Is there a link between aripiprazole and treatment-emergent psychosis?

James J. Gugger, PharmD, BCPP, Courtney L. Tam, PharmD, and Charles R. Ashby, Jr, PhD

Mr. N, age 29, presents to the emergency department at the urging of his family because of poor self-care, bizarre behavior, and disturbed sleep. He first experienced psychiatric symptoms 10 years ago after his mother died. He became dysphoric and paranoid, displaying bizarre responses and behaviors with poor self-care and a gradual functional decline. He has been taking sertraline, 100 mg/d, for 10 years.

Upon arrival at the hospital's inpatient unit, Mr. N is unkempt, oddly related, and paranoid. His affect is constricted. Mr. N displays thought blocking and possibly is responding to internal stimuli. Sertraline is continued and haloperidol, 1 mg/d, is initiated. For the next 2 weeks, Mr. N continues to be oddly related, irritable, and paranoid, and experiences disturbed sleep and thought blocking. After an episode of impulsive aggression, the treatment team initiates aripiprazole, which is titrated to 30 mg/d for 1 week. Mr. N's clinical status worsens; he is menacing toward other patients and his thinking is more disorganized, with loose associations and ideas of reference. He requires 4 injections of IM haloperidol, 5 mg, and several visits to the seclusion room over the next week. Haloperidol is increased to 30 mg/d over the next 10 days, then aripiprazole is discontinued because of a putative drug interaction with haloperidol. Following the medication changes Mr. N demonstrates better behavioral control, but still is grossly psychotic. While awaiting transfer to a state hospital, Mr. N receives a trial of olanzapine, 20 to 40 mg/d, for 2 weeks without significant benefit.

Dr. Gugger is Assistant Clinical Professor, Dr. Tam is Pharmacy Practice Resident, and Dr. Ashby is Professor, St. John's University, College of Pharmacy and Allied Health Professions, Queens, NY.

Several clinical trials demonstrate a significant reduction in intensity of psychotic symptoms with aripiprazole, which has a unique mechanism of action.[1] However, since its FDA approval in 2002, several case reports have described treatment-emergent psychotic symptoms associated with aripiprazole initiation. Over the past 40 years, reports of worsening psychosis associated with antipsychotics have been limited to patients with schizophrenia who were taking high dosages or who had high plasma concentrations, when anticholinergic delirium may have explained increased psychotic symptoms.[2-4]

How can a drug effectively treat psychotic symptoms and occasionally worsen

Practice Points

- **Aripiprazole may interact preferentially** with distinct conformations of the D2 receptor, leading to a spectrum of pharmacologic effects, including acting as a full agonist, partial agonist, or antagonist.
- **Clinical predictors** of aripiprazole-associated worsening of psychosis include low baseline level of psychopathology and previous treatment with high-dose antipsychotics.
- Rapid transition from a medication with significant anticholinergic properties to 1 without these properties **may result in symptoms of activation**, including restlessness, insomnia, and anxiety, which can be mistaken for worsening psychosis.
- **Akathisia**, a common adverse effect of aripiprazole, may masquerade as treatment-emergent worsening of psychotic symptoms.

Vicki L. Ellingrod, PharmD, BCPP, FCCP
Series Editor

them? In this article, we discuss the relevant pharmacology and clinical literature on aripiprazole and try to make sense of this apparent paradox.

Unique pharmacologic profile

Antipsychotics have been reported to be either neutral antagonists or inverse agonists at the D2 receptor, based on *in vitro* data.[5] Aripiprazole and its main metabolite, dehydroaripiprazole, originally were described as partial agonists at D2 dopamine receptors.[6,7] However, it appears aripiprazole's pharmacologic action is better explained by the concept of functional selectivity. Aripiprazole may interact preferentially with distinct conformations of the D2 receptor, leading to a spectrum of pharmacologic effects, including acting as a full agonist, partial agonist, or antagonistic.[5]

