OMNICARE INC.
Professional Services

DATE: June 12, 1997

TO: Regional Clinical Directors

FROM: Mark E. Lehman

RE: Risperdal PSTI Draft 2

Attached for your review and comments is the second draft of the Risperdal PSTI. As you will see, I have added much more emphasis on geriatric behavior use and decreased the emphasis on schizophrenia. I also added a quick "cheat" sheet on differences between the atypicals and the conventional antipsychotic drugs. I need your feedback as soon as possible. I anticipate the GPCG supplement going to print in the next week to ten days, and I (we) need to coordinate the launch of this formulary initiative. Thanks and call if you have questions!

OMNICARE INC.

Patient Specific Therapeutic Interchange Protocol (PSTI - 15)

Diagnoses: Behavioral Disturbances Associated with Dementia

Therapeutic Class: Anti-Psychotic Agents

Selected Agent: Risperidone (Risperdal®)

Approved: June, 1997
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OMNICARE INC.
Risperidone (Risperdal®) Medical Review

When evaluating the selection of one drug from a drug class as the "selected" agent, several critical elements must be evaluated: 1) efficacy, 2) safety, 3) ease of use and related nursing considerations in the long-term care facility, 4) application to a geriatric population, and 5) costs to the payer of the medication bill. The anti-psychotic agents as a class remain an often used modality in long-term care for treating behavioral disturbances associated with dementia. Risperidone (Risperdal®) has several characteristics which make it a "select" agent in the population we serve.

CLINICAL PHARMACOLOGY

1. The mechanism of action of Risperdal, as with other anti-psychotic drugs, is unknown. However, it has been proposed that this drug's anti-psychotic activity is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5-HT2) antagonism. Antagonism at receptors other than D2 and 5HT2 may explain some of the other effects of Risperdal. In general, improvement of negative symptoms and lessened risk of EPS are thought to result from blockade of serotonin $5HT_2$ receptors. Improvement of positive symptoms is thought to result from blockade of dopamine D_2 receptors in the limbic system.
2. Risperdal is a selective monoaminergic antagonist with high affinity for the serotonin type 2 (5HT2), dopamine type 2 (D2), alpha 1 and alpha 2 adrenergic, and H1 histaminergic receptors. Risperdal antagonizes other receptors, but with lower potency. Risperdal has low to moderate affinity for the serotonin 5HT1C, 5HT1D, and 5HT1A receptors, weak affinity for the dopamine D1 and haloperidol-sensitive sigma site, and no affinity for cholinergic muscarinic or beta 1 and beta 2 adrenergic receptors.

PHARMACOKINETICS

1. Risperdal is well absorbed. It is extensively metabolized in the liver by cytochrome P450 IID6 to a major active metabolite, 9-hydroxyrisperidone, which is the predominant circulating specie, and appears approximately equi-effective with Risperdal with respect to receptor binding activity and some effects in animals). Consequently, the clinical effect of the drug likely results from the combined concentrations of Risperdal plus 9-hydroxyrisperidone.
2. Food does not affect either the rate or extent of absorption of Risperdal thus, the drug can be given with or without meals.
3. Following oral administration of Risperdal solution or tablet, mean peak plasma concentrations occurred at about 1 hour. Peak 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. The apparent half-life of Risperdal was three hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers.

4. Steady-state concentrations of Risperdal are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).
5. Risperdal and 9-hydroxyrisperidone are approximately equi-effective, thus, the sum of their concentrations is pertinent. The pharmacokinetics of the sum of Risperdal and 9-hydroxyrisperidone, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.
6. The plasma protein binding of Risperdal was about 90% over the in vitro concentration range of 0.5 to 200 ng/mL and increased with increasing concentrations of alpha1-acid glycoprotein. The plasma binding of 9-hydroxyrisperidone was 77%. Neither the parent nor the metabolite displaced each other from the plasma binding sites.

