Low Risk for Switch to Mania during Treatment with Sleep Promoting Antidepressants

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Key words
- bipolar disorder
- switch to mania
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- trazodone
- mirtazapine
- agomelatine

Abstract

Introduction: Sleep-promoting antidepressants are of interest because they are used not only as antidepressants, but also to promote sleep.
Methods: We reviewed case reports describing the switch to mania during treatment with trazodone, mirtazapine, or agomelatine.
Results: Trazodone, mirtazapine, and agomelatine may induce manic symptoms. However, the risk of switching is related, first of all, to doses recommended for antidepressant treatment, administered without mood-stabilizer co-therapy. Low doses of these antidepressants, used for their hypnotic or sedative effects, were observed to cause mania only in patients with other risk factors for switching. There is no evidence for trazodone or mirtazapine and only sparse evidence for agomelatine, claiming that treatment with these antidepressants is related to an increased risk of switching to mania when administered in combination with a mood stabilizer.
Discussion: These findings suggest that low doses of trazodone and mirtazapine are safe in bipolar disorder, and should still be considered important alternatives to hypnotics when long-term pharmacological treatment of insomnia is necessary. It seems that these antidepressants and agomelatine can also be used safely in antidepressant doses when combined with a mood stabilizer.

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Introduction

Antidepressant drugs have been widely prescribed in patients with bipolar disorder, despite clinicians' concern about antidepressant-induced manic switch and the recommendations of practice guidelines. In a recent report on antidepressant use in bipolar disorder, the task force of the International Society of Bipolar Disorders (ISBD) stated that there is striking incongruity between the wide use of antidepressant drugs in bipolar disorder and the weak evidence base for their efficacy and safety. As the frequency and severity of antidepressant-induced manic switch appears to be greater in bipolar I disorder than bipolar II, it is recommended that antidepressants should only be prescribed to bipolar I patients as an adjunct to mood-stabilizing medications [1].
Although the true rate of antidepressant-induced manic switch in bipolar disorder is a controversial issue, there is a consensus that various antidepressants have differing potential for inducing such a switch. Most studies show that such a potential is higher for tricyclic antidepressants (TCAs) and venlafaxine than for selective serotonin reuptake inhibitors (SSRIs) and bupropion [2–5].
However, there is sparse evidence concerning the risk of switching with other antidepressants, such as trazodone, mirtazapine, and agomelatine. These 3 drugs are of special interest because they are used in bipolar patients not only for their antidepressant effect, but also to promote sleep [6]. Disturbed sleep is a common problem in patients with bipolar disorder, even in interepisode periods [7,8]. For many years, sedative antidepressants were used in such patients as an alternative to benzodiazepine and non-benzodiazepine hypnotics (Z-drugs), because sleep-promoting antidepressants are not related to the risk of hypnotic dependence and can, therefore, be used for a longer time. As the use of antidepressants in bipolar patients has been discouraged in many treatment guidelines, we observe the tendency of these drugs to be replaced by antipsychotics (especially quetiapine), not only in the treatment of bipolar depression, but also as sleep-promoting drugs. Such an approach does not seem to be justified, because evidence for the use of sedative antidepressants in the treatment

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of insomnia is much greater than for sedative antipsychotics. Sedative antidepressants may also be better tolerated [9]. Furthermore, the doses of antidepressants needed to promote sleep are much lower than the doses needed to treat depression [6], so the risk of switching is probably very low.

In this article, we review published case reports describing the switch to mania or hypomania during treatment with trazodone, mirtazapine, or agomelatine, both in monotherapy and in combination with mood stabilizers, and used both in the therapeutic doses for antidepressant effect and in the low doses recommended to promote sleep.

Methods

We performed a literature search in PubMed for articles published in the English language, which were published up to September 2014, using the following search terms in the title or abstract: the antidepressant name (trazodone, mirtazapine, agomelatine) AND mania, hypomania, bipolar disorder, or phase shift. To ensure accuracy, the search performed by the first author of this paper was independently repeated by 2 reviewers (M.J., Ł.O.). Furthermore, references of selected papers and relevant review articles were scanned by all authors in order to locate other reports.

