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Analysis of efficacy and side effects in CATIE demonstrates drug response subgroups and potential for personalized medicine

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Abstract

Objective—This study aims to improve understanding of antipsychotic non/response and assess the potential for personalized schizophrenia treatment.

Methods—We used data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). Efficacy measures included the Positive and Negative Syndrome Scale (PANSS) and neurocognitive functioning. Side effect measures included weight, lipids, glucose, heart rate and QT prolongation. Latent class analysis was conducted for each of the five drugs on the individual treatment effects to study whether there were subgroups of drug responders. The posterior probabilities of belonging to a particular response group were correlated across drugs to examine if patients not responding to one drug are likely to respond to a different drug and whether response to one drug may help to predict response to another drug.

Results—We identified four qualitatively distinct response groups: Optimal Responders, Average Responders, Global Responders and Non-Responders. Different patterns of correlations with demographics and clinical variables across classes provided further support for the validity of these groups. The low correlations between posterior probabilities of the same response groups across drugs implied that patients generally belonged to different response groups for different drugs

Conclusions—Our results demonstrate the existence of subgroups of patients characterized by distinct patterns of drug response. Further, findings suggest that patients who experience a poor response to one drug may be an optimal responder to another antipsychotic. Taken together these findings demonstrate the potential to personalize schizophrenia treatment and highlight the importance of identifying better predictors of drug response.

Keywords

Schizophrenia; CATIE; antipsychotics; latent class analysis; personalized medicine

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1. Introduction

Typically only a portion of the patients suffering from schizophrenia respond to any given antipsychotic (Kane & Correll, 2010). While misdosing, medication error and drug-drug interactions may provide an explanation in some cases, antipsychotic nonresponse is so pervasive that more fundamental underlying factors seem highly probable. Genetic differences among patients represent a likely mechanism, as genes have been shown to play an important role in drug response (Vesell, 1978; Wilke & Dolan, 2011). Specific examples include genes involved in the absorption, distribution, metabolism and excretion of drugs (Evans & McLeod, 2003), so-called ADME genes, as well as genetic variation in pharmacodynamic genes encoding for drug targets (e.g., neurotransmitter receptors). However, given current limitations in knowledge of genomic function, genes of unknown or seemingly unrelated function may also impact drug response (Vesell, 1978; Wilke & Dolan, 2011).

In addition to genetic variation quantitatively moderating drug response, differences in treatment success may also be influenced by categorical differences between subgroups of patients (Kucukalic et al., 2007). That is, rather than being a single disease entity, schizophrenia may be a set of several disorders sharing clinical features but having (partly) heterogeneous etiologies (Fanous & Kendler, 2005; Kennedy et al., 2003; Tsuang & Faraone, 1995). Thus, for certain subgroups of patients, biological systems other than the ones targeted by the prescribed drug could cause the disorder (van den Oord et al., 2007).

Due to nonresponse, physicians often proceed through a lengthy sequence of treatments, with each lasting weeks or months, using drugs within and between drug classes, alone and in polypharmaceutical combinations. During this protracted period, schizophrenia-related suffering may persist or worsen, with consequences including lost income and/or employment, social dysfunction, hospitalizations or drug side effects (McGlashan, 1988). This situation is in need of improvement for millions of schizophrenia patients and their families.

This study aims to improve understanding of antipsychotic nonresponse and assess the potential for personalized schizophrenia treatment by using algorithms to identify the optimal drug for each patient. First, we investigate whether qualitatively different response groups exist or if drug response is merely a quantitative outcome with non-responders being on one end of a single continuum. Second, we study to what extent patients' response profiles differ across treatments, which is an essential prerequisite for personalized medicine. Third, as efforts to predict optimal antipsychotic therapy prior to treatment using clinical and demographic variables have met with limited success (Malhotra et al., 2004), we, alternatively, evaluate whether previous response to one drug may help to predict future response to another drug.

