M. Martín Carrasco[1,2]
J. Ballesteros[2,3]
A. Bulbena[2,4]
G. Baraibar[5]
C. García[6]
L. Mínguez[7]
J. Blanco[8]
J. de Blas[9]
J. A. Agüero[1]
N. Ibarra[2]

Effectiveness of typical and atypical neuroleptics in the control of behavioral and psychopathological symptoms of dementia. Results of a retrospective study

[1] Clínica Psiquiátrica Padre Menni Pamplona (Spain)
[2] Instituto de Investigaciones Psiquiátricas Bilbao (Spain)
[3] Universidad del País Vasco Leioa (Spain)
[4] Universidad Autónoma de Barcelona Barcelona (Spain)
[5] Hospital Aita Menni Mondragón (Spain)
[6] Centro Hospitalario Padre Menni Santander (Spain)
[7] Complejo Hospitalario San Luis Palencia (Spain)
[8] Centro Hospitalario Padre Benito Menni Valladolid (Spain)
[9] Centro Hospitalario Menni Elizondo (Spain)

Introduction. Presence of disruptive behavioural and psychological symptoms in dementia (BPSD) is highly prevalent and, as a consequence, neuroleptics are frequently used in these patients to control BPSD. Several reviews have shown the clinical equivalence of different classes of neuroleptics in BPSD control, although that equivalence has been only indirectly assessed by comparing the combined results of different types of active drugs versus placebo. Thus, little is known on the comparative effectiveness, head to head, of different neuroleptics on BPSD. The aim of this study was to gather preliminary information on the effectiveness of typical (haloperidol, thioridazine) and atypical (olanzapine, risperidone) neuroleptics on BPSD.

Methods. Multicenter, observational and retrospective study using chart reviews of patients with dementia to assess neuroleptic prescriptions and clinical outcomes at 12 weeks on treatment.

Results. No significant differences on BPSD improvement were found by type of neuroleptic (n=78; Kruskal-Wallis exact test; p=0.47). There also were no differences by neuroleptics when the analysis was stratified by levels of cognitive decline (Kruskal-Wallis exact test; p=0.86 and 0.87 for moderate and severe levels of deterioration, respectively). Recorded side effects were worse in the haloperidol group (n=19) regarding rigidity (Fisher's exact; p=0.01), tremor (Fisher's exact; p=0.03) and akathisia (Fisher's exact; p=0.03).

Conclusions. Our findings support the equivalence in effectiveness of several classes of neuroleptics commonly used to treat BPSD. Nevertheless these results need to be confirmed by adequately powered randomized trials and further pharmacoepidemiological studies to assess their safety.

Key words:
Neuroleptics. Antipsychotics. Dementia. Behavioural and psychological symptoms. BPSD.

Actas Esp Psiquiatr 2006;34(4):251-256

Correspondence:
Manuel Martín Carrasco
Clínica Psiquiátrica Padre Menni
Marcelo Celayeta, 10
3104 Pamplona. Spain
E-mail: dmedica@mennipam.com

Efectividad de los neurolépticos típicos y atípicos en el control de los síntomas conductuales y psicopatológicos de la demencia. Resultados de un estudio retrospectivo

Introducción. La presencia de síntomas psicológicos y comportamentales en la demencia (SPCD) es altamente prevalente y los fármacos neurolépticos suelen ser frecuentemente utilizados para su control. Diferentes revisiones han señalado la equivalencia clínica de las distintas familias de neurolépticos en el control de SPCD, aunque dicha equivalencia se ha evaluado sólo indirectamente, comparando sus efectos frente a placebo, por lo que hay poca información comparativa directa de la efectividad de los distintos neurolépticos. Así, el objetivo de este estudio fue el de obtener información preliminar de la efectividad de neurolépticos típicos (haloperidol, tioridazina) y atípicos (olanzapina, risperidona) sobre el control de SPCD.

Métodos. Estudio multicéntrico, observacional y retrospectivo basado en la revisión de los datos de prescripción de neurolépticos en pacientes con demencia y sus resultados a las 12 semanas de tratamiento.

