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After completing this CME activity, the psychiatrist should be able to:

- Review research on the efficacy of neuroleptics for the treatment of behavioral disorders in patients with dementia
- Discuss current issues relative to the safety of using neuroleptics for the treatment of behavioral disorders in patients with dementia
- Compare the efficacy and safety of different types of neuroleptics used for the treatment of behavioral disorders in patients with dementia.

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Efficacy and Safety of Neuroleptics in Behavioral Disorders Associated With Dementia

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Background: Neuroleptics are commonly used to treat behavioral disorders associated with dementia. However, their safety and efficacy have not been well established in these patients.

Method: A meta-analysis of randomized, controlled (either placebo or active drug), double-blind trials published since 1966 (N = 16; 499 treated, 112 active controls, and 123 placebo) was conducted. Data were collected on proportion of patients with clinically significant improvement, significant side effects, and dropout rates.

Results: Pooled mean percentages of patients who improved (95% CI): all neuroleptics, 64% (54% to 74%); low potency, 63% (54% to 72%); moderate potency, 70% (56% to 85%); moderate-high potency, 62% (49% to 75%); and high potency, 69% (49% to 90%). Thus, no differences in efficacy existed between different potencies of neuroleptics. Therapeutic effect (neuroleptic minus placebo) was only 26% (14% to 38%). Treatment-emergent side effects were more common for neuroleptics vs. placebo (mean difference = 25%, 13% to 37%), but pooled mean dropout rates were not different (mean difference = 4%, –7% to 14%). Neither weighting by clinical trial quality (3 raters; weighted agreement, 83% to 92%) nor exclusion of poor quality trials changed the results.

Conclusion: Neuroleptics have small but significant efficacy over placebo in this population, and the efficacy rate is equivalent to the side effect rate. Comparing different neuroleptics shows they have similar efficacy, side effects, and dropout rates. Further study to determine more specific drug-responsive behaviors is needed to maximize benefits of these drugs.

(J Clin Psychiatry 1998;59:550–561)

Received Feb. 11, 1997; accepted March 3, 1998. From the Psychopharmacology Research Program (Drs. Lanctôt and Naranjo and Ms. Best), and the Division of Clinical Pharmacology (Drs. Lanctôt, Mittmann, Liu, and Oh), Sunnybrook Health Science Centre, and the Departments of Pharmacology (Drs. Lanctôt, Mittmann, and Naranjo), Psychiatry (Drs. Lanctôt and Naranjo), and Medicine (Drs. Oh and Naranjo), and the Faculty of Pharmacy (Dr. Einarson), University of Toronto, Toronto, Ontario, Canada.

Supported by the Alzheimer Society of Canada Research Program (Dr. Lanctôt).

An abstract of this work was presented at the 96th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, March 15–17, 1995; San Diego, Calif.

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Dementia has a major impact on the North American health care systems in terms of cost and medical resource utilization.[1,2] Furthermore, as the population ages, the proportion of people with this illness is expected to steadily increase.[1–3] Although the diagnosis of dementia is based on the presence of cognitive impairment, non-cognitive behavioral disorders are also a predominant feature of this condition.[4,5] The behavioral and psychological signs and symptoms of dementia can be divided into 2 groups: those with psychotic features (e.g., delusions and hallucinations) and those without psychotic features (e.g., agitation, wandering, hostility, and uncooperativeness).[6] Behavioral and psychological signs and symptoms are a significant problem for both demented patients and their caregivers.[5,7–10] Behaviors such as agitation and aggression can complicate management and contribute to institutionalization of demented patients.[11,12]

The most common treatment of behavioral disorders associated with dementia is neuroleptic medication.[13,14] Drug utilization studies have shown that neuroleptic medications are used in 39% to 51% of elderly institutionalized patients.[15,16] Despite the high rate of neuroleptic use, the efficacy of these medications has not been well established in the literature. Reviews of the efficacy of neuroleptics in the

treatment of behavioral problems in dementia have found that the majority of the literature consists of open trials, case reports, or poorly designed clinical trials.[13,14,17–21] Furthermore, published studies have not been able to clearly establish efficacy.[20] These contradictory findings combined with questionable quality and small trial sizes have made it difficult to reach conclusions using qualitative reviews.

A meta-analytic review conducted by Schneider et al.[22] suggested that although neuroleptics were significantly more effective than placebo, their effect size was only 18% (difference favoring neuroleptics over placebo). However, this meta-analysis did not consider side effects, dropout rates, or quality of the trial. To date, there has not been a quantitative review published to compare neuroleptic drug classes to examine whether certain types of neuroleptics have advantages in either safety or efficacy over other types of neuroleptics. Furthermore, there are no published meta-analytic reviews that scrutinize included papers by conducting a quality assessment so that the studies of a higher quality could be analyzed separately to produce a more valid estimate of the efficacy and safety of these medications. Hence, we conducted a complete meta-analysis, with a quality assessment, to compare the efficacy and safety of neuroleptics versus placebo in the treatment of behavioral disorders in patients with dementia. Neuroleptics were also grouped by potency and chemical class and compared.

METHOD

A meta-analysis of the English language literature published from 1966 to 1995 was performed. Inclusion criteria were a clinical trial with at least 1 antipsychotic drug, random assignment, double-blind assessment, placebo-control or comparison to an active medication, diagnosis of primary dementia (in > 70% of patients), measurement of behavioral outcomes with any scale (as opposed to only cognitive or other unrelated measures), and length of treatment of at least 4 weeks. The exclusion criterion was inability to extract needed information. Data on proportion of subjects who were responders, had side effects, or dropped out were needed; group statistics do not provide the needed information. Inclusion criteria did not specify dose since the therapeutic dose for this indication is not established, and no requirements were set for the control of concomitant medications. Potential papers were identified by conducting a search in MEDLINE (key words: *antipsychotic agents*, *phenothiazines*, or *butyrophenones*; and *dementia*; and *behavior therapy*; or *behavior*). Manual cross-referencing of recent reviews and all papers retrieved and consultation of experts were also done. Each paper went through 3 stages: (1) assessment for inclusion, (2) quality assessment, and (3) data extraction. All raters were blinded to the authors, date, journal, and place of publication during these 3 phases by selective photocopying to control for bias.[23]

Assessing for Inclusion/Exclusion

Three raters (N.M., B.A.L., T.S.B.) were given a sample of the Method section of the 51 collected papers to assess for adherence to the inclusion criteria. Each rater was given 13 to 15 papers to rate individually plus 10 randomly selected papers to test interrater reliability.