To address these questions, we used latent class analysis, which enables empirical tests for the presence and number of subgroups. Derived subgroups are validated by studying patterns of correlations with demographic and clinical variables. All analyses were conducted using data from the CATIE study, the largest and most comprehensive federally-funded study of antipsychotics conducted to date.

2. Method

2.1. CATIE

We used data from the Clinical Antipsychotic Trials of Intervention Effectiveness, CATIE (Lieberman et al., 2005). In short, CATIE is a multiphase randomized control trial of

antipsychotic medications, including five primary treatments (i.e., olanzapine, perphenazine, quetiapine, risperidone and ziprasidone), which followed patients for up to 18 months. To maximize representativeness, the participants were recruited from 57 clinical settings around the United States. Patients were diagnosed with schizophrenia using the Structured Clinical Interview for DSM-IV (First et al., 1994). All three CATIE phases were used in this study. Further details on the subjects and study design can be found in the Supplemental Material.

2.2. Measures

For the five main CATIE drugs, we studied a wide range of efficacy and side effect outcomes. The Positive and Negative Syndrome Scale (PANSS) (Kay & Opler, 1987) is used to assess improvement of schizophrenia symptoms. The 30 items of the PANSS measure a broad range of the symptoms typical for schizophrenia where five factors are generally preferred to represent its underlying structure (van den Oord et al., 2006; White et al., 1997). More specifically, because of their large sample size ($N = 5,769$), we used the five scales derived by Van der Gaag et al. (2006) labeled Positive symptoms, Negative symptoms, Disorganization symptoms, Excitement, and Emotional distress.

Neurocognition is moderately to severely impaired in patients with schizophrenia. For CATIE, an expert neurocognitive advisory group designed the contents, standardization, and methodology of the neurocognitive assessment battery (R. S. Keefe et al., 2006; R. S. E. Keefe et al., 2003). Eleven neurocognitive tests were administered, resulting in 24 individual scores. Factor analysis supported a model comprised of five domain scores (Processing Speed, Verbal Memory, Vigilance, Reasoning, and Working Memory). The correlations among the five domain scores were medium to high—we therefore analyze the composite score (R. S. Keefe et al., 2006) of these five domains.

Antipsychotic treatments have been associated with a variety of metabolic side effects (Allison et al., 1999; Henderson, 2007), with medical consequences ranging from cosmetic issues to increased rates of cardiovascular disease and diabetes (Henderson & Doraiswamy, 2008). The metabolic measures collected in CATIE have been described in detail previously (McEvoy et al., 2005; Meyer et al., 2008). Blood pressure (mm Hg) was measured as a single, seated determination, and heart rate (bpm) was measured as resting pulse count in 30 seconds $\times 2$. The lipid panel included triglycerides (mg/dL), total cholesterol (mg/dL) and HDL (mg/dL). Fasting blood glucose levels (mg/dL) were also measured.

Antipsychotics, in some cases, cause QT prolongation, an electrocardiogram (ECG) measure associated with an increased risk of cardiac arrhythmias and sudden death (Ray et al., 2001; Stollberger et al., 2005; Welch & Chue, 2000; Zareba & Lin, 2003). Although sudden death is rare, the severity of this event makes QT prolongation one of the most common reasons pharmaceuticals are restricted or removed from the market. Prior to analyses, the QT interval was corrected for the heart rate (QTc) according to Bazett's method (Bazett, 1920). Tardive dyskinesia is often a slow developing, long-term side effect of antipsychotics (Jeste & Caligiuri, 1993). Since tardive dyskinesia can take a long time to develop, it can be difficult to distinguish whether it is caused by a patient's current medication or a previous one. Because the goal of this paper was to examine response to current medication, this side effect was excluded from this study.

Table 1 summarizes the sample sizes and average number of observations/subject for each drug-outcome combination. To make the table as concise as possible, we grouped outcomes with similar number of observations (e.g., all PANSS subscales) and report their average. Table 1 shows that sample sizes ranged from 150-300 subjects, with olanzapine and risperidone at the high end and perphenazine at the low end of this range. Sample sizes

varied across outcome, with average observations/subject ranging around 3-5 for most drug-outcome combinations, and slightly lower for QTc and neurocognitive measures.

