Table 52

Total Number of Days With Normal Eating

Number of Patients and (Percentages)

Factorial Analysis

Number of Days With Normal Eating	Medications Containing Doxylamine	Medications Without Doxylamine	Medications Containing Pyridoxine	Medications Without Pyridoxine	Medications Containing Dicyclomine	Medications Without Dicyclomine
6	224 (27)	157 (20)	188 (24)	193 (24)	181 (22)	200 (25)
5	150 (18)	110 (14)	139 (18)	121 (15)	127 (16)	133 (17)
4	132 (16)	101 (13)	104 (13)	129 (16)	126 (16)	107 (13)
3	88 (11)	84 (11)	90 (11)	82 (10)	86 (11)	86 (11)
2	69 (8)	89 (12)	83 (11)	75 (9)	68 (8)	90 (11)
1	56 (7)	86 (11)	69 (9)	73 (9)	77 (10)	65 (8)
0	110 (13)	143 (19)	115 (15)	138 (17)	140 (17)	113 (14)
Mean	3.7	3.1	3.5	3.4	3.4	3.5

Table 53

Total Number of Days With Normal Daily Activities

Number of Patients (Percentages)

Factorial Analysis

Number of Days With Normal Activities	Medications Containing Doxylamine	Medications Without Doxylamine	Medications Containing Pyridoxine	Medications Without Pyridoxine	Medications Containing Dicyclomine	Medications Without Dicyclomine
6	231 (28)	163 (21)	194 (25)	200 (25)	195 (24)	199 (25)
5	153 (18)	115 (15)	138 (18)	130 (16)	120 (15)	148 (19)
4	112 (14)	113 (15)	108 (14)	117 (14)	117 (15)	108 (14)
3	95 (11)	93 (12)	96 (12)	92 (11)	101 (13)	87 (11)
2	62 (7)	88 (11)	75 (10)	75 (9)	78 (10)	72 (9)
1	69 (8)	71 (9)	73 (9)	67 (8)	69 (9)	71 (9)
0	107 (13)	127 (16)	104 (13)	130 (16)	125 (16)	109 (14)
Mean	3.7	3.3	3.5	3.5	3.4	3.6

Table 54

Effect on Nausea on Eating

(Factorial Analysis)

Effect	Normal Approximation	p*
Main effect of Doxylamine	5.41	<.01
Main effect of Pyridoxine	.87	.19
Main effect of Dicyclomine	-1.60	.94
Doxylamine/Pyridoxine Interaction	1.36	.17
Doxylamine/Dicyclomine Interaction	- .43	>.25
Dicyclomine/Pyridoxine Interaction	-1.13	>.25
Three factor Interaction	.24	>.25

*The test is based on the chi square test for a linear trend in proportions. The main effect p values are one-sided probabilities testing for positive main effects. The interaction p values are two-sided probabilities testing for both positive and negative interactions. A positive value for the normal approximation indicates a positive effect while a corresponding negative value indicates a negative main effect or interaction.

Table 55

Effect of Nausea on Daily Activities

(Factorial Analysis)

Effect	Normal Approximation	p*
Main effect of Doxylamine	3.99	<.01
Main effect of Pyridoxine	.78	.22
Main effect of Dicyclomine	-1.35	.91
Doxylamine/Pyridoxine Interaction	- .91	>.25
Doxylamine/Dicyclomine Interaction	- .17	>.25
Dicyclomine/Pyridoxine Interaction	.81	>.25
Three factor Interaction	.23	>.25

*The test is based on the chi square test for a linear trend in proportions. The main effect p values are one-sided probabilities testing for positive main effects. The interaction p values are two-sided probabilities testing for both positive and negative interactions. A positive value for the normal approximation indicates a positive effect while a corresponding negative value indicates a negative main effect or interaction.

