# A Dose-Outcome Analysis of Risperidone

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***Background:*** Although the establishment of appropriate dosage ranges for antipsychotics has important ramifications for both short-term treatment and long-term therapeutic outcomes, difficulties in dosing persist. Evidence exists that initial dosing recommendations for the titration of risperidone to 6 mg/day in 3 days are excessive. This study examines dosage trends of risperidone and further examines the relationship between dose and outcome by determination of discharge rates among individuals receiving varying doses of the drug.

***Method:*** Records of individuals receiving risperidone in Maryland state psychiatric facilities from March 1994 through February 1997 (N = 1056) were examined. Discharge rates and time to discharge were measured by Kaplan-Meier survival curve analysis.

***Results:*** As risperidone use has risen each year since its introduction, mean doses in both inpatients and discharged patients have steadily declined. Additionally, risperidone doses for discharged patients were significantly lower than those for patients remaining in the hospital. Furthermore, patients receiving 2 and 4 mg/day were significantly more likely to be discharged than those receiving 6 mg/day (log-rank $\chi^2 = 13.54$, df = 2, p = .0011). This difference was seen in patients with similar diagnoses, ages, and racial status.

***Conclusion:*** Patients treated with doses less than the 6-mg/day initial dosing recommendations have better outcomes in terms of discharge. This finding should encourage clinicians to utilize adequate trials of risperidone aimed at stabilizing patients on doses in the 2- to 4-mg/day range before proceeding to higher doses.

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Although the establishment of appropriate dosage ranges for antipsychotics has important ramifications both for short-term treatment and long-term therapeutic outcomes, difficulties in dosing persist. Since the introduction of chlorpromazine in the 1950s, clinicians and researchers have utilized a variety of methods to determine the appropriate dosage ranges for antipsychotics. These methods have remained somewhat unsatisfactory. Decades after the introduction of antipsychotics, optimal dosage ranges remain controversial, with prescribed doses of these agents varying from 25 to 7000 mg/day in chlorpromazine equivalents.[1,2] The subjective nature of psychiatric symptoms, difficulties in diagnosis, and the lack of simple physiologic correlates of response (such as blood pressure or blood glucose levels) further complicate dosing.

Appropriate dosing for the atypical antipsychotics similarly has been difficult to establish. There is no clear biochemical model, such as dopamine $D_2$ receptor occupancy, to help establish appropriate clinical dosing for these drugs. Also, because these drugs have substantially fewer and less prominent extrapyramidal side effects,[3] there is no longer a natural barrier to the use of excessive doses. Furthermore, therapeutic effects of these agents may be confused with lack of effectiveness. When individuals are switched to these agents from conventional antipsychotics, families, support staff, and even clinicians may interpret increased vocalization, improvements in motivation and socialization, and higher activity levels as agitation, anxiety, or excitement and consider increasing the dose.

The current dosing recommendations for atypical antipsychotics originate from doses used in initial clinical efficacy trials. These efficacy trials of 6 to 8 weeks tend to focus on a carefully selected group of acutely psychotic individuals with few or limited comorbid disorders. Patients are often excluded if they require concomitant medications, especially other psychoactive agents. Furthermore, long-term follow-up studies in naturalistic populations are rarely conducted and are generally not available prior to marketing. Efficacy trials may not reflect how patients in "real world" clinical settings will be treated or will respond to treatment. Hence, dosing recommendations based upon stringent efficacy trials may not adequately reflect the most effective doses.

Risperidone is a prime example of a drug whose dosage recommendation and labeling conflict with its current use. The first multicenter study of risperidone displayed a dose-efficacy curve that appeared to peak at 6 mg/day.[4,5] This same trial reported an increasing risk of EPS as the dose increased above 6 mg/day. Thus, the manufacturer recommended administering risperidone 1 mg b.i.d. on the first day, 2 mg b.i.d. on the second day, and 3 mg b.i.d. on the third day. Although the routine dosing titration to 6 mg/day was recommended, product labeling listed the maximum dosage as 16 mg/day, supported by the observation of a few responders at higher levels. However, these pivotal studies examined only a few widely spaced dosage levels: 2 mg, 6 mg, 10 mg, and 16 mg daily.