Data Extraction

Data were extracted for the number of subjects responding and not responding to treatment, overall rates of treatment-emergent adverse symptoms, and dropout rates (due to any cause including adverse drug reactions, lack of efficacy, and noncompliance) by 3 raters (N.M., T.S.B., P.I.O.) from the Results section of each paper.

Quality Assessment

For each of the articles meeting inclusion criteria, 3 raters (N.M., T.S.B., P.I.O.) were given the Method and Results sections, with all identifiers removed, to assess for quality. A quality rating scale was used that scored each paper on the following attributes: study subjects, trial design, results, analysis, and overall quality. Each item could be rated as: 0 = not reported, 1 = poor, 2 = satisfactory, or 3 = good. A sensitivity analysis was done 2 ways to assess the effect of quality on outcome: (1) by eliminating the poor papers and recalculating and (2) by weighting each paper by quality and recalculating.

Statistical Analysis

The method of DerSimonian and Laird[24] with the modification by Velanovich[25] was used to combine study effect sizes. The summary event rates were calculated using this meta-analytical statistical technique, which weighs individual studies by sample size and variance and yields a pooled mean point estimate and 95% confidence level. This method uses a random effects model that accounts for variability among studies by incorporating it into calculations and by weighting according to study variance.[26] Thus, this method generally creates wider confidence intervals than other methods.[26] This approach was felt to be appropriate because heterogeneity of the patient populations included in different clinical trials has been previously identified. Pooled weighted mean percentages

Table 1. List of Double-Blind, Randomized, Controlled Trials for Treatment of Behavioral Disorders in Dementia*

Author(s), Year	Neuroleptic(s), Comparator(s)	Dose (mg/d)	Diagnostic Descriptor (N)	No. Patients (drug 1, drug 2, …)	Behavioral Scale(s)	Treatment Duration	Concomitant Medications
Hamilton and Bennett, 1962[31]	Acetophenazine Placebo	20–60 ...	OBS with psychosis (19), schizophrenia (7), depression and psychosis (1)	27 ® (19, 8) © n/a	"a scale"	3–8 wk	No tranquilizers for 4-wk washout, supporting medications (digitalis, diuretics, and antibiotics)
Hamilton and Bennett, 1962[32]	Trifluoperazine Placebo	4–8 …	CBS with psychosis (27)	27 ® (18, 9) © n/a	MACC	2 mo	Supporting medications only (digitalis, diuretics, and antibiotics)
Sugarman et al, 1964[33]	Haloperidol Placebo	0.5–4.5 …	Senile, arteriosclerosis (18)	18 ® 18 © (9, 9)	Psychotic Reaction Profile	6 wk	Benztropine 2 mg bid for EPS
Kirven and Montero, 1973[34]	Thioridazine Diazepam	38.9 (mean) 9.0 (mean)	Senility (56)	56 ® (28, 28) © n/a	HAM-A, NOSIE, global rating	4 wk	Washout: 2 wk major tranquilizers, 3 d minor tranquilizers; concomitant medications unknown
Smith et al, 1974[35]	Haloperidol Thioridazine	2.0 (1.0–2.17) 106.7 (50–107.7)	CBS with senile psychosis (46)	46 ® (23, 23) 46 © (23, 23)	BPRS, CGI, NOSIE, PEF	6 wk	Antiparkinsonian plus night-time sedation
Covington, 1975[36]	Thioridazine Diazepam	32.9 (mean) 7.2 (mean)	Not available	59 ® 40 © (20, 20)	HAM-A, NOSIE, global rating	4 wk	No psychotropics; other medications (eg, digitalis) allowed
Rada and Kellner, 1976[37]	Thiothixene Placebo	6–15 …	Nonpsychotic OBS (24), psychotic OBS (18)	63 ® 42 © (22, 20)	BPRS, NOSIE	4 wk	Placebo washout for 1 wk; concomitant medications unknown
Cowley and Glen, 1979[38]	Thioridazine Haloperidol	153.2 (75–450) 2.1 (1.5–6.0)	OBS with psychosis (27), senile dementia (11)	40 ® 38 © (19, 19)	BPRS, NOSIE	12 wk	4-wk washout major tranquilizers, 3-d washout minor tranquilizers, biperiden for EPS
Götestam et al, 1981[39]	Haloperidol *cis*(Z)-Clopenthixol	0.5–1 5–10	Senile dementia (29), MID (11), presenile dementia (7)	47 ® (22, 25) 40 © (19, 21)	GCGRS, CGRS, CGI	8 wk	3-wk psychotropic washout, concomitant medications unknown
Petrie et al, 1982[40]	Loxapine Haloperidol Placebo	21.9 (± 1.6) 4.6 (± 0.3) …	Primary degenerative dementia (30), MID (26), other organic (5), not included in analysis (3)	64 ® (19, 20, 22) 37 © (12, 12, 13)	BPRS, CGI, NOSIE, SCAG	8 wk	All psychotropics discontinued, 2-wk placebo washout, antiparkinsonian for EPS, chloral hydrate prn
Barnes et al, 1982[19]	Loxapine Thioridazine	10.5 (mean) 62.5 (mean)	Primary degenerative dementia (33), MID (23), alcoholic dementia (1), head trauma (1), unknown (2)	60 ® 34 © (13, 11, 10)	BPRS, CGI, SCAG, NOSIE	8 wk	Psychotropics discontinued, 2-wk placebo washout, chloral hydrate prn, trihexyphenidyl prn
Ather et al, 1986[41]	Placebo Thioridazine Chlormethiazole	… 80 (60–95) 672 (528–749)	Dementia, Alzheimer, and arteriosclerotic forms (74)	74 ® 60 © (30, 30)	CGBRS, BRS/CAPE, verbal rating scale for agitation	4 wk	Placebo washout for 1 wk, no concomitant psychotropic medications
Lovett et al, 1987[42]	Trifluoperazine Haloperidol	2–6 1–3	Not available	54 ® (26, 28) 44 © (22, 22)	BPRS, CGI, NOSIE, SCAG	6 wk	No psychotropics except chloral hydrate or amobarbital sodium, 7-d washout
Coccaro et al, 1990[43]	Haloperidol Oxazepam Diphenhydramine	0.5–1 (0.9) 30.0 (19.4) …	Senile dementia (37), MID (5), alcoholism (8), Korsakoff (4), major strokes (4), previous depression (1)	59 ® 52 © (18, 17, 17)	BPRS, NOSIE, ADAS	6 wk	No psychotropics, 2-wk placebo washout
Carlyle et al, 1993[44]	Loxapine Haloperidol	36 (mean) 7.0 (mean)	Primary degenerative dementia/Alzheimer's, MID, or senile dementia (40)	40 ® (20, 20) 31 © (17, 14)	"aggression scale"	4 wk	Washout 7 days, chloral hydrate prn, benztropine and lorazepam (restricted) allowed
Finkel et al, 1995[45]	Thiothixene Placebo (crossover)	4.6 (p1) 3.7 (p2) …	Primary dementia (35)	35 ® (17, 18 [p1]) & (14, 17 [p2]) 30 © (p1) & 27 © (p2)	CMAI	11 wk (p1) 6 wk (p2)	1-wk washout, benztropine allowed, psychotropics not stated

