Pharmacoeconomics Made Simple

Risperidone Use in a Teaching Hospital During Its First Year After Market Approval: Economic and Clinical Implications[1]

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Abstract

Risperidone, a new antipsychotic drug, was recently approved by the Food and Drug Administration (FDA) on the basis of its having comparable efficacy and less toxicity than haloperidol. In a preliminary study to evaluate the therapeutic efficiency of this drug, we conducted a survey of risperidone utilization, cost, and safety during its first year of availability at an academic psychiatric hospital. Data were obtained from a computerized, centralized medical record system, from an adverse drug reaction monitoring system, and from pharmacy purchasing records. In its first year of availability, risperidone became the second most widely used antipsychotic agent at our institution. Most of this use extended beyond the adult schizophrenia population, for whom pre-marketing safety and efficacy data are available. The direct institutional cost of risperidone treatment exceeded the entire budget for antipsychotic drugs during the year before its release. Results from the adverse drug reaction reporting system did not indicate a strong advantage of risperidone over more established antipsychotic agents with respect to extrapyramidal side effects. Furthermore, the mean dose of risperidone associated with extrapyramidal symptoms was 3.5 mg/day, considerably lower than that suggested by pre-marketing studies in a more select patient group. These results confirm that new pharmacological agents are generally used in much broader patient populations than those for which efficacy and safety have been established prior to FDA approval. This study also raises questions about the therapeutic efficiency of risperidone compared with other antipsychotic drugs. We conclude that systematic studies of outcome, safety, and cost of new pharmaceuticals in naturalistic settings are needed to provide the data necessary to establish local standards of cost-effective care.

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Introduction

In recent years, dramatic changes in reimbursement for health care services in the United States have prompted the development of novel approaches to the evaluation of new and existing therapies. Pharmaceutical companies routinely collect data on efficacy and tolerance in controlled clinical studies to obtain FDA approval for a product. However, industry generally does not support the evaluation of therapies in naturalistic settings, and there has been a lack of funding from other sources. The result is an enormous gap in our knowledge of the impact of therapeutic agents in clinical practice for areas outside the conditions defined by entry criteria, particularly on low-volume, high-risk populations such as children, adolescents, and the elderly.

There is also an emerging emphasis on the cost-effectiveness of new treatments. For a new treatment to be considered advantageous in comparison to previously available therapies, it must demonstrate its advantages in one or more of three domains: efficacy, safety, and cost. As physicians develop local standards of accepted care, new therapeutic agents that are more costly than previ-

ously available agents must be shown to confer additional advantages in efficacy or safety to be considered therapeutically *efficient.*

Risperidone is only the second new antipsychotic introduced into the United States since 1975 (Kane 1994). The unique pharmacology of the drug reflects its selective action as an antagonist of D_2 and 5-HT_2 receptors in the brain (Ereshefsky 1993). In phase III studies, its therapeutic efficacy has been compared primarily to haloperidol. A Canadian multicenter phase III study (Chouinard et al. 1993) reported that 6 mg/day of risperidone was more effective than 20 mg/day of haloperidol on total ratings on the Positive and Negative Syndrome Scale (PANNS; Kay et al. 1986) and the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham 1988) ratings. The U.S. multicenter study (Marder & Meibach 1994) also reported greater efficacy for 6 and 16 mg/day of risperidone than for 20 mg/day of haloperidol, with significant improvement on negative symptoms noted for risperidone 6 and 16 mg/day but not haloperidol 20 mg/day. A multicenter, multinational European study (Peuskens 1995) reported comparable efficacy for 4, 8, 12, and 16 mg/day of risperidone and 10 mg/day of haloperidol. With regard to EPS, both North American multicenter studies reported dose-related effects in risperidone patients. In the Canadian study, drug-related parkinsonism was no greater for risperidone 2, 6, and 16 mg/day than for placebo. In the U.S. study, risperidone doses of less than 16 mg/day were associated with levels of drug-induced parkinsonism and overall EPS ratings comparable to those seen with placebo treatment. In the European multicenter trial, all risperidone groups except for the 16 mg/day arm experienced less dystonia, akathisia, and drug-related parkinsonism than did the 10 mg/day haloperidol group and required significantly less anticholinergic treatment.

