# The Canadian experience with risperidone for the treatment of schizophrenia: an overview

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**Objective:** To summarize published data to date by Canadian authors and from Canadian sources on risperidone, a novel neuroleptic indicated in the management of schizophrenia and related psychotic disorders. It was introduced in Canada in 1993. **Data sources:** A MEDLINE search was performed using "risperidone" as a keyword. Three Canadian journals were also searched manually. **Study selection:** Articles published between January 1991 and June 1996 by Canadian authors or involving Canadian patients. **Data extraction:** Retrieved articles were categorized according to data on efficacy, safety, resource use/economics and other miscellaneous aspects. Articles were abstracted and summarized. Some non-Canadian sources were used for comparison. **Data synthesis:** The initial Canadian multicentre trial found risperidone (6 mg daily) to be superior to haloperidol (20 mg daily) in reducing positive and negative symptoms, with fewer extrapyramidal side effects (EPS). Various case reports have extended both the clinical use and safety profile of risperidone, while neuro-imaging studies have tried to clarify its mechanism of action. Economic studies suggest substantial cost benefits due to prevention of hospitalization as well as improvement in quality of life. **Conclusions:** Canadian research has contributed considerably to the current knowledge regarding risperidone. Future studies, both controlled and naturalistic, will need to focus on comparisons with the various new compounds now available.

**Objectif :** Résumer des données publiées jusqu'à maintenant par des auteurs canadiens et tirées de sources canadiennes sur la rispéridone, nouveau neuroleptique indiqué dans le traitement de la schizophrénie et des troubles psychotiques connexes. Ce médicament a été lancé au Canada en 1993. **Sources de données :** On a effectué une recherche dans MEDLINE en utilisant «risperidone» comme mot clé, et une recherche manuelle dans 3 journaux canadiens. **Sélection d'études :** Articles publiés entre janvier 1991 et juin 1996 par des auteurs canadiens ou portant sur des patients canadiens. **Extraction de données :** Les articles extraits ont été classés en fonction des données sur l'efficacité, la sûreté, l'utilisation des ressources et l'économie, ainsi que d'autres aspects divers. Les articles ont été abrégés et résumés. On a utilisé quelques sources non canadiennes à des fins de comparaison. **Synthèse des données :** À la suite de la première étude multicentrique réalisée au Canada, on a constaté que la rispéridone (6 mg par jour) est supérieure à l'halopéridol (20 mg par jour) pour ce qui est de réduire les symptômes positifs et

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négatifs et entraîne moins d'effets secondaires extrapyramidaux. Diverses études de cas ont étendu à la fois l'utilisation clinique et le profil de sûreté de la rispéridone tandis que des études de neuro-imagerie visaient à clarifier son mode d'action. Des études économiques indiquent que la prévention des hospitalisations et l'amélioration de la qualité de vie entraînent des avantages importants au plan des coûts. **Conclusions :** La recherche canadienne a contribué énormément aux connaissances actuelles sur la rispéridone. D'autres études, tant contrôlées que naturalistes, devront porter avant tout sur des comparaisons avec les divers composés nouveaux maintenant disponibles.

## Introduction

Schizophrenia affects approximately 1% of the population. The prevalence in Canada has been estimated at 1.04% in men and 0.68% in women.[1] It affects a disproportionately younger population than most other major chronic illnesses, with the age of onset usually 18 to 28 years for men and 23 to 35 years for women.[2] Frequent and lengthy hospitalizations are common in schizophrenia. In 1990/91 in Ontario, for example, schizophrenia accounted for 8003 hospitalizations (with an average stay of 22.2 days), for 13% of total hospitalizations, and for 16% of hospital days for mental disorders.[3]

The treatment of psychoses was revolutionized in 1952 with the introduction of chlorpromazine, after Henri Laborit had observed that it produced "chemical lobotomy" during his experiments in anesthesia.[4] This was a major turning point, which led to the development of a number of conventional neuroleptics. Together, these medications contributed substantially to the process of de-institutionalization, which began in the 1960s.[5] Indeed, in the past 30 years the total number of beds in Canadian psychiatric hospitals has decreased by 68%, and the hospitalization rate in mental institutions by 81%.[6] However, these reductions have been paralleled by an increase in admissions and in stays of shorter duration. The percentage of discharges after stays of less than 1 month increased from 33% in 1965 to 52% in 1981/82.[6] A similar trend has also been documented in the United States, where there has been a decrease of 80% in psychiatric beds in public hospitals since 1955, but a corresponding increase in the number of admissions due to high rates of relapse.[7] The situation seems to have stabilized since the 1980s,[6] although admissions to general hospitals for mental problems, including those for schizophrenia, have further increased in the 1990s.[8] Nonetheless, in 1993/94, schizophrenia was the leading cause of hospitalization in psychiatric hospitals in Canada, accounting for 30% of discharges, up from 28% in 1982/83.[8] Furthermore, these trends seem to have led to "revolving-door" patients: brief-stay patients who tend to be re-admitted sooner than patients treated for longer periods.[7]

