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COMPUTER LIBRARY LITERATURE REVIEW ON EFFECTIVENESS OF  
ANTIMOTION SICKNESS DRUGS\*

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## SUMMARY PAGE

### THE PROBLEM

A computer library of the antimotion sickness drug literature has been established at the Naval Aerospace Medical Institute. A review of this literature is reported here.

### FINDINGS

The over-all effectiveness of the antihistamines was 70.6%; for the belladonnas it was 50.1%, and for the phenothiazines it was 44.9%. The over-all results of British studies indicated a greater effectiveness for the belladonnas than for the antihistamines, the reverse of U. S. studies.

The effectiveness of the individual drugs against motion sickness is also reported. The over-all effectiveness of the drugs is compared in sea, air, and experimental motion studies.

## INTRODUCTION

Computer facilities available today are designed for the storage and retrieval of large amounts of data, and the literature on antinotion sickness drugs is well suited for computer procedures. The large proportion of this literature has been published in the last twenty years, and these studies have been similar in techniques used, methods of reporting, and in drug comparisons. The increased sea and especially air travel, both civilian and military, gives added importance to these drugs. The availability of an up-to-date computer library of reports on these drugs to permit rapid surveys of this literature should be of value.

Such a computer library has been established at the Naval Aerospace Medical Institute, Pensacola, Florida, with information gained from a literature review in preparation for research on these drugs (91,92). The results of a similar review made by the Army-Navy-Air Force Motion Sickness Team preparatory to their Brømerhaven studies also were incorporated into this survey (5,83). The value of such a study is in the large number of subjects studied with the various drugs, the diverse stress conditions, and the variety of investigators presenting the reports (10,30). The obvious disadvantage is that similar emphasis is given to reports with varying degrees of strictness in experimental design. What follows is limited to a literature survey on the antinotion sickness drugs.

## PROCEDURE

The available literature concerning the effectiveness of the antinotion sickness drugs was reviewed. The pertinent facts concerning each study were entered on a form for introduction into the computer. A copy of the form is reproduced on page 2.

The items were coded for the computer program. After these data were entered into the computer, the groupings presented in the results section of this paper were obtained. Only a few special military reports were included as identical data for most reports were found in the published literature. This prevented duplication and also avoided quoting literature that is not generally available.

The percentage effectiveness of the drugs reported here was obtained by use of the following formula (55) except in a few studies where insufficient data were given:

$$\frac{\% \text{ vomiting in placebo group} - \% \text{ vomiting in drug group}}{\% \text{ vomiting in placebo group}} \times 100$$

## COMPUTOR FORM

1. Trade name-----
2. Generic name-----
3. Type of drug-----
4. Author-----
5. Test condition-----
6. Length of exposure-----
7. Placebo/double blind-----
8. Per cent effectiveness-----
9. Per cent vomiting-----
10. Per cent nausea-----
11. Type of subjects-----
- 12/13. Number of subjects-----
14. Side effects reported with drug-----
15. Drowsiness-----
16. Headache-----
17. Fatigue-----
18. Dry mouth-----
19. Blurred vision-----
20. Vertigo-----
21. Dosage-----
22. Therapeutic/prophylactic use-----
23. Route of administration-----
24. Per cent vomiting with placebo-----
25. Side effects reported with placebo-----

## RESULTS AND DISCUSSION

The computations are presented in Tables I-V. The major portion of these drugs can be divided into several large divisions as indicated below. The over-all percentage effectiveness for each drug (Table I) is shown in parenthesis following the drug name in each division.

### ANTIHISTAMINES

The antihistamines have been employed against motion sickness since their introduction by Gay and Carlinger in 1949 (41-43). Literature on the antihistamines surveyed in the present study involved over 14,000 subjects and 53 experiments.\* The most effective and well-established drugs in this group were dimenhydrinate (72.9%) (1,73,74,80,81), cyclizine (71.2%) (60), meclizine (71.5%) (36,39,50,57,62), and diphenhydramine (62.0%) (51). The side effect of drowsiness is reported to be a limiting factor with the use of dimenhydrinate and diphenhydramine (6). Cyclizine and meclizine are reported to produce less drowsiness. A low incidence of side effects is also reported for buclizine (75.0%) (33) and cinnarazine (60.0%) (83) which are promising new additions to this group. The combination of diphenhydramine with hyoscine (66.0%) and with hyoscine aminoxide (50.0%) would tend to indicate that, in general, the combinations are no more effective than the most active principal in them (21,45). Overall, this group of drugs was reported to be 70.6 per cent effective in preventing motion sickness.

