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REVIEW

A systematic review of reported cases involving psychotic symptoms worsened by aripiprazole in schizophrenia or schizoaffective disorder

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Abstract
Rationale Numerous case reports have suggested that aripiprazole can worsen psychotic symptoms in schizophrenia.
Objectives We reviewed reported cases which have suggested that aripiprazole can worsen psychotic symptoms in schizophrenia and evaluated each regarding quality of the causal relationship.
Methods A systematic literature search was conducted on August 18, 2012, using the PubMed and the EMBASE. Twenty-two cases met the following inclusion criteria: (1) diagnosis of schizophrenia or schizoaffective disorder, (2) worsening of psychotic symptoms associated with aripiprazole, and (3) aripiprazole dose ≤30 mg/day. Information about the causal relationship between aripiprazole and increased psychotic symptoms was extracted. The quality of the causal relationship was evaluated according to the modified guidelines for evaluation of drug-associated events and classified as "questionable," "moderately suggestive," or "highly suggestive."
Results Patients were chronic in at least 15 cases, and prior antipsychotic dose exceeded recommended guidelines in 19 cases. Psychotic symptoms worsened after simply adding aripiprazole to the current regimen in eight cases. Besides psychotic symptoms, increasing agitation (nine cases), aggression (11 cases), and/or activation (seven cases) were reported. Clinical resolution occurred after aripiprazole discontinuation in eight cases. Regarding causal relationship, 11 cases were classified as "highly suggestive," three as "moderately suggestive," and eight as "questionable".
Conclusions Clinicians should be vigilant when adding aripiprazole to patients with chronic schizophrenia also receiving relatively high doses of other antipsychotics, and discontinuation of aripiprazole should be considered if psychotic symptoms and/or agitation/aggression/activation increase.

Keywords Aripiprazole · Psychotic symptoms · Worsening · Antipsychotics · Schizophrenia

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Introduction

As a partial dopamine agonist, aripiprazole is pharmacologically unique amongst existing antipsychotic drugs (Burris et al. 2002). It is postulated that this bestows benefits from the standpoint of side effects related to dopamine blockade, including extrapyramidal symptoms (EPS) and hyperprolactinemia in patients with schizophrenia (Marder et al. 2003). Aripiprazole also has a favorable profile in terms of weight gain and associated metabolic disturbances (e.g., disturbances in lipids and glucose) (Marder et al. 2003).

In view of its unique pharmacological and clinical profile, randomized controlled trials have been conducted to investigate the impact of adding, or switching to, aripiprazole to address problems such as hyperprolactinemia (Shim et al. 2007) or metabolic side effects in patients with schizophrenia (Fleischhacker et al. 2010; Newcomer et al. 2008; Stroup et al. 2011). While these studies have reported benefits with such a strategy, there have also been reports of worsening of psychotic symptoms in patients with schizophrenia, for example after adding aripiprazole compared to placebo (Fleischhacker et al. 2010), or switching to aripiprazole versus (L69) continuing olanzapine (Newcomer et al. 2008). The possibility that aripiprazole may worsen psychotic symptoms in patients with schizophrenia dovetails with a body of research suggesting such an association for agents that increase dopaminergic activity (Jaskiw and Popli 2004; Lieberman et al. 1987).

On the other hand, these clinical trials did not provide detailed clinical information on individual patients who experienced a worsening of psychotic symptoms, and thus cannot allow for conclusions regarding aripiprazole and a causal relationship. To date, there have been a number of case reports of psychotic symptoms worsened by aripiprazole in patients with schizophrenia since the first such case was reported in 2004 (Ramaswamy et al. 2004). Contrary to the clinical trials, these cases supply enough information to not only evaluate the quality of the causal relationship between aripiprazole and worsening of psychotic symptoms but also identify the potential risk factors of this phenomenon. Based on these objectives, we carried out a systematic review of reported cases.

