Possible Induction of Mania and Hypomania by Olanzapine or Risperidone: A Critical Review of Reported Cases

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Background: Risperidone and olanzapine are atypical antipsychotics that are now widely used in clinical practice.

Method: A MEDLINE search (1966–1999) showed that, following the introduction of these agents in recent years, 26 cases of induced hypomanic and manic syndromes have been reported during standard olanzapine (N = 10) or risperidone (N = 16) treatment.

Results: A critical analysis of these case reports reveals that the effects on mood were sometimes insufficiently documented and that in about half of them (N = 16) evidence is highly suggestive of a causative role of risperidone or olanzapine in the induction of (hypo)manic symptomatology.

Conclusion: Despite limitations, the available literature confirms intriguing effects of these 2 antipsychotics on mood. The risk factors as well as the mechanisms of action underlying these effects remain to be clarified.

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Risperidone and olanzapine are 2 of the so-called atypical antipsychotics recently marketed for the treatment of psychotic disorders. Both have an extrapyramidal side effect profile superior to that of conventional antipsychotics.[1,2] Although there is not a single hypothesis explaining atypicality, the relative potency for blocking dopamine D_2 and serotonin 5-HT_{2A} receptors is likely to play a role.[3] In fact, animal studies have long shown that reduction in brain serotonergic function can diminish extrapyramidal effects of neuroleptics.[4] Risperidone and olanzapine are characterized by high affinity for 5-HT_2 receptors,[3,5] and it has been suggested that 5-HT_{2A} receptor blockade may be the underlying mechanism for their efficacy to treat the negative signs and symptoms of schizophrenia.[6] In addition to their antipsychotic effects, some available data suggest that risperidone and olanzapine may have antidepressant[7–13] and antimanic properties.[13–17] For example, Tollefson et al.[10] have shown that schizophrenic patients treated with olanzapine had a highly significant improvement in depression rating scale scores compared with patients treated with haloperidol. Regarding olanzapine, an antimanic profile was recently demonstrated in a placebo-controlled, double-blind trial.[16] Berk et al.[17] also suggest therapeutic effects comparable to those of lithium in the treatment of acute mania.

Shortly after the introduction of these atypical antipsychotics, several cases of risperidone- and olanzapine-induced hypomania and mania were reported. To date, based on a MEDLINE search of the literature from 1966 to 1999 using the search terms *atypical antipsychotics*, *risperidone*, *olanzapine*, *hypomania*, and *mania*, 16 such cases have been published with risperidone[18–24] and 10 with olanzapine.[25–33] To our knowledge, no similar cases have been reported until now with other atypical antipsychotics, including clozapine.

In the present article, we critically review and discuss the available evidence on the induction of (hypo)manic symptomatology by these 2 antipsychotics.

CRITICAL REVIEW

Case reports of risperidone- or olanzapine-induced hypomania and mania are presented in Tables 1 and 2, respectively. These tables include a selection of items from the available published data that we consider the most important in evaluating a causal relationship between risperidone or olanzapine treatment and (hypo)mania, i.e., clinical diagnosis at the time of antipsychotic introduction, interval until the occurrence of (hypo)manic symptoms, associated medication, previous drug treatment, and outcome after risperidone or olanzapine withdrawal. The selection of these items has led us to propose a set of questions that should be asked when reading a report on any drug-associated event (Table 3). As described below, when we follow these guidelines, several limitations have to be taken into consideration when analyzing the case reports.

Table 1. Case Reports of Risperidone-Induced Mania[a]

