

TREATMENT OF DUODENAL ULCER

Randomized clinical trials of a decade (1964 to 1974)

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In a review of randomized clinical trials (RCT's) in gastroenterology up to 1964,¹ Truelove and Wright concluded that only one treatment was of proven value in duodenal ulcer: stilbestrol promote healing of the ulcer in men with a history of less than 10 years.² An effect of diet,^{2,3} sedatives,² intragastric milk drip containing sodium carbonate,³ carbenoxolone (Biogastrone),⁴ and anticholinergics^{5,6} had not been demonstrable. Strict bed rest in hospital⁷ and giving up smoking⁸ had effects on the healing of gastric ulcers, but no RCT on the effect in duodenal ulcer had been made.

The purpose of the present analysis was to evaluate RCT's on treatment of duodenal ulcer during the subsequent decade, 1964 to 1974, and their impact on current therapeutic practice.

The relevant citations were obtained from MEDLARS as previously described.⁹ Trials were accepted as RCT's and considered in this review only if (1) patients were allocated to a treatment or a control group at random, (2) the therapeutic effect was evaluated on the basis of clinical variables, (e.g., severity or duration of symptoms, survival), or of variables of indisputable clinical relevance (e.g., disappearance of an ulcer crater, but not on the basis of pure laboratory data, e.g., maximum acidity output), and (3) duodenal ulcer patients were distinguished from gastric ulcer patients in RCT's evaluating both categories. Forty-eight RCT's fulfilling these criteria were obtained by the MEDLARS search, and from their reference lists and from recent surveys 17 additional RCT's were found. The analysis thus comprises 65 RCT's.¹⁰⁻⁷⁷ In 46 of them medical treatments were evaluated, 15 dealt with surgical treatments, and 4

with gastric freezing. A RCT comparing medical and surgical treatments has not been found.

Methodological Evaluation

The purpose of a RCT is to obtain results which can be applied to future patients, and it should be evaluated from this point of view. The perfect RCT probably does not, and never will, exist, and if nothing less than perfection is accepted, this may block therapeutic progress as effectively as blind acceptance of any drug firm's advertisements. The 65 RCT's on duodenal ulcer have been evaluated by the absolute and relative requirements listed in table 1. If the "absolute" requirements are not fulfilled, we find it difficult or impossible to make use of the results of these RCT's. Failure to meet some of the relative requirements may reduce the value of the RCT to a smaller or greater extent, but in most cases this will not invalidate the results completely.

Absolute Criteria

Criterion 1 only states that it is a RCT on duodenal ulcer. Criteria 2 to 4 are self-explanatory. Criterion 5 is a very moderate one, as 1 or 2 years of follow-up is not unreasonable from a clinical point of view. However, for all of the RCT's the median was 3 months, and maximum was 8.6 years. Criterion 6 is further explained in figure 1. It shows the great and often highly significant differences in age, sex, and duration of ulcer history in RCT's in which this information was given. All three factors were stated in only 21 RCT's, but primarily we only excluded 6 in which *none* of them were given. Finally (criterion 7) 8 RCT's were excluded, because the ulcer was not verified by objective methods (radiography was used in 41 RCT's (cf. comments to criterion 16) endoscopy in 2 (one of these used also radiography), and surgery in 6). Thus the absolute requirements eliminated 18 or more than one-fourth, of the RCT's.

Relative Criteria

The experimental design (no. 8) was considered less adequate in eight RCT's, in five because the crossover design was used without an intervening treatment pause, and in three because a large number of groups of patients were compared.

