REVIEW ARTICLE

Drug Safety 2000 Sep; 23 (3): 183-195
0114-5916/00/0009-0183/$20.00/0

A Risk-Benefit Assessment of Risperidone for the Treatment of Behavioural and Psychological Symptoms in Dementia

Michael Zaudig

Windach Institute and Hospital of Neurobehavioural Research and Therapy (WINTR)
Psychosomatic Hospital, Windach, Germany

Contents

Abstract

The importance of behavioural and psychological symptoms in dementia (BPSD) is increasingly being recognised. Symptoms such as verbal and physical aggression, agitation, sleep disturbances and wandering are common, cause great distress to caregivers and are likely to lead to institutionalisation of patients. At present, these symptoms are also more amenable to treatment compared with the progressive intellectual decline caused by dementing illnesses.

The care of individuals with BPSD involves a broad range of psychosocial treatments for the patient and his or her family. If pharmacotherapy is deemed nec-

essary to manage BPSD, a careful balance must be struck between the benefits of symptom control and the inherent risks associated with most psychotropic agents in the elderly. Elderly patients in general, and patients with dementia in particular, are more sensitive to medication adverse effects, including anticholinergic effects, orthostatic hypotension, sedation, parkinsonism, tardive dyskinesia and cognitive impairment than younger patients with dementia or individuals without dementia.

To date, treatment of symptoms of aggression and psychosis has relied on the empirical use of antidepressants, anxiolytics, typical antipsychotics (neuroleptics) and other agents. Treatment-limiting adverse effects are frequently reported with all of these agents. However, it is the typical antipsychotics and the atypical antipsychotic clozapine that are associated with the greatest risk of adverse effects in the elderly.

The present review highlights the issues that limit the use of older psychotropic agents in the elderly, and presents an assessment of the available evidence concerning the efficacy, safety and tolerability of the atypical antipsychotic risperidone, in the treatment of BPSD in elderly patients with dementia.

The extensive clinical development programme for risperidone has shown the drug to be effective and well tolerated in many fragile patients. As a result of its efficacy and safety profile, risperidone can be used for the treatment of behavioural and psychological symptoms in patients with dementia. Risperidone therefore represents a significant addition to the armamentarium for BPSD. While efforts continue in the development of treatment for the cognitive decline associated with dementia, treatment is now available for the noncognitive symptoms. By treating the latter, risperidone has the potential to be of substantial benefit to patients with dementia, their carers and the costs of healthcare.

1. Background

Dementias are generally characterised by a relentless and irreversible deterioration in a patient's intellect, personality and ability to function. Alzheimer's disease and cerebrovascular dementia are the most common primary dementias in the elderly, but many other diseases can have similar effects. These include Lewy body disease, Parkinson's disease, progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome), AIDS-related dementia and multiple sclerosis. Dementia is also associated with rare conditions such as Pick's disease, Wilson's disease, Creutzfeldt-Jakob disease and Huntington's chorea, among others.[1] What these diseases have in common is widespread cortical and/or subcortical pathology, with consequent intellectual deterioration.

Dementia has devastating effects on patients, their carers and their families. It also has a significant impact on healthcare resources and society in general. The burden is growing – changes in the demographic profiles of industrialised societies mean that there is an increasing proportion of elderly people and a consequent rise in the incidence of dementias.

1.1 Behavioural and Psychological Symptoms in Dementia (BPSD)

The progressive decline in cognitive function is regarded as a core feature of dementia.[2-5] However, it is increasingly being recognised that other aspects of the condition have a profound impact on both patients and their carers. The most salient of these are the behavioural and psychological symptoms of dementia (BPSD).[6] BPSD were reported by Alzheimer himself in a 51-year-old woman.[7] Both behavioural and cognitive symptoms are important in the evolution of Alzheimer's disease.[8]

Behavioural and psychological symptoms[9] are commonplace in dementia. At least half of patients attending outpatient dementia clinics and three-quarters of patients in nursing homes have some sort

of psychological or behavioural disturbance. About 80 to 90% of patients with dementia, regardless of aetiology, will exhibit behavioural and psychological symptoms at some time during the course of the disease.[10,11]

The origins of BPSD remain unclear, and there are multiple aetiologies for the symptoms. At present the best aetiological model is one that incorporates neurobiological aspects (neurochemical, neuropathological), psychological aspects (e.g. premorbid personality, response to stress) and social aspects (environmental change and caregiver factors).[12-14]

BPSD are varied. Table I lists the symptoms that are commonly encountered.[15] The most troublesome of these are verbal and physical aggression, agitation, sleep disturbances and wandering. These symptoms, notably aggression, agitation and psychosis, cause great distress to caregivers.

Aggression in particular is very difficult for caregivers to cope with[16] and is common in dementia, with over half of patients being either physically or verbally aggressive.[17] It is the leading cause of hospitalisation and institutionalisation in patients with dementia.[6,18-21] It may be suggested, therefore, that the core aim of treatment for patients with dementia may be to manage the distressing behavioural and psychological symptoms, rather than the progressive intellectual decline.[6,22]

Table I. The behavioural and psychological symptoms of dementia (reproduced from Luxenberg[15] with permission)

Behavioural symptoms	Psychological symptoms
Physical aggression	Delusions
Kicking	'My house is not my home'
Hitting	Suspiciousness
Biting	'People are stealing things'
Hurting self or others	Hallucinations
Verbal aggression	Anxiety
Screaming	Depression
Verbal sexual advances	Sleeplessness
Foul or abusive language	Misidentifications (Capgras' syndrome)
Agitation	Apathy
Wandering, particularly at night	
Sexual disinhibition	
Repetitive questioning	
Shadowing	

1.2 Diagnosis of BPSD

Given the variety of symptoms of BPSD, it can be difficult to diagnose. A consensus statement has been published, however,[22] and further guidelines are available.[15] In addition, a number of instruments have been developed to assess the range and severity of BPSD. These include the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Behaviour Rating Scale for Dementia (C-BRSD),[23,24] and the Neuropsychiatric Inventory (NPI),[25] amongst others. The Brief Psychiatric Rating Scale (BPRS)[26] has also been used, though it was not specifically developed for dementia. Perhaps the most useful, in terms of outcomes assessment, are the Cohen-Mansfield Agitation Inventory (CMAI)[27,28] and the Behavioural pathology in Alzheimer's disease (BEHAVE-AD) rating scale.[29] These last 2 are particularly useful because of their specificity, reliability and validity in BPSD.

