Letter to the Editor

Examination of heterogeneity in treatment response to antipsychotic medications

1. Introduction

Antipsychotic medications effectively treat schizophrenia symptoms, but it is unclear what drives these variations. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study compared oral antipsychotic agents and outcome measures collected over 18 months. No prior analyses of CATIE data have looked specifically at variations in time to all-cause treatment discontinuation or changes in neurocognition by age, sex, the presence of a substance use disorder, symptoms of schizophrenia (PANSS baseline score) and baseline adherence. Due to this significant gap in knowledge, and previous findings of subgroup differences in response to antipsychotic treatments, our novel study tested whether participants responded differently to assigned treatments in CATIE. A prior analysis examining race-ethnicity interactions with treatments on all-cause treatment discontinuation found no effects (Arnold et al., 2013). We investigated heterogeneity of effects on two outcomes: 1) time to all-cause treatment discontinuation, which in the primary analysis from CATIE found that olanzapine had longer time to all-cause treatment discontinuation compared to quetiapine and risperidone (Lieberman et al., 2005), and 2) change in neurocognition from baseline to month 2, which in the primary neurocognitive analysis found no differences between the treatments as measured by a comprehensive neurocognitive battery (Keefe et al., 2007).

2. Methods

Data come from CATIE conducted from January 2001 to December 2004 including individuals with schizophrenia or schizoaffective disorder diagnoses who were randomly assigned to oral olanzapine, quetiapine, risperidone, or perphenazine, and followed up to 18 months. We included 1206 participants from the Phase 1 intent-to-treat sample (i.e., excluding participants with tardive dyskinesia and who did not receive at least one dose of study medication). Ziprasidone was added later, and that cohort was analyzed independently ($N = 742$). Further detail on CATIE design and methods can be found in (Lieberman et al., 2005; Stroup et al., 2003).

2.1. Outcomes

Time to all-cause treatment discontinuation (i.e., discontinuation) in CATIE integrated participants' and clinicians' decisions about efficacy and tolerability of their assigned treatment. We used Kaplan-Meier survival curve estimation (Stel et al., 2011) and Cox proportional-hazards regression models (Cox, 1972) to identify whether the effect of the assigned treatments on discontinuation was modified by: age (continuous ages 18–65 years); sex (female, male); race (white, black, other); presence of a substance use disorder at baseline (a score of ≥3 on the Alcohol Use and/or the Drug Use Scale (Drake et al., 1990)); baseline

schizophrenia symptoms (continuous Positive and Negative Syndrome Scale (PANSS) total score (Kay et al., 1991)), and baseline adherence (continuous brief adherence rating scale proportion of capsules taken (Byerly et al., 2008)). Significance was defined using a Wald χ^2 test with 3 degrees of freedom (df) (4 df for the ziprasidone cohort) and P value <0.05 ($p < 0.05$). Cox proportional hazards regression models were adjusted for treatment site, exacerbation of schizophrenia symptoms in the previous three months and previous treatment status (Essock et al., 2006).

Neurocognitive function was measured using a comprehensive composite neurocognitive Z-score that integrated five cognitive domains (i.e., processing speed, reasoning, verbal memory, working memory and vigilance (Keefe et al., 2006)). We tested whether our six subgroup characteristics modified the effect of assigned treatments on changes in the least squares mean (LSMean) Z-score from baseline to month 2 (Keefe et al., 2007). The sample with both baseline and month 2 neurocognitive scores was $N = 728$. We used analysis of covariance (ANCOVA) and adjusted for baseline neurocognitive composite Z-score, treatment site, exacerbation of schizophrenia symptoms in the previous three months, and previous treatment status. Significance was determined using a Type III sum of squares F-test with 3 df and $p < 0.05$ (4 df for the ziprasidone cohort).

3. Results

Participants' mean age was 39 years, 27% were female, 60% were white, 12% were Hispanic, 28% had an exacerbation of schizophrenia symptoms in the previous 3 months, and baseline mean PANSS total score was 75.

Sex modified the effect of assigned treatment on discontinuation ($\chi^2 = 7.89$, p < 0.05); no other interactions by subgroup characteristics were found. There were differences among the treatments for women ($\chi^2 = 12.62$, $p = 0.0055$, Fig. 1a); when compared to quetiapine, olanzapine ($\chi^2 = 5.1941$, $p = 0.0227$) and perphenazine ($\chi^2 = 11.5672$, $p = 0.0007$) had longer times to treatment discontinuation, but not risperidone. In men ($\chi^2 = 11.00$, $p = 0.0117$, Fig. 1b) only olanzapine had longer time to discontinuation than quetiapine ($\chi^2 = 6.9268$, $p = 0.0085$). Among the individual drugs, only treatment with quetiapine was modified by sex; women had shorter time to discontinuation than men ($\chi^2 = 7.5116$, $p = 0.0061$, Fig. 1c). Post-hoc analyses of the reasons for treatment discontinuation found no difference between women and men.

