Levomepromazine versus chlorpromazine in treatment-resistant schizophrenia: a double-blind randomized trial

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Objective: We compared the effect of levomepromazine (LMP) with chlorpromazine (CPZ) in treatment-resistant schizophrenia (TRS). **Methods:** We carried out a double-blind, parallel group study (n = 19/arm) with balanced randomization in blocks of 4 and stratification by sex. Subjects entered a 30-week trial, of which phases I–III were open: phase I (wk 0–6) baseline; phase II (wk 7–9) stepwise transition to haloperidol (HAL), 30 mg/d, plus benztropine (BT), 4 mg/d; phase III (wk 10–15) HAL, 40–60 mg/d, plus BT, 4–6 mg/d; phase IV (wk 16–20) stepwise transition to LMP or CPZ (500 mg/d) following randomization; phase V (wk 21–28) stepwise increase of LMP or CPZ (600–1000 mg/d, dose reduction permitted) to establish optimum dose; and phase VI (wk 29–30) optimized dose maintained. Criteria for TRS were based on those established by Kane et al in 1988. The criterion for a response to treatment was a reduction of 25% or more in total Brief Psychiatric Rating Scale score. **Results:** Both LMP (p = 0.007) and CPZ (p = 0.030) improved TRS relative to baseline. Although there was no significant difference between the 2 groups in treatment response at study end point, hierarchical linear modelling of longitudinal outcome revealed a significant (p = 0.006) advantage of LMP over CPZ for the BPRS total score. Ten of 19 participants on LMP and 8 of 19 on CPZ met the criterion for treatment response, and 9 of the 18 responders did so on 200–700 mg/d phenothiazine. The mean dose of responders was 710 (standard deviation [SD] 265) mg/d (LMP) and 722 (SD 272) mg/d (CPZ). Akathisia was associated with a nonresponse to phenothiazines (p = 0.010). BPRS scores increased significantly on HAL (p = 0.006). Two of 19 participants on LMP and 5 of 19 on CPZ withdrew early from the study. **Conclusion:** LMP and CPZ may be useful in the management of TRS. A modest advantage of LMP compared with CPZ was seen in longitudinal analysis. High doses of neuroleptics may contribute to TRS; reduction of neuroleptics to modest or moderate doses should be considered before categorizing a patient as treatment resistant.

Objectif : Nous avons comparé l'effet de la lévomépromazine (LMP) à celui de la chlorpromazine (CPZ) dans des cas de schizophrénie résistant au traitement (SRT). **Méthodes :** Nous avons procédé à une étude avec contrôle parallèle (n = 19/groupe) à double insu avec randomisation équilibrée par blocs de quatre et stratification selon le sexe. Les sujets ont entrepris un essai de 30 semaines dont les phases I à III étaient ouvertes : phase I (sem. 0–6), référence; phase II (sem. 7–9), transition graduelle vers l'halopéridol (HAL), 30 mg/j, plus benztropine (BT), 4 mg/j; phase III (sem. 10–15), HAL, 40–60 mg/j, plus BT, 4–6 mg/j; phase IV (sem. 16–20), transition graduelle vers LMP ou CPZ (500 mg/j) après randomisation; phase V (sem. 21–28), augmentation graduelle de LMP ou CPZ (600–1000 mg/j, réduction de la dose autorisée) afin de déterminer la dose optimale; phase VI (sem. 29–30), maintien de la dose optimisée. Les critères de SRT reposaient sur ceux qu'ont établis Kane et ses collaborateurs en 1988. Le critère d'une réponse au traitement était une réduction de 25 % ou plus du score total selon l'échelle abrégée d'appréciation psychiatrique (BPRS). **Résultats :** La LMP (p = 0,007) et la CPZ (p = 0,030) ont toutes deux amélioré la SRT par rapport au niveau de référence. Même s'il n'y avait pas de différence importante entre les deux groupes au niveau de la réponse au traitement à la fin de l'étude, la modélisation linéaire hiérarchique du résultat longitudinal a révélé un avantage important (p = 0,006) de la LMP sur la CPZ dans le cas du score total selon la BPRS. Des 19 participants qui pre-

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naient de la LMP, 10 satisfaisaient au critère de réponse au traitement, et des 19 qui prenaient de la CPZ, 8 y satisfaisaient; chez 9 des 18 sujets qui ont répondu, la réponse a été obtenue avec une dose de phénothiazine variant de 200 à 700 mg/j. La dose moyenne chez ceux qui ont réagi était de 710 (écart type [ET] de 265) mg/j de LMP et de 722 (ET 272) mg/j de CPZ. On a établi un lien entre l'acathisie et la non-réponse aux phénothiazines (p = 0,010). Les scores selon l'échelle BPRS ont augmenté considérablement chez ceux qui prenaient du HAL (p = 0.006); 2 des 19 participants qui prenaient de la LMP et 5 des 19 qui prenaient de la CPZ se sont retirés au début de l'étude. **Conclusion :** La LMP et la CPZ peuvent être utiles pour traiter la SRT. Une analyse longitudinale a révélé un modeste avantage de la LMP sur la CPZ. Des doses élevées d'antipsychotiques peuvent contribuer à la SRT. Il faudrait envisager de ramener les doses d'antipsychotiques à des niveaux modestes ou modérés avant de conclure qu'un patient résiste au traitement.