Researchers have hypothesized that the pathophysiology of schizophrenia may, in part, be caused by dysfunction of mesocorticolimbic dopaminergic neurons characterized by an enhanced sensitivity of postsynaptic D2 receptors and increased sensitivity to dopaminergic drugs.[8,9] In addition, chronic treatment with a D2 receptor antagonist is associated with increases in postsynaptic dopamine receptor density (ie, an increase in receptor reserve).[10,11] Upregulation of D2 receptors may explain several features seen in patients chronically treated with antipsychotics, including tardive dyskinesia[12] and rapid psychotic relapse after discontinuing an antipsychotic (supersensitivity psychosis).[13] Because chronic antipsychotic treatment leads to high postsynaptic receptor reserve, aripiprazole initiation may produce overactivation of D2 receptors, which might worsen a patient's condition.[14] *In vitro* data[15-18] and clinical observations indicate that aripiprazole has intrinsic efficacy at D2 receptors, as do clinical observations, such as:

- its propensity to reduce serum prolactin[19]
- a decreased likelihood of producing extrapyramidal side effects despite >80% occupancy of D2 receptors[6]
- case reports documenting aripiprazole-associated mania,[20] improvement of risperidone-associated cognitive impairment,[21] and pathologic gambling.[22]

Emergence or worsening of psychotic symptoms or a marginal antipsychotic effect may occur if aripiprazole is indeed a postsynaptic D2 receptor agonist. An individual patient's outcome likely would depend on his or her sensitivity to psychosis and concurrent or previous exposure to a D2 receptor antagonist. For example, stimulation of postsynaptic D2 receptors may be further augmented if the dosage of the previous antipsychotic was reduced or withdrawn before initiating aripiprazole because additional receptors would be available for interaction with aripiprazole.

Clinical Point

Aripiprazole initiation may produce overactivation of D2 receptors, which might worsen a patient's condition

Case reports

A literature review revealed 23 reports of treatment-emergent psychosis associated with aripiprazole initiation (***Table, page 56-57***). The mean age of the patients was 47 (range: 17 to 69) and 57% were men. Most patients (87%) were diagnosed with a schizophrenia-spectrum illness before aripiprazole initiation. Most (57%) had mild, stable, or no psychotic symptoms before aripiprazole initiation. Most were receiving relatively high doses of antipsychotics (average chlorpromazine equivalents [CPZE]: 648 mg/d) before aripiprazole initiation. This medication was either decreased or discontinued in 70% of patients.

Emergence or worsening of psychotic symptoms included agitation, aggressive behavior, and increased psychomotor activity. However, akathisia evaluation was described in only 2 reports: 1 author identified akathisia symptoms, but attributed them to a concomitant antipsychotic (fluphenazine)[23] and the other report specifically excluded the possibility of akathisia.[24] Two systematic studies have attempted to establish risk factors for aripiprazole-associated worsening psychosis (***Box***).[14,25]

In our literature review, the mean final dose of aripiprazole was 21.5 mg/d (range: 2 to 60 mg/d). In the cases describing subsequent treatment, all but 1 patient were switched to another antipsychotic, including 2 whose psychotic symptoms

Box

Clinical predictors of aripiprazole-associated psychotic symptoms

Takeuchi et al[14] aimed to establish predictors of worsening psychosis in a naturalistic setting where patients slowly transitioned to aripiprazole from previous antipsychotic treatment. Patients were required to be on a stable dose of an antipsychotic before participating in the study. Aripiprazole was started at 12 mg/d for 2 weeks with flexible dosing from weeks 2 to 52. Previous antipsychotic therapy was reduced biweekly by 25%. The incidence of worsening psychopathology after aripiprazole initiation was higher in the group of patients who had previously received high-dose antipsychotic therapy (average chlorpromazine equivalents [CPZE]: 727 mg/d) compared with the group on low dosages (average CPZE: 382 mg/d). It is possible that previous high-dose antipsychotic therapy was indicative of more significant baseline psychopathology; however, the worsened group and stabilized group had similar baseline Clinical Global Impressions-Severity scores.