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TABLE 1. Absolute (1 to 7) and relative (8 to 17) requirements to randomized clinical trials (RCT's) on the treatment of duodenal ulcer (DU)

Criteria	No. of RCT's fulfilling	
	This require- ment	This and pre- ceding re- quirements
1. a. Random allocation		
b. Effect evaluated by clinical variables	65	
c. DU distinguished from other ulcer		
2. Results tested (or testable) statistically	64	64
3. Group size greater than 10	61	61
4. Treatment schedule and dosage described	59	56
5. Treatment or follow-up period at least 4 wk	59	53
6. Age, sex, or duration of history reported	59	50
7. Ulcer diagnosed by "objective" methods	57	47
8. Adequate experimental design	57	45
9. Ancillary treatment controlled	54	36
10. Specification of symptoms	50	29
11. Number of drop-outs stated	50	26
12. Statistical evaluation	46	20
13. Double blinding	46	14
14. Clearly defined end points	41	12
15. Criteria for exclusion described	34	9
16. Description of radiographic criteria of ulcer	22	4
17. Determination of the type II error (negative RCT's)	4	0

Ancillary treatment (no. 9) was given but not recorded in 11 RCT's. This may cause false-negative results if the ancillary treatment is effective and taken in greater amounts in the control than in the treatment group.

Specification of symptoms (no. 10) was not made in 15 RCT's. Among the RCT's which specified the symptoms, 25 also included unspecific symptoms of nausea, vomiting, stool frequency, etc. In 10 RCT's the consumption of antacids was considered a measure of therapeutic effect.

The number of drop-outs (no. 11) was not stated in 15 RCT's. In 16 RCT's the drop-out rate was more than 20% of the number of included patients.

Statistical evaluation of the results (no. 12) was made in 46 RCT's, but only 32 stated the method used. The type I error (risk of a false-positive result) could be evaluated from the data presented in 60 RCT's with Fisher's exact probability test or Student's *t*-test, and in 9 a claimed significant positive result was not confirmed at the 5% level.

Double blinding (no. 13) was not performed in 19 trials (2 "single blind"). In 5, however, this was motivated and presumably without marked effect on the results.

Clearly defined end points (no. 14) as complete relief from ulcer pain or disappearance of an ulcer crater, were given in 41 RCT's. Among 12 RCT's using radiographic or endoscopic evaluation, only 7 used disappearance of the ulcer as a criterion of success of the treatment.

Criteria for exclusion from the trial (no. 15) were given in 34 RCT's. In five they included an age limit. Ten RCT's reported the percentage of patients excluded. It varied from 0 to 264%, median 35% of the number of patients included in the trial.

A description of the radiographic criteria for duodenal ulcer (no. 16) was given in 22 RCT's but only 10 used the classical ulcer crater as the key criterion.

Calculation of the type II error (no. 17), i.e., the risk of a false-negative result, was made in four RCT's, all using the sequential design which gives this information "automatically." Among 40 "negative" RCT's, i.e., trials with no demonstrable difference between treatments tested, the type II error could be calculated⁷⁸ from the data presented in 31. In 5 RCT's it was less than 10%, and in 20 it was greater than 35%.

The requirements listed in table 1 are ranked according to the frequency with which they are fulfilled in the RCT's studied, but the ranking does not necessarily reflect their general importance. For instance the absence of a calculated (or calculable) type II error in a negative RCT may well make the study useless. On the other hand some requirements with a high ranking on our list may be replaced with others regarding RCT's dealing with other diseases.