Introduction

The efficacy of neuroleptic drugs in the treatment of schizophrenia is well established.[1] However, a significant number of patients, varying from 5% to 25%,[2] or 20%–30% if only patients with chronic disease are considered,[3] respond poorly to typical neuroleptics. Clozapine (CLOZ) is associated with improvement in 30%[4] or more[5,6] of patients with treatment-resistant schizophrenia (TRS), depending on the criteria for TRS and for response, versus only 4% with chlorpromazine (CPZ).[4] Unfortunately, CLOZ is associated with a 2% cumulative incidence of agranulocytosis after 52 weeks of treatment,[7] which limits its use. Further, up to 70% of patients with TRS are nonresponders to CLOZ. In addition, the requirement for frequent monitoring of the hemogram as well as the logistical, administrative and personnel requirements involved in running a CLOZ treatment program are additional restraints on the use of CLOZ. Although beneficial results in TRS with risperidone[8,9] and olanzapine (OLAN)[10] have been reported, others have found either no difference[11] or improvement that was statistically significant but clinically modest.[12]

Lal and Nair[13] observed unexpected improvement in 16 of 23 patients with TRS who were treated with levomepromazine (LMP). Confirmatory observations were reported by Jones et al[14] in 10 of 20 patients. Both these studies were uncontrolled. In a double-blind study comparing LMP with CLOZ in patients with psychosis, 21 of 32 patients showed improvement on LMP (11 became symptom free) and 19 of 32 improved on CLOZ (12 became symptom free).[15] In human brain, LMP has a significantly greater binding affinity for the serotonin-2 (5-HT_2) receptor and the adrenergic α-1 receptor than either CLOZ or CPZ and a significantly greater binding affinity for the adrenergic α-2 receptor than CPZ.[16] Antagonism at these sites has been implicated in the unique therapeutic effect of CLOZ.[17] In addition, LMP has a similar electroencephalogram profile to CLOZ.[18] These findings suggest that LMP might also be effective in the treatment of TRS. Accordingly, we embarked on a double-blind, randomized controlled trial to test the hypothesis that LMP would be superior to CPZ in the treatment of TRS. CPZ was chosen as the comparator, because it has a similar side-effect profile to LMP[19] and was used as a comparator in the study that established the efficacy of CLOZ in TRS.[4]

The present study required a sample size of 86 subjects (43 subjects per arm) to detect a difference in response rates of 30% (power = 80%, α = 0.05, 2-sided), but with the widespread introduction of atypical neuroleptics the trial was prematurely terminated after 38 subjects were enrolled. However, because of the unexpected findings in our sample and the difficulty carrying out studies using typical neuroleptics,[6] we now report our results.

Methods

Subjects

Thirty-eight inpatients (Table 1) at the Douglas Hospital, Montréal, who fulfilled general inclusion and exclusion criteria, as well as historical and severity criteria for TRS, and from whom informed consent was obtained, participated in the study. For subjects considered incompetent, it was necessary for the subject's curator to give consent together with the assent of the patient and also, if available, that of the next of

Table 1: Characteristics of study participants

Characteristic*	Treatment group; no. of patients†	
	Levomepromazine (n = 19)	Chlorpromazine (n = 19)
Mean age, (SD) [and range], yr	38.5 (9.6) [20–54]	39.4 (8.8) [26–54]
Male:female ratio	12:7	12:7
Type of schizophrenia diagnosed		
Paranoid	12	7
Disorganized	3	8
Undifferentiated	4	4
Mean age of onset of illness, (SD) [and range], yr	20.4 (5.2) [13–32]	20.2 (4.1) [15–28]
Mean duration of illness, (SD) [and range], yr	18.7 (9.3) [5–34]	19.3 (7.9) [9–34]
Mean no. of hospital admissions, (SD) [and range]	8.8 (6.2) [2–23]	11.2 (8.1) [3–40]
Three treatment periods completed within		
≤ 5 yr of entry into baseline	16	15
> 5 yr of entry into baseline	3	4
Earlier history		
Clozapine treatment	3	3
Risperidone treatment	5	6
Mean duration of current stay in hospital, (SD) [and range], wk	232 (200) [22–680]	329 (412) [12–1605]

SD = standard deviation.
*Between-group comparisons are not significantly different for any of the variables listed.
†Unless otherwise indicated.

kin, in order to be enrolled. The project was approved by the Research Ethics Board of the Douglas Hospital Research Centre in compliance with the McGill University guidelines for research in human subjects. The study began in January 1994 and ended in April 1998.

General inclusion criteria

Included in the study were men and women aged 20–55 years, who met the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, third edition (DSM-III-R), for chronic schizophrenia (codes 295.12, 295.22, 295.32, 295.92)[20] based on the concurrence of 2 independent psychiatrists and who were sufficiently physically fit to undergo treatment with haloperidol (HAL), CPZ, LMP and benztropine (BT).

Exclusion criteria

Patients who were excluded from the study had mental disorders on Axis I (DSM-III-R)[20] other than schizophrenia; substance or alcohol abuse in the previous 12 months; intolerance of HAL, CPZ, LMP or BT; and clinically significant cardiovascular, hepatic, renal or neurological disease, or other relevant medical disorder. Sexually active women at risk of becoming pregnant were also excluded from the study, unless they were taking oral contraceptives or had an intrauterine device.

Criteria for TRS

Criteria for TRS were based on those of Kane et al[4] and in the present trial consisted of (a) historical criteria: (i) at least 3 periods of treatment with neuroleptics from at least 2 different chemical classes for a period of at least 6 weeks at a dose of at least 1000 mg CPZ equivalents/d, (ii) no good period of functioning in the past 5 years; of (b) severity criteria: (i) total Brief Psychiatric Rating Scale (BPRS)[21] score of at least 45 (18-item version rated 1–7; 1 = absence, 7 = severe) during screening and on each occasion when assessed every 2 weeks during the 6-week baseline phase, (ii) a Clinical Global Impression (CGI) of severity of illness[22] rating of at least 4 or more (4 = moderately ill) during screening and on each assessment during the baseline phase of the study, (iii) item score of at least 4 (4 = moderate) on 2 of the following BPRS items: conceptual disorganization, suspiciousness, hallucinatory behaviour and unusual thought content (4-item psychosis cluster)[4] during screening and on each assessment during the baseline phase; and of (c) prospective criteria: failure to show clinical improvement in an open prospective trial with HAL (up to 60 mg/d in liquid form) plus BT (up to 6 mg/d) to confirm TRS.[4]

Psychiatrists who work on the inpatient services of the Douglas Hospital were approached for potential recruits based on our research criteria and the psychiatrists' opinion of the likelihood of the patient agreeing to participate and being able to tolerate the demands of the protocol. Information on earlier drug treatments was obtained from hospital records. Thirty-five of the subjects had had at least 3 previous adequate pharmacotherapy trials while inpatients at the Douglas Hospital and, of these, 23 had undergone these trials during their current stay in hospital. Of the 3 remaining subjects, 2 had participated in one of the trials before transfer from an affiliated hospital and the other subject had participated in all 3 trials before transfer to the Douglas Hospital.