Pae et al[25] aimed to find predictors of worsening psychosis with aripiprazole in patients whose previous antipsychotic therapy was immediately discontinued. They found lower baseline disease severity was associated with significant worsening during the first month of aripiprazole treatment.

stabilized with continuation of aripiprazole and addition of a second antipsychotic. Interestingly, in the case reported by Adan-Manes et al,[26] initial treatment with aripiprazole monotherapy was efficacious, but a subsequent trial of adjunctive aripiprazole resulted in worsening psychosis.

Other potential explanations

Aripiprazole's manufacturer reported the incidence of psychosis-related adverse events in an analysis of 9 randomized schizophrenia trials.[27] The rates of psychosis-related adverse events ranged from 0.6% to 18%, but there was no apparent relationship to study design or method of transitioning to aripiprazole. Rates of psychosis-related adverse events were similar between aripiprazole and the control group (placebo in 3 studies, another antipsychotic in 2 studies).

Emergence or worsening of psychotic symptoms temporally associated with aripiprazole initiation does not necessarily imply causation. As in Mr. N's case, it is not always possible to determine whether worsening psychosis is the natural disease course or a treatment effect. In addition, it is not possible to differentiate lack of efficacy from a true propensity for aripiprazole to worsen psychosis.

It also is conceivable discontinuation or dosage reduction of a previous antipsychotic would worsen psychotic symptoms or cause side effects. When significant changes in psychopathology or side effects develop during the transition from 1 antipsychotic to another, it is difficult to determine etiology. Specifically, rapid transition from a medication with significant anticholinergic and antihistaminic properties—such as quetiapine or olanzapine—to 1 without these properties—such as aripiprazole—may result in symptoms of activation, including restlessness, insomnia, and anxiety. Consequently, these symptoms could be mistaken for worsening psychosis.[28] Only 1 patient in this series was reported to abruptly discontinue an antipsychotic with significant anticholinergic properties (clozapine) before initiating aripiprazole.[24] Studies by Takeuchi et al[14] and Pae et al[25] did not report the relative baseline use of antipsychotic medication with anticholinergic properties.

In a pooled analysis of treatment-emergent adverse events in 5 randomized clinical trials of patients receiving aripiprazole for acute relapse of schizophrenia, the incidence of akathisia was 10%, although it is not clear if this is a dose-related adverse effect.[29] Because akathisia may be confused for worsening psychosis,[30] it is possible akathisia was mistakenly identified as worsening psychotic symptoms in Mr. N's case, as well as several reports from our literature review.

Covert akathisia is unlikely to explain worsening psychopathology observed in

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Clinical Point

Emergence of psychotic symptoms temporally associated with aripiprazole initiation does not imply causation