Results

Trazodone

Trazodone is an antidepressant of the serotonin antagonist and reuptake inhibitor (SARI) class. Low doses of trazodone (below 150 mg/day) only act via the most potent binding properties, that is, the serotonergic 5HT2A receptors, whereas higher doses recruit additional pharmacological action and result in the blockade of the serotonin transporter (SERT). The ability of trazodone to block SERTs is 100-fold less potent than its ability to block 5HT2A receptors. As both of these actions are considered necessary for an antidepressant effect, the trazodone dose recommended for the treatment of depression is usually above 150 mg/day [10], whereas low doses (25–150 mg/day) are usually sufficient for sleep-promoting effects [6].

The development of switch to mania or hypomania associated with trazodone treatment was described in 17 patients (**Table 1**).

9 of those patients were treated in monotherapy with the antidepressant dose (≥150 mg/day) of trazodone [11–18]. In only 4 cases, monotherapy with a low dose of trazodone (100 mg/day) was found to be associated with switch to mania or hypomania [11, 13, 14]. All of these 4 cases were older patients (over 60 years old), so they could have a slower elimination rate and, therefore, higher trazodone plasma concentrations compared to the younger patients. Furthermore, in 3 of those 4 patients, other factors were present that could increase the risk of switch to mania. 2 patients were treated with other antidepressants before the start of the trazodone treatment, and one patient obtained trazodone treatment during detoxification from benzodiazepines. In only 2 patients, a very low dose of trazodone (50 mg/day) was described as being related to switch to mania or a mixed depressive state. In both cases, treatment with trazodone was combined with other antidepressants, and in one patient additionally with a non-pharmacological intervention (continuous positive airway pressure, CPAP) [19, 20] A non-pharmacological intervention (repetitive transcranial magnetic stimulation, rTMS) added to combined treatment with trazodone (200 mg/day), paroxetine, opipramol, amitriptyline, prazepam and methadone induced a depressive mixed episode in a further patient [21]. In one patient, a switch to hypomania was observed 3 weeks after the discontinuation of trazodone treatment [16]. Additionally, in 2 depressed patients with probable bipolar disorder, who did not respond to trazodone, a switch to mania was described after trazodone was abruptly replaced with imipramine [22]. There are no published cases describing a switch to mania or hypomania in patients who were treated with a mood stabilizer and trazodone as an antidepressant or a sleep-promoting treatment.

The average time until the onset of mania/hypomania after the start of treatment with trazodone was 14.7 days (median 7 days). 9 patients were described as switching to mania, 6 to hypomania, one to hypomania followed by a mixed episode, and one to a mixed depressive episode.

Mirtazapine

Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA). Its mechanism of action involves noradrenergic alpha2-auto- and hetero-receptor blockade, enhancing noradrenaline (NE) and serotonin (5-HT) release, as well as blockade of serotonergic 5-HT2 and 5-HT3 and histaminergic H1 receptors [23]. The recommended dose of mirtazapine for the treatment of depression is 30–45 mg/day because, in this dose range, mirtazapine acts as an alpha2 antagonist and a 5-HT and NE disinhibitor. However, for the sleep-promoting effect, only the antagonistic action of mirtazapine on histaminergic H1 receptors is necessary. For this effect, low doses of mirtazapine of 3.75–15 mg/day are usually sufficient [6].

Development of a switch to mania or hypomania associated with mirtazapine treatment was described in 10 patients (**Table 2**).

3 of those patients were treated in monotherapy with the antidepressant dose (≥30 mg/day) of mirtazapine [24–26]. One of those patients may have been at higher risk of switching, because she was an older patient and the treatment with mirtazapine was started without a period of washout from fluoxetine (20 mg/day) [26]. In 2 further patients, treatment with antidepressant dose of mirtazapine was combined with treatment using SSRIs [27, 28]. In one patient hypomania was observed after a dose of mirtazapine was increased to 60 mg/day [29]. Mirtazapine doses lower than 30 mg/day were found to be associated with switch to mania or hypomania in only 3 cases [30–32]. In the first of those patients, mirtazapine (15 mg/day) was added to a high dose (250 mg/day) of sertraline [32]. The second patient was an older patient, a 68-year-old woman with organic, post-stroke depression [30], and the third patient was a young patient, a 15-year-old girl [31]. In one older depressed patient, a switch to hypomania was observed 2 days after mirtazapine discontinuation, following 35 days of treatment [33]. There are no published cases that describe a switch to mania or hypomania in patients who were treated with a mood stabilizer and mirtazapine either in antidepressant or in a sleep-promoting dose.