FIGURE 6

Daily Percentages of Patients Experiencing No Effects of Nausea on Eating

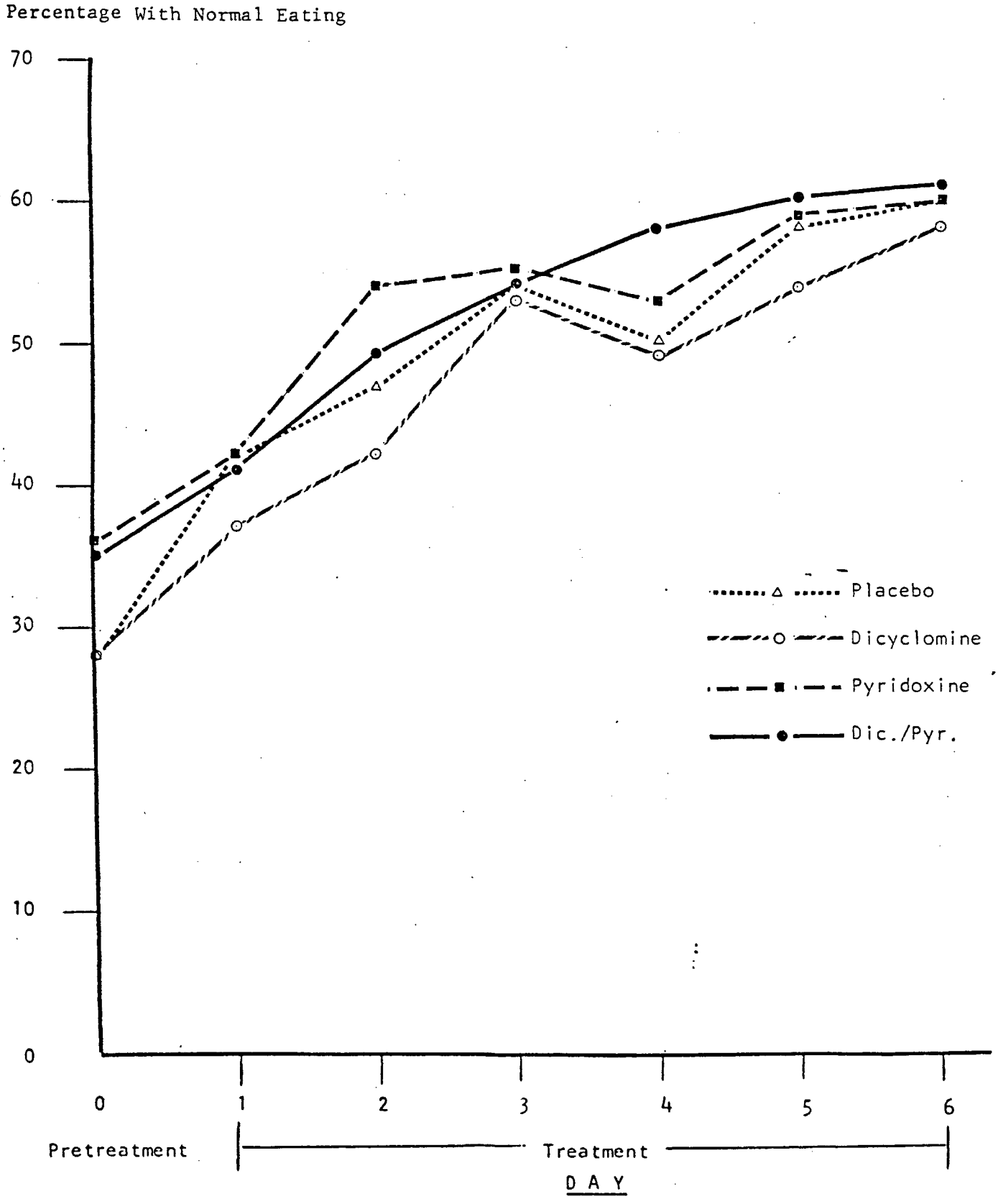


FIGURE 7

Daily Percentages of Patients Experiencing No Effects of Nausea on Eating

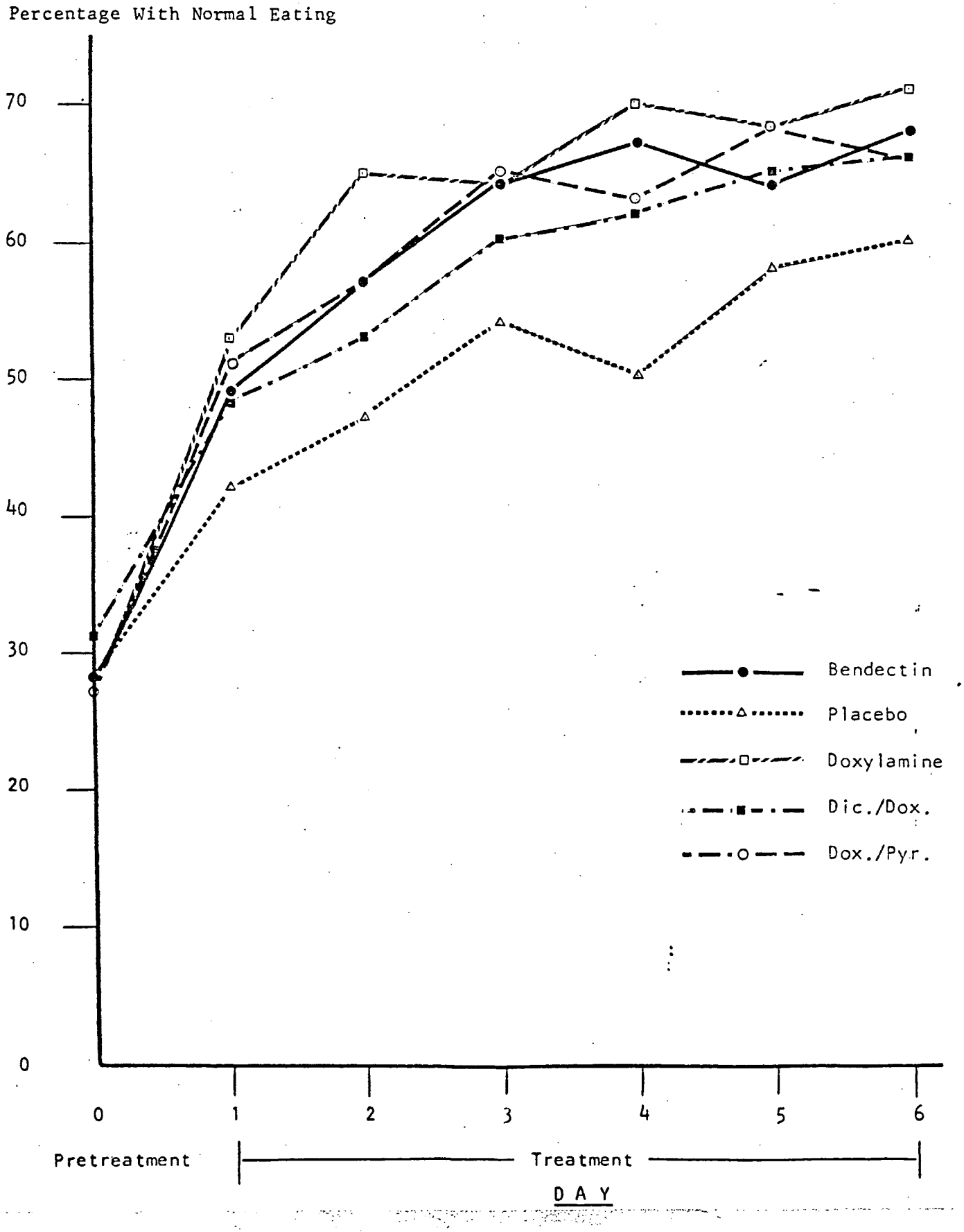
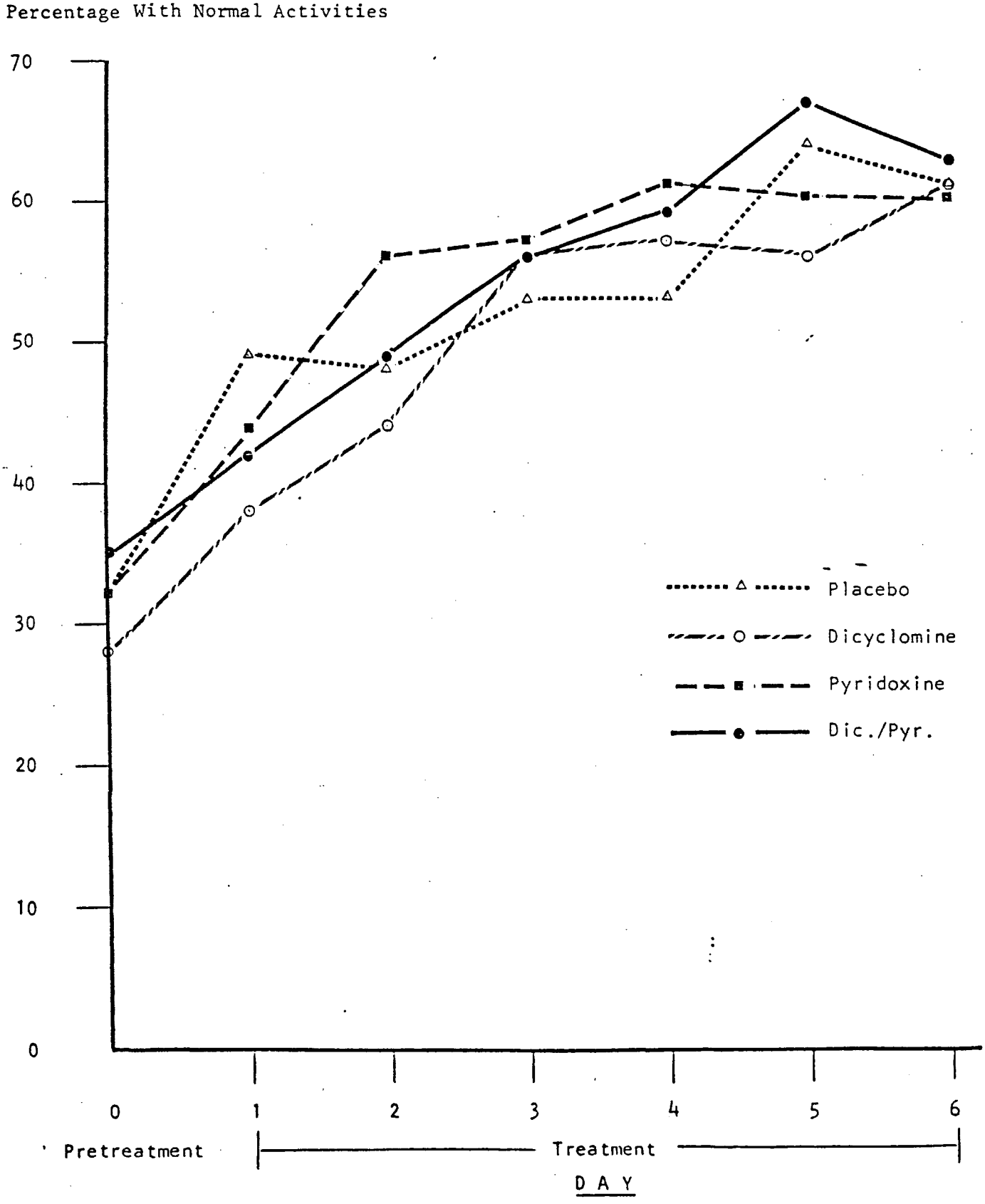