A general idea of functioning was based on the capacity for independent living derived from information from hospital records and family members, if available. None of the subjects had been considered capable of independent living during the previous 5 years. Sixteen patients required continuous care in hospital and 18, when not hospital inpatients, were under supervision in a foster home. Four patients, when not hospital inpatients, lived with their families but required considerable family assistance to be maintained at home.

Study design

Preliminary phase: Psychotropic drugs other than neuroleptics, antiparkinsonian anticholinergic agents and chloral hydrate were gradually withdrawn. In 35 patients, the withdrawal was completed at least 4 weeks before entry into the baseline phase (Table 2). In 4 patients, adjustments to neuroleptic medication were made within the 4-week period before entry into the baseline phase: 3 weeks before in 2 patients, 2 weeks before in 1 and 1 week before in 1.

Phase I (wk 0–6) (baseline): Subjects remained on their regular neuroleptic and antiparkinsonian anticholinergic medication at the same individual doses.

Phase II (wk 7–9) (transition to HAL + BT): Subjects re-

Table 2: Medication taken by study participants before entering the baseline phase of the study

	Treatment group; no. of patients†	
Medication*	Levomepromazine (LMP) (n = 19)	Chlorpromazine (CPZ) (n = 19)
Neuroleptic dose ≥ 1000 mg CPZ equivalents/d	19	18‡
Duration on 1000 mg CPZ equivalents/d		
≥ 12 wk	18	16
< 12 wk	1	3
Mean dose in CPZ equivalents/d at baseline, (SD) [and range], mg	1611 (879) [1000–3900]	1872 (1333) [800–6250]‡
Duration medication was unchanged		
≥ 12 wk	5	3
4 – < 12 wk	10	13
< 4 wk	4	3
Psychotropic medications limited to neuroleptics, anticholinergics and prn chloral hydrate		
≥ 12 wk	10	5
4 – < 12 wk	7	13
< 4 wk	2	1

SD = standard deviation; prn = as needed.
*Between-group comparisons are not significantly different for any of the variables listed.
†Unless otherwise indicated.
‡In 1 subject, the dose was reduced to 800 mg CPZ equivalents/d because of side effects before entry into baseline.

ceived HAL in liquid form (to minimize noncompliance), which was increased stepwise commencing with 10 mg/d in 4 divided doses in week 7, 20 mg/d in week 8 and 30 mg/d in week 9. During this phase, the subjects' regular neuroleptics were decreased by about one-third (in CPZ equivalents) each week. In addition, in subjects who were taking procyclidine or trihexyphenidyl, these were replaced by BT so that all subjects received BT, 1 mg twice a day in week 7, 1 mg 3 times a day in week 8 and 1 mg 4 times a day in week 9.

Phase III (wk 10–15) (HAL + BT phase): Subjects received HAL (40 mg/d in wk 10, 50 mg/d in wk 11 and 60 mg/d in wk 12–15) plus BT (4 mg/d in wk 10, 5 mg/d in wk 11 and 6 mg/d in wk 12–15).

Phases I–III were open phases. At the end of the HAL phase, all subjects who still met the severity criteria for TRS were then randomly allocated to receive either LMP or CPZ under double-blind conditions. The random allocation sequence, stratified by sex and balanced in blocks of 4 patients, was generated by the statistician (G.S.), who had no contact with patients, using a book of random numbers. Independent pharmacists dispensed LMP and CPZ in bottles labelled by patient number only according to the randomization list. Researchers responsible for enrolling subjects, administering treatment and assessing outcome were blind to treatment assignment, as were patients. Commercially obtained LMP and CPZ were encapsulated in identical-looking capsules at strengths of 25 mg, 50 mg and 100 mg. The dose equivalence used was 1 mg LMP = 1 mg CPZ.[23]

Phase IV (wk 16–20) (transition to LMP or CPZ): Subjects began with 100 mg/d LMP or CPZ in 4 divided doses in week 16, and this was increased by 100 mg/wk to a dose of 500 mg/d in week 20. HAL and BT were decreased stepwise to 10 mg/d and 2 mg/d, respectively, in week 20.

Phase V (wk 21–28) (optimization of LMP or CPZ): In week 21, subjects received 600 mg/d of either LMP or CPZ. Doses were increased by 100 mg/wk to a maximum of 1000 mg/d (including as-needed doses). BT was permitted based on clinical judgement to a maximum of 6 mg/d.

Phase VI (wk 29–30) (optimum dose LMP or CPZ): The optimum dose of LMP or CPZ was maintained.

Subjects who were unable to tolerate higher doses of HAL were maintained on a lower dose. If subjects showed clinical deterioration on HAL, they were advanced to week 16 and the last tolerated dose of HAL prescribed. If side effects related to LMP, CPZ or BT occurred, dose reduction was permitted. For agitation, LMP or CPZ as needed in doses of 25 mg was allowed. Chloral hydrate for sleep as necessary was permitted throughout the study. Concomitant medications maintained during the trial are listed in Table 3.