EFFICACY IN SPECIFIC DISEASES/INDICATIONS

A. Schizophrenia:

North American Trial:

The clinical efficacy of Risperdal was documented in over 500 patients in the North American trial. The data from the North American trial formed the basis for the approval of Risperdal by the Food and Drug Administration (FDA). The North American trial was split into United States (Marder, 1994) and Canadian investigators (Chouinard, 1993) for publication purposes.

1. Marder (1994)

Marder (1994) conducted an 8-week multi-center double-blind study to compare the safety and efficacy of Risperdal 2, 6, 10 or 16 mg/day, haloperidol 20 mg/day and placebo in 388 schizophrenic patients. The main efficacy measures included the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression (CGI) scale.

2. Chouinard (1993)

Chouinard (1993) conducted an 8-week multi-center parallel-group double-blind study of 135 chronic schizophrenic patients who were randomized to Risperdal 2, 6, 10, 16 mg/day, haloperidol 20 mg/day or placebo. Efficacy measures included the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression (CGI) of Severity of Illness and Improvement.

3. Results

The combined results of the North American Trial are reported below:

Clinical Improvement: On both the total PANSS and total (PANSS and CGI) scales, Risperdal at a dose of 6 mg was superior to placebo and haloperidol 20 mg in the percentage of patients with clinical improvement.

Positive symptoms: On the PANSS positive subscale, Risperdal at a dose of 6 mg was superior to placebo and haloperidol 20 mg.

Negative symptoms: On the PANSS negative subscale, Risperdal at a dose of 6 mg was superior to placebo and haloperidol 20 mg.

B. Geriatric patients

The results of numerous open trials and case reports in which Risperdal was evaluated in geriatric patients have recently been reported. In general, lower doses of Risperdal were reported in these studies.

A review of published reports is provided below. In addition, a summary of these reports is presented in Table 1.

1. Aronson et al. reported the results of a retrospective study of 32 patients with diagnoses of behavioral disturbances in dementia (BDD), schizophrenia, bipolar, major depressive disorder with psychotic features and delusions disorder. The patients, with a mean age of 74.3 years, received Risperdal at a mean dose of 2.72 mg/day for a mean duration of 6.6 months. Improvement was reported in 31 of the 32 patients. Based on the Clinical Global Impression (CGI) score which was used to assess efficacy, 24 patients were reported to improve to a clinically significant degree. No patients had to discontinue treatment and none reported adverse effects.

2. In an open-label study conducted by Berman et al. in 10 schizophrenic patients with a mean age of 71 years who received Risperdal, statistically significant improvement in psychiatric scores was reported on the PANSS total (positive and negative symptom scale; $p = 0.002$), negative ($p=0.03$) and general symptoms ($p=0.02$). Statistically significant improvement was also reported on cognitive scores (Mini-Mental State Exam, Digit symbol; $p < 0.05$). No changes in vital signs or ECG were reported. Preexisting agitation, constipation, sleep problems and restlessness persisted in some patients. No patient reported significant EPS. One case of syndrome of inappropriate secretion of antidiuretic hormone, which resolved after discontinuation of risperidone, was reported in one patient.

3. Frenchman et al. conducted a chart review of 186 geriatric patients ($\geq$ 65 years) with Alzheimer's dementia, senile dementia NOS, or organic brain syndrome. Sixty patients had been treated with Risperdal (mean 1 mg/day), 83 with haloperidol (mean 2 mg/day) and 43 with thioridazine (mean 33 mg/day). Ninety-five percent of patients who received Risperdal had improvement in their target symptoms which included violence, shouting, delusions, paranoia, pacing, and mixed behaviors. Sixty-six percent and 65% of patients who received haloperidol and thioridazine respectively had improvement in their target symptoms. EPS was reported in fewer patients who received Risperdal(7%) than haloperidol (22%) and thioridazine (18%).