FIGURE 8

Daily Percentages of Patients Experiencing No Effects of Nausea on Usual Daily Activities



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8. Analysis of Subgroups

The eight treatment medications were compared for seven subdivisions of the population which were considered to have potentially important differences in responsiveness to medication. The emphasis in these comparisons was on exploring in greater detail the symptomatology of nausea and vomiting of pregnancy for various subpopulations rather than on tests of significance.

The subdivisions were as follows:

1. Patients who took two tablets at bedtime on each of the nights of the study.
2. Patients who took at least 3 tablets within 24 hours every day of the study.
3. Patients who did not take vitamins during the study.
4. Patients who did not take concomitant medications other than vitamins during the study.
5. Patients who were evaluated by the physician as having moderate or severe nausea and vomiting at pretreatment.
6. Patients in their first pregnancy.
7. Patients with estimated gestation less than 9 weeks.

The physician's overall evaluation of effectiveness of medication was used in the treatment comparisons since this parameter can be easily analyzed and interpreted and provides an overall indication of efficacy. Table 56 lists the percentage with evaluations of moderate or excellent effectiveness for each treatment.

The only subgroup which differed significantly from the total patient population was the group who took 3 or more tablets within 24 hours every day of the study. For this subgroup there was a significantly smaller percentage of patients evaluated as experiencing moderate or excellent effectiveness of medication compared to the total population. This is as expected since each patient was instructed to take an additional tablet in the mornings and/or in the midafternoons if she was still experiencing nausea and/or vomiting.

In the comparisons between medications there are stronger trends indicating the effectiveness of dicyclomine/pyridoxine over placebo for the subpopulation who took 2 tablets at bedtime every night of the study and for the patients who did not take vitamins. There are stronger trends indicating the effectiveness of pyridoxine over placebo for the patients who took 2 tablets at bedtime every night of the study, for the patients who did not take concomitant medications, for the patients with less severe symptoms at pretreatment, and for the patients who did not take vitamins. There are only small differences in effectiveness between the treatments containing doxylamine in all subgroups.

Table 56

Moderate or Excellent Effectiveness of Medication

Based on the Physician's Evaluation

(Percentage of Patients)

Subgroup		Total Sample Size	Placebo	Dicyclomine	Pyridoxine	Dicyclomine/ Pyridoxine	Doxylamine	Dicyclomine/ Doxylamine	Doxylamine/ Pyridoxine	Bendectin
Took 2 tablets at bedtime every night	No	317	69	66	76	46	72	82	66	67
	Yes	1282	54	60	64*	64*	78*	76*	81*	72*
Took at least 3 tablets within 24 hours every day of treatment	No	1008	62	68	69	64	78*	80*	78*	69
	Yes	591	48	52	61	56	73*	73*	77*	74*
Patient took vitamins	No	844	53	57	66*	66*	79*	80*	76*	69*
	Yes	755	64	64	65	55	74	75*	79*	72
Patient took concomitant medication other than vitamins	No	1179	56	61	66*	60	75*	77*	78*	72*
	Yes	420	59	62	66	63	82*	79*	75*	68
Pretreatment moderate or severe nausea and vomiting	No	1160	54	60	66*	62	75*	79*	80*	73*
	Yes	439	62	63	64	58	81*	75	71	65
Gravida	= 1	634	52	62	65	65	82*	82*	77*	70*
	> 1	965	59	60	67	59	73*	75*	78*	72*
Gestation	≤ 8 wks.	995	55	58	66*	63	76*	80*	75*	68*
	> 8 wks.	604	61	67	67	57	78*	74	81*	76*

*$p < .05$. The p values are one-sided probabilities based on chi square tests of each active medication vs. placebo.

