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DOUBLE-BLIND TRIALS OF PROMAZINE IN LABOUR

BY

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A previous study (Matthews, 1961) of patients' responses in this obstetric unit included a questionnaire asking mothers to mention the most disturbing single symptom during labour. Pain accounted for 56% and fear or anxiety for 38%. Inquiry of the staff regarding the reason for administering drugs in labour showed that 49% were given for pain, 26% for fear, and 21% for restlessness or insomnia. This study therefore showed that there were three main groups of symptoms requiring relief in labour: (a) pain, (b) anxiety, and (c) restlessness and insomnia.

Unfortunately the same study made it clear that the drugs given for the relief of these symptoms were not always suitable, as the midwives were confused by the plethora of available agents. They were also governed by principles of treatment and timing of administration unrelated to the symptoms of the patient.

The first step in achieving rational treatment was to give drugs according to patients' requirements, and midwives were therefore asked to abide by the following three general principles: (1) concentrate on relief of symptoms in the first stage irrespective of degree of dilatation of the cervix or time since last drug administration; (2) record symptoms requiring relief and use appropriate agents; and (3) judge dosage according to severity of symptoms.

As a second step suitable drugs were chosen for the control of the major symptoms, enabling the attendant staff to become familiar with a few effective agents and to use them intelligently according to the symptomatic requirements of the patient.

The drugs needed to accomplish this aim in the first stage of labour were an analgesic for the pain group of symptoms, a tranquillizer for the fear group, and a hypnotic for the restlessness and insomnia group. Pethidine was chosen for the relief of pain and promethazine ("phenegan") for overcoming restlessness and insomnia.

After assessing a number of tranquillizers promazine hydrochloride ("sparine") emerged as the most satisfactory. As a result of these pilot trials it was decided to investigate the drug more thoroughly.

Toxicity Study

The first consideration of the drug given in labour must be its safety for both mother and child. Promazine has not been found to increase the length of labour when given intramuscularly or intravenously (Kuntze and Sison, 1957; Sprague, 1957; Pollock *et al.*, 1960). Transient slowing of contractions after intravenous administration with pethidine was noted by Bolton and Benson (1958) and by Pollock *et al.* (1960), but this was not shown by toco-

graphic studies of intravenous promazine alone (Caballero, 1958; MacVicar and Murray, 1960), and under some circumstances promazine appeared to shorten prolonged labour (Donald, 1959). The incidence of forceps delivery and post-partum haemorrhage was not increased. Evaluation of the effect of promazine on the foetus showed no evidence of foetal respiratory depression as assessed by Apgar ratings (Apgar *et al.*, 1958). The only deleterious effects of promazine were maternal tachycardia (Pollock *et al.*, 1960; Fitzpatrick *et al.*, 1960), occasional foetal tachycardia (MacVicar and Murray, 1960), and maternal hypotension (Sprague, 1957), but these appeared to be less frequent with intramuscular administration (Ponzi and Tiengo, 1958).

In order to confirm the apparent safety of intramuscular and oral promazine, a retrospective comparison was made between 500 consecutive cases admitted to the unit before promazine was used and a similar group of 500 mothers given promazine to allay fear and anxiety. In the first group, pethidine, chloral, dichloralphenazone, and methylpentynol were used, according to the individual preference of the attendant. In the second group, promazine was administered for fear and anxiety according to the patients' requirements, the usual dose being 50 to 100 mg. intramuscularly. The other drugs given were pethidine for pain and promethazine for insomnia.