1.3 Management of BPSD

The care of individuals with BPSD involves a broad range of psychosocial treatments for the patient and his or her family.[30-32] These include thorough diagnostic evaluations, careful consideration of the aetiology of the dementia and the exclusion of other symptom causes, such as drug-induced delirium or adverse effects of treatment of comorbid conditions.[22] Environmental adjustments, such as improved accommodation and lifestyle support are generally first-line interventions.[32,33] Treatment for psychosis is guided by the patient's level of distress, agitation or aggression, and the risk that those behaviours present to the patient and the caregiver. Most cases of aggression, agitation and psychotic symptoms will require pharmacotherapy.[34]

If pharmacotherapy is deemed necessary to control behavioural or psychological symptoms of dementia, a careful balance must be struck between the benefits of symptom control and the inherent risks associated with most psychotropic agents in the elderly.[35,36] Changes in pharmacokinetics and pharmacodynamics, and alterations in the structure

and function of vital organs all conspire to create problems in the rational prescribing of therapeutic agents in the elderly.

To date, treatment of symptoms of aggression and psychosis has relied on the empirical use of antidepressants, anxiolytics, typical antipsychotics (neuroleptics) and other agents. Unfortunately, there has been a lack of systematic studies supporting the use of these drugs in BPSD.[36,37] The few randomised, placebo-controlled trials that have been carried out have generally been small scale and of short duration. Thus, there is little, in evidence-based medicine terms, to recommend the majority of drugs currently used for BPSD.

An exception is risperidone, a balanced serotonin (5-hydroxytryptamine, 5-HT)-dopamine antagonist (SDA). This is the first agent that has been proven to be effective for the behavioural and psychological symptoms of dementia.[38,39] The trial reported by Katz et al.[38] was the first large scale, double-blind, placebo-controlled assessment of the efficacy and safety of risperidone in the treatment of BPSD. The results demonstrate that risperidone is effective in controlling aggression, agitation and psychotic symptoms in patients with many different forms of dementia. In addition, risperidone was well tolerated, was not associated with an increased risk of extrapyramidal symptoms (EPS) or tardive dyskinesia, and did not further impair the daily function of elderly patients with dementia.

The present review highlights the issues that limit the use of older psychotropic agents in the elderly, and presents an assessment of the available evidence concerning the efficacy, safety and tolerability of risperidone in the treatment of BPSD in elderly patients with dementia.

2. Special Requirements for Prescribing in Elderly Patients with Dementia

In planning the treatment of behavioural and psychological symptoms associated with dementia, it is important to recognise the special needs of elderly patients. Aging is characterised by progressive loss of the functional capacities of all the vital organs, including the brain. There is a also an alteration in body composition.[40,41] These developments mean that elderly patients are more sensitive to both the therapeutic and adverse effects of drug treatment.

One of the most important pharmacokinetic changes in old age is a decrease in the excretory capacity of the kidney, causing many drugs to be eliminated from the body more slowly. Changes in drug distribution are also important. Age-related reductions in liver mass, hepatic blood flow and hepatocyte function also mean that drugs metabolised in the liver will have a delayed clearance. For many medications, this means that lower starting doses, smaller dose increments and longer dose-escalation periods must be used to avoid potentially toxic drug accumulation.[40]

Concurrent illnesses and associated polypharmacy are extremely common in elderly patients. Consideration of potential drug-drug interactions is therefore often unavoidable. General medical conditions and other medications may alter the binding, metabolism and excretion of drugs used to treat BPSD. This can result in adverse effects when 1 drug interferes with the action or metabolism of another, causing elevated plasma concentrations.[42]

Elderly patients in general, and patients with dementia in particular, are more sensitive to certain medication adverse effects, including anticholinergic effects (e.g. dry mouth, constipation, agitation and delirium), orthostatic hypotension, sedation, parkinsonism, tardive dyskinesia and cognitive impairment than younger patients with dementia or individuals without dementia.[43-47] In the case of tardive dyskinesia, for example, patients beginning treatment with typical antipsychotics in their fifth decade are 3 to 5 times more likely to experience this adverse effect than younger patients, despite the lower dosages used.[47] Elderly patients are also particularly prone to falls, and drugs that cause sedation, postural hypotension or EPS have been found to cause an increased incidence of falls.[48-51] The elderly are also likely to experience more serious consequences of falls, such as fractures.[52]

Table II. Receptor affinities of 4 antipsychotic agents

Receptor	Risperidone	Olanzapine	Quetiapine	Haloperidol
Muscarinic M_1	–	+++++	+++	–
Histamine H_1	++	++++	++++	–
α_1-adrenergic	+++	+++	++++	++
Dopamine D_2	++++	+++	++	+++++
Serotonin 5-HT_2	+++++	++++	+	+

5-HT = 5-hydroxytryptamine; – = no affinity; + = very low affinity; ++ = low affinity; +++ = moderate affinity; ++++ = high affinity; +++++ = very high affinity.

3. Treatment-Limiting Adverse Effects of Antipsychotics and Other Agents

Historically, several different classes of drugs have been used in an empirical manner to treat behavioural and psychological symptoms associated with dementia. These include antidepressants, anxiolytics, anticonvulsants, lithium, typical antipsychotics and the first atypical antipsychotic to be developed, clozapine.[53] Although clinical experience has suggested that such treatments may provide some benefits in patients with dementia,[54-59] no systematic studies of these drugs in the management of BPSD have been conducted.[36,37]

Treatment-limiting adverse effects are frequently reported with all of these agents. Antidepressants (particularly the tricyclic antidepressants) are associated with a risk of hypotension and potentially severe anticholinergic effects. Anxiolytics, notably the benzodiazepines, may produce over-sedation and impairment of cognitive function, or increased aggression and confusion, exacerbating patient management problems. However, it is the typical antipsychotics and clozapine that are associated with the greatest risk of adverse effects in the elderly.[59,60] Furthermore, despite perceptions to the contrary, typical antipsychotics are relatively ineffective. A meta-analysis conducted in 1990[57] indicated that treatment with thioridazine and haloperidol benefitied only 18% of patients (beyond the effect of placebo). This is consistent with the modest efficacy reported in previous qualitative reviews.[35,36]

Typical antipsychotics are associated with a high risk of adverse effects.[35,59,60] These agents are the most commonly used to treat aggression, agitation and psychotic symptoms associated with dementia – the most difficult symptoms, but also the most amenable to treatment. The problem is that the dosages that are sufficient to be effective are associated with a high rate of troublesome or serious adverse effects.[59,60] There is also evidence that typical antipsychotic drugs can hasten the progression of Alzheimer's disease and worsen the patient's already compromised cognitive function.[61,62] McShane et al.[63] reported that the rate of decline in patients who took typical antipsychotics was double that of patients who did not. The difference was not explained by cortical Lewy body pathology, which was investigated at necropsy (typical antipyschotics have serious, potentially fatal, consequences in patients with Lewy body disease) (see section 3.1).

