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CONTROL OF AGGRESSION AND AGITATION IN PATIENTS WITH DEMENTIA: EFFICACY AND SAFETY OF RISPERIDONE

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INTRODUCTION

Until recently, the main focus of pharmacological research related to dementia was on the improvement of cognitive functioning. This resulted in the introduction of several symptomatically active cognitive enhancers with acceptable safety profiles. However, behavioural and psychological symptoms of dementia (BPSD) are among the most predominant and pervasive features of dementia, and increasingly form a target for therapeutic intervention in this cognitively impaired population (Reisberg *et al.*, 1986, 1987; Jost and Grossberg, 1996). Aggression and other behavioural symptoms of dementia (e.g. agitation, purposeless activity, wandering and pacing symptoms) are important features of the illness and have a severe impact on the quality of life of patients and caregivers, thus complicating effective medical management (Reisberg *et al.*, 1987; Tariot and Blazina, 1994; Tariot *et al.*, 1995; Reisberg, 1992; Eastley and Wilcock, 1997). Behavioural symptoms have been described as the primary predictor of caregiver burden (Coen *et al.*, 1997; Donaldson *et al.*, 1997). In fact, the behavioural symptoms of dementia (in particular, aggression and agitation) may be the most common reason for patients being admitted to hospital or residential care (Ferris *et al.*, 1987; O'Donnell *et al.*, 1992).

A variety of pharmacological agents have been evaluated for the treatment of BPSD, including cholinergic agents, anticonvulsants, antidepressants, anxiolytics, hormonal preparations and neuroleptic drugs. Unfortunately, the reports often rely on anecdotal observations and/or open-label clinical trials (Porsteinsson *et al.*, 1997; Mintzer *et al.*, 1998). Neuroleptics have been studied more intensively than other agents have. Although available evidence supports the efficacy of the conventional neuroleptics, side effects, including the risk of irreversible movement disorders, extrapyramidal symptoms (EPS), anticholinergic effects and adverse drug interactions, are particularly problematic in this elderly patient population (Stoppe *et al.*, 1999; Schneider *et al.*, 1990).

Case-study reports of risperidone in elderly patients with dementia suggest that this agent may help to reduce behavioural symptoms, particularly agitation and aggression, and may increase interest in social activities, without substantial risk of EPS or sedation (Kopala and Honer, 1997; Jeanblanc and Davis, 1995; Madhusoodanan *et al.*, 1995). A recent open-label study of 109 nursing home patients with dementia demonstrated that risperidone may be useful for the treatment of behavioural symptoms (i.e. agitation, verbal outbursts, and physical aggression) (Goldberg and Goldberg, 1997).

The utility of risperidone in elderly patients with dementia and behavioural symptoms has been evaluated in two multi-centre, placebo-controlled, double-blind clinical trials (RIS-INT-24 and RIS-USA-63) (De Deyn *et al.*, 1999; Katz *et al.*, 1999). The primary objective of both studies was to compare the efficacy and tolerability of risperidone with that of placebo in the treatment of behavioural symptoms in patients with dementia. The

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secondary objective of the RIS-INT-24 study was to compare the tolerability (particularly with regard to EPS) and the general safety of risperidone with that of haloperidol. This section contains a review and comparison of the studies, together with additional analyses of the integrated dataset from the two studies. In addition, data on two long-term efficacy and safety studies (RIS-INT-26 and RIS-USA-70) are briefly presented. Our conclusion from these studies is that risperidone is an effective treatment for aggression and agitation in these patients. Risperidone also has a beneficial safety and tolerability profile, and so is particularly suitable for the treatment of aggressive behaviour in elderly people with dementia.