Resultados. No se observaron diferencias significativas en la mejora de SPCD según los distintos neurolépticos evaluados (n=78; test exacto de Kruskal-Wallis; p=0,47). Tampoco se observaron diferencias al estratificar el análisis por niveles de deterioro cognitivo (test exacto de Kruskal-Wallis; p=0,86 y 0,87, respectivamente, para los niveles moderados y graves de deterioro cognitivo). Los efectos secundarios más importantes se recogieron en el grupo de pacientes tratados con haloperidol (n=19) y fueron, fundamentalmente, rigidez (test exacto de Fisher; p=0,01), temblor (test exacto de Fisher; p=0,03) y acatisia (test exacto de Fisher; p=0,03).

Conclusiones. Nuestros resultados apoyan la equivalencia en efectividad para los distintos tipos de neurolépticos habitualmente utilizados para tratar los SPCD, aunque estos resultados necesitan ser confirmados por ensayos clínicos prospectivos con adecuado poder estadístico y estudios de farmacovigilancia para evaluar su seguridad.

Palabras clave:
Neurolépticos. Antipsicóticos. Demencia. Síntomas psicológicos y comportamentales.

INTRODUCTION

Symptomatic association including behavior problems and psychiatric symptoms (the so-called «behavioral and psychological symptoms of dementias» or BPSD) occurs in high prevalence in patients who suffer from middle and advanced stage dementia syndrome, especially in those caused by degenerative conditions, such as Alzheimer's disease. More than 70% of patients with dementia in assisted care residences have BPSD, agitation and aggression being the most common symptoms[1-3]. BPSD tend to be maintained over time[1]. Behavior alterations are especially refractory to change while psychiatric manifestations (e.g., depression, psychotic symptoms) may remit spontaneously[4]. As a consequence of these problems, antipsychotic or neuroleptic drugs are generally used with relative frequency in dementia patients. Consensus protocols are used for it as a base given that there is generally lack of formal therapeutic indication in BPSD[5].

Up to now, different systematic reviews and meta-analysis have pointed out the efficacy of neuroleptics in the control of BPSD, especially psychotic symptoms. The same reviews have mentioned the clinical equivalence of different neuroleptics in relationship to their efficacy[6-8]. The results of a combined analysis we conducted (table 1) based on the data presented in Lanctôt et al.[7] complemented with studies done after that review[9-12] confirm that neuroleptics are more effective than placebo in the management of BPSD (14 studies; risk difference [RD]=0.17; 95% confidence interval [95% CI]: 0.12 to 0.23; $p<0.001$). Based on these results, it can be estimated that the number of patients needed to treat (NNT) with neuroleptics to control a BPSD episode would be 6 (95% CI for the NNT: 5 to 9). Previous results on clinical equivalence of the different neuroleptic classes are also confirmed in this analysis (table 1).

Table 1 Combined analysis of the efficacy of neuroleptics in the control of BPSD

Comparisons	Risk differences (95% CI)	Heterogeneity (Q test)
Any neuroleptic vs placebo (14 studies)	0.17 (0.12 to 0.23)	17.75 (13 gl) ($p=0.17$)
Phenothiazines* vs placebo (3 studies)	0.24 (0.05 to 0.43)	(0.05 a 0.43) ($p=0.44$)
Butyrophenones** vs placebo (4 studies)	0.19 (0.09 to 0.30)	1.32 (3 gl) ($p=0.72$)
Other neuroleptics*** vs placebo (4 studies)	0.27 (0.13 to 0.40)	6.14 (3 g.l) ($p=0.10$)
Atypical neuroleptics**** vs placebo (3 studies)	0.13 (0.05 to 0.20)	4.09 (2 gl) ($p=0.13$)

*Acetophenazine, trifluoperazine, thioridazine. **Haloperidol. ***Thiothixene, loxapine. ****Risperidone, olanzapine.