### BELLADONNAS<sup>+</sup>

The belladonnas have had long and extensive use as motion sickness preventives and as a group in this survey were 50.1 per cent effective in 25 experiments involving 3015 subjects. Hyoscine was 62.9 per cent (32,46), followed by benztropine (58.0%), atropine (50.0%), trihexyphenidyl (36.0%), and hyoscine aminoxide (24.0%) (31) among others. Hyoscine has long had the support of British investigators as being one of the most effective antimotion sickness preparations. The side effects of dry mouth, blurred vision, and drowsiness have been reported with its use. With prolonged use disturbing dreams have also been reported (24,51). The synthetic belladonnas have fewer side effects (17,71) but also appear to be less effective, with the possible exception of benztropine (one study) (5). Hyoscine in the 0.6 mg dose seems to be the drug of choice in this group.

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\*(refs. 3,4,7,8,11,16-19,20,22,23,25-29,37,38,51,53,56,59,66,70,82,93,94)

<sup>+</sup>(refs. 14,15,34,48,49,52,55,56,61,63,64,67-69,75-78,89,90)

Table 1

Effectiveness of Drugs in Preventing Motion Sickness Listed by Generic Names

Drug	No. of Subjects	Effectiveness Per Cent	No. of Studies
Benactyzine	61	3.50	1
Benztropine	264	58.00	1
Buclizine	587	75.00	2
Caramiphen	86	1.50	1
Cyclizine	2128	71.24	6
Cycrimine	95	47.00	1
Chlorpromazine	139	21.80	1
Chlorcyclizine	193	37.50	2
Diethazine	803	2.00	1
Dimenhydrinate	5184	72.91	15
Dimenhydrinate + Hyoscine	1234	66.02	9
Diphemanil	93	8.00	1
Dimenhydrinate + Hyoscine Aminoxide	117	50.00	1
Ethopropazine	960	45.52	2
Hyoscine Aminoxide	302	24.41	3
Hyoscine	2713	62.96	22
Meclizine	2736	67.98	12
Meprobamate	440	75.00	1
Nislamide	127	19.70	1
Orphenadrine	94	7.00	1
Promazine	67	5.00	1
Promethazine	3977	64.33	14
Perphenazine	73	25.00	1
Procyclidine	192	30.09	2
Prochlorperazine	518	39.81	4
Pyrathiazine	821	62.05	2
Pheniramine	1156	59.82	3
Phenyltatoxamine	111	5.00	1
Trifluoperazine	468	69.00	2*
Trimethobenzamine	43	0.50	1
Trihexyphenidyl	625	36.44	5
Diphenhydramine	2053	62.11	9
Promethazine + d-Amphetamine	80	50.00	1
Glutethimide	150	21.20	2
d-Amphetamine	168	64.00	4
Thiethylperazine	425	35.00	2

\*Tested for therapeutic effect and not for prophylactic effect.

## PHENOTHIAZINES\*

The phenothiazines have proven to be excellent antiemetics for chemically induced nausea; however, this does not appear to be directly related to potency in preventing motion sickness. Chlorpromazine which is reported to be only 21.8 per cent effective against motion sickness is an example of this. Promethazine appears to be the best established preparation in this group (9). It has an over-all effectiveness of 64.3 per cent in 14 studies (44). Prochlorperazine (39.8%) (12,88) and trifluoperazine (69.0%) (35,84), which was tested for therapeutic effect and not for prophylactic effect, appear to be promising drugs; however, at present too few reports on them are available. Part of the success of this group of drugs against motion sickness may be due to relief of some of the psychic factors which are of great importance in susceptibility to motion sickness. Side effects of drowsiness, decreased alertness, and hypotension have been reported with these preparations. This is a very active area of drug research, however, and it is possible that other effective drugs will be found here. At present, however, further investigation is indicated before the phenothiazines are well established as antimotion sickness drugs. Other tranquilizer drugs such as the rauwolfias have not proven to be effective against motion sickness (30,86).

## MONAMINE OXIDASE INHIBITORS

The monamine oxidase inhibitors have not proven to be significantly effective against motion sickness. In fact, some studies have reported a heightened susceptibility with them (5,30).

## VITAMINS

Vitamin preparations, although they have reported effectiveness against vertigo from atherosclerosis and against nausea of pregnancy, have been uniformly unsuccessful against motion sickness (5).

## MISCELLANEOUS

There is one report that meprobamate was 75 per cent effective, but again further investigation seems indicated before its use is established in this area (40).

Trimethobenzamide has been used against motion sickness; however, in the only study available to this survey it was ineffective as a prophylactic measure (89).

The use of d-amphetamine against motion sickness has been reported in four studies in which it was 64.0 per cent effective (2, 13, 54, 58). When combined with other drugs its effectiveness is not diminished (16), and therefore it may be of value in counteracting the drowsiness reported with several of the preparations.