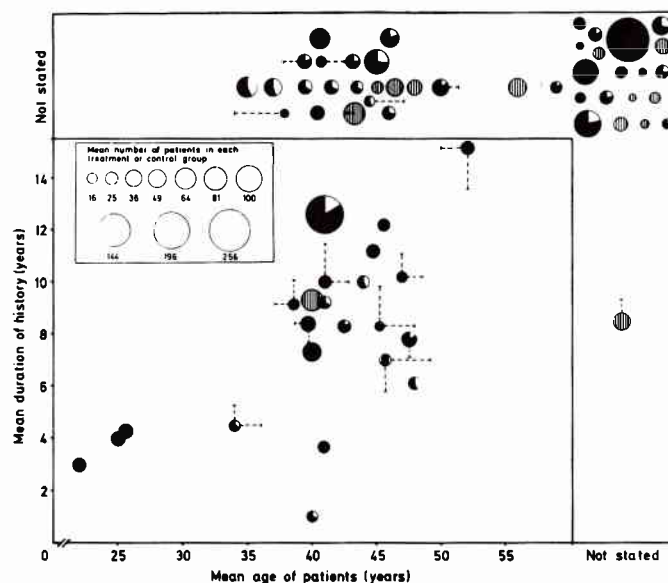


FIG. 1. The 65 randomized clinical trials (RCT's) illustrated by their data on mean age, mean length of history, female-male ratio, and mean size of treatment and control groups of patients included in the RCT's. Where possible the SEM of the mean length of history and the mean age have been calculated and indicated as vertical and horizontal dotted lines, respectively. The female-male ratio is given by the proportion of the white-black sectors of each circle. Hatched circles indicate that information about sex was not given.

TABLE 2. Randomized clinical trials (RCT's) on anticholinergics versus placebo

Blinded-ness (reference)	Anticholinergic	Daily dosage	Age, mean or range	Female/male ratio	Length of history, mean	Percentage of patients with previous complications	Duration of RCT	Mean size of treatment and control group	Main types of evaluation	Result (+: $P = 2\alpha < 0.05$, -: $P = 2\alpha > 0.05$)
		<i>mg</i>	<i>yr</i>		<i>yr</i>		<i>wk</i>			
DB ^a (13)	Glycopyrrolate	OED ^b (4-16)	38.6	0	9.2	73	78	18.5	Prevention of recurrence of ulcer-like symptoms	+
DB (14)	Glycopyrrolate	6	52.1	0	15.2	57	72-104	23	Decrease of symptoms	-
DB (15)	Oxyphen-cyclimine	20	13-53	0.20	2	?	52	25	Absence of pain	-
DB (16)	Propantheline	60	43.3	0.08	11.2	61	52	17	Healing of ulcer	-
									Prevention of recurrence of ulcer	-
SB ^c (17)	Glycopyrrolate	OED ^b (1-11)	39	0	8.4	26	52	30	Decrease of pain	-
SB (17)	<i>l</i> -Hyoscyamine	OED ^b (0.4-3.0)	40	0	9.7	26	52	31.5	Healing of ulcer	-
SB (18)	<i>l</i> -Hyoscyamine	OED ^b	47.6	0.18	7.8	?	104	29	Decrease of pain	-
									Healing of ulcer	-
									Prevention of recurrence of ulcer crater	+
									Prevention of recurrence of pain	-
DB (19)	Propantheline	75	46.6	0	?	11	48	15	Healing of ulcer	-

^a DB, RCT double blind.

^b OED, optimal effective dose, i.e., highest individual dose not giving side effects.

^c SB, RCT single blind.

The following analysis of different types of treatment, studied by RCT's during the decade 1964 to 1974, only includes the 47 trials which meet our absolute requirements. In cases where the reported and the recalculated statistics differed, the latter have been used.

Clinical Evaluation

Eleven RCT's, published in 10 reports, evaluated anticholinergics.¹⁰⁻¹⁹ One RCT¹⁰ compared the effects of two different anticholinergics, one¹¹ compared an anticholinergic versus an antacid, and one¹² compared high doses versus low doses of an anticholinergic. These three RCT's were all negative (i.e., the difference between the treatments was not significant at the 5% level) when tested with Fisher's exact probability test. In eight RCT's¹³⁻¹⁹ the effect of anticholinergics was compared with that of placebo (table 2). The two "positive" RCT's (i.e., showing a significant difference between the treatments at the 5% level) and one negative RCT evaluated the effect on prevention of recurrence of ulcers already healed by other means. No statistically significant difference between positive and negative RCT's with regard to clinical variables, duration of the RCT, sample size, dosage administered or dosage recommended by manufacturer,⁷⁹ and the main type of evaluation could be found. It should be noted that the total number of patients treated with anticholinergics

in these RCT's was less than 200. It appears from figure 2 that the net effect on symptoms and healing of duodenal ulcer has stabilized around zero as more RCT's have been made. An effect has been demonstrated on prevention of ulcer recurrence (table 5).

