A 3-Month, Randomized, Placebo-Controlled, Neuroleptic Discontinuation Study in 100 People With Dementia: The Neuropsychiatric Inventory Median Cutoff Is a Predictor of Clinical Outcome

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Background: Although few placebo-controlled neuroleptic discontinuation studies have been conducted in people with dementia, such studies are essential to inform key clinical decisions.

Method: A 3-month, double-blind, placebo-controlled, neuroleptic discontinuation study (June 2000 to June 2002) was completed in 100 care-facility residents with probable or possible Alzheimer's disease (according to National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria) who had no severe behavioral disturbances and had been taking neuroleptics for longer than 3 months. The Neuropsychiatric Inventory (NPI) was used to measure changes in behavioral and psychiatric symptoms. Quality of life was evaluated using Dementia Care Mapping.

Results: Eighty-two patients completed the 1-month assessment (36 placebo, 46 active). The number of participants withdrawing overall (N = 14 [30%] placebo, N = 14 [26%] active treatment) and because of exacerbation of behavioral symptoms (N = 6 [13%] placebo, N = 5 [9%] active treatment) was similar in the neuroleptic- and placebo-treated patients. As hypothesized, patients with baseline NPI scores at or below the median (≤ 14) had a particularly good outcome, with a significantly greater reduction of agitation in the patients receiving placebo (Mann-Whitney U test, $z = 2.4$, $p = .018$), while patients with higher baseline NPI scores were significantly more likely to develop marked behavioral problems if discontinued from neuroleptics ($\chi^2 = 6.8$, $p = .009$). There was no overall difference in the change of quality of life parameters between groups.

Discussion: A standardized evaluation with an instrument such as the NPI may be a clinical indicator of which people with dementia are likely to benefit from discontinuation of neuroleptic treatment.

(J Clin Psychiatry 2004;65:114–119)

Received Feb. 7, 2003; accepted June 20, 2003. From the Wolfson Research Centre, Newcastle General Hospital, Newcastle, U.K. (Drs. Ballard, Thomas, Lana, Swann, O'Brien and Ms. Lee) and the University Department of Old Age Psychiatry, Warneford Hospital, Oxford, U.K. (Drs. Fossey, Jacoby, Bannister, McShane, and Juszczak).

Funding for this study was provided by Research into Ageing (London, U.K.) and Age Concern (London, U.K.).

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As the age of the population increases, so does the number of people with dementia. Many of these individuals require residential or nursing home care at some stage of their illness, with dementia patients occupying a large proportion of care facilities.[1] More than 35% of dementia sufferers living in residential or nursing home care are prescribed neuroleptic drugs.[2,3] One of the key issues is the optimal discontinuation of these treatments. Placebo-controlled treatment trials of neuroleptics in people with dementia indicate modest benefit over 6 to 12 weeks,[4] but there are no studies over a longer period. Of concern, 2 naturalistic studies have suggested a possible detrimental effect of neuroleptics on the outcome of behavioral symptoms in some patients,[5,6] although, as neither study was randomized, confounding factors may have explained the apparent impact.

Neuroleptic drugs can have substantial adverse effects in people with dementia, including an increased risk of falls and drowsiness, parkinsonism,[7] akathisia, tardive dyskinesia, risk of cardiac arrhythmias,[8] severe neuroleptic sensitivity reactions,[9] and the possibility that neuroleptic agents may accelerate cognitive decline[10] and neuronal loss.[11,12] As a consequence of the potentially harmful side effects of these agents, in the United States, legislation has been introduced to regulate the prescription of neuroleptics to nursing home patients,[13] and, in the United Kingdom, the Chief Medical Officer has recommended particular caution when prescribing neuroleptics to people with dementia.[14]

Behavioral and psychiatric symptoms occur in more than 50% of nursing home patients with dementia.[15] They can be very distressing for patients[16] and caregivers,[17] and anecdotal clinical experience indicates that some patients may benefit from maintenance therapy. However, long-term pharmacotherapy has the potential for serious adverse consequences. Clinicians are hence caught on the horns of a dilemma, facing the almost impossible task of balancing the potential risk of adverse events with neuroleptic treatment against the potential exacerbation of behavioral symptoms if neuroleptics are discontinued without the benefit of an evidence base informing practice. Evidence-based clinical criteria to inform decisions regarding when a trial of neuroleptic discontinuation is the best management strategy are a priority.