After exclusion of patients not in labour, there were 495 patients in the promazine group and 498 controls. The groups were comparable with regard to age and parity, but

TABLE I.—Results of Retrospective Comparison
Delivery

Group	Total Patients	Surgical Induction	Epi-siotomy	Lacerations	Forceps	Caesarean Sections
Control	498	58	147	120	49	21
Promazine	495	41	155	113	42	23

Duration of Labour

Group	1st Stage (Hours)					2nd Stage (mins.)				3rd Stage (mins.)		
	<5	5–	10–	20–	40+	<15	15–	60–	120+	<15	15–	60+
Control	70	153	166	77	32	127	252	83	15	429	37	11
Promazine	60	150	171	85	29	102	261	87	22	433	33	6

Complications

Group	Maternal Tachycardia	Foetal Distress	Post-partum Blood Loss (oz.)			Manual Removal of Placenta	Vomiting	Intra-venous Fluids	Fresh Stillbirths
			<10	10–	20+				
Control	18	41	367	78	32	14	27	15	6
Promazine	32	42	368	78	26	10	5	3	5

there were rather heavier babies in the promazine group, which also had more abnormal presentations.

The results of this retrospective comparison are shown in Table I; these confirm the safety of promazine suggested by the literature. They also show the greater tendency towards maternal tachycardia (120 per minute and over) with promazine, and the drug's anti-emetic effect. Vomiting was not specifically recorded in the case-notes used in this retrospective trial and it is likely that only repeated vomiting was noted.

Double-blind Assessment of Condition of Mother in Labour

Once the safety criteria of promazine had been satisfied, it remained to establish the drug's value in treating fear and apprehension in labour, under conditions typical of obstetrical units in this country. A review of previous trials of phenothiazines in labour revealed that the majority were uncontrolled assessments and that even the controlled comparisons were not double-blind, so that the assessors knew the medication that had been given, and in many cases the mothers also realized that a new drug was being administered. There was also a tendency to give the drugs in fixed dosages and at certain stages of labour rather than according to the symptomatic requirements of the patient. The only controlled trial of promazine in labour conducted in the United Kingdom was that of MacVicar and Murray (1960), who gave the drug intravenously, but although this comparative trial showed that promazine provided adequate sedation for most mothers, it did not confirm the very high success rate of previous uncontrolled assessments (Sprague, 1957; Kuntze and Sison, 1957; Pollock *et al.*, 1960). In view of these differences which have been noted in other phenothiazine trials in labour (Savage, 1955; Norton *et al.*, 1956) it seemed essential to conduct a double-blind trial.

Method

Six groups of tablets and ampoules were made and labelled sparine A to F. Three of these contained promazine (A, D, and F) and the other three lactose (tablets) or saline (ampoules), but the active and placebo medications were identical in every other respect. The midwives carrying out the trial were told that the effects of different tranquillizing drugs were being compared. At no time was the question of a placebo mentioned.

Random selection was ensured by allocating patients to groups A to F in rotation, according to their order of admission to hospital. The only cases excluded were those admitted for elective caesarean section. Throughout labour each patient received only the tablets and ampoules bearing the same letter as her group.

Treatment was given according to the principles laid down in the introduction, pethidine being used for the relief of pain and the trial drug (promazine or placebo) for fear and anxiety. In order to minimize the difficulties of interpreting results, no promethazine or other drugs were given during the trials. Inhalation analgesics were used only in the second stage, but as it was customary to hand the mask to each patient during crowning of the head, comparative results for the use of inhalant gases showed no difference in the two groups.

It was difficult to decide upon a satisfactory method of assessment. The majority of trials in this field have made an overall evaluation of the effect of the drug, but this is clearly unsatisfactory when the nature of the drug is known, and even in a double-blind trial it has marked limitations. The main disadvantages are that drugs are

often given infrequently and act for a relatively short time while symptoms in labour may persist for 24 hours or more, and one assessor is rarely present for the whole labour. Despite these possible sources of error, this method of evaluation had been extensively employed and was therefore chosen. Midwives were asked to classify the mental state of the patient on admission, during the first stage of labour and again during the second stage. The gradings available were: agitated and uncooperative, agitated but co-operative, afraid but calm, and calm and confident.

In addition, mothers were asked after delivery for a relative assessment of "pain in labour" (less than expected, more than expected, or as expected), "sedation in labour" (too sleepy, not sleepy enough, or just right), and "pain-relieving drugs" (too many, too few, or just enough). In an initial study these questions were asked immediately after delivery while the patients were still in the labour ward and again after six days, but as there proved to be no significant difference between the two sets of answers a single questionnaire was filled in four days after delivery during this study.