The average time until the onset of mania/hypomania after the start of the treatment or a dose increase of mirtazapine was 15.7 days (median 7 days). 5 patients were described as switching to mania, 4 to hypomania, and one to a mixed depressive episode.

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Table 1 Reports of switching to mania or hypomania during treatment with trazodone.

Study	Patient (age/ gender/diagnosis)	Dose (mg/day)	Concomitant treatment	Time to switch onset (days)	Affective symptoms	Actions taken
Escobar et al.1980 [12]	middle-aged depressed man	400	none	14	mania	no data
Warren & Bick 1984 [17]	57-year-old woman, major depression	150	none	7	mania	discontinuation of trazodone, treatment with lithium and thiothixene
Warren & Bick 1984 [17]	25-year-old depressed woman	400	alprazolam 4 mg/day	28	mania	discontinuation of trazodone, treatment with chlorpromazine
Arana & Kaplan 1985 [11]	66-year-old man, recurrent depression	100	8 days earlier discontinuation of desipramine 75 mg/day due to switch to mania	4	mania	discontinuation of trazodone
Arana & Kaplan 1985 [11]	47-year-old depressed woman	400	2 weeks earlier discontinuation of desipramine 125 mg/day due to switch to mania	17	mania	discontinuation of trazodone
Theilman & Christenbury 1986 [16]	33-year-old woman, major depression	300	none	21 after discontinuation of trazodone	hypomania	treatment with thioridazine and lithium
Knobler et al. 1986 [14]	82-year-old man, bipolar disorder	100	after 10 days of treatment with maprotiline,	14	mania	discontinuation of trazodone, treatment with haloperidol
Knobler et al. 1986 [14]	35-year-old woman, bipolar disorder	300	after 6 weeks of treatment with chlorimipramine, up to 250 mg/day, followed by treatment with imipramine, up to 300 mg/day, for another 6 weeks, 5 days of wash out	5	mania	discontinuation of trazodone, treatment with haloperidol
Knobler et al. 1986 [14]	84 year-old woman, major depression	300	none	56	mania	trazodone dose reduction to 150 mg/day
Zmitek 1987 [18]	58-year-old woman, major depression	150	none	7	mania	discontinuation of trazodone, treatment with haloperidol
Lennhoff 1987 [15]	53-year-old man, major depression	150	alcohol detoxification 17 days earlier, treatment doxepin 150 mg/day for 10 days, 3 days of wash out	4	hypomania	trazodone decreased to 50 mg/day, lithium carbonate 900 mg/day
Jabeen & Fisher 1991 [13]	61-year-old man, severe depression	100	after 7 days of benzodiazepine withdrawal from chlordiazepoxide (7.5 mg/day) and temazepam (20 mg/day)	4	hypomania	discontinuation of trazodone, treatment with lithium, trazodone restarted at 200 mg/day, benzodiazepines were gradually withdrawn
Jabeen & Fisher 1991 [13]	24-year-old woman, postnatal depression	150	none	4	hypomania	reduction of trazodone dose to 100 mg/day, after 7 days again increased to 150 mg/day
Jabeen & Fisher 1991 [13]	70-year-old depressed man	100	none	28	transient hypomania	trazodone dose increase to 200 mg/day
Horiguchi & Sai 2001 [19]	55-year-old man, major depression	50	fluvoxamine 50 mg/day added to stable treatment with trazodone and sulpiride 150 mg/day		hypomania	cessation of fluvoxamine
Hilleret et al. 2001 [20]	50-year-old man, bipolar disorder, right hemiplegia from birth with persisting motor deficiency	50	venlafaxine 300 mg, CPAP	4 weeks after start of CPAP	hypomania, mixed episode	continuation CPAP, cessation of venlafaxine and trazodone, 6 days interruption of pharmacological treatment, treatment with valproic acid and levomepromazine
Rachid et al. 2006 [21]	39-year-old woman, refractory major depression	200	paroxetine 40 mg/day, opipramol 150 mg/day, amitriptyline 50 mg/day, prazepam 100 mg/day, methadone 7.5 mg/day rTMS	second week of rTMS treatment, depressive mixed episode	mixed episode	rTMS treatment was discontinued, treatment with valproic acid

Not all details given in reports, rTMS = repetitive transcranial magnetic stimulation, CPAP = continuous positive airway pressure

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Table 2 Reports of switching to mania or hypomania during treatment with mirtazapine.