In the years since risperidone's introduction, many clinicians have recognized that routine titration to 6 mg/day in 3 days is not appropriate for most patients. A European multicenter study[6] of 1362 patients reported risperidone to have a bell-shaped dose-response curve peaking at about 4 mg/day for its therapeutic effects. This study did not receive the attention or publicity received by the North American clinical trials. This trial was replicated by another European study[7] in chronic patients with schizophrenia, which found the 4-mg/day dose to be the most efficacious dose. Recently, another trial reported as well that the optimal dose of risperidone, in terms of both efficacy and safety, was 4 mg/day.[8]

Investigators have examined risperidone dosing trends in a few naturalistic studies using large databases. Bouchard et al.[9] found a correlation between higher doses of risperidone and poorer response of both positive and negative symptoms. The Alpha project in Germany (N = 2000) has found a mean dose of 4.7 mg/day of risperidone.[10] Likewise, the Cleveland Veteran's Affairs Medical Center has found the mean dose of risperidone to be around 5 mg/day.[11] Studies utilizing existing data involve analyses on large numbers of subjects whose illness is complicated by unclear diagnoses, comorbid conditions, and other factors normally excluded from efficacy studies. Although naturalistic studies do not provide response rates in terms of standard rating scales, they do allow for the examination of dosing in relation to other commonly accepted outcome measures such as discharge or rehospitalization.

This study examines dosing trends for risperidone in a state hospital population from March 1994 through February 1997. It further examines the relationship between dose and outcome by determining discharge rates among individuals receiving varying doses of the drug.

## METHOD

This study was designed to prospectively evaluate the effect of the introduction of all novel antipsychotics in Maryland state inpatient facilities with regard to hospitalization status and dosing trends. Records of inpatients in State of Maryland psychiatric hospitals were included in the analysis. In accordance with Federal Regulation 45 CFR 46.101.b, this protocol was reviewed and determined exempt from written informed consent by the University of Maryland Institutional Review Board. All patients within state facilities prescribed risperidone from March 1994 through February 1997 were evaluated. This antipsychotic database, consisting of 1056 records for inpatients who received risperidone, comprises 6 major public psychiatric facilities located throughout the state that account for 92% (2024/2205) of beds in the state facilities in Maryland. These facilities comprise an ethnically and geographically diverse group of patients. To classify appropriate diagnoses, chart reviews were performed by 2 members of the investigative team to verify most recent diagnoses according to DSM-IV criteria.

Mean doses of risperidone for patients discharged, patients retained, and total patients were assessed for each year from 1994 through 1996. Each patient's maximum stabilized dose during inpatient treatment, defined as the highest dose that a patient received for at least 2 weeks during hospitalization, was the dose used in the analysis. This was also the dose the patient was discharged on in > 99% of cases (in only 2 of 1056 cases was the discharge dose different than the maximum stabilized dose). Further, we examined the 1996 data set to determine dose by age and diagnosis. Finally, we compared discharge rates on various low doses (≤ 6 mg/day) of risperidone.

Two-tailed unpaired Student t tests were used to compare mean doses and demographic variables between those who were discharged and those who remained hospitalized. Means among 3 variables were analyzed by 1-way analysis of variance (ANOVA). Changes of risperidone dosing over time were analyzed by repeated-measures ANOVA using Greenhouse-Geisser–corrected degrees of freedom. The Fisher exact test was used to compare the percentage of patients discharged on higher doses versus lower doses. To measure time to discharge, we used survival analysis. Survival curves were estimated by the product-limit (Kaplan-Meier) formula. Significance of difference between the dosing ranges was measured by the log-rank chi-square test.