9. Pooling of Investigators' Results

The variation among the results from different investigators was tested in a formal statistical analysis for a parameter taken from the patient's daily diary card (the daily duration of nausea, section 3) and for a parameter taken from the physician's final evaluation form (the evaluation of effectiveness of medication, section 5). For both of these parameters a significant portion of the variation in the experiment was attributed to investigator groups treated as blocks. However, there was no evidence of a significant treatment by investigator interaction for either parameter.

These results can be interpreted as providing supporting evidence for combining the results from all investigators since an analysis of the total population, while potentially increasing the unexplained variation in the population, does not appear to bias the overall comparisons among medications. Further justifications for pooling of results are the fact that a single protocol was used for all investigators and that separate treatment randomizations were carried out for each investigator. Furthermore, individual analyses may be misleading since 16 of the 29 investigators had fewer than 5 patients in at least one treatment group (see Table 1).

As a further check on the consistency of the investigators' results, tables were constructed which list for each investigator a statistic based on each of the seven efficacy variables. The seven parameters are as follows:

Physician's Evaluation

1. Effectiveness of medication - percentage evaluated moderate or excellent (Table 57).
2. Nausea - percentage improved (Table 58).
3. Vomiting - percentage improved (Table 59).

Patient's Daily Diary Card

4. Nausea - percent reduction from pretreatment (Table 60).
5. Vomiting - percentage with no vomiting on 5 or more treatment days (Table 61).
6. Eating - percentage with normal eating on 5 or more treatment days (Table 62).
7. Daily activities - percentage with normal daily activities on 5 or more treatment days (Table 63).

The patients who were asymptomatic for vomiting at pretreatment were not included in the tables relating to the analysis of vomiting. The patients of investigators having a small number of patients evaluated for the parameter under analysis were pooled into one group. The numbers in these tables include only those investigators where the active medication or placebo was ranked higher for the parameter under analysis, i.e., the investigators with ties were excluded.

The tables show that there are differences between investigators, as expected, but also indicate a consistent trend in favor of the active medications over placebo. Table 64 lists for each parameter the number of investigators for which the active medications were evaluated to be better than placebo. This table indicates a similar ranking of the medications by order of effectiveness as shown by the analysis of the total patient population.

Table 57

Moderate or Excellent Effectiveness of Medication

Based on the Physician's Evaluation

Investigator	Placebo		Dicyclomine		Pyridoxine		DIC/PYR		Doxylamine		DIC/DOX		DOX/PYR		Bendectin	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Berry	6	50	6	33	5	60	4	100	4	100	6	100	5	80	4	86
Cameron	10	50	15	53	14	71	14	71	13	69	15	73	16	69	13	62
Ficklen	4	75	4	75	4	100	3	0	4	100	4	75	3	67	4	75
Phillips	7	57	8	50	7	71	3	67	8	88	10	90	9	67	8	63
Bolding	10	60	13	69	15	73	15	80	9	89	14	86	15	93	12	67
Balin	4	100	6	83	3	67	3	100	4	100	3	100	4	50	3	33
Greenblatt	5	40	6	50	7	71	5	80	7	57	7	100	8	100	7	71
Greer	8	75	9	67	6	67	8	38	9	89	9	78	9	89	6	33
Malinak	5	60	3	33	6	50	5	80	6	67	7	71	4	100	5	100
McQuarrie	16	31	14	50	16	44	15	40	17	65	16	56	14	57	17	53
Weed	7	43	6	83	7	86	5	60	9	67	8	63	8	63	9	78
Taylor	8	75	9	67	8	63	8	50	10	90	9	78	8	100	10	70
Celnicker	13	85	14	71	13	69	14	86	16	75	12	83	15	87	12	75
Kritzer	7	71	8	25	3	0	7	57	9	67	10	70	6	50	9	89
Robison	13	77	17	65	14	93	21	71	14	86	17	82	15	87	11	82
Rowley	8	25	10	80	10	60	9	56	10	70	10	80	12	83	8	63
Rush	4	25	4	100	5	80	6	33	7	71	6	100	5	80	3	100
Salter	8	75	10	70	7	71	7	100	6	83	8	88	8	100	8	88
Deruiter	4	50	8	63	9	33	7	29	12	75	10	70	11	64	9	78
Kuhn	11	55	15	53	13	69	15	33	12	67	15	67	12	92	13	92
Other Investigators	23	43	18	56	19	100	21	57	23	78	22	73	26	62	15	53
Total Population	181	56	203	61	191	66	195	61	209	77	218	78	213	78	189	71

