Possible Induction of Mania or Hypomania by Atypical Antipsychotics: An Updated Review of Reported Cases

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Background: Atypical antipsychotics are widely used in clinical practice for several psychiatric disorders. Between 1994 and 1999, 26 cases of manic and hypomanic syndromes were reported with olanzapine and risperidone and were described in a previous review article.

Method: An updated MEDLINE search (1999–2003) using the terms *atypical antipsychotics, amisulpride, aripiprazole, clozapine, flupenthixol, olanzapine, quetiapine, risperidone, sertindole, ziprasidone, zotepine, hypomania,* and *mania* showed that 34 new cases of induced hypomanic or manic syndromes have been published, not only with olanzapine (N = 5) and risperidone (N = 6), but also with quetiapine (N = 5) and ziprasidone (N = 11) treatment. Six cases have been reported with flupenthixol and 1 with amisulpride, two antipsychotics considered as "partial" atypicals.

Results: A critical analysis of these case reports revealed that the effects on mood were insufficiently documented in some of the reports but that for 20 of them, evidence is highly suggestive of a causative role of atypical antipsychotics in the induction of manic/hypomanic symptomatology.

Conclusion: This updated review continues and extends the results of the initial review and suggests that atypical antipsychotics have some intriguing effects on mood. Such effects have never been reported with conventional antipsychotics. The mechanisms involved in this phenomenon of mood switch remain to be elucidated.

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Atypical antipsychotics are widely prescribed for the treatment of psychotic disorders, particularly schizophrenia. They are also used as adjunctive[1,2] or as sole agents in the management of a variety of neuropsychiatric conditions including manic episodes of bipolar disorder. Olanzapine, for example, was approved by the U.S. Food and Drug Administration in 2000 for the treatment of acute mania, and several randomized controlled studies have demonstrated its superiority over placebo for that condition.[3,4] It was also found to be as effective as lithium or divalproex sodium for acute mania.[5,6] In addition, several open and controlled studies have demonstrated the efficacy of risperidone as monotherapy or in conjunction with mood stabilizers for the treatment of mania.[7–12] Preliminary randomized controlled studies have also suggested that quetiapine[13,14] and ziprasidone[15] are effective in the treatment of acute mania.

On the other hand, it has been suggested that some atypical antipsychotics like risperidone and olanzapine may have a role in the augmentation of antidepressant treatment[16] of both nonpsychotic[17] and psychotic depression[18] or even as single agents in the management of treatment-resistant psychotic depression.[19,20] Also, quetiapine and risperidone have demonstrated efficacy in the treatment of depressive symptoms in psychosis.[21] Such potential antidepressant effects raise the question of whether atypical antipsychotics could have a propensity to induce mania in susceptible individuals. In fact, in 2000, we published a critical review of 26 cases of olanzapine-induced (N = 10) or risperidone-induced mania/hypomania (N = 16) which showed that more than half of these cases were highly suggestive of a causal link between the use of such agents and the development of manic/hypomanic symptomatology.[22]

To update our review, we recently performed a MEDLINE search of the literature from January 1999 to December 2003 using the terms *atypical antipsychotics, amisulpride, aripiprazole, clozapine, flupenthixol, olanzapine, quetiapine, risperidone, sertindole, ziprasidone, zotepine, hypomania,* and *mania*. We found 34 new cases of mood switch, 6 with risperidone[23,24]; 5 with olanzapine[25–29]; 5 with quetiapine[30–34]; 11 with ziprasidone[35–40]; 6 with flupenthixol,[41] a "partial" atypical[42,43];

and 1 with amisulpride.[44] This article is a critical review of these 34 cases and also discusses the available evidence for putative mechanisms of action involved in the induction of manic/hypomanic symptomatology by atypical antipsychotics.

Case reports of mania/hypomania induced by risperidone, olanzapine, quetiapine, ziprasidone, flupenthixol, or amisulpride are presented in Tables 1 through 6. As described in our previous article,[22] these tables are based on what we selected as the most important items to consider in evaluating a causal relationship between the use of these drugs and mania/hypomania (Table 7). Based on these guidelines, we will first outline the limitations of these case reports.