The RD for the comparison of phenothiazines versus placebo (three studies) is 0.24 (95% CI: 0.05 to 0.43; $p=0.01$). For the butyrophenones versus placebo (four studies), the RD is 0.19 (95% CI: 0.09 to 0.30; $p<0.001$), while for other neuroleptics versus placebo (four studies), the RD is 0.27 (95% CI: 0.13 to 0.40; $p=0.0001$). RD for the atypical neuroleptics versus placebo is 0.13 (95% CI: 0.05 to 0.20; $p<0.001$).

However, beyond these comparisons versus placebo, there is little data on comparative efficacy, head to head, of the different neurolepetic classes in the control of BPSD. Thus, this study aimed to evaluate the effectiveness of typical neuroleptics (haloperidol (haloperidol, thioridazine) and atypical ones (olanzapine, risperidone) in the control of BPSD in patients with institutionalized dementia.

METHODS

Study design

This is a multicenter, observational and retrospective study that includes four treatment conditions: risperidone and olanzapine as atypical neuroleptics, haloperidol and thioridazine as typical ones. The study was conducted in six psychiatric sites that belong to the same health care organization (Hermanas Hospitalarias del SCJ). Information on treatment effectiveness was obtained with an extensive review of the clinical records of all the patients whose age was ≥ 65 years, who had a clinical diagnosis of dementia according to the ICD-10, with a prescription of neuroleptics for BPSD and who were treated for a time period ≤ 12 weeks.

The study was conducted according to the recommendations for observational studies on the use of psychopharmacological treatments[13] and was approved by the corresponding ethics committees.

Evaluations

The measurement used to assess effectiveness of the treatments was the BEHAVE-AD scale[14], one of the instruments used most for psychopathological assessment of dementias. The score on this scale is either collected routinely from the clinical records of patients with dementia or, on the other hand, is easily deducible from the information collected on psychiatric and behavior disorders. Its total score assesses severity on the BPSD on an ordinal scale of 4 points, going from value 0 (no problem with the caretaker nor danger for the patient) to value 3 (serious problems or intolerable for the caretaker or dangerous for the patient). The assessment of effectiveness was based on the difference of score between baseline and final values. A negative score, or a 0 value, was assessed as indication of no improvement; value 1 indicates moderate improvement; while a value of ≥ 2 indicates substantial improvement. All the patients also

had baseline assessments of the stage of their dementia syndrome according to the Global Deterioration Scale (GDS), that has an ordinal scale of 7 points (from no cognitive deterioration to advanced dementia)[15]. Neurologic side effects were collected from the information present in the clinical records by the psychiatrists caring for the patients, using the UKU scale as a registry guideline[16]. As a way to control possible information biases, it was agreed that the clinicians (psychiatrists) who assessed the final severity of the BPSD episode would not be the psychiatrists who were directly responsible for the patient care.

Statistical analysis

The demographic or clinical differences between the different treatment arms in the baseline situation and the side effects were evaluated with Fisher's exact test or the simple analysis of the variance. Due to the moderate size of the samples included, effectiveness of the treatment was only analyzed with exact tests, based on permutations. All the likelihood values presented are associated to bilateral statistical tests. The analyses were conducted with the Stata 7 and StatXact 5 programs.

RESULTS

Characteristics of the patients

A total of 87 patients who had a clinical diagnosis of dementia according to the ICD-10 and an associated episode of BPSD were included in the study. The main demographic and clinical characteristics of the sample are given in table 2. Most of the patients had serious or very serious cognitive deterioration and moderate or serious behavior problems according to their responsible psychiatrist. These behavior problems (mainly aggressiveness, agitation and daytime rhythm disorder) were the reasons mainly collected for the prescription of neuroleptics in patients with dementia. There were no significant differences between the different interventions according to age (F 3.82 = 0.25; $p = 0.86$), gender (Fisher's exact test; $p = 0.11$), type of dementia (Fisher's exact test; $p = 0.78$), years passed from the clinical diagnosis of dementia (F 3.81 = 0.83; $p = 0.48$), and total score on the BEHAVE-AD scale (Fisher's exact test; $p = 0.35$). On the contrary, the contrast for the different cognitive deterioration levels according to the GDS reached statistically significant differences between the different treatment arms (F 3.83 = 5.70; $p = 0.001$). *A posteriori* statistical contrasts indicated that patients treated with olanzapine had lower scores on the GDS scale than patients treated with risperidone or thioridazine and that they were not different from patients treated with haloperidol. According to these analyses, the scores on the GDS scale were dichotomized into moderate (until moderately serious cognitive deterioration) and serious levels (serious and very serious cognitive deteriorations) to use it as a stratification variable in the effectiveness analyses.

