from 14 days to 9 years (no evidence of any patient having periods of discontinuation), although 5 cases occurred within 4 months of initiating treatment. No one was on high-dose clozapine (>600 mg/d), but concurrent medications were frequently present and 1 patient was receiving electroconvulsive therapy. Several types of colitis were reported, including 2 cases each of necrotizing and pseudomembranous, and one each of microscopic, acute, and eosinophilic. One of the 7 patients died as a result of colitis, and 3 required major bowel surgery. In 3 cases, clozapine was restarted, with 2 patients experiencing a recurrence of colitis and no follow-up was reported in the third case.

The growing body of case reports suggests a need for more detailed research into both frequency of serious intestinal sequelae and mechanism of any possible causative link with clozapine treatment. In particular, whether colitis may be a distinct pathological process from the risk of clozapine causing bowel obstruction or pseudo-obstruction. In the interim, it remains imperative that intestinal symptoms in patients receiving clozapine be taken seriously and addressed early.

AUTHOR DISCLOSURE INFORMATION

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Keith Richard Linsley, FRCPsych
Tees Esk and Wear Valleys NHS Foundation Trust
Durham, UK
keith.linsley@tewv.nhs.uk

Octavia Williams, MBBS, MRCPsych
NHS Foundation Trust
Durham, UK

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Dopaminergic Genes Influence Early Response to Atypical Antipsychotics in Patients With First Presentation of Psychosis

To the Editors:

Antipsychotics are the mainstay of treatment for psychotic episodes. The evidence that they all block dopamine D2 receptors and that sustained exposure to dopamine D2 receptor antagonists induces psychosis-like symptoms have led to the classical dopamine hypothesis of schizophrenia. The theory postulates that hallucinations and delusions arise from the hyperstimulation of dopamine D2 receptors caused by an excess of subcortical dopamine. Second-generation antipsychotics, such as risperidone and quetiapine, act as antagonists at both dopaminergic (in particular D2) and serotonergic receptors and show some improvement on 50% to 80% of patients. However, treatment response is largely unpredictable and discontinuation rates are high. Limited evidence from twin and family studies suggest that response to antipsychotic medication is a heritable complex trait influenced by a number of genes and environmental factors.

The genetic variants mostly reported are dopamine receptors, in particular, D2 and D3; in general, alleles associated with lower expression are also associated with poorer response. The D2 receptor is the major target of antipsychotic blockade and is present in high density in the basal ganglia. The A>G rs1800497 single nucleotide polymorphism (SNP) (aka Taq1A) in DRD2 encodes a cysteine-to-thiamine amino acid change. The A allele has been associated with reduced receptor density in the striatum and related structures in vitro and in vivo but with higher D2 density in patients with schizophrenia after antipsychotic use. The dopamine D4 receptor is highly expressed in the prefrontal cortex, which in turn influences striatal function, and may thus influence treatment response to dopamine antagonists. It may also directly regulate striatal tonic dopamine release. Its gene contains an A>G SNP (rs4680) that causes a valine-to-methionine change that results in a 2- to 3-fold reduction in enzymatic activity and stability. The dopamine D4 receptor is highly expressed in the prefrontal cortex and, like D2, is a target of antipsychotic drugs. The DRD4 gene contains a T>C SNP in the promoter region (rs1800955, aka C-521T) that influences expression: the T allele has been associated with about 40% lower transcription levels, although this finding has not been consistently demonstrated.

Given the importance of dopaminergic transmission blockade by antipsychotics in the early response (up to 4 weeks) of first onset psychosis patients, and that treatment response is influenced by genetic variability, we hypothesized that commonly occurring variation in genes relevant to the dopaminergic system (COMT [rs4680], DRD4 [rs1800955], and DRD2 [rs1800497]) would have an impact on symptom improvement. Based on current evidence, we predicted that the COMT A, the DRD2 A, and the DRD4 C alleles would be associated with greater improvement in symptoms (compared with their opposite alleles). We further hypothesized that the effect of these genetic variants would be greatest for positive symptoms, given that these are thought to arise from a hyperdopaminergic state in the basal ganglia and that they typically subside within 4 weeks of effective antipsychotic...
administration (in contrast to negative symptoms that frequently take longer to treat). In view of the multiple parameters influencing treatment response, drug-naive first-presentation psychosis patients represent an ideal group for exploratory pharmacogenetic studies. Using a multivariate analysis of variance in SPSS v15, we tested for main and epistatic effects of these polymorphisms and genotype by drug type interactions on symptom improvement (total, positive, and negative using the Positive And Negative Syndrome Scale (PANSS) and calculated as (follow-up raw score – baseline raw score)/baseline raw score in a cohort of 55 subjects with a first presentation of untreated psychosis at 1-month follow-up (see Supplemental Data for further details, Supplemental Digital Content 1, http://links.lww.com/JCP/A136). This cohort is a subset (those providing consent and a sample for DNA extraction) of a cohort studied in a randomized controlled trial of risperidone and quetiapine. Medication dose and ethnicity were included as covariates of no interest. There were no statistically significant differences in terms of sex, ethnicity, or age with respect to any of the polymorphisms or a main effect of medication type.

