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Association between type-three metabotropic glutamate receptor gene (*GRM3*) variants and symptom presentation in treatment refractory schizophrenia†

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Objective Positive associations between polymorphisms in the type-three metabotropic glutamate receptor gene (*GRM3*) and the pathogenesis of schizophrenia as well as response to antipsychotic treatment have been reported. The objective of this study was to determine whether refractory psychiatric symptoms in antipsychotic non-responders are related to polymorphisms in *GRM3*.
Methods Ninety-five treatment refractory schizophrenia participants were enrolled. Prior to a medication switch, global psychopathology and negative symptoms were rated. These participants were genotyped for seven markers in *GRM3*. Genotype associations with symptoms were assessed.
Results Two markers in *GRM3* (rs1989796 and rs1476455), were associated with the presence of refractory global symptoms as measured by the Brief Psychiatric Rating Scale (BPRS) Total scores. Participants with an rs1476455_CC genotype had significantly higher BPRS scores than A-carriers (55.1 ± 10.4 vs. 48.3 ± 9.2; $F = 7.6$, $p = 0.0071$). Additionally, participants with the rs1989796_CC genotype had significantly higher BPRS scores than T-carriers (50.1 ± 5.7 vs. 55.8 ± 10.5, $F = 7.1$, $p = 0.0091$). No evidence for significant associations with negative symptoms was observed.
Conclusions Polymorphisms in the *GRM3* gene may be associated with refractory global psychosis symptoms but not negative symptoms in persons with schizophrenia. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS — metabotropic; glutamate; antipsychotic; pharmacogenetics; schizophrenia

INTRODUCTION

Glutamate disposition and signaling in the brain is increasingly recognized as an essential component of the pathogenesis and treatment of schizophrenia (Harrison *et al.*, 2008; Tamminga, 2006). Furthermore, variants in glutamate system genes are associated with cognitive function, medication response, medication dosing, and in some studies with genetic risk for schizophrenia (Bishop *et al.*, 2005; Egan *et al.*, 2004; Fijal *et al.*, 2009; Fujii *et al.*, 2003). Efforts to identify specific genetic variants that predict disease risk, symptom presentation, and medication response in psychiatric disorders have begun to focus on the components of the glutamate system and are helping to improve our understanding of the biology of schizophrenia, risk for disease, and targets for new drug treatments.

Many second generation antipsychotics have either direct or indirect effects on the glutamate system that may partially account for their mechanisms of action and effectiveness in treating the cognitive and negative symptoms of schizophrenia (Moghaddam, 2004; Tamminga, 2006). Investigational pharmacologic agents for schizophrenia that stimulate selected metabotropic glutamate receptors (mGluRs) as well as agents that modulate N-methyl-D-aspartate (NMDA) receptors have antipsychotic properties in both humans and animal models of disease (Javitt, 2006; Patil *et al.*, 2007). Due to the complex nature of glutamate signaling in the brain, including interactions with dopamine and other neurotransmitter systems, genetic variants in glutamate receptors are likely contributors

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to the variability seen in symptom presentation and antipsychotic drug response (Bishop *et al.*, 2005).

GRM3 has been localized to chromosome 7q21.1-21.2 and spans 220.1 kb (Scherer *et al.*, 1996). *GRM3* codes for the mGluR3 protein which is a G-protein coupled receptor. Along with the structurally similar mGluR2 protein, mGluR3 is localized to the periphery of both pre- and post-synaptic neurons and is essential for optimal signaling of glutamate in the brain (Cartmell and Schoepp, 2000). Initial studies of genetic variation in *GRM3* suggest association with schizophrenia in some studies (Egan *et al.*, 2004; Fujii *et al.*, 2003) but not others (Albalushi *et al.*, 2008; Bishop *et al.*, 2007; Jonsson *et al.*, 2009; Marti *et al.*, 2002; Norton *et al.*, 2005; Schwab *et al.*, 2008; Tochigi *et al.*, 2006).