Author/Case	Diagnosis (age and gender)	Symptom	Dose (mg/day)	Interval Until Onset	Medication Until Risperidone's Onset	Comedication	Outcome
Dwight et al, 1994[19]							
1	Schizoaffective, bipolar type, mixed (?, ?)	Mania	8	7 ± 3 d[b]	?	?	Addition of valproate; decrease of symptoms with ongoing risperidone
2	Schizoaffective, bipolar type, depressed (?, ?)	Mania	6	7 ± 3 d[b]	?	?	Remission with ongoing risperidone
3	Schizoaffective, bipolar type, mixed (?, ?)	Mania	8	7 ± 3 d[b]	?	?	Addition of valproate; decrease of symptoms with ongoing risperidone
4	Schizoaffective, bipolar type, manic (?, ?)	Mania	8	7 ± 3 d[b]	?	?	?
5	Schizoaffective, bipolar type, depressed (?, ?)	Mania	6	7 ± 3 d[b]	?	?	Remission with ongoing risperidone
6	Schizoaffective, bipolar type, depressed (?, ?)	Mania	6	7 ± 3 d[b]	?	?	Remission with ongoing risperidone
Diaz, 1996[18]							
7	Schizophrenia (50, male)	Mania	9	40 d	Haloperidol, tapered	None	Addition of clonazepam, 2 mg/d, haloperidol, lithium + valproate; stop risperidone 2 wk after onset of mania; remission after several wk
Koek and Kessler, 1996[20]							
8	Recurrent depression, psychotic; posttraumatic stress disorder (44, male)	Mania	4	7–8 d	None	Doxepin, 250–300 mg/d; alprazolam, 1 mg/d	Stop risperidone after 2 wk; remission within 3 d
Schnierow and Graeber, 1996[21]							
9	Schizoaffective, depressed type, (42, male)	Mania	4	2 d	Perphenazine and lithium	None	Stop risperidone; reinstitution of perphenazine + lithium; remission within 2 wk
10	Chronic, disorganized schizophrenia (44, male)	Mania	6	Few days?	Fluphenazine (high doses)	None	Risperidone decreased to 5 mg/d, followed by "rapid remission"
11	Bipolar type I, manic (47, male)	Mania	6	Few days?	Lithium; valproate	Lithium (? mg/d); valproate (? mg/d)	Stop risperidone with remission of mania; rechallenge with 3 mg/d followed by new manic symptoms; then decrease to 2 mg/d with remission
Tomlinson, 1996[22]							
12	Schizophrenia (46, male)	Mania	6	15 d	Haloperidol, tapered from 25 to 10 mg/d	Haloperidol, 10 mg/d	Haloperidol, 30 mg/d, up to 80 mg/d; risperidone? remission after 2 mo
Barkin et al, 1997[23]							
13	Bipolar type I, manic (32, female)	Mania	6	3 d	Haloperidol, 20 mg/d; valproate (76 mg/L); lithium (0.8 mEq/L)	Valproate (76 mg/L); lithium (0.8 mEq/L)	Stop risperidone; addition of perphenazine, 28 mg/d; remission within 36 h
14	Schizoaffective, depressed type (29, male)	Mania	2.5	Days?	?	Valproate (95 µg/L)	Stop risperidone; addition of thiothixene, 15 mg/d; remission with 2 d
Lane et al, 1998[24]							
15	Schizophrenia (48, male)	Mania	3	40 d	None	None	Stop risperidone; "rapid remission"; rechallenge with 2 mg/d followed by hypomanic state within 2 d; decrease of risperidone to 1.5 mg/d; remission within 3 d
16	Chronic schizophrenia (36, male)	Mania	6	20 d	Conventional antipsychotic (dose?)	None	Decrease risperidone to 4 mg/d after 10 d with hypomanic mood; gradual remission

[a]Symbol: ? = information not available or imprecise.
[b]For cases 1–6, interval until onset of symptomatology is expressed as mean ± SD.

Table 2. Case Reports of Olanzapine-Induced (Hypo)Mania[a]