Study	Patient (age/ gender/diagnosis)	Dose (mg/day)	Concomitant treatment	Time to switch onset (days)	Affective symptoms	Actions taken
Soutullo et al. 1998 [32]	45-year-old, woman, MDE	15	sertraline 250 mg/day	4	hypomania	discontinuation of mirtazapine
De Leon et al., 1999 [30]	68-year-old, man, poststroke depression	15	after 10 days of wash out from paroxetine 60 mg/day	3	hypomania	mirtazapine was discontinued, treatment with carbamazepine and haloperidol
MacCall & Callender 1999 [33]	65-year-old, woman, MDE	30	none	2, after mirtazapine discontinuation after 35 days of treatment	hypomania	symptoms remitted after 6 weeks
Bhanji et al. 2002 [29]	43-year-old woman, MDE	60	after washout form venlafaxine 225 mg/day, topiramate 400 mg/day	7, after dose increase to 60 mg/day	mania	mirtazapine dose reduced to 45 mg/day, lithium carbonate 600 mg/day, topiramate 400 mg/day
Ng 2002 [27]	48-year-old depressed woman	30	fluoxetine 40 mg/day, alprazolam 1 mg/day	35	mania	discontinuation of fluoxetine, dose mirtazapine reduced to 15 mg/day and discontinued, valproate 2 000 mg/day and clonazepam 0.5 mg/day at bedtime
Prost & Abraham 2004 [28]	35-year-old woman, major depression	45	paroxetine 50 mg/day	56	hypomania	mirtazapine discontinued
Goyal & Sinha 2008 [31]	15-year-old girl, severe depressive episode	22.5	none	14	mania	lithium 900 mg/day after discontinuing mirtazapine, haloperidiol 5 mg/day
Liu et al. 2009 [26]	66-year-old women with late life depression	30	switch from fluoxetine 20 mg/day without a period of tapering-off, washout or cross-titration	3	mania	mirtazapine discontinued, treatment with valproate and low-dose risperidone
Habermeyer et al. 2010 [25]	51-year-old patient, major depression	45	none	5 after dose increase to 45 mg/day	mixed episode	mirtazapine discontinued, treatment with olanzapine and lithium
Basavraj et al. 2011 [24]	42-year-old woman, recurrent depressive disorder	30	after tapering down escitalopram 20 mg/day	14	mania	discontinuation of mirtazapine, treatment with lithium 900 mg/day, quetiapine 100 mg/day

MDE – major depressive episode

Agomelatine

Agomelatine is an antidepressant with a novel non-monoaminergic mechanism of action. It is a melatonin agonist at both melatonin receptors MT1 and MT2 and a serotonin antagonist at 5-HT2C receptors. The recommended dose of agomelatine to treat depression is 25–50 mg/day [34]. So far, it is unknown whether lower doses of agomelatine can be used to have only a sleep-promoting effect.

Recently, a switch to hypomania has been described in a 52-year-old female patient with the diagnosis of a recurrent major depressive disorder and comorbid panic disorder. The patient was treated with paroxetine 20 mg/day and trazodone 100 mg/day. As no improvement was observed after 1 month, the patient was admitted to hospital and the paroxetine treatment was shifted to agomelatine 25 mg/day, while 100 mg/day trazodone was maintained. After 4 days, the symptoms of hypomania occurred, and the agomelatine was discontinued 2 days later. One week after stopping the agomelatine treatment, the hypomanic symptoms remitted [35]. In a study that evaluated the efficacy of agomelatine in patients with bipolar I disorder, who were experiencing a major depressive episode during treatment with lithium or valpromide, there were 3 of 13 agomelatine and lithium treated patients who experienced manic or hypomanic episodes during an optional observation period of up to 46 weeks Only one of those cases was rated as treatment-related [36].

Discussion

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The described cases suggest that trazodone, mirtazapine, and agomelatine may induce manic symptoms in some patients. It happens most frequently at an early stage of treatment, which has been already noticed before [37]. The risk of a switch to mania or hypomania during treatment with trazodone or mirtazapine seems to be related, first of all, to the doses recommended for antidepressant treatment, administered without concomitant mood-stabilizer therapy. Low doses of these antidepressants, which can be used for their hypnotic or sedative effects, were observed to cause a switch to mania or hypomania only in patients with other risk factors for switching, such as treatment with other antidepressants, organic origin of the depressive symptoms, and being of an older or very young age.