CRITICAL REVIEW

Concerning the described symptomatology prior to the onset of the induced manic/hypomanic episode, 1 patient (case 33) was already developing a manic episode prior to the initiation of flupenthixol while she was still on fluoxetine treatment, although the manic symptoms continued worsening for an unspecified period of time after discontinuation of the antidepressant. Since fluoxetine and its active metabolite norfluoxetine have relatively long half-lives, the above episode might represent antidepressant-induced rather than flupenthixol-induced mania in a patient with a history of several manic episodes, some of which might have been related to the use of antidepressants, as described by the authors of this large series.[41] It should also be pointed out that the same patient was prescribed fluoxetine in the absence of a mood stabilizer despite a suggested diagnosis of bipolar disorder. It is possible, nonetheless, that flupenthixol may have contributed to the worsening clinical course of the described episode, particularly because the symptoms abated soon after it was discontinued and haloperidol was added.

The description of premorbid clinical features is insufficiently documented in several cases (cases 1, 2, 4, 6–8, 17–19, and 26). The same applies to the description of the manic/hypomanic episode in 11 cases (cases 1, 7, 8, 11, 12, 17–19, 25, 26, and 29). In addition, 2 patients suggested by authors to have mania (cases 1 and 7) instead presented with hypomanic symptoms during risperidone and olanzapine treatment, respectively. In case 8, although the patient was described by the authors[26] as having increased psychomotor activity and excessive speech, the absence of an elated and/or irritable mood and of some other characteristic manic symptoms (decreased need for sleep, distractibility, or racing thoughts) despite the presence of grandiose delusions and related auditory hallucinations could merely represent the exacerbation of a psychotic illness different from the delusional disorder suggested by the authors. In case 13, although hypomania is suggested, the fact that the patient endorsed delusions

Table 1. Case Reports of Risperidone-Induced Mania/Hypomania

Case No.	Author	Diagnosis (age [y], gender)	Symptom	Dose (mg/d)	Interval Until Onset	Medication Until Start of Risperidone	Comedication	Outcome
1	Zolezzi and Badr, 1999[23]	Schizophrenia (21, female)	Mania	2 then 5 gradually	Within 3 weeks	?	?	Reduce risperidone dose, then stop; add carbamazepine, benzodiazepines, and, as needed, neuroleptics; remission of mania
2	Zolezzi and Badr, 1999[23]	Schizophrenia, chronic (45, female)	Mania	2 to 6 gradually	Within 4 weeks	Unknown antipsychotic	Nitrazepam	Start chlorpromazine; stop risperidone; resolution of mania after 7 days
3	Zolezzi and Badr, 1999[23]	Schizophrenia, paranoid type (35, female)	Mania	2 to 6 gradually	10 days	Trifluoperazine	None	Stop risperidone; remission of mania
4	Zolezzi and Badr, 1999[23]	Schizoaffective disorder (25, female)	Mania	2	Shortly after	Valproic acid Fluoxetine	Valproic acid Fluoxetine	Increase dose of valproic acid; stop risperidone; slow remission of mania
5	Güzelcan et al, 2002[24]	Schizophrenia, disorganized type, chronic (24, male)	Mania	4 then 5	"Acute"	Risperidone 3 mg/d stopped 2 months prior to hospitalization	?	After dose of risperidone increased to 5 mg/d, worsening of mania; stop risperidone and start haloperidol, lithium, and lorazepam; remission of mania within 3 weeks
6	Güzelcan et al, 2002[24]	Schizophrenia, paranoid type, chronic (21, female)	Mania	8 then 4 over period of 14 days	"Acute"	Temazepam 20 mg/d Trihexyphenidyl 4 mg/d	Temazepam 20 mg/d Trihexyphenidyl 4 mg/d	Onset of mania after dose of risperidone decreased from 8 mg/d to 4 mg/d; stop risperidone; start haloperidol 3 mg/d; remission of mania within 3 days

Symbol: ? = information not available or imprecise.

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Table 2. Case Reports of Olanzapine-Induced Mania/Hypomania