The adverse effects associated with all antipsychotics vary according to the potency of the drugs and their affinity for different receptors.[64,65] Table II summarises the receptor affinities of 3 atypical antipsychotics and haloperidol. Sections 3.1 to 3.4 examine the adverse effects that may be linked to these different receptor-binding profiles.

3.1 Extrapyramidal Symptoms and Tardive Dyskinesia

EPS, e.g. akathisia, akinesia, parkinsonism and tardive dyskinesia (antipsychotic-induced oral-buccal dyskinesia) are most strongly associated with high potency antipsychotics, such as haloperidol and fluphenazine.[37] It is generally believed that dopamine D_2 receptor blockade in the nigrostriatal system gives rise to EPS, whereas D_2 receptor blockade in the mesolimbic system is associated with antipsychotic efficacy. In comparison with the typical antipsychotics, atypical antipsychotics are mostly se-

lective for the mesolimbic system and are therefore effective, but are associated with much lower rates of EPS.

The symptoms of EPS are very distressing for both the patient and their caregiver and can result in an increased incidence of falls.[48-50] The probability of developing tardive dyskinesia after antipsychotic treatment is also known to be higher in the elderly than in younger patients,[47,66,67] with an annual incidence of 25 to 30% being reported.[44,47,66,68] One recent report[69] concluded that the risk of tardive dyskinesia in older outpatients is high, even with relatively short treatment courses of low dose typical antipsychotics.

It should be noted that EPS are generally worse in patients with Lewy body dementia[70] and can be exacerbated by antipsychotic treatment. Severe and often fatal sensitivity to typical antipsychotics has been described in patients with this condition and these drugs should not be given to such patients.[71,72]

3.2 Anticholinergic Adverse Effects

Anticholinergic adverse effects are mediated by central and peripheral binding to cholinergic muscarinic receptors. The morbidity and management issues associated with unwanted anticholinergic activity are underestimated and frequently overlooked.[43] Anticholinergic adverse effects are common and are often viewed as 'unavoidable' or as a normal part of the ageing or disease process. Psychotropic agents that have anticholinergic adverse effects can increase the toxicity associated with co-administered antidepressants, including the selective serotonin reuptake inhibitors and tricyclic antidepressants, and drugs commonly used for other geriatric conditions, such as Parkinson's disease.[73] Low potency typical antipsychotics (e.g. thioridazine, chlorpromazine) are associated with the most severe anticholinergic adverse effects.[37] Table III provides a summary of body systems affected by anticholinergic adverse effects and their potential consequences in elderly patients.[43]

Peripheral anticholinergic effects include decreased secretions, slowed gastrointestinal motility, blurred vision and increased heart rate. These may be uncomfortable for a younger patient in relatively good health, but they may be disastrous for older patients.[43] The most common adverse effect, dry mouth, appears trivial at first sight, but can lead to increased risk of serious respiratory infection, dental or denture problems, impaired nutritional status and a reduction in the ability to communicate.

Table III. Systems affected by cholinergic impairment and patient outcomes (reproduced from Feinberg[43] with permission)

System impairment	Potential outcome
Vision	Impaired activities of daily living
	Falls and other accidents
Oral cavity	Decreased nutritional status
	Increased risk of infection
	Impaired communication
Gastrointestinal tract	Decreased nutritional status
	Worsening of disease
	Anxiety, pain
Cardiovascular system	Worsening of disease
	Anxiety
Urinary tract	Incontinence
	Infection
	Loss of independence
CNS	Cognitive dysfunction
	Impaired activities of daily living

Other peripheral anticholinergic effects include constipation, causing pain, faecal compaction and increased use of laxatives,[43,74] and urinary retention, resulting in discomfort, urinary tract infections and an increased need for catheterisation. Catterson et al.[40] note the potential for a 'vicious circle' of treatment and adverse effects. Faecal impaction occurs frequently in patients with dementia and can cause agitation because of the associated discomfort. If the agitation is treated with an antipsychotic that has anticholinergic properties, then this will worsen the impaction and aggravate the agitation. Finally, visual impairments, such as mydriasis, may increase the risk of accidents and can precipitate narrow-angle glaucoma in patients predisposed to this condition.[43]

Central anticholinergic effects range from sedation, confusion and inability to concentrate to frank delirium, agitation, hallucinations and severe cognitive decline.[43,45] Even mild central effects can reduce cognitive function and so increase depend-

ency, resulting in greater caregiver burden, increased costs, reduced quality of life and impaired activities of daily living.[43,45] At the other end of the spectrum, delirium, which is present in 10 to 25% of elderly inpatients, has an associated mortality rate of up to 40%.[45] Anticholinergic drugs are implicated in at least 40% of delirium cases among the hospitalised elderly.[75] Hallucinations are particularly common in patients with Lewy body disease[76] and are likely to be treated with typical antipsychotics – a course of action that can potentially result in fatal sensitivity reactions.[71,72]

Sedation caused by anticholinergic drugs can be worsened if symptoms of BPSD are treated with sedative agents, such as benzodiazepines. This increases the patient's risk of falls and other accidents.[51,52]

Alzheimer's disease is the most common primary dementia in the elderly. A number of mechanisms have been suggested for the disease process, but the fall in acetylcholine level is the most consistent change associated with the condition and the only one that correlates closely with both the characteristic neuropathological changes and with the severity of the disease.[77] The most successful treatment strategy for Alzheimer's dementia so far is to increase the available acetylcholine by inhibiting the enzyme responsible for its metabolism. It is clear that adding a drug with anticholinergic effects is likely to worsen the disease process, and this may account for the decline in patients treated with certain agents.[45,61,62,63]

3.3 Postural Hypotension

Orthostatic (postural) hypotension resulting from adrenergic α_1-receptor blockade may result in more clinically serious consequences for older patients. Low potency typical antipsychotics, such as thioridazine and chlorpromazine, and clozapine are associated with a high risk of postural hypotension.[78] This adverse effect has been found to increase the risk of falls in the elderly. As previously mentioned, falls in the elderly are associated with serious consequences.[51,52] It is not difficult to imagine a chain of events such as sedation or postural hypotension leading to a fall, subsequent hip fracture and more serious sequelae – hospitalisation and pneumonia, for example.