In studies of cognition (Egan *et al.*, 2004) and drug response in schizophrenia (Bishop *et al.*, 2005; Fijal *et al.*, 2009) *GRM3* variants have accounted for a portion of the variability seen in these outcome measures. The mGluR3 receptor product of this gene has subsequently become one glutamate receptor targeted by potential antipsychotics (Patil *et al.*, 2007). The heterogeneity of the disease association studies alongside growing evidence for the role of *GRM3* in cognition, symptom profile, and response to drug treatment further suggests that variants in this gene may influence disease presentation and potentially interact with other genetic (Nicodemus *et al.*, 2007; Tan *et al.*, 2007) and perhaps non-genetic factors as opposed to being solely a disease risk gene.

Collectively, research to date indicates that single nucleotide polymorphisms (SNPs) in *GRM3* may be useful to study as genetic markers with potential influence on response to antipsychotics in persons with schizophrenia. In addition to traditional pharmacogenetic analyses of drug response, it is also informative to identify and characterize the biological underpinnings of antipsychotic non-response. Genetic association studies of disease presentation and symptoms that are resistant to drug treatment may provide important information on treatment strategies and drug development efforts for difficult to treat patients. Building on our initial research of treatment response pharmacogenetics and disease association studies of *GRM3* in schizophrenia, we investigated the relationship between variants in this gene with symptomatology in a uniquely characterized cohort of treatment refractory patients with the goal of identifying genetic determinants of antipsychotic resistant symptoms that may drive non-response to initial therapies.

METHODS

Participants

Ninety-five unrelated persons meeting DSM-IV criteria for schizophrenia were recruited for this study. Individuals were assessed in this study prior to initiating treatment with a medication regimen for treatment refractory schizophrenia (predominantly clozapine). All participants gave written informed consent to an IRB-approved protocol. Inclusion criteria consisted of having a DSM-IV diagnosis of schizophrenia, being at least 18 years of age, and refractory to prior antipsychotic treatment according to the operationally defined criteria of Kane *et al.* (1988) (i.e., persistent psychotic symptoms for at least 2 years despite adequate separate trials with three antipsychotic drugs from two biochemical classes at doses >1000 chlorpromazine equivalents for 6 weeks) ($n = 93$) or inadequate response to at least two prior antipsychotic agents ($n = 2$). Previously utilized second generation antipsychotics were clinically estimated to exceed >1000 equivalents (Woods, 2003). Participants were recruited from inpatient and outpatient clinics in this single site study. Potential subjects were excluded if they had a DSM-IV diagnosis of organic mental disorder, suicidal ideation, other serious medical condition, or had previously been treated with clozapine.

Assessments

Participants were evaluated by a trained rater prior to the initiation of their treatment refractory regimen. with the 18-item Brief Psychiatric Rating Scale (BPRS) with each item rated 1–7, with 1 = not present and 7 = severe. In addition, ratings of negative symptoms were conducted with the Scale for Assessment of Negative Symptoms (SANS), with SANS score defined as the sum of the alogia, anhedonia, avolition, attention, and affective flattening global ratings with each item rated 0–5, with 0 = not present and 5 = severe.

Genotyping

Genomic DNA was isolated from whole blood with the salt precipitation method (Lahiri and Nurnberger, 1991). Genotyping was done with Pyrosequencing™ Technology. Polymerase chain reaction (PCR) primers were designed using Oligo 6 (MBI, Cascade, CO, USA). Pyrosequencing primers were designed using Pyrosequencing Primer Design Version 1.01 software (http://www.pyrosequencing.com). Seven SNPs (rs274622, rs724226, rs917071, rs6465084, rs1468412, rs1989796, and rs1476455) in *GRM3* (Egan *et al.*, 2004; Fujii

