antibacterial agents, topical salicylate and silver sulfadiazine.

Effects of antihistamines on memory [Tables 1 and 4]

When the effect of chlorpheniramine on memory was observed at 1 week as compared to baseline, the mental balance ($P = 0.006$), attention and concentration ($P = 0.002$) and total PGIMS scores ($P = 0.000$) were significantly decreased. Immediate recall ($P = 0.021$) score was increased significantly at 4 week as compared to 1 week. Mental balance ($P = 0.002$), attention and concentration ($P = 0.005$), delayed recall ($P = 0.016$) and total PGIMS ($P = 0.029$) scores were significantly decreased at 4 week as compared to baseline.

When the effect of levocetirizine on memory was observed at 1 week as compared to baseline, the remote memory ($P = 0.029$), mental balance ($P = 0.010$) and total PGIMS ($P = 0.026$) scores were significantly decreased. Delayed recall ($P = 0.002$) scores were significantly decreased at 4 week as compared to 1 week. Mental balance ($P = 0.047$), delayed recall ($P = 0.001$), visual retention ($P = 0.044$) and total PGIMS ($P = 0.007$) scores were significantly decreased at 4 week as compared to baseline.

When the effect of fexofenadine on memory was observed at 1 week as compared to baseline, the verbal retention of similar pairs ($P = 0.017$), recognition ($P = 0.004$) and total PGIMS ($P = 0.019$) scores were significantly increased. Delayed recall ($P = 0.042$), immediate recall ($P = 0.025$), visual retention ($P = 0.016$) and total PGIMS ($P = 0.000$) scores were significantly increased at 4 week as compared to 1 week. Attention and concentration ($P = 0.003$), delayed recall ($P = 0.002$), immediate recall ($P = 0.039$), verbal retention of similar ($P = 0.004$) and dissimilar ($P = 0.019$) pairs, visual retention ($P = 0.022$), recognition ($P = 0.045$) and total PGIMS ($P = 0.000$) scores were significantly increased at 4 week as compared to baseline.

When the effect of bepotastine on memory was observed at 1 week as compared to baseline, remote memory score ($P = 0.017$) was significantly decreased. However, at 4 week, remote memory score ($P = 0.02$) increased significantly as compared to baseline. Verbal retention of dissimilar pairs' score increased significantly at 4 week as compared to 1 week ($P = 0.012$) and baseline ($P = 0.007$). Recognition score increased significantly at 4 week as compared to 1 week ($P = 0.029$) and baseline ($P = 0.035$). Total PGIMS score ($P = 0.001$) increased significantly at 4 week as compared to 1 week.

Effects of antihistamines on psychomotor functions [Tables 2 and 4]

When the effect of chlorpheniramine on psychomotor functions was observed at 1 week as compared to baseline, the psychomotor function test scores showed no significant difference. Digit letter substitution test score (P = 0.043) was significantly increased at 4 week as compared to 1 week. At 4 week as compared to baseline: single-letter cancellation test (0.033) and hand steadiness test (0.007) scores were significantly increased at 4 week as compared to baseline.

When the effect of levocetirizine on psychomotor functions was observed, the psychomotor function test scores showed no significant difference.

When the effect of fexofenadine on psychomotor functions was observed at 1 week as compared to baseline, the digit letter substitution test (P = 0.027) and critical flicker fusion at 20 Hz (P = 0.042) scores showed significant increase. Single-letter cancellation test (P = 0.008) and digit letter substitution test (P = 0.021) scores increased, and critical flicker fusion at 20 Hz (P = 0.042) decreased at 4 weeks as compared to 1 week. Single-letter cancellation (P = 0.000) and digit letter substitution (P = 0.005) showed significant increase in scores and hand steadiness test (P = 0.008) score significantly decreased at 4 weeks as compared to baseline.

When the effect of bepotastine on psychomotor functions was observed at 4 week as compared to baseline, hand steadiness test score (P = 0.016) showed significant decrease.