*Abbreviations and symbols: © = completers, i.e., patients who completed the study; ® = randomized patients; ADAS = Alzheimer's Disease Assessment Scale; BPRS = Brief Psychiatric Rating Scale; BRS/CAPE = Behavior Rating Scale of the Clifton Assessment Procedures for the Elderly; CBS = chronic brain syndrome; CGBRS = Crichton Geriatric Behavioral Rating Scale; CGI = Clinical Global Impression; CGRS = Crichton Geriatric Rating Scale; CMAI = Cohen-Mansfield Agitation Inventory; EPS = extrapyramidal symptoms; GCGRS = Gottfries-Cronholm Geriatric Rating Scale; HAM-A = Hamilton Rating Scale for Anxiety; MACC = Motility Affect Cooperation Communication Scale; MID = multi-infarct dementia; NOSIE = Nurses' Observation Scale for Inpatient Evaluation; OBS = organic brain syndrome; p1, p2 = phase 1, phase 2 trials; PEF = psychiatric evaluation form; SCAG = Sandoz Clinical Assessment-Geriatric.

of patients who improved were calculated for subgroups of neuroleptics according to chemical structure (i.e., butyrophenones and phenothiazines) and degree of potency (low, moderate, moderate-high, and high). Potency was based on the number of milligrams required to produce a clinical effect[27] such that chlorpromazine and thioridazine would have low potency; acetophenazine and loxapine would have moderate potency; perphenazine, trifluoperazine, and thiothixene would have moderate-high potency; and fluphenazine and haloperidol would have high potency. Homogeneity of the studies being combined was tested using the method of Breslow and Day[28] that calculates a Q value, which follows a chi-square distribution.

Dose Analysis

Doses were converted to standardized units using the defined daily dose (DDD) methodology. The DDD is the mean daily dose of a medication when prescribed for its major indication. For example, if the DDD for haloperidol is 8 mg orally and a patient is taking 4 mg p.o. per day, that patient is receiving 0.5 DDDs. This methodology is recommended by the World Health Organization to make dose comparisons.[29] The mean dose of neuroleptic or midpoint of the range of doses used in each clinical trial was correlated to each of the major outcome variables (efficacy, side effect rate, and dropout rate) using both raw and placebo-adjusted rates, and a Pearson correlation coefficient was calculated.

RESULTS

Eligible Studies

Seventeen studies met inclusion criteria[19,30–45] and all but 1 of these[30] had extractable data (Table 1). The 16 remaining studies involved 499 neuroleptic-treated patients, 112 active controls, and 123 placebo-treated patients. An additional 34 studies were excluded[46–79] based on their Method sections for the following reasons: not an original clinical trial (N = 1), no random treatment allocation (N = 15), not controlled (N = 9), not double-blind (N = 10), inadequate diagnosis of dementia (N = 10), too few subjects diagnosed with dementia (< 75%) (N = 15), insufficient length of treatment (< 4 weeks) (N = 10), and no behavioral outcomes (N = 1). Papers were also excluded if information needed to confirm inclusion criteria was not extractable by the raters. Table 2 shows the data extracted from the 16 studies that met inclusion criteria and did not meet the exclusion criterion. The proportion of subjects who improved could be extracted from 13 of 16 studies that involved 20 different neuroleptic treatment arms and 393 patients in total. Improvement was defined by the majority of papers by using Clinical Global Impression (CGI) scores rather than a clinically significant drop on 1 of the standardized behavioral outcome scales. CGI scores used were blinded ratings of a clinically significant improvement in overall behavioral pathology.

Comparative Analysis

Comparative data were available for 7 studies that compared a neuroleptic with a placebo, 3 studies comparing phenothiazines (thioridazine, trifluoperazine, and acetophenazine) with placebo, 6 studies comparing a butyrophenone (haloperidol) with another neuroleptic, and 3 studies comparing haloperidol with a phenothiazine. For these comparative studies, the pooled mean percentage of patients who improved for all neuroleptics was 61% (95% CI: 47% to 75%) and for placebo was 34% (95% CI: 18% to 50%). The therapeutic effect (neuroleptic minus placebo) was 26% (95% CI: 14% to 38%) ($Z = 4.26$, $p < .0001$) (Figure 1). Phenothiazines were more efficacious than placebo (therapeutic effect = 22% [95% CI: 5% to 39%], $p = .01$) but they were not significantly different from the butyrophenone (i.e., haloperidol) (Table 3). Furthermore, the butyrophenone demonstrated no significant advantage over other neuroleptics (Table 3). Quality-weighted mean differences were similar to raw differences. Pooled studies were homogeneous ($Q = 1.76$ to 7.88, NS).