2.3. Treatment Effect Estimation

In previous research we have developed (van den Oord et al., 2009), and applied (McClay et al., 2011b) a novel method for estimating treatment effects in clinical trial data. Using mixed modeling (Goldstein, 1995; Searle et al., 1992), our method first determines the optimal functional form of over-time drug response, then screens many possible covariates to select those that improve the precision of the treatment effect estimates, and finally generates the individual treatment effect estimates based on the best-fitting model using best linear unbiased predictors (BLUPs) (Pinheiro & Bates, 2000). As our approach condenses all information collected during the trials in an optimal, empirical fashion, and it results in more precise estimates than traditional approaches that estimate treatment effects using only two assessments (e.g., subtracting pre- from post-treatment observations).

Specifically, to determine the optimal drug response trajectory for each outcome we fit a series of models specifying linear change for a given number of days on drug and flat thereafter. This series began with a model assuming that maximal drug response was achieved at day one. Each subsequent model specified an incrementally longer duration until maximal drug response, with the final model assuming that the drug effect did not plateau (i.e. linear change throughout trial). The best-fitting model of the series was selected to determine the average number of days until maximal drug response (through optimizing the likelihood across the series). After determining the optimal functional form of the drug response trajectories, 36 covariates were screened to identify those that improved the precision of the treatment effect estimates. Covariates included design characteristics, socio-demographic measures, clinical information, confounding medications and baseline antipsychotic treatment. The number of selected covariates ranged from zero (e.g., BMI) to four or greater (e.g., blood lipids), with design characteristics most commonly selected. Finally, treatment effects were generated as random effects. To elaborate, mixed models estimates two types of parameters, coefficients that describe the predictors' sample average effects, and deviations from the average effects for each subject (i.e., random effects). Thus, for each of the five trial drugs investigated, subject-level treatment effects were generated by specifying random effects for the drug response variable. Intuitively, these treatment effects quantify how much, for instance, each subject's metabolic phenotypes change in response to a given drug, relative to the average effect for all subjects taking the drug. All treatment effects used here have been previously described in published genomewide association studies of CATIE (Aberg et al., 2010; Adkins et al., 2011; McClay et al., 2011a; McClay et al., 2011b).

2.4. Latent Class Analysis

This study uses latent class analysis (LCA), which classifies individuals into unobserved subgroups, called latent classes, based on their observed response pattern for all efficacy and side effect measures. Currently, there is no agreed upon "best" method for comparing models with differing numbers of classes (Muthén & Asparouhov, 2008; Nylund et al., 2007). Because standard chi-square difference tests cannot be used in this setting (McLachlan & Peel, 2000), formal tests of model fit to the data cannot be conducted (Vermunt & Magidson, 2003), and so LCA cannot prove the existence of latent classes, but only describe the putative latent classes (Borboom et al., 2003; Steinley & Brusco, 2011; Vermunt & Magidson, 2002). One method for selecting models with different numbers of latent classes is to use information criteria, which compute an index that is a function of the log-likelihood with a penalty for model complexity. We follow this approach, utilizing the commonly used Bayesian Information Criterion, BIC (Schwarz, 1978). Thus, number of

subgroups for each drug was chosen based on the lowest BIC along with substantive interpretation of the classes. After selecting the best fitting model, the posterior probabilities of subgroup membership were calculated for each patient.

3. Results

3.1. Drug Response Groups

Using efficacy and side effect measure treatment effects, LCA was conducted within each of the five drugs to test for heterogeneous drug response groups. Fig. 1 shows the percentage improvement in the BIC over the one-group LCA model by drug. A one-group solution was indicated for olanzapine, a two-group solution was indicated for quetiapine, and a three-group solution was indicated for the remaining drugs.