Table 1: Effects of antihistamines on memory

Test	Chlorpheniramine Mean ± SEM						Levocetirizine Mean ± SEM						Fexofenadine Mean ± SEM					
	Baseline		1 Week		4 Week		Baseline		1 Week		4 Week		Baseline		1 Week		4 Week	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Remote memory	7.95	0.04	7.55	0.18	7.82	0.08	8.0	0.0	7.65*	0.15	7.83	0.10	7.85	0.15	7.80	0.09	7.95	0.05
Recent memory	4.95	0.04	4.82	0.08	4.91	0.06	4.96	0.04	4.83	0.08	4.83	0.08	4.85	0.08	5.00	0.00	5.00	0.00
Mental balance	5.32	0.47	4.41*	0.47	4.05@	0.47	4.91	0.57	3.83*	0.5	4.04@	0.45	5.20	0.50	5.20	0.45	5.60	0.48
Attention and concentration	3.73	0.57	2.50*	0.35	2.55@	0.36	4.04	0.57	4.09$	0.54	3.87	0.48	3.45	0.48	3.90$	0.41	4.15@	0.47
Delayed recall	8.36	0.4	7.82	0.33	7.59@	0.40	8.48	0.33	8.17	0.42	7.74#@	0.38	7.70	0.36	7.85	0.37	8.25#@	0.32
Immediate recall	6.41	0.69	5.68	0.51	6.36#	0.49	6.70	0.63	6.43	0.59	6.39	0.52	6.80	0.54	7.00	0.46	7.45#@	0.42
Verbal retention of similar pairs	3.91	0.22	3.68	0.17	3.86	0.21	3.91	0.15	3.91	0.14	3.83	0.15	4.00	0.18	4.40*$	0.13	4.50@^	0.15
Verbal retention of dissimilar pairs	8.0	0.71	7.91	0.73	8.36	0.60	8.70	0.62	8.57	0.66	8.61	0.69	9.50	0.39	9.95	0.35	10.10@	0.35
Visual retention	7.14	0.66	6.91	0.58	7.14	0.7	6.74	0.58	6.39	0.51	6.09@	0.54	7.35	0.6	7.25	0.48	8.25#@	0.62
Recognition	8.23	0.45	7.95	0.47	8.27	0.47	8.43	0.26	8.39	0.21	8.48	0.23	8.55	0.22	9.10*$	0.16	9.10@	0.18
PGI memory score	64.0	2.47	59.23*	2.06	60.91@	2.38	64.87	2.07	62.26*	2.03	61.70@	2.01	65.25	1.27	67.45*$	0.81	70.35#@^	1.01

Footnote: Paired sample *t*-test was used for intragroup comparison and ANOVA followed by post hoc analysis was used for intergroup comparison. In intragroup comparison, * depicts significance at 1 week as compared to baseline, # depicts significance at 4 week as compared to 1 week, and @ depicts significance at 4 week as compared to baseline. In intergroup comparison (shaded boxes represent comparison groups showing significance), $ depicts significance at 1 week and ^ depicts significance at 4 week