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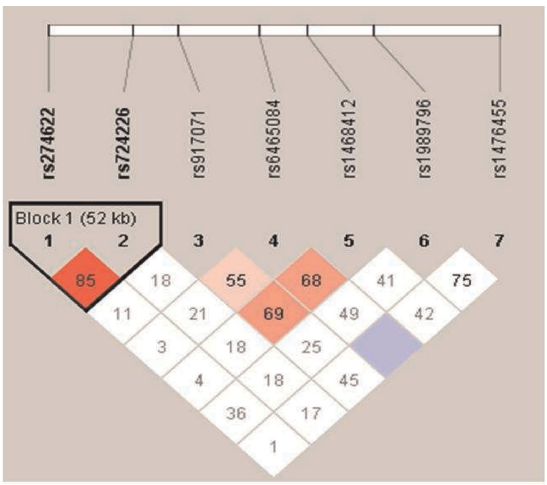
et al., 2003) were analyzed for their relationships to BPRS or SANS scores. Genotyping assays for six of the *GRM3* variants were done as described previously (Bishop *et al.*, 2005). Assays for rs6465084 were completed with 45 PCR cycles per reaction in a 50 μl volume with 1.5 mM Mg^{2+}. PCR products were visualized by electrophoresis on 1.5% agarose gels stained with ethidium bromide prior to Pyrosequencing. Forward, reverse, and Pyrosequencing primers for the variants are as follows: rs6465084 (TTGCCTT AATGACACAAAGTTCTC, CCGGTGCTCTTTCCA TATTGA, and TCCATGAAAAAGGCAC). Genotyping was done blind to symptom ratings. All genotyping assays were validated with direct sequencing.

Statistical analysis

Allele and genotype frequencies, Hardy–Weinberg equilibrium (HWE), and genotype association tests were conducted with PLINK software (Purcell *et al.*, 2007). Linkage disequilibrium (LD) plots were created with Haploview version 4.2 software (Barrett *et al.*, 2005) (displayed as *D*') with solid spine $D' > 0.8$ used to define haplotype blocks (see Figure 1). Genotype associations with BPRS and SANS scores as quantitative traits were conducted with PLINK using the genotypic (2df) association procedure which assesses an additive effect model. The mperm 1000 permutations option was selected to assess significance by controlling for multiple genetic markers and the LD between SNPs. Subsequent one-way Analysis of Variance (ANOVA) tests were completed for markers rs1989796, and rs1476455 which were identified as significant from the PLINK procedures to quantify differences across genotype groups. Student's *t*-tests were performed to test for differences in BPRS and SANS scores between males and females. ANOVA was used to test for differences in SANS and BPRS scores across racial groups. Pearson's correlation coefficient was used to examine relationships between age and SANS/BPRS scores. Power calculations were carried out using Quanto 1.2.4; http://hydra.usc.edu/gxe using our lowest minor allele frequency (0.12 for rs1476455) as a conservative estimate of our ability to detect associations in this sample. At a minor allele frequency of 0.12, using the means and standard deviations for BPRS and SANS scores obtained in our study sample of 95 subjects and a two-tailed 0.05 level of significance for an additive effect model, we had 80% power to detect R^2 for genotypes as low as 0.08 and a mean difference of difference of 2.65 points on SANS and BPRS scores across genotype groups.



Linkage disequilibrium for *GRM3* SNPs (displayed as D') with solid spine D'>0.8 used to define haplotype blocks

Figure 1. Linkage disequilibrium structure *GRM3*

Policy and ethics

The work described in this article was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

RESULTS

Ninety-five participants with schizophrenia volunteered to take part in this study. Our study population consisted of $n = 85$ (90%) Caucasian, $n = 8$ (8%) African American, $n = 1$ (1%) Asian, and $n = 1$ (1%) participants of unknown race. One participant was Hispanic. Participants were predominantly male $n = 61$ (64%) with a mean age of 37.9 ± 10.2 years. Mean BPRS Total scores were in the moderately severe range (53.5 ± 10.5 points), as were negative symptoms as measured by the SANS (13.9 ± 4.3 points). In this treatment refractory sample, age was not significantly associated with BPRS or SANS scores and scores did not differ across race/ethnic groups (all p's > 0.05). SANS scores were significantly higher in female participants (15.1 ± 4.3) versus males (13.2 ± 4.2) ($t = 2.1$, 1df, $p = 0.04$). BPRS scores did not differ between males and females.