Across drugs, four response types were found (Fig. 2). For each drug we found a group, termed Average Responders, which showed no divergence, in either efficacy or side effects, from the drug's average response pattern (red line, Fig. 2a). A group of Optimal Responders was found in all drugs, except olanzapine, showing favorable response with above average efficacy and below average side effects (blue line, Fig. 2c). Global Responders, characterized by higher than average levels of both efficacy and side effects, were found in perphenazine, risperidone and ziprasidone (green line, Fig. 2d). A Non-Responder group was found in perphenazine (purple line, Fig. 2b) and is composed of patients who have lower than average response on both efficacy and side effect measures.

In order to investigate the criterion validity of subgroups, their posterior probabilities were correlated with demographic and clinical effects (Supplemental Material). Correlations ranged from -0.43 to 0.33 . Non-zero correlations support subgroup validity, as substantively interpretable correlation patterns with demographic and clinical characteristics would not be expected if extracted classes were artifactual. Further, whereas the within responder group pattern of correlations are consistent, they differ across different responder classes. This finding supports the discriminant validity of the classes, as different groups have divergent characteristics, which are generally substantively consonant with expectations. For example, in Fig. 3, the correlations for the Optimal Responder group for different drugs generally have the same sign and magnitude (e.g., all drugs have positive correlations for number of days on drug). But, when compared to the Non-Response group, the correlations with various outcomes are clearly different. For example, the Non-Response group has negative correlations with the quality of life measure while Optimal Response groups have positive correlations.

3.2. Potential for Personalized Medicine

In order to ascertain if non/responders to one drug may respond to another, the posterior probabilities for each drug and class combination were correlated (Table 2). These correlations are generally close to zero, especially for correlations between the same response class on different drugs (e.g. Blocks II, V and VII). This suggests that patients will generally have different responses to different drugs. These low absolute correlations illustrate the potential for personalized medicine, because if patients belonged to the same response group for each drug there would be no opportunity for tailoring drugs to individual patients. More specifically, Block II has low correlations between Optimal Responder groups of different drugs suggesting that finding an optimal drug is patient-specific as opposed to the same patients having optimal response to multiple drugs.

3.3. Predicting Drug Response

In an effort to predict what type of patient belongs to each responder group prior to treatment, the posterior probabilities of group membership were regressed on various background characteristics, such as age, sex, race/ethnicity and clinical outcomes (Supplemental Material). Across all regressions, extremely few of the background characteristics were significant predictors of response group. This finding is consistent with previous research and suggests that demographic and clinical variables do not predict drug response well. The low correlations in Table 2 suggest that while patients often experience variable response patterns across antipsychotics, the best treatment for a patient cannot be predicted with any certainty based on prior drug response. That said, there are a few moderate correlations in Table 2 that should be highlighted.

In Block I, because olanzapine had a one-group solution, the average effects of the efficacy and side effects measures were correlated with the posterior probabilities of responder groups from other drugs. The olanzapine efficacy average has mostly negative correlations with the other drug response groups suggesting that if an individual has good efficacy on olanzapine they are unlikely to be an Average Responder or Global Responder on other drugs. In general, Global Responder groups are more likely to show olanzapine side effects while the Optimal Responder groups are less likely to show olanzapine side effects. Thus, patients experiencing problematic side effects with olanzapine are apt to experience improvement, without loss of efficacy, with some other drugs.

In Block VIII, there are negative correlations between the perphenazine Non-Response group and the Optimal Response groups suggesting that perphenazine Non-Response patients are unlikely to find a better drug among those drugs with Optimal Response groups. However, olanzapine may be a good alternative because the correlation with the efficacy average is large and positive, while the correlation with the side effect average is negative, suggesting that perphenazine Non-responders are likely to respond well to olanzapine with few side effects.