Table 2 Principal characteristics of the patients included (n = 87)

Variables	Values
Age, years (mean, SD)	80,0 (7.4)
Gender (n, %)	
Man	32 (36.8)
Woman	55 (63.2)
Clinical diagnosis (n, %)	
Probable Alzheimer	70 (80.5)
Other causes of dementia	17 (19.5)
Years from diagnosis (mean, SD)	3.3 (3.3)
Scores on GDS (n, %)	
Moderate	17 (19.5)
Moderate serious	16 (18.4)
Serious	40 (46.0)
Very serious	14 (16.1)
Total score on BEHAVE-AD scale (n, %)	
Mild problems/dangerous for the patient	24 (27.6)
Moderate problems/dangerous for the patient	53 (60.9)
Serious problems/dangerous for the patient	10 (11.5)
Indications for neuroleptic prescription (n, %)*	
Paranoid ideation and delusions	42 (48.3)
Hallucinations	23 (26.4)
Agitation	56 (64.4)
Aggressiveness	77 (88.5)
Daytime rhythm disorders	55 (63.2)
Affective disorders	30 (34.5)
Anxiety and phobias	43 (49.4)
Neuroleptic prescription (n, %)	
Olanzapine	16 (18.4)
Risperidone	30 (34.5)
Thioridazine	22 (25.3)
Haloperidol	19 (21.8)

*Non-independent percentages.

Neuroleptic dose

The mean neuroleptic dose for the maximum dose collected in the clinical records was 7.8 mg/day (SD: 4.4) for olanzapine (range from 5 to 20 mg/day), 1.8 mg/day (SD: 1.5) for risperidone (range from 0.5 to 6 mg/day), 55.5 mg/day (SD: 59.7) for thioridazine (range from 7 to 260 mg/day) and 7.8 mg/day (SD: 14.4) for haloperidol (range from 0.1 to 60 mg/day).

Effectiveness analysis

Table 3 shows the comparative results of the different neuroleptics in the control of BPSD. No significant differen-

Table 3 Results of effectiveness according to cognitive deterioration levels evaluated with the GDS scale

Treatment	Improvement		
	Without improvement n (%)	Moderada n (%)	Substantial n (%)
All the patients			
Olanzapine	5 (31.2)	0 (0.0)	11 (68.8)
Risperidone	9 (30.0)	11 (36.7)	10 (33.3)
Haloperidol	4 (21.0)	9 (47.4)	6 (31.6)
Thioridazine	3 (13.6)	13 (59.1)	6 (27.3)
Patients with moderate cognitive deterioration			
Olanzapine	4 (30.8)	0 (0.0)	9 (69.2)
Risperidone	3 (42.9)	0 (0.0)	4 (57.1)
Haloperidol	1 (11.1)	5 (55.6)	3 (33.3)
Thioridazine	0 (0.0)	3 (75.0)	1 (25.0)
Patients with serious cognitive deterioration			
Olanzapine	1 (33.3)	0 (0.0)	2 (66.7)
Risperidone	6 (26.1)	11 (47.8)	6 (26.1)
Haloperidol	3 (30.0)	4 (40.0)	3 (30.0)
Thioridazine	3 (16.7)	10 (55.6)	5 (27.8)

ces were found between neuroleptics for clinical improvement (Kruskal-Wallis exact test; $p=0.47$), and the same occurred when patients were stratified according to cognitive deterioration based on the GDS scale scores (Kruskal-Wallis exact test; $p=0.86$ and 0.87, respectively for moderate and serious cognitive deterioration). A secondary analysis was conducted to compare global effectiveness of atypical neuroleptics (olanzapine plus risperidone) versus the typical ones (thioridazine plus haloperidol), but the results also did not show any significant differences (Kruskal-Wallis exact test; $p=0.76$, 0.50 and 0.98, respectively, for all the patients and for the patients with moderate and severe cognitive deterioration).

