Supplemental Material for "Effectiveness of Switching Antipsychotic Medications" by Essock et al. (Am J Psychiatry 2006; 163:2090–2095)

CATIE Study Design

Individuals were randomly assigned to receive one of the five study antipsychotics under double-blind conditions, without consideration for their current antipsychotic treatment. The randomization was stratified such that individuals with tardive dyskinesia at baseline were excluded from randomization to perphenazine. The dose of the medications was flexible, ranging from one to four capsules daily, and was based on the study doctor's judgment.

"Stayers" and "Switchers"

Individuals who were taking two or more antipsychotic medications at study entry and who were assigned to take something different than either of their study entry medications were categorized as "switchers." We excluded individuals who could not be categorized as "stayers" or "switchers." Specifically, we excluded individuals who were taking more than one antipsychotic at study entry if one of their antipsychotic medications included the medication to which they were randomly assigned—these individuals neither stayed on their study entry medication regimen (because they discontinued one of their antipsychotic medications) nor did they switch medications (because the antipsychotic medication they were assigned to take was one of the medications they were taking at study entry). Hence, we excluded from the olanzapine group 16 individuals who were taking olanzapine plus one other antipsychotic

medication at study entry, and we excluded from the risperidone group 12 individuals who were taking risperidone plus one other antipsychotic medication at study entry, for a final total of 635 study participants (96% of the original sample of individuals assigned to either olanzapine or risperidone).

Reasons for Discontinuation Among Phase 1 CATIE Participants Whose Random Assignment to Olanzapine or Risperidone Meant Staying With or Switching From Their Baseline Treatment

Rates of discontinuation for lack of efficacy were lowest for those who were randomly assigned to olanzapine (13% among those whose double-blind assignment meant staying with olanzapine and 14% among those for whom olanzapine was a switch) relative to those who received double-blind risperidone (21% among those whose double-blind assignment meant staying with risperidone and 29% among those for whom risperidone was a switch). Results of the Cox proportional hazards model revealed that time to discontinuation of treatment for lack of efficacy was lower for olanzapine compared with risperidone (hazard ratio=0.43, $p<0.001$). Due to loss of power, stay versus switch status was not significant in this analysis (hazard ratio=0.69, $p=0.11$), although the hazard ratio was identical to that found in analyses of all-cause discontinuation. The interaction between double-blind treatment and stay versus switch status was not significant.

Rates of discontinuation for tolerability were lower for individuals assigned to stay with the antipsychotic medication they were taking at study entry (hazard ratio=0.49, $p=0.018$), although this finding appears to be mostly due to individuals assigned to olanzapine (who had discontinuation rates of 9% when staying with olanzapine and 22%

when switching to olanzapine). For those assigned to risperidone, 10% discontinued because of intolerability whether their assignment meant staying or switching. Despite this, the interaction between treatment condition (olanzapine versus risperidone) and stay versus switch status was not significant (p=0.18). The power to find an interaction was not strong, with just seven events among olanzapine stayers and six events among risperidone stayers. Results of the Cox proportional hazards model also revealed a significant effect for double-blind treatment (olanzapine versus risperidone, hazard ratio=1.6, p=0.03), with risperidone showing lower rates of discontinuation due to intolerability.

Rates of discontinuation due to patient decision mirrored the findings of all-cause discontinuation. Specifically, rates of discontinuation for patient decision were lowest for those who were assigned to continue taking the antipsychotic medication they were taking at study entry (19% for those assigned to stay with olanzapine and 24% for those assigned to stay with risperidone) relative to those for whom the assignment was a switch (25% for those switched to olanzapine and 31% for those assigned switched to risperidone). Significant Cox proportional hazards ratio results were seen for stay versus switch status (hazard ratio=0.67, p=0.05) and for double-blind olanzapine versus risperidone (hazard ratio=0.72, p=0.03) but not the interaction.