Table 2: Effects of antihistamines on psychomotor functions

Test	Chlorpheniramine Mean±SEM						Levocetirizine Mean±SEM						Fexofenadine Mean±SEM					
	Baseline		1 Week		4 Week		Baseline		1 Week		4 Week		Baseline		1 Week		4 Week	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Six-letter cancellation test	23.82	1.44	24.50	1.93	27.00@	1.78	25.17	2.02	25.04	1.54	24.22	1.76	21.80	1.49	22.70	1.28	24.70#@	1.43
Digit letter substitution test	23.45	1.64	21.91	1.37	23.36#	1.65	19.87	2.13	20.48	2.67	19.78	2.32	21.25	1.7	22.35*	1.56	24.15#@	1.85
Choice reaction time audio	1.68	0.15	1.56	0.11	1.57	0.08	1.60	0.07	1.64	0.09	1.74	0.08	1.37	0.08	1.34	0.07	1.25^	0.05
Choice reaction time video	1.62	0.11	1.59	0.10	1.61	0.09	1.6	0.12	1.64	0.08	1.58	0.09	1.30	0.11	1.34	0.09	1.3^	0.1
Hand steadiness test	59.90	4.83	55.20	4.79	54.20@	3.99	59.7	7	62.20	7.72	59.50	6.05	51.70	5.78	47.70	4.84	45.70@	4.88
Critical flicker fusion test 20 Hz	47.73	0.16	47.950	0.21	47.73	0.16	47.50	0.27	47.61	0.29	47.72	0.15	47.50	0.0	48.00*	0.23	47.50#	0.0
Critical flicker fusion test 50 Hz	47.61	0.11	47.61	0.11	47.61	0.11	47.50	0.16	47.28	0.35	47.61	0.11	47.50	0.0	47.50	0.0	47.50	0.0

Footnote: Paired sample *t*-test was used for intragroup comparison and ANOVA followed by post hoc analysis was used for intergroup comparison. In intragroup comparison, * depicts significance at 1 week as compared to baseline, # depicts significance at 4 week as compared to 1 week, and @ depicts significance at 4 week as compared to baseline. In intergroup comparison (shaded boxes represent comparison groups showing significance), $ depicts significance at 1 week and ^ depicts significance at 4 week

Effects of antihistamines on sleep [Tables 3 and 4]

When the effect of chlorpheniramine on sleep was observed at 1 week as compared to baseline, Epworth sleepiness scale showed significant increase ($P = 0.006$), while with levocetirizine, the score ($P = 0.026$) showed significant increase at 1 week and at 4 weeks ($P = 0.019$) as compared to baseline. When the effect of fexofenadine on sleep was observed, Epworth sleepiness scale score ($P = 0.019$) showed decrease in score at 4 week as compared to baseline, while with bepotastine the score showed no significant difference.

Effects of antihistamines on mood [Tables 3 and 4]

When the effect of chlorpheniramine on mood was observed at 1 week as compared to baseline, no significant difference was observed. Arousal calm ($P = 0.040$) and positive tired ($P = 0.038$) mood scores were significantly decreased at 4 week as compared to 1 week. Arousal calm ($P = 0.006$) and positive tired ($P = 0.006$) mood scores were significantly decreased at 4 week as compared to baseline.

When the effect of levocetirizine on mood was observed at 1 week as compared to baseline, positive tired ($P = 0.004$) mood score was decreased significantly. Pleasant unpleasant mood score ($P = 0.013$) decreased significantly at 4 week as compared to 1 week. Positive tired ($P = 0.001$) and pleasant unpleasant ($P = 0.18$) mood scores decreased significantly at 4 week as compared to baseline.

Table 3: Effects of antihistamines on mood and sleep

Test	Chlorpheniramine Mean±SEM						Levocetirizine Mean±SEM						Fexofenadine Mean±SEM					
	Baseline		1 Week		4 Week		Baseline		1 Week		4 Week		Baseline		1 Week		4 Week	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Epworth sleepiness scale	4.41	0.68	5.82*	0.66	5.41	0.72	3.39	0.56	4.70*	0.57	4.65$^{@}$	0.46	4.65	0.70	4.25	0.63	4.00$^{@}$	0.57
Brief mood introspection scale (BMIS) Pleasant unpleasant score	53.77	1.46	54.00	0.91	52.91	0.64	54.70	1.60	54.13	1.5	52.30$^{\#@}$	1.26	54.85	0.87	55.45	0.84	53.00$^{\#}$	0.80
BMIS arousal calm score	28.32	0.78	27.95	0.84	25.50$^{\#@}$	0.70	28.52	0.47	27.65	0.76	27.83	0.72	27.85	0.45	29.05	0.75	26.05$^{\#}$	0.79
BMIS positive tired score	22.23	0.52	21.64	0.46	19.95$^{\#@}$	0.51	23.22	0.59	21.78*	0.62	20.87$^{@}$	0.72	22.75	0.47	22.45	0.42	20.20$^{\#@}$	0.71
BMIS negative relaxed score	8.86	0.87	8.18	0.63	7.82	0.47	8.52	0.68	8.43	0.67	8.61	0.63	8.10	0.38	8.20	0.55	7.40	0.52