Adverse effects

Table 4 collects the neurological adverse effects gathered by the psychiatrists responsible for the patients during the BPSD episode assessed. The only significant differences appear in rigidity (Fisher's exact test; p=0.01), tremor (Fisher's exact test; $p=0.03$) and akathisia (Fisher's exact test; $p=0.03$). For all these adverse effects, haloperidol had more moderate or serious problems than the remaining neuroleptics included in this study.

Table 4 Adverse neurologic effects observed in patients with dementia according to neuroleptic prescription

Adverse effects	None or in mild grade	Moderate or in severe grade
Dystonia		
Olanzapine	14	0
Risperidone	17	2
Thioridazine	16	0
Haloperidol	13	0
Rigidness		
Olanzapine	14	0
Risperidone	18	1
Thioridazine	15	1
Haloperidol	10	3
Hypokinesis/akinesis		
Olanzapine	13	1
Risperidone	17	2
Thioridazine	13	3
Haloperidol	11	2
Hyperkinesis		
Olanzapine	14	0
Risperidone	19	0
Thioridazine	15	1
Haloperidol	12	1
Tremor		
Olanzapine	14	0
Risperidone	19	0
Thioridazine	16	0
Haloperidol	11	2
Akathisia		
Olanzapine	14	0
Risperidone	18	1
Thioridazine	16	0
Haloperidol	11	2

DISCUSSION

Our results indicate clinical improvement in BPSD seriousness in at least 70% of patients with dementia who were treated with neuroleptics. On the contrary to other retrospective studies[17,18] we have not found any differences in effectiveness for the different neuroleptics evaluated. Frenchman and Prince[17] describe better results for risperidone (n=60; improvement in 95% of the cases) than for haloperidol (n=83; 66% improvement) or thioridazine (n=43; 65% improvement); while Edell and Tunis[18], in the analysis of groups of behavioral or psychological results, find an advantage for olanzapine (n=209) versus haloperi-

dol (n = 289) and risperidone (n = 500). Several methodological problems of the retrospective designs, discussed further on, could explain the different results found in these observational studies. In our study, the adverse effects recorded are the only important difference between the different neuroleptics, haloperidol being that which has the worst safety profile. In summary, our results support that described in previous studies and reviews in regard to equivalence between different neuroleptics in the control of BPSD and regarding the lower frequency of presentation of neurological adverse effects in atypical neuroleptics[6-8,10,19-22].

Several limitations of the study should be considered when comparing our results with those of other previous observational studies. These limitations depend on the observational and retrospective design we have used. This study, as others[17,18], depends on the information collected in the clinical records of the patients to obtain information on effectiveness and safety. The BEHAVE scale was used to systematize the collection of information. This instrument was not designed for this purpose since it was originally created for the current and prospective assessment of the patient, collecting the psychopathological manifestations present in the two weeks prior to the examination by the information supplied by a reliable informer[23]. As a consequence, the validity of the findings mainly depends on a correct and systematic registry of clinical information by the psychiatrists and other health care professionals responsible for the patients' medical care. However, the use of this methodology as a way to extract relevant information from existing clinical material is not rare in the literature[24]. On the other hand, the fact that all the hospitals included in this study belong to the same non-profit health care organization and share similar evaluation and treatment protocols in patients with dementia assures us of at least some common procedures for the registry of clinical information. The possibility of screening biases in these types of studies is much more problematic, given that allotment to treatment is not random but decided by the psychiatrist responsible for the patient. Another possible source of biases, related with the previous, is lack of blinding during the study. Unfortunately, there is no direct way to control these possible sources of biases in retrospective studies. We have attempted to minimize both problems as much as possible using psychiatrists other than those related with the clinical care of the patients included in the study as evaluators of the result. However, we cannot assure that we have eliminated the presence of possible information or selection biases in our study. On the other hand, given that the effectiveness of the treatments was evaluated by independent evaluators and not by the psychiatrists caring for the patients, we believe that it is unlikely that said biases may have a differential impact on our results since, in any event, their effects would be distributed similarly among all the study groups.