4. Discussion

Using LCA, we identified four qualitatively distinct efficacy and side effect response groups: Optimal Responders, Average Responders, Global Responders and Non-Responders. The different patterns of correlations with demographic and clinical variables provided further support for the validity of these groups. The results also suggested that patients generally belong to different response groups for different drugs. More specifically, the low absolute correlations between optimal response groups of different drugs (i.e., optimal response groups do not overlap between drugs) indicate that different patients may show optimal response to different drugs. Given the large number of currently available antipsychotic medications, this observation suggests that an optimal drug may exist for a sizeable group of schizophrenic patients. For example, assume that 5% of the patients belong to the optimal response group of drug A and another 5% of patients belong to the optimal response group of drug B. Because the optimal response groups hardly overlap, about 10% of patients would belong to an optimal response group.

Unlike the other four drugs, olanzapine had a one-group solution where efficacy and side effects were positively correlated. This one-group solution does not suggest that everyone taking olanzapine will have the same exact response, instead it says that overall, patients responses to olanzapine tend to trend in the same direction relative to the average effect for all patients who took olanzapine. So, while clinicians may have some hope of attaining efficacy without side effects with some drugs, with olanzapine they should expect weight gain (Meyer et al., 2008; Newcomer, 2005) to accompany efficacy in most cases.

Our finding that patients generally belong to different response groups for different drugs also implies that previous response to one drug cannot typically be used to predict response to another drug. However, some exceptions were found and warrant further study, including the possibility of switching patients showing little response to perphenazine to olanzapine, and avoiding switching quetiapine average responders to ziprasidone, as the correlation between quetiapine average responders and ziprasidone optimal responders is negative.

4.1. Limitations

Our findings must be interpreted in the context of potential limitations. First, the CATIE sample may not be generalizable to all schizophrenia patients. The CATIE patients were, overall, chronically ill and relatively stable, yet considered to be in clinical need for a medication change. Second, because of the CATIE design, patients would generally be kept on a drug to which they show an optimal response. So a subgroup of patients who respond favorably to multiple antipsychotic drugs may exist, but were undetectable because of the CATIE design. Because these patients may have shown an optimal response to another drug but were never switched once they achieved optimal response, the correlations in Table 2 for optimal response groups may be underestimated.

The statistical analyses presented in this paper were conducted on previously collected data, and used to make inferences about relationships between different antipsychotic response groups. Findings pertaining to the relationships between different response groups should be viewed as hypothesis-generating for future research, as rigorous testing of these hypotheses (e.g., how a patient will respond to a second drug following an initial treatment failure) will require novel clinical trial data collection.

4.2. Conclusions

Our results showed that qualitatively different subgroups of response exist and demonstrated the potential for personalized medicine. However, our findings also confirm results from previous studies showing that it is difficult to make reliable predictions of the optimal drug for individual patients. This raises the question of how to improve predictive power. Given that drugs impact biological systems, it seems reasonable to search for predictive biomarkers in these biological systems. Historically, the search for such biomarkers has been hampered by limited knowledge of drugs' mechanisms of action (MOA) and how biological variation in relevant pathways affects clinical response.

Novel high-throughput biological investigations that systematically screen (hundreds of) thousands of genotypes, transcripts, methylation markers and metabolites for association with drug response offer a promising avenue toward improving our ability to personalize antipsychotic treatment. Genetic sequence variation is particularly appealing for predicting drug response because genetic markers can be inexpensively and noninvasively measured prior to treatment. DNA methylation markers represent a complementary class of predictors. Similar to sequence variation, methylation markers are accessible at the stable DNA level and can therefore be measured cost-effectively in biosamples that are easy to collect, which makes them potentially usable in clinical settings. In contrast to sequence variation, methylation is directly related to gene expression, which could potentially increase predictive power. Furthermore, because methylation levels can be influenced by drugs, they could provide early biomarkers of drug efficacy and toxicity before they are clinically \phenotypically apparent. A third example is metabolomics. Metabolites are small, non-proteinaceous, endogenously-synthesized molecules, such as glucose, cholesterol, amino acids and small molecule neurotransmitters. There are approximately 700-800 metabolites for any given tissue; they represent the final products of many cellular regulatory processes and are, therefore, closer to the clinical response than any other biomarker. This makes