Single-Arm Estimates

Meta-analysis was also used to estimate overall proportion of patients who improved with each treatment group. Pooled mean percentages of patients who improved are shown in Table 4. Phenothiazines, butyrophenones, and thioxanthenes showed similar efficacy rates (62% to 69%) and overlapping confidence intervals, suggesting no significant differences. However, when grouped this way, the studies showed significant heterogeneity for phenothiazine and butyrophenone groups ($Q = 28.8, 45.7$; $p < .001$).

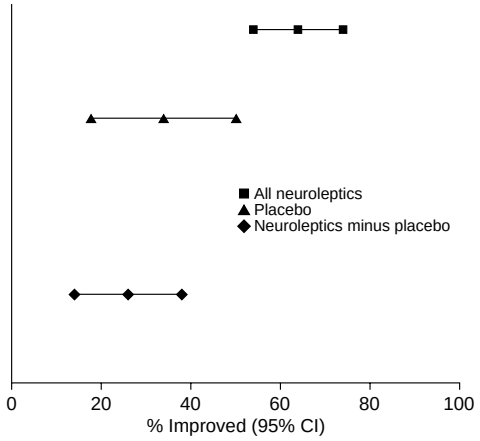
Next, the neuroleptics were grouped by potency. Pooled mean percentages of patients improving with placebo, low, moderate, moderate-high, and high potency neuroleptics are also shown in Table 4. Again, the neuroleptic groups produced similar rates of efficacy with overlapping confidence intervals suggesting no significant differences (Figure 2). Heterogeneity was statistically significant within the high potency group ($Q = 45.7$, $p < .001$) and within the placebo group ($Q = 28.8$,

Table 2. Data Extracted From Papers Included in Meta-Analysis*

Author(s), Year	Neuroleptic(s), Comparator(s)	Neuroleptic Dosage DDDs	Proportion Improved	Proportion With Adverse Events	Proportion of Dropouts	Mean Quality Score (1 to 3)
Hamilton and Bennett, 1962[31]	Acetophenazine	0.4–1.2	13/19	5/19	n/a	1
	Placebo	…	2/8	0/8	…	
Hamilton and Bennett, 1962[32]	Trifluoperazine	0.2–0.4	4/18	n/a	n/a	1.67
	Placebo	…	0/9	…	…	
Sugarman et al, 1964[33]	Haloperidol	0.06–0.56	8/9	n/a	0/9	1
	Placebo	…	6/9	…	0/9	
Kirven and Montero, 1973[34]	Thioridazine	0.13	16/28	2/28	n/a	2
	Diazepam	0.9	14/28	5/28	…	
Smith et al, 1974[35]	Haloperidol	0.25	19/23	n/a	0/23	2
	Thioridazine	0.36	14/23	…	0/23	
Covington, 1975[36]	Thioridazine	0.11	13/20	0/20	n/a	1
	Diazepam	0.72	6/20	0/20	…	
Rada and Kellner, 1976[37]	Thiothixene	0.2–0.5	13/22	10/22	n/a	1.67
	Placebo	…	11/20	6/20	…	
Cowley and Glen, 1979[38]	Thioridazine	0.51	14/19	2/19	n/a	2.33
	Haloperidol	0.26	11/19	1/19	…	
Götestam et al, 1981[39]	Haloperidol	0.06–0.125	4/19	n/a	3/22	2.67
	cis(Z)-Clopenthixol	0.05–0.1	6/21	…	4/25	
Petrie et al, 1982[40]	Loxapine	0.22	11/19	18/20	8/20	3
	Haloperidol	0.58	13/20	19/21	9/21	
	Placebo	…	8/22	12/22	9/22	
Barnes et al, 1982[19]	Loxapine	0.105	13/19	9/20	4/20	2
	Thioridazine	0.21	10/17	6/18	3/18	
	Placebo	…	8/17	3/19	2/19	
Ather et al, 1986[41]	Thioridazine	0.27	n/a	n/a	3/30	2
	Chlormethiazole	0.45	…	…	0/30	
Lovett et al, 1987[42]	Trifluoperazine	0.1–0.3	19/22	n/a	4/26	2
	Haloperidol	0.125–0.375	20/22	…	6/28	
Coccaro et al, 1990[43]	Haloperidol	0.06–0.125	n/a	n/a	2/18	2.33
	Oxazepam	0.6	…	…	2/19	
	Diphenhydramine	…	…	…	…	
Carlyle et al, 1993[44]	Loxapine	0.36	14/17	5/20	3/20	2
	Haloperidol	0.88	11/14	11/20	6/20	
Finkel et al, 1995[45]	Thiothixene	0.14	20/31	n/a	n/a	1.33
	Placebo	…	6/35	…	…	

*Abbreviations: DDD = defined daily dose for major indication (i.e., antipsychosis); n/a = data not available or could not be extracted; … = not applicable, listed comparator was not a neuroleptic.

Figure 1. Therapeutic Effect of Neuroleptics*



*Pooled estimate with 95% confidence intervals.

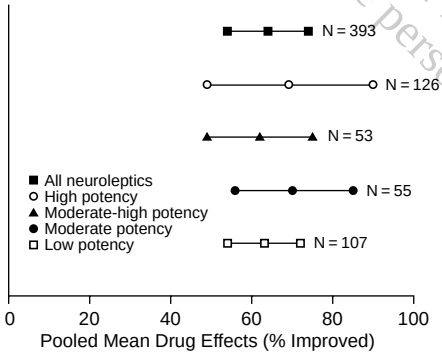
p < .001), but not in low and moderate potency groups. A search for outliers showed that in the high potency group heterogeneity was due to a single study by Götestam et al.[39] This study was rated as having good quality and had characteristics similar to those of the other studies in the group (Table 1); however, the proportion of patients who improved with haloperidol was very low (21%). Removing that study from the analysis of high potency drugs slightly increased the pooled mean percentage of patients who improved to 77% (95% CI: 56% to 99%) and eliminated heterogeneity (Q = 9.7, p = .08). In the placebo group, the outlier was the Finkel et al. study,[45] which had a low placebo response rate (17%). That study was a crossover study as opposed to a parallel group, but was similar to the other placebo-controlled studies in other ways (Table 1). Elimination of this study from the analysis of the placebo group increased the placebo response rate