Method

A literature search was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement (Moher et al. 2009) on August 18, 2012, in the PubMed and the EMBASE using the following search terms: "aripiprazole AND schizophreni*". Our literature search was limited to "case reports," "humans," and "English" in the PubMed, and "letters," "human," and "English language" in the EMBASE. The reference lists of the relevant reports were also examined.

Inclusion criteria were as follows: (1) diagnosis of schizophrenia or schizoaffective disorder; (2) worsening of psychotic symptoms in conjunction with aripiprazole, including hallucinations, delusions, disorganization, and/or bizarre behavior; and (3) aripiprazole ≤30 mg/day (i.e., maximum recommended therapeutic dose).

Each of the cases meeting inclusion criteria were screened for the following information: age and gender, diagnosis, onset or history of illness/treatment, rationale for initiating aripiprazole, previous antipsychotic medication(s)/dose(s), concomitant psychotropic medication(s)/dose(s), switching strategies to aripiprazole until psychotic worsening commences, duration until psychotic worsening commences since initiation of aripiprazole, nature of psychotic/non-psychotic symptoms that increased, effective/ineffective strategies for managing increased psychotic symptoms, and duration until psychotic worsening resolves.

Psychotic symptoms were defined by the following symptoms: hallucinations, delusions, disorganization, and bizarre behavior. Increased anxiety, hostility, and psychomotor activity were also recorded under the following categories, respectively: agitation, aggression, and activation.

The quality of the causal relationship between aripiprazole and increased psychotic symptoms was systematically evaluated for each case according to "the guidelines for evaluation of drug-associated events" developed by Aubry et al. (2000). These guidelines, developed to evaluate the relationship between atypical antipsychotics and mania/hypomania, were modified to specifically evaluate psychotic symptoms and are detailed in Table 1.

Items 1–7 of the original guidelines were maintained, with item 8 excluded based on the original definition (Aubry et al. 2000). In line with the original scale, the total number of fulfilled items was used to categorize each case as follows: 1–3 as "questionable," 4 as "moderately suggestive," and 5–7 as "highly suggestive" (Aubry et al. 2000).

Results

A total of 22 cases in 16 reports (Adan-Manes and Garcia-Parajua 2009; Ahuja and Lloyd 2007; Avari et al. 2011; Barnas et al. 2005; Burke and Lincoln 2006; Chiu et al. 2011; DeQuardo 2004; Glick et al. 2006; Grover et al. 2006; Kapusta et al. 2007; Lea et al. 2007; Letmaier et al. 2012; Ponde and Novaes 2007; Raja 2007; Ramaswamy et al. 2004; Reeves and Mack 2004) were identified (Fig. 1); a summary is provided in Table 2. Case reports have been published almost yearly since 2004 when aripiprazole became available in the USA.

Case characteristics

Age ranged from 23 to 72 years (median, 48), and cases were evenly split based on gender. Most cases (15 cases) were diagnosed with schizophrenia, with the remainder (seven cases) schizoaffective disorder. Patients were characterized as being chronic and/or ill >10 years in most cases (15 cases).

The reasons for introducing aripiprazole included persistent symptoms (12 cases), side effects (seven cases), both (one case), or other reasons (two cases). Previous antipsychotic treatment included atypical antipsychotic monotherapy (15 cases), typical antipsychotic monotherapy (four cases), combinations of atypical and typical antipsychotics (two cases), and combinations of atypical antipsychotics (one case). The prior antipsychotic dose exceeded the recommended maximum therapeutic dose (Gardner et al. 2010) in seven cases, and did so by one daily defined dose (DDD) (WHO Collaborating Centre for Drug Statistics Methodology, available at http://www.whocc.no/atc_ddd_index/) in most cases (15 cases). Mood stabilizers, used in eight cases of 12 cases, represented the most frequent concomitant medication class. Anticholinergic drugs were used in two cases.