3.4 Agranulocytosis

Clozapine causes a decline in white blood cell counts in some patients, leaving them highly vulnerable to infection. This decline can lead to the life-threatening and occasionally fatal condition, agranulocytosis. Consequently, complete blood counts need to be monitored vigilantly throughout treatment. Among the antipsychotic agents, this particular adverse effect was thought to be peculiar to clozapine. However, recent case reports have suggested that neutropenia and agranulocytosis may also occur with the structurally similar drug, olanzapine.[79,80]

4. What is the Evidence that Risperidone is Effective?

The novel antipsychotic, risperidone, transformed the treatment of schizophrenia when it was first introduced in 1993.[81] Risperidone is the first SDA to have been shown in a series of well controlled clinical trials to be effective and well tolerated in the management of BPSD, including symptoms such as aggression, agitation, hallucinations and delusions.

Risperidone has a generally favourable receptor binding profile. It has a high affinity for D_2 receptors and for 5-HT_{2A} receptors. Risperidone has no detectable muscarinic activity and only moderate activity at histamine H_1 and α_1-adrenergic receptors.[64] These characteristics mean that it is effective in treating BPSD, but is not associated with the poor tolerability and adverse effects caused by older antipsychotic drugs, particularly in the elderly.[82]

4.1 Risperidone and the Control of Aggressive Behaviour and Psychosis

Risperidone is the first novel antipsychotic shown to be effective for behavioural and psychological symptoms associated with dementia.[38,39] The good efficacy and tolerability of the drug is supported by an extensive clinical trials programme –

the first large scale, well controlled clinical evaluation of any pharmacological treatment for behavioural and psychotic symptoms associated with dementia. Investigations include the following: 3 open studies;[83-85] an open, comparative retrospective investigation;[86] a double-blind, placebo-controlled study in patients with Alzheimer's disease;[87] and 2 pivotal, double-blind, placebo-controlled, parallel-group phase III studies.[38,39] Clinical trials have mainly examined patients with Alzheimer's disease, vascular dementia or mixed dementia – these 3 conditions comprise over 90% of patients with dementia.

The phase III pivotal studies[38,39] were the first to demonstrate the efficacy of an SDA in BPSD under-rigorously controlled conditions. De Deyn et al.,[39] for example, reported a study involving 344 patients with dementia (Alzheimer's disease, vascular dementia or mixed dementia). Patients were randomised to receive placebo or flexible doses (0.5 to 4.0mg) of risperidone or haloperidol. Efficacy was assessed using the BEHAVE-AD, the CMAI and the Clinical Global Impression (CGI) scale. A number of tolerability assessments were carried out, including the Extrapyramidal Symptom Rating Scale (ESRS).

At the end of the 13-week study (12 weeks of treatment following a 1-week placebo washout), the mean dosage of risperidone was 1.1 mg/day and the mean dosage of haloperidol was 1.2 mg/day. Statistical analyses showed that improvements in the BEHAVE-AD total score were significantly greater in patients who received risperidone compared with those in the placebo group, particularly for aggressive symptoms (BEHAVE-AD and CMAI aggression clusters). A *post hoc* analysis showed significantly greater reductions in the BEHAVE-AD aggressiveness score and the CMAI total and verbal aggressive scores in patients treated with risperidone compared with the haloperidol group at week 12. The severity of EPS with risperidone did not differ from placebo and was less than that encountered with haloperidol.

A pooled analysis of the 2 phase III trials showed that risperidone produced a significant improvement over placebo on all efficacy parameters.[88] Aggressive behaviour, agitation, psychotic symptoms, physical destructiveness, verbal disruption, pacing and aimless wandering, negativism and sexually inappropriate behaviour were all significantly reduced in patients taking risperidone.[88] The beneficial effects of risperidone on BPSD were shown to be independent of sedation and EPS, and were not linked to psychosis or an improvement in psychotic symptoms.[38]

The long term benefits associated with risperidone in the management of aggressive behaviour and psychosis have also been demonstrated in an open-label extension study.[89]

5. What Are the Risks Associated with Risperidone?

The safety and tolerability of risperidone in the treatment of this fragile patient population has been excellent in all clinical studies to date. Safety and tolerability in the 2 pivotal trials were evaluated using the ESRS, ratings of sedation, Functional Assessment Staging scores, Mini-Mental State Examination (MMSE), adverse event recording, laboratory tests, electrocardiogram, bodyweight and vital signs. The results of these assessments are discussed in sections 5.1 to 5.7.

5.1 Extrapyramidal Symptoms

Because of their importance, EPS have been closely monitored in studies of novel antipsychotics, including those of risperidone. One of the most reliable and sensitive investigative tools for EPS is the ESRS.[90] The ESRS is comprehensive, with provision for rating all neurological syndromes associated with the use of antipsychotics. It allows for evaluation of subjective symptoms as well as signs, has defined anchor points sufficiently widely spread to render the scale sensitive to change, and rates hyperkinetic disorder on the twin axes of frequency and amplitude, thus offering the prospect of enhanced reliability in these items. Furthermore, the various subscales allow different manifestations of drug-related movement disorders to be considered separately.

In the 2 pivotal trials, the risk of EPS associated with risperidone at the recommended clinical dosage of 1.0 mg/day (for symptoms of aggression and psychosis in the elderly) was not significantly different from that associated with placebo.[38,39] ESRS scores indicated that the risk of EPS was significantly lower with risperidone (mean dosage = 1.1 mg/day) than with haloperidol (mean dosage = 1.2 mg/day; $p < 0.05$)[39] (figs 1 and 2).

Katz et al.[38] reported that the severity of parkinsonism and hypokinesia, as measured by the ESRS, did not differ significantly between patients treated with risperidone, 0.5 to 1.0 mg/day, and placebo. They did note, however, that the effect of risperidone, 2 mg/day, was significantly different from placebo on these scales. Figure 3 illustrates these findings.