Conventional neuroleptics rapidly came to represent the mainstay of treatment for schizophrenia, although it has been reported that schizophrenia is refractory to pharmacotherapy with these agents in approximately 5% to 25% of patients,[9-11] who may need to be admitted to hospital intermittently as a result. Furthermore, conventional neuroleptics have 2 major disadvantages: a relative lack of efficacy in treating negative symptoms of schizophrenia, and extrapyramidal side effects (EPS).[12-14]

Recent advances have led to the development of "novel" neuroleptics, such as clozapine, quetiapine, sertindole, risperidone and olanzapine. In Canada, clozapine, risperidone, quetiapine and olanzapine are currently available. Studies of clozapine have established it as the prototype of the novel compounds, indicating it to be beneficial in the management of positive symptoms refractory to conventional neuroleptic therapy.[15,16] In addition, it appears to have a benefit in treating negative symptoms and demonstrates a markedly diminished risk of EPS.[15-17]

Risperidone is a benzisoxazole derivative with a high affinity for the serotonin type 2 ($5\text{-}HT_2$), dopamine $D_2$, and $\alpha_1$-adrenergic receptors (according to the Risperdal product monograph). It is well absorbed after oral administration, and peak plasma concentrations are reached within 2 hours of ingestion. The major metabolite is 9-hydroxy-risperidone, which has activity similar to the parent drug. Concentration of the active moiety (risperidone plus 9-hydroxy-risperidone) is similar between extensive and poor metabolizers, and the elimination half-life is approximately 24 hours. Risperidone carries no increased risk of agranulocytosis, an adverse effect seen with clozapine. In Canada, risperidone is indicated

for the management of schizophrenia and related psychotic disorders.

## Objectives

As the first country to approve the use of risperidone for the treatment of schizophrenia, Canada has played a leading role in its development and in ongoing research. It is worth noting that risperidone has since become the most widely prescribed neuroleptic by psychiatrists in North America.[18]

The purpose of this article was to review and update the Canadian contribution to the medical and scientific literature pertaining to the use of risperidone. The objectives were to summarize efficacy and safety data and compare the results with worldwide general trends, to review resource use and economic reports, and finally to analyze the economic implications of efficacy and safety of risperidone from a Canadian perspective.

## Methods

A MEDLINE search was performed using "risperidone" as a keyword. The abstracts from this search were manually reviewed in order to retrieve articles by Canadian authors and articles involving Canadian patients. The main method for identifying Canadian authors was their affiliation as reported on MEDLINE. We also used a list of Canadian researchers prepared from a previous literature search. We also performed a manual search of 3 Canadian medical and scientific journals: the *Canadian Journal of Psychiatry*, the *Canadian Medical Association Journal* and the *Journal of Psychiatry and Neuroscience*. The search period was January 1991 to June 1996. It was assumed that studies reported by Canadian authors or in Canadian journals targeted Canadian populations or institutions, unless clearly specified otherwise.

Retrieved articles were then categorized according to their content: efficacy, safety, resource use/economics, and miscellaneous. Articles were abstracted and all relevant information summarized. Some non-Canadian sources were also used for comparison and reference purposes.

## Results

There were 52 articles that fit the above criteria. There was 1 panel report on current schizophrenia research in Canada.[2] There were 7 articles that reported or critiqued clinical trials reflecting the experience of Canadian patients,[19–25] 5 review articles of the experience with risperidone (including the Risperdal product monograph),[26–29] 16 case reports of patient experience with risperidone,[30–45] 3 papers addressing the economic impact of risperidone treatment,[46–48] and 2 papers reviewing the literature and methodology of economic evaluation in schizophrenia.[49,50] There were also 12 articles whose main focus was the pharmacology or mechanism of action of risperidone,[51–62] and 6 articles on disease management impact and issues with the use of risperidone and other novel neuroleptics.[29,63–67] These articles are summarized in the tables.