Table 58

Physician's Evaluation of Nausea

Percentage Improved

Investigator	Placebo		Dicyclomine		Pyridoxine		DIC/PYR		Doxylamine		DIC/DOX		DOX/PYR		Bendectin	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Berry	6	17	6	33	5	40	4	25	4	75	6	83	5	60	7	29
Cameron	10	60	15	67	14	71	14	64	13	77	15	60	16	100	13	77
Ficklen	4	50	4	50	4	75	3	33	4	75	4	50	3	67	4	75
Phillips	7	100	8	50	7	57	3	100	8	88	10	70	9	78	8	88
Bolding	10	60	13	77	15	87	15	40	9	100	14	93	15	100	12	75
Balin	4	0	6	17	3	67	3	0	4	100	3	67	4	25	3	0
Greenblatt	5	20	6	17	7	71	5	60	7	29	7	57	8	50	7	57
Greer	8	75	9	78	6	83	8	75	9	100	9	89	9	78	6	33
Malinak	5	20	3	33	6	50	5	80	6	17	7	57	4	75	5	60
McQuarrie	16	44	14	57	16	81	15	47	17	59	16	63	14	71	17	65
Weed	7	43	6	50	7	43	5	100	9	56	8	63	8	50	9	22
Taylor	8	75	9	78	8	88	8	75	10	80	9	67	8	88	10	50
Celnicker	13	69	14	78	13	62	14	57	16	75	12	58	15	93	12	75
Kritzer	7	57	8	50	3	67	7	43	9	89	10	70	6	50	9	78
Robison	13	54	17	71	14	79	21	62	14	71	17	65	15	67	11	82
Rowley	8	25	10	40	10	50	9	33	10	30	10	60	12	83	8	38
Rush	4	50	4	25	5	20	6	50	7	86	6	67	5	60	3	100
Salter	8	50	10	70	7	57	7	71	6	67	8	38	8	75	8	88
Deruiter	4	75	8	88	9	67	7	86	12	92	10	90	11	91	9	89
Kuhn	11	55	15	80	13	85	15	53	12	92	15	93	12	75	13	85
Other Investigators	23	43	18	50	19	58	21	57	23	57	22	82	26	65	15	53
Total Population	181	52	203	61	191	68	195	57	209	69	218	71	213	75	189	65

Table 59

Physician's Evaluation of Vomiting

Percentage Improved

Investigator	Placebo		Dicyclomine		Pyridoxine		DIC/PYR		Doxylamine		DIC/DOX		DOX/PYR		Bendectin	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Cameron	7	57	13	69	10	80	11	73	10	100	12	83	14	93	10	80
Phillips	5	80	5	60	5	60	2	100	5	100	6	100	7	71	7	86
Bolding	6	83	5	60	7	71	6	100	6	100	7	71	9	67	9	89
Greer	5	80	7	100	4	50	6	17	7	71	9	67	5	100	4	75
McQuarrie	11	45	9	44	11	91	11	55	8	50	12	58	10	70	8	88
Taylor	2	50	3	67	3	100	6	50	4	100	4	75	3	33	3	67
Celnicker	9	89	6	83	10	70	6	71	6	83	8	75	7	100	4	100
Robinson	5	60	6	83	5	40	10	60	5	80	9	78	7	86	4	100
Rowley	6	17	6	83	6	17	6	50	8	37	5	80	7	43	5	40
Salter	7	71	3	67	2	50	3	67	4	75	6	17	2	50	4	75
Deruiter	3	100	5	80	4	50	3	33	9	89	5	80	9	67	6	83
Kuhn	5	80	4	100	6	100	4	75	5	80	7	100	6	83	6	83
Other Investigators	32	66	28	61	37	62	28	64	40	75	48	77	34	65	32	69
Total Population	103	66	99	71	110	66	103	62	116	78	137	74	120	73	102	77

Table 60

Average Percent Reduction in Daily Hours of Nausea

Investigator	Placebo		Dicyclomine		Pyridoxine		DIC/PYR		Doxylamine		DIC/DOX		DOX/PYR		Bendectin	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Berry	6	-18	6	45	5	18	4	40	4	43	6	6	5	90	7	75
Cameron	10	58	15	32	14	26	14	41	13	55	15	-2	16	55	13	34
Ficklen	4	11	4	-2	4	-26	3	-26	4	76	4	94	3	39	4	47
Phillips	7	66	8	42	7	41	3	42	8	59	10	40	9	75	8	64
Bolding	10	11	13	46	15	35	15	65	9	78	14	73	15	83	12	62
Balin	4	86	6	70	3	49	3	73	4	85	3	88	4	59	3	84
Greenblatt	5	21	6	26	7	36	5	84	7	74	7	59	8	86	7	69
Greer	8	49	9	72	6	87	8	53	9	83	9	54	9	72	6	22
Malinak	5	54	3	-49	6	-13	5	49	6	37	7	57	4	-38	5	58
McQuarrie	16	57	14	35	16	57	15	47	17	45	16	48	14	62	17	63
Weed	7	44	6	61	7	-5	5	44	9	53	8	45	8	-3	9	42
Taylor	8	44	9	43	8	27	8	44	10	61	9	50	8	57	10	48
Celnicker	13	26	14	43	13	48	14	58	16	45	12	55	15	68	12	62
Kritzer	7	-36	8	-30	3	-383	7	38	9	67	10	68	6	31	9	59
Robison	13	35	17	41	14	45	21	17	14	47	17	23	15	69	11	46
Rowley	8	-3	10	-5	10	-14	9	1	10	12	10	41	12	48	8	68
Rush	4	0	4	-9	5	-7	6	25	7	46	6	34	5	37	3	90
Salter	8	1	10	62	7	23	7	66	6	55	8	43	8	62	8	68
Deruiter	4	62	8	51	9	37	7	12	12	73	10	60	11	67	9	70
Kuhn	11	11	15	26	13	48	15	21	12	60	15	54	12	76	13	71
Other Investigators	23	2	18	43	19	26	21	56	23	65	22	60	26	66	15	9
Total Population	181	31	202	36	191	35	195	44	209	56	218	50	213	64	189	57

A negative change indicates an increase of nausea during treatment.

