Alteration in the Recommended Dosing Schedule for Risperidone

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Objective: *The authors' goal was to study the recommended dose schedule for risperidone.* *Method:* *They obtained computerized pharmacy data on 1,283 inpatients with the diagnoses of schizophrenia or schizoaffective disorder who were treated with risperidone. Continuance on risperidone was defined as remaining on the drug for 16 days or until discharge.* *Results:* *The majority of the patients (84%) continued on risperidone. Use of the recommended dose schedule decreased greatly over time. Patients were more likely to continue on risperidone if they had a higher maximum dose (5.7 mg/day versus 4.7 mg/day), a longer number of days to maximum dose (5.7 days versus 3.9 days), and a maximum rise in dose of 0.5–2 mg/day.* *Conclusions:* *These findings suggest that the recommended dose schedule should be altered to one that recommends a less rapid titration (over 6 days to a week) and that the dose increments consist of 0.5–2 mg/day.*

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The research that establishes the safety and effectiveness of a new psychotropic agent may not provide adequate information to determine which dose and, even more so, which dose schedules produce optimal benefits (1–3). For example, risperidone is marketed with the following information in the package insert: "Risperidone should be administered on a BID schedule, generally beginning with 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day" (1996 edition of *Physician's Desk Reference*). Subsequent clinical experience indicated that this drug regimen was probably too aggressive for most patients. A slower increase is encouraged, and many patients respond optimally to doses other than 6 mg/day (4). However, we are unaware of any systematic study to support these clinical impressions.

The availability of a pharmacy database serving more than 2,000 beds in state-operated facilities in Illinois allowed us to assess the clinical appropriateness of the recommended dose schedule and to inform us regarding alternative dose regimens.

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METHOD

Subjects. Subjects included all patients with DSM-IV diagnoses of schizophrenia or schizoaffective disorder who received a prescription for risperidone between February 1994 and February 1996 (N=1,283).

Measures: prescribing variables. We first looked at the use of what has been the recommended dose schedule for risperidone. Other measures were used to characterize dosing patterns. The maximum rise in dose between any 2 days was calculated for the first 8 days. In addition, we looked at the maximum dose achieved within the first 16 days and the number of days to maximum dose.

Measures: outcome variables. The major outcome examined was continuation on risperidone for at least 16 days or until discharge if this occurred earlier. This time period provided physicians the opportunity to assess the patients' tolerance for the medication.

Measures: trends over time. Dosing patterns were examined over 10 time periods; the first nine time periods were for 75 days each, and the last was limited to 55 days because the study period ended.

RESULTS

Subjects. The majority of the subjects (N=834, 65%) had schizophrenia; the remainder (N=449, 35%) had schizoaffective disorder. Two-thirds of the patients were men (N=854), and their average age was 39 years (SD=11).

Use of Recommended Dose Schedule

1. Change over time. Overall, only 13% of the patients (N=167) received the recommended dose schedule during the study period. Rate of use of the recommended dose schedule decreased greatly from 24% (N=55) in the first 75 days to 3% (N=2) in the last period.

2. Discontinuance. For the majority of the study periods examined, the rate of discontinuation on the recommended dose decreased over time relative to discontinuation on other doses as the rate of prescribing the recommended dose decreased. The initial discontinuation rate for the recommended dose schedule was 15%, but in the second to the seventh time period, discontinuance on the recommended dose schedule decreased to 0%. At that point, it looked as if physicians were using this pattern more judiciously and therefore more successfully. However, for the last three time periods the recommended dose schedule fell into relative disuse; it was used only twice per period.

Other Dose Measures

1. Maximum dose and number of days to maximum dose. The maximum dose achieved within the first 16 days averaged 5.5 mg/day (SD=2.4). The mean number of days to maximum dose was 5.4 days (SD=4.3).

Relationship to continuation. Overall, 84% of the subjects (N=1,072) continued on risperidone. Patients who received higher maximum doses (mean=5.7 mg/day, SD=2.3) were more likely to continue than those receiving lower doses (mean=4.7 mg/day, SD=2.6) ($t=5.09$, df=235, $p<0.001$, Student's t test). Patients were also more likely to continue when the maximum dose was reached over a longer period of time. Patients who continued had a mean number of days to maximum dose of 5.7 days (SD=4.4), compared with a mean of 3.9 days (SD=3.5) among those who discontinued ($t=–6.41$, df=292, $p<0.001$, Student's t test).

2. Maximum rise in dose. The mean maximum rise in dose was 1.4 mg/day (SD=1.3).

Relationship to continuation. For the purpose of the analysis of the relationship between continuation and dose increases, patients were included only if they did not have a decrease in dose that might have compensated for too much of an increase (N=1,139). The maximum rise in dose was divided into five levels: 0 mg/day, 0.5–1 mg/day, greater than 1–2 mg/day, greater than 2–4 mg/day, and greater than 4 mg/day. Discontinuation was most frequent in individuals with dose increases of greater than 2–4 mg/day (33%, N=376) and less in those with increases of 0.5–1 mg/day (16%, N=182) or greater than 1–2 mg/day (11%, N=125) ($\chi^2=26.84$, df=4, $p<0.0001$). Both no increase and extreme increases (greater than 4 mg/day) were associated with discontinuance rates of about 20%.

3. Multivariate analysis. Logistic regression was used to examine the relative influence of dose factors on the continuation of risperidone, including the first-day dose, the maximum rise in dose, the maximum dose, and the number of days to maximum dose. Demographic variables (age and gender) were also included. Forward step-wise regression with the likelihood ratio test was used to identify those variables with the strongest relationship to continuation on risperidone. A Bonferroni correction was used to allow for the use of six variables, requiring a p value of 0.008 as the criterion for statistical significance. The number of days to maximum dose was strongly related to continuation (Wald statistic=12.71, df=1, $p<0.001$). Once this variable was entered, no other variables were significant. The model 2 likelihood chi-square for all variables at this point in the equation was 36.29 (df=2, $p<0.0001$). This represented an improvement in chi-square of 11.05 (df=1, $p<0.001$).

DISCUSSION

There appear to be four main findings. First, over time, the recommended dose schedule was used in a smaller proportion of patients to the point of almost not being used at all. This suggests that physicians viewed this schedule with increasing skepticism and were far more selective in their use of this aggressive regimen.

Second, we found that patients who continued on risperidone had a mean dose of 5.7 mg/day, which is very close to the recommended dose. Patients who discontinued had lower doses, suggesting an inability to achieve a more therapeutic dose, perhaps due to side effects.

Third, patients who continued on risperidone had a mean number of days to maximum dose of 6 days, but those who discontinued had a mean of 4 days. Although the initial titration schedule called for achieving a therapeutic dose within 3 days, a period of almost twice that long might be optimal.

Fourth, a maximum increase of 0.5–2 mg/day was associated with lower rates of discontinuation, but increases of greater than 2 mg/day were associated with higher rates of discontinuation.

With this in mind, we suggest that the recommended dose schedule be changed to one that recommends a less rapid titration schedule (over 6 days to a week) and that dose increments consist of 0.5–2 mg/day rather than a general recommendation of 2 mg/day.

This study also suggests that the use of large pharmacy databases to monitor the actual clinical experience of newly introduced drugs can be helpful in devising more appropriate dose schedules.

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