Table 1. BEHAVE-AD scoring for the aggressiveness cluster

Verbal outbursts
- 0—Not present
- 1—Present (including unaccustomed use of foul or abusive language)
- 2—Present and accompanied by anger
- 3—Present, accompanied by anger, and clearly directed at other persons

Physical threats and/or violence
- 0—Not present
- 1—Threatening behaviour
- 2—Physical violence
- 3—Physical violence accompanied by vehemence

Agitation (other than above)
- 0—Not present
- 1—Present
- 2—Present with emotional component
- 3—Present with emotional and physical component

MATERIALS AND METHODS

Design and patients

In the RIS-INT-24 trial, the effects of risperidone were compared with those of placebo (efficacy and tolerability) and haloperidol (tolerability). This 13-week double-blind study involved a total of 344 institutionalised elderly patients in centres across seven European countries and Canada. The patients, who had moderate to severe dementia (Alzheimer's disease, 67%; vascular dementia, 26%; mixed dementia, 7%), were randomly assigned to receive either placebo or flexible doses (0.5–4 mg/day) of risperidone or haloperidol. Behavioural symptoms were assessed using the Behavior Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), the Cohen-Mansfield Agitation Inventory (CMAI), and the Clinical Global Impression (CGI) scale (Guy, 1976; Reisberg *et al*., 1987; Cohen-Mansfield *et al*., 1989). (See Appendices 1 and 2 of this supplement for copies of the BEHAVE-AD and CMAI scales.) The BEHAVE-AD is a 25-item scale that measures behavioural symptoms in a total of seven clusters: paranoid and delusional ideation; hallucinations; activity symptoms; aggressiveness; diurnal rhythm symptoms; affective symptoms; anxieties and phobias. All items are scored on a four-point scale of increasing severity. The aggressiveness subscale score is the sum of three symptom scores (Table 1). Minor adaptations were made to the scale for use in an institutional setting. The BEHAVE-AD global score is a measure of behaviour deemed to be disturbing or dangerous to the patient or to those in their environment. The ratings are based on a four-point scale of increasing severity, as follows: 0, not disturbing or dangerous; 1, mildly disturbing or dangerous; 2, moderately disturbing or dangerous; and 3, severely disturbing or dangerous. The CMAI is a rating scale developed in nursing homes to assess a total of 29 agitated behaviours on a seven-point scale of increasing frequency. The cluster scores include physical, verbal and total aggression, and physical, verbal and total non-aggressive scores. CGI ratings by the investigator measured behavioural symptoms on a seven-point scale of increasing severity.

Tolerability assessments included Extrapyramidal Symptom Rating Scale (ESRS) scores (Chouinard *et al*., 1980), level of sedation, Functional Assessment Staging (FAST) scores, Mini-Mental State Examination (MMSE) scores, incidence of adverse events, laboratory tests, electrocardiogram, and vital signs.

The RIS-USA-63 trial was a US-based study in which the effects of fixed doses of risperidone (0.5 mg/day, 1 mg/day and 2 mg/day) were compared with those of placebo. The study involved 625 institutionalised elderly patients with severe dementia (Alzheimer's disease, 73%; vascular dementia, 15%; mixed dementia, 12%). The design, efficacy and safety outcome parameters of the study were very similar to those of the RIS-INT-24 study.

RESULTS

RIS-INT-24

A total of 344 patients completed washout and were randomly assigned to double-blind treatment with risperidone ($N = 115$), haloperidol ($N = 115$), or placebo ($N = 114$). Of these, 194 patients (56%) were women. The patients' median age was 81 years (range 56–97 years); the median time from the onset of dementia to trial entry was 4.3 years, and the median duration of institutionalisation was 4 months. Two hundred and twenty-nine patients (67%) had Alzheimer's dementia according to DSM-IV criteria, 90 (26%) had vascular dementia, and 25 (7%) had mixed dementia.

The three study groups were comparable at baseline with respect to demographic and disease characteristics. Most enrolled individuals had severe dementia [FAST stage 6 in 210 (61%); stage 7 in 106 (30.8%)] with poor cognitive function (mean MMSE scores of 7.9–8.8). The overall mean BEHAVE-AD total score at baseline was 16.5. Aggressiveness was the dominant symptom in these patients. The mean aggressiveness cluster score was 4.9 (more than 50% of the possible total score). The mean dose of medication received at endpoint was 1.1 mg/day in the risperidone group and 1.2 mg.day in the haloperidol group. At endpoint, 111 (96.5%) patients in the risperidone group were receiving a dose less than 2 mg/day, whereas only four patients (3.5%) were receiving 2 mg/day or more.