## RESULTS

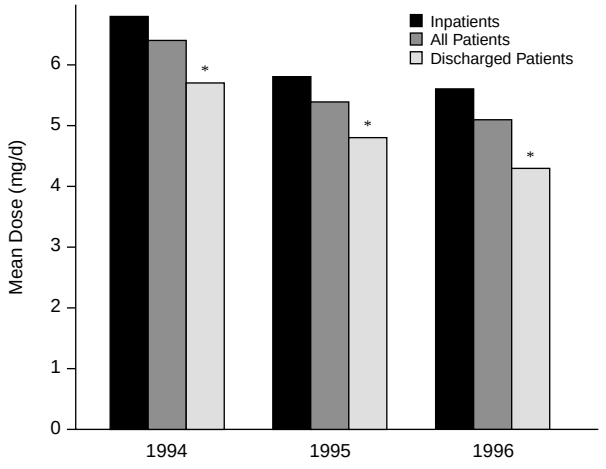
The study group represented by this computerized database contained 1056 patient records. Patients ranged in age from 13 to 91 years (mean ± SD = 41.36 ± 15.31 years). The population was 59% male and 41% female. The mean ± SD time on risperidone treatment during hospitalization was 175.32 ± 226.46 days (range, 2–991 days).

The use of risperidone in the Maryland Mental Health System increased each year after its introduction in 1994. Two hundred sixty-two patients in the system began treat-

Table 1. Risperidone Use in Maryland by Age and Diagnosis in 1996

| Variable | % of Patients Using Risperidone |
|---|---|
| Age (y) | |
| < 20 | 8 |
| 20–39 | 47 |
| 40–64 | 37 |
| > 64 | 8 |
| Diagnosis | |
| Schizophrenia | 34 |
| Schizoaffective disorder | 28 |
| Bipolar disorder | 13 |
| Dementia | 2 |
| Other | 23 |

Figure 1. Mean Risperidone Dose Per Year[a]

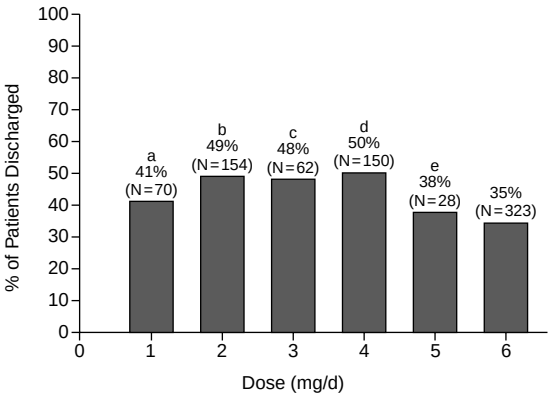



[a]A significant decrease occurred in dose over time for all patients (ANOVA: F = 13.91, df = 2,1054; p < .001), for inpatients (ANOVA: F = 7.21, df = 2,658; p < .001), and for discharged patients (ANOVA: F = 7.94, df = 2,393; p < .001).
*p < .05, discharge dose vs. inpatient dose.

ment with risperidone in the first year of its availability (1994), increasing to 345 in 1995 and 449 in 1996, despite a stable or dropping census in the 8 facilities surveyed. Table 1 demonstrates the 1996 usage of risperidone by patient age and diagnosis.

Overall, the mean risperidone dose declined significantly in the first 3 years of its availability (Figure 1). The mean ± SD dose in 1994 was 6.4 ± 3.6 mg/day, followed by mean ± SD doses of 5.4 ± 3.1 mg/day in 1995 and 5.1 ± 2.9 mg/day in 1996 (ANOVA: F = 13.91, df = 2,1054; p = .0001). Doses for those who were discharged and those who remained hospitalized both declined significantly as well (F = 7.94, df = 2,393; p < .001 and F = 7.21, df = 2,658; p < .001, respectively). The mean ± SD dose by age group was 3.1 ± 1.8 mg/day for those aged < 20 years, 5.3 ± 2.8 mg/day for those aged 20 to 39 years, 5.5 ± 3.1 mg/day for those aged 40 to 64 years, and 4.3 ± 3.0 mg/day for those over the age of 64. In 1996,

Figure 2. Twelve-Month Discharge Rates for Patients Receiving Low Doses of Risperidone



