

low dopamine neurotransmission. This keeps prolactin levels normal, spares cognition, and obviates extrapyramidal signs.

This letter provides data on the off-rates of additional newer atypical antipsychotics, using methods similar to those reported for the human cloned D₂Long receptor in tissue culture cells (1, 2) and drug concentrations found in the spinal fluid of patients (4). The times for 50% dissociation from D₂ were the following: 42 seconds for 4 nM S-(-)-amisulpride, 66 seconds for 40 nM amoxapine, 52 seconds for 10 nM aripiprazole, 30 minutes for 1.5 nM chlorpromazine, 15 seconds for 200 nM clozapine, 38 seconds for 1 nM domperidone, 38 minutes for 2 nM haloperidol, 16 minutes for 20 nM loxapine, 17 minutes for 5 nM olanzapine, 24 seconds for 140 nM perlapine, 16 seconds for 200 nM quetiapine, 23 minutes for 4 nM raclopride, 13 seconds for 5 nM remoxipride, 27 minutes for 2 nM risperidone, and 60 seconds for 2 nM paliperidone (9-hydroxy-risperidone).

The data for the rapidly dissociating antipsychotics (amoxapine, aripiprazole, clozapine, perlapine, quetiapine, remoxipride, and paliperidone) are compatible with their low extrapyramidal signs. The extent of risperidone-associated extrapyramidal signs may depend on the proportions of risperidone and its metabolite, paliperidone, in the patient. Olanzapine has a slow off-rate from D₂, compatible with its dose-dependent incidence of extrapyramidal signs; however, the potent anticholinergic action of olanzapine (its dissociation constant of 2.1 nM matches that of benztropine at the muscarinic receptor) provides an effective anti-extrapyramidal-sign mechanism (1).

References

1. Seeman P: Atypical antipsychotics: mechanism of action. *Can J Psychiatry* 2002; 47:27–38
2. Seeman P, Tallerico T: Rapid release of antipsychotic drugs from dopamine D₂ receptors: an explanation for low receptor occupancy and early clinical relapse upon withdrawal of clozapine or quetiapine. *Am J Psychiatry* 1999; 156:876–884
3. Kapur S, Seeman P: Does fast dissociation from the dopamine D₂ receptor explain the action of atypical antipsychotics? a new hypothesis. *Am J Psychiatry* 2001; 158:360–369
4. Seeman P, Corbett R, Van Tol HHM: Atypical neuroleptics have low affinity for dopamine D₂ receptors or are selective for D₄. *Neuropsychopharmacology* 1997; 16:93–110

PHILIP SEEMAN, M.D., Ph.D.
Toronto, Ont., Canada

Research Paradigms of Psychiatric Genetics

TO THE EDITOR: In his article, Kenneth S. Kendler, M.D. (1), identified “four major research paradigms,” consisting of 1) “basic genetic epidemiology,” 2) “advanced genetic epidemiology,” 3) “gene finding methods,” and 4) “molecular genetics.” Dr. Kendler argued that although “a substantial portion” of gene association claims “do not survive the test of replication,” family, twin, and adoption studies have found “genetic risk factors... for every psychiatric and drug use disorder that has ever been the subject of serious study” (p. 6). Moreover, “Unless there are strong and consistent methodologic biases operating across study designs, this growing body of work indicates that genetic risk factors are of substantial etiologic importance for all major psychiatric and drug use disorders” (p. 6).

However, as I argued in detail in my recent book (2), family, twin, and adoption studies do indeed suffer from “strong and consistent methodologic biases operating across study designs,” not the least of which is the twin method’s questionable “equal-environment assumption.”

Dr. Kendler noted that the “low” replication level for linkage findings “contrasts strikingly with the high level of consistency seen in the results of genetic epidemiologic studies—for example, the results of family and twin studies of schizophrenia” (p. 7). In fact, there is no “striking contrast” between these results if they are viewed as evidence supporting a purely environmental etiology for psychiatric disorders. Environmental theories predict 1) familial clustering, 2) a higher concordance of identical versus fraternal twins, and 3) a failure to find genes, and this is what we find (2, 3). Rather than consider a purely environmental explanation as a competing paradigm, Dr. Kendler argued that linkage and association studies cannot be used to test “whether a twin or adoption study was correct in its conclusion that disorder X is heritable” (p. 8). I agree, but negative results could at least compel researchers to take a second look at these methods. Although Dr. Kendler views his four strategies as “competing paradigms,” all four are components of the same biological/genetic paradigm, in contrast to what we might call the “environment/treatment/stress” paradigm.

Finally, Dr. Kendler called for integrating his four “paradigms,” which would “require an appreciation of the complementary sources of information obtained by genetic epidemiologic and gene identification approaches” (p. 9). Thus, a “striking contrast” was transformed into “complimentary sources of information” in the space of three pages. Dr. Kendler called his synthesis “explanatory pluralism” (p. 10), but what this means in practice is falling back on family, twin, and adoption results to explain the unexpected failure to find genes. Far better, in my view, would be a reexamination of the assumptions and biases of twin and adoption studies (Dr. Kendler’s paradigms 1 and 2) in the context of considering the possibility that genes for the major psychiatric disorders do not exist.