Case No.	Author	Diagnosis (age [y], gender)	Symptom	Dose (mg/d)	Interval Until Onset	Medication Until Start of Olanzapine	Comedication	Outcome
7	Fahy and Fahy, 2000[25]	Major depressive disorder, recurrent (55, female)	Mania	2.5	3 days	?	?	Stop olanzapine; rapid remission of mania
8	Narayan and Puranik, 2000[26]	Delusional disorder, paranoid type (85, female)	Mania	10	Within 4 months	Risperidone Trifluoperazine Thyroxine 100 µg/d	Thyroxine 100 µg/d	Stop olanzapine; start haloperidol 1 mg/d on an as-needed basis; remission of mania within 2 weeks
9	Borysewicz and Borysewicz, 2000[27]	Schizophrenia (31, male)	Mania	10	5 days	Risperidone Clozapine 400 mg/d Zuclopenthixol	Clorazepate Clonazepam Diazepam Nifedipine	Reduce dose of olanzapine to 5 mg/d; start haloperidol; remission of mania; then continue olanzapine 5 mg/d with haloperidol decanoate 100 mg every 2 weeks
10	Lykouras et al, 2001[28]	Schizophrenia, paranoid type (36, female)	Mania	15	3 weeks	None	?	Reduce dose of olanzapine to 10 mg/d, then to 5 mg/d, then stop; start ? conventional antipsychotic; remission of mania over next 4 weeks
11	Henry and Demotes-Mainard, 2002[29]	Bipolar I disorder (57, male)	Mania	5	Within 1 week	Amisulpride 200 mg/d Lithium	Lithium	Stop olanzapine; restart amisulpride with lithium; remission of mania over next 4 weeks

Symbol: ? = Information not available or imprecise.

Table 3. Case Reports of Quetiapine-Induced Mania/Hypomania

Case No.	Author	Diagnosis (age [y], gender)	Symptom	Dose (mg/d)	Interval Until Onset	Medication Until Start of Quetiapine	Comedication	Outcome
12	Benazzi, 2001[30]	Schizoaffective disorder, depressive type (43, female)	Hypomania	100 then 300	2 to 3 weeks	Chlorpromazine 100 mg/d Fluoxetine 20 mg/d Diazepam 5 mg/d	Fluoxetine 20 mg/d Diazepam 5 mg/d	Stop quetiapine; start chlorpromazine 100 mg/d; remission of hypomania after 1 week
13	Atmaca et al, 2002[31]	Schizophrenia, paranoid type (33, female)	Hypomania	50, then within 4 days 400	Within 2 weeks	Haloperidol 5 mg/d Chlorpromazine 75 mg/d Lithium 900 mg/d	None	Reduction of dose of quetiapine to 100 mg/d; remission of mania within 5 days; start haloperidol 5 mg/d and diazepam 5 mg/d
14	Lykouras et al, 2003[32]	Schizophrenia, paranoid type (26, male)	Mania	100, then 200 in 3 days, then to 400 2 days later, then 600	2 days	Lorazepam	Lorazepam	Worsening of mania with increased dose of quetiapine; gradual reduction of dose of quetiapine, then stop; remission of mania as of next day
15	Biancosino et al, 2003[33]	Schizophreniform disorder (23, female)	Mania	400 within 3 weeks	Gradual; within 1 week?	Haloperidol 10 mg/d Venlafaxine 75 mg/d Diazepam 2 mg/d	Diazepam 2 mg/d	Stop quetiapine; start zuclopenthixol and lorazepam; remission of mania within 10 days
16	Pacchiarotti et al, 2003[34]	Schizophrenia, paranoid type (21, male)	Mania	100 to 300 in 2 weeks	Within 3 weeks	Haloperidol 4.5 mg/d	Haloperidol initially	Stop quetiapine; start haloperidol 9 mg/d, chlorpromazine 300 mg/d, and clonazepam 9 mg/d; persistence of psychosis and mania; start clozapine 50 mg/d followed by valproate 600 mg/d; remission of mania within 10 days