Footnote: Paired sample *t*-test was used for intragroup comparison and ANOVA followed by post hoc analysis was used for intergroup comparison. In intragroup comparison, * depicts significance at 1 week as compared to baseline, # depicts significance at 4 week as compared to 1 week, and @ depicts significance at 4 week as compared to baseline. In intergroup comparison (shaded boxes represent comparison groups showing significance), $ depicts significance at 1 week and ^ depicts significance at 4 week

Table 4: Effects of bepotastine on memory, psychomotor functions, sleep and mood

	Baseline		1 week		4 week	
	Mean	SEM	Mean	SEM	Mean	SEM
Remote memory	8	0	7.39*	0.231	7.94$^{\#}$	0.056
Recent memory	4.89	0.076	4.94	0.056	4.94	0.056
Mental Balance	4.5	0.55	4.28	0.636	4.22	0.613
Attention and concentration	3.78	0.552	3.5	0.414	3.83	0.493
Delayed recall	8.44	0.372	8.33	0.45	8.5	0.345
Immediate recall	6.5	0.682	6.17	0.612	6.72	0.516
Verbal retention of similar pairs	3.83	0.167	4.11	0.159	4.11	0.196
Verbal retention of dissimilar pairs	8.89	0.816	9.06	0.906	10$^{\#,@}$	0.82
Visual retention	6.83	0.48	7.5	0.525	7.78	0.558
Recognition	8.06	0.521	8.22	0.552	8.56$^{\#,@}$	0.55
PGIMS score	63.72	1.97	63.5	2.43	66.61$^{\#}$	2.416
Single letter cancellation test	22.17	1.253	23.72	1.643	24	1.563
Digit letter substitution test	19.78	1.689	19.94	2.173	20.17	1.844
Choice reaction time audio	1.51	0.09593	1.37507	0.076186	1.39339$^{\wedge}$	0.074468
Choice reaction time video	1.4	0.11132	1.37507	0.076186	1.39339	0.074468
Hand steadiness test	61.15	9.42	58.2	9.86	53.35 $^{@}$	8.01
Critical flicker fusion threshold at 20 Hz	47.64	0.14	47.78	0.19	47.64	0.14
Critical flicker fusion threshold at 50 Hz	47.64	0.14	47.64	0.14	47.64	0.14
Epworth sleepiness scale	4.72	0.69	5.89	0.69	5.06	0.569
Pleasant unpleasant score	53.22	2.209	54.39	1.753	53.72	1.604
Arousal calm score	28.94	0.857	27.11*	0.766	26.67$^{@}$	0.804
Positive tired score	22.5	0.857	21.72	0.804	20.89$^{@}$	0.9
Negative relaxed score	9.11	0.976	7.67	0.695	7.44	0.677

Footnote: Paired sample *t*-test was used for intragroup comparison. Here, * depicts significance at 1 week as compared to baseline, # depicts significance at 4 week as compared to 1 week, @ depicts significance at 4 week as compared to baseline. The shaded area represents the difference observed in intragroup comparison and ^ depicts significance at 4 week

When the effect of fexofenadine on mood was observed at 1 week as compared to baseline, no significant difference was observed. Pleasant unpleasant (P = 0.012), arousal calm (P = 0.009) and positive tired (P = 0.005) mood scores decreased significantly at 4 week as compared to 1 week. Positive tired mood score (P = 0.003) decreased significantly at 4 week as compared to baseline.