Three hundred consecutive patients were included in this trial, but mothers not established in labour and those with very rapid labours not requiring any drugs were excluded from the analysis of results. A breakdown of the promazine and control groups included in the trial shows these to be comparable (Table II).

TABLE II.—First Double-blind Trial

	Primiparae		Multiparae	
	Control	Promazine	Control	Promazine
Total patients	82	73	57	68
Age in years:				
20 and less	34	22	3	4
21 to 25	37	37	35	28
26 to 30	22	22	25	29
31 to 35	2	15	23	23
36 and over	5	4	14	16
Maternal data:				
Unmarried	4	3	3	1
Married in pregnancy	27	31	0	3
Toxaemia or hypertension	15	23	17	9
Other complications	5	3	5	9
Attended relaxation classes	24	27	5	4
Parity 4 and over	—	—	12	10
Foetal data:				
Twins	0	0	4	4
Abnormal presentation	2	8	3	3
5½ lb. (2,500 g.) and under	9	8	5	1
8 lb. (3,630 g.) and over	25	30	40	26

Apart from "total patients," all results are expressed as percentages.

Results

There were slightly more agitated cases on admission in the promazine (28%) as opposed to the control (20%) group, but when the average condition in the first stage was compared with the state on admission there was no difference. The change between admission and first stage was as follows: improved, 9% of both groups; deteriorated, 38% of the promazine group and 41% of the controls. Assessments in the second stage similarly failed to demonstrate any difference between the two groups.

The opinions of the mothers after labour were made in an exactly similar way both in this and in the subsequent trial and the data from both series are dealt with together, after the description of the second trial.

It was not altogether surprising that the general assessment of the mother's state in labour failed to show any difference between groups under double-blind conditions. As mentioned earlier, a drug effect could well have been

diluted by the untreated hours of labour and observers could have changed, so that no significant difference resulted. Under rather similar circumstances Masson (1962) tested analgesics in post-operative patients. He found it impossible to distinguish between 100 mg. of pethidine given intramuscularly and saline, and suggested that retrospective analysis and changing observers invalidated the record. A second trial using a constant observer noting pain relief demonstrated a significant difference between pethidine and saline.

With these points in mind, a second double-blind trial was carried out on a further series of 300 consecutive admissions to the unit.

Double-blind Assessment of Drug Effect

This second double-blind trial was conducted in exactly the same way as the first, apart from the method of assessing drug effect. The midwife giving the medication returned 45 minutes after each administration to assess the response under two headings, "pain" and "mental state." For each of these factors she was asked to indicate whether there was a marked or moderate improvement, no change, or deterioration. In this way there was a single observer, and other factors such as the variable lengths of labour and the traditional timing of drug administrations were of no importance in the assessment of results. These recordings were all made in the first stage before the use of inhalation analgesia.

After exclusion of false labours, 292 mothers were included in the trial and were divided into promazine and placebo groups as in the first trial. A breakdown of the two groups (Table III) shows them to be comparable.

TABLE III.—*Second Double-blind Trial*

	Primiparae		Multiparae	
	Control	Promazine	Control	Promazine
Total patients	78	75	65	74
Age in years:				
20 and less	31	36	8	8
21 to 25	38	38	34	33
26 " 30	17	19	31	24
31 " 35	13	7	12	16
36 and over	1	0	15	19
Maternal data:				
Unmarried	11	8	2	0
Married in pregnancy ..	28	33	0	1
Toxaemia or hypertension ..	18	21	14	11
Other complications	6	3	14	11
Attended relaxation classes ..	30	32	6	1
Parity 4 and over	—	—	14	9
Foetal data:				
Twins	0	0	2	3
Abnormal presentation ..	4	8	3	0
5½ lb. (2,500 g.) and under ..	8	7	3	3
8 lb. (3,630 g.) and over ..	22	27	26	36

Apart from "total patients," all results are expressed as percentages.