Psychotic symptoms worsened after adding aripiprazole to current treatment, left unchanged, in eight cases. In most of these (six cases), psychotic symptoms worsened at a dose before/without aripiprazole titration. Doses of aripiprazole associated with a worsening of psychotic symptoms ranged from 5 to 30 mg/day (mode, 15 mg/day), which suggests no

Table 1 The modified guidelines for evaluation of drug-associated events for psychotic symptoms worsened by aripiprazole in schizophrenia or schizoaffective disorder

Original items	Definition	Original descriptions	Criteria to be fulfilled
1. Symptomatology and diagnosis before onset	Symptoms are confined to psychotic symptoms and diagnosis is confined to schizophrenia or schizoaffective disorder	(a) Were the symptoms already present and since when? (b) Are the clinical features and the diagnosis sufficiently documented?	Well documented and asymptomatic
2. Diagnostic evaluation at the time of side effect	Confined to psychotic symptoms	(a) Well documented? symptom severity	Well documented
		(b) Differential diagnosis; organic causes?	Not considered
		(c) Drug and/or substance abuse?	Not considered
3. Interval until onset	Duration until psychotic worsening commences since initiation of aripiprazole	(a) Is the interval precisely documented? (b) Rapid (hours to a few days) or slow onset (weeks to months)?	Well documented and ≤1 months
4. Dose	At the time psychotic worsening commences	(a) Titration (rapid escalation?)	Not considered
		(b) Standard posology?	Dose of aripiprazole is ≤30 mg/day
		(c) Blood levels available?	Not considered
5. Medication until introduction of suspected treatment	Confined to antipsychotics	(a) Abrupt withdrawal or tapering of previous medication? (b) Newly introduced treatment inefficacy versus prior treatment?	Previous antipsychotics are not changed and no other antipsychotics are initiated
6. Comedication (polypharmacy)	Confined to psychotropic medications other than antipsychotics	Drug(s) with potential of inducing similar associated events; drug(s) prescribed for the remission of induced symptomatology; dosage; pharmacokinetic interaction?	Concomitant psychotropic medications are not changed
7. Outcome	Also identify duration until psychotic worsening resolves since discontinuation of aripiprazole	Remission? Spontaneous? With dose reduction or discontinuation, with/without adjunctive treatment?	Resolved by discontinuation of aripiprazole without changing any other psychotropic medications (including antipsychotics) in ≤1 months
8. Rechallenge	Confined to aripiprazole	With/without reappearance of suspected drug-induced symptoms?	Worsened by rechallenge of aripiprazole

After assessing items 1–7 according to each criteria, quality of the causal relationship between aripiprazole and increased psychotic symptoms is concluded based on the total number of fulfilled items as follows: 1–3 as "questionable," 4 as "moderately suggestive," and 5–7 as "highly suggestive." Psychotic symptoms: hallucinations, delusions, disorganization, or bizarre behavior

clear relationship between aripiprazole dose and worsening of psychotic symptoms. Duration of aripiprazole exposure until increased psychotic symptoms ranged from days to months (median and mode, 2 weeks). Specifically identified symptoms included hallucinations (11 cases), delusions (19 cases), disorganization (two cases), and/or bizarre behavior (two cases). Intensity of increased psychotic symptoms was described as "significantly worsened/increased" (case 2, 4, and 20), "outbreak" (case 15), "dramatically increased" (case 17 and 21), "severely exacerbated" (case 22), "intensely paranoid" (case 5), or "overtly paranoid" (case 6). Other symptoms noted were agitation (10 cases), aggression (11 cases), and/or activation (seven cases).

The worsening of psychotic symptoms was not improved by increasing or decreasing aripiprazole, while leaving other medications unchanged, in approximately half the cases (six cases out of 13 cases). Further to this point, increasing aripiprazole dose was implicated in further worsening in four cases. On the other hand, discontinuation of aripiprazole, without changing other medications, resulted in resolution in most instances where this was implemented (eight cases). Just as time to onset of psychotic worsening was quite variable, duration until improvement of psychotic symptoms after effective intervention ranged widely, from days to months (median, 8 days; mode, 1 week). Table 2 provides details of each case.

Besides the 22 cases, 4 cases were identified as rechallenge trials (Table 2). In all, psychotic symptoms worsened after simply adding aripiprazole across a wide range of doses (2.5–15 mg/day) to the current regimen and resolved shortly after discontinuation of aripiprazole.