Only 1 case of tardive dyskinesia was reported in the pivotal phase III studies, and that occurred in the placebo treatment group.[38,39] In addition, during two 12-month, open-label extensions to these studies involving 413 patients, only 1 case of *de novo* tardive dyskinesia was observed – an incidence of 0.2%.[88] This rate is comparable to that reported in studies of younger patients treated for psychosis.[91]

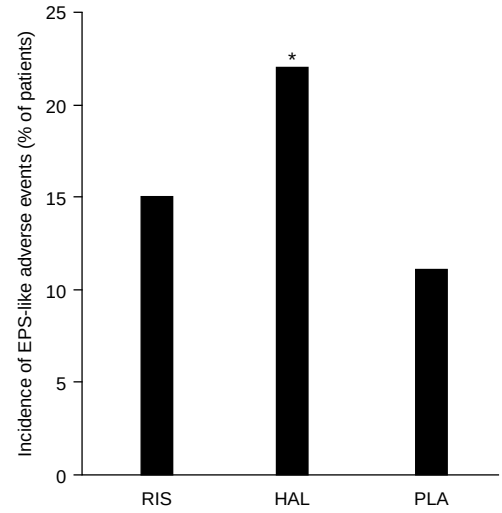

Fig. 1. Occurrence (total incidence) of extrapyramidal symptoms (EPS) in patients receiving risperidone (RIS) [mean dose = 1.1mg], haloperidol (HAL) [mean dose = 1.2mg] or placebo (PLA).[39] *$p < 0.05$ versus placebo.

5.2 Sedation and Cognitive Function

In the clinical trials, sedation was rated on a 7-point rating scale.[39] Ratings of sedation were very low at the start of the study and remained so over the course of the study. At all the time points tested, in all groups (risperidone, haloperidol and placebo), the mean scores were in the range 1 to 2 ('not present' to 'very mild'). The very small changes in the sedation rating scores that were observed were not considered to be clinically relevant. Overall, only 15% of patients in the phase III studies reported somnolence as an adverse event.[88]

Cognitive function in these studies was measured by the MMSE. At the end of the study by Katz et al.,[38] mean MMSE scores were reduced by 0.74 in patients receiving risperidone, 1 mg/day, and by 0.64 in those receiving the 2 mg/day dosage. There were no significant differences between these changes and those in the patients who received placebo. Similarly, De Deyn et al.[39] report no decline in cognition, as measured by the MMSE. Furthermore, there was no evidence of an association between risperidone and a deterioration in functional status (Functional Assessment Staging).

5.3 Anticholinergic Effects

Unsurprisingly, treatment with risperidone was not associated with any significant change in the incidence of anticholinergic effects.[38,39] The incidence of symptoms such as abnormal vision, dry mouth, constipation and urinary retention in patients treated with risperidone was comparable with placebo.[38,39]

Because risperidone has no affinity for muscarinic receptors, and consequently no anticholinergic effects, its withdrawal does not cause cholinergic rebound.[92,93] The symptoms of cholinergic rebound can range from nausea and vomiting to severe agitation and delirium. These effects occur on withdrawal of anticholinergic agents including some novel antipsychotics, such as clozapine.[94,95] When patients are switched from an anticholiner-

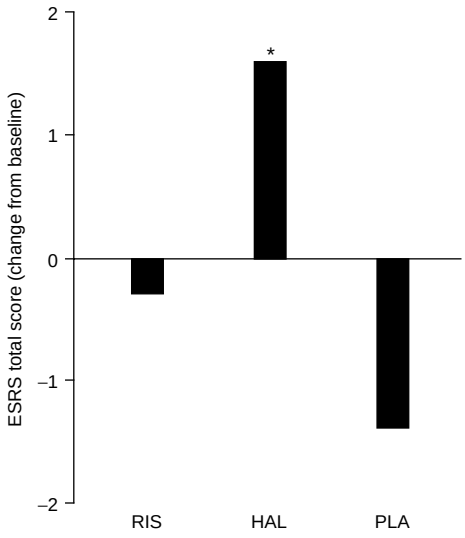

Fig. 2. Changes from baseline in the severity of extrapyramidal symptoms [Extrapyramidal Symptoms Rating Scale (ESRS) total score] in patients receiving risperidone (RIS) [mean dose = 1.1mg], haloperidol (HAL) [mean dose = 1.2mg] or placebo (PLA).[39] *p < 0.05 versus risperidone and placebo.

gic antipsychotic drug to risperidone, care should therefore be taken to avoid cholinergic rebound, as risperidone will not suppress the sudden increase in acetylcholine that occurs as part of the withdrawal phenomena.

5.4 Cardiovascular Safety

No clinically relevant changes in blood pressure or heart rate were seen in the phase III studies.[38,39] A minor dose-dependent increase in the proportion of patients with hypotension has been observed in some studies, so caution is advised when treating patients with cardiovascular disease.[88] No differences between risperidone and placebo have been observed in the occurrence of electrocardiogram abnormalities (including prolonged QTc interval) in these studies.[38,39,88]

5.5 Bodyweight

No clinically significant changes in bodyweight were seen after risperidone treatment.[38,39] The increase in bodyweight recorded in patients treated with risperidone ranged from 0 to 0.6kg after 12 weeks of treatment, whereas placebo and haloperidol recipients lost 1.2kg and 0.3kg, respectively.[88] It has been suggested that a small bodyweight gain may be advantageous in frail elderly patients. However, the bodyweight gain generally seen with antipsychotics – mainly the older antipsychotics but also some atypical antipsychotics, such as olanzapine and clozapine[96] – is probably attributable to an increase in body fat, rather than muscle mass. If this is the case, then bodyweight gain is unlikely to have clinically beneficial effects.

5.6 Laboratory Parameters and Drug Interactions

No consistent abnormalities in laboratory parameters have been identified after risperidone treatment.[38,39]

A number of drug-drug interaction studies have been undertaken.[97] No clinically significant interactions between risperidone and digoxin, aspirin, lactulose, levothyroxine, lorazepam or paracetamol have been observed.

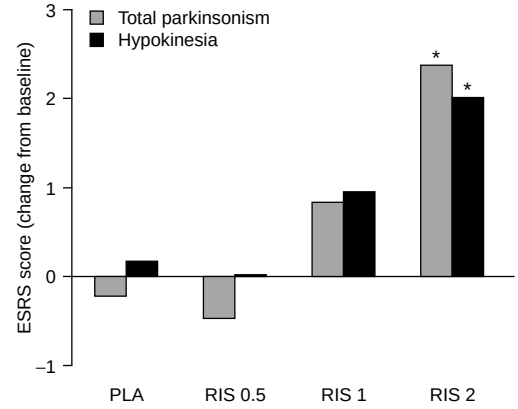

Fig. 3. Changes from baseline in scores on the total parkinsonism and hypokinesia scales of the Extrapyramidal Symptom Rating Scale (ESRS) for risperidone 0.5 mg/day (RIS 0.5), 1.0 mg/day (RIS 1), 2.0 mg/day (RIS 2), and placebo (PLA)[38] *p < 0.001 versus placebo.