Differences between the risperidone and placebo groups were tested for statistical significance at endpoint and, for completers, at week 12 (Table 2). The therapeutic effect was most evident for aggressive symptoms. Risperidone was associated with significantly greater improvements than placebo in both the BEHAVE-AD aggression cluster score and the CMAI aggressiveness scores (total, physical, and verbal cluster) at both endpoint and week 12. The superior effect of risperidone was seen as early as week 2 of treatment, and was maintained over the next 10 weeks. Patients receiving risperidone also exhibited significantly greater global improvements (CGI severity ratings) than placebo-treated patients did, at both week 12 and endpoint.

The study focused on the effects of risperidone in a typical group of dementia patients, and so included patients with Alzheimer's disease, vascular dementia and mixed dementia. However, a sub-analysis was also performed, excluding patients with vascular dementia (Table 3). The results (mean shifts on BEHAVE-AD and CMAI scores) were consistent with those observed in the mixed group of dementia patients. At endpoint and at week 12, there were significantly greater improvements with risperidone than placebo on BEHAVE-AD aggressiveness score ($p = 0.03$ and $p = 0.01$, respectively) and CMAI total aggress-

Table 2. RIS-INT-24 study. Mean BEHAVE-AD and CMAI aggressiveness scores at baseline, and mean changes at week 12 and endpoint

	Baseline	Endpoint	Week 12
BEHAVE-AD aggressiveness			
Placebo	5.0	−0.8	−1.5
Risperidone	5.0	−1.7**	−2.99**†
Haloperidol	4.7	−1.6[a]	−1.8
CMAI total aggressive			
Placebo	27.5	−1.6	−4.9
Risperidone	25.6	−3.9**	−8.3*†
Haloperidol	26.3	−3.3	−3.6
CMAI physical aggressive			
Placebo	19.7	−0.7	−3.5
Risperidone	18.9	−2.7**	−5.9*
Haloperidol	19.3	−2.3	−2.8
CMAI verbal aggressive			
Placebo	7.7	−0.8	−1.4
Risperidone	6.8	−1.2**	−2.5**††
Haloperidol	7.0	−1.0	−1.8

* $p \leqslant 0.05$ vs placebo, ** $p \leqslant 0.01$ vs placebo. Additional analysis: [a] $p \leqslant 0.01$ vs placebo, † $p \leqslant 0.05$ vs haloperidol, †† $p \leqslant 0.01$ vs haloperidol.

Table 3. RIS-INT-24 study. Alzheimer's disease patients only. Mean BEHAVE-AD and CMAI aggressiveness scores at baseline, and mean changes at week 12 and endpoint

	Baseline	Endpoint	Week 12
BEHAVE-AD aggressiveness			
Placebo	4.7	−1.2	−1.8
Risperidone	4.9	−2.1*	−3.5**
Haloperidol	4.7	−2.2*	−2.2
CMAI total aggressive			
Placebo	27.1	−2.1	−4.8
Risperidone	25.7	−5.4*	−9.5*
Haloperidol	26.1	−4.4	−4.4