The effect of carbenoxolone capsules (Duogastrone) having fewer side effects than the Biogastrone preparation, was compared with that of placebo in eight RCT's.²⁰⁻²⁷ Some details of these appear from table 3. As with anticholinergics, no statistically significant difference was found between the positive and negative RCT's. Figure 2 shows that the cumulated net cure rates approach a level of 20 to 30%, showing that carbenoxolone is significantly better than placebo in relieving symptoms and promoting healing of ulcers. As with anticholinergics these conclusions are based on observations in less than 200 treated patients. The agent is not available in the United States.

Three RCT's evaluated antacids.²⁸⁻³⁰ A concentrated antacid (Ducon) was compared to a standard antacid (Maalox) in one RCT.²⁸ This study did not include a placebo-treated group of patients. Ducon was found significantly more effective than Maalox in bringing about complete relief of pain ($P = 0.03$), but if one considers the effect on bringing about "complete" as well as "definite" relief of pain no significant difference is found ($P = 0.92$). Two RCT's tested antacids versus placebo^{29, 30}

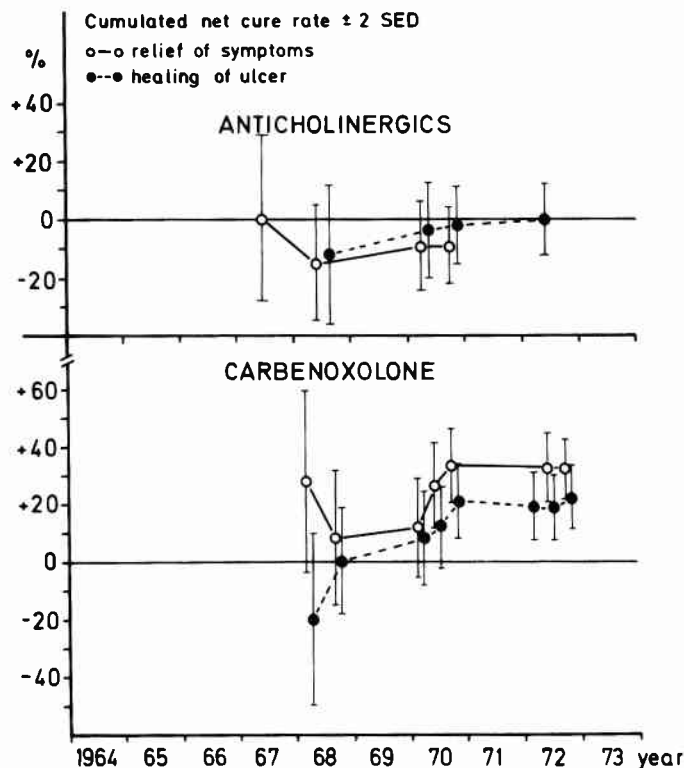


FIG. 2. Net effect of anticholinergics and carbenoxolone on symptoms and healing of duodenal ulcer calculated as the accumulated net cure rate ± 2 SED (standard error of the difference).⁸⁰ The net cure rate is the difference between percentage of patients cured in the treatment and the control group. The accumulated cure rates are calculated from accumulated number of patient cured as percentage of accumulated number of patients treated.

(table 4). Both the RCT testing antacids in liquid form,²⁹ and the RCT testing antacids in tablet form³⁰ were negative in regard to effect on symptoms and ulcer healing.