### *Clinical studies*

There has been a single large clinical Canadian trial of the use of risperidone compared with placebo and haloperidol. Chouinard et al[21] reported the results of the Canadian Risperidone Study, which was a double-blind randomized study comparing daily dosages of 2 mg, 6 mg, 10 mg and 16 mg of risperidone with placebo and with 20 mg of haloperidol. One hundred and thirty-five patients with a diagnosis of chronic schizophrenia according to DSM-III criteria were treated in an 8-week trial. The authors found that there was a curvilinear dose–response relation, and that the most efficacious and safe dosage of those studied in this patient population was 6 mg of risperidone daily. The primary efficacy measure was clinical improvement at the end point, defined as at least a 20% reduction in the Positive and Negative Symptom Scale (PANSS) total score from baseline to end point. The proportion of patients showing a clinical response to risperidone 6 mg (72.7%) was 25% greater than for haloperidol 20 mg (47.6%), but this difference did not reach statistical significance. When the average change from baseline to study termination in PANSS total and subscale scores was considered, risperidone 6 mg was significantly better than haloperidol in reducing the total PANSS score. Risperidone 6 mg was found to be significantly more efficacious than haloperidol in reducing negative symptoms, and was found to have similar efficacy in reducing positive symptoms. On the general psychopathology subscale, risperidone was found to be significantly more beneficial than haloperidol. One observation worth reporting is the difference in the percentage of patients who dropped out of the trial due to lack of efficacy. While this figure was 4.5% for the 6 mg risperidone group,

52% of the subjects taking haloperidol and 63% of those taking placebo withdrew in the early stages of the trial. This finding may have implications for the risk of patient noncompliance.

In this study, risperidone 6 mg was not associated with any increased risk of parkinsonism over placebo, and with significantly less risk of parkinsonism than haloperidol. A secondary analysis of this study was performed to assess the effect of risperidone in tardive dyskinesia.[19] In patients who had at least moderately severe dyskinesia at baseline, risperidone showed a beneficial effect in reducing dyskinesia compared with both placebo and haloperidol.

The Canadian risperidone study produced results

**Table 1: Efficacy and safety studies — Canadian clinical studies of risperidone in schizophrenia**

| Study | Article type | Detail | Summary |
|---|---|---|---|
| Chouinard et al, 1993[21] | Clinical trial | Study population | Canadian Risperidone Study involving 135 patients compared risperidone (2, 6, 10, 16 mg/d) with haloperidol (20 mg/d) and placebo |
| | | Efficacy | Risperidone (6 mg/d) best dosage; total Positive and Negative Symptom Scale (PANSS) and negative symptoms improved over haloperidol treatment |
| | | Safety | No increased parkinsonism over placebo, beneficial effect on dyskinesia; significantly less parkinsonism, dyskinesia than with haloperidol treatment |
| Chouinard et al, 1994[20] | Open clinical trial | Study population | Schizophrenic patients with supersensitivity psychosis resistant to treatment; 6 patients received risperidone and 5 patients received clozapine |
| | | Efficacy, safety | Both patients taking risperidone and clozapine had good response |
| Chouinard, 1995[19] | Clinical trial | Study population | Canadian Risperidone Study: subgroup of 49 patients with tardive dyskinesia at baseline |
| | | Safety | Dyskinesia — risperidone (6 mg/d) resulted in greater reduction than placebo or haloperidol; antiparkinsonian medication — risperidone (6 mg/d) similar to placebo, less effective than haloperidol |
| Kopala et al, 1996[22] | Open study | Study population | 22 severely ill patients with first-episode schizophrenia, who had never received neuroleptics, were given lower doses of risperidone (average 4.7 mg/d) |
| | No controls | Efficacy, safety | 59% of patients showed clinical improvement (20% reduction in total PANSS); statistically significant reduction in overall symptoms on positive and negative subscales |
| McEvoy, 1994[23] | Clinical trial | Study population | North American Risperidone Study (combined Canadian, US data on 513 patients); compared risperidone (6 mg/d) with haloperidol (20 mg/d) and placebo |
| | | Efficacy | With risperidone (6 mg/d), significantly more patients showed clinical improvement than with haloperidol or placebo; risperidone better than haloperidol on most measures of positive symptoms |
| Moller et al, 1995[24] | Clinical trial | Study population | North American Risperidone Study, compared risperidone (6 mg/d) with haloperidol (20 mg/d); path analysis to see if effect on negative symptoms can be explained by effect on positive symptoms and/or extrapyramidal side effects (EPS) |
| | | Efficacy | Risperidone has a more potent direct effect on negative symptoms than haloperidol |
| Musser and Kirisci, 1995[25] | Critique | Comments | Multiple comparisons adjustment, repeated measures analysis of variance suggested |