Table 61

Percentage of Patients with No Vomiting

on 5 or More Treatment Days

Investigator	Placebo		Dicyclomine		Pyridoxine		DIC/PYR		Doxylamine		DIC/DOX		DOX/PYR		Bendectin	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Berry	3	33	2	0	5	60	2	50	1	100	2	0	3	67	2	50
Cameron	4	25	5	60	6	83	4	75	5	80	7	86	4	75	5	20
Phillips	2	50	3	0	3	33	2	50	3	100	2	100	5	40	4	25
Greenblatt	2	50	3	67	3	67	3	67	3	67	3	67	1	100	5	40
Greer	4	25	6	33	4	100	3	33	6	83	7	86	5	60	4	25
McQuarrie	8	13	8	25	4	25	8	38	5	60	9	33	7	43	6	33
Taylor	2	50	3	67	2	0	3	0	3	33	4	25	3	67	2	50
Celnicker	8	38	6	67	6	33	5	100	4	50	6	67	5	80	4	50
Kritzer	2	50	2	0	1	0	2	50	4	75	3	67	4	75	1	100
Robison	4	50	4	25	4	50	9	33	3	100	8	38	5	80	3	67
Rowley	2	0	2	0	2	0	3	0	2	50	1	0	5	60	4	75
Rush	2	0	2	50	1	0	3	33	2	100	1	100	1	0	2	100
Deruiter	2	50	4	25	4	50	1	0	3	100	4	75	7	71	2	100
Kuhn	4	50	4	75	2	0	1	100	2	0	1	0	2	50	4	100
Other Investigators	19	37	6	50	17	24	15	60	17	76	24	71	20	60	16	69
Total Population	67	28	60	30	64	29	61	39	63	54	82	49	76	48	63	46

Table 62

Percentages of Patients with Normal Eating

on 5 or More Treatment Days

Investigator	Placebo		Dicyclomine		Pyridoxine		DIC/PYR		Doxylamine		DIC/DOX		DOX/PYR		Bendectin	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Berry	6	50	6	33	5	40	4	50	4	75	6	67	5	40	7	100
Cameron	10	50	15	40	14	50	14	64	13	85	15	60	16	69	13	54
Ficklen	4	50	4	50	4	50	3	0	4	100	4	75	3	67	4	50
Phillips	7	43	8	38	7	57	3	33	8	50	10	60	9	56	8	50
Bolding	10	60	13	62	15	60	15	60	9	78	14	57	15	73	12	47
Balin	4	100	6	100	3	100	3	100	4	100	3	100	4	100	3	100
Greenblatt	5	40	6	83	7	71	5	100	7	71	7	57	8	88	7	71
Greer	8	50	9	44	6	67	8	38	9	56	9	78	9	33	6	67
Malinak	5	80	3	33	6	50	5	80	6	83	7	57	4	25	5	80
McQuarrie	16	63	14	43	16	44	15	53	17	59	16	50	14	36	17	47
Weed	7	57	6	33	7	29	5	20	9	56	8	50	8	50	9	78
Taylor	8	50	9	33	8	25	8	13	10	70	9	33	8	50	10	60
Celnicker	13	38	14	43	13	23	14	50	16	69	12	50	15	80	12	67
Kritzer	7	43	8	25	3	33	7	29	9	67	10	40	6	50	9	78
Robison	13	38	17	29	14	43	21	43	14	64	17	47	15	40	11	55
Rowley	8	38	10	50	10	60	9	44	10	30	10	40	12	75	8	63
Rush	4	50	4	25	5	20	6	33	7	57	6	67	5	40	3	67
Salter	8	25	10	50	7	29	7	57	6	50	8	38	8	50	8	63
Deruiter	4	25	8	50	9	33	7	29	12	83	10	90	11	82	9	67
Kuhn	11	45	15	60	13	62	15	47	12	50	15	80	12	75	13	69
Other Investigators	23	48	18	44	19	58	21	62	23	61	22	59	26	46	15	47
Total Population	181	33	203	32	191	37	195	37	209	49	218	41	213	47	189	44

Table 63

Percentage of Patients with Normal Daily Activities on 5 or More Treatment Days

Investigator	Placebo		Dicyclomine		Pyridoxine		DIC/PYR		Doxylamine		DIC/DOX		DOX/PYR		Bendectin	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Berry	6	67	6	17	5	60	4	50	4	100	6	67	5	60	7	86
Cameron	10	70	15	47	14	64	14	64	13	77	15	67	16	81	13	54
Ficklen	4	50	4	50	4	25	3	33	4	100	4	75	3	67	4	50
Phillips	7	71	8	38	7	57	3	33	8	63	10	70	9	56	8	50
Bolding	10	60	13	46	15	60	15	73	9	78	14	64	15	80	12	58
Balin	4	100	6	100	3	67	3	100	4	100	3	100	4	100	3	100
Greenblatt	5	20	6	50	7	86	5	60	7	57	7	57	8	88	7	71
Greer	8	63	9	56	6	83	8	75	9	67	9	78	9	44	6	67
Malinak	5	80	3	67	6	50	5	80	6	67	7	43	4	25	5	80
McQuarrie	16	63	14	43	16	50	15	33	17	53	16	56	14	21	17	41
Weed	7	43	6	33	7	86	5	60	9	44	8	50	8	63	9	55
Taylor	8	50	9	44	8	38	8	13	10	50	9	44	8	63	10	20
Celnicker	13	54	14	50	13	23	14	50	16	63	12	50	15	80	12	67
Kritzer	7	43	8	38	3	67	7	43	9	67	10	60	6	50	9	78
Robison	13	54	17	24	14	29	21	43	14	64	17	41	15	40	11	45
Rowley	8	38	10	30	10	50	9	44	10	10	10	30	12	58	8	50
Rush	4	50	4	25	5	40	6	50	7	29	6	50	5	40	3	67
Salter	8	25	10	50	7	57	7	57	6	67	8	38	8	50	8	63
Deruiter	4	50	8	88	9	56	7	57	12	83	10	80	11	64	9	67
Kuhn	11	55	15	60	13	62	15	40	12	67	15	80	12	75	13	77
Other Investigators	23	39	18	50	19	42	21	52	23	65	22	45	26	54	15	60
Total Population	181	42	203	50	191	44	195	49	209	37	218	38	213	32	189	36

Table 64

Number of Investigators Evaluating the Active Medications to be Better Than or Equal to Placebo

Efficacy Parameters	Dicyclomine	Pyridoxine	Dicyclomine/ Pyridoxine	Doxylamine	Dicyclomine/ Doxylamine	Doxylamine/ Pyridoxine	Bendectin
Nausea (Patient's Diary Card)	11/21	9/20	11/19	16/21	16/21	17/21	16/21
Vomiting (Patient's Diary Card)	9/14	5/11	9/12	13/15	10/14	12/13	10/13
Nausea (Physician's Evaluation)	16/20	16/20	11/16	19/21	15/19	19/21	16/20
Vomiting (Physician's Evaluation)	6/13	4/12	5/11	9/12	8/13	7/13	11/13
Effectiveness of Medication (Physician's Evaluation)	9/20	13/21	13/20	18/20	17/19	18/21	16/20
Daily Activities (Patient's Diary Card)	5/19	9/21	8/17	14/19	10/18	13/20	12/18
Eating (Patient's Diary Card)	7/19	9/17	9/17	17/20	14/20	12/19	15/18

The first number in each square is the number of investigators ranking the active medication to be better than placebo. The second number is the total number of investigators excluding the investigators where the active medication and placebo were tied based on the efficacy parameter. Patients of investigators having a small number of patients evaluated for the parameter under analysis were pooled into one group.

