4. Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, Fishman SA: A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain 2008; 9:506–521
5. Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, Gamsa A, Bennett GJ, Collet JP: Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 2010; 182:E694–E701
6. Corey-Bloom J, Wolfson T, Gamst A, Jin S, Marcotte TD, Bentley H, Gouaux B: Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. CMAJ 2012; 184:1143–1150
7. Harper S, Strumpf EC, Kaufman JS: Do medical marijuana laws increase marijuana use? Replication study and extension. Ann Epidemiol 2012; 22:207–212
8. Grant I, Atkinson JH, Gouaux B, Wilsey B: Medical marijuana: clearing away the smoke. Open Neurol J 2012; 6:18–25

IGOR GRANT, M.D.
J. HAMPTON ATKINSON, M.D.
BEN GOUAUX, B.A.
La Jolla, Calif.

Dr. Atkinson is a member of a scientific advisory board for Eli Lilly Pharmaceuticals, Inc. Mr. Gouaux is an employee of the Center for Medicinal Cannabis Research at the University of California, San Diego, funding of which is provided entirely by the State of California. Dr. Grant reports no financial relationships with commercial interests.

This letter (doi: 10.1176/appi.ajp.2012.12060791) was accepted for publication in July 2012.

Response to Grant et al. Letter

TO THE EDITOR: While we did not mention the Center for Medicinal Cannabis Research at the University of California, ably headed by Dr. Grant for the past decade, we did not suggest that the "evidence for marijuana's efficacy is anecdotal"—just the large majority of it! We did say that "indications with the most evidence include spasticity secondary to neurological diseases such as multiple sclerosis (and) pain management, especially neuropathic pain." These in fact are the subject of the references cited by Grant et al. to prove their point about marijuana efficacy. These also are the relatively rare conditions that most applicants claim as the reason they need medical marijuana cards, and less than 3% of applicants claim such conditions.

Finally, as we noted in our commentary, in 2011 daily marijuana use among high school seniors reached the highest level in 30 years, according to the Monitoring the Future survey conducted annually by researchers at the Institute for Social Research at the University of Michigan. Researchers found, as we pointed out, that "the rate of marijuana use in youths is inversely related to 'perceived risk' and 'perceived social disapproval.'" Surely Grant et al. are not suggesting that the "medical marijuana" referenda and the dispensaries are unrelated to this increase.

We commend Grant et al. for their attempt to evaluate marijuana scientifically and look forward to the day when there will be FDA submissions.

HERBERT D. KLEBER, M.D.
New York
ROBERT L. DUPONT, M.D.
Rockville, Md.

The authors' disclosures accompany the original commentary.

This reply (doi: 10.1176/appi.ajp.2012.12060791r) was accepted for publication in July 2012.

Serum IgG Antibodies Against the NR_1 Subunit of the NMDA Receptor Not Detected in Schizophrenia

TO THE EDITOR: A consensus exists that schizophrenia is not a single disease, but the final pathway of a variety of still unknown neurobiological derangements. Several treatable autoimmune brain disorders have been identified that present with psychotic symptoms that, in some cases, resemble those found in schizophrenia (1). Antibodies target synaptic proteins, interrupting synaptic transmission in brain networks supporting cognition and emotion. Particularly relevant are autoantibodies against the NR_1 subunit of the *N*-acetyl methyl D-aspartate (NMDA) receptor, which result in diminished NMDA receptor activity, now considered a hallmark of schizophrenia (2). In patients harboring these antibodies, initial psychiatric symptoms are usually followed by dyskinetic movements or seizures and decreased respiratory drive, with a reduced level of consciousness often requiring intensive care (1). However, it could be postulated that a limited form of the disease may result in a milder syndrome akin to schizophrenia. We tested this hypothesis using serum from patients with a first psychotic episode referred to the regional psychiatric center of the province of Alava, Spain, and from healthy comparison subjects. All participants were enrolled after giving written informed consent according to protocols approved by the local institutional review board. Blood was drawn and sera were frozen for subsequent study, blinded to patient-control status. After a 1-year follow-up, sera of patients who then met DSM-IV-TR criteria for schizophrenia spectrum disorders were tested for antibodies to NR_1 and other cell surface antigens using three criteria (immunohistochemistry on rat brain slices and dissociated rodent hippocampal neurons, and a cell-based assay in which human embryonic kidney cells recombinantly express NMDA receptor), as previously reported (1). Patients (N=80) and healthy comparison subjects (N=40) did not differ statistically in age (mean age=29.4 years [SD=9.9] and 30.7 years [SD=9.4], respectively) or sex (28% and 38% women, respectively). Anti-NR_1 IgG antibodies were not detected in either group. Both groups had four cases with sera reactive to other still unidentified neuronal surface antigens. Our findings and a study of seven patients with schizophrenia (3) fail to support the hypothesis that NMDA receptor IgG antibodies are present in the sera of patients with schizophrenia. Although another study (4) reported NMDA receptor antibodies in the sera of some schizophrenia patients, it was performed without a control group, and test specificity was lower (only one of the above criteria was applied); differences in the clinical diagnosis could also explain the discrepant findings. It should be noted, however, that our study does not rule out the possibility that some patients have antibodies in only the cerebrospinal fluid, but not in serum (1). Additionally, antibodies could be present in patients with acute psychosis not meeting DSM-IV-TR criteria at 1 year.

References

1. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, Dessain SK, Rosenfeld MR, Balice-Gordon R, Lynch DR: Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008; 7:1091–1098
2. Moghaddam B, Javitt D: From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. Neuropsychopharmacology 2012; 37:4–15