**Table 2: Efficacy and safety studies — Canadian review articles of risperidone in schizophrenia**

| Study | Article type | Summary |
|---|---|---|
| Addington, 1994[26] | Review | Maintain dose in optimal range; bell-shaped response curve, linear EPS curve |
| Chouinard and Arnott, 1993[27] | Review | With 4 to 8 mg/d, risperidone has rapid onset, improves positive, negative and general symptoms better than traditional neuroleptics, with fewer EPS; also improves dyskinesia |
| Jones, 1993[28] | Review of current research foci | Review of the clinical results with risperidone and its receptor affinity, with implications for understanding of the disease |
| Remington, 1993[29] | Review | Review of disease process and recent clinical results with the newer neuroleptics and their receptor activity |
| Risperdal Product Monograph, 1993 | Monograph | Includes summary of published material |

consistent with the US arm of the clinical trial, which also showed superior improvement in positive and negative symptoms among patients taking risperidone when compared with both haloperidol and placebo, without the same degree of EPS experienced by those taking haloperidol.[24,68] In contrast, a large European trial confirmed the advantage of risperidone over haloperidol with respect to EPS, but was unable to show a clear advantage of risperidone over haloperidol in terms of positive, negative and general symptoms of schizophrenia.[69]

Two open studies in Canada have since investigated risperidone in more specific indications. Chouinard et al[20] compared risperidone to clozapine in an open trial involving 11 schizophrenic patients with supersensitivity psychosis that was resistant to treatment. Six of these patients received risperidone for 2 to 25 months, and 5 patients received clozapine for 7 to 16 months. Of the patients receiving risperidone, treatment outcome for 4 patients was reported as "extremely" improved, and for the remaining 2 "very much" improved. Of the patients receiving

**Table 3: Efficacy and safety studies — Canadian case reports of risperidone in schizophrenia**

| Study | Article type | Detail | Summary |
|---|---|---|---|
| Addington et al, 1995[30] | Case report | Safety | 28-year-old woman with no history of tardive dyskinesia showed good symptom control and no EPS but moderate tardive dyskinesia on risperidone (10 mg/d) |
| Chong et al, 1996[32] | Case report | Safety | 36-year-old woman with 16-year history of schizophrenia; clozapine yielded no improvement; addition of risperidone (6 mg/d) resulted in no change in psychosis but worsening of hoarding |
| Dickson et al, 1994[33] | Case report | Efficacy, safety | 36-year-old man responded well to clozapine for control of positive symptoms, with no EPS; after change to risperidone he experienced relapse, dystonic reaction |
| Dickson et al, 1995[34] | Case report | Safety | Five premenopausal women prescribed risperidone experienced markedly elevated prolactin levels and amenorrhea; 3 of the 5 experienced galactorrhea; when changed to typical neuroleptic treatment, prolactin levels dropped |
| Drugs Directorate, Health Canada, 1995[31] | Case reports | Safety | Number of reported adverse effects of risperidone from July 1993 to Sept. 1994 (39 reported adverse events included 11 EPS, 7 parkinsonian, 6 dystonia and 2 akathisia reactions). During those 14 months there were 68 206 filled prescriptions for risperidone |
| Emes and Millson, 1994[35] | Case report | Safety | 50-year-old man with 30-year history of schizophrenia and polydipsia developed priapism requiring surgical intervention while receiving risperidone (10 mg/d). He was also receiving lithium and lorazepam |
| Jones et al, 1994[36] | Case report | Efficacy | Severely ill 26-year-old man with schizophrenia refractory to treatment had such severe withdrawal that he required restraint to feed; he responded well to clozapine, then to risperidone |
| Kopala and Honer, 1994[38] | Case report | Efficacy, safety | 40-year-old woman with severe psychotic symptoms and tardive dyskinesia was receiving long-term haloperidol treatment; on risperidone (4 mg/d), psychosis and dyskinesia improved significantly |
| Kopala and Honer, 1994[37] | Case report | Safety | 22-year-old man with schizophrenia and obsessive–compulsive features; on risperidone (6 mg/d) psychosis improved, but obsessive–compulsive symptoms increased, then decreased again when fluvoxamine was added |
| Landry, 1995[39] | Case report | Safety | 53-year-old man with 28-year history of schizophrenia receiving long-term haloperidol and procyclidine treatment, with 10-year history of polydipsia and 33-month history of hyponatremia; after risperidone was started, the polydipsia and hyponatremia resolved |
| Meterissian, 1996[40] | Case report | Safety | 53-year-old woman with 15-year history of schizoaffective disorder developed neuroleptic malignant syndrome after starting risperidone treatment |
| O'Croinin and Zibin, 1995[41] | Case report | Safety | 31-year-old woman with 13-year history of chronic paranoid schizophrenia and no history of mania; risperidone (6 mg/d) resulted in hypomanic symptoms, which resolved after switching to haloperidol |
| Purdon et al, 1994[42] | Case report | Efficacy, safety | 2 men with pervasive developmental disorder were treated with risperidone and showed improvement in general intellectual functioning and reduced stereotyped speech and agitation |
| Remington and Adams, 1994[43] | Case report | Safety | 56-year-old man with obsessive–compulsive disorder and schizophrenia started receiving risperidone; he remained nonpsychotic and had reduced tardive dyskinesia but obsessive–compulsive symptoms returned |
| Stip et al, 1995[44] | Case report | Efficacy | 15 patients in whom initially positive response "wore off" and the patients reverted to former symptomatic state despite verified compliance and dosage alteration/combination |
| Takhar and Manchanda, 1996[45] | Case report | Safety | 17-year-old man who had never taken neuroleptics received risperidone (2 mg/d) for 2 days and developed acute dystonic reaction and subsequent delirium with an anticholinergic agent |