metabolites potentially powerful predictors (Frank & Hargreaves, 2003; Goodacre et al., 2004). Although successful examples exist (e.g., glucose, cholesterol), the dynamic nature and sensitivity to environmental changes (e.g., diet) of metabolites present challenges to use in clinical settings. However, because metabolomics provide a comprehensive picture of a drug's MOA, identifying all activated pathways, this knowledge could subsequently be reverse-engineered to identify biomarkers that are easier to measure in clinical settings. Overall, the emerging omics technologies offer several interlocking approaches toward actualizing the promise of personalized schizophrenia treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Percentage Improvement in the BIC over the One-Class Latent Class Analysis Model by Antipsychotic. Because a lower value of the BIC indicates a better fitting model, any improvement in fit from one model to the next should be a negative value. So the best-fitting model for each drug is at the lowest point on that drug's line.

Fig. 2.

Latent Class Analysis Response Profile by Antipsychotic (AR = Average Responder, GR = Global Responder, OR = Optimal Responder, NR = Non-responder). The efficacy, PANSS and neurocognitive (Neuro), and side effect measures, Weight, Lipid, Blood Pressure (BP), Glucose, Heart and QTc, are on the x-axis, and the y-axis represents the average treatment effect. The numbers in the legend are the proportion of patients taking that specific drug who are in that class (i.e. for Perphenazine, 8.4% of patient taking Perphenazine are in the non-responder class).

Fig. 3. Correlations between Posterior Probability of Belonging to Response Class with Background and Clinical Variables. The minimum value at which a correlation is significant at the 5% level (e.g. $p < 0.05$) for each drug is: olanzapine = 0.09, perphenazine = 0.13, quetiapine = 0.10, risperidone = 0.10, ziprasidone = 0.12.

Table 1

Sample Sizes and Average Number of Observations per Antipsychotic-Outcome

	Disease Symptoms		Neuro-cognitive		Metabolic outcomes				QTc prolong.	
	N	Obs	N	Obs	N	Obs	N	Obs	N	Obs
Olanzapine	254	4.86	222	2.05	282	4.30	281	2.69	249	1.59
Perphenazine	130	4.68	108	2.04	144	4.16	142	2.52	121	1.65
Quetiapine	238	3.98	197	1.64	276	3.40	266	2.25	224	1.51
Risperidone	254	4.33	211	1.93	281	3.90	272	2.47	239	1.55
Ziprasidone	168	3.63	137	1.83	198	2.99	195	1.97	189	1.62

Posterior Probability Correlations Between Antipsychotic Response Classes

Olanzapine		Optimal Responders (OR)		Global Responder (GR)		Average Responder (AR)	
Efficacy Side Effects		Quetiapine	Risperidone	Ziprasidone	Perphenazine	Risperidone	Ziprasidone
I							
Olan.	Eff.	1.000					
	SE	0.880	1.000				
II							
OR	Quet	0.166	-0.016	1.000			
	Risp	-0.142	-0.223	0.057	1.000		
	Zipr	-0.005	-0.025	0.226	-0.036	1.000	
III							
GR	Perp	-0.345	0.400	-0.071	-0.057	-0.135	1.000
	Risp	-0.037	0.339	-0.015	-0.051	-0.069	1.000
	Zipr	0.062	0.149	-0.126	-0.081	-0.120	-0.070
IV							
AR	Perp	-0.425	0.190	0.104	0.099	0.200	-0.071
	Quet	-0.166	0.016		0.057	-0.226	0.071
	Risp	0.206	-0.039	0.055	0.052	0.070	0.073
Zipr	-0.044	-0.097	-0.050	0.092	0.197	0.089	0.050
	VIII						
NR	Perp	0.545	-0.210	-0.074	-0.079	-0.135	0.215
V							
Zipr							
VI							
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VII							
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