Assessment scales

In addition to the BPRS, subjects were rated on the Positive and Negative Syndrome Scale (PANSS).[24] Additional scales included the CGI of severity of illness scale[22] and the Nurses' Observation Scale for Inpatient Evaluation (NOSIE).[25] Tardive dyskinesia was rated using the Abnormal Involuntary Movement Scale (AIMS).[26] Items 1–5 and 7 of the Parkinsonism Objective Examination (section II) of the Extrapyramidal Symptom Rating Scale (ESRS)[27] were used to assess parkinsonism; item 6 of section II was used to assess akathisia (range 0–6).

Subjects were rated at weeks 0, 2, 4, 6, 9, 11, 13, 15, 16, 18, and then weekly from weeks 20–30 inclusive. Raters were previously trained. To minimize the issue of interrater reliability, each subject was rated by the same rater throughout the subject's participation. Vital signs and side effects were assessed weekly. Routine laboratory tests and electrocardiograms were obtained at weeks 0 and 30.

Data analysis

All subjects were included in the analysis on an intention-to-treat basis. In subjects who were advanced in study week or dropped out because of side effects or clinical deterioration, the last scores rated were carried forward and used in the analysis. The primary outcome was the proportion of patients who achieved a 25% or greater improvement in BPRS scores from baseline to week 30. The proportion of subjects who met the strict criteria reported by Kane et al[4] for improvement was also evaluated. Secondary outcomes were the following: mean change in BPRS and PANSS total and factor scores, CGI and NOSIE scores; longitudinal outcome as measured by BPRS total scores at each evaluation following random allocation to LMP or CPZ; mean change in extrapyramidal symptoms and tardive dyskinesia as measured by the ESRS; and the proportion of subjects who reported adverse effects. Proportions were analyzed by the χ^2 test with the Yates correction for continuity where appropriate. Rating scale scores were submitted to analysis of variance (ANOVA) or analysis of covariance (ANCOVA), with mean baseline (wk 0–6) scores as covariate in order to control for the effect of any differences at baseline. For each ANCOVA, the homogeneity of slopes by treatments was tested in a separate analysis. Data showing heterogeneity of variance were analyzed by the Mann–Whitney *U* test. Hierarchical linear modelling (HLM) was employed to compare treatments with respect to longitudinal outcome observed during the randomized treatment phase; missing data were not replaced in this analysis. Data for means are presented as the mean (and standard deviation [SD]). An α of 0.05 was used throughout as a threshold for statistical significance, and all tests were 2-tailed. Because of inflation of type 1 error, testing

Table 3: Concomitant medications maintained during study

Medication	Treatment group; no. of patients	
	Levomepromazine (*n* = 19)	Chlorpromazine (*n* = 19)
None	9	10
Laxatives	7 (5)*	5 (4)*
Birth control pills	2	3
Niacinamide	1	1
Fenofibrate	1	1
Gemfibrozil, glyburide and metformin†	1	0

*Number in parenthesis refers to subjects taking laxatives as the sole concomitant agent.
†One subject with stable diabetes mellitus was taking all 3 agents.

of BPRS factor scores and PANSS subscale scores was regarded as exploratory.

Results

Early withdrawals

All subjects entered the randomization phase (Table 4). Seventeen in the LMP group and 14 in the CPZ group completed the trial. Two patients on LMP were withdrawn from the study prematurely: one because of syncope from orthostatic hypotension, and the other temporarily ran away. Five patients on CPZ were withdrawn prematurely for the following reasons: clinical deterioration ($n = 2$), withdrawal of consent ($n = 1$), physical aggression ($n = 1$) and one temporarily ran away ($n = 1$). There was no significant difference between treatments with respect to the incidence of early withdrawal (Yates $\chi^2_1 = 0.70$, $p = 0.40$).

LMP and CPZ dosage

The mean final dose in patients who completed the trial was 799 (SD 234) mg/d LMP and 764 (SD 215) mg/d CPZ, which is in each case significantly lower in CPZ equivalents than at their respective baselines of 1624 (SD 914) mg/d and 1623 (SD 856) mg/d ($F_{1,16} = 16.00$, $p < 0.001$; and $F_{1,13} = 11.70$, $p < 0.005$, respectively).

End point

At study end point, 10 of 19 (52.6%) patients on LMP and 8 of 19 (42.1%) on CPZ showed a 25% or greater decrease in the primary outcome variable, the BPRS total scores; namely, 18 of 38 subjects (47.4%) enrolled in the study met the criterion for response. There was no significant difference between treatments in response rate (Yates $\chi^2_1 = 0.11$, $p = 0.75$). In 9 of 18 responders (5 on LMP and 4 on CPZ), response was obtained at a dose level of 200–700 mg CPZ equivalents/d, that is, 9 of 38 patients (23.7%) enrolled responded at this dose range. The mean final dose in all responders was 710 (SD 265) mg/d ($n = 10$) for LMP and 722 (SD 272) mg/d ($n = 8$) for CPZ, which were significantly lower than their respective baseline values ($F_{1,9} = 14.37$, $p = 0.004$ and $F_{1,7} = 7.89$, $p = 0.026$, respectively) (Table 4). Eleven of 38 subjects at baseline were on doses of 1750 mg CPZ equivalents/d or more; of these, 6 improved on either LMP or CPZ (3 on 350–600 mg/d and 3 on 1000 mg/d).

On the PANSS, a 25% decrease in total scores was seen in 11 of 19 patients (57.9%) on LMP and 6 of 19 (31.6%) on CPZ (Yates $\chi^2_1 = 1.70$, $p = 0.19$). Two additional subjects on CPZ showed an improvement of 21% and 24%, respectively. Using the criteria reported by Kane et al,[4] the figures for improvement were 6 of 19 (31.6%) on LMP and 4 of 19 (21.1%) on CPZ (Yates $\chi^2_1 = 0.14$, $p = 0.71$).