Table 3. Comparative Efficacy Data From Meta-Analysis of Neuroleptics in the Treatment of Behavioral Disorders*

Groups Being Compared	Group 1 [95% CI]	Group 2 [95% CI]	Difference in % Improved [95% CI]	Standard Error	Z-score (p value)	Quality-Weighted Mean Difference [95% CI]	Heterogeneity Q (p value)[a]	Total Subjects (group 1, group 2)
Neuroleptics vs placebo	0.61 [0.47, 0.75]	0.34 [0.18, 0.50]	0.26 [0.14, 0.38]	0.06	4.26 (< .0001)	0.23 [–0.04, 0.54]	7.88 (.25) NS	295 (174, 121)
Phenothiazines vs placebo	0.50 [0.22, 0.75]	0.24 [–0.03, 0.52]	0.22 [0.05, 0.39]	0.09	2.57 (.01)	0.21 [–0.07, 0.56]	1.76 (.42) NS	90 (55, 35)
Butyrophenone vs other neuroleptics	0.66 [0.45, 0.88]	0.65 [0.48, 0.83]	0.02 [–0.08, 0.13]	0.05	0.43 (.66) NS	0.01 [–0.25, 0.28]	4.54 (.47) NS	238 (117, 121)
Butyrophenone vs phenothiazines	0.79 [0.62, 0.96]	0.75 [0.60, 0.90]	–0.05 [–0.23, 0.14]	0.09	–0.50 (.62) NS	–0.02 [–0.28, 0.21]	3.56 (.16) NS	128 (64, 64)

*All values in columns 4 to 9 are for differences between the 2 groups being compared.
[a]Nonsignificance indicates that studies were homogeneous.

Figure 2. Pooled Mean Drug Effects for Different Potencies of Neuroleptics*



*Pooled estimate with 95% confidence intervals.

from 34% (95% CI: 18% to 0.50%) to 46% (95% CI: 33% to 58%) and removes heterogeneity in the group (Q = 5.15, p = .27). The studies that allowed the use of restricted concomitant medications[19,35,40,42,44] (see Table 1) had a trend toward a higher efficacy compared with the group as a whole (75% improved [95% CI: 67% to 83%] vs. 64% [95% CI: 54% to 74%]) (Table 4).

Safety Analysis

Side effect rates and rate of dropout for various neuroleptics were also compared (Table 5). Treatment-emergent side effects were significantly more common for neuroleptics versus placebo. The pooled mean difference was equal to 25% (95% CI: 13% to 37%). There were no detectable differences between classes of neuroleptics according to the available information (Table 5). Pooled mean dropout rates were no different for neuroleptics versus placebo. The mean difference in dropout rates was equal to 4% (95% CI: –7% to 14%). This was not statistically significant. The information available from the trials was not sufficient to compare the studies for specific side effects of interest, for example, movement disorders. However, important side effects such as sedation in 21% (95% CI: 13% to 29%, N = 392), movement disorders in 13% (95% CI: 6% to 20%, N = 429), and orthostatic hypotension in 8% (95% CI: 1% to 15%, N = 429) of patients were reported. There was significant heterogeneity between studies for these pooled estimates.

Quality Analysis

Three raters assessed the quality of each clinical trial (N = 16) on a 4-point scale, as was described above. Interrater weighted agreement was good (82% to 94%) and the kappa score showed that overall agreement between raters was moderate and significant ($\kappa = 0.52$, p = .002). Only 1 trial received a score of 3 (“good”); the rest were either satisfactory (mean score ≥ 2, N = 9) or poor (mean score < 2, N = 6) (Table 2). Weighting of trials by quality did not change the trend of the results (see quality-weighted mean difference versus difference in Tables 3 and 5). Exclusion of poor quality articles also did not change the results. In general, the confidence intervals of the quality-weighted mean difference spanned 0, such that the results became nonsignificant. In contrast, exclusion of poor quality trials tended to increase the magnitude of the difference between groups and narrow the confidence interval (Figure 3).

Dose Analysis

Mean or midpoint dose was neither correlated to efficacy, therapeutic effect, side effect rate, dropout rate nor with or without placebo (r = –0.31 to 0.29).

Table 4. Pooled Efficacy Data for Different Groups of Neuroleptics

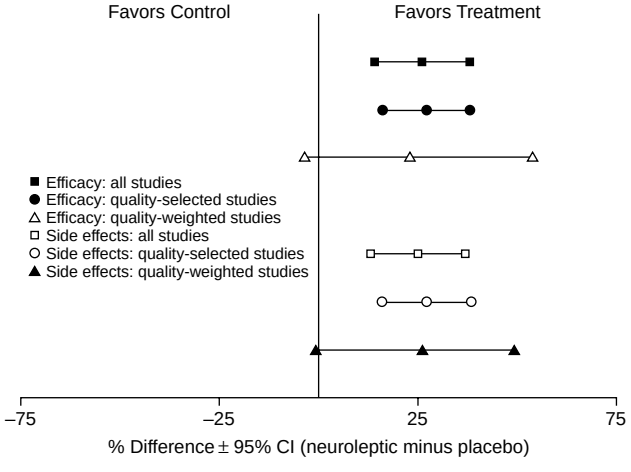
Group	No. of Studies	No. of Patients	Efficacy Rate	[95% CI]	Heterogeneity Q (p value)
All neuroleptics	13	393	0.64	[0.54, 0.74]	97.8 (p < .001)
Placebo	7	120	0.34	[0.18, 0.50]	28.8 (p < .001)
By structure					
Phenothiazines	7	138	0.63	[0.46, 0.79]	28.8 (p < .001)
Butyrophenone	7	126	0.69	[0.49, 0.90]	45.7 (p < .001)
Thioxanthenes	2	53	0.62	[0.49, 0.75]	0.2 (p = .69) NS
By potency at D_2 receptor					
Low (thioridazine)	5	107	0.63	[0.54, 0.72]	1.7 (p = .79) NS
Moderate (loxapine)	3	55	0.70	[0.56, 0.85]	2.9 (p = .23) NS
Moderate-high (thiothixene)	2	53	0.62	[0.49, 0.75]	0.2 (p = .69) NS
High (haloperidol)	7	126	0.69	[0.49, 0.90]	45.7 (p < .001)
Studies allowing use of concomitant psychotropic medications					
Neuroleptics + other	5	144	0.75	[0.67, 0.83]	162 (p < .001)