Table 4. Case Reports of Ziprasidone-Induced Mania/Hypomania

Case No.	Author	Diagnosis (age [y], gender)	Symptom	Dose (mg/d)	Interval Until Onset	Medication Until Start of Ziprasidone	Comedication	Outcome
17	Davis and Risch, 2002[35]	Major depressive disorder, recurrent (43, male)	Hypomania	40 for 1 week, then 80	1 to 2 weeks?	Lamotrigine	None	Reduce dose of ziprasidone to 40 mg/d; complete remission of hypomania
18	Davis and Risch, 2002[35]	Major depressive disorder, recurrent; generalized anxiety disorder; attention-deficit/ hyperactivity disorder (31, male)	Hypomania	40 for 2–3 weeks, then 20	4 days	Bupropion	?	Reduce dose of ziprasidone to 20 mg/d, then development of severe depression; stop ziprasidone; persistence of depression
19	Davis and Risch, 2002[35]	Major depressive disorder, recurrent; panic disorder? (33, female)	Hypomania	40	10 hours and 3 days	Bupropion	Bupropion?	Hypomania then depression; stop ziprasidone; start risperidone dose to 3 mg/d; remission of depression
20	Lu et al, 2002[36]	Schizoaffective disorder bipolar type (41, male)	Mania	Titrated to 120 in 10 days	10 days	Olanzapine Divalproex	Divalproex	Stop ziprasidone; increase dose of divalproex; add quetiapine; remission of mania after 15 days
21	Baldassano et al, 2003[37]	Bipolar I disorder, rapid cycling, current episode depressed (26, male)	Mania	40	7 days	Carbamazepine 800 mg/d Clonazepam 2 mg/d Quetiapine 25 mg/d	Carbamazepine Clonazepam	Ziprasidone self-discontinued with partial remission of mania in 4 days
22	Baldassano et al, 2003[37]	Bipolar I disorder, current episode depressed (45, male)	Mania	40	3 days	Tolcapone 400 mg/d Lithium 1500 mg/d Lamotrigine 300 mg/d Oxcarbazepine 200 mg/d Clonazepam	Lithium Lamotrigine Oxcarbazepine Clonazepam	Stop ziprasidone; start perphenazine; full remission of mania in 4 days
23	Baldassano et al, 2003[37]	Bipolar I disorder, current euthymia (25, male)	Mania	40	4 days	Lithium 1200 mg/d Clonazepam 2 mg/d Lamotrigine 250 mg/d Olanzapine 20 mg/d	Lithium Clonazepam Olanzapine 10 mg/d	Reduce dose of ziprasidone to 20 mg/d; increase olanzapine dose back to 20 mg/d; full remission of mania in 1 week
24	Baldassano et al, 2003[37]	Bipolar II disorder, current episode depressed; posttraumatic stress disorder (29, female)	Mania	40 to 100 in 5 days	5 days	Sertraline 200 mg/d Valproic acid 1000 mg/d Venlafaxine 25 mg/d Quetiapine 25 mg/d	Sertraline Valproic acid Venlafaxine	Reduce dose of ziprasidone to 80 mg/d; remission of mania in 3 days
25	Nolan and Schulte, 2003[38]	Schizophrenia (20, male)	Mania	40 to 160 in 4 days, then to 80	1 day	Haloperidol Risperidone	None	Stop ziprasidone; add lorazepam; start olanzapine; remission of mania within 48 hours
26	Larson and Hauser, 2003[39]	Schizophrenia (17, female)	Mania	20 to 160 within 1 week	3 days	None	None	Stop ziprasidone; remission of mania
27	Privitera and Maharaj, 2003[40]	Major depressive disorder, generalized anxiety disorder, panic disorder without agoraphobia, alcohol dependence in remission (52, female)	Mania	Risperidone 0.5, then 1 4 days later	Few days	Quetiapine Nefazodone Alprazolam (vitamins C and D, estradiol, calcium, prednisone, ipratropium bromide inhaler, ipratropium bromide nebulizer[a])	Fluoxetine 20 mg/d Alprazolam	Stop risperidone; remission of mania within days
			Mania (2 months later)	Ziprasidone 20	Few days	Fluoxetine 20 mg/d Alprazolam	Paroxetine 20 mg/d Alprazolam 4 mg/d	Stop ziprasidone; remission of mania within days
			Mania (time of onset unspecified)	Ziprasidone 5	“Quickly”	Paroxetine 20 mg/d Alprazolam 4 mg/d	Paroxetine 10 mg/d Alprazolam 4 mg/d	Stop ziprasidone; remission of mania and onset of depression and anxiety within days; stop paroxetine; add ziprasidone 5 mg/d; no mania

[a]These medications were also taken during risperidone treatment and the 2 periods of ziprasidone treatment.
Symbol: ? = Information not available or imprecise.