4. Gierz et al. presented in a poster, the pooled results of three open-label studies conducted in 35 older patients with schizophrenia, organic delusional disorder, bipolar and dementias of different etiologies. The ranges of the mean age and Risperdal dose for the three studies were respectively 55.6-71 years and 1.75-5.64 mg/day. Sixty percent (21/35) of the patients were considered to improve considerably with only 6% showing signs of worsening of symptoms. Side effects which occurred in some patients were considered tolerable.

5. In a poster, Goldberg reported the use of Risperdal in dementia-related disturbed behavior in nursing home residents. Sixty-four patients with dementia-related behavioral disturbances were treated with low doses of Risperdal (0.25-0.5 mg twice daily) for 6 months. Their ages ranged from 43-98 years with a mean of 80.4 years. The patients' behavior was recorded on questionnaires by the nursing staff for up to 6 months. Symptoms that showed the greatest improvements included agitation, verbal outbursts, physical aggression, depressed mood, anxiety, and abnormal movements. In general, Risperdal was well-tolerated and reported to be very helpful in 26 (41%) patients, moderately helpful in 17 (27%), slightly helpful in 10 (16%), and not helpful in 11 (17%) patients.

6. In a letter to the editor, Jeanblanc and Davis reported the use of Risperdal in five elderly patients (4 with dementia of the Alzheimer's type and 1 with vascular dementia). The age range was 70-91 years. A marked reduction or elimination of the patients' dementia-related agitation or violent behavior was observed within 7-10 days at Risperdal doses of 1.5-2.5 mg/day. Mild extrapyramidal symptoms were reported in two patients.

7. Kopala and Honer reported the use of Risperdal(1.5 mg) for persistent vocalizations in two elderly patients (92 and 78 years) with combined Alzheimer-vascular dementia. Vocalizations were reported to decrease to less than 20% of baseline ratings with Risperdal. Moreover, a decrease in Extrapyramidal System Rating Scale (ESRS) score was noted in one patient with dyskinesia.

8. Lacro et al. reported the results of 4 pooled open-label independent studies involving 47 patients (mean age 67.9) with schizophrenia, dementia, delusional disorder and mood disorder with psychotic features who received Risperdal at a mean dose of 3.2 mg/day for a mean duration of 10.8 weeks. Target symptoms which included psychotic symptoms and severe behavioral disturbances were reported to improve in 85% of the patients after Risperdal was initiated. Statistically significant ($p < 0.01$) improvement in cognitive function (mean scores on the Mini-mental State Exam) was also reported in a subsample of 19 patients. Adverse effects reported included hypotension (5), sedation (5), salivation (3) and EPS (1).

9. Lavretsky et al. conducted a 10-week open-label study of Risperdal for the treatment of agitation in 15 elderly patients (mean 78 years) with dementia. The range of Risperdal dose was 0.5 - 3.0 mg. All patients who received Risperdal were improved or very much improved at 10 weeks based on the Clinical Global Impression scale (CGI). After 2 weeks of treatment, 50% of patients were reported to improve on the Overt Aggression Scale (OAS) while 50% improvement was reported on the Cohen-Mansfield Agitation Inventory (CMAI) after 8 weeks treatment with Risperdal. Four patients reported EPS. Mean Mini-Mental State Exam (MMSE) scores decreased and Unified Parkinson's Disease Rating Scale (UPDRS) scores increased over 10 weeks.

10. In a letter to the editor published in the Lancet, Allen et al. described three patients with Lewy body dementia (LBD) who were treated with low dose Risperdal (0.5 to 1 mg per day). All three patients showed improvement in their behavioral and psychotic symptoms as measured by the Alzheimer's disease rating scale. Cognitive function either improved or stayed the same during Risperdal therapy.

11. Lee et al. reported the use of Risperdal in a 74-year-old female patient with senile dementia of Lewy body type (SDLBT). The patient received Risperdal 5 mg/day which was titrated over 10 days. Due to drowsiness and increased confusion, Risperdal was reduced to 1 mg bd. The patient's mental and cognitive state showed a gradual improvement after the dose reduction. In a letter to the editor, Mc Keith et al. cautioned about the possibility of sensitivity reactions to Risperdal in Lewy body dementia.