It is known that neuroleptics have significantly greater efficacy than placebo in the control of BPSD (table 1), however there is still not enough knowledge accumulated on comparative efficacy (head to head) of the different types of neuroleptics in this problem. Few controlled studies have covered this aspect and those that have done so have mainly used haloperidol as comparison treatment[10,25-27]. Our results support the equivalence of effectiveness on the control of BPSD of different types of neuroleptics. However, the final word in this sense can only be had by randomized clinical trials. These controlled trials, with adequate statistical power, and designed to compare directly the different relevant treatment arms are necessary to be able to adequately assess the possible therapeutic equivalence of the different classes of neuroleptics. On the other hand, the recent news on cerebrovascular type adverse effects may be associated with some neuroleptic treatments in patients with dementias[22], justify the development of prospective pharmacovigilance studies, with large patient samples, to be able to assess the middle and long term safety of these treatments. BPSDs are a frequent and common problem among patients with institutionalized dementia and thus we urgently need objective scientific evidence that may be used to develop better and safer treatments for our patients.

ACKNOWLEDGEMENTS

Study financed with a research grant given by Lilly, Spain.

REFERENCES

1. Ballard CG, Margallo-Lana M, Fossey J, Reichelt K, Myint P, Potkins D. A 1-year follow-up study of behavioural and psychological symptoms in dementia among people in care environments. J Clin Psychiatry 2001;62:631-6.
2. Brodaty H, Draper B, Saab D, Low LF, Richards V, Paton H. Psychosis, depression and behavioural disturbances in Sidney nursing home residents: prevalence and predictors. Int J Geriatr Psychiatry 2001;16:504-12.
3. Margallo-Lana M, Swann A, O'Brien J, Fairbairn A, Reichelt K, Potkins D. Prevalence and pharmacological management of behavioural and psychological symptoms amongst dementia sufferers living in care environments. Int J Geriatr Psychiatry 2001; 16:39-44.
4. Haupt M, Kurz A, Janner M. A 2-year follow-up of behavioural and psychological symptoms in Alzheimer's disease. Dement Geriatr Cogn Disord 2000;11:147-52.
5. Defilippi JL, Crismon ML. Antipsychotic agents in patients with dementia. Pharmacotherapy 2000;20:23-33.
6. Schneider LS, Pollock VE, Lyness SA. A meta-analysis of controlled trials of neuroleptic treatment in dementia. J Am Geriatr Soc 1990;38:553-63.
7. Lanctôt KL, Best TS, Mittmann N, Liu BA, Oh PI, Einarson TR. Efficacy and safety of neuroleptics in behavioural disorders associated with dementia. J Clin Psychiatry 1998;59:550-61.
8. Hemels ME, Lanctôt KL, Iskedjian M, Einarson TR. Clinical and economic factors in the treatment of behavioural and psychological symptoms of dementia. Drugs Aging 2001;18: 527-50.