Table 5. Case Reports of Flupenthixol-Induced Mania/Hypomania

Case No.	Author	Diagnosis (age [y], gender)	Symptom	Dose (mg/d)	Interval Until Onset	Medication Until Start of Flupenthixol	Comedication	Outcome
28	Becker et al, 2002[41]	Schizoaffective disorder (33, male)	Mania	9	?	?	None	Stop flupenthixol; start risperidone up to 3 mg/d; remission of mania after few days
29	Becker et al, 2002[41]	Schizophrenia, paranoid type (48, male)	Mania	3	Abrupt	?	None	Stop flupenthixol; start perphenazine 48 mg/d; remission of manic-like symptoms within 1 week
30	Becker et al, 2002[41]	Schizoaffective disorder, borderline personality disorder (43, female)	Mania	3	2 weeks	?	Lithium	Stop flupenthixol; continue lithium; remission of mania within few days
31	Becker et al, 2002[41]	Bipolar disorder (43, female)	Mania	3	2 weeks	Moclobemide Clonazepam	Moclobemide? Clonazepam?	Stop flupenthixol; start clopenthixol; remission of mania within few days
			Mania (2 years later)	After 2 years, 2	5 days	Tricyclics SSRIs Lithium	?	Stop flupenthixol; start zuclopenthixol; almost complete remission of mania in few days
32	Becker et al, 2002[41]	Schizoaffective disorder (33, male)	Mania	9	3 weeks	?	Clonazepam 2 mg/d	Stop flupenthixol; start fluphenazine; rapid remission of mania
33	Becker et al, 2002[41]	Bipolar disorder (58, female)	Mania	3	Within days?	Fluoxetine 20 mg/d	None	Stop flupenthixol; start haloperidol up to 7.5 mg/d; remission of mania in 4 days

Abbreviation: SSRI = selective serotonin reuptake inhibitor. Symbol: ? = Information not available or imprecise.

of grandeur strongly points to a case of psychotic mania. Moreover, in cases 12 and 29, the described symptoms could represent severe akathisia or even agitated depression (case 12) rather than hypomanic or manic symptomatology, respectively.

Several cases lack precise information about the interval until the onset of mania/hypomania (cases 4–6, 12, 17, 28, 29, and 33), about medication use shortly before the introduction of the atypical antipsychotic drug (cases 1, 2, 7, 8, 29, 30, and 32), about concomitant medication use (cases 1, 5, 7, 8, 10, and 18), and about dosage or plasma levels of comedication (cases 4, 19, 21–24, and 30).

Further complicating the interpretation of the data is that some cases involved the use of drugs known to induce mania (cases 4, 12, 19, 24, 27, 31, 33, and 34), sometimes with the concomitant use of a mood stabilizer (cases 4 and 24). For example, in case 4, although manic symptoms developed shortly after the introduction of risperidone, the patient was already on fluoxetine treatment, which could have triggered these symptoms. In addition, despite the close temporal relationship between the initiation of risperidone and the onset of mania, it was only after having discontinued risperidone and having increased the dose of valproic acid that the manic episode slowly remitted. This case tends to weaken the role of risperidone in inducing the manic episode either by itself or through a synergistic effect with fluoxetine.

Many cases of mania/hypomania (cases 1, 2, 5, 6, 8–12, 15, 16, 19, 20, 22, 23, 25, 28, 29, and 31–34) remitted soon after dose reduction or discontinuation of the suspected mood-elating agent, albeit with the addition or substitution of other atypical or conventional antipsychotics, benzodiazepines, and/or mood stabilizers. The implication of a possible effect of other medications makes it difficult to attribute the remission of mood changes solely to the discontinuation of the offending drug and could point to the ineffectiveness of the drug to prevent manic symptoms.

In some cases, discontinuation of antipsychotic treatment and/or the initiation of an atypical antipsychotic possibly ineffective for the prevention of a manic/hypomanic episode may have led to the conclusion that the latter had in fact caused such an episode (cases 3, 11–13, 16, 22–24, and 26). It is also noteworthy to mention that in 2 cases (cases 6 and 25), mania/hypomania emerged only after decreasing the doses of risperidone and ziprasidone, respectively, which could indicate ineffectiveness of the antipsychotic rather than mood switch.

In case 18, although the patient developed hypomania shortly after the introduction of ziprasidone, cutting the dose in half resulted in a depressive clinical picture that persisted despite discontinuation of the drug. Also, in case 19, the patient developed hypomania followed by depression while being kept on treatment with the same dose of ziprasidone.