When the effect of bepotastine on mood was observed at 1 week as compared to baseline, arousal calm score (P = 0.027) showed significant increase. Arousal calm score (P = 0.015) and positive tired score (P = 0.045) were significantly increased at 4 week as compared to baseline.

Intergroup comparison of effects of antihistamines on memory, psychomotor functions, sleep and mood [Tables 1–5]

Memory

A comparison between groups showed that all the parameters of PGIMS scores at baseline were comparable.

Attention and concentration scores at 1 week were significantly high in levocetirizine (mean difference = 1.587 ± 0.598, P = 0.01) and in fexofenadine (mean difference = 1.400 ± 0.62, P = 0.02) groups as compared to chlorpheniramine group (Post hoc analysis).

Table 5: Intergroup comparison of effects of antihistamines on memory, psychomotor functions, sleep and mood

	Baseline		1 Week		4 Week	
	F	Sig.	F	Sig.	F	Sig.
Remote memory	0.839	0.477	0.987	0.403	0.814	0.49
Recent memory	0.721	0.542	1.76	0.162	1.487	0.224
Mental balance	0.45	0.718	1.266	0.292	2.235	0.091
Attention and concentration	0.2	0.896	2.746	0.048	2.588	0.059
Delayed recall	0.985	0.404	0.389	0.762	1.291	0.283
Immediate recall	0.078	0.972	1.007	0.394	1.067	0.368
Verbal retention of similar pairs	0.129	0.943	4.116	0.009	3.013	0.035
Verbal retention of dissimilar pairs	0.91	0.44	1.588	0.199	2.04	0.115
Visual retention	0.224	0.88	0.825	0.484	2.406	0.073
Recognition	0.319	0.811	1.706	0.173	0.883	0.454
PGIMS score	0.119	0.948	3.137	0.03	4.679	0.005
Single-letter cancellation test	0.938	0.426	0.385	0.764	0.725	0.54
Digit letter substitution test	0.903	0.444	0.3	0.826	1.272	0.29
Choice reaction time audio	1.654	0.184	2.576	0.06	8.764	0
Choice reaction time video	1.898	0.137	1.927	0.132	2.798	0.045
Hand steadiness test	0.387	0.763	0.779	0.509	0.988	0.403
Critical flicker fusion threshold at 20 Hz	0.387	0.762	0.58	0.63	0.632	0.597
Critical flicker fusion threshold at 50 Hz	0.357	0.784	0.617	0.606	0.332	0.802
Epworth sleepiness scale	0.924	0.433	1.616	0.192	1.049	0.375
Pleasant unpleasant score	0.228	0.876	0.259	0.855	0.265	0.851
Arousal calm score	0.452	0.717	1.012	0.392	1.895	0.137
Positive tired score	0.511	0.676	0.401	0.753	0.454	0.715
Negative relaxed score	0.318	0.812	0.238	0.869	0.974	0.409

Footnote: One-way ANOVA. P value<0.05 is considered statistically significant

Verbal retention of similar pairs score at 1 week was significantly high in fexofenadine group as compared to chlorpheniramine (mean difference = 0.718 ± 0.212, P = 0.001) and levocetirizine (mean difference = 0.674 ± 0.25, P = 0.008) groups (Post hoc analysis).

Verbal retention of similar pairs score at 4 week was high in fexofenadine group as compared to chlorpheniramine (mean difference = 0.636 ± 0.252, P = 0.014) and levocetirizine group (mean difference = 0.674 ± 0.248, P = 0.008) (Post hoc analysis).

Total PGIMS score at 1 week was high in fexofenadine group as compared to chlorpheniramine group (mean difference = 8.223 ± 2.714, P = 0.003). Total PGIMS score was high in fexofenadine group at 4 week as compared to chlorpheniramine (mean difference = 9.441 ± 2.889, P = 0.002) and levocetirizine (mean difference = 8.654 ± 2.859, P = 0.003) groups.

