

support the hypothesis that compulsive hoarding is a discrete syndrome (5, 6).

Drs. van Grootheest and Cath correctly state that genetic linkage results must be replicated "before we can conclude that there is a [specific] susceptibility locus for hoarding." However, as with most other psychiatric disorders, there are probably several genes that confer risk for compulsive hoarding. The OCD Collaborative Genetics Study is the third study to find genetic markers specifically associated with compulsive hoarding, indicating that it is a distinct and heritable phenotype. Other studies have confirmed that compulsive hoarding is strongly familial (7) and appears to breed true (8). Future genetic studies should be conducted on populations with the more homogeneous and well-defined categorical phenotype of compulsive hoarding syndrome in order to identify the specific genes involved in its etiology.

References

1. Grisham JR, Brown TA, Savage CR, Steketee G, Barlow DH: Neuropsychological impairment associated with compulsive hoarding. *Behav Res Ther* 2007; 45:1471-1483
2. Wincze JP, Steketee G, Frost RO: Categorization in compulsive hoarding. *Behav Res Ther* 2007; 45:63-72
3. Wu KD, Watson D: Hoarding and its relation to obsessive-compulsive disorder. *Behav Res Ther* 2005; 43:897-921
4. Clarke DJ, Boer H, Whittington J, Holland A, Butler J, Webb T: Prader-Willi syndrome, compulsive and ritualistic behaviours: the first population-based survey. *Br J Psychiatry* 2002; 180:358-362
5. Saxena S, Brody A, Maidment K, Smith EC, Zohrabi N, Katz E, Baker SK, Baxter LR: Cerebral glucose metabolism in obsessive-compulsive hoarding. *Am J Psychiatry* 2004; 161:1038-1048
6. Frost R, Hartl T: A cognitive-behavioral model of compulsive hoarding. *Behav Res Ther* 1996; 34:341-350
7. Mathews CA, Nievergelt CM, Azzam A, Garrido H, Chavira DA, Wessel J, Bagnarello M, Reus VI, Schork NJ: Heritability and clinical features of multigenerational families with obsessive-compulsive disorder and hoarding. *Am J Med Genet B Neuropsychiatr Genet* 2007; 144:174-182
8. Cullen B, Brown CH, Riddle MA, Grados M, Bienvenu OJ, Hoehn-Saric R, Shugart YY, Liang KY, Samuels J, Nestadt G: Factor analysis of the Yale-Brown Obsessive Compulsive Scale in a family study of obsessive-compulsive disorder. *Depress Anxiety* 2007; 24:130-138

SANJAYA SAXENA, M.D.
San Diego, Calif.

The author's disclosures accompany the original editorial.

This letter (doi: 10.1176/appi.ajp.2007.07030425r1) was accepted for publication in May 2007.

Dr. Samuels Replies

TO THE EDITOR: We agree with Drs. Grootheest and Cath that hoarding behavior may be heterogeneous, "possibly with subtypes related and subtypes unrelated to OCD." Indeed, on page 498 of our article, we noted that hoarding behavior can occur in conditions other than OCD, and we wrote that "we suspect that hoarding behavior itself is heterogeneous, and that the etiology of hoarding behavior is different in various syndromes." However, as noted by Dr. Saxena, all of the families in our cohort were recruited because they had two or more relatives affected with OCD, and thus OCD was over-

represented in the hoarding participants. On page 497, we suggested that Zhang et al. (1) may have found different linkage peaks for hoarding in their study because they selected families with multiple siblings affected with Tourette's syndrome, not OCD (1). Certainly, more work is needed in order to refine the phenotypic definition of hoarding, including the clinical features outlined by Dr. Saxena.

As pointed out by Drs. Van Grootheest and Cath, there was a range of severity in the hoarding individuals in our cohort, but the majority (68%) reported spending at least 1 hour per day and/or experiencing moderate, severe, or extreme distress that was frequent and disturbing during the worst period of their hoarding behavior.