5.7 Long Term Safety

Long term observations of the safety of risperidone are compatible with the data derived from the randomised, controlled trials. Open extensions to the phase III studies have found no clinically significant adverse events or changes in vital signs or laboratory parameters with the long term use of risperidone for up to 1 year.[89,98]

6. Conclusions: the Risks and Benefits of Risperidone in Clinical Practice

The extensive clinical development programme for risperidone in the treatment of behavioural and psychotic symptoms associated with dementia has shown the drug to be effective and well tolerated in many fragile patients. Risperidone is effective in controlling psychosis and aggressive behaviour in dementias caused by Alzheimer's disease, vascular dementia or mixed dementias.

As a result of its efficacy and safety profile, risperidone can be used for the treatment of behavioural and psychological symptoms in patients with dementia who have symptoms such as aggressiveness (e.g. verbal outbursts, physical violence), activity disturbances (e.g. agitation) or psychotic symptoms (e.g. delusions, hallucinations). The recommended starting dosage of risperidone for all patients with BPSD patients is 0.5 mg/day, which should be used for at least 2 days. The dosage can then be individually adjusted by increments of 0.5 mg/day. The optimum dosage is 1.0 mg/day for most patients.

Risperidone is the first SDA to be established as having proven efficacy and safety in the treatment of the behavioural and psychological symptoms of dementia. As such, it represents a significant addition to the armamentarium for BPSD. While efforts continue in the development of treatment for the cognitive decline associated with dementia, treatment is now available for the noncognitive symptoms. By treating the latter, risperidone has the potential to be of substantial benefit to patients with dementia, their carers and the costs of healthcare.

Acknowledgements

Preparation of this article was supported by funding from the Janssen Research Foundation, Beerse, Belgium.

References

1. Peretz, JA, Cummings JL. Subcortical dementia. In: Holden U, editor. Neuropsychology and ageing. London: Croom Helm, 1988: 70-120
2. Reisberg B, Ferris SH, de Leon MJ, et al. The Global Deterioration Scale (GDS): an instrument for the assessment of primary degenerative dementia. Am J Psychiatry 1982; 139: 1135-9
3. Rosen WG, Mohs RC. Evolution of cognitive decline in dementia. In: Corkin S, editor. Alzheimer's disease: a report of progress. Ageing, Vol 19, New York (NY): Raven Press, 1982: 183-8
4. Roth M, Tomlinson BE, Blessed G. Correlation between scores for dementia and counts of 'senile plaques' in cerebral grey matter of elderly subjects. Nature 1966; 209: 109-10
5. Miller E, Morris R. The psychology of dementia. Chichester: John Wiley & Sons Ltd., 1993: 1-63
6. Victoroff J, Mack WJ, Nielson KA. Psychiatric complications of dementia: impact on caregivers. Dement Geriatr Cogn Disord 1998; 9: 50-5
7. Alzheimer A. Über einen eigenartigen schweren Erkrankungsprozeß Hirnrinde. Neurologisches Centralblatt 1906; 23: 1129-36
8. Alzheimer A. Über eigenartige Krankheiten des späteren Alters. Zeitschrift für die gesamte Neurologie und Psychiatrie 1911; 4: 356-85
9. Finkel SI, Luxenberg J, Zaudig M, et al. Behavioral and psychological symptoms of dementia. Educational pack. Macclesfield: Gardiner-Caldwell Communications Limited, 1998
10. Finkel SI. The significance of the behavioural and psychological symptoms of dementia. Clinician 1998; 16: 33-42
11. Tariot PN, Blazina L. The psychopathology of dementia. In: Morris JC, editor. Handbook of dementing illnesses. New York (NY): Marcel Dekker Inc., 1994: 461-75
12. Zaudig M. Assessing behavioral symptoms of dementia of the Alzheimer type. Categorical and quantitative approaches. Int Psychogeriatr 1996; 8 Suppl. 2: S183-S200
13. Zaudig M. Behavioral disturbances of dementia in DSM-IV and ICD-10: fact or fiction? Int Psychogeriatr 1996; 8 Suppl. 3: S285-S288
14. Zaudig M. Etiology of BPSD. Module 3. In: Finkel SI, Luxenberg J, Zaudig M, et al., editors. Behavioral and psychological symptoms of dementia. Educational pack. Macclesfield: Gardiner-Caldwell Communications Limited, 1998
15. Luxenberg J. Clinical issues in BPSD. Module 2. In: Finkel SI, Luxenberg J, Zaudig M, et al., editors. Behavioral and psychological symptoms of dementia. Educational pack. Macclesfield: Gardiner-Caldwell Communications Limited, 1998
16. Argyle N, Jestice S, Brook CPB. Psychogeriatric patients: their supporters' problems. Age Ageing 1985; 14: 355-60
17. Eastley R, Wilcock GK. Prevalence and correlates of aggressive behaviours occurring in patients with Alzheimer's disease. Int J Geriatr Psychiatry 1997; 12: 484-7
18. Burgio L. Interventions for the behavioural complications of Alzheimer's disease: behavioural approaches. Int Psychogeriatr 1996; 8 Suppl. 1: S45-S52
19. Colerick EJ, George LK. Predictors of institutionalization among caregivers of patients with Alzheimer's disease. J Am Geriatr Soc 1986; 34: 493-8