Table 5. Comparative Safety Data From Meta-Analysis of Neuroleptics in the Treatment of Behavioral Disorders*

Groups Being Compared	Group 1 [95% CI]	Group 2 [95% CI]	Difference [95% CI]	Z-score (p value)	Quality-Weighted Mean Difference	Heterogeneity Q (p value)[a]	Total Subjects (group 1, group 2)
Side effect rate							
Neuroleptics vs placebo	0.51 [0.18, 0.85]	0.25 [0.05, 0.46]	0.25 [0.13, 0.37]	4.06 p < .001	0.26 [–0.01, 0.49]	1.34 p = .72 NS	189 (120, 69)
Phenothiazines vs placebo	0.30 [0.16, 0.45]	0.10 [–0.01, 0.21]	0.20 [0.02, 0.38]	2.14 p < .05	0.19 [–0.06, 0.46]	0.06 p = .81 NS	106 (59, 47)
Butyrophenone vs other neuroleptics	0.40 [–0.03, 0.82]	0.40 [0.002, 0.79]	–0.013 [–0.19, 0.16]	–0.14 p = .89 NS	–0.02 [–0.21, 0.22]	8.40 p = .04	166 (82, 84)
Dropout rate							
Neuroleptics vs placebo	0.20 [0.05, 0.35]	0.16 [0.01, 0.30]	0.04 [–0.07, 0.14]	0.67 p = .50 NS	0.04 [–0.19, –0.26]	0.42 p = .94 NS	165 (106, 59)
Butyrophenone vs other neuroleptics	0.20 [0.05, 0.35]	0.15 [0.04, 0.27]	0.02 [–0.05, 0.08]	0.47 p = .64 NS	0.04 [–17, 0.25]	1.53 p = .82 NS	226 (113, 113)

*All values are for differences between the 2 groups being compared.
[a]Nonsignificance (NS) of the Q indicates that studies were homogeneous.

Figure 3. Effect of Quality on Neuroleptic Minus Placebo Differences for Efficacy and Side Effects



DISCUSSION

This meta-analysis has shown that neuroleptics are moderately effective in the treatment of behavioral problems in dementia and that no one particular type of neuroleptic is more efficacious than any other. Although the efficacy rate was 61%, the therapeutic effect was only 26% above placebo. This is consistent with other qualitative and quantitative reviews in this area in which the therapeutic effect was described as small or modest.[13,14,17–22] The nonresponder rate (39%) is slightly higher than that found when these drugs are administered for the treatment of psychosis where nonresponders account for about 10% to 30% of patients treated.[80–82]

The placebo response rate was 34%, which is relatively high compared with the efficacy of the active medications, but similar to that found when these medications are used for schizophrenia (39%).[81] Although the litera-

ture in this area is dominated by open-label trials and non–placebo-controlled trials, the magnitude of the placebo response together with the variability (95% CI: 18% to 50%) and significant heterogeneity between clinical trials indicate that placebo controls are necessary in this population. Actual blinding may be difficult to achieve for inactive placebo controls due to characteristic side effects; thus, active controls are also important. The placebo response rate in this population may be due to nonpharmacologic factors such as the added attention that clinical trials place both on patients and on the staff who are recording and monitoring the behavior of patients as required by the study. Indeed, in a study by Nilsson et al.,[83] the rate of aggressive incidents decreased by 82% during the 6-week piloting of a new instrument administered by psychogeriatric ward staff to monitor aggression. The instrument required staff to record antecedents, behaviors, and consequences of the behavior as is done during nonpharmacologic interventions. These findings indicate that enrollment in a clinical trial may mimic a behavioral intervention and lead to dramatic changes in patient behavior. The wide range of placebo response rates found may also reflect differences in the severity of behavioral disorders between studies. These between-study sample differences may make the detection of the drug-placebo difference more difficult. However, combining the studies using meta-analysis overcame this noise and detected a statistically significant difference.

Neuroleptics have been shown to be associated with a variety of potentially serious adverse drug reactions such as oversedation, extrapyramidal symptoms (akathisia, tardive dyskinesia, pseudoparkinsonism), orthostatic hypotension, and anticholinergic symptoms[27] and are prescribed with caution in the elderly.[84–87] However, it has been suggested that acute side effects in this population are no different from those in any other psychiatric population when these medications are used in low doses.[14] As expected, our safety analysis was able to detect that neuroleptics were more likely to cause side effects compared with placebo. However, dropout rates for the 2 treatment groups were similar. Comparison between classes of neuroleptics showed that phenothiazines and butyrophenones had similar side effect and dropout rates. When neuroleptics were grouped according to potency, there were also no differences in side effect and dropout rates. Side effect profiles between drugs of various potency are known to be different, and this can be the driving factor in selection of medications. Therefore, although no one neuroleptic showed advantages over another when data were grouped by overall rates, type of side effect is still an important consideration. These studies showed that at least 21% of patients had an important side effect such as EPS, sedation, or orthostatic hypotension. The low dropout rate supports the fact that these low doses of neuroleptics are well tolerated in this patient population, but may also be an artifact of inpatient enrollment in a clinical trial. Movement disorders were reported; however, in most instances these events were described as mild and controllable. The short length of these clinical trials in combination with the low dosages used makes detection of these events less likely. A need exists for longer follow up of these patients.