Several studies reporting educational or liaison interventions into care facilities have indicated that the level of behavioral symptoms remains the same or improves following neuroleptic discontinuation,[6,18,19] although drug withdrawal was not double-blind in these studies. Of particular interest, Thapa et al.[19] reported that the outcome was especially favorable in people scoring below the median on a standardized evaluation of behavioral symptoms at baseline. There have been, however, only 2 placebo-controlled trials. In a preliminary, 4-week, double-blind, withdrawal study of 36 people with dementia residing in care facilities, only 10% of patients assigned to placebo experienced significant worsening of behavioral symptoms,[20] and there was a nonsignificant reduction in the severity of behavioral problems. In a more comprehensive, 6-week, placebo-controlled, crossover study of 58 patients, there was again a nonsignificant improvement of behavioral symptoms when pharmacologic treatment was discontinued, although within the context of this study, an intensive psychosocial intervention was undertaken.[21]

These studies provide exciting preliminary data, but there is an urgent need for a larger, longer-term, placebo-controlled trial that better reflects usual clinical practice and that includes patients receiving atypical as well as typical neuroleptics. Importantly, existing trials indicate that overall there is no detrimental effect from neuroleptic discontinuation within the groups as a whole, but differences in outcome for individual patients may be masked within global effects. This issue needs to be clarified in order to effectively identify patients most or least likely to benefit from neuroleptic discontinuation.

Quality of life is a key outcome parameter to judge any treatment intervention. A cross-sectional study[22] indicated that neuroleptics were associated with a significant reduction in well-being. Therefore, in addition to the consideration of behavioral symptoms and side effects, the withdrawal of unnecessary neuroleptics may also have an impact on quality-of-life parameters.

We completed a 3-month, double-blind, placebo-controlled, discontinuation study of 100 care-facility residents with dementia receiving long-term treatment with 1 of 5 commonly prescribed neuroleptic agents, including the atypical antipsychotic risperidone. On the basis of preliminary work,[19] we hypothesized that stopping neuroleptic drugs would be beneficial for people scoring below the median score for behavioral symptoms at baseline. In addition, we examined the impact of neuroleptic withdrawal on quality of life.

METHOD

A sample of 100 people with dementia who had been taking neuroleptics (thioridazine, chlorpromazine, haloperidol, trifluoperazine, or risperidone) for more than 3 months (median prescription time > 1 year) were recruited from residents of residential or nursing home facilities in 2 centers (Newcastle and Oxford, U.K.). Participants were aged > 65 years, met National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable or possible Alzheimer's disease,[23] had a Clinical Dementia Rating scale (CDR)[24] severity of stage 1 or greater, and had no severe behavioral symptoms (no individual symptom scores > 7 on the Neuropsychiatric Inventory [NPI][25]) at the time of evaluation.

The study was conducted using a double-blind design. All study neuroleptics were encapsulated by an independent company to maintain blind, and dispensing was coordinated by the pharmacy departments at the 2 centers. Prescriptions were written prior to randomization in a twice-daily regimen, allocating to each participant the closest dose to their preexisting prescription from the doses encapsulated (risperidone 0.5 mg, chlorpromazine 12.5 mg, thioridazine 12.5 mg, trifluoperazine 0.5 mg, haloperidol 0.25 mg). Subjects were then randomized to neuroleptic (N = 54) or placebo (N = 46). Study medication replaced existing medication on the day of commencement; there was no dose reduction or tapering. Treatment was continued for a 3-month period.

The standardized assessments included the NPI,[25] which covers 12 domains of behavioral and neurovegetative symptoms, the Mini-Mental State Examination (MMSE),[26] and the CDR.[24]

Well-being was evaluated as a measure of quality of life using Dementia Care Mapping (DCM),[27] a reliable[28,29] and valid,[29,30] direct, operationalized, observational method based on the theoretical sociopsychological theory of personhood in dementia.[31] The method quantifies activities using activity category codes, which are recorded every 5 minutes over a 6-hour period of observation during 1 day, measuring key quality-of-life parameters such as social withdrawal and engagement in constructive activities. Raters within the current study had to achieve kappa values for interrater reliability of greater

than 0.8 with each other and with a senior care mapper in a 6-hour practice assessment for DCM measures before the main study evaluations were commenced. All raters had completed a training course to ensure that the operationalized rules were applied consistently.