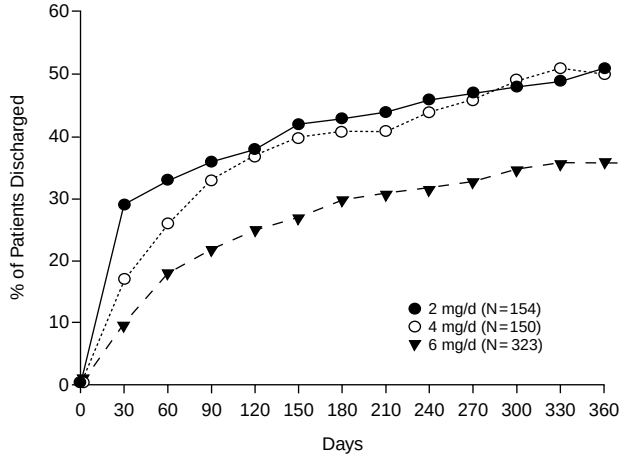

[a]1 vs. 6 mg/day; log-rank $\chi^2 = 1.80$, df = 1, p = .1801.
[b]2 vs. 6 mg/day; log-rank $\chi^2 = 11.08$, df = 1, p = .0009.
[c]3 vs. 6 mg/day; log-rank $\chi^2 = 4.90$, df = 1, p = .0269.
[d]4 vs. 6 mg/day; log-rank $\chi^2 = 7.89$, df = 1, p = .0050.
[e]5 vs. 6 mg/day; log-rank $\chi^2 = 0.02$, df = 1, p = .8925.

individuals with a diagnosis of schizophrenia received the highest doses, a mean ± SD of 6.2 ± 3.0 mg/day, while those with schizoaffective disorder received a mean ± SD dose of 5.6 ± 3.0 mg/day, those with bipolar disorder received 3.9 ± 2.1 mg/day, and those with dementia 3.5 ± 1.6 mg/day.

In each year, patients successfully discharged on risperidone therapy were treated with significantly lower mean ± SD doses than those who remained inpatients (1994: 5.7 ± 3.5 vs. 6.8 ± 3.7 mg/day; t = 2.39, df = 261, p < .05; 1995: 4.8 ± 2.3 vs. 5.8 ± 3.4 mg/day; t = 3.45, df = 334.2, p < .01; 1996: 4.3 ± 2.5 vs. 5.6 ± 3.0 mg/day; t = 4.77, df = 406.3, p < .01) (see Figure 1). A greater percentage of patients receiving 6 mg/day or less were discharged than of those receiving greater than 6 mg/day (42% [328/787] vs. 25% [67/269]; Fisher exact test, p < .001).

We examined the rates of discharge for doses up to 6 mg/day. The total percentages of patients discharged by dose at 1 year following the start of treatment are listed in Figure 2. The 6-mg/day dose was used as a comparator arm to the other doses. The 2-, 3-, and 4-mg/day cohorts were found to have significantly higher rates of discharge than the 6-mg/day cohort. A total of 38%, 34%, 38%, and 54% of patients in the 2-, 3-, 4-, and 6-mg/day groups, respectively, had a schizophrenic diagnosis at discharge. Thus, we analyzed these dosage groups within the schizophrenia diagnosis to test whether diagnosis was driving the significant differences in the overall group. Both the 2- and 4-mg/day groups were found to have higher discharge rates than the 6-mg/day group within the schizophrenic cohort (2 vs. 6 mg/day: log-rank $\chi^2 = 10.12$, df = 1, p = .0015; 4 vs. 6 mg/day: log-rank $\chi^2 = 6.87$,

Figure 3. Discharge Rate by Risperidone Dose[a]




[a]Log-rank $\chi^2$ (3 doses) = 13.54, df = 2, p = .0011; 2 vs. 6 mg/day: log-rank $\chi^2$ = 11.08, df = 1, p = .0009; 4 vs. 6 mg/day: log-rank $\chi^2$ = 7.89, df = 1, p = .0050; 2 vs. 4 mg/day: log-rank $\chi^2$ = 0.21, df = 1, p = .6455.

df = 1, p = .0088). The percentages of patients discharged at 1 year with a schizophrenic diagnosis at 2, 4, and 6 mg/day were 51%, 52%, and 32%, respectively. The group of schizophrenic patients who received 3 mg/day did not have a significantly higher discharge rate than the 6-mg/day group (49%, log-rank $\chi^2 = 1.37$, df = 1, p = .2416) most likely owing to the small sample size of the 3-mg/day group. In patients with other diagnoses, the rates were similar: 48%, 49%, and 35% in the 2-, 4-, and 6-mg/day groups, respectively.