12. In a case series, Madhusoodanan et al. reported the efficacy of Risperdal in 11 geriatric patients (mean age 69.4 years) with schizophrenia, schizoaffective, bipolar and senile dementia. The mean dose of Risperdal was 4.9 mg/day. Overall, 8 patients responded to Risperdal and 7 had marked decreases in their positive and negative symptoms. Decreases in EPS and tardive dyskinetic symptoms were also reported in 4 patients. Adverse events reported such as hypotension, orthostatic hypotension, somnolence, headache, abdominal cramps and dizziness were considered negligible.

13. Madhusoodanan et al. reported the results of a 12-week open multicenter study to evaluate the efficacy and safety of Risperdal used at a mean dose of 2.4 mg/day in 103 elderly (mean age 71 years) with schizophrenia or schizoaffective disorder. Statistically significant reductions in severity of symptoms were reported on the Positive and Negative Symptoms Scales (PANSS) total and subscales. When efficacy was assessed by the Clinical Global Impression Scale (CGI), 62% of the patients were reported to at least minimally improved at endpoint (11% very much improved, 24% much improved, 27% minimally improved). Patients who received Risperdal $\leq$ 3 mg/day (64% improved) were more likely to improve than > 3 mg/day (58% improved). The most frequently reported side effects were dizziness, insomnia, agitation, somnolence and injury. EPS was reported to decrease from baseline to endpoint.

14. In a letter to the editor, Meco et al. suggested that Risperdal(range 0.25-1.25) may be effective for hallucinations in six levodopa-treated elderly (mean age 71.17 years) patients with Parkinson's disease. No worsening of EPS was reported.

15. Raheja et al. reported the successful use of Risperdal in two geriatric (76 and 82 years) patients to control behavioral disorders. The Risperdal dose in the two patients was 3 mg/day.

16. Reyntjens et al. conducted a 5-week pilot study to evaluate the effect of Risperdal in forty geriatric patients with behavioral disturbances. Risperdal was started at 0.5 mg bid and the dose was adjusted based on therapeutic response and side effects. The results suggested that Risperdal is an effective and well tolerated drug for the management of behavioral symptoms in geriatric patients.

17. Zarate et al. conducted a retrospective study to evaluate the use of Risperdal in 122 elderly patients with diagnoses of dementia, mood and psychotic disorders. The mean dose of Risperdal was 1.6 mg. Risperidone was effective in 85% of the 108 patients who continued treatment based on the Clinical Global Impression improvement scale (CGI-I).

The common adverse events reported included hypotension (29%), EPS (11%) and symptomatic orthostasis (10%).

18. Borison et al. reported on the use of Risperdal in 22 elderly patients with schizophrenia or dementia (Alzheimer's disease).

19. Czobor P, et al. reported on the positive effect of Risperdal on hostility in elderly with schizophrenia.

INDICATIONS, USES, DOSE RECOMMENDATIONS

1. Risperdal is indicated for the management of the manifestations of psychotic disorders.
2. ***Elderly:*** In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and a greater tendency to postural hypotension. In healthy elderly subjects renal clearance of both Risperdal and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients.
3. The recommended **initial dose** is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. **Dosage increases in these patients should be in increments of no more than 0.5 mg bid.** Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients slower titration may be medically appropriate. Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate Risperdal than normal adults. Patients with impaired hepatic function may have increases in the free fraction of the Risperdal, possibly resulting in an enhanced effect. Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored.

SAFETY ISSUES

1. The favorable safety profile of Risperdal demonstrated in 6-8 week short-term studies has been confirmed in seven 1-year safety studies involving over 1100 patients. The most common side effects reported with Risperdal in short-term studies are insomnia, agitation, EPS, headache, anxiety, rhinitis .