Psychomotor functions

When the comparison was done between groups, the psychomotor function tests' scores at baseline showed that all parameters were comparable. The comparisons of effects of drugs on all the parameters were made at 1 and 4 weeks.

Choice reaction time audio test scores at 4 week were significantly improved in fexofenadine group as compared to chlorpheniramine (mean difference = 0.321 ± 0.103, P = 0.003) and in levocetirizine group (mean difference = 0.493 ± 0.102, P = 0.000). Choice reaction time audio test scores at 4 week were significantly improved in bepotastine group as compared to levocetirizine group (mean difference = 0.350 ± 0.105, P = 0.001) (post hoc analysis).

Choice reaction time video test scores were significantly improved in fexofenadine group as compared to chlorpheniramine (mean difference = 0.314 ± 0.133, P = 0.021) and in levocetirizine group (mean difference = 0.284 ± 0.131, P = 0.033) (post hoc analysis).

Sleep

Epworth sleepiness scale scores at baseline between groups showed that all parameters were comparable and no significance at 1 and 4 weeks.

Mood

The BMIS scores at baseline showed that all parameters were comparable and showed no significance at 1 and 4 weeks in between the groups.

Adverse drug reactions (ADRs)

A total of 21 ADRs were observed, out of which 12 patients in chlorpheniramine group and 9 patients in levocetirizine group complained of drowsiness. All ADRs were possibly related to suspected drug as assessed for causality using the WHO-UMC

criteria and Naranjo's score. All ADRs were mild (level 1) as assessed by Modified Hartwig and Siegel scale. The ADRs were not preventable as assessed by Modified Schumock and Thornton criteria. Seven patients in chlorpheniramine group and six in levocetirizine group recovered from ADR within 7 days, whereas five patients in chlorpheniramine group and three in levocetirizine group did not recover from ADR at 28 days. No patients in fexofenadine group complained of ADRs.

Discussion

Family physicians are involved in treating a large proportion of patients on a daily basis specially to manage allergic diseases.[2] Assessment of cognitive and psychomotor performance of an individual depends on four essential components, that is, the sensory processing aspects, the central integration and processing mechanisms, the motor responses and sensori–motor coordination. Research so far have studies effect only on acute and subchronic effect of AHs. Though computerised neuropsychological test batteries are available, the study tools were selected on the basis of the population to be tested and lack of infrastructure in public health set-up.[13]

Six-letter cancellation test assesses the perceptual processing of sensory stimulus; recoding and recognition of sensory information was assessed by digit letter substitution test, fine motor control in hand by hand steadiness test and flicker fusion threshold assess the overall integrity, that is, the speed at which cognitive components are able to process information and arousal of CNS and critical flicker fusion tests. This coordination was checked by the choice reaction time tests.[14-16] Though 123 patients were enrolled, only 83 patients completed the study as patients were lost to follow-up which may be due to time-consuming tests, symptomatic relief in their illness or lack of time.

Effects on cognitive and psychometric tasks

The results of our study showed that chlorpheniramine and levocetirizine have deteriorating effects on cognitive and psychomotor performance, whereas fexofenadine and bepotastine showed positive effect on various cognitive and psychometric tasks.

Our study showed that with chlorpheniramine, mental balance; attention and concentration; and total PGIMS scores deteriorated at 1 week as compared to baseline. All the parameters on memory scale tend to increase at 4 weeks as compared to 1 week though not significant. At 4 weeks, mental balance, attention and concentration, delayed recall and total PGIMS deteriorated as compared to baseline. The deteriorating effects of chlorpheniramine on memory corroborated with the study conducted by Okamura *et al.* in 2000.[17] The increasing trend of scores of various parameters at 4 weeks as compared to 1 week is in line with studies conducted by Schweitzer *et al.*[18] in 1994 and Mattila MJ *et al.*[19] in 1986, which indicated tolerance to the CNS effects of chlorpheniramine.