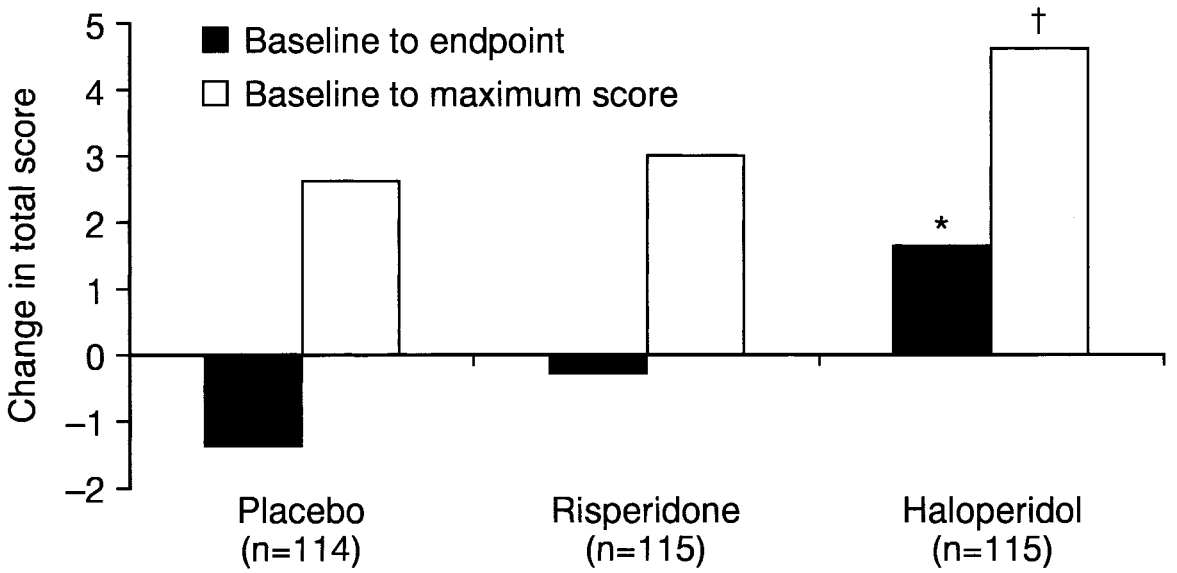

Fig. 1. RIS-INT-24 study. Mean change in ESRS total score from baseline to endpoint and from baseline to maximum score in the placebo, risperidone and haloperidol treated groups. * $p < 0.05$, † $p = 0.055$ vs risperidone

iveness scores ($p = 0.04$ and $p = 0.01$, respectively).

An additional post-hoc analysis compared haloperidol to risperidone and placebo on BEHAVE-AD and CMAI change scores. There were significantly greater improvements with risperidone than haloperidol on the BEHAVE-AD aggressiveness score ($p = 0.05$) and the CMAI total and verbal aggressive scores ($p = 0.02$ and $p = 0.01$, respectively) at week 12 (Table 2).

The severity of EPS (as measured by the ESRS total score) at endpoint was not significantly different between the risperidone and placebo groups; EPS associated with haloperidol was significantly greater than with risperidone (Fig. 1). Moreover, the incidence of EPS-related adverse events was not significantly different between patients receiving risperidone (15%) or placebo (11%); the incidence was significantly higher in those receiving haloperidol (22%) compared with placebo. Adverse events occurring in $\geqslant 10\%$ of patients in any one group were fall, injury, agitation, somnolence, and purpura. Of these, only somnolence occurred in more patients receiving active treatment than in those receiving placebo. There was no significant difference between the risperidone and placebo groups with respect to the change in MMSE score, during the study (Fig. 2). Thus risperidone maintained cognition during the trial period. However, the decline in MMSE scores with haloperidol was greater than that with placebo ($p < 0.05$), suggesting that haloperidol led to cognitive toxicity (mean changes: risperidone -0.5; placebo $+0.5$; haloperidol -2.1). There were no consistent changes or clinically relevant abnormalities in vital signs (blood pressure and heart rate), laboratory safety parameters, body weight, or ECG.

Lorazepam was the only permitted concomitant psychopharmacological agent (limited to 4 days a week during the first 4 weeks of double-blind treatment). The use of lorazepam was similar in the three groups (risperidone, $N = 34$, 30%; haloperidol, $N = 33$, 29%; and placebo, $N = 31$, 27%). Ratings of sedation, measured on a seven-point severity scale, remained low throughout the trial. There was a slight increase from baseline in the risperidone ($+0.5$) and haloperidol ($+0.5$) groups compared with placebo (-0.1) that was not considered to be clinically relevant. Based on the scores at endpoint, ratings of sedation in all three groups were between 'not present' and 'very low' (risperidone 1.8; placebo 1.4; haloperidol 1.9). To determine whether somnolence or sedation had