Amylopectin sulfate (SN-263) has been tested in 3 RCT's.^{11, 16, 19} In a big multinational RCT, amylopectin sulfate was found to be 22% more effective than antacids in bringing about rapid relief of pain ($P = 0.003$).¹¹ This study did not include a placebo-treated group. In two RCT's the effect was compared with that of placebo (table 3). In one of these amylopectin sulfate was 59% more effective than placebo in preventing recurrence of already healed ulcers,¹⁶ the other showed no advantage of the agent over placebo on symptoms or healing of ulcers.¹⁹ This drug is not available for use in the United States.

Of three RCT's testing the effect of deglycyrrhized liquorice versus placebo³¹⁻³³ (table 4), only one was positive with regard to relief of symptoms.³¹ By addition of the results (table 5) deglycyrrhized liquorice appears to be slightly more effective than placebo.

Estriol succinate, an estrogen without significant feminizing side effects, was compared with placebo in a rather small sample of male duodenal ulcer patients (table 4).³⁴ The effect on ulcer symptoms was not significant (table 5), but the effect on healing of ulcers was close to statistical significance ($P = 0.07$).

The surface analgesic oxethazaine in combination with antacids has been tested versus antacids alone in two RCT's. One showed no effect,³⁵ the other was positive regarding relief of symptoms after 4 weeks ($P < 0.05$), but the patients included had an ulcer history of no more than 2 years.³⁶ The cumulated results of the oxethazaine-treated groups was not significantly better than that of the control groups (table 5).

The musculotropic-antispasmodic mebeverine has been tested in one RCT (table 4).³⁷ Mebeverine was significantly more effective than placebo in bringing about "complete relief," but if one considers the effect in bringing about "complete" as well as "partial" relief the difference is not significant ($P = 0.10$).

Carbamide (Carbamine) in one RCT has been shown to be no more effective than placebo in relieving ulcer symptoms (table 4).³⁸

Gastric freezing has been tested in 4 RCT's.³⁹⁻⁴² All showed no significant superiority of the procedure over sham procedures on relief of symptoms.

Surgical treatments. Selective and truncal vagotomy were compared in two RCT's.^{43, 44} After a follow-up period of 5 years no significant differences in regard to recurrence of ulcers, dumping, and weight change could be found. However, diarrhea was significantly more frequent after truncal than after selective vagotomy.^{43, 44}

The Finney pyloroplasty and the Heinecke-Mikulicz pyloroplasty were compared in patients having a truncal vagotomy.⁴⁵ No significant difference was found between the two procedures after 6 months or after 5.2 years.⁴⁶ The preliminary results of another RCT comparing the effects of the Finney pyloroplasty with no pyloroplasty in patients having a proximal selective vagotomy revealed no significant difference in the rate of recurrence of ulcers.^{47, 48} The frequency of dumping or other side effects was not significantly different in the two groups when tested with Fisher's exact probability test. On the basis of these preliminary results neither the presence nor the type of pyloroplasty significantly modifies the effect of a vagotomy.

Gastrojejunostomy and pyloroplasty were compared in patients with vagotomy in two RCT's.^{49, 50} Bilious vomiting occurred more often after gastrojejunostomy than after pyloroplasty in patients with truncal vagotomy.⁴⁹ In patients with selective vagotomy that difference was not present, but pyloroplasty led to slightly more frequent bowel movements than did gastrojejunostomy.⁵⁰

Antrectomy versus pyloroplasty in vagotomized patients was analyzed in three RCT's.⁵¹⁻⁵³ Antrectomy led to fewer ulcer recurrences than did pyloroplasty when combined with truncal vagotomy,^{51, 52} but apparently not in combination with selective vagotomy, as shown in a preliminary report.⁵³ These RCT's indicate that antrectomy should be preferred to pyloroplasty when truncal vagotomy is performed.