Table

Case reports: Treatment-emergent psychosis associated with aripiprazole

Study	Age, sex	Diagnosis	Before aripiprazole initiation
Chiu et al, 2011[a]	39, M	Schizophrenia	Psychiatrically stable, tardive dystonia
Ekinci et al, 2010[b]	17, M	ADHD	Inattention and impulsive aggression
Selvaraj et al, 2010[c]	49, F	Chronic depression	Depressive symptoms, suicidal ideation
Adan-Manes et al, 2009[d]	23, M	Schizophrenia	No psychotic symptoms
Cho et al, 2009[e]	45, F	Schizophrenia	Persistent psychotic symptoms, new onset diabetes with acute ketoacidosis
Ahuja et al, 2007[f]	35, F	Schizoaffective disorder	Stable before medication change
Lea et al, 2007[g]	57, M	Schizophrenia	Persistent psychotic symptoms, treatment resistance, recent recovery from NMS
Lea et al, 2007[g]	49, M	Schizoaffective disorder	Delusions, verbal aggression, substance abuse, HCV
Lea et al, 2007[g]	60, M	Schizophrenia	Delusions, labile mood, aggression
Raja, 2007[h]	30, M	Schizoaffective disorder	Negative symptoms, otherwise stable, recent citalopram discontinuation
Raja, 2007[h]	69, F	Bipolar disorder	History of multiple relapses; presented with tremor, akathisia, weight gain
Raja, 2007[h]	59, F	Schizophrenia	Negative symptoms, otherwise stable
Thone, 2007[i]	31, M	Schizophrenia	Confusion, agitation, delusions worsened with aripiprazole dose increase
Glick et al, 2006[j]	55, F	Schizophrenia	Stable before medication change
Glick et al, 2006[j]	52, M	Schizophrenia	Negative symptoms
Barnas et al, 2005[k]	57, F	Schizoaffective disorder	Stable before medication change
DeQuardo, 2004[l]	54, M	Schizophrenia	History of aggression, residual paranoia, severe EPS
DeQuardo, 2004[l]	51, M	Schizophrenia	History of aggression, persistent psychotic symptoms, treatment resistance
Ramaswamy et al, 2004[m]	43, F	Schizoaffective disorder	Psychiatrically stable, multiple medication changes, including substituting carbamazepine for valproic acid
Ramaswawamy et al, 2004[m]	57, F	Schizoaffective disorder	History of multiple hospitalizations, but stable before medication change
Ramaswawamy et al, 2004[m]	67, F	Schizophrenia	Remote hospitalizations, recent worsened psychosis
Ramaswamy et al, 2004[m]	46, M	Schizophrenia	Persistent delusions while receiving risperidone, TD
Reeves et al, 2004[n]	50, M	Schizoaffective disorder	Relatively stable with nonthreatening delusions, hallucinations

ADHD: attention-deficit/hyperactivity disorder; EPS: extrapyramidal symptoms; HCV: hepatitis C virus; NMS: neuroleptic malignant syndrome; TD: tardive dyskinesia

Source: For reference citations, see this article at CurrentPsychiatry.com

Clinical Point

It is not possible to differentiate lack of efficacy from a true propensity for aripiprazole to worsen psychotic symptoms

Pre-aripiprazole treatment	Aripiprazole dose	Concomitant psychotropic treatment	Subsequent treatment
Clozapine, 300 mg/d	10 mg/d	Valproic acid, 1,000 mg/d, clonazepam, 2 mg/d, mephenoxalone, 800 mg/d	Clozapine
Tapered and discontinued risperidone, 2.5 mg/d	5 mg/d	Methylphenidate, 54 mg/d	Risperidone, 2 mg/d, methylphenidate, 36 mg/d
None stated	2 mg/d	Duloxetine, 80 mg/d, clonazepam, 2 mg/d	Duloxetine, 120 mg/d
Abrupt decrease of amisulpride dose from 800 mg/d to 400 mg/d	20 mg/d	Biperiden, 4 mg/d	Amisulpride, 800 mg/d
Haloperidol, 20 mg/d, abrupt clozapine discontinuation	15 mg/d	Valproic acid, nortriptyline	Molindone, 150 mg/d
Tapered amisulpride, 400 mg/d, over 6 weeks	15 mg/d	None	Amisulpride, 600 mg/d
Discontinued ziprasidone, 200 mg/d	30 mg/d	Lorazepam, 2 mg/d, amantadine, 100 mg, sertraline, 50 mg/d	Clozapine
Decreased quetiapine dose from 800 mg/d to 400 mg/d	15 mg/d	Divalproex, 1,000 mg/d, fluvoxamine, 200 mg/d, clonazepam, 2 mg/d	Lithium, quetiapine, 500 mg/d, haloperidol, 2 mg/d
Risperidone, 3 mg/d, interruption of fluphenazine, 75 mg/d	20 mg/d	Divalproex, 4,500 mg/d, benztropine, 3 mg/d	Not discussed
Discontinued amisulpride, 800 mg/d over 2 weeks	30 mg/d	Lithium	Amisulpride, 500 mg/d
Discontinued risperidone, 2 mg/d, over 2 weeks	15 mg/d	Lithium	Risperidone, 4 mg
Reduced risperidone dosage from 5 mg/d to 4 mg/d	7.5 mg/d	None	Risperidone, 5 mg/d
None	60 mg/d	None	Aripiprazole dose reduction to 15 mg/d, olanzapine, 10 mg/d
Tapered and discontinued thioridazine, 600 mg/d, over 3 months	30 mg/d	None	Chlorpromazine, 200 mg/d, aripiprazole, 30 mg/d
Decreased olanzapine dose from 30 mg/d to 20 mg/d	30 mg/d	None	Olanzapine, 30 mg/d
Discontinued perphenazine, 8 mg/d	30 mg/d	None	Quetiapine, 350 mg/d
Haloperidol, 200 mg/d	15 mg/d	Benztropine	Haloperidol
Olanzapine, 60 mg/d	10 mg/d	None	Olanzapine
Discontinued ziprasidone, 160 mg/d, discontinued quetiapine, 400 mg/d, over 2 weeks	30 mg/d	Propranolol, 30 mg/d, l-thyroxine, .05 mg/d, carbamazepine, 600 mg/d	Not available
Decreased olanzapine dose from 20 mg/d to 15 mg/d	30 mg/d	Valproic acid, 2,000 mg/d	Ziprasidone
Decreased ziprasidone dose from 200 mg/d to 160 mg/d 2 months previously	30 mg/d	Carbamazepine, 200 mg/d	Not discussed
Risperidone, 3 mg/d	15 mg/d	Valproic acid, 1,500 mg/d	Risperidone, 3 mg/d
Quetiapine, 800 mg/d	30 mg/d	Divalproex, 2,000 mg/d	Olanzapine, 20 mg/d