2. The long-term safety of Risperdal has been reported in 1,156 patients enrolled in seven 1-year clinical trials (Brecher, 1996). Adverse events reported in these 1-year trials were consistent with the findings from short-term double-blind studies. The range of the mean dose of Risperdal in the long term trials was 7.6-9.4 mg/day. Although the mean dose of Risperdal was higher than the doses used in practice (avg. dose for schizophrenia: 4.7 mg/day; all conditions: 3.2 mg/day) and found to be optimal in clinical trials (4-6 mg), the adverse events' profile of Risperdal from the long-term studies was similar to that reported in short-term pivotal trials.

Extrapyramidal symptoms/Tardive dyskinesia

3. Risperdal's potent effects at $5HT_{2A}$ receptors may be responsible for the low incidence of neurological adverse effects, such as EPS, associated with its use. Importantly, Risperdal at a dose of ≤10 mg/day has demonstrated an incidence of extrapyramidal symptoms (EPS) comparable to placebo (Risperdal product labeling). Marder (1994) reported that there was no significant differences in Extrapyramidal Symptom Rating Scale (ESRS) score between patients receiving placebo and Risperdal ≤ 6 mg.

4. In a study of 36 schizophrenic patients, Borison (1992) concluded that Risperdal decreased the signs of tardive dyskinesia. Chouinard (1995) determined that Risperdal had a significant beneficial effect on tardive dyskinesia in the Canadian Multi-center Risperdal study of 135 schizophrenic patients. In a post hoc analysis, Chouinard (1995) further examined the effects of Risperdal in patients with tardive dyskinesia from the Canadian Multi-center Risperdal study. The author reported that Risperdal at 6mg/day had the most beneficial effect on tardive dyskinesia.

5. Brecher (1996) evaluated the long-term safety of Risperdal (mean dose 7.6-9.4 mg/day) in 1156 patients enrolled in seven 1-year clinical trials. Only four cases (0.3 %) of tardive dyskinesia were reported in the long term studies.

Anticholinergic side effects

6. Risperdal's low affinity for muscarinic receptors is consistent with the relatively low incidence of anticholinergic adverse events reported in clinical trials conducted to evaluate its safety and efficacy. In these trials, the incidence of constipation was 3% in the placebo group and 7% in patients who received Risperdal in a dose of less than 10 mg/day, and 13% of patients who received 16 mg/day (Risperdal Product labeling). In a study conducted by Marder and Meibach (1994), the incidence of constipation was reported as 1.6% for both 2 and 6 mg daily doses of Risperdal.

Orthostatic hypotension

7. Risperdal may induce orthostatic hypotension especially during the initial dose-titration period, which is reflective of its alpha-adrenergic antagonistic properties. Orthostatic hypotension may be minimized, however, by following the recommended dose titration schedule. Syncope was reported in 0.2% (6/2670) of Risperdal-treated patients (Risperdal Product labeling).

Weight gain

8. Brecher (1996) reported a small weight gain with a mean increase in body weight per patient of 2.6 kg over the 1 year time period.

Sedation/Somnolence

9. The incidence of somnolence was reported as 3.2% and 3.1% respectively for 2 and 6 mg daily doses of Risperdal by Marder (1994) and is consistent with Risperdal's relatively low affinity for histamine H_1 receptors.

Laboratory monitoring

10. Laboratory monitoring, such as liver enzymes or white blood cell count is not required during Risperdal therapy since increased liver enzymes or white blood cells disorders have not consistently been reported in the pre-marketing studies or the post-marketing experience.

Other adverse effects

11. The most common adverse events reported in patients treated with Risperdal in pre-marketing clinical trials were insomnia, agitation, EPS, headache, anxiety, and rhinitis.