clozapine, 4 were rated as having "marked response" and 1 as "minimally improved." These results indicate that atypical neuroleptics may be beneficial in treatment-resistant schizophrenia when classic neuroleptics are no longer effective.

Kopala et al[22] described a study of 22 patients with schizophrenia who had not previously received neuroleptics and who had been admitted to hospital for the first time. They found that, although this series of patients was globally more severely ill than patients described in previous clinical trials of chronically ill patients, the risperidone dosage required for treatment ranged from 2 to 8 mg daily, with a mean dosage of 4.7 mg daily. Fifty-nine percent of the patients showed clinical improvement at study end (1.8 to 14.1 weeks of treatment). The effectiveness of a lower dosage is consistent with another report suggesting that patients in the early stages of treatment may respond to dosages of neuroleptics below those used in chronically ill individuals.[70]

The Canadian literature also includes a number of case reports related to the clinical experience with risperidone. Although case reports lack the validity of large randomized blinded studies, and generally portray a very small proportion of patients taking the medication in everyday practice, their value resides in the fact that they document rare, but important, adverse drug events. They also describe beneficial aspects of a therapy that can, in turn, be tested in further research.

In one report by Jones et al,[36] a man with schizophrenia had severe and life-threatening negative symptoms and withdrawal, which responded well to clozapine and then to risperidone. In a report of 15 cases, the patients had an initial good response to risperidone, followed by slow return to pretreatment condition, despite verified adherence to the medication regimen.[44] In another case, a patient responded well to clozapine for control of positive symptoms with no EPS but had a relapse and marked dystonic reaction after discontinuation of clozapine and initiation of risperidone.[33] In a related indication, there was a report of 2 men with pervasive developmental disorder treated with risperidone who showed improvements in general intellectual functioning, reduced stereotyped speech and agitation.[42] In another case report, Kopala and Honer[38] described a woman who had severe dyskinetic and dystonic movements after haloperidol treatment. After switching to treatment with risperidone (4 mg daily), there was significant

**Table 4: Resource use and economics — review papers**

| Study | Article type | Summary |
|---|---|---|
| Wasylenki, 1994[49] | Review | Review of burden of illness of schizophrenia in several countries and economic evaluations; focus on prevention of relapse as a key factor in economic impact of interventions, including novel neuroleptics such as risperidone |
| Williams and Dickson, 1995[50] | Review | Review and discussion of the economic analysis of drugs used in schizophrenia, including risperidone, and burden of illness evaluations in US, UK, Australia and Canada |