Performance of patients on digit letter substitution test and six-letter cancellation test deteriorated significantly at 4 weeks in chlorpheniramine group, which signifies the deteriorating effects on perception, recognition and recoding of sensory stimulus.[15] In chlorpheniramine group, performance of patients deteriorated in hand steadiness test at 4 week as compared to baseline indicating the effect on fine motor control.

Our study showed that in patients on levocetirizine, remote memory, mental balance and total PGIMS scores deteriorated at 1 week. Delayed recall deteriorated at 4 week as compared to 1 week. At 4 week mental balance, delayed recall, visual retention and total PGIMS scores deteriorated as compared to baseline. The findings for levocetirizine group were contradictory to the study conducted in Netherlands on 48 healthy volunteers to assess the acute (day 1) and subchronic effects (day 4) of levocetirizine (5 mg) on cognitive and psychomotor functions, which showed that there was no significant effect of levocetirizine on memory (recognition and word learning test), attention and tracking performance at day 1 or 4.[20] There was no difference observed in psychometric performance in levocetirizine group.

In our study, it was observed that there was overall a positive effect of fexofenadine on memory, similar to a study conducted in Bangladeshi population on 100 healthy volunteers which showed that there was slight increase in cognitive functions in subjects on fexofenadine on day 1, especially in word memory test.[14]

In fexofenadine group, digit letter substitution test and single-letter cancellation tests showed significant improvement at 4 weeks as compared to baseline. This signifies the positive effect of fexofenadine on perceptual processing, recoding and recognition of sensory stimulus. Choice reaction time audio/video test scores were significantly improved in fexofenadine group as compared to chlorpheniramine and levocetirizine groups. The sedative effects of chlorpheniramine and levocetirizine can possibly explain the increase in reaction time. This finding was similar to the study done to assess the effects of chlorpheniramine on reaction time, which showed increase in the reaction time. However, the finding was contradictory in levocetirizine group.[17] However, these studies assessed only the acute effects of AHs and that too mainly on healthy volunteers. Studies for comparison of effects of AHs on memory at 4 weeks are not available. Moreover, the study conducted by Gandon J *et al.*[16] 2002 showed that choice reaction time was decreased with levocetirizine at day 1 and day 5.

Our study showed that in bepotastine group, remote memory score decreased at 1 week as compared to baseline. However, at 4 week, remote memory score increased significantly as compared to baseline. Verbal retention of dissimilar pairs', recognition scores increased significantly at 4 week as compared to 1 week and baseline. Total PGIMS score increased significantly at 4 week as compared to 1 week. Hand steadiness test showed improvement at 4 week as compared to baseline contradictory to findings of

study conducted by Takahashi *et al.* in 2004, wherein bepotastine showed no effect on psychomotor performance.[30]

Comparison of chlorpheniramine and levocetirizine groups showed that attention and concentration scores improved in levocetirizine group as compared to chlorpheniramine group. Previous studies' findings corroborated with the findings of our study in which levocetirizine in comparison to cetirizine and other first generation AHs has showed better cognitive functioning.[14,20,21] However, these studies assessed only the acute and subchronic effects of levocetrizine. Comparisons between four groups showed that the patients in fexofenadine group did better than those on chlorpheniramine or levocetirizine mainly in verbal retention of similar pairs; attention and concentration; and total PGIMS scores. Choice reaction time audio and video test scores at 4 week were significantly improved in fexofenadine group as compared to chlorpheniramine and levocetirizine groups. Choice reaction time audio test scores improved at 4 week in bepotastine group as compared to levocetirizine group. There were no studies found for comparison of intergroup findings.