Antrectomy and gastroenterostomy were compared in patients with truncal vagotomy.⁵⁴ Antrectomy led to dumping and weight loss more often than did gastroenterostomy. Recurrence of ulcer tended to occur less fre-

TABLE 3. Randomized clinical trials (RCT's) on carbenoxolone versus placebo

Blinded-ness (reference)	Daily dosage	Age, mean or range	Female/male ratio	Length of history, mean	Percentage of patients with previous complications	Duration of RCT	Mean size of treatment and control group	Main types of evaluation	Result (+: $P = 2\alpha < 0.05$; -: $P = 2\alpha > 0.05$)
	mg	yr		yr		wk			
DB ^a (20)	200	41	0	10	?	6	17	Absence of pain Healing of ulcer	- -
O ^b (21)	200	42.5	0.22	8.4	0	26	20	Absence of pain Healing of ulcer	- -
DB (22)	200	22	0	3	?	26	26	Improvement of symptoms Healing of ulcer	- -
DB (23)	200	34	0.47	4.5	0	12	14	Absence of pain Healing of ulcer	+ -
DB (24)	200	17-68	0.32	?	?	4	25	Absence of symptoms Healing of ulcer	+ +
DB (25)	300	43	0.33	?	?	4	26	Healing of ulcer	-
DB (26)	300	45.3	0.16	8.3	?	12	13.5	Decrease of pain Healing of ulcer	- -
DB (27)	200-100	?	?	8.3	18	24	40 18.5	Absence of pain Healing of ulcer	+ +

^a DB, RCT double blind.

^b O, RCT "open" and not strictly placebo controlled.

quently among patients with antrectomy, but the differences were not statistically significant. The over-all assessment (Visick grading) showed no significant differences between the two procedures.

Gastric resection and vagotomy and drainage were compared in three RCT's.^{52, 54, 55} Gastric resection with Polya reconstruction was associated with epigastric fullness more frequently than were truncal vagotomy and gastroenterostomy in one⁵⁵ but not in another RCT.⁵⁴ In the latter RCT episodic diarrhea was less frequent after gastric resection. However, in both RCT's the differences were small and the over-all results were similar. In another large RCT gastric resection, predominantly with Billroth II reconstruction, implied more frequent occurrence of dumping, early satiety, small pouch syndrome, and anemia than did vagotomy and drainage (pyloroplasty or gastroenterostomy).⁵² However, mortality and ulcer recurrence were not significantly different in the two groups, nor were the over-all clinical results.

The Billroth I and the Billroth II reconstruction (gastroenterostomy) were compared in one RCT.⁵⁶ The Billroth II reconstruction implied fewer ulcer recurrences.

Different procedures for management of massively bleeding duodenal ulcers were evaluated in two RCT's^{57, 58} In one of these nearly identical mortality rates were found whether treatment consisted of no operation, immediate gastrectomy, or "selective gastrectomy" (i.e., surgery if transfusion did not combat shock),⁵⁷ but the criterion for "massive hemorrhage" was rather mild (i.e., loss of more than 1/2 liter of blood in 48 hr). In the other RCT the mortality rate of massively bleeding patients with duodenal ulcer was significantly lower after immediate ligation of the bleeding artery plus vagotomy and pyloroplasty than after "expectant" treatment.⁵⁸ In this study the criterion for

massive bleeding was shock, and on average the patients received 4 1/2 units of blood within 5 hr (immediately operated patients) or 9 units of blood within 32 hr (patients receiving "expectant" treatment).

The above-mentioned results from RCT's on surgical treatments of duodenal ulcer do not clearly demonstrate which method is preferable. Some discrepancies may be attributable to differences in patient material, surgical technique, and evaluation of the patients after the operation. However, some conclusions seem warranted: when both procedures can be safely performed, selective vagotomy should be preferred to truncal vagotomy; when selective vagotomy is performed drainage operation seems not to be very important. Massively bleeding ulcers should be treated surgically as soon as possible. Ligation of the bleeding artery, truncal vagotomy, and pyloroplasty are preferable to gastric resection. Among the more recent procedures the highly selective vagotomy without drainage or resection, which in uncontrolled trials and preliminary RCT's has given encouraging results (fewer side effects, no statistically significant difference in recurrence rate, when tested with Fisher's test)^{76, 77} should be tested more extensively. Furthermore, the very important but unsolved dilemma of surgical versus conservative treatment should be subjected to RCT's.