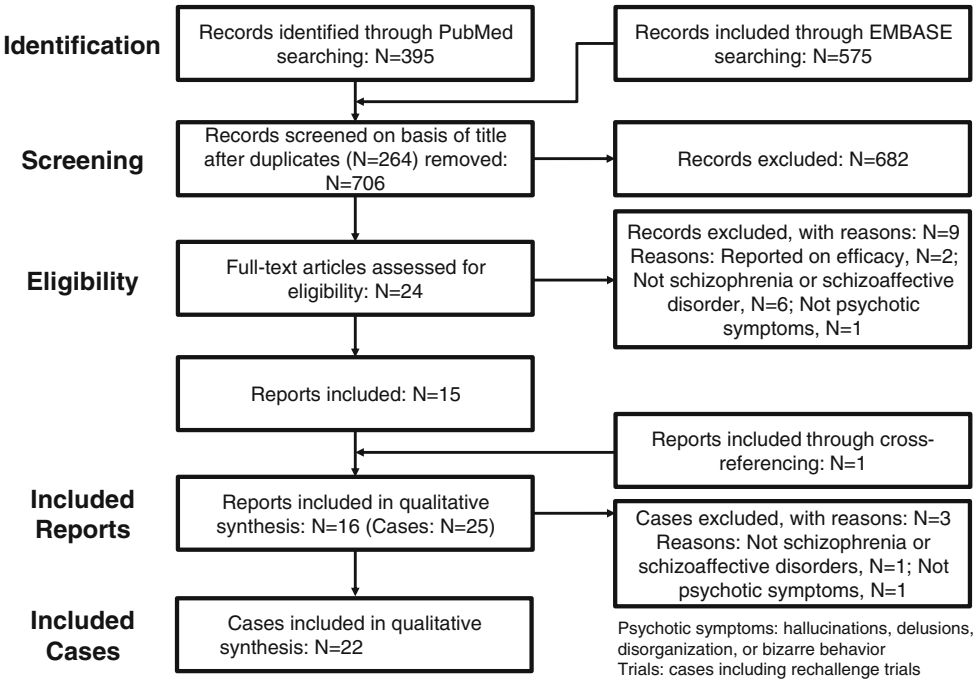

Fig. 1 PRISMA flow diagram of the literature search

Quality of causal relationship between aripiprazole and psychotic worsening for cases

Causal relationship between aripiprazole and worsening of psychotic symptoms is summarized as follows: 11 cases, "highly suggestive"; three cases, "moderately suggestive"; and eight cases, "questionable" (Table 2). All four rechallenge cases were classified as "highly suggestive."

Discussion

Our main findings from this systematic review are as follows: (1) approximately half of reported cases demonstrated a robust causal relationship between aripiprazole and a worsening of psychotic symptoms, (2) approximately one third of cases reported psychotic symptoms worsened after simply adding aripiprazole to the current treatment regimen, and (3) approximately one third of cases showed resolution of psychotic worsening was achieved by discontinuing aripiprazole without changing other medications. Aripiprazole also exacerbated psychotic symptoms across a wide range of doses. Taken together, the evidence seems to substantiate a causal relationship between aripiprazole and a worsening of psychotic symptoms in a proportion of patients with schizophrenia or schizoaffective disorder.

What is less clear is whether there are predictors of those at risk; to date, there have been few studies examining risk factors for aripiprazole-induced psychotic worsening. One study reported 40 % of patients worsened following a switch to aripiprazole, and patients already receiving relatively high antipsychotic doses may be at greater risk compared to those on lower doses (727 vs. 382 mg/day, respectively) (Takeuchi et al. 2009). A second study indicated that approximately 30 % of patients did not complete a switch to aripiprazole; descriptively, they received more typical antipsychotics and higher doses (≥1 DDD), were more ill, and had a longer course of illness compared to those who successfully completed the switch (Lin et al. 2009). Summarizing, it would seem that increased risk occurs in patients with chronic schizophrenia who are more ill and, as a result, are receiving relatively high antipsychotic doses. However, we are also reminded that these studies involved individuals undergoing a switch to aripiprazole, in contrast to reports where aripiprazole is added to existing treatment. Data drawn from switching studies must also factor in the possibility that the new drug, in this case aripiprazole, is not as effective as the antipsychotic the individual had been taking.