The results of these controlled clinical studies suggest that risperidone is an effective antipsychotic agent that is relatively well tolerated and relatively free from EPS when used in doses around 6 mg/day. Whether these same results would be obtained in a broader treatment setting is entirely unknown. The participants in the phase III studies described above were typical for such protocols—physically healthy young adults with an unambiguous diagnosis of schizophrenia. Patients with schizoaffective disorder, concurrent mood disorder, substance abuse disorder, or seizure disorder were excluded from all three protocols.

In capitated systems of reimbursement, where fixed amounts of funding are available to pay for hospital care, aftercare, and medications, increased medication costs may necessitate cuts in other areas such as case management or psychosocial programs. Thus, the potential therapeutic advantages of an expensive new drug treatment such as risperidone need to be weighed along with its cost to assess the pharmacoeconomic impact of its use. In the only published study that specifically addresses the issue of direct cost, Davis (1994) reported that 4 mg of risperidone cost $4.38/day, while 10 mg of haloperidol cost $1.61 and 10 mg of fluphenazine cost $1.82. While these figures suggest that the direct cost impact of the introduction of risperidone should be modest, the author of this study acknowledges that this assessment may not be valid where lower cost, generic forms of haloperidol and fluphenazine are available. Therefore, pharmacoeconomic analyses of risperidone utilization should include collection of data on efficacy, tolerance, and local cost in the actual population of patients who receive treatment with the drug.

Risperidone's reputation for efficacy with low toxicity, which is based on pre-marketing studies conducted in patients with chronic schizophrenia, has resulted in a rapid increase in its use. But an assessment of risperidone's therapeutic *efficiency* requires an assessment of its efficacy, toxicity, and cost in routine clinical practice. We present results of a survey of drug utilization, cost, and reports of significant adverse drug reactions (ADRs) associated with the first year of risperidone use in a large psychiatric teaching hospital. Our first goal in presenting these data was to characterize the pattern of use of this new antipsychotic in clinical practice in contrast with its approved indication (chronic schizophrenia in adults). Second, we sought to determine the direct cost impact on the institution of risperidone use during this period. Finally, we attempted to obtain preliminary data on risperidone's potential advantage with regard to EPS, suggested by the published premarketing studies of this drug. While these results should be considered preliminary and subject to the limitations of collecting data in a naturalistic setting, they are also provocative and should serve to stimulate further systematic study of this new antipsychotic as it is used in the community. This reflects the work being done at the University of Pittsburgh's Center for Education and Research in Therapeutics (CERT), which has been established to conduct outcome-based pharmacoepidemiological research relating to the effective, safe and cost-efficient use of drugs.

Methods

These data examine the cost and tolerance of risperidone in patients treated at Western Psychiatric Institute and Clinic (WPIC) during its first year of use. WPIC is a 279-bed psychiatric teaching hospital affiliated with the University of Pittsburgh Medical Center (UPMC). It provides acute psychiatric care to a large urban catchment area and also serves as a referral center for psychiatric patients from suburban and rural southwestern Pennsylvania. The results of this study were obtained from existing computerized databases within the WPIC/UPMC pharmacy system. The number of hospitalized patients prescribed each of the five most commonly used antipsychotics (including risperidone) at our institution was generated from a hospital wide Medical Archival Retrieval System (MARS; Vries et al. 1994; Yount et al. 1991) in three-month quarters for 24 months. This includes three quarters prior to the marketing of risperidone, the quarter during which it was introduced (first quarter of 1994), and the four quarters following its introduction. The ages and discharge diagnoses of risperidone-treated patients were also obtained from the MARS. To provide information on the cost of risperidone use, the total expenditure by the pharmacy for each of these agents for 1993 and 1994 was generated from pharmacy purchasing records. ADRs for the first year of risperidone use (2/14/94–2/13/95) were identified from a pharmacist-initiated ADR monitoring system. At our institution, whenever an adverse event requires discontinuation of a drug, a dose reduction, or treatment with another agent such as an antidyskinetic, an antiparkinsonian agent, or a beta-blocker, a hospital pharmacist approaches the patient's physician to determine whether an ADR has occurred. In accordance with requirements of the Joint Commission on Accreditation of Healthcare Organizations, our institution defines an ADR as any reaction associated with a drug that adversely affects outcome, requires treatment, or prolongs hospitalization. The physician completes the report, which describes the ADR as well as medication dose, concomitant medications, and patient demographic information. This report is then reviewed at the monthly meeting of the Pharmacy and Therapeutics Committee, where a decision is made as to whether to report the ADR to the FDA. *It is important to note that the ADR system is entirely pharmacist-initiated and triggered by relatively standardized events. Its initiation does not depend on the judgment of the treating physician.* Finally, a chart review of patients experiencing EPS associated with risperidone treatment was conducted by one of the authors (C.S.C.) to identify whether a previous history of EPS associated with antipsychotic treatment had been documented and to confirm the dose of risperidone at the time of the ADR. Data related to the presence of concomitant medications as well as any other clinically relevant information related to these patients were also recorded.