20. Everitt DE, Fields DR, Soumerai SS, et al. Resident behavior and staff distress in nursing homes. J Am Geriatr Soc 1991; 39: 792-8
21. Steele C, Rovner B, Chase GA, et al. Psychiatric symptoms and nursing home placement of patients with Alzheimer's disease. Am J Psychiatry 1990; 147: 1049-51
22. Finkel SI, Costa E, Silva J, et al. Behavioral and psychological signs and symptoms of dementia: a consensus statement on current knowledge and implications for research and treatment. Int Psychogeriatr 1996; 8 Suppl. 3: S497-S500
23. Tariot PN, Mack JL, Patterson MB, et al. The behavior rating scale for dementia of the consortium to establish a registry for Alzheimer's Disease. Am J Psychiatry 1995; 152: 1349-57
24. Welsh KA, Butters N, Mohs RC, et al. The consortium to establish a registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. Neurology 1994; 44: 609-14
25. Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. Neurology 1997; 48 Suppl. 6: S10-S16
26. Hafkenscheid A: Psychometric evaluation of a standardized and expanded brief psychiatric rating scale. Acta Psychiatr Scand 1991; 84: 294-300
27. Cohen-Mansfield J. Conceptualization of agitation: results based on the Cohen-Mansfield Agitation Inventory and the Agitation Behavior Mapping Instrument. Int Psychogeriatr 1996; 8 Suppl. 3: S309-S315
28. Koss E, Weiner M, Ernesto C, et al. Assessing patterns of agitation in Alzheimer's disease patients with the Cohen-Mansfield agitation inventory. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997; 11 Suppl. 2: S45-S50
29. Reisberg B, Auer SR, Monteiro IM. Behavioral pathology in Alzheimer's disease (BEHAVE-AD) rating scale. Int Psychogeriatr 1996; 8 Suppl. 3: S301-S308
30. American Psychiatric Association. Practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Am J Psychiatry 1997; 154 Suppl. 5: S1-S39
31. Brodaty H. Caregivers and BPSD. Module 4. In: Finkel SI, Luxenberg J, Zaudig M, et al., editors. Behavioral and psychological symptoms of dementia. Educational pack. Macclesfield: Gardiner-Caldwell Communications Limited, 1998
32. Rabins P. Non-pharmacological management of BPSD. Module 5. In: Finkel SI, Luxenberg J, Zaudig M, et al., editors. Behavioral and psychological symptoms of dementia. Educational pack Macclesfield: Gardiner-Caldwell Communications Limited, 1998
33. Leibovici A, Tariot PN. Agitation associated with dementia: a systematic approach to treatment. Psychopharmacol Bull 1988; 24: 49-53
34. Ray WA, Federspiel MR, Schaffner W. A study of antipsychotic use in nursing homes: epidemiologic evidence suggesting misuse. Am J Pub Health 1980; 70: 485-91
35. Lawlor B. Pharmacological management of BPSD. Module 6. In: Finkel SI, Luxenberg J, Zaudig M, et al., editors. Behavioral and psychological symptoms of dementia. Educational pack. Macclesfield: Gardiner-Caldwell Communications Limited, 1998
36. Sunderland T. Treatment of the elderly suffering from psychosis and dementia. J Clin Psychiatry 1996; 57 Suppl. 9: S53-S56
37. Finkel SI. Managing the behavioral and psychological signs and symptoms of dementia. Int Clin Psychopharmacol 1997; 12 Suppl. 4: S25-S28
38. Katz IR, Jeste DV, Mintzer JE, et al. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. J Clin Psychiatry 1999; 60: 107-15
39. De Deyn PP, Rabheru K, Rasmussen A, et al. A randomized trial of risperidone, placebo, and haloperidol for behavioural symptoms of dementia. Neurology 1999; 53: 946-55
40. Catterson ML, Preskorn SH, Martin RL. Pharmacodynamic and pharmacokinetic considerations in geriatric psychopharmacology. Psychiatr Clin North Am 1997; 20: 205-18
41. Turnheim K. Drug dosage in the elderly. Is it rational? Drugs Aging 1998; 13: 357-79
42. Harvey AT, Preskorn SH. Cytochrome P450 enzymes: interpretation of their interactions with selective serotonin reuptake inhibitors. Part II. J Clin Psychopharmacol 1996; 16: 345-55
43. Feinberg M. The problems of anticholinergic adverse effects in older patients. Drugs Aging 1993; 3: 335-48
44. Kane JM, Woerner M, Lieberman J. Tardive dyskinesia: prevalence, incidence, and risk factors. J Clin Psychopharmacol 1988; 8 Suppl.: S52-S56
45. Mach Jr JR, Dysken MW, Kuskowski M, et al. Serum anticholinergic activity in hospitalized older persons with delirium: a preliminary study. J Am Geriatr Soc 1995; 43: 491-5
46. Naranjo CA, Herrmann N, Mittmann N, et al. Recent advances in geriatric psychopharmacology. Drugs Aging 1995; 7: 184-202
47. Woerner MG, Alvir JM, Saltz BL, et al. Prospective study of tardive dyskinesia in the elderly: rates and risk factors. Am J Psychiatry 1998; 155: 1521-8
48. Swearer JM. Behavioral disturbances in dementia: In: Morris JC, editor. Handbook of dementing illnesses. New York (NY): Marcel Dekker Inc., 1994: 499-527
49. Deutsch LH, Bylsma FW, Rovner BW, et al. Psychosis and physical aggression in probable Alzheimer's disease. Am J Psychiatry 1991; 148: 1159-63
50. Salzman C. Treatment of the agitated demented elderly patient. Hosp Commun Psychiatr 1988; 39 Suppl.: S1143-S1144
51. Thapa PB, Gideon P, Fought RL, et al. Psychotropic drugs and risk of recurrent falls in ambulatory nursing home residents. Am J Epidemiol 1995; 142: 202-11
52. Ray WA, Griffin MR, Schaffner W, et al. Psychotropic drug use and the risk of hip fracture. N Engl J Med 1987; 316: 363-9
53. Gilleard CJ, Morgan K, Wade BE. Patterns of neuroleptic use among the institutionalized elderly. Acta Psychiatr Scand 1983; 68: 419-25
54. Reifler BV, Teri L, Raskind M, et al. Double-blind trial of imipramine in Alzheimer's disease patients with and without depression. Am J Psychiatry 1989; 146: 45-9
55. Simpson DM, Foster D. Improvement in organically disturbed behavior with trazodone treatment. J Clin Psychiatry 1986; 47: 191-3
56. Petrie WM, Ban TA, Berney S, et al. Loxapine and psychogeriatrics: a placebo and standard controlled clinical investigation. J Clin Psychopharmacol 1982; 2 Suppl. 2: S122-S126
57. Schneider LS, Pollock VE, Lyness SA. A meta-analysis of controlled trials of neuroleptic treatment of dementia. J Am Geriatr Soc 1990; 38: 553-63
58. Schneider LS, Sobin PB. Non-neuroleptic medications in the management of agitation in Alzheimer's disease and other dementias. A selective review. Int J Geriatr Psychiatry 1991; 6: 691-708
59. Sunderland T, Silver MA. Neuroleptics and the treatment of dementia. Int J Geriatr Psychiatry 1988; 3: 79-88
60. Devanand DP, Levy SR. Neuroleptic treatment of agitation and psychosis in dementia. J Geriatr Psychiatry Neurol 1995; 8 Suppl. 1: S18-S27