RISPERDAL SHORT AND LONG TERM SAFETY

	Risperdal Safety Information	
Adverse effects	Short term safety	Long term safety

Anticholinergic side effects	• No affinity for muscarinic cholinergic receptors
	• Minimal risk of anticholinergic side effects
	e.g, constipation:
	  • 3% placebo
	  • 7% RIS ≤ 10 mg/day
	  • 13% RIS 16 mg/day
		• The rate of anticholinergic side effects is comparable to short term studies

Extrapyramidal symptoms	• The incidence of EPS with Risperdal at doses ≤ 10 mg is comparable to placebo.
	• Incidence of EPS:
	  • Placebo 16%
	  • RIS ≤ 10 mg/day: 17%
	  • RIS 16 mg: 34%
		• Long term data indicates that the risk of EPS does not increase with extended use

Tardive dyskinesia	• Risperdal may have a beneficial effect on tardive dyskinesia in some patients	• Only four cases of (0.3%) of tardive dyskinesia reported in long term studies
Somnolence	• Risperdal causes minimal somnolence at ≤ 10 mg/day • RIS ≤ 10 mg/day: 3% • RIS 16 mg/day: 8% • Placebo: 1%	• The rate of somnolence is comparable to short term studies
Weight gain	• The incidence of weight gain (≥7% of body weight) with Risperdal has been reported as 18% compared to 9% with placebo	• Weight gain data from long term studies revealed a mean increase in body weight of 2.6 kg (range 1.8 - 3.3 kg) or 5.72 lb. (range 3.96 - 7.26 lb.). The mean duration of exposure was 213 days

	Risperdal safety information	
Adverse effects	Short term safety	Long term safety
Prolactin	• Greater plasma prolactin elevations than haloperidol • No correlation between prolactin-related adverse effects (e.g., gynecomastia, galactorrhea, oligomenorrhea, erectile and ejaculatory dysfunction) and prolactin levels in men and women	• Limited available data are similar to short term data • Long term study in progress
Electrocardiographic changes	• Mean QTc changes: Range -5.5 to + 2.7 msec Clinically insignificant	• Mean QTc changes: Range -0.9 to + 4.4 msec Clinically insignificant
Liver enzymes monitoring	• No monitoring required	• No monitoring required
White blood cell monitoring	• No monitoring required	• No monitoring required

DRUG INTERACTIONS

1. There have been no systematic evaluations of interactions between Risperdal and other drugs, to date. Given the primary central nervous system effects of Risperdal, caution should be used when Risperdal is taken in combination with other centrally acting drugs or alcohol.

2. Risperdal may antagonize the effects of levodopa and dopamine agonists.

3. Chronic administration of carbamazepine with Risperdal may increase the clearance of Risperdal.

4. Chronic administration of clozapine with Risperdal may decrease the clearance of Risperdal.

DRUG ADMINISTRATION FACTORS

1. Risperdal 1 mg/ml oral solution has been approved by the Food and Drug Administration (FDA) and is commercially available.

2. Data submitted to the FDA demonstrated that the Risperdal 1 mg/ml oral solution is bioequivalent to the 1 mg tablets. Gutierrez presented, in a poster, the results of an open-label, randomized, two-way crossover study comparing the bioavailability of Risperdal as a 1-mg tablet and 1-mg/ml oral solution in 23 healthy male subjects. The tablet and the oral solution were given as a single 1-mg dose and were separated by a 10-day washout period. The 90% confidence intervals on the relative bioavailability for Risperdal, 9-hydroxyrisperidone, and total Risperdal for Cmax and AUC were within the equivalence range of 80-120%. Both formulations are bioequivalent and were well tolerated.
3. The oral solution is supplied in 100 ml bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL., while the maximum calibrated volume is 3 mL.
4. **Tests indicate that Risperdal oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea.**

COST

1. Utilizing Risperdal as the branded anti-psychotic of choice in behavioral disturbances associated with dementia will provide cost savings to the payer of the pharmacy bill. When compared to the other branded anti-psychotic currently available on the market (Zyprexa®).