Impact

The impact of the RCT's on therapeutic practice is difficult to measure directly. However, the recommendations for treatments in textbooks appearing around 1964 and 1974 gives an indication of the impact of the RCT's from the intervening period.

The nonsurgical treatments recommended by standard medical and gastroenterological textbooks are re-

TABLE 4. Randomized clinical trials (RCT's) on other medications versus placebo

Blinded-ness (reference)	Agent	Daily dosage	Age, mean or range	Female/male ratio	Length of history, mean	Percentage of patients with previous complications	Duration of RCT	Mean size of treatment and control group	Main type of evaluation	Result (+: $P = 2\alpha < 0.05$; -: $P = 2\alpha > 0.05$)
DB ^a (29)	Aluminum hydroxide + magnesium trisilicate in skim milk powder	? (20 g each hr)	15-63	0.54	?	0	7	30	Healing of ulcer	-
DB (30)	Calcium carbonate + glycine	12.6 g; 5.4 g	38.4	0.28	?	?	4	25	Healing of ulcer Pain relief	- -
DB (16)	Amylopectin sulfate	2 g	48.5	0.09	10.0	63	52	17.5	Prevention of recurrence of ulcer	+
DB (19)	Amylopectin sulfate	3 g	42	0	?	13	48	15	Healing of ulcer	-
DB (31)	Deglycyrrhizinated liquorice	2.28 g	48	0.8	6.1	?	4	24	Relief of symptoms	+
DB (32)	Deglycyrrhizinated liquorice	2.28 g	41.2	0.47	9.2	13	4	23.5	Pain relief	-
DB (33)	Deglycyrrhizinated liquorice	2.28 g	40	0	7.3	?	6	45	Relief of symptoms	-
DB (34)	Estriol succinate	10 mg	41.0	0	3.7	?	8	20	Healing of ulcer Relief of symptoms	- -
DB (35)	Oxethazaine hydrochloride	8 tea-spoons	?	0.25	?	?	8	30	Relief of symptoms	-
DB (36)	Oxethazaine hydrochloride	44 mg	40	0.48	1	0	4	17	Relief of symptoms	+
DB (37)	Mebeverine	150 mg	10-45	0.29	?	?	26	17	Complete or partial relief of pain	-
DB (38)	Carbamide	9.3 g	45.7	?	7.0	?	4	17	Relief of symptoms	-

^a DB, RCT double blind.

TABLE 5. Cumulated net effect^a of nonsurgical treatments in randomized clinical trials (RCT's) 1964 to 1974 (%)

Treatment	Type of evaluation			
	Relief of symptoms	Healing of ulcer	Prevention of recurrence	Prevention of complications
Anticholinergics	-9 ^b	0	37 ^c	7
Carbenoxolone	30 ^c	22 ^c		
Antacids	17	16		
Amylopectin sulfate		13	59 ^c	
Deglycyrrhizinated liquorice	18 ^c			
Estriol succinate	17	33		
Oxethazaine	17			
Mebeverine	36			
Carbamide	9			
Gastric freezing	-2			

^a Cumulated value of the net cure rates (percentage of cured patients in treatment group minus percentage of cured patients in placebo group) from RCT's evaluating the same treatments.

^b Type II error⁷⁸ less than 5%.