Differences were identified between cases where aripiprazole was added to current treatment (eight cases) and those where individuals were switched to aripiprazole from current treatment (14 cases). The main reason for introducing aripiprazole was efficacy (six cases) in the former, while efficacy (six cases) and side effects (six cases) were equally represented in the latter. In addition, number of cases where prior antipsychotic dose exceeded 1 DDD was slightly higher in cases where aripiprazole was added to existing antipsychotic treatment (six of eight cases) versus cases where individuals were being switched to aripiprazole (nine of 14 cases). Not surprisingly, it would appear that aripiprazole is added to current treatment in patients with treatment-resistant schizophrenia.

Table 2 Cases of psychotic symptoms worsened by aripiprazole in schizophrenia or schizoaffective disorder

Case no.	Authors, year	Age (years) Gender	Diagnosis Onset or history of illness/treatment	Previous antipsychotic medication(s) (mg/day)	Concomitant psychotropic medication(s) (mg/day)	Switching strategies to APZ until psychotic worsening commences (mg/day)	Duration until psychotic worsening commences since initiation of APZ
1	Ramaswamy et al. 2004	43 F	SAD ?	ZIP 160 QTP 400	VPA 1500 Propranolol 30 Levothyroxine 0.05	Add APZ 15 and increase to 30 Taper QTP to 100 (as needed) Switch from VPA to CBZ 600	?
2	Ramaswamy et al. 2004	57 F	SAD 20 years old	OLZ 20	VPA 2,000	Add APZ 30 Then, decrease OLZ to 15	≤4–6 months
3	Ramaswamy et al. 2004	67 F	S 35-years history	ZIP 160	CBZ 200	Add APZ 7.5 and increase to 30	2 months
4	Ramaswamy et al. 2004	46 M	S Chronic course	RIS 3	VPA 1500	Add APZ 15	?
5	DeQuardo 2004	54 M	S >25 years ago	HD 200 (every 4 weeks)	Benztropine ?	Add APZ 15	4 weeks
6	DeQuardo 2004	51 M	S >30 years ago	OLZ 60	None	Add APZ 10	9 days
7	Reeves and Mack 2004	50 M	SAD Mid-20s	QTP 800	VPA 2,000	Add APZ 15	1 week
7 (Rechallenge)	Reeves and Mack 2004	50 M	SAD Mid-20s	QTP 800	VPA 2,000	Add APZ 15	6 days
8	Barnas et al. 2005	57 F	SAD Long history	Perphenazine 8	None	Add APZ 10 and increase to 20 Discontinue perphenazine	2–3 weeks
9	Glick et al. 2006	55 F	S Early 20s	RIS 3 Thioridazine 600	None	Add APZ 15 Taper off RIS Then, taper off thioridazine	≥4 months
10	Glick et al. 2006	52 M	S 24 years old	OLZ 30	None	Add APZ 15 Decrease OLZ to 20	≤2 weeks
11	Burke and Lincoln 2006	30 M	S ?	APZ 10 HPD 10	None	Increase APZ to 30	?
12	Grover et al. 2006	24 F	S 5 years ago	HPD up to 30	None	Add APZ up to 20	≤2 months
13	Raja 2007	30 M	SAD Years treatment history	AMI 800	Li ? Citalopram 30	Cross-titrate from AMI to APZ 15 Then, discontinue citalopram	≥2 months
13 (Rechallenge)	Raja 2007	30 M	SAD Years treatment history	AMI 500	Li ?	Add APZ 7.5	Days
14	Raja 2007	59 F	S ≥30-years treatment history	RIS 5	None	Add APZ 7.5 Decrease RIS to 4	2 weeks
15	Ponde and Novaes 2007	72 F	S 30 years ago	HPD 1	Estazolam 2 Clonazepam 2 (as needed) Promethazine 25	Add APZ 7.5	5 months