Results

Antipsychotic utilization patterns (total number of oral prescriptions written) are shown in Figure 1. The overall increase in the total number of patients treated per quarter reflects shorter lengths of stay with constant bed occupancy. Prior to the introduction of risperidone, perphenazine was the most frequently prescribed agent and haloperidol the second most frequently prescribed. Over the following year, risperidone became the second most frequently prescribed antipsychotic.

During its first year of use at WPIC, risperidone was given to 285 patients: 12 (4%) were under age 18, 231 (81%) were 18 to 60 years of age, and 42 (15%) were over age 60. Almost 20 percent were children, adolescents, or elderly. Table 1 shows the *DSM-IV* (American Psychiatric Association 1994) diagnoses of risperidone-treated patients during this period. Risperidone was

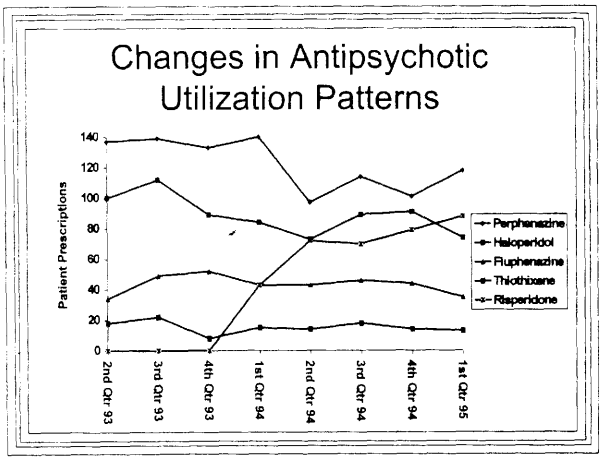

FIGURE 1. Number of patients prescribed each of the five most commonly used antipsychotic drugs for the last 3 quarters of the year before and the first year of risperidone use.

TABLE 1. Number of Patients (%) Treated with Risperidone (*n*=285) by Diagnostic Group for First Year of Use at Western Psychiatric Institute and Clinic.

Disorder	*n* (%)
Schizophrenia/schizophreniform	68 (24)
Schizoaffective	49 (17)
Psychotic disorder not otherwise specified	16 (6)
Mood	90 (32)
Organic mental	36 (13)
Childhood	7 (2)
Other	19 (7)

widely used in the treatment of disorders other than schizophrenia, although pre-marketing efficacy and safety studies were conducted exclusively in patients with this diagnosis.

Figure 2 shows the total expenditure for each of the most commonly used antipsychotics at WPIC during 1993 and 1994, the first year of risperidone availability. It should be noted that competitive bidding for generic preparations of perphenazine, fluphenazine, and thiothixene permitted greater reduction in cost for these three drugs than did reduced utilization between these 2 years. Although risperidone was being ordered in significant quantities for only the last 8 months of 1994, it accounted for 76.7 percent of the total cost of antipsychotics purchased during this year, and its cost during this period exceeded the total expenditure for all antipsychotics for the previous year.

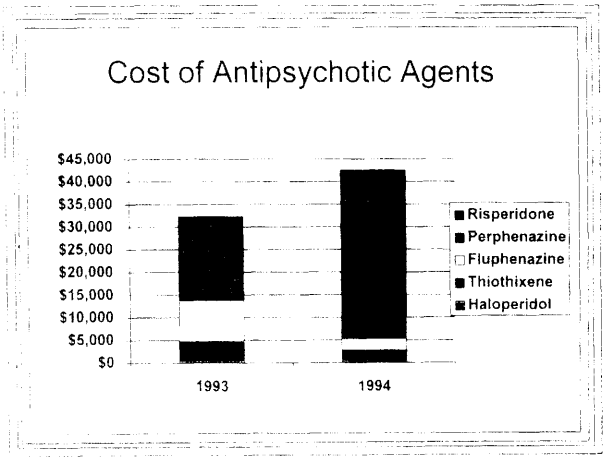

FIGURE 2. Comparison of the total cost for each of the five most commonly used oral antipsychotic agents during 1993 and 1994. (Based on Western Psychiatric Institute and Clinic pharmacy purchasing records.)