GRM3 genotypes

Allele and genotype frequencies are presented in Table 1. Genotypes for *GRM3* did not deviate from HWE, with the exception of rs1468412 ($p = 0.024$),

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Table 1. Characteristics of SNPs assessed for association with refractory symptoms

SNP	Position	HWE, *p*-value	MAF	Alleles	Genotype count
rs274622	85917591	0.8154	0.34 (C)	T:C	12/41/42
rs724226	85970025	0.4917	0.34 (A)	G:A	13/39/43
rs917071	85998432	0.1928	0.34 (T)	C:T	14/36/45
rs6465084	86048126	0.9842	0.28 (G)	A:G	7/40/48
rs1468412	86078102	0.0313	0.35 (T)	A:T	17/33/45
rs1989796	86118964	0.8735	0.37 (T)	C:T	14/43/48
rs1476455	86196391	0.5059	0.12 (A)	C:A	0/22/73

HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency.

which has been previously associated with risk for schizophrenia (Egan *et al.*, 2004). Markers in *GRM3* were in moderate LD (denoted as *D*') with one haplotype block consisting of two SNPs with $D' > 0.80$ as indicated in Figure 1.

Relationship between symptoms and genetic variability

Genotype associations between *GRM3* variants and BPRS and SANS scores are summarized in Tables 2 and 3. Two markers (rs1989796 and rs1476455) in the 3′ end of *GRM3* were significantly associated with BPRS Total scores, but not SANS scores. BPRS and SANS scores across rs1989796 and rs1476455 genotype groups were then assessed. Mean (SD) BPRS Total scores for rs1989796 CC, CT, and TT were 50.1 (10.0), 55.0 (9.9), and 58.2 (12.2) ($F = 4.07$, 2df, $p = 0.02$). Participants with the rs1989796_CC genotype had significantly higher BPRS scores than T-carriers (50.15.7 vs. 55.810.5, $F = 7.1$, $p = 0.0091$). Mean (SD) BPRS scores for rs1476455 AC, and CC were 48.3 (9.2) and 55.1 (10.4) ($F = 7.6$, 1df, $p = 0.007$) (see Figure 2). Mean (SD) SANS scores for rs1989796 CC, CT, and TT were 13.4 (4.0), 14.1 (4.6), and 14.5 (4.2) ($F = 0.44$, 2df, $p = 0.64$). Mean (SD) SANS scores for rs1476455 AC, and CC were 12.7 (4.3) and 14.3 (4.3) ($F = 2.4$, 1df, $p = 0.13$). Adjusting these relationships with SANS scores for sex did not alter the significance of these findings.

Table 2. Genotype associations between type-3 metabotropic glutamate receptor (*GRM3*) SNPs and total scores of the Brief Psychiatric Rating Scale (BPRS)[a]

SNP	BETA	SE	R^2	*T*-score	*p*-value	Corrected *p*-value[b]
rs274622	−0.58	1.58	0.0015	−0.37	0.71	1.0
rs724226	−0.19	1.55	1.6E−4	−0.12	0.90	1.0
rs917071	−1.93	1.50	0.018	−1.29	0.20	0.69
rs6465084	−0.67	1.73	0.0016	−0.39	0.70	1.0
rs1468412	−1.60	1.43	0.013	−1.12	0.27	0.80
rs1989796	4.24	1.49	0.080	2.84	0.0055	0.04
rs1476455	−6.79	2.47	0.075	−2.75	0.0071	0.04

[a]Additive model.
[b]Permuted *p*-value correcting for multiple comparisons and linkage disequilibrium between SNPs.

Table 3. Genotype associations between type-3 metabotropic glutamate receptor (*GRM3*) SNPs and negative symptom scores as assessed by the Scale for Assessment of Negative Symptoms (SANS)[a]

SNP	BETA	SE	R^2	*T*-score	*p*-value	Corrected *p*-value[b]
rs274622	−0.65	0.64	0.011	−1.01	0.32	1.0
rs724226	−0.41	0.63	0.0045	−0.64	0.52	0.90
rs917071	0.083	0.62	1.94E−4	0.13	0.89	0.99
rs6465084	0.27	0.71	0.0016	0.38	0.70	1.0
rs1468412	−0.14	0.59	6.30E−4	−0.24	0.81	1.0
rs1989796	0.59	0.64	0.0092	0.93	0.36	0.93
rs1476455	−1.60	1.038	0.025	−1.54	0.13	0.56

[a]Additive model.
[b]Permuted *p*-value correcting for multiple comparisons and linkage disequilibrium between SNPs.