Author/Case	Diagnosis (age and gender)	Symptom	Dose (mg/day)	Interval Until Onset	Medication Until Olanzapine's Onset	Comedication	Outcome
Lindenmayer and Klebanov, 1998[27]							
17	Schizophrenia, chronic undifferentiated type (38, male)	Mania	10, 15, then 20	21 d	Loxapine, tapered	None	Decrease to 15 mg/d, then 10, with remission within ?
18	Schizophrenia, chronic undifferentiated type (43, male)	Mania	5–20 over 4 wk	28 d	None	Clonazepam, 3 mg/d	Decrease to 10 mg/d, then stop 4 mo later; risperidone, 16-mg/d trial, then rechallenge with 10 mg/d olanzapine; new manic symptoms, stop olanzapine; remission
Benazzi and Rossi, 1998[25]							
19	Schizophrenia disorder, depressed type (60, female)	Mania	10, then 20	Few days	Risperidone, tapered	None	Add chlorpromazine, 200 mg/d; lorazepam, 4.5 mg/d for a week; then, stop olanzapine; remission within 48 h
Reeves et al, 1998[29]							
20	Schizoaffective disorder (40, male)	Mania	10	7 d	Valproate (75.2 µg/mL); haloperidol, 5 mg/d risperidone	Haloperidol, discontinued after several days; valproate	Stop olanzapine; restart haloperidol, 5 mg/d; remission within several days
Pozo and Alcantara, 1998[28]							
21	Schizophrenia, paranoid type (50, female)	Mania	10	7 d	Zuclopenthixol decanoate	None	Stop olanzapine; introduce haloperidol, 30 mg/d; diazepam, 30 mg/d; valproic acid, 1500 mg/d; remission within 7 d. Replacement of haloperidol with risperidone
London, 1998[26]							
22	Pervasive developmental disorder? (16, male)	Mania	7.5	14–21 d	None?	None	Stop olanzapine; remission within ? then valproate and trifluoperazine trial
John et al, 1998[30]							
23	Chronic paranoid schizophrenia (38, female)	Mania	10, then 20	35 d	Haloperidol, 30 mg/d, haloperidol decanoate (100 mg once)	None	Olanzapine decreased to 10 mg/d; risperidone, 6 mg/d; remission "rapid"
Fitz-Gerald et al, 1999[31]							
24	Schizophrenia, paranoid type (44, male)	Mania	20	28 d	Fluphenazine decanoate, fluphenazine hydrochloride	Fluphenazine decanoate	Stop olanzapine; add valproate + clonazepam; remission within 1 wk
Simon et al, 1999[32]							
25	Not otherwise specified psychotic disorder (31, female)	Hypomania	20	2 d	Haloperidol, 23 mg over 24 h	None	Decrease olanzapine to 15 mg/d, then replace with risperidone, 6 mg/d; remission within 5 d
Benazzi, 1999[33]							
26	Bipolar schizoaffective (55, female)	Mania	20	7 d	Haloperidol, 6 mg/d; levomepromazine, 100 mg/d; flurazepam, 30 mg/d	Clonazepam, 2 mg	Stop olanzapine; valproate, 600 mg/d; haloperidol, 6 mg/d; lorazepam, 10 mg/d; remission within a few days

[a]Symbol: ? = Information not available or imprecise.

Table 3. 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?
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 our study, but they can be followed to evaluate any case report describing a suspected drug-induced side effect.

Regarding the described symptomatology before the onset of the induced manic episode, it should be pointed out that several cases (cases 1, 3, 11, and 13) were already manic (mixed state for cases 1 and 3) and 1 case (case 4) was at least hypomanic with a score of 18 on the Young Mania Rating Scale (YMRS)[34] prior to initiation of risperidone. Therefore, for these patients, the described increase in manic symptomatology could simply be due to a spontaneous worsening evolution of symptoms attributed to treatment inefficacy, rather than to risperidone's effect on mood. Moreover, in the large series of Dwight et al.,[19] according to the score of the YMRS that they used to evaluate the presence and severity of manic symptoms, 2 patients (cases 2 and 5) presented with hypomanic symptoms (scores of 10 and 14) during risperidone treatment, and not with the suggested manic episode. Still considering symptomatology, as mentioned by the authors[27] of case reports 17 and 18, the described symptoms could represent severe akathisia instead of a manic episode. The description of the premorbid state or of the manic episode is also insufficiently documented for some cases (cases 1–6, 22, and 23).

It is noteworthy that several of the cases lack precise information about the interval until onset of mania (cases 1–6, 10, 11, 14, 18, and 22), about comedication (cases 1–6), about dosage or plasma levels of comedication (cases 1–6, and 11), and about medication shortly before introduction of risperidone or olanzapine (cases 1–6, 16, and 22).

Interpretation of the data is further complicated by several cases of polypharmacy with medications that can be involved in the emergence (cases 8 and 9) or the remission (cases 1, 3, 20, 21, 25, and 26) of a manic syndrome. For example, comedication with an antidepressant (doxepin) could have contributed or been responsible for the induction of a manic episode in case 8. However, in this case, manic symptoms rapidly remitted after olanzapine withdrawal despite ongoing antidepressant treatment, which speaks in favor of a minor link between doxepin and the mood switch. In case 9, manic symptomatology followed the cessation of lithium treatment, known to enhance the risk of manic relapse, which can occur after a brief interval.[35] Additionally, in that particular case, if remission occurred following cessation of risperidone, it should be taken into consideration that risperidone was immediately replaced by lithium and perphenazine. Thus, it is difficult to attribute the remission of manic symptoms to the withdrawal of risperidone and/or to the initiation of a mood stabilizer and a conventional antipsychotic. Similarly, for cases 1, 3, 7, 12, 19–21, and 24–26, the addition or replacement of risperidone or olanzapine by benzodiazepines, antipsychotics, and/or mood stabilizers renders the remission of symptomatology more difficult to interpret.

