

Mirtazapine-Related Manic / Hypomanic Shift: Mini Review and Case Report

Mustafa Dincer¹, Ahmet Gul²,
Hesna Gul¹, Mehmet Sinan Aydin³,
Sahin Bodur¹, Yasemin Tas Torun¹,
Mehmet Ayhan Congologlu¹,
Kamil Nahit Ozmenler³

¹Gulhane Training and Research Hospital, Department of Child and Adolescent Mental Health and Diseases, Ankara - Turkey

²Ufuk University, Department of Psychiatry, Ankara - Turkey

³Gulhane Training and Research Hospital, Department of Psychiatry, Ankara - Turkey

ABSTRACT

Mirtazapine-related manic / hypomanic shift: mini review and case report

Mirtazapine is a pharmacological agent frequently used both as an antidepressant and as a hypnotic sedative agent. However, manic shift, an important side effect of other antidepressants, has not been adequately addressed in the treatment of mirtazapine, and the evidence has been only available from case reports. This mini-review and case report aimed to compile case reports on mirtazapine related manic shifts and to report a case where a manic shift was determined relatively early compared to that in these cases.

Keywords: Dose, manic shift, mirtazapine

ÖZ

Mirtazapin ilişkili manik / hipomanik kayma: Mini derleme ve olgu sunumu

Mirtazapin hem antidepresan olarak hem de hipnotik sedatif etkisi nedeni ile sıkça kullanılan bir farmakolojik ajandır. Ancak diğer antidepresanlarda önemli bir yan etki olan manik kayma, mirtazapin tedavisinde yeterince ele alınmamış, kanıtlar genellikle olgu sunumu aşamasında kalmıştır. Bu mini-derleme ve olgu sunumunda mirtazapinle ilişkili manik kayma ile ilgili olgu sunumlarını derleyerek, bu olgulara göre çok daha kısa sürede manik kaymanın izlendiği bir vakanın sunulması planlanmıştır.

Anahtar kelimeler: Doz, manik kayma, mirtazapin



How to cite this article: Dincer M, Gul A, Gul H, Aydin MS, Bodur S, Tas-Torun Y, Congologlu MA, Ozmenler KN. Mirtazapine-related manic / hypomanic shift: mini review and case report. Dusunen Adam The Journal of Psychiatry and Neurological Sciences 2018;31:209-214. <https://doi.org/10.5350/DAJPN2018310210>

Address reprint requests to / Yazışma adresi:
Hesna Gul,
Gulhane Training and Research Hospital,
Child and Adolescent Mental Health and
Diseases Department, Ankara, Turkey

Phone / Telefon: +90-312-304-2000

E-mail address / Elektronik posta adresi:
drhesnagul@gmail.com

Date of receipt / Geliş tarihi:
September 19, 2017 / 19 Eylül 2017

Date of the first revision letter /
İlk düzeltme öneri tarihi:
October 2, 2017 / 2 Ekim 2017

Date of acceptance / Kabul tarihi:
October 17, 2017 / 17 Ekim 2017

INTRODUCTION

Mirtazapine is one of the antidepressants that increase both noradrenaline (NA) and serotonin release. This effect is mediated by blockage of noradrenergic alpha-2 auto- and heteroreceptors and inhibition of serotonergic 5-HT_{2A} and 5-HT₃, and histaminic H₁ receptors (1). The recommended dose of mirtazapine for the treatment of depression is

30-45mg/day, within which range acts as a disinhibitor of serotonin and NA and antagonist of alpha-2. Nevertheless, the dose range of 3.75-15mg is usually sufficient for insomnia as the latter only requires the blockade of H₁ receptors (2).

Although the underlying mechanism has not yet been elucidated, all antidepressants has the potential to cause development of manic episodes (3).

Previous studies and case reports have suggested

tricyclic antidepressants, monoamine oxidase inhibitors and selective serotonin reuptake inhibitors among the antidepressants with highest risk for developing manic episodes (4-6). In particular, mirtazapine needs special attention as implied by many case reports that suggested the occurrence of manic episodes under mirtazapine combination therapy, or in an add-on setting for sleeping problems in mixed depressive disorders, or after discontinuance of the drug (7-10).