Table 2 (continued)

Case no.	Authors, year	Age (years) Gender	Diagnosis Onset or history of illness/treatment	Previous antipsychotic medication(s) (mg/day)	Concomitant psychotropic medication(s) (mg/day)	Switching strategies to APZ until psychotic worsening commences (mg/day)	Duration until psychotic worsening commences since initiation of APZ
						Then, increase to 15 and discontinue HPD, clonazepam, and promethazine	
16	Ahuja and Lloyd 2007	35 F	SAD ?	AMI 400	None	Add APZ 10 and lorazepam 1 (as needed) Then, taper AMI to ? Then, increase APZ to 15 and taper AMI to ?	≤4 weeks
17	Kapusta et al. 2007	37 M	S 20 years old	RIS 6	None	Add APZ 15	3 days
17 (Rechallenge)	Kapusta et al. 2007	37 M	S 20 years old	RIS 9	None	Add APZ 2.5 and increase to 15	20 days
18	Lea et al. 2007	49 M	S Chronic course	QTP 800	VPA 1,000 Fluvoxamine 200	Add APZ 10, decrease QTP to 400 and fluvoxamine to ?, and start clonazepam 1	≤2 days
19	Adan-Manes and Garcia-Parajua 2009	23 M	S ≥2 years ago	AMI 800	Biperiden 4	Add APZ 10 Then, increase to 20 and decrease AMI to 400	17 days
19 (Rechallenge)	Adan-Manes and Garcia-Parajua 2009	23 M	S ≥2 years ago	AMI 800	Biperiden 4	Add APZ 10	5 days
20	Chiu et al. 2011	39 M	S >10 years ago	CLZ 300	VPA 1,000 Clonazepam 2 Mephenoxalone 800	Add APZ 10	1 week
21	Letmaier et al. 2012	39 F	SAD ?	RIS 4	Venlafaxine 225 Mirtazapine 30 Bisoprolol 5	Add APZ 5 and HPD 5 Discontinue RIS 4	5 days
22	Avari et al. 2011	47 F	S Late adolescence	CLZ 700	None	Add APZ ? and increase to 15	2 weeks

Case no.	Nature of symptoms that increased	Ineffective strategies for managing increased psychotic symptoms (outcome)	Effective strategies for managing increased psychotic symptoms (mg/day)	Duration until psychotic worsening resolves	Modified Aubry"s criteria: fulfilled items	Modified Aubry"s criteria: conclusion
1	Psychotic symptoms (?)	Trifluoperazine (as needed) (Worsened)	N/A	N/A	(None)	Questionable
2	Hallucination Delusion	N/A	Discontinue APZ Start ZIP ?	?	2, 4, 6	Questionable
3	Hallucination	N/A	N/A	N/A	2, 4, 5, 6	Moderately suggestive

Table 2 (continued)