Table 6. Case Report of Amisulpride-Induced Mania/Hypomania

Case No.	Author	Diagnosis (age [y], gender)	Symptom	Dose (mg/d)	Interval Until Onset	Medication Until Start of Amisulpride	Comedication	Outcome
34	Murphy, 2003[44]	Schizophrenia (17, female)	Mania	400 over 4 weeks	3 months	Olanzapine Citalopram 20 mg/d	Citalopram 20 mg/d	Stop citalopram; no improvement of mania; reduce dose of amisulpride to 200 mg and start olanzapine 15 mg; reduction of mania; stop amisulpride; remission of mania within days

Table 7. Proposed Guidelines for Evaluation of Drug-Associated Events[a]

1. Symptomatology and diagnosis before onset
   - Were the symptoms already present and since when?
   - Are the clinical features and the diagnosis sufficiently documented?
2. Diagnostic evaluation at the time of side effect
   - Well documented? Symptom severity?
   - Differential diagnosis; organic causes?
   - Drug and/or substance abuse?
3. Interval until onset
   - Is the interval precisely documented?
   - Rapid (hours to a few days) or slow onset (weeks to months)?
4. Dose
   - Titration (rapid escalation?)
   - Standard posology?
   - Blood levels available?
5. Medication until introduction of suspected treatment
   - Abrupt withdrawal or tapering of previous medication?
   - Newly introduced treatment inefficacy versus prior treatment?
6. Comedication (polypharmacy)
   - Drug(s) with potential of inducing similar associated events; drug(s) prescribed for the remission of induced symptomatology; dosage; pharmacokinetic interaction(s)?
7. Outcome
   - Remission? Spontaneous? With dose reduction or discontinuation, with/without adjunctive treatment?
8. Rechallenge
   - With/without reappearance of suspected drug-induced symptoms?

[a]These selected questions were used to critically assess the case reports analyzed in this study, but they can be followed to evaluate any case report describing a suspected drug-induced side effect.

Although there are a number of limitations in the case reports reviewed in this article, there are also several factors suggestive of a causative role of risperidone, olanzapine, quetiapine, ziprasidone, flupenthixol, and amisulpride in the emergence of mania/hypomania.

In cases 13, 17, and 24, remission of mania/hypomania occurred after quetiapine or ziprasidone dose reduction, suggesting a causal relationship between the use of these agents and the occurrence of mania in such cases. That same suggestion applies to case 34, in which the described manic symptoms decreased after cutting the dose of amisulpride in half.

An important factor to consider is the close temporal relationship between the introduction or upward titration of the dose of the atypical antipsychotic and the development of manic/hypomanic symptoms (cases 3–7, 9, 11, 14, 15, 16, 18–29, 31, and 33). For example, in case 28, it was only after the dose of flupenthixol was increased to 9 mg/day that the patient "abruptly" developed mania.[41] Moreover, the worsening of mania/hypomania associated with an increase in the dose of the atypical agent (cases 5, 9, and 14) as well as the rapid remission (partial or complete) of symptomatology on discontinuation or reduction of its dose, mostly without the introduction of adjunctive treatment (cases 3, 7, 13, 14, 18, 21, 26, 27, and 30), are clear indications of a causal link. Additionally, rechallenge with the same drug implicated in the development of the mood episode (cases 27 and 31) followed by rapid reemergence of mania/hypomania is strongly suggestive of a role of that agent in mood elevation.

DISCUSSION

A critical review of 34 cases of mania/hypomania induced by risperidone, olanzapine, quetiapine, ziprasidone, flupenthixol, or amisulpride reported from 1999 to December 2003 shows that more than half of the cases (N = 20) are highly suggestive of a causal link, 10 are moderately suggestive, and 4 are questionable (summarized in Table 8). This percentage of highly suggestive cases is similar to what we found in our first review, published in 2000.[22] If we combine the results of both critical reviews, we have 36 cases with strong evidence regarding induction of mania/hypomania by atypical antipsychotics.

In a recently published pooled analysis of 2 large placebo-controlled trials investigating the efficacy of olanzapine versus placebo for the treatment of mania, Baker et al.[45] underlined the fact that there was no report of an association between olanzapine and exacerbation of mania, although some patients' mania clearly worsened while on olanzapine treatment but to a lesser extent than with placebo. However, it should be kept in mind that the 2 analyses are based on 2 different types of patient groups: patients already with a manic episode in studies evaluating the therapeutic effects of atypical antipsychotics versus patients without hypomanic or manic symptoms, or even past histories of mood disorders, in a majority of the case reports of mood switch reviewed here.