By chance, after randomization, mean baseline BPRS and PANSS total scores, as well as some of the BPRS factor and PANSS subscale scores, were higher in the CPZ than the LMP group (Table 5). Analysis of covariance, controlling for differences in baseline scores, revealed no significant difference between the 2 treatments at end point (week 30) for either the BPRS Total Score ($F_{1,35} = 1.77$, $p = 0.19$; adjusted mean treatment difference = 6.0, 95% confidence limits –3.1, 15.1) or the PANSS Total Score ($F_{1,35} = 2.98$, $p = 0.09$; adjusted mean treatment difference = 12.8, 95% confidence limits –2.3, 27.9). However, exploratory analysis of covariance on BPRS factors and PANSS

Table 4: Treatment outcome*

Variable	Treatment group; no. of patients† Levomepromazine $n = 19$	Chlorpromazine $n = 19$
Completed HAL phase, 60 mg/d × 4 wk	12	13
Advanced after HAL, 60 mg/d × 1–3 wk‡	6	2
Advanced after HAL, < 60 mg/d‡	1	4
Randomization phase completed	17	14
Premature withdrawal	2	5
Mean baseline neuroleptic dose (and SD), mg/d§	1611 (879) ($n = 19$)	1872 (1333) ($n = 19$)
Mean final neuroleptic dose (and SD), mg/d	813 (225)	762 (199)
p value¶	< 0.001	< 0.002
Mean baseline neuroleptic dose (and SD), mg/d (completers)§	1624 (914) ($n = 17$)	1623 (856) ($n = 14$)
Mean final neuroleptic dose (and SD), mg/d (completers)	799 (234)	763 (215)
p value¶	< 0.001	< 0.005
BPRS total decrease ≥ 25%	10	8
Criteria of Kane et al[4] for response	6	4
PANSS (total) decrease ≥ 25%	11	6**
Mean baseline neuroleptic dose of responders (and SD), mg/d§	1715 (966) ($n = 10$)	1763 (921) ($n = 8$)
Mean final neuroleptic dose of responders (and SD), mg/d††	710 (265)	722 (272)
p value¶	< 0.005	0.026
Mean weight at baseline (and SD), kg	71.5 (12.2) ($n = 17$)	70.5 (20.2) ($n = 12$)
Mean weight at wk 30 (and SD), kg	75.6 (12.9)	75.4 (18.4)
p value¶	0.046	0.015
Mean baseline QTc interval (and SD)	0.446 (0.053) ($n = 11$)	0.424 (0.025) ($n = 12$)
Mean QTc interval at wk 30 (and SD)	0.429 (0.025)	0.437 (0.024)
p value¶	0.29	0.12

BPRS = Brief Psychiatric Rating Scale; HAL = haloperidol; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.
*None of the between-group comparisons are significantly different.
†Unless otherwise indicated.
‡Subjects advanced to randomized phase without reaching HAL, 60 mg/d × 4 wk.
§Chlorpromazine equivalents.
¶Within-group comparisons.
**Two additional subjects improved 21% and 24%, respectively.
††Subjects showing a ≥ 25% reduction in total BPRS.

subscale scores at end point showed a borderline difference favouring LMP for the PANSS Negative Symptoms subscale ($F_{1,35}$ = 4.00, p = 0.05; but this is not significant if the Bonferroni correction for multiple testing is applied). No significant differences (p > 0.05) were found between treatments on the other BPRS factors or PANSS subscales at end point. Analysis of covariance also showed no significant difference (p > 0.05) between the 2 treatments with respect to BPRS and PANSS endpoint scores in the subgroup of completers.

Longitudinal outcome

The course over time of the BPRS total scores (mean and SD) in the group treated with LMP is shown in Figure 1, and for the group treated with CPZ in Figure 2. Analysis of longitudinal BPRS total scores by HLM for the period when subjects received randomly allocated treatment (wk 21–30) revealed a significant treatment ∞ time interaction ($F_{1,374}$ = 3.08, p = 0.006), with the advantage of LMP treatment over CPZ increasing as time progressed (Fig. 1, Fig. 2).

Comparison of mean BPRS total scores during weeks 21 to 30, when patients were treated with only 1 of the phenothiazines (with or without BT) with their respective mean baseline scores indicated that there were significant improvements in both LMP-treated ($F_{1,18}$ = 9.39, p = 0.007) and CPZ-treated ($F_{1,18}$ = 5.56, p = 0.030) groups (Fig. 1, Fig. 2). However, at end point, exploratory analyses revealed that significant (p < 0.05) decreases for BPRS Factors I, II, III and V and the BPRS 4-item psychosis cluster occurred on LMP, but only for Factor II on CPZ (Table 5). On the PANSS, significant (p < 0.05) improve-

Table 5: Effect of levomepromazine (LMP) and chlorpromazine (CPZ) on psychopathology