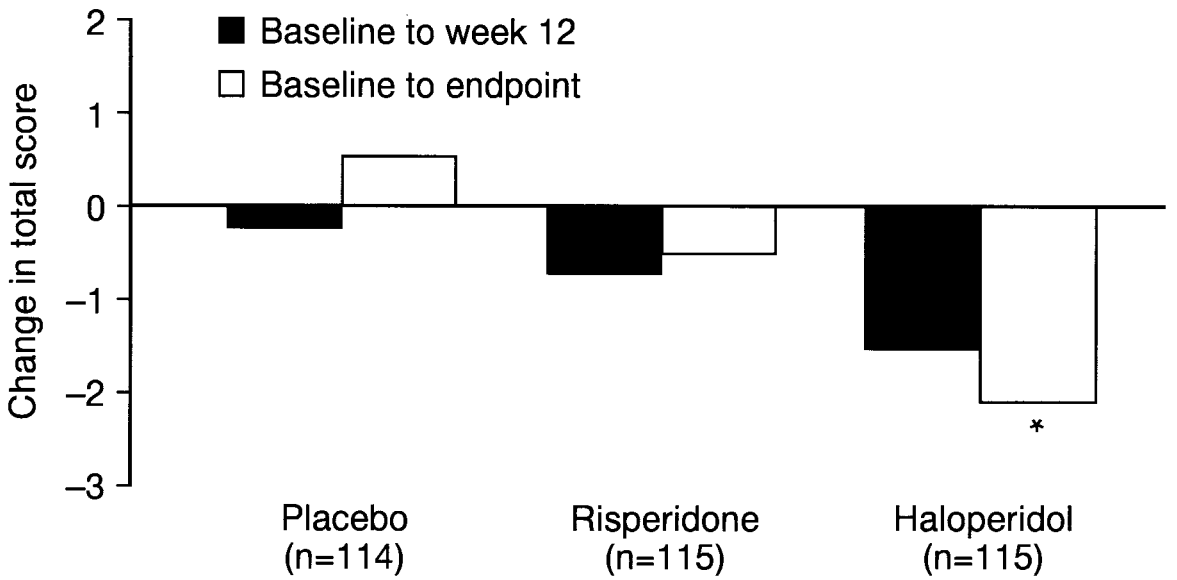

Fig. 2. RIS-INT-24 study. Mean change in MMSE total score from baseline to endpoint and from baseline to week 12 in the placebo, risperidone and haloperidol treated groups. * $p < 0.05$ vs placebo

influenced the outcome of the treatment with regard to behavioural symptoms, a post-hoc analysis was conducted, excluding those patients who had reported somnolence. The analysis showed that the reduction in behavioural symptoms with risperidone remained significantly greater than placebo, thus demonstrating that the effect of risperidone is not attributable to sedation.

RIS-USA-63

Treatment responses (defined post-hoc as a 50% or greater reduction in BEHAVE-AD total score) occurred in more patients receiving risperidone 1 mg/day (45%; $p = 0.02$) or risperidone 2 mg/day (50%; $p = 0.002$) compared with those receiving placebo (33%). At endpoint, patients receiving risperidone (1 or 2 mg/day) improved significantly more than placebo-treated individuals, as assessed by the BEHAVE-AD total and aggressiveness scores. In addition, treatment with risperidone (0.5 mg/day) was associated with a significant improvement on the BEHAVE-AD aggressiveness subscale at week 12. Effects of treatment on the CMAI score paralleled those on the BEHAVE-AD total score: patients receiving either 1 or 2 mg/day of risperidone exhibited significantly greater improvements than did placebo-treated patients at week 12 and endpoint on the verbal, physical, and total aggression scales of the CMAI. A sub-analysis excluding those individuals presenting somnolence or EPS also demonstrated significant improvements with risperidone. The effects of risperidone on the target symptoms could not therefore be attributed to indirect effects resulting from changes in somnolence or EPS. There were no significant changes in the severity of parkinsonism and hypokinesia (ESRS scores) in patients receiving 0.5 or 1 mg/day risperidone compared with placebo. At the highest dose of risperidone (2 mg/day) there were significant increases in scores on the parkinsonism total and hypokinesia scales compared with placebo. Tardive dyskinesia (TD) emerged in one patient receiving placebo and in none of the patients receiving risperidone. Other dose-related events included mild somnolence and peripheral oedema.