Clinical Point

Covert akathisia may not explain worsening psychopathology observed in all patients in our literature review

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Related Resource

- Abilify [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2011.

Drug Brand Names

Amantadine • Symmetrel
Aripiprazole • Abilify
Benztropine • Cogentin
Biperiden • Akineton
Carbamazepine • Tegretol
Chlorpromazine • Thorazine
Clonazepam • Klonopin
Clozapine • Clozaril
Divalproex • Depakote
Duloxetine • Cymbalta
Fluphenazine • Permitil, Prolixin
Fluvoxamine • Luvox
Haloperidol • Haldol
Lithium • Eskalith, Lithobid
Lorazepam • Ativan
Nortriptyline • Aventyl, Pamelor
Methylphenidate • Concerta
Molindone • Moban
Olanzapine • Zyprexa
Perphenazine • Trilafon
Propranolol • Inderal
Quetiapine • Seroquel
Risperidone • Risperdal
Sertraline • Zoloft
Thioridazine • Mellaril
Thyroxine • Synthroid
Valproic acid • Depakene
Ziprasidone • Geodon

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Clinical Point

Aripiprazole's activity is on a pharmacologic continuum between a neutral antagonist and full agonist

all patients in our literature review because confusion of akathisia and worsening psychosis is not a widespread phenomenon. In a post hoc analysis of pooled safety data from aripiprazole trials, Kane et al[31] did not find a correlation between presence of akathisia and aripiprazole efficacy as measured by the Positive and Negative Syndrome Scale (PANSS) total, PANSS positive, PANSS negative, Clinical Global Impressions-Severity, Clinical Global Impressions-Improvement, and percentage of responders. Pae et al[25] also noted there was no correlation between scores on the Barnes Akathisia Rating Scale and worsening psychopathology in patients switched to aripiprazole.

An antagonist always is an antagonist and clinicians have appreciated this concept since the days of chlorpromazine. The activity of aripiprazole, however, is on a pharmacologic continuum between a neutral antagonist and full agonist and currently there is no way to precisely determine the level of D2 receptor agonist action in a patient.