Results

Results of the drug effects vary with the dosage used and comparisons can only be made between one dose of promazine and pethidine and a comparable dose of placebo and pethidine. In the 149 patients in the promazine group there were 232 injections and 37 oral administrations; in the 143 patients in the control group there were 213 injections and 40 oral administrations.

The subgroups of oral administration were too small for valid comparison and even when added together there was no significant difference between the two groups. Improvement was noted in mental state in 76% of the promazine group and 60% of the controls, while improvement in pain was claimed in 73% of the promazine group and 59% of the controls.

Where the intramuscular route was used, only 13 administrations of promazine or placebo were not combined with pethidine, which made the groups too small for comparison, and the results of the combined injections are given in Table IV. Taking all dosage levels, 58.5% of promazine cases and 36.1% of placebo cases showed marked improvement in pain. The corresponding figures for "Mental State" were 63.2% for promazine and 36.2% for placebo cases. These show the therapeutic effect of promazine in relieving anxiety and also in potentiating the analgesic effect of pethidine. As pethidine has been the standard agent used in obstetrics for many years for the relief of pain and to some extent for the relief of anxiety, a measure of improvement in both pain and mental state was to be expected in the control group. However, the addition of promazine produced a significant increase in the percentage of patients showing marked improvement of mental state and pain at all dosage levels tested.

TABLE IV.—*Assessment of Subjective Relief in Second Double-blind Trial*

Intramuscular Administrations		Mental State (Percentages)				Pain (Percentages)			
Dosage	No.	Marked Improv.	Mod. Improv.	No Change	Worse	Marked Improv.	Mod. Improv.	No Change	Worse
Pethidine { Placebo	91	25	56	17	2	22	57	18	3
50 mg. { Promazine	107	51†	38	7	4	47†	44	7	2
Pethidine { Placebo	92	47	37	15	1	48	43	8	1
100 mg. { Promazine	81	65*	31	2	1	63*	33	2	1
Pethidine { Placebo	25	40	44	16	0	44	50	6	0
100 mg. { Promazine	36	67*	22	11	0	83†	14	3	0

* Significantly better than control at 5%.

† Significantly better than control at 1%.

Calculated by chi-squared test taking proportion of "marked improvement" only.

Additional Data

As the two double-blind trials gave the same data, apart from the main assessments, the other results were analysed from the combined data of both trials. The comparison of populations in both groups is given in Tables II and III and will not be repeated apart from the total numbers: control group 282 (160 primigravidae, 122 multigravidae) and promazine group 290 (148 primigravidae, 142 multigravidae).

The additional data cover the effects of the medication on labour, on the condition of the foetus, and on the dosage of pethidine used, and the mother's own retrospective assessment.

The effects of the medication on labour are given in Tables V, VI, and VII, which show that the inclusion of promazine resulted in no prolongation of labour and no

TABLE V.—*Effect of Medication on Duration of Labour*

	Primiparae		Multiparae	
	Control	Promazine	Control	Promazine
Total patients	160	148	122	142
Duration of 1st stage:				
< 5 hours	4	5	18	22
5 to 12 hours	30	28	53	45
Over 12 to 24 hours ..	40	41	21	25
Over 24 hours	26	26	8	8
Duration of 2nd stage:				
< 15 mins.	7	7	59	56
15 to 60 mins.	59	63	36	38
61 " 120 "	29	26	4	5
Over 120 mins.	5	4	1	1
Duration of 3rd stage:				
½ to 1 hour	1	3	2	1
Over 1 hour	2	2	0	0

Apart from "total patients," all results are expressed as percentages.

TABLE VI.—*Effect of Medication on Delivery and Complications*

	Primiparae		Multiparae	
	Control	Promazine	Control	Promazine
Total patients	160	148	122	142
Delivery:				
Forceps	16	15	2	4
Caesarean section	2	3	1	2
General anaesthetic	10	8	1	4
Complications:				
Post-partum haemorrhage	6	3	6	8
Manual removal of placenta	4	2	1	1
Vomiting	36	11	15	11

Apart from "total patients," all results are expressed in percentages.