SUMMARY

Risperdal possess several characteristics that make it a "select" agent for use in the geriatric population. Risperdal has been proven effective for the positive and negative symptoms of psychosis while exhibiting an excellent safety profile, unlike the older, first generation anti-psychotic agents. Risperdal can be administered by tablet or liquid, can be given in a twice daily regimen, and, when compared to the other branded anti-psychotic, provides a cost savings to the payer of the pharmacy bill. For these reasons we are initiating an intervention program to:

1. **Initiate anti-psychotic therapy with Risperdal when a new, atypical agent is selected for use.**

2. **Suggest Risperdal as the anti-psychotic of choice when a resident has experienced adverse effects or therapeutic failure with a trial of a conventional anti-psychotic.**

REFERENCES

Available for review.

CONVENTIONAL VS. ATYPICAL ANTIPSYCHOTICS

The new atypical antipsychotic agents include clozapine (Clozaril ®), risperidone (Risperdal ®) and olanzapine (Zyprexa)®. Although there is no universally accepted definition for atypicality, in general an atypical antipsychotic has a higher 5HT2 (serotonin 2) to D2 (dopamine 2) ratio resulting in less extrapyramidal symptoms and improved efficacy against the negative symptoms associated with schizophrenia. In addition the atypical antipsychotic drugs carry a lower risk of tardive dyskinesia than the conventional antipsychotic agents.

Mechanism of action...

1. The conventional antipsychotics primarily block the *dopamine* D_2 receptors
2. The atypical antipsychotics block the *dopamine* D_2 and *serotonin* $5HT_2$ receptors to various degrees
3. The atypical antipsychotics have higher $5HT_2$ to D_2 ratios than the conventional antipsychotics

Safety...

1. The conventional antipsychotics, especially the high-potency agents, frequently cause extrapyramidal side effects such as pseudoparkinsonism, acute dystonia, and akathisia
2. The atypical antipsychotics cause less extrapyramidal side effects due to a higher $5HT_2$ to D_2 ratio
3. The atypical antipsychotic agents have a lower risk of tardive dyskinesia

RISPERDAL...

* **Extra Pyramidal Symptoms**

Short term studies have shown that the incidence of EPS with Risperdal at doses $\leq$ 10 mg is comparable to placebo

- **Placebo: 16%;**
- **RIS $\leq$ 10 mg/day: 17%**
- **RIS 16 mg: 34%**

Long term data indicates that the risk of EPS does not increase with extended use

* **Tardive dyskinesia**

- **Low incidence (0.3%) in long term studies**
- **Risperdal may have a beneficial effect on tardive dyskinesia**

References

1. Kane JM. Schizophrenia. N Eng. J Med 1996; 334(1): 34-41.
2. Love RC. Novel versus conventional antipsychotic drugs. Pharmacotherapy 1996; 16(1 Pt 2): 16S-10S.
3. Risby BR, Donnigan D, et al. Formulary considerations for treating psychiatric disorders: Schizophrenia. Formulary 1997; 32:142-55.

Table 1: Summary of published reports on the use of Risperidone in the geriatric population

Study	Patients	Risperidone dosing	Efficacy results	Safety results
Aronson et al. Retrospective	**n=32; mean age 74.3 yrs Behavioral disturbances in dementia, schizophrenia, bipolar, major depressive disorder with psychotic features, delusional disorders**	**mean=2.72 mg/day Duration 6.6 months**	**Improved CGI (31) Clinically significant improvement CGI scores (24)**	**None reported**
Berman et al. Open-label	**n=10, mean age 71 years Schizophrenia**	**Maximum 6 mg/day**	**Statistically significant improvement in psychiatric scores: PANSS total (p=0.002), negative (p=0.03), general score (p=0.02) Statistically significant improvement on cognitive scores (MMSE, Digit Symbol; p<0.05)**	**Preexisting agitation, constipation, sleep problems and restlessness persisted No patient reported significant EPS Syndrome of inappropriate secretion of antidiuretic hormone (1)**
Frenchman et al. Retrospective	**n=186; ≥ 65 years Alzheimer's disease, senile dementia, organic brain syndrome.**	**RIS: 1 mg/day Haloperidol: 2 mg/day Thioridazine: 33 mg/day**	**Target symptoms improvement: RIS: 95% Haloperidol: 66% Thioridazine: 65%**	**EPS: RIS 7% Haloperidol 22% Thioridazine 18%**
Gierz et al. Open-label	**n=35; Age: 55.6-71 years Schizophrenia, organic delusional disorder, bipolar, dementias**	**Range: 1.75-5.64**	**60% improved considerably (21/35)**	**6% showed signs of worsening of symptoms Side effects tolerable**
Jeanblanc & Davis Case reports	**n=5; Age: 70-91 years Alzheimer's and vascular dementia**	**1.5-2.5 mg/day**	**Marked reduction in dementia-related agitation/violence in all patients**	**No sedation Mild EPS (2)**