		Time of treatment; mean score (and standard deviation)			*p value	
Scale	Treatment	Week 0–6 (baseline phase)	Week 15 (haloperidol phase)	Week 30 (LMP or CPZ phase)	Week 15 v. baseline	Week 30 v. baseline
CGI (severity)	LMP	5.1 (0.4)	5.5 (1.0)	4.0 (0.9)	0.80	< 0.001
	CPZ	5.4 (0.8)	5.5 (0.8)	4.8 (1.3)	0.59	0.025
BPRS						
Total	LMP	55.8 (4.8)	61.0 (10.8)	45.2 (11.6)	0.024	0.001
	CPZ	61.1 (8.3)	64.4 (8.2)	54.2 (14.8)	0.49	0.041
4-item psychosis cluster†	LMP	16.9 (1.5)	18.4 (3.0)	14.1 (4.3)	0.020	0.017
	CPZ	18.4 (2.6)	19.5 (2.7)	16.8 (4.9)	0.005	0.15
Factor I: anxiety–depression	LMP	2.9 (0.6)	3.1 (0.6)	2.2 (0.6)	0.09	0.001
	CPZ	2.8 (0.9)	2.9 (0.9)	2.5 (0.9)	0.33	0.10
Factor II: anergia	LMP	2.7 (0.6)	3.1 (0.7)	2.3 (0.8)	0.017	0.016
	CPZ	3.0 (0.7)	3.0 (0.8)	2.6 (0.9)	0.73	0.026
Factor III: thought disturbance	LMP	3.8 (0.4)	4.1 (0.9)	3.3 (1.0)	0.13	0.036
	CPZ	4.3 (0.8)	4.6 (0.8)	3.9 (1.2)	0.007	0.14
Factor IV: activation	LMP	2.6 (0.5)	2.7 (0.7)	2.2 (0.9)	0.72	0.08
	CPZ	3.3 (0.8)	3.5 (0.9)	2.9 (1.4)	0.23	0.10
Factor V: hostile–suspiciousness	LMP	3.4 (0.8)	4.1 (1.4)	2.6 (1.0)	0.06	0.014
	CPZ	3.6 (1.2)	4.0 (1.0)	3.3 (1.4)	0.07	0.40
PANSS						
Total	LMP	100.8 (9.8)	108.8 (18.1)	81.1 (21.2)	0.048	0.001
	CPZ	107.9 (16.6)	112.8 (12.9)	97.0 (24.0)	0.14	0.06
Positive	LMP	25.7 (2.4)	28.0 (5.8)	21.9 (6.6)	0.10	0.022
	CPZ	28.8 (4.5)	30.3 (4.3)	26.8 (7.7)	0.08	0.27
Negative	LMP	25.7 (4.9)	27.2 (4.9)	19.7 (5.2)	0.14	0.002
	CPZ	25.8 (5.7)	26.8 (4.2)	23.7 (5.2)	0.46	0.22
General	LMP	49.4 (5.1)	53.7 (9.6)	39.4 (10.6)	0.036	0.001
	CPZ	53.3 (9.8)	55.6 (8.2)	46.5 (12.9)	0.18	0.018
NOSIE (total assets)	LMP	187.8 (23.8)	176.1 (26.8)	201.6 (30.1)	0.016	0.09
	CPZ	177.6 (23.3)	175.4 (27.0)	180.3 (26.7)	0.74	0.60
AIMS (total)	LMP	4.0 (2.7)	3.7 (2.5)	2.6 (2.7)‡	0.60	0.13
	CPZ	6.0 (4.6)	8.3 (6.0)	6.5 (3.9)	0.016	0.54
ESRS						
Section II (excluding item 6): parkinsonism	LMP	11.7 (7.3)	10.8 (6.3)	8.7 (8.6)	0.55	0.16
	CPZ	11.4 (9.4)	13.6 (10.9)	8.4 (7.7)	0.028	0.12
Section II, item 6: akathisia	LMP	1.0 (1.1)	1.0 (0.9)	0.4 (0.8)§	0.81	0.10
	CPZ	1.8 (1.1)	1.6 (1.4)	1.7 (1.7)	0.48	0.97

AIMS = Abnormal Involuntary Movement Scale; ANCOVA = analysis of covariance; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression of severity of illness; ESRS = Extrapyramidal Symptom Rating Scale; NOSIE = Nurses' Observation Scale for Inpatient Evaluation; PANSS = Positive and Negative Syndrome Scale.
*Within-group comparisons.
†Combined item scores for conceptual disorganization, suspiciousness, hallucinatory behaviour and unusual thought content.
‡p = 0.005 (between-group comparisons tested by ANCOVA with mean baseline score as covariate).
§p = 0.016 (between-group comparisons tested by ANCOVA with mean baseline score as covariate).

ment occurred on the total score and on the Negative, Positive and General Psychopathology subscores on LMP, but only on the General Psychopathology subscale on CPZ (Table 5). CGI scores improved significantly with both drugs (Table 5). Neither treatment was associated with significant ($p > 0.05$) improvement on the NOSIE (total assets).

The mean peak dose of HAL was 58.4 (SD 6.7, range 30–60) mg/d and 54.7 (SD 12.6, range 10–60) mg/d for LMP and CPZ groups, respectively, and for BT, 5.8 (SD 0.7) mg/d[3–6] and 5.6 (SD 0.8) mg/d.[4–6] During the HAL + BT treatment phase, comparison of mean BPRS total scores at the end of the HAL phase with mean baseline scores showed a significant worsening during HAL treatment ($n = 38$) ($F_{1,37} = 8.40$, $p = 0.006$).

Extrapyramidal symptoms and outcome

At the end of the study, 3 of 19 and 8 of 19 subjects on LMP and CPZ, respectively, were on BT (Yates $\chi^2_1 = 2.05$, $p = 0.15$). Akathisia scores were significantly lower after LMP than CPZ ($F_{1,37} = 6.43$, $p = 0.016$) (Table 5). At baseline, 4 of 19 patients in the LMP group had akathisia scores of 2 or more compared with 9 of 19 in the CPZ group (Yates $\chi^2_1 = 1.87$, $p = 0.17$); at week 30, the numbers were 1 of 19 on LMP and 9 of 19 on CPZ (Yates $\chi^2_1 = 6.65$, $p = 0.010$). Of the subjects who responded on either drug, only 1 of 18 had an akathisia score of 2 or more at week 30 compared with 9 of 20 who failed to respond (Yates $\chi^2_1 = 5.70$, $p = 0.017$); all of the 9 subjects who showed no improvement were in the CPZ treatment group. Total AIMS scores were significantly lower after LMP than CPZ ($F_{1,37} = 9.22$, $p = 0.004$). There was no significant difference ($p > 0.05$) between the 2 drugs with respect to parkinsonism (Table 5).