Table 2 shows the proportion and characteristics of patients treated with antipsychotic medications in the year following risperidone's introduction for whom an ADR report associated with EPS was filed. In all cases the dose of risperidone associated with EPS was 6 mg/day or less. The mean dose was only 3.5 mg/day, which is considerably lower than the 10 to 16 mg range associated with EPS in the controlled clinical trials described above. The demographic and diagnostic characteristics of the 6 patients experiencing EPS during risperidone treatment, together with concomitant medications, are shown in Table 3. Of these patients, 1 had been identified as being highly sensitive to EPS, while 2 others had histories of EPS during previous antipsychotic treatment; 1 patient had been previously treated with neuroleptics without developing EPS; the 2 remaining patients were neuroleptic naive. Regarding concomitant medications, 1 patient was being concurrently treated with fluphenazine 7.5 mg/day and benztropine mesylate (Cogentin) 1 mg b.i.d. and 2 were concurrently receiving paroxetine 20 mg/day, which may be associated with increased plasma concentrations of risperidone.

Discussion

Since receiving FDA approval in 1994, risperidone has rapidly become a first-line choice in antipsychotic therapy. This change in the standard of practice in the treatment of psychosis is reflected at our institution. The number of patients treated with risperidone increased steadily while the numbers treated with the two most commonly prescribed agents, perphenazine and haloperidol, decreased during this time period. By the end of the first quarter of 1995 more patients were treated with risperidone than with haloperidol.

The pattern of risperidone use confirms this, despite the fact that therapeutic efficacy has been demonstrated only for the short-term treatment of (predominantly) young adults with schizophrenia. Once this agent became commercially available, it was quickly introduced to a broad patient population. Only 24 percent of risperidone-treated patients had schizophrenia or schizophreniform disorder. Similarly, while 4 percent of patients were under 18 years of age and 15 percent were 60 years of age or older, no data relating to efficacy or safety in children, adolescents, or the elderly are available. Clearly, more data are needed on both the efficacy

TABLE 2. Adverse Drug Reaction (ADR) Reports at WPIC During First Year of Risperidone Use.

Antipsychotic	Number[a]	Age[b]	Gender F:M	Mean Dose (mg/day)	Syndrome, *n*
Perphenazine	8/462 (1.7%)	43.0 (10.4)	6:2	16.6 (8.5)	Akathisia, 5 Parkinsonism, 2 Dystonia, 1
Risperidone	6/285 (2.1%)	31.5 (14.1)	3:3	3.5 (1.0)	Parkinsonism, 2 Dystonia, 3 Akathisia, 1
Fluphenazine	3/165 (1.8%)	36.0 (1.0)	2:1	6.1 (1.3)	Akathisia, 3
Haloperidol	6/341 (1.8%)	32.2 (8.9)	1:5	7.3 (2.9)	Akathisia, 3 Dystonia, 3

NOTE: Where numerical means are given standard deviations are in parentheses.
No ADRs were filed for thiothixene.
[a]Denominators and percentages refer to the total number of patients prescribed these agents from 2/14/94 through 2/13/95.
[b]Values are mean (± standard deviation).

TABLE 3. Characteristics of Patients for Whom Risperidone-Related Adverse Drug Reactions for Extrapyramidal Symptoms (EPS) Were Reported.