An extensive literature search found only 16 randomized, controlled trials of neuroleptics with extractable efficacy data on 393 patients receiving active medications and 120 placebo controls. Surprisingly, neuroleptics are the most well-studied of all the treatments for behavioral disorders in dementia. Our original intent was to compare serotonergic medications with neuroleptics. Despite the fact that selective serotonin drugs are emerging as a first-line treatment for these disorders, we were unable to compare neuroleptics with selective serotonin reuptake inhibitors (SSRIs) or trazodone because none of the serotonergic papers that met inclusion criteria had extractable data. Only 3 double-blind, randomized, controlled clinical trials of SSRIs have been published to date,[88–90] and only 1 with trazodone.[91] The SSRI studies involved 184 patients, and, although 1 showed significant efficacy,[92] the others showed only trends favoring the drug[89] or no significant efficacy.[90] A pooled estimate of the efficacy of serotonergic medications would be useful because of the small numbers of patients who have been rigorously studied and because of the conflicting results. Unfortunately, data on proportion of patients with a clinically significant response were not extractable from these papers. Data on other psychotropics for the treatment of behavioral disorders are also very preliminary. Alternatives that have been studied in small numbers of randomized, controlled trials include buspirone,[93] trazodone,[94] selegiline,[95] valproate,[96] carbamazepine,[97] β-blockers,[98,99] and benzodiazepines.[43] The use of the newer atypical neuroleptics such as risperidone,[100–102] olanzapine, quetiapine, and others can be expected to afford lower incidences of EPS and other side effects, depending on the pharmacologic profile, although randomized, controlled trials are not yet published.

Much of the literature on pharmacotherapies for behavioral disorders suffers from major flaws, including lack of a homogeneous population of well-characterized demented patients and inappropriate study design.[13,14,17–19,22] Some of the methodological issues in these studies include failure to randomize, failure to include a control

group, failure to include blinding techniques, inadequate sample size, improper dosing and duration of treatment, inclusion of a heterogeneous population (patients have varied etiologies for their dementias and are at varied stages of the illness), inappropriate statistical analysis, and insensitive methods used to identify and track target behaviors. Of the 51 published studies, only 17 met our basic inclusion criteria and only Petrie et al.[40] was rated as having "good" quality for the purposes of this analysis by all 3 raters. They studied haloperidol (mean daily dose = 4.6 mg/day) and loxapine (mean daily dose = 22 mg/day) in an 8-week, double-blind, placebo-controlled trial in 64 hospitalized psychogeriatric patients with behavioral disorders. Significant improvement was noted in both the loxapine (32%) and haloperidol (35%) groups compared with placebo (9%) ($p < .05$). Drug responsive symptoms included hostility, hallucinations, uncooperativeness, and excitement. Side effects included increased incontinence, confusion, and social withdrawal in association with oversedation. In the study by Barnes et al.[19] where thioridazine, loxapine, and placebo were compared over 8 weeks in 56 nursing home patients with either primary degenerative dementia or multi-infarct dementia, there was modest but significant improvement with thioridazine (68%) and loxapine therapy (59%) versus placebo (47%). Drug-responsive behaviors included anxiety, excitement, emotional lability, and uncooperativeness, with no differential response by dementia subtype.[19] These 2 relatively large, placebo-controlled studies show different magnitudes of response and record different behaviors illustrating the difficulty in generalizing from the literature. With the addition of "lower" quality studies (e.g., fewer numbers of patients), the results become even more difficult to interpret. Meta-analysis can serve to combine such data in an overall synthesis to provide global, quality-rated, quantitative results. This analysis showed that the overall trend did not change when the quality of these trials was incorporated into the estimates.

The doses used in these 16 clinical trials were all low, ranging from 0.06 DDDs to 1.2 DDDs, with a mean ± SD dose of 0.31 ± 0.21 DDDs, and 83% of the doses were less than one half of the standard daily doses. Dose was not correlated to the response rate, therapeutic response rate, rate of adverse events, or proportion of dropouts. Since no dose-response relationship was found in these clinical trials, the studies to date do not provide rationale to use higher doses of neuroleptics in this population. It can be expected that subtherapeutic doses of neuroleptic would lead to lack of efficacy and minimal dose-related side effects and higher doses would confer greater efficacy at the expense of severe side effects. In these studies, a range of dosages and titration by the clinician were allowed by each protocol. Thus, although there is a possibility that all of the doses were subtherapeutic, the toxicity of these drugs limited the use of higher doses. The range of doses used both within and between individual studies reflects the increased variability and sensitivity seen with aging, as well as the known variability in the drug metabolizing enzymes responsible for metabolizing many of these drugs (e.g., cytochrome P450 2D6) at any age. Thus, the current literature cannot answer the question of optimal dosing since as a general rule, dosage should be individualized.

Although meta-analysis has many advantages compared with unstructured, qualitative reviews, it is unrealistic to imagine that simple statistical answers will solve complex clinical problems.[103] The role of a meta-analysis is to provide evidence about safety or efficacy that cannot be drawn from individual trials due to small numbers or conflicting results or to combine data for a class of drugs or treatments to allow a general, qualitative conclusion. As with any other review, it cannot tell clinicians how to treat an individual patient, but rather provides information that facilitates evidence-based decision-making. Meta-analysis increases the statistical power by using a pooled estimate. However, there may be difficulty in integrating the results from various studies because of the diverse nature of the studies, in terms of both study design and methods employed.[24] Lack of homogeneity in the trials included in a meta-analysis can affect the validity of the results. In this study, the inclusion/exclusion criteria were adequate in selecting trials to be pooled that were generally homogeneous, and heterogeneity was measured.

More research needs to be conducted to examine which behavioral disorders respond to certain types of medications. Currently, the literature lacks comparative studies for different types of medications (e.g., neuroleptics versus SSRIs) and specific behaviors (e.g., aggression versus psychosis). Presently, most experts recommend the use of neuroleptic medications for alleviating psychotic behavioral problems such as hallucinations and delusions and for the treatment of other severe behavioral problems such as aggression, hostility, and "sundowning" (agitation/confusion beginning at sundown and continuing through the night).[4,14,17–19,21,40,85,104,105] Their use in the treatment of disruptive or nuisance behaviors such as wandering, pacing, and crying out is regarded as inappropriate; however, this is not based on any convincing published evidence, but is mostly extrapolated from clinical experience.

Future research should be aimed at developing more appropriate pharmacologic treatments for specific behavioral subtypes. A better understanding of the neurotransmitter alterations in Alzheimer's disease and multi-infarct dementia and their link with particular behavioral subtypes may provide the basis for rational therapeutics. This approach would lead to more effective treatments and would have tremendous implications with regard to health care costs and patient care.