**Table 5: Resource use and economics — original research**

| Study | Article type | Detail | Summary |
|---|---|---|---|
| Addington et al, 1993[46] | Chart review | Study population | 27 patients from Canadian Risperidone Study who were taking risperidone for 1 year (treatment successes) to compare days in hospital for the year on risperidone with the previous year |
| | | Results | 20% reduction in hospital days; for "revolving-door" patients, 73% reduction in hospital days |
| Albright et al, 1996[47] | Database review | Study population | Compared resource use before and after initiation of risperidone using Saskatchewan Health linkable databases, covering an average of 10 months before and after initiation of risperidone therapy; risperidone indication in Saskatchewan is failure of other treatment |
| | | Results | Hospital admissions decreased by 60%, physician visits decreased by 22%, increased costs of antipsychotic agents; total decrease in cost of $7925 per patient per year after start of risperidone |
| Chouinard and Albright, 1997[48] | Cost–utility analysis | Study population | Patients in Canadian Risperidone Study categorized by mild, moderate and severe symptoms; utility was measured through an interview with health care professionals, and utility change based on category change was combined with cost per year to compare treatments |
| | | Results | Incremental cost–utility ratio of risperidone compared with haloperidol is $24 250 per quality-adjusted life year gained |

improvement in both psychotic illness and all aspects of movement disorder.

From July 1993 to September 1994 the Health Canada Drugs Directorate received reports of 39 adverse events associated with risperidone,[31] of which 11 were EPS reactions (7 involving parkinsonism, 6 dystonia, and 2 akathisia). Individual cases of adverse events reported in the literature included: tardive dyskinesia,[30] acute dystonic reaction,[45] neuroleptic malignant syndrome[40] and priapism.[35] There was 1 report of worsening of hoarding behaviour,[32] 2 cases of worsening of obsessive–compulsive symptoms,[37,43] and 1 report of hypomania.[41] There was also a case report of resolution of long-standing polydipsia and hyponatremia following initiation of risperidone treatment,[39] and 1 report reviewing 5 cases of markedly elevated prolactin levels in premenopausal women.[34] This small number of reports may be due to underreporting by treating physicians, who tend to report only severe or unusual adverse events. A more extensive re-

**Table 6: Miscellaneous articles — pharmacology as main focus**

| Study | Article type | Summary |
|---|---|---|
| Andrew et al, 1994[51] | Review | Review of the relation between EPS and tardive dyskinesia; dopamine hypofunction resulting in EPS may lead to development of dopamine receptor hypersensitivity, increasing the risk of tardive dyskinesia |
| Ereshefsky, 1993[52] | Review | Detailed pharmacokinetics, pharmacodynamics of risperidone |
| He and Richardson, 1995[53] | Review | Review of pharmacokinetics of risperidone, and review of efficacy and safety from Canadian study |
| Kapur et al, 1995[55] | Positron emission tomography study | Benefits of risperidone (6 mg/d) with respect to EPS cannot be explained in terms of lower $D_2$ binding; EPS superiority may be related to its 5-$HT_2$ blocking ability |
| Kapur et al, 1996[54] | Review | Review of the neurological basis for serotonin–dopamine interaction and its clinical relevance |
| Keegan, 1994[56] | Review | Pharmacology — basic and clinical review |
| Miller and Chouinard, 1993[57] | Review | Pathophysiological mechanism for dyskinesia, neuroleptic-induced supersensitivity psychosis and refractory schizophrenia |
| Remington, 1995[67] | Review | Pharmacology review — trends and questions for future research |
| Seeman, 1990[59] | Review | Mechanisms of action of atypical neuroleptics — discussion of multiple receptor roles |
| Shriqui, 1995[60] | Review | Review of dose levels for neuroleptics |
| Sigmundson, 1994[61] | Review | Review of studies of the pharmacology of novel neuroleptics |
| Villeneuve, 1994[62] | Review | Concludes that clinical effects on negative symptoms are presumably related to activity at serotonin receptors |

**Table 7: Miscellaneous articles — disease management and outcomes**

| Study | Article type | Summary |
|---|---|---|
| Clarke and Yaeger, 1994[63] | Case report | Addresses the needs of patients for socialization and support once negative symptoms of schizophrenia are relieved and patients are more aware |
| Jeffries, 1993[65] | Opinion | Ethical issues in drug selection for schizophrenia : assessing primary and secondary negative symptoms, responsibility to provide best treatment with least side effects, maximizing patient competence and insight, and societal allocation of resources |
| MacEwan, 1993[64] | Review | Addresses application of research results to clinician populations |
| Naranjo et al, 1995[66] | Review | The elderly are extremely sensitive to EPS; risperidone may be useful in this indication but has not been studied in this group |
| Remington, 1993[29] | Guidelines | Guidelines regarding neuroleptic (risperidone) treatment re: correct diagnosis, noncompliance, nonresponsiveness, excessive dosage, drug interactions, side effects, dose adjustments, other medications |
| Remington, 1995[67] | Review | Discussion of the role of neuroleptics, compliance, depot neuroleptics, psychosocial rehabilitation and psychosocial support — a balanced approach is needed |