The changes (sometimes rapid) from high- to low-dosage antipsychotics (cases 12, 13, 23, and 25) or the complete cessation of antipsychotic treatment (cases 7, 9, 10, 16, 19, 20, 21, 25, and 26) shortly before introduction of olanzapine or risperidone could account for the emergence of manic symptomatology due to treatment ineffectiveness. In this context, it is interesting to point out that if withdrawal of conventional antipsychotics is unassociated with the occurrence of important mood change, a case of manic and psychotic symptoms following risperidone withdrawal was recently reported.[36]

Another somewhat surprising point in several cases concerns the remission of manic symptomatology with ongoing risperidone (cases 1–3, 5, and 6). For these cases, the fact that manic symptoms declined during ongoing risperidone treatment suggests that they could not be the sole provoking agents. With some other cases (cases 10, 11, 15–17, and 23), remission of symptomatology occurred after risperidone or olanzapine dose reduction, which is more conceivable. However, with case 10 for example, a decrease of risperidone from 6 to 5 mg/day was followed by rapid remission of symptoms. For this particular case, it is difficult to imagine that such a small dose reduction could allow for complete and rapid remission of symptoms. An alternative hypothesis to explain the disappearance of drug-induced symptomatology with ongoing medication is a transient paradoxical idiosyncratic behavioral response during the first days or weeks

Table 4. Summary of the Critical Review of 26 Cases of Risperidone- or Olanzapine-Induced (Hypo)mania[a]

Author	Case	Items Fulfilled	Conclusion[b]
Dwight et al, 1994[19]	1	2,4	Questionable
	2	4	Questionable
	3	2,4	Questionable
	4	2,4	Questionable
	5	4	Questionable
	6	2,4	Questionable
Diaz, 1996[18]	7	1,2,3,4	Moderately
Koek and Kessler, 1996[20]	8	1,2,3,4,5,7	Highly
Schnierow and Graeber, 1996[21]	9	1,2,3,4,7	Highly
	10	1,2,4,6	Moderately
	11	2,4,5,7,8	Highly
Tomlinson, 1996[22]	12	1,2,3,4	Moderately
Barkin et al, 1997[23]	13	2,3,4,6,7	Highly
	14	1,2,4,6,7	Highly
Lane et al, 1998[24]	15	1,2,3,4,5,6,7,8	Highly
	16	1,2,3,4,6,7	Highly
Lindenmayer and Klebanov, 1998[27]	17	1,3,4,5,6,7	Highly
	18	1,4,5,6,7,8	Highly
Benazzi and Rossi, 1998[25]	19	1,2,3,4,7	Highly
Reeves et al, 1998[29]	20	1,2,3,4,7	Highly
Pozo and Alcantara, 1998[28]	21	1,2,3,4,7	Highly
London, 1998[26]	22	2,4,6	Questionable
John et al, 1998[30]	23	1,3,4,6,7	Highly
Fitz-Gerald et al, 1999[31]	24	1,2,3,4,7	Highly
Simon et al, 1999[32]	25	1,2,3,4,7	Highly
Benazzi, 1999[33]	26	1,2,3,4,7	Highly

[a]For each case, we checked whether the 8 items presented in Table 3 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 3, 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; more than 3 weak points make for a questionable case.

of treatment, as has been described with the selective serotonin reuptake inhibitors (SSRI).[37]

Besides the aforementioned limitations of the reports available to date, there are also several factors supporting a causative role of risperidone and olanzapine in the development of (hypo)mania. For example, the close temporal relationship between the introduction of olanzapine or risperidone and the onset of (hypo)manic symptoms (cases 9, 13, 19, and 25), as well as the rapid remission of symptomatology after discontinuation of treatment (cases 8, 13, 14, 19, 20, and 25), is clearly suggestive of a causal relationship. Moreover, rechallenge with risperidone (cases 11 and 15) or olanzapine (case 18), followed by rapid resurgence of manic symptomatology, strongly suggests their etiologic role in mood elevation.