All evaluations were undertaken at baseline. The NPI and DCM assessments were also completed at 1- and 3-month follow-up.

In the case of any clinically significant worsening of behavioral symptoms, the center coordinator, blinded to neuroleptic status, decided whether the patient needed to be withdrawn from the study to receive additional "rescue" medication.

Study withdrawals and the proportion of people developing marked behavioral symptoms are described and compared between groups using the chi-square test. People who did not develop any marked behavioral problems were considered to "remain stable." For all participants who completed at least 1 follow-up assessment, the last evaluation was carried forward. The main NPI behavioral factors were derived using a principal components analysis; subscales not included in any of the factors were evaluated as individual symptoms in a secondary analysis. The changes in the key measures (NPI factor scores, total NPI scores) were compared between the placebo and neuroleptic groups using the Mann-Whitney U test. These analyses were repeated for patients scoring above and below the median at the baseline assessment. Changes in the DCM well-being score were compared between groups using the Mann-Whitney U test. The SPSS computerized statistics package[31] was used for all statistical analyses.

RESULTS

The study was fully approved by the local research ethics committee at each center. In addition to receiving informed consent from participants, we also requested assent from the next of kin. One hundred people participated (risperidone N = 39, thioridazine N = 41, haloperidol N = 17, trifluoperazine N = 2, chlorpromazine N = 1). Fifty-four patients received active treatment and 46 patients received placebo. There were no significant differences in any of the baseline sample characteristics (Table 1) (active vs. placebo: mean ± SD age = 83.1 ± 7.1 years vs. 83.6 ± 9.3 years, z = 0.2, p = .83; percentage of women = 76% vs. 87%, $\chi^2 = 1.8$, p = .18; mean ± SD MMSE score = 5.5 ± 6.8 vs. 5.5 ± 6.5, z = 0, p = .97; mean ± SD CDR score = 2.5 ± 0.7 vs. 2.5 ± 0.7, z = 0.2, p = .84; mean ± SD total NPI score = 13.3 ± 9.3 vs. 15.7 ± 8.3, z = 1.3, p = .19; mean ± SD percentage of time socially withdrawn = 6.2 ± 8.6 vs. 5.8 ± 6.4, z = 0.3, p = .80; mean ± SD well-being score = 2.7 ± 1.7 vs. 2.5 ± 1.4, z = 0.8, p = .45).

Fourteen patients (26% active treatment, 30% placebo) withdrew from the study in each group ($\chi^2 = 0.25$, p = .62). There were only 6 withdrawals in the placebo-treated group (13%) and 5 withdrawals in the active treatment group (9%) because of behavioral deterioration ($\chi^2 = 0.36$, p = .55). Other withdrawals were because of physical health problems (active N = 3 [6%], placebo N = 2 [4%]), death (active N = 3 [6%], placebo N = 3 [7%]), protocol violation (active N = 2 [4%], placebo N = 1 [2%]) or withdrawal of consent (active N = 3 [6%], placebo N = 2 [4%]). Eighty-two (82%) of the patients completed at least 1 follow-up evaluation and were included in the primary outcome analysis.