10. Patients Not Included in the Primary Analysis

There were 132 patients from the total population of 2308 who did not return for a final evaluation visit. From the remaining 2176 patients, 577 were excluded from the primary statistical analysis because they failed to satisfy one or more of the six criteria listed in section 1. An analysis based on the physician's evaluation of effectiveness of medication was calculated to discover whether the results were biased in favor of any medication by not including those patients.

The evaluations of effectiveness for those patients not included in the primary analysis are listed in Table 65. There was a large number of evaluations of no effectiveness of medication (ranging between 25% and 51%) for this subgroup compared to the patients included in the primary analysis given in Table 30 (ranging between 7% and 21%).

In the statistical analysis treatment comparisons were made using an analysis of categorical data by linear models as outlined in section 5. The pairwise comparisons (Table 66) show trends which are similar to the pairwise comparisons based on the patients who were included in the primary statistical analysis (Table 31).

The results from the total population were pooled and are given in Table 67. The results of the pairwise comparisons (Table 68) show that the trends in favor of dicyclomine and pyridoxine over placebo reach statistical significance at the 5% level when the excluded patients are included in the analysis (dicyclomine vs. placebo, $p = .05$; pyridoxine vs. placebo, $p = .02$). Dicyclomine/pyridoxine was also evaluated as more effective than placebo ($p = .09$).

The results are consistent with the results in the primary analysis in showing a statistically significant difference in the effectiveness of Bendectin, doxylamine/pyridoxine, dicyclomine/doxylamine, and doxylamine over placebo ($p<.01$). The percentages of moderate or excellent evaluations of effectiveness are 75% for doxylamine/pyridoxine and dicyclomine/doxylamine, 72% for doxylamine, and 68% for Bendectin. In the statistical analysis the differences in favor of doxylamine/pyridoxine ($p = .18$) and dicyclomine/doxylamine ($p = .34$) over doxylamine are not statistically significant.

Factorial Analysis

Table 69 lists the evaluations of effectiveness for the total population grouped by medications containing and not containing each of the three ingredients. The factorial analysis is given in Table 70. There is a significant positive main effect of doxylamine ($p<.01$). The main effects of pyridoxine and dicyclomine are not significant. There is a statistically significant negative interaction between doxylamine and pyridoxine ($p = .01$). None of the other interaction terms was significant.

Table 65

Physician's Evaluation of Effectiveness of Medication
Patients Who Were Not Included in the Primary Statistical Analysis

Treatment	Not Stated	None	Slight	Moderate	Excellent
Placebo	17	45 (51)	11 (13)	16 (18)	16 (18)
Dicyclomine	17	31 (47)	9 (14)	10 (15)	16 (24)
Pyridoxine	19	30 (38)	18 (23)	11 (14)	21 (26)
Dicyclomine/Pyridoxine	21	30 (43)	12 (17)	11 (16)	17 (24)
Doxylamine	17	19 (31)	7 (11)	17 (28)	18 (30)
Dicyclomine/Doxylamine	18	16 (25)	7 (11)	20 (31)	22 (34)
Doxylamine/Pyridoxine	20	15 (29)	3 (6)	13 (25)	20 (39)
Bendectin	25	23 (31)	7 (9)	17 (23)	28 (37)

Number of patients and (percentages).

Table 66

Physician's Evaluation of Effectiveness of Medication

Patients Who Were Not Included in the Primary Statistical Analysis

	PLACEBO	DICYCLOMINE	PYRIDOXINE	DOXYLAMINE	DICYCLOMINE/ PYRIDOXINE	DICYCLOMINE/ DOXYLAMINE	DOXYLAMINE/ PYRIDOXINE
Dicyclomine	.25						
Pyridoxine	.08						
Doxylamine	<.01						
Dicyclomine/ Pyridoxine	.18	.59	.64				
Dicyclomine/ Doxylamine	<.01	<.01		.20			
Doxylamine/ Pyridoxine	<.01		.02	.21			
Bendectin	<.01	<.01	.03	.69	.01	.64	.80

The test is based on an analysis of categorical data by linear models. The values in tha table are one-sided probabilities to determine whether the row treatment is superior to the column treatment in each comparison. If $p < .50$ ($p > .50$) the row (column) treatment is superior in each comparison.

Table 67

Physician's Evaluation of Effectiveness of Medication

Total Patient Population

Treatment	Not Stated	None	Slight	Moderate	Excellent
Placebo	17	80 (30)	54 (20)	71 (26)	64 (24)
Dicyclomine	17	71 (26)	48 (18)	66 (24)	84 (31)
Pyridoxine	19	66 (24)	47 (17)	77 (28)	81 (30)
Dicyclomine/Pyridoxine	21	71 (27)	47 (18)	70 (26)	77 (29)
Doxylamine	17	36 (13)	39 (14)	90 (33)	105 (39)
Dicyclomine/Doxylamine	19	32 (11)	39 (14)	104 (37)	107 (38)
Doxylamine/Pyridoxine	20	35 (13)	31 (12)	81 (31)	117 (44)
Bendectin	25	43 (16)	41 (16)	76 (29)	103 (39)

Number of patients and (percentages)

Table 68

Physician's Evaluation of Effectiveness of Medication

Total Patient Population

	Placebo	Dicyclomine	Pyridoxine	Doxylamine	Dicyclomine/ Pyridoxine	Dicyclomine/ Doxylamine	Doxylamine/ Pyridoxine
Dicyclomine	.05						
Pyridoxine	<.02						
Doxylamine	<.01						
Dicyclomine/ Pyridoxine	.09	.61	.73				
Dicyclomine/ Doxylamine	<.01	<.01		.34			
Doxylamine/ Pyridoxine	<.01		<.01	.18			
Bendectin	<.01	<.01	<.01	.75	<.01	.88	.95

The test is based on the chi square test for an analysis of categorical data by linear models. The values in the table are one-sided probabilities to determine whether the row treatment is superior to the column treatment in each comparison. If $p<.50$ ($p>.50$) the row (column) treatment is superior in each comparison.