DISCUSSION

After a critical review of the 26 cases of risperidone- or olanzapine-induced (hypo)mania reported to date (summarized in Table 4), more than half of them (N = 16) remain highly suggestive of a causal relationship, the others being moderately suggestive (N = 3) or questionable (N = 7). None of the above-mentioned weaknesses of reported cases refute the induction of (hypo)manic symptomatology by risperidone or olanzapine but underline the necessity for precise and detailed presentation of all aspects (diagnosis, clinical presentation, medication dosage, and modification) that make a case report compelling and conclusive.[38] To this end, we propose a decision tree with a set of guideline questions that should be asked when reading a report on drug-induced side effect (Table 3). Interestingly, apart from our report of olanzapine-induced hypomania (case 25), we observed in our daily practice 3 other cases suggestive of (hypo)manic switch during olanzapine treatment (unpublished observations). However, in these cases, because the mood change occurred in a context of complex polypharmacy, it could not be clearly attributed to olanzapine.

The emergence of (hypo)manic symptomatology during treatment with risperidone or olanzapine raises the question of the effect of other atypical antipsychotics on mood. Clozapine has been suggested to be effective in the treatment of resistant bipolar disorder and has been reported to have some antidepressant properties.[39–42] Like risperidone and olanzapine, it also has a high 5-HT_2/D_2 occupancy. However, we did not find any reported case of (hypo)manic switch during clozapine treatment or with the newer atypical antipsychotics sertindole or quetiapine (MEDLINE search).

Regarding the mechanisms involved in olanzapine and risperidone effects on mood, Lane et al.[24] have proposed that the mood state may be a function of the ratio of 5-HT_2 receptor occupancy to D_2 receptor occupancy. According to this hypothesis, low doses of risperidone are associated with a high 5-HT_2/D_2 receptor occupancy. Therefore, at low doses, the 5-HT_2 antagonistic effect, as well as its ensuing forebrain dopamine disinhibiting effect, could influence the mood state. At high doses, dopaminergic blockade action could counteract the dopamine disinhibiting effects. This hypothesis has been made following the occurrence of risperidone-induced manic switch, but the same mechanism could apply to olanzapine. Although this 5-HT_2/D_2 receptor occupancy hypothesis is attractive, it only partly fits with the data of the published case reports. In fact, barely one third of risperidone-induced mania cases (cases 8, 9, 14, and 15) were treated with low-to-moderate doses (2.5 to 4 mg/day). All the other cases were receiving from 6 to 9 mg/day before mood elevation. Regarding olanzapine, only 1 patient (case 22) had less than 10 mg/day, and a majority of cases were treated with the maximum recommended dose of 20 mg/day at the time of the mood switch. Thus, other mechanisms are likely to be involved in olanzapine's and risperidone's effects on mood. This is supported by the

fact that in some cases of mood change during olanzapine treatment (cases 18, 21, and 25), olanzapine was replaced by risperidone without induction of (hypo)manic symptomatology. On the contrary, rechallenge with olanzapine (case 18) or risperidone (cases 11 and 15) was followed by reemergence of (hypo)manic symptoms within a few days (cases 11 and 18), even though the interval until onset of initial mood change had been up to 40 days (case 15). Interestingly, when we compared the mood-elevating propensity of risperidone with that of olanzapine, we did not identify any particular factors relating specifically to either medication (i.e., interval until onset, dose range, outcome). Regarding diagnosis, schizoaffective disorder or schizophrenia represented a large majority (80%) of cases reported for both risperidone and olanzapine.

It is also of interest that for some patients (cases 8, 13–15, and 19), remission of manic symptoms occurred rapidly (36 to 72 hours) after risperidone or olanzapine treatment was stopped, suggesting that the occurrence of manic symptoms is linked to a direct effect of the medication. In contrast, for some other cases (cases 7, 9, and 12), it took several weeks or months for the manic syndrome to resolve, as though once triggered, the manic episode was little influenced by withdrawal of risperidone. It is of interest to note that the same observation can be made about antidepressant-induced manic episodes in bipolar patients.[43]

In conclusion, future studies are clearly needed to further clarify the intriguing effects of risperidone and olanzapine on mood as well as the risk of (hypo)manic switch associated with these 2 atypical antipsychotics. The risk factors as well as the mechanisms of action underlying these effects also deserve further investigations.

Drug names: alprazolam (Xanax and others), chlorpromazine (Thorazine and others), clonazepam (Klonopin and others), clozapine (Clozaril and others), diazepam (Valium and others), doxepin (Sinequan and others), haloperidol (Haldol and others), lorazepam (Ativan and others), loxapine (Loxitane and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane), trifluoperazine (Stelazine), valproic acid (Depakene).

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