61. Chui HC, Lyness SA, Sobel E, et al. Extrapyramidal signs and psychiatric symptoms predict faster cognitive decline in Alzheimer's disease. Arch Neurol 1994; 51: 676-81
62. Stern Y, Mayeux R, Sano M, et al. Predictors of disease course in patients with probable Alzheimer's disease. Neurology 1987; 37: 1649-53
63. McShane R, Keene J, Gedling K, et al. Do neuroleptic drugs hasten cognitive decline in dementia? Prospective study with necropsy follow up. BMJ 1997; 314: 266-70
64. Pickar D. Prospects for pharmacotherapy of schizophrenia. Lancet 1995; 345: 557-61
65. Casey DE. The relationship of pharmacology to side effects. J Clin Psychiatry 1997; 58 Suppl. 10: S55-S62
66. Jeste DV, Caligiuri MP, Paulsen JS, et al. Risk of tardive dyskinesia in older patients: a prospective longitudinal study of 266 outpatients. Arch Gen Psychiatry 1995; 52: 756-65
67. Glazer WM, Morgenstern H, Douchette JT. Predicting the long-term risk of tardive dyskinesia in outpatients maintained on neuroleptic medications. J Clin Psychiatry 1993; 54: 133-9
68. Saltz BL, Woerner MG, Kane JM, et al. Prospective study of tardive dyskinesia incidence in the elderly. JAMA 1991; 266: 2402-6
69. Jeste DV, Lacro JP, Palmer B, et al. Incidence of tardive dyskinesia in early stages of low-dose treatment with typical neuroleptics in older patients. Am J Psychiatry 1999; 156: 309-11
70. Gnanalingham KK, Byrne EJ, Thornton A, et al. Motor and cognitive function in Lewy body dementia: comparison with Alzheimer's and Parkinson's diseases. J Neurol Neurosurg Psychiatry 1997; 62: 243-52
71. McKeith I, Fairbairn A, Perry R, et al. Neuroleptic sensitivity in patients with senile dementia of lewy body type. BMJ 1992; 305: 673-8
72. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996; 47: 1113-24
73. Kumar V. Neuropsychopharmacology of antipsychotics: past, present and future. Clin Geriat 1997; Suppl. A: S21-S28
74. Monane M, Avorn J, Beers MH, et al. Anticholinergic drug use and bowel function in nursing home patients. Arch Intern Med 1993; 153: 633-38
75. Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. JAMA 1990; 263: 1097-101
76. Weiner MF, Risser RC, Cullum CM, et al. Alzheimer's disease and its Lewy body variant: a clinical analysis of postmortem verified cases. Am J Psychiatry 1996; 153: 1269-73
77. Levy R. Is there life in the neurotransmitter approach to the treatment of Alzheimer's disease? In: Levy R, Howard R, Burns A, editors. Treatment and care in old age psychiatry. Petersfield: Wrightson Biomedical Publishing Ltd., 1993: 39-46
78. Retz W, Rosler M, Sitzmann L, et al. Clozapine in treatment of neuropsychiatric diseases in the elderly. Fortschr Neurol Psychiatr 1997; 65: 347-53
79. Benedetti F, Cavallaro R, Smeraldi E. Olanzapine-induced neutropenia after clozapine-induced neutropenia. Lancet 1999; 354: 566-7
80. Naumann R, Felber W, Heilemann H, et al. Olanzapine-induced agranulocytosis [letter]. Lancet 1999; 354: 566-7
81. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994; 151: 825-35
82. Stanniland C, Taylor D. Tolerability of atypical antipsychotics. Drug Saf 2000; 22: 195-214
83. Heylen S, Gelders Y. Risperidone in the treatment of behavioural disturbances in psychogeriatric patients: a multicentre open dose-finding study. Beerse: Janssen Research Foundation; 1989. Report no.: RIS-BEL-6
84. Mertens C. Risperidone in psychogeriatric patients with behavioural disturbances: an open long-term follow-up study. Beerse: Janssen Research Foundation; 1990. Report no.: RIS-BEL-9
85. Davidson M, Borison R, Grebb J, et al. The tolerance and safety of risperidone in geriatric patients with behavioural disturbances. Beerse: Janssen Research Foundation; 1995. Report no.: RIS-USA-34
86. Frenchman IB, Prince T. Clinical experience with risperidone, haloperidol, and thioridazine for dementia-associated behavioral disturbances. Int Psychogeriatr 1997; 9: 431-5
87. Mertens C. Risperidone in the treatment of behavioural disturbances in patients with Alzheimer's dementia: a double-blind placebo-controlled trial. Beerse: Janssen Research Foundation; 1993. Report no.: RIS-BEL 14
88. De Smedt G, Lemmens P, Wyffels V, et al. Clinical expert report of risperidone in the treatment of behavioural disturbances in patients with dementia. Beerse: Janssen Research Foundation; 1997. Clinical Trial Report no.: R-64766
89. De Deyn PP. Long-term efficacy and safety of risperidone in the treatment of behavioural disturbances in patients with dementia. An open label, follow-on to RIS-INT-24. Beerse: Janssen Research Foundation; 1998. Clinical Research Report no.: RIS-INT-26
90. Chouinard G, Ross-Chouinard A, Annable L, et al. The extrapyramidal symptom rating scale [abstract]. Can J Neurol Sci 1980; 7: 233
91. Gutierrez-Esteinou R, Grebb JA. Risperidone: an analysis of the first three years in general use. Int Clin Psychopharmacol 1997; 12 Suppl. 4: S3-S10
92. Tracy JI, Monaco CA, Abraham G, et al. Relation of serum anticholinergicity to cognitive status in schizophrenia patients taking clozapine or risperidone. J Clin Psychiatry 1998; 59: 184-8
93. Borison RL. Changing antipsychotic medication: guidelines on the transistion to treatment with risperidone. The Consensus Study Group on Risperidone Dosing. Clin Ther 1996; 18: 592-607
94. Shiovitz TM, Welke TL, Tigel PD, et al. Cholinergic rebound and rapid onset psychosis following abrupt clozapine withdrawal. Schizophr Bull 1996; 22: 591-5
95. Stanilla JK, de Leon J, Simpson GM. Clozapine withdrawal resulting in delirium with psychosis: a report of three cases. J Clin Psychiatry 1997; 58: 252-5
96. Wirshing DA, Wirshing WC, Kysar L, et al. Novel antipsychotics: comparison of weight gain liabilities. J Clin Psychiatry 1999; 60: 358-63
97. Data on file, Janssen Research Foundation, Beerse, 1998
98. Brecher M, Okamoto A, Napolitana J, et al. Low frequency of tardive dyskinesia in elderly patients with dementia exposed to risperidone for up to one year [poster]. 96th Collegium Internationale Neuro-Psychopharmacologicum Congress; 1998 Jul 12-16; Glasgow

Correspondence and offprints: Dr *Michael Zaudig*, Windach Institute and Hospital of Neurobehavioural Research and Therapy (WINTR) Psychosomatic Hospital, Schützenstrasse, 16 D-86949 Windach, Germany.
E-mail: zaudig@klinik.windach.de