Although it is interesting to speculate that aripiprazole's D2 receptor agonist action may contribute to worsening psychosis,[32-34] there are other plausible explanations to consider. Rapid transition from a drug with significant anticholinergic properties and aripiprazole-associated akathisia may contribute to worsening psychopathology in patients starting aripiprazole. Because covert side effects may be incorrectly identified as psychotic agitation, we cannot exclude this as a possible etiologic factor in Mr. N's case as well as the cases in our literature review.

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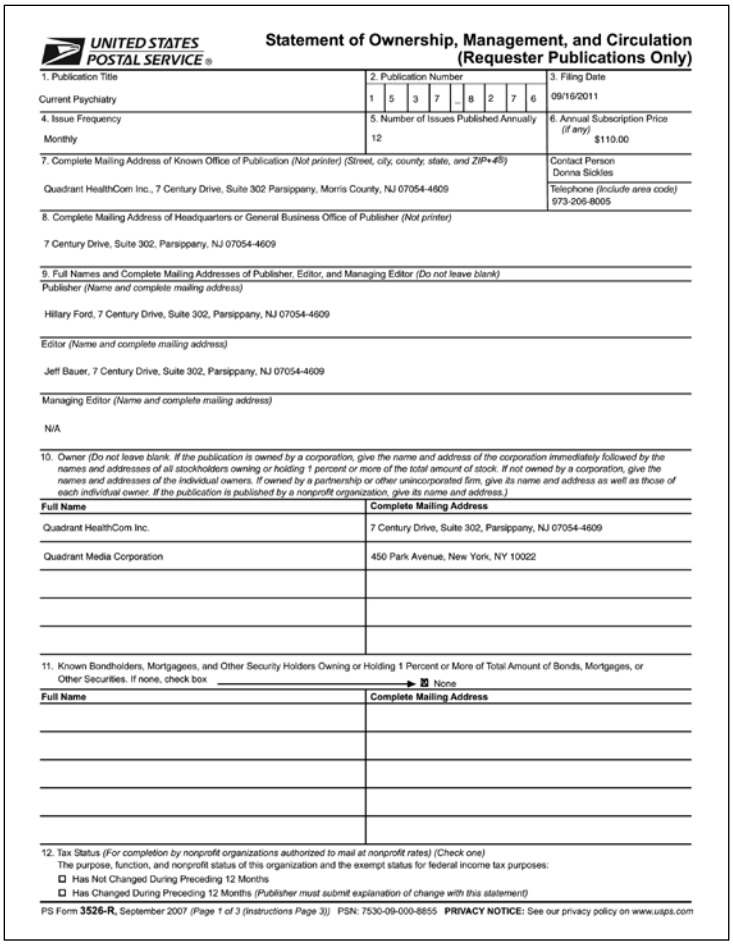

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1. Publication Title	2. Publication Number	3. Filing Date
Current Psychiatry	1 5 3 7 - 8 2 7 6	09/16/2011
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price (if any)
Monthly	12	$110.00

7. Complete Mailing Address of Known Office of Publication *(Not printer) (Street, city, county, state, and ZIP+4®)*: Quadrant HealthCom Inc., 7 Century Drive, Suite 302 Parsippany, Morris County, NJ 07054-4609 — Contact Person: Donna Sickles; Telephone *(Include area code)*: 973-206-8005

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not printer)*: 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do not leave blank)*

Publisher *(Name and complete mailing address)*: Hillary Ford, 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609

Editor *(Name and complete mailing address)*: Jeff Bauer, 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609