There is no evidence for trazodone and mirtazapine, and only sparse evidence for agomelatine [36], claiming that treatment with these antidepressants is related to an increased risk of

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switch to mania when administered in combination with a mood stabilizer. This last finding of our review is supported by results of a recent study based on Swedish national registries, which examined the risk of antidepressant-induced manic switch in patients with bipolar disorder who were being treated either with antidepressant monotherapy or with an antidepressant in conjunction with a mood stabilizer. Although an increased risk of manic switch was found among patients with bipolar disorder on antidepressant monotherapy, the risk of manic episodes was not increased in the short or long term for patients treated with an antidepressant and a concurrent mood stabilizer [38].

To interpret the findings from the case reports reviewed by us, we have to take into account that switching to mania or hypomania related to treatment with trazodone, mirtazapine, or agomelatine may be more common, but underreported. The reason may be, for example, the relatively mild intensity of the hypomanic symptoms. In many described case reports, the described symptoms did not require any other action than stopping or reducing the dose of the administered antidepressant. Some authors even claimed that, in their experience, trazodone-induced hypomanic symptoms may be transient and that immediate withdrawal of trazodone may not always be necessary [13]. In some cases, switching to mania or hypomania may also be considered as resulting from illness progression [39] or stressful life events [40].

However, at least for mirtazapine, the low risk of a switch to mania was also found in studies that analyzed data from clinical trials. In a review of the initial clinical trials, manic symptoms associated with mirtazapine treatment were described in 3 (0.25%) of 1299 patients [41]. In a study that analyzed data from 2 clinical trials in patients with rapid-cycling bipolar disorder, the rate of treatment-derived mania/hypomania was 30.1% for SSRIs (highest for fluoxetine 42.1%, lowest for fluvoxamine 0%), 35.7% for bupropion, 30.6% for venlafaxine, 18.8% for nefazodone (a drug with similar pharmacological action to trazodone), and there were no cases of switching observed for mirtazapine [42].

All of these data suggest that low doses of trazodone and mirtazapine are safe in patients with bipolar disorder and should still be considered as important alternatives to hypnotics when long-term pharmacological treatment of insomnia is necessary. We believe that such a use of sleep-promoting antidepressants can even decrease the risk of switching, because the effective treatment of insomnia in bipolar patients improves the course of the disorder and quality of life. It also seems that trazodone, mirtazapine, and agomelatine can be used safely in antidepressant doses when combined with a mood stabilizer, especially in patients with bipolar II disorder.

Further work should clarify whether doxepin, the only sedative antidepressant approved by the FDA for the treatment of insomnia characterized by difficulty with sleep maintenance, can also be used to treat insomnia in bipolar disorder. Although TCAs are regarded as antidepressants with the highest risk of a switch to mania [43], there is no evidence to claim that low doses (3 and 6 mg) of doxepin, which show only antihistaminergic effects [6, 44], are related to treatment-emergent mania or hypomania. Another interesting tricyclic antidepressant worthy of consideration as sleep-promoting drug is trimipramine. Trimipramine is regarded as an atypical antidepressant with antipsychotic and sedative properties. It has been studied in monotherapy in delusional depression [45] and in low dose to treat primary insomnia [46]. In some countries it is frequently used to induce sleep, also as adjuvant therapy to other drugs [47].

It is also noteworthy that the sleep-promoting effect may not be the most relevant feature for estimating the switch risk and choice of an antidepressant. In patients with bipolar disorder without sleep problems a dopaminergic antidepressant bupropion may be a reasonable first-line treatment. Bupropion has lower rates of manic switch than tricyclic and tetracyclic antidepressants and norepinephrine-serotonin reuptake inhibitors [1] and is especially useful, e.g., in bipolar disorder comorbid with attention-deficit/hyperactivity disorder [48].

Conflict of Interest

During last 3 years Adam Wichniak has received speaker honoraria and consultancies, congress and educational grants from Angelini, Lundbeck, Servier. Janusz K. Rybakowski has participated in advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, and Sanofi-Aventis and has lectured for Janssen-Cilag, Lundbeck, and Servier.

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