We stand by our conclusion that the findings of our study suggest that a region on chromosome 14 is linked to compulsive hoarding behavior in these OCD families. We hypothesize that there is a genetic variant in this region that increases the risk of hoarding behavior in individuals who are susceptible to OCD. Additional genetic studies are required to replicate these findings and to characterize the genetic variant that may be involved.

Reference

1. Zhang H, Leckman JF, Pauls DL, Tsai CP, Kidd KK, Campos MR; Tourette Syndrome Association International Consortium for Genetics: Genomewide scan of hoarding in sib pairs in which both sibs have Gilles de la Tourette syndrome. *Am J Hum Genet* 2002; 70:896-904

JACK SAMUELS, PH.D.
Baltimore, Md.

The author's disclosures accompany the original article.

This letter (doi: 10.1176/appi.ajp.2007.07030425r2) was accepted for publication in May 2007.

Aripiprazole-Induced Tardive Dyskinesia: The Role of Tamoxifen

TO THE EDITOR: Aripiprazole is the newest atypical antipsychotic, which acts as a partial dopamine D₂ receptor agonist, partial 5-HT_{1A} agonist, and 5-HT_{2A} antagonist (1). There has been one case report of aripiprazole-induced tardive dyskinesia (2). We report a unique case of aripiprazole-induced tardive dyskinesia, with a possible role of concomitant tamoxifen use.

"Ms. A" was a 54-year-old female with a history of breast cancer while receiving hormonal therapy with tamoxifen for 4 years. She suffered with schizoaffective disorder and had been receiving olanzapine for 5 years, which was discontinued because of weight gain. Aripiprazole was started at 15 mg/day and then titrated to 20 mg/day, with good clinical effect. Ten months after initiation of aripiprazole, the patient presented with complaints of "tongue heaviness, talking with a lisp," and lip smacking for a 6-week period. She had tongue protrusion and lingual writhing movements on examination. Aripiprazole was discontinued. Her dyskinetic movements completely resolved within 1 month. She was successfully maintained on quetiapine without return of dyskinesia for 1 year.

There have been case reports on improvement of tardive dyskinesia with aripiprazole (2, 3). The partial agonist effect

on dopamine D₂ receptors and the lack of dopamine receptor upregulation at the nigrostriatal dopamine system were hypothesized as favorable effects of aripiprazole in patients with tardive dyskinesia (3).

Tamoxifen, a selective estrogen receptor modulator with mixed agonist/antagonist action, is used in the prevention and treatment of breast cancer (4). Animal studies have shown a neuroprotective role of estrogen and tamoxifen at the nigrostriatal dopamine pathway; however, this finding has not been ubiquitous (5, 6). Increased dopamine release (directly or indirectly through modulating dopamine receptor function) and modulation of membrane dopamine transporter activity have been postulated as some of the neuroprotective mechanisms of estrogen (5, 6).

We hypothesize that, in our patient—in addition to known risk factors (i.e., female gender, advanced age)—tamoxifen-induced dopaminergic action in the nigrostriatal dopamine system resulted in the loss of partial dopamine agonist effect of aripiprazole, which contributed to the development of tardive dyskinesia. Presently, the exact mechanisms remain unclear to us. In contradiction, estrogen has been previously reported to reduce tardive dyskinesia by suppressing dopamine receptor supersensitivity induced by typical antipsychotics (7).

In conclusion, it is important to note that aripiprazole can be associated with tardive dyskinesia. The relationship between estrogen, antipsychotics, and tardive dyskinesia remains to be examined.