Table 69

Physician's Evaluation of Effectiveness of Medication

Total Patient Population

(Factorial Analysis)

Effect	Normal Approximation	p*
Main effect of Doxylamine	8.93	<.01
Main effect of Pyridoxine	.76	.22
Main effect of Dicyclomine	- .07	.53
Doxylamine/Pyridoxine Interaction	-2.07	.01
Doxylamine/Dicyclomine Interaction	-1.15	.13
Dicyclomine/Pyridoxine Interaction	-1.00	.16
Three factor Interaction	.19	>.25

*The test is based on an analysis of categorical data by linear models. The main effect p values are one-sided probabilities testing for positive main effects. The interaction p values are two-sided probabilities testing for both positive and negative interactions. A positive value for the normal approximation indicates a positive effect while a corresponding negative value indicates a negative effect or interaction.

Table 70

Physician's Evaluation of Effectiveness of Medication

Total Patient Population

Factorial Analysis

Number of Patients and Percentages

	None	Slight	Moderate	Excellent
Medication containing Doxylamine	146 (13)	150 (14)	351 (33)	432 (40)
Medication without Doxylamine	288 (27)	196 (18)	284 (26)	306 (28)
Medication containing Pyridoxine	215 (20)	166 (16)	304 (29)	378 (35)
Medication without Pyridoxine	219 (20)	180 (17)	331 (30)	360 (33)
Medication containing Dicyclomine	217 (20)	175 (16)	316 (29)	371 (34)
Medication without Dicyclomine	217 (20)	171 (16)	319 (30)	367 (34)

APPENDIX 4

CLINICAL STATUS OF DEBENDOX FORMULATION CONTAINING DOXYLAMINE AND PYRIDOXINE (WITHOUT DICYCLOMINE).

Following a request from the United States Food and Drug Administration to confirm the efficacy of all the ingredients in Bendectin (Debendox), an 8-way study was set up to discover which of the ingredients were the most effective and whether synergism occurred. (Details of this study were recently resubmitted [redacted] on 16th November, 1981). The whole product containing 10 mg of doxylamine, 10 mg pyridoxine and 10 mg dicyclomine was compared with placebo and also with the following combinations:

doxylamine and pyridoxine
pyridoxine alone
dicyclomine alone
dicyclomine and doxylamine
doxylamine alone
dicyclomine and pyridoxine.

A total of 1599 patients out of 2308 selected were considered suitable for statistical analysis. The objective of the study was to determine the effectiveness of the product as assessed by the physician and the patient, and there was an overall rating, and one covering nausea, vomiting, dieting and daily activities. In the case of the first three assessments the physician gave an opinion as well as the patient. As assessed by the physician in terms of percentage response, 57% did well on the global rating, 52% did well in terms of improvement of nausea, and 66% in terms of improvement of vomiting when given placebo. This large placebo response made the assessment of all formulations difficult. However, with the large sample involved, it was possible to demonstrate significant benefit over placebo for the whole original formulation when the physician rated overall effectiveness, nausea, and vomiting, and for all the questions directed at the patient. There was no doubt that the total formulation was effective.

The other combinations were largely effective except for dicyclomine combined with pyridoxine, or dicyclomine alone, but doxylamine alone gave a result as assessed by the physician of the same order as was obtained with the triple combination. When the patient's assessment was considered, doxylamine alone, or doxylamine with pyridoxine showed overall efficacy for all symptoms whereas in some areas dicyclomine with doxylamine, dicyclomine with pyridoxine, pyridoxine or dicyclomine alone did not produce statistically significant benefit.

As a next step a factorial analysis was undertaken to assess the contribution of the three ingredients, and to deduce those producing a main effect. For all physician and patient assessments there was a main effect for doxylamine and pyridoxine, but this was not the case for dicyclomine.

Following this study and the assessment of these results, the Food and Drug Administration decided that the best combination was doxylamine with pyridoxine. A change was made in 1976 in the USA to introduce the two-ingredient formulation, and subsequently in Canada a similar change was made.

It is upon the basis of this one large clinical study that we would like to change the formula to doxylamine 10 mg and pyridoxine 10 mg, omitting dicyclomine.

One other practical point is that all the prospective studies, currently being undertaken on the incidence of teratogenic effects from Bendectin, are concerned with the 2-ingredient formula. These studies are still continuing in the U.S.A., and will provide more information about the

safety of the product. In the U.K. there have been three studies published describing the incidence of teratogenic effects, and these have already been submitted to the CSM following an appeal to the Licensing Authority by Mr. Jack Ashley, MP for an investigation of this product. In the appendix you will find publications describing the epidemiology studies conducted in this country. First of all by Professor Smithells covering Leeds and Liverpool; and secondly, in Northern Ireland by Professor Shanks, which was a comprehensive description, again covering many years, relating to the incidence of birth defects recorded in Northern Ireland; and finally a report by Fleming and Knox describing a GP study conducted in Scotland and England published recently in the British Medical Journal.

None of the UK published studies has indicated an increase in the incidence of congenital malformations occuring in users of the three ingredient formulation of Debendox.

On-going studies in the U.S.A. have been the subject of publications in The Journal of the American Medical Association in the Summer of 1981, and all the relevant papers are attached. Two issues have been outstanding: one has been the report on congenital heart defects by Rothman and the second relates to a personal report supplied to the FDA at a public hearing by Dr. Golding indicating an increased incidence of hare lip and cleft palate in the Oxford region associated with exposure to Debendox. Both the findings have not been repeated in other studies mentioned, and there are in all 13 published epidemiological studies concerning Debendox in both formulations.