References

1. Kendler KS: Psychiatric genetics: a methodologic critique. *Am J Psychiatry* 2005; 162:3–11
2. Joseph J: *The Gene Illusion: Genetic Research in Psychiatry and Psychology Under the Microscope*, North American ed. New York, Algora, 2004 (Ross-on-Wye, UK, PCCS Books, 2003)
3. Joseph J: *The Missing Gene: Psychiatry, Heredity, and the Fruitless Search for Genes*. New York, Algora (in press)

JAY JOSEPH, Psy.D.
Berkeley, Calif.

Dr. Kendler Replies

TO THE EDITOR: In this brief letter, I cannot respond fully to the issues raised by Dr. Joseph or provide detailed references to support my position. Dr. Joseph and I disagree in four ways in the interpretation of the accumulating literature in psychiatric genetics. First, in examining family twin and adoption studies of the major psychiatric disorders, I concluded in my article that the evidence strongly supports the hypothesis that genetic factors play a significant role in the etiology of these conditions. I did not assert that individual studies are free

from methodologic problems. Indeed, in studying human populations by observational means, there can be no such thing as a perfect study. However, in examining the studies carefully and knowing—for example, that twin and adoption studies have different potential biases but reach the same conclusion for the disorders in which both methods have been used—it becomes very unlikely that the pattern of observed results could have arisen from methodological biases alone.

Second, Dr. Joseph is concerned about the equal-environment assumption as a significant bias in twin studies. I share his concern, but the equal-environment assumption has been examined in a number of empirical studies. Although there is a bit of evidence that this bias might be operative in some disorders, studies that have corrected for its effects typically find only small changes in heritability estimates. Although the equal-environment assumption is probably not perfectly true, evidence to date strongly suggests that the biases introduced thereby are quite modest.

Third, Dr. Joseph argues that current efforts at gene finding for psychiatric disorders have been unsuccessful. Although there certainly have been problems with replication, I disagree with his interpretation. For example, a recent well-done meta-analysis of schizophrenia linkage studies identified a number of genomic regions with substantial cross-study agreement (1). Several susceptibility genes for schizophrenia are beginning to be replicated at rates that are hard to explain if the original findings were false positive (2). I recently summarized this evidence for dysbindin in the *Journal* (3), and since then, two further positive reports have been published (4, 5).

Fourth, unlike Dr. Joseph, I judged that it is a priori likely that genes do contribute to variation in human behavior and the risk for psychiatric disorders. Behavior is instantiated in our brains, which are the product of evolution. The evidence that genetic factors influence behavior in other animals is overwhelming. As Darwin recognized, behavior is as much the subject of evolution as physical traits. Is it really plausible

that humans would be the only species whose behavior is unrelated to our genetic makeup? It is one thing to criticize the methodology of specific studies. It is quite another to suggest, as Dr. Joseph does, that we reject the results of an entire field of scientific inquiry. This might have been warranted for some pseudoscientific systems, such as astrology, alchemy, and the Ptolemaic astronomic system. It is highly unlikely that modern psychiatric genetics will be judged by future historians of science to be in such company.

References

1. Lewis CM, Levinson DF, Wise LH, DeLisi LE, Straub RE, Hovatta I, Williams NM, Schwab SG, Pulver AE, Faraone SV, Brzustowicz LM, Kaufmann CA, Garver DL, Gurling HM, Lindholm E, Coon H, Moises HW, Byerley W, Shaw SH, Mesen A, Sherrington R, O'Neill FA, Walsh D, Kendler KS, Ekelund J, Paunio T, Lonnqvist J, Peltonen L, O'Donovan MC, Owen MJ, Wildenauer DB, Maier W, Nestadt G, Blouin JL, Antonarakis SE, Mowry BJ, Silverman JM, Crowe RR, Cloninger CR, Tsuang MT, Malaspina D, Harkavy-Friedman JM, Svrakic DM, Bassett AS, Holcomb J, Kalsi G, McQuillin A, Brynjolfsson J, Sigmundsson T, Petursson H, Jazin E, Zoega T, Helgason T: Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: schizophrenia. *Am J Hum Genet* 2003; 73:34–48
2. Owen MJ, Williams NM, O'Donovan MC: The molecular genetics of schizophrenia: new findings promise new insights. *Mol Psychiatry* 2004; 9:14–27
3. Kendler KS: Schizophrenia genetics and dysbindin: a corner turned? (editorial). *Am J Psychiatry* 2004; 161:1533–1536
4. Numakawa T, Yagasaki Y, Ishimoto T, Okada T, Suzuki T, Iwata N, Ozaki N, Taguchi T, Tatsumi M, Kamijima K, Straub RE, Weinberger DR, Kunugi H, Hashimoto R: Evidence of novel neuronal functions of dysbindin, a susceptibility gene for schizophrenia. *Hum Mol Genet* 2004; 13:2699–2708
5. Funke B, Finn CT, Plocik AM, Lake S, DeRosse P, Kane JM, Kucherlapati R, Malhotra AK: Association of the DTNBP1 locus with schizophrenia in a US population. *Am J Hum Genet* 2004; 75:891–898

KENNETH S. KENDLER, M.D.
Richmond, Va.

Reprints are not available; however, Letters to the Editor can be downloaded at <http://ajp.psychiatryonline.org>.