References

1. Shapiro DA, Renock S, Arrington E, Chiodo LA, Liu LX, Sibley DR, Roth BL, Mailman R: Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. *Neuropsychopharmacology* 2003; 28:1400–1411
2. Mantal G, Ostacher M, Stern TA: Aripiprazole-related tardive dyskinesia. *CNS Spectr* 2006; 11:435–439
3. Duggal HS: Aripiprazole-induced improvement in tardive dyskinesia. *Can J Psychiatry* 2003; 48:771–772
4. Grese TA, Dodge JA: Selective estrogen receptor modulators. *Curr Pharm Des* 1998; 4:71–92
5. Liu B, Dluzen DE: Effects of estrogen and related agents upon methamphetamine-induced neurotoxicity within an impaired nigrostriatal dopaminergic system ovariectomized mice. *Neuroendocrinology* 2006; 83:295–302
6. Le Saux M, Di Paolo T: Influence of estrogenic compounds on monoamine transporters in rat striatum. *Neuroendocrinol* 2006; 18:25–32
7. Benarf PJ, Langelier P, Villeneuve A: Estrogens and extrapyramidal system. *Lancet* 1977; 2:1367–1368

YESNE ALICI EVCIMEN, M.D.
New York, N.Y.
HARUN EVCIMEN, M.D.
Philadelphia, Pa.
JIMMIE HOLLAND, M.D.
New York, N.Y.

The authors report no competing interests.

This letter (doi: 10.1176/appi.ajp.2007.07030469) was accepted for publication in May 2007.

Paradoxical Motor Syndrome Following a Switch From Atypical Neuroleptics to Aripiprazole

TO THE EDITOR: The reciprocal influence on distinct dopamine transmission systems is putatively responsible for the clinical efficacy of aripiprazole in the treatment of psychiatric disorders. Thus, this partial agonist of the dopamine D₂- and serotonin 5-HT_{1A} receptors and antagonist of the 5-HT_{2A} receptor is thought to reinforce the cortical circuitry while blocking the mesolimbic pathway (1). Aripiprazole is often used as a second-line agent, raising the question of an optimized therapeutic switch after prolonged treatment with typical/atypical neuroleptics. This may account for diverse clinical issues, as the one we describe in the case presented below.

“Ms. A,” a 54-year-old woman who suffered with bipolar disorder for 35 years without any history of drug abuse, was treated with lithium at therapeutic rates for 25 years and olanzapine for 1 year. Three years before, she received risperidone for several months. Because the patient reported being unsatisfied, diurnal tiredness, increase of appetite, and weight gain, olanzapine was substituted to amisulpride up to 200 mg/day. One month later, amisulpride was progressively discontinued, since weight gain was persistent, and aripiprazole (5 mg then 10 mg) was started.

Rapidly, an akineto-hypertonic parkinsonian syndrome developed in the patient, with shaking of her upper limbs and stiffness of her four limbs, impeding her from lying down, getting up, walking, and feeding herself. This contrasts with the expected clinical consequences of switching from an antagonist to a partial agonist of D₂ receptors. Soon after this episode, the patient showed facial, oral, and axial dystonia, which is consistent with enhanced activity in the nigrostriatal pathway. Meanwhile, she experienced a recurrence of hallucinations with paranoid symptoms. Aripiprazole was then discontinued. The patient's motor symptoms were treated with trihexyphenidyl (anticholinergic) (15 mg), and olanzapine (5 mg) was reintroduced. Lithium was maintained under therapeutic values. Three months were needed for her motor and psychotic symptoms to disappear, and her appetite increased again.

According to classical receptor theory, the density of receptors directly influences the intrinsic activity of partial agonists (2, 3). It is therefore difficult to predict the response to such drugs in a given tissue, especially under pathological circumstances. Accordingly, one would predict that prior exposures to neuroleptics would increase the tissue responsiveness and favor the agonist profile of aripiprazole. Based on these concepts, we hypothesize that the chronic administration of atypical antipsychotics leads to dopamine D₂ receptor hypersensitivity in the nigrostriatal pathway. This would promote the activation of dopamine D₂ receptors by aripiprazole, explaining the emergence of dystonic symptoms.

These observations reveal that the clinical consequences of a switch between distinct neuroleptics can be more unpredictable than suggested. Fundamental studies might be needed in order to understand the underlying mechanisms.

References

1. Tamminga CA, Carlsson A: Partial dopamine agonists and dopaminergic stabilizers, in the treatment of psychosis. *Curr Drug Targets CNS Neurol Disord* 2002; 1:141–147