**Table 8: Panel Report of Canadian Research in Schizophrenia**

| Study | Article type | Summary |
|---|---|---|
| Annable et al, 1994[2] | Review/report | Reviews strengths and weaknesses of schizophrenia research in Canada; new research foci included novel antipsychotics such as risperidone; identifies new priorities in research such as negative symptoms and refractory schizophrenia |

view of adverse events can be found in the product monograph.

At recommended dosages, risperidone demonstrates an EPS profile comparable to placebo, with a possible beneficial effect on tardive dyskinesia. In order to investigate the pharmacological basis for this improved safety profile, as related to $D_2$ dopamine receptor occupancy, Kapur et al[55] carried out a positron emission tomography (PET) study of 9 patients receiving a 7- to 14-day course of risperidone in fixed daily dosages of 2 to 6 mg of risperidone. $D_2$ receptor occupancy for risperidone was similar to that for conventional neuroleptics, and higher than that for clozapine. Moreover, the authors reported a dose–response relation for EPS. Their findings suggest that the low rate of EPS reactions may be related to risperidone's high 5-$HT_2$ affinity.

Our review could not find any published Canadian study of the use of risperidone in the elderly. However, a review article supported the view that risperidone may represent a worthwhile alternative in elderly patients, given their sensitivity to EPS and their slower or impaired elimination of medications.[66] This hypothesis is supported by a US study that found risperidone well tolerated at an average dosage of 3.8 mg in elderly patients with chronic psychosis.[71]

*Resource use/economics studies*

Wasylenki[49] and Williams and Dickson[50] reviewed the cost and economics of treatment in schizophrenia. Both reports indicated that there is a considerable burden of illness in this disease, which is related to relapse and hospitalization. Both reviewed the economic contribution of risperidone, based on a previously published study by Addington et al.[46]

A costly, but more effective, neuroleptic may be expected to result in net cost savings if relapses are prevented, as one of the highest components of the cost of treatment of patients with schizophrenia is the cost of re-hospitalizations following relapse. Addington et al[46] compared hospitalizations 1 year before risperidone treatment with hospitalizations during 1 year of risperidone treatment and found a statistically significant 20% reduction in days of stay with risperidone treatment. Virtually all of this benefit involved the patients who were hospitalized for part of the previous year; that is, the "revolving-door" patients. In these patients, there was a 73% reduction in the number of days hospitalized. This study indicates the magnitude of benefit from successful treatment in a subset of patients. However, it did not control for confounding factors. Furthermore, a parallel comparison group of patients treated with conventional neuroleptics is needed to compare the number of hospitalization days saved. Patients who are unable to continue taking either type of treatment may need to be included in the comparison, for follow-up of resource use.

Albright et al[47] compared health care resource utilization before and after initiation of risperidone treatment through the use of data from the Saskatchewan Health linkable databases. They found that risperidone treatment resulted in a decrease in hospital days and physician visits, and an increase in antipsychotic medication costs. The total decrease in cost after the start of risperidone treatment, compared with an equivalent period before treatment, was $7925 per patient per year. A comparison with patients receiving conventional neuroleptic treatment or other novel neuroleptics may again be necessary to help interpret this difference.

Chouinard and Albright[48] performed a cost–utility analysis based on the data from the Canadian Risperidone Study, and estimated the utility of treatment in terms of mild, moderate and severe symptoms using an interview method with health care professionals known as the "standard gamble" technique. They combined the quality-adjusted life years (QALY) gained through treatment with risperidone versus haloperidol with the difference in acquisition cost of risperidone and haloperidol to obtain a cost–utility ratio of $24 250 per QALY gained. A cost of less than $20 000 per QALY gained is regarded as strong evidence supporting the adoption of a new technology or therapeutic agent, and a range of $20 000 to $100 000 per QALY gained is considered moderate evidence supporting adoption.[72] While the result for risperidone falls into the second category, it leans favourably toward the lower cost range.

*Comparison with other novel neuroleptics*

With the increased availability of novel neuroleptics, clinicians may need comparative safety and efficacy data for selection of an appropriate novel agent for their patients. However, in clinical trials, newer agents have traditionally been compared with older drugs such as haloperidol, and only rarely with other drugs in their own group of novel neuroleptics.