CONCLUSION

This meta-analysis has shown that neuroleptics have moderate efficacy compared with placebo in treating behavioral disturbances associated with dementia. The therapeutic effect (drug above placebo) (26%) and the risk of side effects (25%) are approximately equivalent in this study. Different types and potencies of neuroleptics have similar side effect and dropout rates. Since the efficacy of neuroleptics has been established but the overall therapeutic effect is modest, further study of patterns of response for different behavioral reactions and different subtypes of dementia is needed to try to maximize the benefit-risk ratio of these medications. As well, further rigorous study of atypical neuroleptics and nonneuroleptic medications (such as cognitive enhancers) is needed. Improved knowledge of the pathophysiology of different subtypes of behavioral manifestations of this disease is necessary to facilitate the development of more appropriate medications and allow linkage to specific treatment interventions. Only then can the goal of evidence-based practice be reached.

Drug names: acetophenazine (Tindal), amobarbital (Amytal), benztropine (Cogentin and others), biperiden (Akineton), buspirone (BuSpar), carbamazepine (Tegretol and others), chloral hydrate (Noctec), chlorpromazine (Thorazine and others), diazepam (Valium and others), diphenhydramine (Benadryl and others), haloperidol (Haldol and others), loxapine (Loxitane), olanzapine (Zyprexa), oxazepam (Serax and others), perphenazine (Etrafon, Triavil), quetiapine (Seroquel), risperidone (Risperdal), selegiline (Eldepryl), thioridazine (Mellaril and others), thiothixene (Navane), trazodone (Desyrel and others), trifluoperazine (Stelazine), trihexyphenidyl (Artane and others).

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DISCLOSURE OF OFF-LABEL USAGE

Psychotropics are not specifically approved for the treatment of behavioral disorders in dementia. The use of neuroleptics is as recommended in Expert Consensus Guidelines of March 1998 (see reference 105).

Instructions

Psychiatrists may receive 1 hour of Category 1 credit toward the American Medical Association Physician's Recognition Award by reading the article starting on page 550 and correctly answering at least 70% of the questions in the posttest that follows.

1. Read each question carefully and circle the correct corresponding answer on the Registration form.
2. Type or print your full name, address, phone number, and Social Security number in the spaces provided.
3. Mail the Registration form along with a check, money order, or credit card payment in the amount of $10 to: Physicians Postgraduate Press, Office of CME, P.O. Box 752870, Memphis, TN 38175-2870.
4. For credit to be received, answers must be postmarked by the deadline shown on the CME Registration form. After that date, correct answers to the posttest will be printed in the next issue of the *Journal*.

All replies and results are confidential. Answer sheets, once graded, will not be returned. Unanswered questions will be considered incorrect and so scored. Your exact score can be ascertained by comparing your answers with the correct answers to the posttest, which will be printed in the *Journal* issue after the submission deadline. The Physicians Postgraduate Press Office of Continuing Medical Education will keep only a record of participation, which indicates the completion of the activity and the designated number of Category 1 credit hours that have been awarded.

1. The most common treatment of behavioral disorders associated with dementia is which type of medication?
a. β-Blocker
b. Atypical neuroleptic
c. SSRI
d. Neuroleptic
e. Benzodiazepine

2. Neuroleptics have been associated with a variety of potentially serious adverse drug reactions. Which of the following was *not* shown in this study to be a serious adverse drug reaction to neuroleptics?
a. Oversedation
b. Hypertension
c. Orthostatic hypotension
d. Extrapyramidal symptoms
e. Anticholinergic symptoms

3. Since no dose-response relationship was found in the clinical trials analyzed, the studies to date do not provide a rationale to ____ for treating behavioral disorders of dementia in an elderly population.
a. Use higher doses of neuroleptics
b. Use lower doses of neuroleptics
c. Discontinue use of neuroleptics
d. Use other psychotropics
e. Use newer atypical neuroleptics

4. The current literature cannot answer the question of optimal dosing for neuroleptic treatment of behavioral disorders associated with dementia since, as a general rule, dosage should be:
a. Standardized
b. Minimized
c. Maximized
d. Individualized
e. Randomized

5. Presently, most experts recommend the use of neuroleptic medications for alleviating which of the following severe behavioral problems in elderly patients with dementia?
a. Wandering
b. Delusions
c. Aggression
d. "Sundowning"
e. Answers b, c, and d

6. The use of neuroleptics is regarded as inappropriate for treatment of disruptive or nuisance behaviors. Which of the following behaviors *is* considered appropriate to treat with neuroleptics?
a. Wandering
b. Pacing
c. Hostility
d. Crying out
e. None of the above

7. This meta-analysis has shown that neuroleptics have ____ efficacy when compared with placebo in treating behavioral disturbances associated with dementia.
a. The same
b. Moderate
c. Low
d. High
e. No

Answers to the April 1998 CME posttest

1. b 2. e 3. d 4. a 5. b 6. e 7. e

Circle the one correct answer for each question.

1.	a	b	c	d	e
2.	a	b	c	d	e
3.	a	b	c	d	e
4.	a	b	c	d	e
5.	a	b	c	d	e
6.	a	b	c	d	e
7.	a	b	c	d	e

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Retain a copy of your answers and compare them with the correct answers, which will be published after the submission deadline.

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1. Was the educational content relevant to the stated educational objectives? ❑ Yes ❑ No

2. Did this activity provide information that is useful in your clinical practice? ❑ Yes ❑ No

3. Was the format of this activity appropriate for the content being presented? ❑ Yes ❑ No

4. Did the method of presentation hold your interest and make the material easy to understand? ❑ Yes ❑ No

5. Achievement of educational objectives:

   A. Enabled me to review research on the efficacy of neuroleptics for the treatment of behavioral disorders in patients with dementia. ❑ Yes ❑ No

   B. Enabled me to discuss current issues relative to the safety of using neuroleptics for the treatment of behavioral disorders in patients with dementia. ❑ Yes ❑ No

   C. Enabled me to compare the efficacy and safety of different types of neuroleptics used for the treatment of behavioral disorders in patients with dementia. ❑ Yes ❑ No

6. Did this CME activity provide a balanced, scientifically rigorous presentation of therapeutic options related to the topic, without commercial bias? ❑ Yes ❑ No

7. Does the information you received from this CME activity confirm the way you presently manage your patients? ❑ Yes ❑ No

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