Table 1. Baseline Characteristics of a Sample of 100 Patients With Dementia

Characteristic	Placebo (N = 46)	Neuroleptic (N = 54)
Age, mean (SD), y	83.6 (9.3)	83.1 (7.1)
Gender, N (%)		
Male	6 (13.0)	13 (24.1)
Female	40 (87.0)	41 (75.9)
MMSE score, median (min–max)	3.0 (0–21.0)	2.5 (0–23.0)
CDR score, N (%)		
Stage 1	4 (8.7)	6 (11.1)
Stage 2	15 (32.6)	13 (24.1)
Stage 3	27 (58.7)	35 (64.8)
Neuroleptic (mean ± SD dose, mg), N (%)		
Risperidone (1.3 ± 0.7)	17 (37.0)	22 (40.7)
Thioridazine (38.0 ± 26.2)	20 (43.5)	21 (38.9)
Haloperidol (0.9 ± 0.4)	7 (15.2)	10 (18.5)
Trifluoperazine (3.0 ± 1.4)	2 (4.4)	0 (0.0)
Chlorpromazine (20)[a]	0 (0.0)	1 (1.9)
NPI total score, median (min–max)	16.0 (0–35.0)	14.0 (0–48.0)
Agitation factor	4 (0–16)	4 (0–16)
Psychosis factor	0 (0–16)	0 (0–16)
Mood factor	16.0 (0–35.0)	14.0 (0–48.0)
Well-being score, median (min–max)	2.35 (0.26–6.40)	2.39 (0.25–10.40)

[a]No SD value, as there was only 1 patient taking chlorpromazine.
Abbreviations: CDR = Clinical Dementia Rating scale, MSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory.

NPI Principal Components Analysis

A principal component analysis was completed, entering the scores for the 12 NPI subscales on all 100 participants at the baseline assessment. Six factors emerged with Eigenvalues > 1.0. Symptoms with a correlation coefficient > 0.4 were considered to be a component of that factor. The first 3 factors (all with Eigenvalues > 1.5) appeared distinct. Factor 1 included subscales D (depression, r = 0.5), E (anxiety, r = 0.4), G (apathy, r = 0.6), K (sleep, r = 0.5), and L (appetite, r = 0.8) and focused on symptoms related to altered mood. Factor 2 was associated with subscales A (delusions, r = 0.5) and B (hallucinations, r = 0.6) and was hence focused on psychosis. Factor 3 was associated with subscales C (agitation/aggression, r = 0.6), F (elation, r = 0.5), and I (irritability, r = 0.6) and focused on symptoms of agitation. The re-

Table 2. Differences in Change in Behavioral Symptoms Between Placebo (N = 36) and Neuroleptic (N = 46) Groups of Patients With Dementia Enrolled in a 3-Month Discontinuation Trial: Statistical Evaluation

	Mean ± SD Change			
Variable	Placebo	Neuroleptic	z Value[a]	p Value
Behavioral factors				
NPI total score	–1.3 ± 9.4	0.2 ± 12.0	0.73	.46
Agitation	–1.0 ± 5.1	–1.0 ± 5.3	0.14	.89
Mood	–1.1 ± 7.7	–0.62 ± 8.1	0.19	.85
Psychosis	–0.5 ± 3.2	–0.9 ± 3.5	0.83	.41
Quality of life				
Well-being	–0.18 ± 1.72	0.35 ± 2.41	0.77	.44

[a]Mann-Whitney U test.
Abbreviation: NPI = Neuropsychiatric Inventory.

maining 3 factors included only 1 individual symptom, each of which had already been included in 1 of the first 3 factors. These 3 subscales were used in addition to the total NPI score for the evaluation of outcome. The items not associated with any of the factors (disinhibition, aberrant motor behavior, nighttime disturbances, and eating and appetite disorders) were evaluated separately as individual symptoms in a secondary analysis.

Placebo-Neuroleptic Comparisons

The 46 patients receiving active treatment and 36 receiving placebo who completed at least 1 month of follow-up were included in the primary evaluation. There were no significant differences between groups in the change on the NPI total score or the key psychiatric /behavioral factors of agitation, mood, and psychosis (Table 2), although in the secondary evaluations there was a trend toward a better outcome for appetite and eating disorders in the placebo-treated group (–0.5 ± 3.1 vs. 0.9 ± 3.0, z = 1.8, p = .08) but no difference for disinhibition (z = 0.6, p = .55), aberrant motor behavior (z = 0.9, p = .41), or nighttime disturbances (z = 0.6, p = .55). Twenty-four (67%) of the placebo-treated and 35 (76%) of the neuroleptic-treated patients remained "stable" over the treatment period ($\chi^2 = 0.89$, p = .36). The median baseline NPI score was 14 for patients receiving active treatment.