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\*(refs. 47, 65, 72, 87)

## COMMENTS

In Table II it is noted that drug effectiveness diminished with exposure to motion of more than twenty-four hours. This would be expected as susceptibility is increased with time in exposure.

Table II

Length of Exposure as Related to Effectiveness Against Motion Sickness

	No. of Subjects	Effectiveness Per cent	No. of Studies
Less than 24 hrs.	13162	67.32	69
24 hrs. or more	16273	55.35	68

The type of motion is also an important consideration. The drugs were more effective in flying studies than in studies at sea. It is noted that, with experimentally produced motion, which eliminates the milder test situations, the antmotion sickness drugs were generally less effective (Table III). A more careful selection for susceptibility of subjects in the experimental conditions may have also been a factor.

Table III

Effectiveness of all Types of Antmotion Sickness Drugs as Related to Type of Exposure

	No. of Subjects	Effectiveness Per cent	No. of Studies
Sea	16502	55.77	74
Air	8467	72.74	29
Exp. Sea	353	33.84	5
Exp. Air	3776	59.54	24
Swing	141	39.33	2

In Table IV the antihistamines are listed as 70 per cent effective while hyoscine was 50 per cent effective. Table V, however, indicates reverse results when the British and U. S. studies are considered separately. These were in the main all military studies using placebos and double-blind conditions; therefore, it is difficult to explain these differences. A variation in the strength of stimulus in the various studies may be part of the answer. It may be that the antihistamines have adequate effects against only the milder stresses due to motion, while hyoscine is effective not only in mild but also in the more severe stresses. In carefully controlled studies on effectiveness of antimotion sickness drugs at the Naval Aerospace Medical Institute utilizing the Slow Rotation Room the results were in general agreement with the British reports (89).

Table IV  
Type of Drugs as Reported for Over-All Effectiveness

Type	No. of Subjects	Effectiveness Per cent	No. of Studies
Antihistamines	14402	70.58	53
Antihistamine + Belladonna	1301	65.27	9
Belladonna	3015	50.10	25
Synthetic Belladonnas	2678	23.19	14
Moncamine Oxidase Inhibitors	127	19.70	1
Phenothiazines	1363	44.91	7
Tranquilizers	822	63.33	4
Vitamins	336	5.00	3

Table V

## Comparison of British and U. S. Reports of Effectiveness

	No. of Subjects	Effectiveness Per cent	No. of Studies
Antihistamines			
British	807	39	11
U. S.	2496	70	36
Hyoscine			
British	417	83	6
U. S.	997	52	19

In some of the studies reported in this survey, the proper research conditions of placebos and double blind (85) were not used. The computer cannot improve upon poorly collected data; therefore, a test design incorporating these features is strongly recommended for any future studies. The computer library is continuing to be expanded by additional studies from the literature and by new reports as they are published.

Motion sickness is a complex and unique response. There appears to be no correlation between potency as an antimotion sickness preparation and effectiveness of the same drugs as antihistamines against Parkinsonism, with other types of nausea and vertigo, and even as antiemetics against chemically induced nausea. It is therefore important that these drugs be tested against conditions which evoke motion sickness before any recommendations are made for their use against motion sickness.

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<b>4. DESCRIPTIVE NOTES (Type of report and inclusive dates)</b>			
<b>5. AUTHOR(S) (Last name, first name, initial)</b>  Wood, Charles D.; Kennedy, Robert S.; Graybiel, Ashton; Wherry, Robert J. Jr., and Trumbull, Richard			
<b>6. REPORT DATE</b>  15 November 1965		<b>7a. TOTAL NO. OF PAGES</b>  15	<b>7b. NO. OF REFS</b>  94
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<b>10. AVAILABILITY/LIMITATION NOTICES</b>  Qualified requesters may obtain copies of this report from DDC. Available, for sale to the public, from the Clearinghouse for Federal Scientific and Technical Information, Springfield, Virginia 22151.			
<b>11. SUPPLEMENTARY NOTES</b>		<b>12. SPONSORING MILITARY ACTIVITY</b>	
<b>13. ABSTRACT</b>  A computer library of the antimotion sickness drug literature has been established at the Naval Aerospace Medical Institute. A review of this literature is reported here. The over-all effectiveness of the antihistamines was 70.6 per cent; for the belladonnas it was 50.1 per cent, and for the phenothiazines it was 44.9 per cent. The over-all results of British studies indicated a greater effectiveness for the belladonnas than for the antihistamines, the reverse of U. S. studies. The effectiveness of the individual drugs against motion sickness is also reported. The over-all effectiveness of the drugs is compared in sea, air, and experimental motion studies.			

14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Motion sickness						
Pharmacology						
Therapeutic effect of drugs						
Computer techniques						
Literature review						

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