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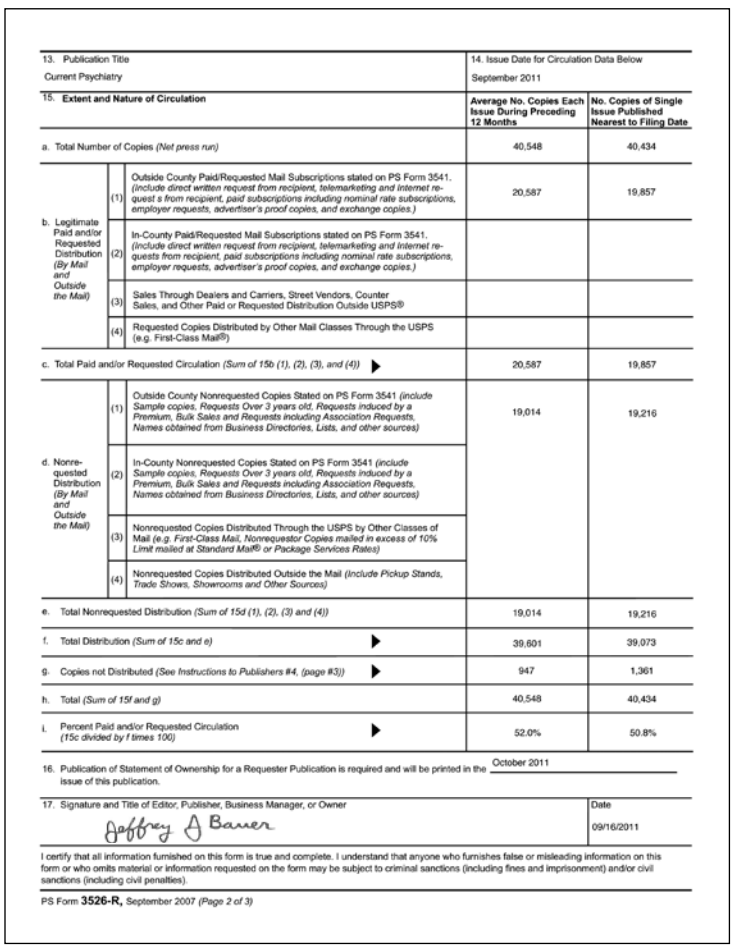

13. Publication Title	14. Issue Date for Circulation Data Below
Current Psychiatry	September 2011

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b. Legitimate Paid and/or Requested Distribution *(By Mail and Outside the Mail)*	(1)	Outside County Paid/Requested Mail Subscriptions stated on PS Form 3541. *(Include direct written request from recipient, telemarketing and Internet request from recipient, paid subscriptions including nominal rate subscriptions, employer requests, advertiser's proof copies, and exchange copies.)*	20,587	19,857
	(2)	In-County Paid/Requested Mail Subscriptions stated on PS Form 3541. *(Include direct written request from recipient, telemarketing and Internet requests from recipient, paid subscriptions including nominal rate subscriptions, employer requests, advertiser's proof copies, and exchange copies.)*		
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c. Total Paid and/or Requested Circulation *(Sum of 15b (1), (2), (3), and (4))* ▶			20,587	19,857
d. Nonrequested Distribution *(By Mail and Outside the Mail)*	(1)	Outside County Nonrequested Copies Stated on PS Form 3541 *(include Sample copies, Requests Over 3 years old, Requests induced by a Premium, Bulk Sales and Requests including Association Requests, Names obtained from Business Directories, Lists, and other sources)*	19,014	19,216
	(2)	In-County Nonrequested Copies Stated on PS Form 3541 *(include Sample copies, Requests Over 3 years old, Requests induced by a Premium, Bulk Sales and Requests including Association Requests, Names obtained from Business Directories, Lists, and other sources)*		
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	(4)	Nonrequested Copies Distributed Outside the Mail *(Include Pickup Stands, Trade Shows, Showrooms and Other Sources)*		
e. Total Nonrequested Distribution *(Sum of 15d (1), (2), (3) and (4))*			19,014	19,216
f. Total Distribution *(Sum of 15c and e)* ▶			39,601	39,073
g. Copies not Distributed *(See Instructions to Publishers #4, (page #3))* ▶			947	1,361
h. Total *(Sum of 15f and g)*			40,548	40,434
i. Percent Paid and/or Requested Circulation *(15c divided by f times 100)* ▶			52.0%	50.8%

16. Publication of Statement of Ownership for a Requester Publication is required and will be printed in the October 2011 issue of this publication.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Jeffrey J Bauer — Date: 09/16/2011

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including civil penalties).

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Table

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