Patients With Higher Levels of Behavioral Disturbance (NPI Score > 14)

In people whose NPI score was > 14, those who were assigned to continue neuroleptic treatment were significantly less likely than were those taking placebo to develop marked behavioral disturbance ($\chi^2 = 6.8$, p = .009), but there were no significant differences in the changes of total NPI scores or factor scores (Table 3). In the comparisons of other symptoms, the people continuing with neuroleptic treatment had a significantly better outcome with respect to aberrant motor behavior (0.6 ± 2.7 vs. –0.3 ± 1.0, z = 2.0, p = .047), but there were no differences in disinhibition (z = 1.0, p = .31), appetite and eating disturbances (z = 0.2, p = .83), or nighttime disturbances (z = 1.2, p = .25).

Patients With Lower Levels of Behavioral Disturbance (NPI Score ≤ 14)

In a comparison of active treatment and placebo in the group with NPI scores ≤ 14, the patients assigned to placebo had a significantly better outcome with respect to agitation (z = 2.4, p = .018). In the primary comparisons, there were no other significant differences, although a trend was found for those taking placebo to be less likely to develop marked behavioral or psychiatric symptoms ($\chi^2 = 3.6$, p = .06) and have a greater reduction in total NPI score (z = 1.7, p = .09) (Table 3). There were no significant differences in the secondary comparisons (disinhibition, z = 0.6, p = .52; aberrant motor behavior, z = 1.3, p = .17; appetite and eating disturbances, z = 0.7, p = .46; nighttime disturbances, z = 1.4, p = .16).

Comparison of People With Higher and Lower Levels of Behavioral Disturbance Assigned to Placebo

Patients with NPI scores > 14 in the placebo group were significantly more likely to develop marked behavioral disturbances ($\chi^2 = 12.3$, p < .0001) and had significantly worse outcomes with respect to mood (z = 2.3, p = .02) and psychosis (z = 2.1, p = .038), with a trend toward a less favorable outcome for well-being (Mann-Whitney U, z = 1.9, p = .06). There were no differences in total NPI score (Mann-Whitney U, z = 1.6, p = .12) or agitation (Mann-Whitney U, z=0.1, p=.93).

Quality of Life

The descriptive data for quality of life are shown in Table 2. Although there was a 15% improvement in well-being in people withdrawn from neuroleptics compared with a slight worsening in patients continuing to take neuroleptic treatment, there were no significant differences between groups in either the overall cohort or those with NPI scores above the median or at or below the median.

DISCUSSION

The present study, the largest and longest duration placebo-controlled discontinuation study of neuroleptics in people with dementia, utilized standardized measures to evaluate behavioral and psychiatric symptoms. Most people (67%) with dementia who had stable behavior and had been receiving more than 3 months of treatment with a neuroleptic experienced no deterioration of their behavioral symptoms when the neuroleptic agents were discon-

Table 3. Statistical Comparison of Participants Receiving Neuroleptic or Placebo According to Baseline Neuropsychiatric Inventory (NPI) Scores Above the Median (> 14) or at or Below the Median (≤ 14)

	Change in Score From Baseline to Endpoint							
	NPI ≤ Median				NPI > Median			
Item	Placebo (N = 17)	Neuroleptic (N = 21)	z Value	p Value	Placebo (N = 19)	Neuroleptic (N = 25)	z Value[a]	p Value
Total NPI	–3.2 ± 11.7	–6.2 ± 8.7	1.7	.09	–3.3 ± 5.7	–2.9 ± 8.0	0.34	0.73
Psychiatric/Behavioral Factors								
Agitation	–1.0 ± 3.1	1.5 ± 2.5	2.4	.018*	–1.0 ± 6.9	–3.3 ± 5.7	0.82	.38
Mood	1.6 ± 5.2	0.6 ± 6.0	0.39	.70	–2.5 ± 9.7	–2.7 ± 8.8	1.0	.31
Psychosis	–0.3 ± 3.6	0.3 ± 2.9	0.7	.47	–1.9 ± 3.1	–0.7 ± 3.4	1.6	.11
Well-being	0.4 ± 1.5	0.6 ± 1.7	0.15	.88	1.1 ± 2.9	0.2 ± 2.7	0.42	.68

[a]Mann-Whitney U test.
*Significance set at $p < .05$.

tinued. In the current study, the discontinuation was abrupt, with an immediate withdrawal of neuroleptic in patients allocated to placebo. Although this method was selected because of the generally small doses of neuroleptic agents received by dementia patients, it may have led to a possible exaggeration of withdrawal symptoms. Because of the entry criteria for the study, the level of behavioral disturbance was modest and the impact of neuroleptic withdrawal on people with more severe symptoms was not evaluated.