TABLE VII.—*Cardiovascular Changes*

	Primiparae		Multiparae	
	Control	Promazine	Control	Promazine
Total patients	160	148	122	142
Maximum foetal heart rate:				
139 and less	3	5	5	6
140 to 149	63	55	68	69
150 to 159	22	22	22	19
160 to 169	9	13	5	5
170 and over	3	5	0	1
Foetal distress (heart rate of 100 or less)	4	6	1	1
Maximum maternal heart rate:				
110 to 119	9	7	6	5
120 and over	11	24	7	11
Rise in maternal heart rate of 20 min. or more	42	50	19	30

Apart from "total patients," all results are expressed as percentages.

TABLE VIII.—*Foetal Condition*

	Primiparae		Multiparae	
	Control	Promazine	Control	Promazine
Total babies	140	126	118	137
Apgar rating:				
4 or less	2	3	2	6
5 to 6	10	6	3	7
7 to 8	14	21	14	12
9 to 10	74	70	81	75

Apart from "total babies," all results are expressed as percentages.

increase in complications, except for some maternal tachycardia. The anti-emetic action of promazine demonstrated in the pilot study is confirmed.

Altogether 585 babies were delivered; these included one neonatal death in the control group and one fresh stillbirth in the control group and one in the promazine group. In order to avoid influencing Apgar ratings, non-cephalic presentations, babies delivered under general anaesthesia, and those born with the cord looped tightly round the neck are omitted from the totals given in Table VIII. This table suggests a trend towards foetal depression in the promazine group of multiparae, although this is not statistically significant.

Analgesic Requirements

The total amount of pethidine given to a patient is clearly related to the duration of labour, and a comparison of the amount of pethidine given during the first stages of similar length in the two groups is shown in the Chart. This tends to confirm the analgesic-potentiating effects of promazine but it also shows the relatively small increases in the dosages of pethidine used in the longer labours. In an earlier study (Matthews, 1961) it was found that pain and fear were directly proportional to the length of labour and therefore the analgesic requirements rose sharply during longer labours. Thus it appears that the efforts to overcome traditional timing of drug administrations had not

been entirely successful. The data shown in the Chart also invalidate the conclusions drawn from trials where results are judged by the total dosages of drugs given or by the average condition of the patient.

Amount of pethidine given during first stage of labour in promazine and control groups.

Retrospective Maternal Assessment

The retrospective maternal assessment of pain, analgesics, and sedatives in labour resulted in no significant difference between the promazine and control groups. This is of some interest as it is a form of assessment commonly used in trials, and when compared with the marked effect of promazine shown in Table IV the validity of the method is in some doubt. In addition 75 to 80% of patients in the control group were satisfied with the analgesia given, whereas uncontrolled trials often quote such figures as evidence of efficacy for a new therapeutic agent.

Discussion

The two main points which arose from these studies were the trial methods used and the place of promazine in obstetrics.

The majority of trials of phenothiazines in obstetrics have been general assessments, usually with a very high success rate for the drug under consideration. Controlled trials on the same drugs have shown a much lower rate of benefit; indeed some have failed to demonstrate any benefit at all. This occurred with both chlorpromazine (Savage, 1955; Norton *et al.*, 1956) and promazine (MacVicar and Murray, 1960). In view of these variable results and the subjective nature of the symptoms under study, it seemed desirable to conduct a controlled double-blind trial of promazine and a placebo.

Double-blind trials, whether using the overall condition of the mother as observed in labour or the retrospective opinion of the mother after labour, failed to show any difference between the drug and the placebo groups. When, however, the assessment of the patient's condition was made by one observer at an optimum time after the administration of the drug, a highly significant difference was found. This striking contrast between the two groups casts doubt on the validity of obstetrical trials in which only the first methods were used. These limitations were also noted by Modell and Houde (1958) in two consecutive double-blind trials of aspirin, in which they used similar methods of assessing analgesic effect.

Unless treatment is given in repeated doses according to the patients' needs, the only way to assess the effect of a drug is to ensure that a single observer gives the drug when symptoms are present and returns during the time of drug activity to assess the degree of change.