Analysis of the integrated dataset from the RIS-INT-24 and RIS-USA-63 trials

The assessments conducted in the two large phase III trials were very similar, so that an analysis of the combined data could be conducted. Demographic and baseline data for the RIS-INT-24 and RIS-USA-63 study populations were very

Table 4. Integrated dataset from the RIS-INT-24 and RIS-USA-63 combined populations. Mean BEHAVE-AD and CMAI aggressiveness scores at baseline, and percentage improvements at week 12 and endpoint

		Treatment			
		Placebo	Risperidone		
Behavioural score		$N = 275$	< 0.75 mg $N = 193$	$0.75 < 1.5$ mg $N = 203$	$\geqslant 1.5$ mg $N = 175$
BEHAVE-AD scores					
Aggressiveness	Baseline	4.9	4.6	5.0	5.0
	Week 12	29	48**	48**	62**
	Endpoint	16	28	36**	46**
Activity disturbances	Baseline	3.2	2.3	3.2	2.6
	Week 12	25	41*	31	42
	Endpoint	16	24	25*	27
Global rating	Baseline	1.8	1.8	1.9	1.8
	Week 12	22	33	37**	44**
	Endpoint	11	22	26**	33**
CMAI scores					
Physical aggressive	Baseline	19.6	19.2	20.1	19.4
	Week 12	34	44	59**	70**
	Endpoint	9	18	38**	48**
Verbal aggressive	Baseline	7.2	6.5	7.3	7.0
	Week 12	21	49**	47**	60**
	Endpoint	10	31**	30**	45**
Total aggressive	Baseline	26.8	25.7	27.4	26.5
	Week 12	30	45	56**	66**
	Endpoint	9	24	36**	46**

* $p \leqslant 0.05$, ** $p \leqslant 0.01$ vs placebo, ANCOVA with treatment, baseline, and trial interactions, when appropriate.

comparable. Sixty-five per cent of individuals in the studies were female; 91% were Caucasian, the mean age was 83 years (range 58–105 years); 72% suffered from Alzheimer's disease and 18% from vascular dementia. Mean baseline BEHAVE-AD scores were 16.5 and 15.5 for the RIS-INT-24 and RIS-USA-63 studies, respectively.

For the analysis of the integrated data, patients were categorised to one of four groups, based on the treatment which they had received: one placebo group and three risperidone groups (< 0.75 mg/day, 0.75–1.5 mg/day and > 1.5 mg/day). Risperidone was associated with dose-dependent improvements in aggressive/agitated symptoms as reflected by changes in the BEHAVE-AD aggressiveness and activity disturbances clusters, and also the CMAI physical, verbal and total aggression scores (Table 4). Figure 3 illustrates the beneficial effects of risperidone on BEHAVE-AD aggressiveness scores, in patients who did not report somnolence. Again, this demonstrates that the improvements which were associated with risperidone were not related to a sedative effect.

Open label extension studies (RIS-INT-26 and RIS-USA-70)

Each of the two phase III risperidone trials were followed by a planned 1-year open-label extension period, which allowed the long-term efficacy and safety of risperidone to be assessed in this elderly demented population. A total of 413 patients were enrolled in these extension protocols. Extended treatment with risperidone resulted in sustained efficacy in both trials. Figure 4 shows the CGI severity ratings made by the investigators during the extension study which followed RIS-INT-26. In addition, special attention was paid to the appearance of EPS, and in particular to TD.

Only one case of clinically observed TD was reported in the placebo-treated group of the RIS-USA-70 trial. Using a change of $\geqslant 2$ points on two