Kopala and Honer Case reports	n=2, Age=92-78 Combined Alzheimer-vascular dementia	1.5 mg	Vocalizations decreased by 20% of baseline ratings Decrease in ESRS score in one patient with dyskinesia	None
Lacro et al. Pooled open studies	n=47; mean age 67.9 Schizophrenia, dementia, delusional disorder, mood disorder with psychotic features	Mean 3.2 mg/day 10.8 weeks	Target symptom improvement in 85% of patients MMSE improved in subsample of 19 patients, $p<0.01$	Hypotension (5) Sedation (5) Salivation (3) EPS (1)
Lavretsky et al. Open-label	n=64; Mean age 78 Agitation in dementia	Range 0.5-3.0 mg	All patients improved or very much improved via CGI at 10 wk CMAI: 50% improvement after 8 wks OAS: 50% improvement after 2 wks	EPS (4) Mean MMSE decreased over 10 wks Mean UPDRS increased over 10 wks
Allen et al Case reports	n=3; Age 66-78 Lewy body dementia	range 0.5-1 mg/day	All three patients improved in their behavioral and psychotic symptoms via Alzheimer's rating scale Cognitive function improved or stayed the same	Worsening in EPS (1)
Lee et al. Case reports	n=1; 74 years Lewy body type dementia	1 mg bd	Gradual improvement in mental and cognitive state	Drowsiness and confusion

Madhusoodanan et al. Case reports	n=11; mean age 69.4 Schizophrenia, schizoaffective, bipolar, senile dementia	4.9 mg/day	8 patients responded 7 had marked decrease in positive and negative symptoms Decrease in preexisting EPS and tardive dyskinesia (4)	No changes in ECG/vital signs Hypotension Orthostatic hypotension Somnolence, headache, abdominal cramps, dizziness
Madhusoodanan et al. Open label, multicenter	n=103; Mean age 71 Schizophrenia and schizoaffective	2.4 mg/day	Statistically significant reductions in PANSS total and subscales 62% minimally improved via CGI Patients who received RIS ≤ 3 mg/day (64% improved) more likely to improve than > 3 mg/day (58% improved).	Most frequently adverse effects: dizziness, insomnia, agitation, somnolence, injury EPS decreased from baseline to endpoint
Meco et al. Letter to the Editor	n=6; Mean 71.17 years Hallucinations / parkinson's disease	range 0.25-1.25 mg/day	Effective for hallucinations in L-dopa-treated patients	No worsening of EPS
Raheja et al. Case reports	n=2, 76, 82 years Behavioral disorders	3 mg/day	Symptoms improvement in both patients	No adverse events reported
Reyntjens et al. Open-label	n=40; Behavioral disturbances	Starting dose 0.5 mg bid. Titrated based on response and side effects	Effective for the management of behavioral disturbances	None reported
Zarate et al. Retrospective	n=122; ≥ 65 years old Dementia, mood and psychotic disorders	mean 1.6 mg/day	Effective in 85% of patients via CGI-I	Hypotension (29%) EPS (11%) Orthostasis (10%)