Adverse effects

Only 6 subjects reached a maximum dose of 1000 mg/d LMP. Reasons for dose restriction or reduction were systolic blood pressure below 100 mm Hg on standing immediately after being recumbent ($n = 7$), drowsiness or fatigue ($n = 4$), and irritability or agitation ($n = 2$). Five patients reached a maximum dose of 1000 mg/d on CPZ. Reasons for dose restriction or reduction were the following: systolic blood pressure below 100 mm Hg on standing immediately after being recumbent ($n = 8$), drowsiness ($n = 2$), agitation ($n = 1$), seizure ($n = 1$) and premature withdrawal from the study ($n = 2$). The side effects present in subjects who completed the study on their optimized dose during the final week of treatment are given in Table 6. One patient on LMP developed a 3-fold increase in hepatic transaminases. No other clinically significant changes in routine laboratory tests or electrocardiograms were noted with either drug. Both treatments resulted in weight gain. The final mean systolic and diastolic blood pressures (lying and standing) were not significantly lower than their respective mean baseline values (data not shown).

Discussion

Several reports in the early literature pointed to improvement with LMP in patients who failed to respond to CPZ or other treatment modalities,[28–32] but studies were limited in terms of either being uncontrolled or in using assessment tools less rigorous than the BPRS.

In the present study in patients with TRS, when data were analyzed by ANCOVA, controlling for the effect of baseline differences, there was little difference in outcome between the 2

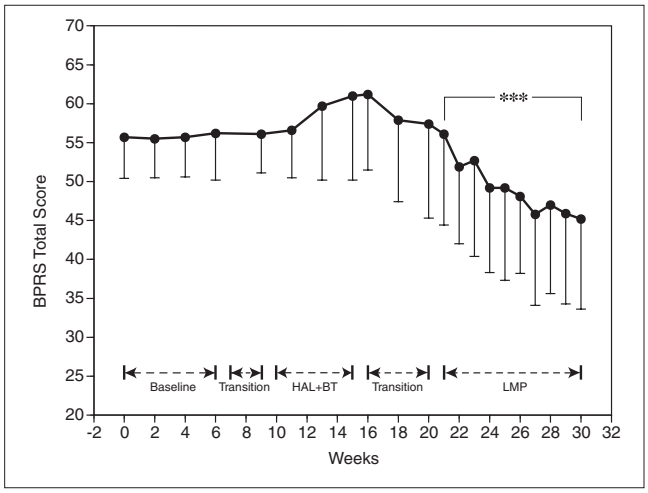

Fig. 1: Effect of levomepromazine (LMP) on the Brief Psychiatric Rating Scale (BPRS) total scores. Data are presented as the mean (and standard deviation). Baseline represents observations while subjects were taking their regular neuroleptic medication. The first transition period represents the gradual switch from baseline neuroleptics to haloperidol (HAL) plus benztropine (BT). The second transition phase represents the gradual switch from HAL + BT to LMP. ***$p = 0.007$ refers to the difference between mean baseline value and mean value for weeks 21–30 inclusive.

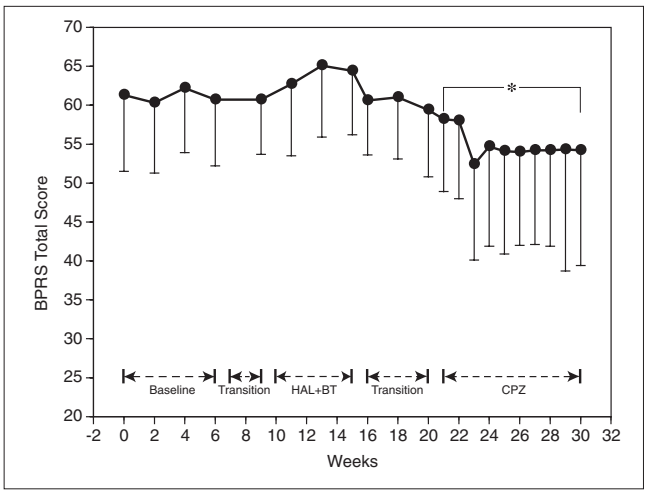

Fig. 2: Effect of chlorpromazine (CPZ) on the Brief Psychiatric Rating Scale (BPRS) total scores. Data are presented as the mean (and standard deviation). Baseline represents observations while subjects were taking their regular neuroleptic medication. The first transition period represents the gradual switch from baseline neuroleptics to haloperidol (HAL) plus benztropine (BT). The second transition phase represents the gradual switch from HAL + BT to CPZ. *$p = 0.030$ refers to the difference between mean baseline value and mean value for weeks 21–30 inclusive.

groups at end point. However, longitudinal analysis of outcome by HLM revealed a trend toward superiority of LMP over CPZ as time progressed. Both phenothiazines improved TRS; LMP improved both negative and positive symptoms. Unlike the present study in which 8 of 19 patients (42.1%) on CPZ responded (total BPRS 25% decrease), 3 published studies have shown little or no response to CPZ. Kane et al,[4] using a 20% reduction in total BPRS as one of the necessary criteria for improvement, found 38 of 126 individuals (30%) improved on CLOZ versus only 5 of 139 (4%) on CPZ. Conley et al,[11] who used similar criteria for TRS and for response as Kane et al,[4] noted an improvement in 3 of 42 individuals (7.1%) on OLAN versus 0 of 42 on CPZ. In the study by Hong et al,[33] which used less rigorous criteria for TRS and for response, 6 of 21 individuals (28.6%) improved (> 20% reduction in total BPRS) on CLOZ versus 0 of 19 on CPZ. Difference in outcome in comparison with our study may have been related to the higher doses used in those 3 trials. In the study by Kane et al,[4] the doses of CPZ and CLOZ compared were in a ratio of 2:1. During the 6-week double-blind phase, the mean peak doses exceeded 1200 mg/d CPZ (max 1800 mg/d) and 600 mg/d CLOZ (max 900 mg/d). Side effects of hypotension and dry mouth were considerably higher for CPZ. In the study by Conley et al,[11] the mean dose of CPZ was 1173 mg/d versus 25 mg/d OLAN. CPZ plus BT caused significantly more orthostatic hypotension, unsteady gait and dry mouth than OLAN. Hong et al[33] used an average dose of 1163 (SD 228) mg/d CPZ and 543 (SD 157) mg/d CLOZ.