Severity of schizophrenia symptoms at baseline modified assigned treatment's effects on participants' neurocognition increases by month 2 (F = 2.66, $p < 0.05$), but no other interactions by other subgroup characteristics were found. We dichotomized participants by their baseline PANSS total score median of 73. Increases in neurocognition at month 2 were not different between the treatments among participants with fewer symptoms at baseline, but among participants with more symptoms, those assigned risperidone (LSMean = 0.30) and perphenazine (LSMean = 0.34) had
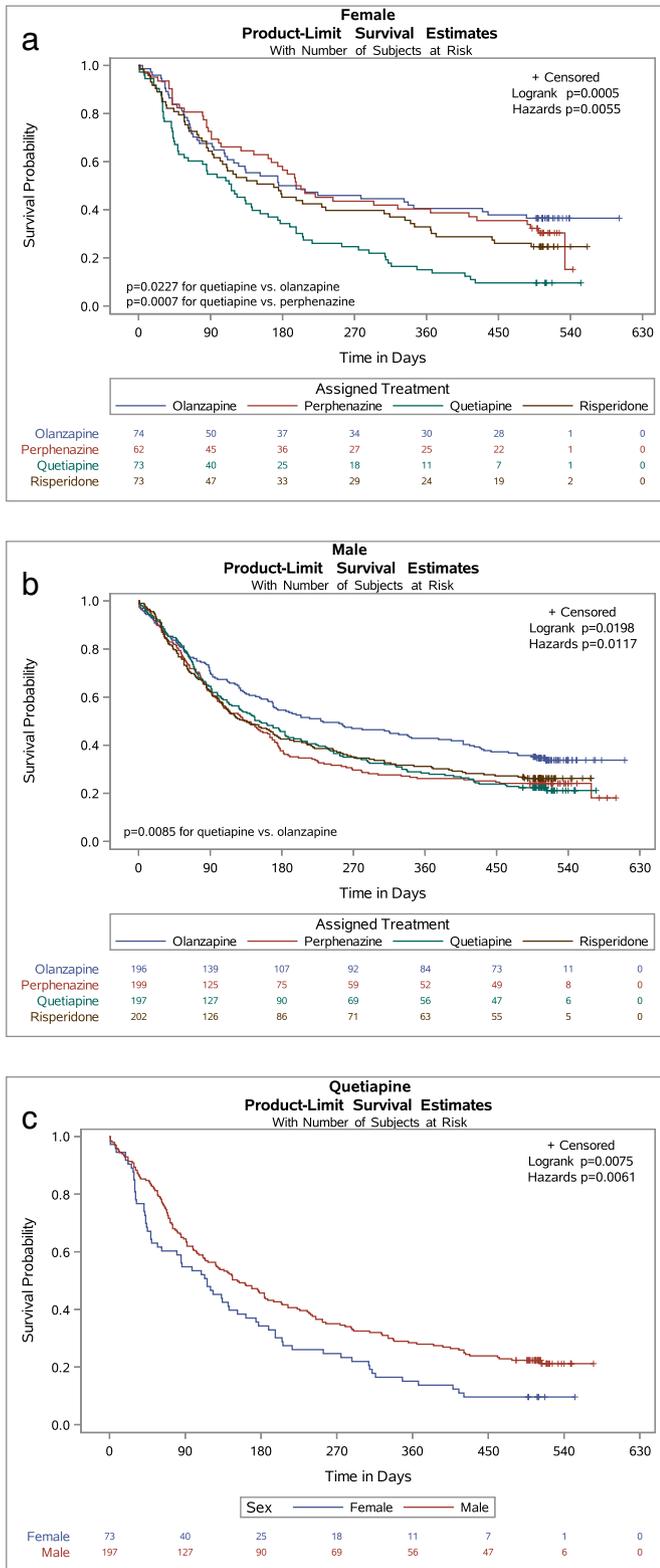
a

Female
Product-Limit Survival Estimates
With Number of Subjects at Risk

Assigned Treatment			
Olanzapine	Perphenazine	Quetiapine	Risperidone

Olanzapine	74	50	37	34	30	28	1	0
Perphenazine	62	45	36	27	25	22	1	0
Quetiapine	73	40	25	18	11	7	1	0
Risperidone	73	47	33	29	24	19	2	0

b

Male
Product-Limit Survival Estimates
With Number of Subjects at Risk

Assigned Treatment			
Olanzapine	Perphenazine	Quetiapine	Risperidone

Olanzapine	196	139	107	92	84	73	11	0
Perphenazine	199	125	75	59	52	49	8	0
Quetiapine	197	127	90	69	56	47	6	0
Risperidone	202	126	86	71	63	55	5	0

c

Quetiapine
Product-Limit Survival Estimates
With Number of Subjects at Risk

Sex	Female	Male

Female	73	40	25	18	11	7	1	0
Male	197	127	90	69	56	47	6	0

Fig. 1. a–c. Modification of time to all-cause treatment discontinuation by sex.

greater increases at month 2 than olanzapine ($p = 0.0345$ and $p = 0.0150$ respectively) or quetiapine ($p = 0.0403$ and $p = 0.0154$ respectively).

If adjusted for multiple comparisons using a Bonferroni correction ($0.05/12 = 0.004$) then the difference between perphenazine and quetiapine on treatment discontinuation remains significant ($p = 0.0007$). We assessed whether the randomization held, and results

indicated no differences between the treatments on the six subgroup characteristics in the survival and neurocognitive analyses.

No interactions between the subgroup characteristics and assigned treatments on the outcomes in the smaller ziprasidone cohort ($N = 728$) were found.

4. Discussion

A possible explanation for treatment discontinuation differences between sexes is heterogeneous adverse effects. For example, (McEvoy et al., 2005) found an association between women and multiple measures of metabolic syndrome status; a higher percentage met a greater number of syndrome criteria. Similarly, (McEvoy et al., 2014) found women had much greater increases in serum prolactin than men. The desire for more personalized treatment choices has led to efforts to identify predictors and moderators of heterogeneity in treatment response. Modification of treatment effects by sex for all-cause treatment discontinuation and by severity of schizophrenia symptoms at baseline for neurocognition may be clinically important, if replicated.

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