The only published Canadian comparative study, which we discussed earlier, is an open-label study comparing risperidone with clozapine in only 11 patients with a secondary indication, supersensitivity psychosis.[20]

The literature on international research comparing risperidone with clozapine has also been very limited.[73,74]

Studies comparing risperidone with other novel neuroleptics available in Canada are also scarce. Our review of the literature could not find any study comparing risperidone to quetiapine, a dibenzothiazepine derivative, since this agent seems to have been compared only with placebo or conventional neuroleptics (Seroquel product monograph).[75] Furthermore, only one non-Canadian study has compared risperidone with olanzapine, a thienobenzodiazepine recently introduced in Canada.[76,77]

## Discussion

There is a considerable burden of illness associated with schizophrenia, which is reflected in the direct and indirect costs to the health care system, patients and their families. Prevention of both relapse and hospitalization has been identified as a key factor in containing costs, and the patient population in which this prevention may be most attainable is the "revolving-door" group. Factors in preventing relapse and rehospitalization include community support and case management services, in addition to maintenance of adequate and appropriate neuroleptic treatment. Patient and physician education, and the availability of novel neuroleptics, all contribute to improved adherence to therapy and have the potential to be cost-effective strategies, particularly in patients with schizophrenia resistant to treatment.

Experience to date within controlled clinical trials of risperidone indicates that a dosage of 6 mg per day results in improved efficacy in terms of the positive and negative symptoms of schizophrenia, including fewer EPS and a possible beneficial effect on tardive dyskinesia compared with conventional neuroleptics such as haloperidol.

At the same time, risperidone is a newer agent and is more expensive than conventional agents. However, schizophrenia being a chronic illness, the cost of risperidone treatment may be offset by its potential benefits. This position has been supported by the findings of a recent study performed for the Canadian Coordinating Office for Heath Technology Assessment.[78] In this study, the savings on expected costs resulting from risperidone treatment were estimated at $6510 per year per patient, and the benefit was estimated at an additional 0.04 QALY, when compared with haloperidol.

Furthermore, as indicated by Jeffries,[65] ethical patient treatment requires consideration of the optimal treatment for the patient and must be balanced by responsible choices regarding societal allocation of resources. Unfortunately, as of yet few studies have investigated the impact of risperidone on resource use and cost of care. Although they have indicated possible savings with risperidone, their results need further validation with proper controls and comparisons.

All aspects of neuroleptic therapy should be considered when performing an economic evaluation: efficacy, safety, effectiveness in target populations, as well as impact on quality of life. Recently, Glazer and Ereshefsky[79] developed a hypothetical model to compare the cost-effectiveness of a novel neuroleptic (e.g., risperidone) with a depot neuroleptic (e.g., haloperidol decanoate) and an oral conventional neuroleptic (e.g., haloperidol) in "revolving-door" patients with schizophrenia. Their model was sensitive to changes in patient adherence rates and cost of medications. In a scenario which assigned the novel neuroleptic an adherence rate of 65% versus 50% for the conventional neuroleptic and 80% for the depot neuroleptic, the novel neuroleptic was the most expensive option. However, in another scenario that estimated an adherence rate of 80% for the novel neuroleptic and a reduction of 25% of its acquisition cost, it was the least expensive option. However, in this model adherence rates were not empirically evaluated but estimated by the authors, and quality of life aspects were omitted.

As noted, data on risperidone indicate that it has an improved safety profile and superior clinical efficacy when compared with haloperidol. It has also been shown to reduce rates of hospitalization in certain psychiatric populations. Taken together, these factors should translate into improved quality of life and utility, as well as a decrease in relapse rates. Although risperidone costs more than haloperidol, the cost per QALY gained is comparable to that for many other acceptable health care interventions.

Further economic research is warranted to compare risperidone and existing conventional neuroleptics, in

addition to the various novel agents now available. As suggested by Curtis and Kerwin,[80] in the future newer agents should be compared with existing novel neuroleptics rather than with placebo or haloperidol.

## Conclusion

Canadian research has played a significant role in the investigation of risperidone. At the same time, there is a need for continuing research on risperidone, focusing on efficacy, long-term outcomes, and impact on resource use and quality of life. Furthermore, risperidone and newer neuroleptics should be compared with other novel neuroleptics. Canadian researchers are well positioned to continue their integral role in such research.

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