Baseline Medication Group Differences

As might be expected given the number of comparisons being made, several differences with respect to baseline characteristics were found between the medication groups at study entry. First, individuals who were taking agents other than olanzapine, risperidone,

or quetiapine and those taking no antipsychotic medications at study entry were slightly older (mean age was about 42 years) compared with individuals in other groups (average ranged from 39 to 40 years of age; F=3.81, df=5, p=0.002). Second, individuals receiving risperidone monotherapy at baseline had slightly shorter durations of prior antipsychotic therapy (mean=12.6 years) than individuals in other groups (average ranged from 13.7 to 15.9 years; F=2.62, df=5, p=0.03). Third, groups differed with respect to gender, with the lowest proportion of women (20%) within the group receiving olanzapine monotherapy at baseline and the highest (34%) within the group taking a treatment other than olanzapine, quetiapine, or risperidone (χ^2=18.3, df=5, p=0.003). Fourth, groups differed with respect to race with the largest proportion of non-whites (50%) within the group of individuals receiving no antipsychotic medication at baseline and the least (27%) within the group taking more than one antipsychotic including olanzapine, quetiapine, or risperidone (χ^2=37.6, df=5, p<0.0001). Fifth, groups differed with regard to whether they experienced an exacerbation of schizophrenia in the prior 3 months with the lowest proportion of individuals with an exacerbation (21%) within the group receiving a treatment other than olanzapine, quetiapine, or risperidone and the most (38%) within the group receiving quetiapine monotherapy at baseline (χ^2=22.9, df=5, p<0.001). Sixth, groups differed in baseline tardive dyskinesia status with the lowest proportion of individuals with tardive dyskinesia (10%) within the group receiving risperidone monotherapy at baseline and the highest (24%) within the group receiving quetiapine monotherapy at baseline (χ^2=27.4, df=5, p<0.0001).

Time to Discontinuation Differences Among Patients Receiving Olanzapine at Study Entry Between Those Whose Random Assignment Meant Staying With Olanzapine Versus Switching to a Different Antipsychotic

Post hoc analyses of time to discontinuation for patients entering the study receiving olanzapine monotherapy indicated that individuals who stayed with olanzapine had much longer time to discontinuation than did those who switched to risperidone (hazard ratio=0.48, $p<0.001$), quetiapine (hazard ratio=0.43, $p<0.001$), perphenazine (hazard ratio=0.49, $p=0.002$), or ziprasidone (hazard ratio=0.26, $p<0.0001$). For these individuals, switching to risperidone, perphenazine, or quetiapine were similar, but switching to ziprasidone resulted in the shortest time to all-cause discontinuation. This finding remained the same in auxiliary analyses that excluded individuals with tardive dyskinesia at baseline or were limited to the cohort of patients enrolled after ziprasidone was added to the study

Reasons for Discontinuation Including and Excluding Phase 1 CATIE Participants Whose Random Assignment Meant Staying With Their Baseline Treatment

Consistent with the main study findings, there was a statistically significant overall difference in discontinuation due to lack of efficacy even with stayers removed ($p=0.002$), and olanzapine continued to show significantly lower discontinuation rates (14%) relative to perphenazine (25% [hazard ratio=0.45, $p=0.001$]), quetiapine (28% [hazard ratio=0.41, $p<0.0001$]), and risperidone (29% [hazard ratio=0.41, $p<0.0001$]) but

not ziprasidone after adjustment for multiple comparisons (25% [hazard ratio=0.58, p=0.04]) .

When examining discontinuation for intolerability with stayers removed, there was an overall difference (p=0.012), and olanzapine showed significantly higher discontinuation rates (22%) compared with risperidone (10% [hazard ratio=1.92, p=0.009]f).

Mirroring the pattern of all-cause discontinuation rates, discontinuation rates for patient decision after removing stayers were 25% for those assigned to olanzapine, 30% for those assigned to perphenazine, 31% for those assigned to risperidone, 34% for those assigned to quetiapine, and 33% for those assigned to ziprasidone. Results of the Cox proportional hazards model revealed no significant overall group differences (p=0.13).

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