More importantly, there were very clear differences between people scoring above and below the median score on the NPI at baseline. People with scores less than 14 experienced a significantly better outcome with respect to agitation and showed a trend toward being less likely to develop marked behavioral problems if they were discontinued from neuroleptic treatment. In contrast, patients with scores higher than the median at baseline were significantly more likely to develop marked behavioral problems if they did not continue to receive neuroleptic treatment and in secondary analysis experienced a significant worsening in motor restlessness. The differences in outcome between patients with baseline NPI scores above the median and those with scores at or below the median were also evident from a direct comparison of people with scores above and those with scores at or below this threshold who were allocated to placebo treatment and had hence been discontinued from their neuroleptic treatment. People with baseline scores at or below the median had significantly better outcomes with respect to mood, psychosis, and the development of marked behavioral problems and a trend toward a more favorable quality-of-life outcome than did those with higher baseline scores.

Concern regarding the potential exacerbation of behavioral symptoms is a major factor perpetuating long-term neuroleptic treatment of people with dementia; the current data strongly indicate that this exacerbation does not occur in the majority of people with NPI scores of 14 or less. Given the potential side effects and other adverse consequences of neuroleptic treatment, such as sedation, parkinsonism, falls, and the possibility of accelerated cognitive decline, the current findings strongly support the recommendation that a trial discontinuation of neuroleptic treatment is indicated for most dementia patients with stable behavior problems indicated by low NPI scores. For people with higher levels of behavioral disturbance, the decision probably requires a detailed clinical evaluation on an individual patient basis, with the likelihood that many patients will benefit from ongoing treatment.

Although the largest study of its kind, the modest sample size limits the statistical power. For example, there was a > 1-point advantage for placebo treatment in the overall group for total NPI score and for both total NPI score and mood disorder score in patients with below-median baseline levels of behavioral/psychiatric symptoms. With a larger sample, some of these differences may also have been significant, although the overall profile of change supports the conclusion of no significant worsening of symptoms in the overall patient group, with some advantages of placebo in the less disturbed patients but some benefits of ongoing neuroleptic treatment in patients with higher levels of behavioral symptoms. In the current study, key side effects such as extrapyramidal symptoms, involuntary movements, and falls were not systematically measured. The reduction of side effects is another potential benefit of discontinuing neuroleptics and should be evaluated more systematically in future studies.

The current cohort comprised dementia patients living in residential and nursing-home facilities. Typical of this group of individuals, most people had moderate or severe dementia, and the majority were under the treatment of primary care physicians. Although the dosage of neuroleptic agents was what would be expected for the management of neuropsychiatric and behavioral symptoms in dementia, the selection of agents may differ from that seen in specialist practice and the severity of symptoms may be less marked than in specialist settings. The results cannot therefore automatically be generalized to dementia patients under the management of specialist services or to people living in the community with less severe dementia.

The current study clearly indicates the benefit of standardized clinical evaluation of behavioral symptoms, suggesting that a cutoff on the NPI can provide a useful clinical indication for deciding which patients with dementia receiving long-term neuroleptic therapy are most likely to benefit from a trial of treatment discontinuation.

Although there was a 15% improvement in well-being in patients allocated to placebo compared with a slight deterioration for those continuing to receive neuroleptics, these differences were not statistically significant. There is hence no evidence from the current study that discontinuing neuroleptic treatment improves quality of life.

In conclusion, there may be particular benefits of treatment discontinuation in patients with a low threshold of behavioral symptoms (NPI scores ≤ 14). Our findings indicate that ongoing monitoring of behavioral and psychiatric symptoms with a brief standardized tool is valuable and can form the basis for clear treatment recommendations.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), haloperidol (Haldol and others), risperidone (Risperdal), trifluoperazine (Stelazine and others).

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