The positive effect of fexofenadine on cognitive and psychomotor performance can be explained on the dopamine transporter hypothesis, which suggests to have enhanced effect on various components like executive functioning, attention and behaviour. The dopamine transporter is a presynaptic receptor, which recollects dopamine when released into the synaptic cleft. So, when the dopamine transporter is blocked, the availability of dopamine in the synaptic cleft increases. Studies which previously demonstrated the inhibition of dopamine reuptake by AHs have been performed in animals *in vitro* and in vivo.[22,23] Another assumption is based on the finding that histamine stimulates GABA neurons and that this excitation is blocked by the AH. GABA has an inhibiting effect on dopamine release, so when GABA is inhibited, this leads to excitation of dopamine cells due to disinhibition.[24] Another suggestion is that the H_3-autoreceptor is blocked by fexofenadine, leading to an increase in histamine, which causes an increased level of arousal.[25] Another reason for the reduced penetration of second-generation H_1-AHs into the brain is because their translocation across the blood–brain barrier is under the control of active transporter proteins, of which the ATP-dependent efflux pump, P-glycoprotein, is the best known. The P-glycoprotein pump will export the AH out of the CNS even if it crosses the BBB.[26] The study results regarding the fexofenadine group could also be possibly due to the better sleep quality and no next day hangover drowsiness effects as opposed to chlorpheniramine and levocetirizine groups in which patients had daytime drowsiness.[27]

Effects on sleep

Our study results showed chlorpheniramine and levocetirizine to be having sedative effects, whereas fexofenadine and bepotastine are nonsedating collaborating with the findings of study conducted by Tashiro *et al.*[28] in 2004 and Takahashi *et al.*[30] in 2004. In chlorpheniramine group, the sleepiness score increased at 1 week, but at 4 weeks, there was no significant change as compared to baseline, which may indicate the tolerance to sedative effects of chlorpheniramine.[20] A meta-analysis done by Snidvongs *et al.*[29] in 2017 to study the sedative effects of levocetirizine has shown that levocetirizine though thought to be devoid of sedative effects tend to show modest sedative effects which corroborated with our study.

Effects on mood

Our study showed that all the three drugs had negative effects on mood however, no significant difference was observed in between chlorpheniramine, levocetirizine and fexofenadine groups while in bepotastine group, arousal calm and positive tired scores increased at 4 week as compared to baseline. A study by Ozdemir *et al.*[31] showed partially similar findings with higher scores on the depression, anxiety and fatigue subscales in cetirizine, chlorpheniramine, than those who received levocetirizine. However, the mechanisms which lead to these mood effects are largely unknown.

Adverse drug reactions

Our study reported a total of 21 ADRs related to study drugs during the study period. A total of 12 (54.54%) patients in chlorpheniramine group and 9 (39.13%) patients in levocetirizine group complained of drowsiness. Our study findings were similar to the findings of a study conducted by Leynadier *et al.*[32] in 2001, which showed with levocetirizine; somnolence was found in 10.2% patients with 10 mg and in 1.7% patients with 5 mg.

Conclusions

The present study assessed acute, subchronic and long-term effects of AHs on cognitive and psychomotor, which concludes that chlorpheniramine causes deteriorating effects on mental balance, attention and concentration, delayed recall, fine motor skills, perception, recognition and recoding abilities; levocetirizine causes deteriorating effects on mental balance, delayed recall and visual retention; and improvement was observed with fexofenadine on attention and concentration, delayed and immediate recall, verbal retention of similar and dissimilar pairs, visual retention and recognition and perception, recognition and recoding ability, sensorimotor coordination on long term; and bepotastine showed improvement in remote memory, verbal retention of dissimilar pairs, recognition and total PGIMS scores. Drug groups except bepotastine had negative effect on mood, while increased sleepiness was observed with chlorpheniramine and levocetirizine. Patients involved in heavy machinery working, driving or are tasks requiring alertness should be prescribed fexofenadine or bepotastine. Chlorpheniramine and levocetrizine should not be preferred in such patients. Also, patients requiring long-term use of AHs; it is suggested that cognitive and psychological functions should be evaluated periodically for better quality of life.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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