In the present study, for all enrolled subjects the mean final dose of CPZ was 762 (SD 199) mg/d (and for LMP 813 [SD 225] mg/d). Baldessarini et al[1] in a review of dose–response studies of antipsychotic drugs noted an inverse "U"-shaped relation between neuroleptic drug dose and therapeutic efficacy; doses of 500–700 mg/d CPZ equivalents appear to be optimal. With high doses, a worse overall effect may occur because of drug-induced toxicity.[34] In our study, 18 of 38 subjects responded at a significantly lower dose (CPZ equivalents) than at their respective baseline, a finding that is compatible with this view. Further, 9 of these subjects responded at a dose range of 200–700 mg/d. This suggests that a subgroup of patients has a low-dose therapeutic window. At baseline, 11 of 38 patients were taking 1750 mg/d CPZ equivalents; of these patients, 6 improved on either LMP or CPZ. These findings raise the possibility that high doses of neuroleptics may contribute to TRS and that subjects should be given a trial of 200–700 mg/d CPZ equivalents of typical low-potency neuroleptics before they are considered to be treatment resistant.

Table 6: Side effects on optimized dose of phenothiazine*

	Treatment group; no. of patients	
Side effects†	Levomepromazine (n = 17)	Chlorpromazine (n = 14)
Insomnia	8	8
Constipation	6	2
Drowsiness	5	3
Dry mouth	5	3
Fatigue	4	0
Hypotension‡	3	3
Dizziness	3	1
Headache	2	3
Agitation	1	3

*Side effects present in final week of subjects completing the study on levomepromazine (LMP) or chlorpromazine (CPZ) with or without benztropine.
†In addition to those listed, heartburn and nasal stuffiness were experienced by 1 patient on LMP and anxiety in 1 patient on CPZ. Galactorrhoa present at baseline persisted on LMP in 1 patient.
‡Systolic blood pressure < 100 mm Hg on standing immediately after being recumbent.

Lieberman et al[35] reported that reducing HAL from 50 mg to 20 mg or less per day in 13 patients with TRS was associated with a reduction in BPRS scores. Two of the 13 patients, however, were unable to tolerate substantial dose reduction. Their study would support the idea that in many patients high doses of HAL worsen psychopathology. In a prospective study in patients with TRS using up to 60 mg/d HAL plus BT, 6 mg/d, Kane et al[4] found that 5 of 305 patients improved and 52 of 305 terminated prematurely. BPRS scores were reported on average as being unchanged. Data, however, were not provided. In the present study, using the same doses and duration of HAL + BT as Kane et al,[4] there was a significant deterioration in total BPRS and in some of the subscales. This again points to the deleterious effect of high-dose neuroleptic therapy.

In a double-blind multicentre study, the mean effective dose in the treatment of schizophrenia was 300 mg/d for CLOZ and 350 mg/d for CPZ.[36] In addition, Angst et al[15] in a double-blind, 4-week study showed that patients with psychosis showed improvement on CLOZ at a dose of 140 mg/d or 180 mg/d LMP. Although neither of these studies investigated patients with TRS, they do suggest that in studies comparing LMP or CPZ with CLOZ a ratio closer to 1:1 would appear more appropriate. Further, Petit and Dollfus[37] concluded that based on published data on binding affinity to dopamine-2 (D_2) receptors 600 mg CPZ is equivalent to 500 mg CLOZ. Clearly, CLOZ has advantages over low-potency phenothiazines in terms of side-effect profile, especially the absence of risk for tardive dyskinesia. However, to determine whether CLOZ has a specific antipsychotic effect in TRS compared with other neuroleptics, it is necessary to conduct studies using a more appropriate dose of comparator.

An additional factor that may account for the lack of effect of CPZ in earlier studies may have been the short duration of treatment. Petit and Dollfus[37] cite data showing that of 182 patients considered resistant to CPZ at 3 months, at 6 months the number had dropped to 83 and at 9 months to 59.

In our study, the presence of akathisia was associated with failure to improve. This suggests that combining phenothiazines with anti-akathisic agents such as propranolol might augment the response rate in patients with TRS.

The direction of changes on the NOSIE scores was compatible with changes in total BPRS scores but, unlike total BPRS, NOSIE scores only reached significance versus baseline in the LMP group during the HAL + BT phase. The reason for this is unclear but may represent a lower sensitivity of the NOSIE instrument.

The present study is limited by its small sample size. A further limitation is that it is possible that treatment with high doses of HAL altered brain receptor function such that subsequent exposure to phenothiazines accounted for improvements

in subjects' responding. However, this would imply that such changes persist for at least 10 weeks after discontinuation of HAL. Interestingly, in the study by Kane et al,[4] improvement with CLOZ also followed a prospective phase with high doses of HAL. Inclusion of a HAL + BT phase may make comparison with other studies using typical antipsychotic agents difficult.

Ideally, the study should have included a group of patients with TRS who, following the haloperidol phase, were gradually switched back to their baseline type and dose of neuroleptic to eliminate the possibility that the attention of the staff and duration of the study resulted in the therapeutic benefit observed.

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Contributors: Drs. Lal, Thavundayil, Nair, Annable and Ng Ying Kin designed the study. Drs. Thavundayil and Gabriel acquired the data. Drs. Lal, Nair, Annable, Ng Ying Kin and Schwartz analyzed the data. Drs. Lal and Annable wrote the article. All authors critically reviewed the article and gave final permission for its publication.

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