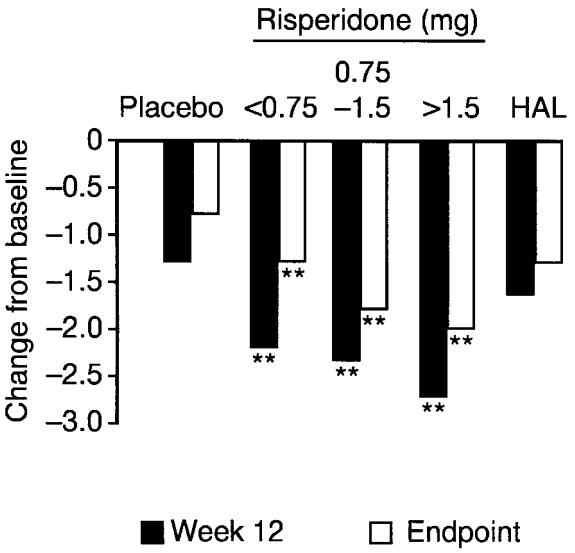

Fig. 3. BEHAVE-AD aggressiveness cluster scores. Mean changes from baseline to week 12 and baseline to endpoint in patients without somnolence. Integrated dataset from the RIS-INT-24 and RIS-USA-63 combined populations. * $p \leqslant 0.05$, ** $p \leqslant 0.01$ vs placebo

items of the ESRS or $\geqslant 3$ points on one item of the ESRS as the criterion for TD, a calculated 1-year incidence of 2.6% was observed in 255 patients. This is in contrast to expectations based on historical data observed in older populations where the incidence with typical neuroleptics is approximately an order of magnitude greater (Jeste *et al.*, 1995).

DISCUSSION

Risperidone is a selective dopamine D_2 and 5-HT_{2A} receptor antagonist, without affinity for muscarinic acetylcholine receptors, and is used widely as an antipsychotic. The clinical efficacy and safety profile of risperidone in the treatment of schizophrenia is well established and very favourable. We have reviewed the efficacy and safety data from two large randomised phase III clinical trials (total number of patients: 969) of risperidone in the treatment of BPSD, the RIS-INT-24 and RIS-USA-63 trials, and data from two long-term, 1-year follow-up trials, RIS-INT-26 and RIS-USA-70.

In the RIS-INT-24 trial (which included a total

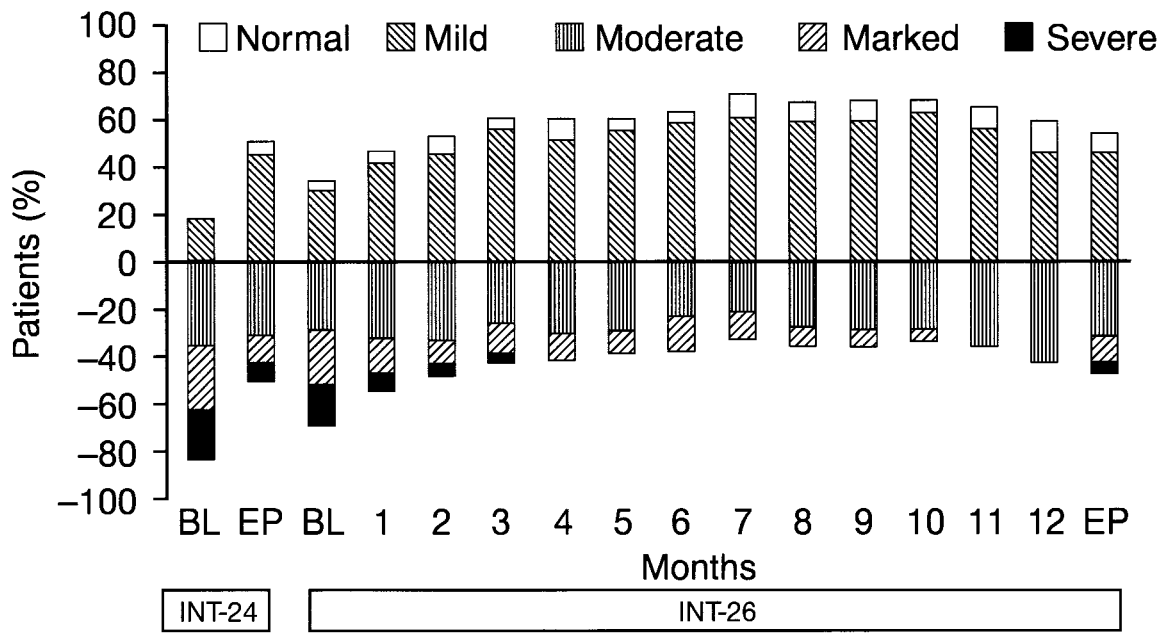

Fig. 4. Investigators' ratings of the severity of behavioural disturbances (CGI severity scale) in RIS-INT-24 and the 1-year open-label extension period (RIS-INT-26). The results shown are the percentage of patients rated as having severe, marked, moderate or mild disturbance, or not disturbed. BL: baseline; EP: endpoint