^c Percentage significantly higher than zero ($P = 2\alpha < 0.05$ (Fisher's exact probability test)).

viewed in table 6. It appears that antacids and anticholinergics still are being recommended in spite of practically no support from RCT's. Antacids and anticholinergics are still considered the mainstays in the therapy of duodenal ulcer and the consumption is enormous, the annual cost being about 110⁸⁸ and 60⁷⁹ million dollars, respectively, in the United States. On the other hand, carbenoxolone and amylopectin sulfate which have been shown to be effective in RCT's, are not recommended. These drugs are unfortunately not available in the United States. Table 6 also shows that other treatments not tested (bed rest, giving up smoking), or tested very little with a negative result (diet, sedatives), are being recommended in some textbooks.

The recommendations for surgical treatments have changed very little in the decade 1964 to 1974.^{81-86, 88-92} The major development in the period seems to be the more common recommendation of vagotomy plus drainage and vagotomy plus antrectomy. However, gastrectomy is still considered an acceptable procedure.

Thus, the total impact of the performed RCT's on the recommendations has been very small.

TABLE 6. Recommendations for nonsurgical treatment of duodenal ulcer compared with results of randomized clinical trials (RCT's)

Treatment	Result of RCT's before 1964	Recommendation for treatment \approx 1964 ^a	Result of RCT's 1964-1974	Recommendation for treatment \approx 1974 ^b
Anticholinergics	- ^c	+ ^d	-	+
Antacids	No RCT	+	-	+
Diet	-	+	No RCT	(+) ^e
Bed-rest	No RCT	+	No RCT	(+)
Sedatives	-	+	No RCT	(+)
Giving up smoking	No RCT	+	No RCT	+
Carbenoxolone	-	None	+	-
Deglycyrrhizinated liquorice			+	None
Amylopectin sulfate			+	None
Estrogens	+	None	-	None
Oxethazaine			-	None
Mebeverine			-	None
Carbamide			-	None
Gastric freezing			-	None

^a Based on References 81 to 83.

^b Based on References 84 to 89.

^c -, cumulated result of RCT's negative i.e., $P = 2\alpha > 0.05$, or treatment not recommended, respectively.

^d +, cumulated result of RCT's positive, i.e., $P = 2\alpha < 0.05$, or treatment recommended, respectively.

^e (+), treatment recommended in some textbooks but not in other textbooks.

Perspectives

The analysis has revealed that the RCT's on treatment of duodenal ulcer in the decade 1964 to 1974 are very heterogeneous. They have included small and sometimes rather highly selected samples of the duodenal ulcer population. The diversity as to design, blinding, selection of patients, duration of treatment or observation periods, type of evaluation, and interpretation of the results indicates that many RCT's were not sufficiently well planned or performed. The contribution of the RCT's to our present knowledge on the effect of the various treatments has been rather small, and the information obtained from the best RCT's has had practically no impact on current therapeutic practice, which is predominantly based on uncontrolled observations. The explanations for these discrepancies are numerous. Results from individual RCT's are often contradictory and it may be necessary to combine results of many RCT's to get a clearer picture. The RCT's are few in number,⁹ and some may be overlooked because they "drown" in the flood of uncontrolled therapeutic information. The results of a RCT may not be accepted if deserved criticism can be raised against it but even if it is beyond methodological criticism the results may be neglected if they clash with "clinical experience" or uncontrolled "knowledge." Doctors may be reluctant to leave treatments proved to be ineffective in RCT's if their patients think they help, even if this is a pure placebo effect.⁹³

To improve the situation, more well-planned and well-conducted RCT's must be produced and the results should be communicated more effectively to the medical

profession. Future RCT's should include larger⁷⁸ and less selected samples of duodenal ulcer patients, in whom the diagnosis is confirmed and the effect evaluated by duodenoscopy. The duration of RCT's should be longer and the results should be evaluated statistically for both type I and type II errors.

Presently the effect of H₂ blockers such as cimetidine⁹⁴ and of bismuth compounds such as De-Nol⁹⁵ is being evaluated in RCT's and the preliminary results are favorable.

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