9. Devanand DP, Marder K, Michaels KS, Sackheim HA, Bell K, Sullivan MA. A randomised, placebo-controlled dose-comparison trial of haloperidol for psychosis and disruptive behaviors in Alzheimer's disease. Am J Psychiatry 1998;155: 1512-20.
10. De Deyn PP, Rabheru K, Rasmussen A, Bocksberger JP, Dautzenberg PH, Eriksson S. A randomised trial of risperidone, placebo and haloperidol for behavioural symptoms of dementia. Neurology 1999;53:946-55.
11. Katz IR, Jeste DV, Mintzer JE, Clyde C, Napolitano J, Brecher M. Comparison of risperidone and placebo for psychosis and behavioural disturbances associated with dementia: a randomised, double-blind trial. J Clin Psychiatry 1999;60:107-15.
12. Street JS, Clark WS, Gannon KS, Cummings JL, Bymaster FP, Tamura RN. Olanzapine treatment of psychotic and behavioural symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomised, placebo-controlled trial. Arch Gen Psychiatry 2000;57:968-76.
13. Linden M, Baier D, Beitinger H, Kohnen R, Osterheider M, Philipp M. Guidelines for the implementation of drug utilization observation (DUO) studies in psychopharmacological therapy. Pharmacopsychiatry 1997;30:65-70.
14. Reisberg B, Borenstein J, Salob SP, Ferris SH, Franssen E, Georgotas A. Behavioral symptoms in Alzheimer´s disease: phenomenology and treatment. J Clin Psychiatry 1987;48:9-15.
15. Reisberg B. The brief cognitive rating scale and global deterioration scale. In: Crook T, Ferris S, Bartus R, editores. Assessment in geriatric psychopharmacology. New Canaan, con: Mark Powley Associates, 1983; p. 19-35.
16. Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side-effects in neuroleptic-treated patients. Acta Psychiatr Scand 1987; (Suppl. 76):1-100.
17. Frenchman IB, Prince T. Clinical experience with risperidone, haloperidol and thioridazine for dementia-associated behavioural disturbances. Int Psychogeriatr 1997;9:431-5.
18. Edell WS, Tunis SL. Antipsychotic treatment of behavioural and psychological symptoms of dementia in geropsychiatric inpatients. Am J Geriatr Psychiatry 2001;9:289-97.
19. De Deyn PP, Katz IR. Control of aggression and agitation in patients with dementia: efficacy and safety of risperidone. Int J Geriatr Psychiatry 2000;15(Suppl. 1):14-22.
20. Fontaine CS, Hynan LS, Koch K, Martín-Cook K, Svetlik D, Weiner MF. A double-blind comparison of olanzapine versus risperidone in the acute treatment of dementia related behavioral disturbances in extended care facilities. J Clin Psychiatry 2003; 64:726-30.
21. Brodaty H, Ames D, Snowdon J, Woodward M, Kirwan J, Clarnette R, et al. A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. J Clin Psychiatry 2003;64:134-43.
22. Pwee KH, Shukla VK, Herrmann N, Skidmore B. Novel antipsychotics for agitation in dementia: a systematic review. Ottawa: Canadian Coordinating Office for Health Technology Assessment, 2003.
23. Reisberg B, Auer SR, Monteiro I, Boksay I, Sclan SG. Behavioral disturbances of dementia: an overview of phenomenology and methodologic concerns. Int Psychogeriatr 1996;8 Suppl. 2:169-80.
24. Draper B, Brodaty H, Low LF, Saab D, Lie D, Richards V, et al. Use of psychotropics in Sydney nursing homes: associations with depression, psychosis, and behavioral disturbances. Int Psychogeriatr 2001;13:107-20.
25. Allain H, Dautzenberg PH, Schuck S, Bonhomme D, Gerard D. Double blind study of tiapride versus haloperidol and placebo in agitation and aggressiveness in elderly patients with cognitive impairment. Psychopharmacology (Berl) 2000;148:361-6.
26. Chan WC, Lam LC, Choy CN, Leung VP, Li SW, Chiu HF. A double-blind randomised comparison of risperidone and haloperidol in the treatment of behavioural and psychological symptoms in Chinese dementia patients. Int J Geriatr Psychiatry 2001;16:1156-62.
27. Meehan KM, Wang H, David SR, Nisivoccia JR, Jones B, Beasley CM. Comparison of rapidly acting intramuscular olanzapine, lorazepam and placebo: a double-blind, randomised study in acutely agitated patients with dementia. Neuropsychopharmacology 2002;26:494-504.