DISCUSSION

The principal finding of this study is that global psychosis symptoms as measured by BPRS Total scores were significantly related to two gene variants in the 3′ end of the *GRM3* gene. Significant genotype associations between rs1989796 and rs1476455 and BPRS Total scores were observed, with potentially clinically meaningful and statistically significant differences across genotype groups. No significant associations between *GRM3* variants and negative symptoms were observed in this study sample. To our knowledge this is the first association between *GRM3* variants and clinical symptoms in treatment refractory schizophrenia.

Relationship of the glutamate system to schizophrenia and antipsychotic pharmacology

Currently, there are eight known metabotropic glutamate genes (*GRMs*) coding for mGluRs 1–8 one through eight (*GRM1–GRM8*). The eight individual mGluRs are subdivided into three groups (Group-I, Group-II, and Group-III) based on amino acid sequence and second messenger signaling similarities (Nakanishi, 1992). *GRM1* and *GRM5* are the two members of Group I, *GRM2* and *GRM3* comprise Group II, with the rest falling into Group III. These receptors mediate signal transduction through G-protein second messenger systems which distinguishes

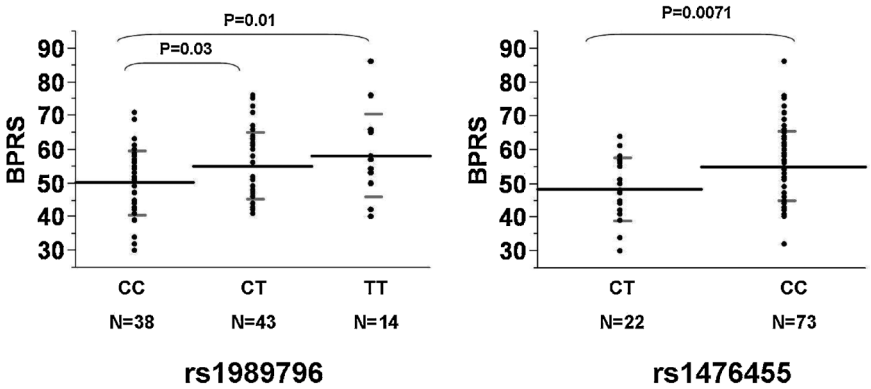

Figure 2. *GRM3* variants and BPRS Total scores analysis of variance and Student's *t*-tests were used to compare mean BPRS values ± standard deviation across genotype groups

them from their ionotropic counterparts, the NMDA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), and kainate receptors. mGluRs seem to ''fine tune'' glutamate transmission, while ionotropic receptors regulate large scale glutamate fluctuations in the brain (Conn and Pin, 1997).

A number of studies have investigated the relationship between *GRM3* and risk for schizophrenia with mixed results. Collectively these data do not provide strong evidence that variants in these genes on their own confer an increased risk for developing this disease. Previous investigations of *GRM3* variants as potential predictors of antipsychotic response in schizophrenia (Bishop *et al.*, 2005; Fijal *et al.*, 2009) while not associated with disease risk (Bishop *et al.*, 2007; Marti *et al.*, 2002; Norton *et al.*, 2005) suggests that *GRM3* variants are associated with drug response and symptom presentation rather than the disease. The results obtained from the cohort of treatment refractory persons with schizophrenia studied here is consistent with this possibility.