Figure 3 illustrates the time course to discharge in the 2-, 4-, and 6-mg/day cohorts for all diagnoses. The mean ± SD ages of the 2-, 4-, and 6-mg/day groups were 39.72 ± 16.02, 41.86 ± 17.53, and 40.77 ± 13.71 years, respectively (1-way ANOVA: F = 0.750, df = 2,624; p = .4730. The sex breakdown in all 3 dose groups was 60% male. The mean ± SD lengths of hospitalization prior to starting risperidone were 563.3 ± 2054.3, 771.3 ± 1644.3, and 771.1 ± 1670.5 days in the 2-, 4-, and 6-mg/day dosage groups, respectively. Thus, the 2- and 4-mg/day doses were associated with significantly higher discharge rates than the 6-mg/day dose; the differences were not accounted for by age, diagnosis, length of prior hospital stay, or sex.

## DISCUSSION

To our knowledge, this is the first study to examine dose-outcome relationships for a second generation antipsychotic in a large population. The data generated in the Maryland Mental Health System is particularly relevant for several reasons. The population studied is large and inclusive of essentially all use within state inpatient facilities. Furthermore, the population studied consists of all individuals receiving antipsychotic drugs prescribed by over 100 clinicians in 6 different facilities from throughout the state, eliminating the bias of reporting data from only a small number of prescribers.

We observed a trend toward progressively lower doses over the years since the introduction of risperidone. This trend might reflect the learning curve of clinicians, who have established optimal dosing strategies by experience rather than by reliance on product labeling. This decrease in dosing is not accounted for by an increase in the proportion of older patients receiving risperidone. In fact, in Maryland's inpatient system, use in older individuals has declined since 1994 in concert with the census of the facilities. The doses of risperidone employed in both those discharged and those remaining hospitalized have also declined significantly since its introduction in 1994. Differential efficacy between high and low doses, a greater rate in side effect occurrence, or a tendency to treat more refractory patients with higher doses may explain these findings. However, the finding that doses lower than 6 mg/day are used in similar patient groups argues against this possible confound of refractory patients. If one accepts length of hospital stay prior to starting risperidone as a proxy for chronicity, this measure demonstrates that the dosage groups had no significant differences. However, lengths of stay were long in all of the groups. This finding points to the fact that dosage selection was independent of the chronicity of illness or of episode.

The North American trials failed to consider risperidone doses between 2 and 6 mg/day.[10,11] Perhaps this failure led the manufacturer to misinterpret the dose-response curve as being shifted to the right and recommend higher-than-necessary doses. Our study found that lower doses are associated with better outcomes. Specifically, the 2- and 4-mg/day doses were found to be statistically superior to the 6-mg/day dose in discharge rates. This finding is similar to other more recently published randomized and naturalistic studies,[10–12] which state that most patients are receiving less than 6 mg/day of risperidone. Although these data suggest that a therapeutic dose-response window exists for risperidone, it is possible that an increased incidence of adverse effects affects outcomes at higher doses. In any case, our finding that low doses of risperidone are associated with superior discharge rates should encourage clinicians to utilize adequate trials of risperidone aimed at stabilizing patients on doses in the 2- to 4-mg/day range before proceeding to higher doses. The finding may also indicate that individuals who previously failed to respond to higher doses of risperidone may benefit from a dosage reduction or a retrial at a lower dose.

Although the focus of this study is not economic, it is obvious that lower doses may also result in reductions in drug costs. Since hospital costs are one of the primary determinants of the total cost of care, the differences seen in

discharge rates when lower doses are employed may lead to substantial overall savings. At a time when cost management is playing an increasing role in decisions regarding care, it is essential that both clinicians and policy makers recognize the potential savings that can be accrued when promoting appropriate dosing of risperidone.

In conclusion, this study demonstrates a consistent reduction in the dosing of risperidone employed since its introduction in the state of Maryland. It further demonstrates that lower doses, in the 2- to 4-mg/day range, are associated with a significantly greater likelihood of discharge than the 6-mg/day dose, which was promoted in the product labeling. Additional studies are under way to prospectively examine similar trends with other novel antipsychotics.

*Drug names:* chlorpromazine (Thorazine and others), risperidone (Risperdal).

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