Since this work was completed, Powe *et al.* (1962) have published the results of a double-blind trial of pheno-

thiazines in obstetrics, in which they assessed the patients' response after one dose of the drug under test and demonstrated a significant difference between the phenothiazines and the placebo.

These present trials were, however, designed to assess therapy under normal labour ward conditions, which is a more realistic method than the single-dose test. So far as promazine was concerned the double-blind trials confirmed the safety suggested by a pilot study and showed it to be an effective agent for controlling agitation and potentiating analgesics in labour. An anti-emetic effect was also shown.

Maternal tachycardia was the only adverse effect, but this did not appear to have any clinical significance. Hypotension is a recognized risk of phenothiazine administration, but although no serial blood-pressure readings were made there were no cases of clinical hypotension in the 785 patients in the series treated with promazine.

Summary

Three consecutive controlled clinical trials of promazine (sparine) were carried out on 1,565 maternity cases in the same unit. The first, a retrospective toxicity study of 993 consecutive cases, confirmed the safety of promazine suggested by the literature, despite a tendency towards maternal tachycardia. The reduction in vomiting from 5% to 1% and a corresponding reduction in the need for intravenous fluids suggested a powerful anti-emetic effect in the promazine group.

In the first double-blind trial of 280 cases subjective relief was assessed by the average condition of the patient at various stages of labour. This method failed to demonstrate any significant difference between placebo and promazine groups.

In a second double-blind trial of 292 cases subjective relief was assessed at a fixed time after each drug administration. The results showed a significant difference between the promazine and placebo groups (see Table IV).

Taking all dosage levels, 58.5% of promazine cases and 36.1% of placebo cases showed marked improvement in pain. The corresponding figures for "mental state" were 63.2% for promazine cases and 36.2% for placebo cases.

The methods of conducting and interpreting the results of obstetric trials are discussed in some detail.

In conclusion it is suggested that promazine, with its tranquillizing, analgesic-potentiating, and anti-emetic properties, is a useful adjunct to therapy in labour. Statistically, no increased risks were noted to mother or child and it appears that this phenothiazine derivative is a valuable addition to the therapeutic agents used in hospital obstetric practice.

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AMPHETAMINE AND PHENMETRAZINE ADDICTION

PHYSIOLOGICAL ABNORMALITIES IN THE ABSTINENCE SYNDROME

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Amphetamine addiction is common, though the readiness with which such addiction develops is not as widely recognized as one could wish. Those addicted often take large quantities of short-acting barbiturates as well, and of the tablets containing both, "drinamyl" (dexamphetamine sulphate 5 mg. with amylobarbitone, 32 mg.), popularly known as "purple hearts," is in most common use. A popular substitute or equivalent for amphetamine is phenmetrazine ("preludin") "known in London as 'sweeties' . . . available in any quantity . . . at the rate of £1 for 24 tablets" (Kellock, 1962). This compares with the price of £1 for 25 tablets among Edinburgh factory-workers (Case 4 below). Experience of addiction to these drugs (Bell and Trethowan, 1961) in New South Wales led Trethowan (1962) to emphasize the progressive deterioration in character associated with such addiction. He also pointed out that to claim, as many do, that they are drugs not of addiction but only of "habituation" is to engage in a semantic quibble.

The Interdepartmental Committee appointed by the Ministry of Health and the Department of Health for Scotland (1961), though remarking that in 1959 there were no fewer than 5,600,000 prescriptions for preparations of amphetamine and phenmetrazine, "formed the impression that . . . abuse is not widespread." The committee drew a distinction between addiction and habituation, partly on the grounds of "physical dependence on the effects of a drug" in the case of addiction and "absence of physical dependence and hence of an abstinence syndrome" in the case of habituation.

Addiction to these drugs is common in Edinburgh, and it is our purpose to demonstrate that *physical dependence* and characteristic, persisting, and easily measurable "physical" or physiological abnormalities form part of the *abstinence syndrome*.