The null hypothesis that variation in genes involved in the dopaminergic system has no effect on symptom response to dopamine antagonists was disproved (see Supplemental Table 1, Supplemental Digital Content 2, http://links.lww.com/JCP/A137). The COMT genotype effect explained 33% and 25% of the total variance (partialing out other factors from the total nonerror variance) in total and positive PANSS improvements, respectively (Fig. 1). Consistent with our prediction, the response of Met158 homozygotes (ie, A/A) patients was significantly (\(P < 0.05\)) greater than that of Val158 homozygotes (ie, G/G) patients. Furthermore, the rate of improvement of the heterozygotes was intermediate between those groups (except in the quetiapine-administered patients in relation to positive PANSS) that was also expected as it concurs with previous evidence of allelic codominance at the molecular, behavioral, and brain activation level.\(^4,12\) Consistently, the Met158-containing enzyme has been repeatedly associated with better response to antipsychotics in total,\(^2,13\) positive,\(^2,13\) and cognitive\(^2\) symptoms, as well as fewer side effects.\(^2\) As this enzyme is lower functioning, it allows for higher dopamine synaptic availability than its
The COMT’s impact in the frontal cortex is relatively greater than in striatal areas (60% of dopamine turnover vs 15% in the striatum). It is possible that the beneficial effect of Met158-COMT on positive symptoms improvement is caused by its lower metabolism of tonic dopamine in the striatum, which increases phasic stimulation or, more probably, to an indirect effect via the prefrontal cortex as follows. Because of a decrease in the signal-to-noise ratio in the prefrontal function, the higher functioning Val158-COMT is shown to disinhibit (ie, increase) dopamine synthesis in the midbrain, leading to increased dopaminergic stimulation of the striatum. The latter has long been associated with an increased rate of positive symptoms. Deriving from that, an antidepressant, given the same dose, would less efficiently antagonize striatal dopamine activity in Val158 rather than Met158 homozygotes and at an intermediate level in heterozygotes, which is what we report. In a clinical setting, this may mean that a higher medication dose would be needed for Val158 homozygotes to reach the same level of improvement as Met158 homozygotes and, thus, prescribed dosage should depend on allele load. This may be especially relevant for risperidone because we found that for both total and positive PANSS, the symptom improvement was greater (at a trend level) in the risperidone group (in which it was statistically significant) than in the quetiapine group (in which it was not). This is consistent with risperidone having, in general, a higher affinity than quetiapine to all types of dopamine receptors and, in particular, to DRD2 and a rarer and of DRD2 variant, which may mask the subtle genetic effects on receptor availability that mediate antipsychotic response. This may give rise to inconsistencies when comparing studies with chronic and first-episode psychosis drug-naïve cohorts. Additional (secondary) analyses are reported as Supplemental Data (Supplemental Digital Content 1) for completeness.

The observed impact of COMT, DRD4, and as a trend, of DRD2 variation on improvement in the positive symptoms subscale score, but not the negative symptoms subscale score, is consistent with our prediction. Our prediction was based on the theory that positive symptoms, rather than negative symptoms, are directly related to dopaminergic imbalance in the striatum (where dopamine antagonists preferentially act) and that their improvement within 2 to 4 weeks of treatment onset (and in general) is greater than that of negative symptoms. This is concordant with previous studies of the mechanism of action of these drugs and with the revised dopamine hypothesis of schizophrenia. One improvement to this study design would be to assess serum levels of drug metabolites to more precisely monitor dose effect and patient compliance. The study also has limitations in terms of its small sample size and ethnic heterogeneity (although we corrected our analyses for ethnicity) and, hence, it should be interpreted with caution. Nevertheless, the main effects of DRD4 and COMT remain statistically significant after applying a Bonferroni correction for multiple comparisons, taking into account the number of genetic variants tested (N = 3): these results survive a corrected significance threshold of P = 0.017, which is obtained by dividing the consensual P = 0.05 by a factor of 3. We focused our analysis on 3 polymorphisms to avoid excessive multiple comparisons; future larger cohorts would be needed to address other possible epistases. Findings for individual polymorphisms are of limited clinical value as a combination of information in key genes has been shown to predict treatment response. The present study may inform further development of such biomarkers into pharmacogenetic tests to guide antipsychotic drug prescription.

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AUTHOR DISCLOSURE INFORMATION

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Short-Term Treatment of Catatonia With Amantadine in Schizophrenia and Schizoaffective Disorder

To the Editors:

Catatonia is a common syndrome that was first described by Karl Kahlbaum in 1874 and whose classification, diagnosis, and pathophysiology are still matters of debate in the scientific literature today, posing a challenge to clinicians. There are symptomatic similarities between catatonia and Parkinson disease with regard to akinesia rigidity and odd behavior. The most well-established treatment options for catatonia consist of lorazepam and electroconvulsive therapy (ECT). Guidelines list these biological treatments as effective in acute and chronic catatonia, but a large number of patients do not respond to them. Among patients with comorbid affective disorders, catatonic signs typically respond dramatically to benzodiazepine therapy. Nevertheless, patients with schizophrenia (SZ) usually have a poor response compared with patients with affective disorders, suggesting different underlying processes causing catatonia in each disorder. A recent open trial for catatonia treatment in patients with psychosis reports that ECT, benzodiazepines, and clozapine had beneficial effects on catatonic features, whereas typical antipsychotic drugs resulted in worsening of clinical condition. Contraindications, family denial, and transient response are limitations to the use of lorazepam and ECT. Amantadine was introduced for the pharmacological management of neuroleptic malignant syndrome because of its beneficial effects in Parkinson disease, which were attributed to its dopaminominetic properties. Although the dopaminominetic effects of amantadine are weak under experimental conditions, it has been reported that amantadine is an antagonist at the N-methyl-D-aspartate (NMDA) type of the glutamate receptor. It has been increasingly suggested that glutamate dysregulation may be involved in the neuropathology of SZ in general, and in catatonia in particular, mainly through NMDA receptor...