The primary mechanisms of action for antipsychotics are hypothesized to center on striatal dopamine-2 (D2) and mesolimbic serotonin-2A (5HT2A) receptor antagonism, but an increasing body of animal and human research indicates that these agents may also affect glutamate neurotransmission via regulating gene expression (Girgenti *et al.*, 2010; Molteni *et al.*, 2009). The relationship of genetic variability in the *GRM3* region with the effects of second generation antipsychotic medications is not surprising. Second generation antipsychotics influence the expression of *GRM3* mRNA as well as serum glutamate concentrations. Serum glutamate concentrations increase significantly after subjects are switched from conventional antipsychotic agents to olanzapine (Goff *et al.*, 2002). While not affecting NMDA or AMPA gene expression in rats (Riva *et al.*, 1997; Tascedda *et al.*, 2001), clozapine and olanzapine appear to upregulate the expression of *GRM3* mRNA after chronic administration. This upregulation may explain our earlier results with rs274622 (Bishop *et al.*, 2005) which is a T/C variant residing in the ''T'' of a CCAAT box of the *GRM3* promoter region (Corti *et al.*, 2001). This variant may contribute to a state of glutamate hypofunction that is reversed by antipsychotic treatment. In the current study sample of treatment refractory patients, we did not observe any associations between SNPs in the 5′ end of *GRM3* with either negative or global symptoms. This is not surprising, as the reasons why an individual is refractory to antipsychotic agents likely involve a number of variables. It is plausible that these SNPs at the 3′ end of the gene are in LD for unstudied variants in the 3′untranslated region of *GRM3*, which may be targeted by epigenetic regulatory mechanisms that have increased activity or importance after long-term antipsychotic exposure, or which may be general markers for treatment resistance.

These results may shed light on the heterogeneity seen in studies investigating associations between *GRM3* and schizophrenia. At the current time, eleven studies have investigated the association of *GRM3* SNPs with schizophrenia, seven in Caucasian samples and four in Asian samples (Albalushi *et al.*, 2008; Bishop *et al.*, 2007; Chen *et al.*, 2005; Egan *et al.*, 2004; Fallin *et al.*, 2005; Fujii *et al.*, 2003; Jonsson *et al.*, 2009; Marti *et al.*, 2002; Norton *et al.*, 2005; Schwab *et al.*, 2008; Tochigi *et al.*, 2006). These studies have resulted in mixed associations between SNPs and/or haplotypes and disease. Additional evidence suggests that *GRM3* may interact with the catechol-*o*-methyltransferase (*COMT*) Val158Met variant to confer risk for schizophrenia (Nicodemus *et al.*, 2007; Tan *et al.*, 2007). Our results may provide additional insight into these heterogeneous findings if there are differential relationships between

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GRM3 and clinical outcomes for schizophrenia subtypes.

Study limitations

This study describes the association of variation in one candidate gene with symptoms in treatment refractory schizophrenia patients prior to a medication switch. The reasons for non-response to prior antipsychotic treatment are unknown. Further, because of heterogeneity of prior antipsychotic treatment, we were unable to determine the relationships of exposure to specific agents and doses with the outcomes assessed in this study. In addition, the long-standing nature of illness in the subjects limited our ability to reliably estimate illness duration. This study sample is predominantly Caucasian, so we were unable to determine unequivocally whether the relationships between *GRM3* SNPs and symptom presentation hold across other racial and ethnic groups. Of note, our results did not change significantly when non-Caucasian races were excluded from our analyses.

CONCLUSION

We observed that two variants in the 3′ end of *GRM3* were associated with global symptoms of psychosis as assessed by the BPRS, but not negative symptoms in this study sample. This suggests that variation in *GRM3* may be related to a mechanism of treatment resistance in a subset of patients. However, it is important to note that not all subjects with these genotypes had higher measures of global psychosis symptoms as measured by the BPRS; rather on average they were higher across selected genotype groups. As previously noted, there may be many reasons why a patient has an inadequate response to antipsychotic therapy. Dosing, treatment adherence, intolerance to side effects, and agent selection are some modifiable factors that may influence this outcome.

The identification of genetic biomarkers of medication non-response is potentially useful, but the interpretation of this information needs to be considered carefully. However, it is conceivable that the results of this type of study, if replicated, may be useful in agent selection for schizophrenia. It is plausible that the use of treatment strategies reserved for later in treatment, such as clozapine, may be considered earlier in therapy if we identify markers of non-response to other therapeutic options.

CONFLICT OF INTEREST

Dr. Bishop has received research grant support from Ortho-McNeil Janssen and honoraria from Eli Lilly. Dr. Miller has served on data safety monitoring boards for Otsuka Pharmaceuticals and GlaxoSmithKline, and received research grant support in the form of medical supplies from Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Janssen Pharmaceutica and Pfizer. Dr. Ellingrod has served on an advisory board for Eli Lilly. Mr. Holman has no potential conflicts to disclose.

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