Table 8. Summary of the Critical Review of 34 Cases of Risperidone-, Olanzapine-, Quetiapine-, Ziprasidone-, Flupenthixol-, or Amisulpride-Induced Mania/Hypomania[a]

Case No.	Author	Items Fulfilled	Conclusion[b]
1	Zolezzi and Badr, 1999[23]	3, 4, 6	Questionable
2	Zolezzi and Badr, 1999[23]	2, 3, 4, 6	Moderately suggestive
3	Zolezzi and Badr, 1999[23]	1, 2, 3, 4, 6, 7	Highly suggestive
4	Zolezzi and Badr, 1999[23]	1, 2, 4, 5	Moderately suggestive
5	Güzelcan et al, 2002[24]	1, 2, 4, 5, 6	Highly suggestive
6	Güzelcan et al, 2002[24]	2, 4, 5, 6	Moderately suggestive
7	Fahy and Fahy, 2000[25]	1, 3, 4, 7	Moderately suggestive
8	Narayan and Puranik, 2000[26]	1, 5, 6	Questionable
9	Borysewicz and Borysewicz, 2000[27]	1, 2, 3, 4, 5, 6	Highly suggestive
10	Lykouras et al, 2001[28]	1, 2, 4, 5, 6	Highly suggestive
11	Henry and Demotes-Mainard, 2002[29]	1, 3, 4, 6	Moderately suggestive
12	Benazzi, 2001[30]	1, 3, 4	Questionable
13	Atmaca et al, 2002[31]	1, 2, 3, 6, 7	Highly suggestive
14	Lykouras et al, 2003[32]	1, 2, 3, 4, 5, 6, 7	Highly suggestive
15	Biancosino et al, 2003[33]	1, 2, 3, 4, 6	Highly suggestive
16	Pacchiarotti et al, 2003[34]	1, 2, 3, 4, 6	Highly suggestive
17	Davis and Risch, 2002[35]	1, 4, 6, 7	Moderately suggestive
18	Davis and Risch, 2002[35]	1, 3, 4, 7	Moderately suggestive
19	Davis and Risch, 2002[35]	1, 3, 4, 5	Moderately suggestive
20	Lu et al, 2002[36]	1, 2, 3, 4, 6	Highly suggestive
21	Baldassano et al, 2003[37]	1, 2, 3, 4, 5, 6, 7	Highly suggestive
22	Baldassano et al, 2003[37]	1, 2, 3, 4, 6	Highly suggestive
23	Baldassano et al, 2003[37]	1, 2, 3, 4, 6	Highly suggestive
24	Baldassano et al, 2003[37]	1, 2, 3, 4, 7	Highly suggestive
25	Nolan and Schulte, 2003[38]	1, 2, 3, 4, 5, 6	Highly suggestive
26	Larson and Hauser, 2003[39]	1, 3, 6, 7	Moderately suggestive
27	Privitera and Maharaj, 2003[40]	1, 2, 3, 4, 5, 7, 8	Highly suggestive
28	Becker et al, 2002[41]	1, 2, 4, 5, 6	Highly suggestive
29	Becker et al, 2002[41]	1, 4, 5, 6	Moderately suggestive
30	Becker et al, 2002[41]	1, 2, 3, 4, 5, 6, 7	Highly suggestive
31	Becker et al, 2002[41]	1, 2, 3, 4, 5, 8	Highly suggestive
32	Becker et al, 2002[41]	1, 2, 3, 4, 5, 6	Highly suggestive
33	Becker et al, 2002[41]	2, 4	Questionable
34	Murphy, 2003[44]	1, 2, 3, 4, 5	Highly suggestive

[a]For each case, we checked whether the 8 items presented in Table 7 could be answered satisfactorily. For item 8, we did not consider rechallenge as a weak point when untested, since a rechallenge is obviously not proposed to the patient when there is a suspected drug-induced side effect.

[b]The conclusion about the compellingness of the cases was made using the following criteria: of the items (except the rechallenge) presented in Table 7, we consider that a case with no more than 1 or 2 weak points can be considered to be highly suggestive of a causal relationship; 3 weak points make for a moderately suggestive case; and more than 3 weak points make for a questionable case.

As a matter of fact, the majority of the cases reported in the present review did not have a diagnosis of bipolar disorder. Forty-four percent (N = 15) of these cases, about two thirds of them highly suggestive, and 46% (N = 12) in our previous review[22] had a diagnosis of schizophrenia or schizophreniform disorder. To investigate whether some patients are inherently at greater risk than others for atypical antipsychotic–induced mood switch, as has been shown in the case of antidepressant-induced mania, we carefully analyzed various demographic and clinical parameters described in the cases reviewed such as gender, age, schizophrenia subtype, and duration of illness. However, we were not able to identify a particular risk factor in schizophrenic or other non–mood disorder patients who developed secondary mania/hypomania.