Demographics Age (yrs), sex	Diagnosis	Risperidone Dose	EPS Type	Previous EPS	Concomitant Medication
41, female	Chronic schizophrenia	1 mg b.i.d.	Dystonia	Yes, highly sensitive	None
20, male	Bipolar disorder (first episode)	2 mg b.i.d.	Dystonia	None	None
17, female	Chronic schizophrenia, Mild mental retardation	1 mg q a.m. 2 mg q h.s.	Parkinsonism	Yes	None
52, male	Major depression, Organic mental disorder	2 mg q h.s.	Dystonia	None	Paroxetine 20 mg q a.m.
21, male	Organic personality disorder, Mental retardation	2 mg b.i.d.	Parkinsonism	None	Paroxetine 20 mg q a.m.
38, female	Chronic schizophrenia, Polysubstance dependence	3 mg b.i.d.	Akathisia	Yes	Fluphenazine 7.5 mg/day, benztropine 1 mg b.i.d.

and safety of risperidone treatment in a broader population than that in the published pre-marketing studies.

Given the broad diagnostic and demographic population in which risperidone was used during its first year of availability and the prominent role it has assumed in the treatment of psychosis, it is important to begin to evaluate the therapeutic efficiency of this compound. This evaluation will require the systematic collection of data related to efficacy, toxicity, and cost *in the local setting*. Significant advantages in efficacy or toxicity must be evident to justify a costly agent as the local standard of care. While we did not collect data on the comparative efficacy of risperidone, our survey results on its relative cost and toxicity, discussed below, raise questions about the therapeutic efficiency of this agent.

It is striking that the direct cost to the institution during the first year for risperidone exceeded the previous year's entire expenditure for the four most frequently prescribed antipsychotic drugs. One would expect that a new drug would be required to confer a

decided advantage in either efficacy or safety to justify this kind of cost differential. Addington and colleagues (1993) reported on a small group of patients (n=27) who completed a 1-year open-label trial of risperidone therapy. They showed a significant reduction in the number of days of hospitalization during their year on risperidone compared with the previous year. However, the overall attrition rate was very high (64% of patients dropped out), and there was no control group. Except for this one inconclusive study, there are no published data to suggest that risperidone is likely to yield a cost advantage over other drugs as a result of reduced hospitalization rates. In view of the observed tremendous cost differential associated with risperidone treatment, it is critical to undertake a controlled pharmacoeconomic analysis of long-term, community-based risperidone treatment versus conventional antipsychotic treatment.

While equivalent efficacy to haloperidol was demonstrated in the phase III studies, risperidone's chief advantage over haloperidol 10 and 20 mg/day was its lower prevalence of EPS in the lower dosage ranges (6 to 8 mg/day). Thus, one major clinical rationale for using risperidone rather than an older antipsychotic drug is the expectation that risperidone is less likely to cause significant EPS. This may explain the large use of risperidone we observed for conditions and in patient populations for which controlled data supporting its efficacy and safety are not yet available. However, the profile of ADRs in the naturalistic setting of the present study suggests that risperidone produced rates of EPS-related ADR's comparable to those seen with other antipsychotics. This finding must be interpreted cautiously, however. Overall, the rate of ADRs was low, presumably because EPS are expected side effects of antipsychotic medications and may be tolerated to some degree by patients and clinicians in our institution. However, while our mechanism for identifying EPS may have underestimated their prevalence, it should not have affected the relative number of cases attributed to risperidone versus other antipsychotics. It is also possible that patients may have been selected for risperidone treatment because of a history of heightened sensitivity to EPS, although our chart review suggests that this was the case for only 1 of the 6 observed cases of risperidone-associated EPS. It is noteworthy that the mean dose of risperidone associated with EPS of sufficient severity to generate an ADR was less than 4 mg per day, clearly below the dose range associated with EPS in the pre-marketing studies. This may be explained in part by differences between patients who received risperidone at our institution and those studied in the clinical trials. Table 3 indicates that only 1 of the patients for whom an EPS-related ADR was reported would have met entry criteria for the phase III studies. This intriguing finding should stimulate further systematic post-marketing studies to establish how well the phase III results relate to clinical experience in the broader patient population for whom risperidone is being prescribed.

The results of this study confirmed the widespread, "off-label" use of the new antipsychotic agent risperidone during its first year of availability. Our results indicate a strikingly high cost associated with the use of this drug. While we did not collect data on efficacy in this preliminary study, our data on toxicity did not appear to confer a strong advantage for risperidone over other agents with respect to EPS related ADRs. Thus, the therapeutic efficiency of risperidone compared with other antipsychotic drugs remains to be determined. Clearly, further systematic studies that address efficacy as well as toxicity are needed before the appropriate role for risperidone in the treatment of psychosis is established.

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