Case no.	Nature of symptoms that increased	Ineffective strategies for managing increased psychotic symptoms (outcome)	Effective strategies for managing increased psychotic symptoms (mg/day)	Duration until psychotic worsening resolves	Modified Aubry"s criteria: fulfilled items	Modified Aubry"s criteria: conclusion
	Agitation					
4	Delusion	N/A	Discontinue APZ	≤Several weeks	2, 4, 5, 6, 7	Highly suggestive
5	Delusion Aggression	N/A	Discontinue APZ	4 weeks	2, 3, 4, 5, 6, 7	Highly suggestive
6	Hallucination Delusion Aggression	N/A	Discontinue APZ	Weeks	2, 3, 4, 5, 6, 7	Highly suggestive
7	Delusion Bizarre behavior Agitation Aggression	Increase APZ to 30 (Worsened)	Discontinue APZ	1 week	2, 3, 4, 5, 6, 7	Highly suggestive
7 (Rechallenge)	Hallucination Delusion Aggression	N/A	Discontinue APZ	4 days	2, 3, 4, 5, 6, 7	Highly suggestive
8	Bizarre behavior Aggression Activation (Under APZ 30, Delusion, Agitation)	Increase APZ to 30 (Worsened)	Discontinue APZ Start QTP 200 and increase to 350	?	2, 3, 4, 6	Moderately suggestive
9	Delusion Agitation Aggression Activation	Increase APZ to 30 (Temporarily improved)	Add thioridazine 100 (Afterward, two times APZ monotherapy trials worsened, and adding thioridazine 100 or CPZ 200 improved)	2 weeks	2, 4, 6	Questionable
10	Hallucination Delusion Agitation Activation	Increase APZ to 30 ("Strikingly" worsened)	Discontinue APZ Increase OLZ to 40	"Rapidly"	1, 2, 3, 4, 6	Highly suggestive
11	Delusion Agitation	Increase HPD to 20 ("Marginally" improved)	Discontinue APZ	4 days	2, 6, 7	Questionable
12	Psychotic symptoms (?)	Increase HPD up to 60 (Not changed)	Discontinue APZ	?	6	Questionable
13	Hallucination Delusion Agitation Aggression	Increase APZ to 30 (Worsened)	Discontinue APZ Restart AMI 800	1 month	1, 2, 4	Questionable

Table 2 (continued)

Case no.	Nature of symptoms that increased	Ineffective strategies for managing increased psychotic symptoms (outcome)	Effective strategies for managing increased psychotic symptoms (mg/day)	Duration until psychotic worsening resolves	Modified Aubry"s criteria: fulfilled items	Modified Aubry"s criteria: conclusion
	Activation					
13 (Rechallenge)	Delusion Aggression Activation	Decrease APZ to 5 (Worsened)	Discontinue APZ Increase AMI to 1,000	"Promptly"	1, 2, 3, 4, 5, 6	Highly suggestive
14	Hallucination Delusion Activation	Decrease APZ to 2.5 (Worsened)	Discontinue APZ Increase RIS to 5	?	1, 2, 3, 4, 6	Highly suggestive
15	Delusion Aggression	N/A	Add trifluoperazine 7.5	3 months	2, 4	Questionable
	Activation					
	Hallucination	Discontinue APZ	Increase AMI to 600	7-9 weeks	1, 2, 3, 4, 6	Highly suggestive
16	Delusion Agitation	(Partially worsened)				
17	Hallucination Delusion Aggression	N/A	Discontinue APZ Increase RIS to 9	≤10 days	2, 3, 4, 5, 6	Highly suggestive
17 (Rechallenge)	Hallucination Agitation	N/A	Discontinue APZ	4 days	2, 3, 4, 5, 6, 7	Highly suggestive
	Aggression					
18	Delusion Disorganization Agitation	Increase APZ to 15 Discontinue VPA Start Li ? Start hydroxyzine 50 (Not changed)	Discontinue APZ Increase QTP to 500 Start HPD to 2	1 week	2, 3, 4	Questionable
19	Hallucination Delusion	Decrease APZ to 10 Increase AMI to 800 (Partially improved)	Discontinue APZ	5 days	1, 2, 3, 4, 6, 7	Highly suggestive
19 (Rechallenge)	Hallucination	N/A	Discontinue APZ	1 week	1, 2, 3, 4, 5, 6, 7	Highly suggestive
20	Hallucination Delusion	N/A	Discontinue APZ	Weeks	2, 3, 4, 5, 6, 7	Highly suggestive
	Aggression					
21	Delusion Disorganization	APZ Increase to 30 HPD Increase to 7.5	Discontinue APZ Discontinue HPD	1 week	2, 3, 4, 6	Moderately suggestive
	Agitation Aggression	(Worsened)	Start OLZ 5			
22	Hallucination	N/A	Discontinue APZ	5 weeks	1, 2, 3, 4, 5, 6	Highly suggestive

Table 2 (continued)