of 344 patients), which was a flexible dose trial, the mean doses at endpoint were 1.1 mg/day for risperidone and 1.2 mg/day for haloperidol. The most important symptom in these patients was aggression. During the period of the study, BEHAVE-AD and CMAI aggression cluster scores, as well as CGI scores, were significantly reduced in the risperidone group compared with placebo at endpoint and week 12. Risperidone had a significantly greater effect than haloperidol in completers, as indicated by week 12 improvements in the BEHAVE-AD aggressiveness score and the CMAI physical aggressive and verbal aggressive scores. A subanalysis excluding the patients who presented some degree of somnolence also demonstrated that risperidone was significantly superior to placebo in reducing aggressive symptoms. This indicates that the therapeutic effects demonstrated here were not caused by sedation, but are rather related to a specific pharmacological effect, possibly mediated in part via 5-HT_{2A} receptor antagonism (Mintzer *et al*., 1998).

The MMSE data presented in the RIS-INT-24 trial exclude significant adverse effects on cognition. The fact that risperidone has no anticholinergic effect may be important in this cognitively impaired population. In contrast, haloperidol led to significant cognitive decrements in this study.

Risperidone was well tolerated in this older frail population. In particular, the severity of EPS with risperidone did not differ from that with placebo and was significantly less than with haloperidol. In addition, fewer risperidone-treated patients (12%) reported somnolence, compared with those who received haloperidol (18%). The lack of interaction of risperidone with muscarinic receptors predicts a lack of peripheral (i.e. dry mouth, constipation, urinary retention) and central cholinergic side effects (i.e. cognitive impairment). Indeed, risperidone did not decrease performance on the MMSE and, other than minor EPS at higher dosages, the incidence of adverse events with risperidone was similar to that with placebo.

The RIS-USA-63 trial compared the efficacy and tolerability of fixed doses of risperidone (0.5 mg/day, 1 mg/day and 2 mg/day) vs placebo (Katz *et al*., 1999). The study included 625 patients with dementia (73% Alzheimer's disease, 15% vascular dementia and 12% mixed dementia), with significant behavioural and psychological symptoms. Similar outcome parameters were used as in the RIS-INT-24 trial. At endpoint, significantly greater reductions in BEHAVE-AD total score, and aggressiveness subscale scores, were observed in patients receiving 1 and 2 mg/day of risperidone compared with placebo-treated patients. However, more adverse events (EPS, somnolence and mild peripheral oedema) were reported in patients receiving 2 mg/day than with 1 mg/day risperidone. EPS were not significantly greater in patients receiving 1 mg/day of risperidone compared with placebo-treated patients.

Two long-term follow-up trials, involving a total of 413 patients who were treated for up to 12 months, yielded favourable data on the long-term efficacy and tolerability of risperidone, especially with regard to the low incidence of EPS, with an extremely low incidence of TD.

Findings from the two studies are consistent. Although we recognise the difficulties in combining data from fixed- and variable-dose studies, we have presented findings from analyses on the combined data set because the larger subject population of the combined data set may support more precise estimation of the benefits and risks of treatment. As with the individual studies, findings from the combined data suggest that doses of 0.75–1.5 mg/day of risperidone may optimise the therapeutic effects of treatment while minimising side effects. For most patients, the target dose will be 1 mg/day.

CONCLUSION

It is concluded that relatively low doses of risperidone (approximately 1 mg/day) are effective in reducing the severity and frequency of aggressive symptoms in elderly patients with dementia, and are very well tolerated by these elderly patients. Based on an extensive analysis of the data from these two innovative and well controlled clinical trials, together with extensive clinical experience with risperidone, an average dose of 1 mg/day per day is recommended for the treatment of the dementia patient with prominent aggressive behaviour.

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