As in our last review, despite the use of clozapine in the treatment of resistant bipolar disorder based on its suggested efficacy for such conditions,[46,47] its potential antidepressant properties,[48,49] and its rather high 5-HT_{2A}/D_2 occupancy ratio, we found no reported case of clozapine-induced mania/hypomania in our MEDLINE search. We also found no case report concerning sertindole or aripiprazole, possibly reflecting the low number of world prescriptions for them at the present time.

It has been suggested that risperidone-induced mania/hypomania is primarily related to dose, with lower doses possibly resulting in blockade of 5-HT_{2A} but not D_2 receptors, in turn leading to disinhibition of frontal dopamine release and induction of manic symptomatology.[50] Another speculation is that the combined blockade of 5-HT_{2A} and of D_2 receptors enhances the ability of 5-HT_{1A} receptors to cause frontal dopamine release.[51] However, in the first cases of risperidone-induced mania/hypomania reviewed in our previous article,[22] moderate to high doses of this drug were used. In the present article, only 2 cases of risperidone-induced mania (cases 4 and 27) are reported with low dosage. Regarding olanzapine, the same is true as far as dosage is concerned. In fact, only 2 out of 5 cases (cases 7 and 11) were prescribed low doses of olanzapine (2.5 and 5 mg/day, respectively) prior to the development of mania/hypomania. In the case of quetiapine and ziprasidone, only 1 case used low doses of such agents (case 27: ziprasidone 20 mg/day, then 5 mg/day).

These observations question the role of 5-HT_{2A} receptor antagonism as the main explanation for risperidone- or other atypical antipsychotic–induced mood alterations. For example, ziprasidone has both the highest 5-HT_{2A} affinity and the highest 5-HT_{2A}/D_2 binding ratio among atypical antipsychotics.[52–54] Such pharmacodynamic properties coupled with somewhat potent noradrenergic and less potent serotonergic reuptake inhibiting actions as well as high agonist 5-HT_{1A} affinity compared with D_2 receptors[55] could be involved in the antidepressant/anxiolytic effects of ziprasidone as well as its potentially increased propensity to cause mood elevation in susceptible individuals. In fact, in this review, almost a third of the cases of mania/hypomania suggested to have been induced by atypical antipsychotics were ziprasidone-related, of which 7 were highly suggestive of a causal link. On the other hand, quetiapine has the lowest 5-HT_{2A} affinity and 5-HT_{2A}/D_2 binding ratio,[52,56] but with a higher affinity for 5-HT_{2A} than D_2 receptors at lower doses,[57] it also seems to be involved in the induction of mania/hypomania.

An interesting situation is mania induced by amisulpride, an antipsychotic that is generally considered to have some atypical properties and that causes minimal

extrapyramidal side effects despite the lack of 5-HT_{2A} receptor affinity. As suggested by Murphy,[44] low doses of amisulpride have presynaptic D_2 and D_3 autoreceptor–blocking activities, thus enhancing dopamine transmission in the prefrontal cortex, resulting in possible antidepressant effects and potential mania induction. However, the case described by that author[44] was not prescribed a low dose of amisulpride.

In conclusion, one limitation of our review is that it is based on the evaluation of case reports that by themselves do not provide us with a strong level of evidence in comparison to that of controlled studies. However, considering the number of highly suggestive cases presented, clinicians should still be aware of the possible occurrence of mood switches with all atypical antipsychotics, with the probable exception of clozapine (for sertindole and aripiprazole, more information is needed), notably in patients suffering from schizophrenia and schizoaffective disorder. Despite this potential adverse effect on mood, it should be emphasized that, to date, the net effect of atypical antipsychotics is clearly antimanic.

Drug names: alprazolam (Xanax and others), aripiprazole (Abilify), bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Thorazine, Sonazine, and others), citalopram (Celexa), clonazepam (Klonopin and others), clorazepate (Gen-Xene, Tranxene, and others), clozapine (Clozaril, Fazaclo, and others), diazepam (Valium and others), divalproex sodium (Depakote), estradiol (Estrace, Climara, and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), ipratropium bromide (Atrovent and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), nefazodone (Serzone and others), nifedipine (Procardia, Adalat, and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal), paroxetine (Paxil and others), perphenazine (Trilafn and others), prednisone (Deltasone and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), temazepam (Restoril and others), thyroxine (Synthroid, Levo-T, and others), tolcapone (Tasmar), trifluoperazine (Stelazine and others), valproic acid (Depakene and others), venlafaxine (Effexor), ziprasidone (Geodon).

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