Case no.	Nature of symptoms that increased	Ineffective strategies for managing increased psychotic symptoms (outcome)	Effective strategies for managing increased psychotic symptoms (mg/day)	Duration until psychotic worsening resolves	Modified Aubry's criteria: fulfilled items	Modified Aubry's criteria: conclusion
	Delusion Aggression Activation		Increase CLZ to 800			

Psychotic symptoms: hallucination, delusion, disorganization, or bizarre behavior; *?* not documented

SAD schizoaffective disorder, *AMI* amisulpride, *APZ* aripiprazole, *CBZ* carbamazepine, *CLZ* clozapine, *CPZ* chlorpromazine, *FD* fluphenazine decanoate, *FPZ* fluphenazine, *HD* haloperidol decanoate, *HPD* haloperidol, *Li* lithium, *OLZ* olanzapine, *QTP* quetiapine, *RIS* risperidone, *ZIP* ziprasidone, *VPA* valproic acid or divalproex

In terms of mechanism of action, exacerbation of psychotic symptoms by aripiprazole is most readily explained by its partial dopamine agonist properties (Burris et al. 2002); indeed, all 14 case reports that discuss the possible mechanism also implicate it. Notably, aripiprazole has a very high affinity for D_2 receptors (Burris et al. 2002), in contrast to low affinities for other receptors other than 5-HT_{1A} and 5-HT_{2A} (DeLeon et al., 2004). That the cases occur in chronically treated individuals also calls into question the impact of long-term antipsychotic administration and dopamine upregulation (Silvestri et al. 2000), possibly resulting in increased sensitivity to dopaminergic perturbations (i.e., supersensitivity psychosis) as may occur with partial agonist activity via the addition of aripiprazole. To this point, 11 case reports posit a role for upregulation of postsynaptic dopamine receptors or supersensitivity psychosis (Moncrieff 2006).

The worsening of psychosis associated with aripiprazole, as detailed in these case reports, was not improved by altering the dose of aripiprazole, although resolution occurred frequently after aripiprazole discontinuation. This certainly offers at least indirect evidence supporting a causal relationship between aripiprazole and psychotic worsening.

Finally, from a clinical standpoint, it is also important to recognize that the symptoms related to the addition of aripiprazole were not confined to psychotic symptoms per se, but also included agitation, aggression, and activation. Indeed, cases have been reported where the central features were agitation (Cho and Lindenmayer 2009) or mania (Ducroix et al. 2008; Padala et al. 2007; Traber et al. 2007). Regarding mania induced by atypical antipsychotics, some reviews (Aubry et al. 2000; Benyamina and Samalin 2012; Michalopoulou and Lykouras 2006; Rachid et al. 2004) have suggested all types of atypical antipsychotics can induce mania or hypomania; thus, this phenomenon is not specific to aripiprazole. Notwithstanding, clinicians must also be vigilant of these symptoms and the possible need to consider aripiprazole discontinuation should they appear.

Unfortunately, a series of case reports does not allow us to establish the exact risk of aripiprazole for worsening psychotic symptoms, and predicting who is liable also remains an unanswered question. Any interpretation of the data is qualified by the diversity of the cases (e.g., illness severity, types and doses of prior antipsychotics, or concomitant medications) and variables beyond pharmacotherapy. For example, there is the possibility that factors such as natural course of illness or environmental stress play a role, although the quality of the causal relationship between aripiprazole and increased psychotic symptoms was evaluated according to the modified guidelines for evaluation of drug-associated events.

In conclusion, evidence suggests that at least a small number of patients with schizophrenia or schizoaffective disorder risk an exacerbation of psychotic symptoms if aripiprazole is added to existing antipsychotic treatment. Many of the cases reported involve patients who are quite ill and have been exposed to long-term antipsychotic treatment, but it may also be that this population is simply more likely to be exposed to augmentation strategies. There appears to be no relationship between its occurrence and age or gender; similarly, it can occur across all doses of aripiprazole and anytime from days to weeks after treatment commences. At this point, clinicians must simply be cognizant of the risk, vigilant of clinical worsening in the context of such a scenario, and aware that aripiprazole discontinuation appears the preferred strategy should it occur.

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