This mini-review aimed to evaluate the case reports that could be reached when screening using the keywords "mirtazapine", "manic shift", "mania", and "hypomania" in PubMed, Google Scholar, PsychINFO, and Cochrane search engines. Among the case reports published until August 2017, those in English or accessible in full text were examined. Afterwards, a patient developing manic shift after a two-day course of mirtazapine therapy during his hospitalization in Department of Psychiatry of Gulhane Training and Research Hospital was introduced to point to potential risk factors.

Case Reports on Mirtazapine Use and Discontinuance

The literature search showed nine reports where manic or hypomanic episode was described during mirtazapine treatment and two reports where manic episode was described after it was discontinued. These patients who developed manic episodes were classified in four groups based on pharmacological differences and manic episodes:

1. Manic episode after mirtazapine monotherapy (n=4)
2. Manic episode during therapy with ≥ 30 mg/day mirtazapine added on to SSRI (n=2),
3. Manic/hypomanic episode during therapy with < 30 mg/day mirtazapine (n=3),
4. Manic episode after mirtazapine discontinuance (n=2).

1. Manic shift after mirtazapine monotherapy

The first group was characterized manic symptoms observed during mirtazapine monotherapy (< 30 mg/day)

used for depression. In two cases that aged 42 and 66 years old, fluoxetine and escitalopram were used before mirtazapine monotherapy was initiated, where the latter was tapered and fluoxetine was abruptly discontinued prior to mirtazapine (11,12). The other case was antidepressant-naive before mirtazapine, yet received a higher dose (45mg/day) (13). The most distinguishing feature of these three cases was the time to the manic episode. It was shown that higher dose of mirtazapine monotherapy led to accelerated development of manic episode when initiated before fluoxetine cessation and not allowing for a washout period. Another case to be considered in this group in terms of antidepressant monotherapy was a 43-year-old female patient with major depression. This case started with venlafaxine treatment where no response led to switching into mirtazapine after discontinuance and appropriate washout period. As no improvement was seen after titration up to 45mg/day after 4 weeks, topiramate 400mg/day was added. And finally when mirtazapine was escalated to 60mg/day, symptoms of mania were reported to be observed (14).

2. Manic episode during therapy with ≥ 30 mg/day mirtazapine added on to SSRI

The second group of case reports were those receiving mirtazapine in antidepressant doses combined to SSRI therapy. It was reported that the drug was added onto fluoxetine or paroxetine, where manic/hypomanic symptoms occurred within 45 days in average, and that hypomanic symptoms were spontaneously resolved after mirtazapine discontinuance and manic symptoms with valproate and clonazepam treatment (15,16).

3. Manic/hypomanic shift during therapy with < 30 mg/day mirtazapine

The third group described manic/hypomanic episodes where mirtazapine doses were below the antidepressant level (< 30 mg/day). The first case initiated 15mg/day of mirtazapine in addition to high-dose sertraline treatment (250mg/day), (17). The other

68-year-old male patient was followed up with post-stroke depression (9). Ten-day course of mirtazapine that was initiated after paroxetine discontinuance was reported to trigger hypomania symptoms, which could be relieved with carbamazepine and haloperidol. The last case was a 15-year-old adolescent patient. The most interesting feature of this manic episode triggered by 22.5mg/day of mirtazapine regimen was that no other treatment had been used. Extra intervention was needed to relieve this episode, including lithium and haloperidol after mirtazapine cessation (18).

4. Manic shift after mirtazapine discontinuance

The last group was those developing manic episode after mirtazapine cessation. There were two case reports in this group. The first case, a 65-year-old female patient, was being followed up with major depression and developed hypomanic episode two days after discontinuance of mirtazapine that she received for 35 days (19). The second case was a male patient who was diagnosed with bipolar disorder 20 years ago and received 800mg/day of lithium and 15mg/day of mirtazapine for the last six months. This patient also developed mania seven days after mirtazapine cessation, where the episode could only be resolved with olanzapine 10mg/day added on to the lithium treatment (20).

Case Report Manic Shift After Two-Day Course of Mirtazapine

Secondary to his wife's infidelity, 31 years old male patient was diagnosed with major depression after having feelings of unhappiness and anhedonia, complaints of continuous crying and inability to sleep, and thoughts of self-harm; and hospitalized to Gulhane Training and Research Hospital. Past medical history showed venlafaxine 75mg/day due to obsessive compulsive disorder two years ago and then sertraline 75mg/day for anxiety disorder. These modalities were reported to help him to resolve symptoms and he discontinued the drugs voluntarily.

It was determined that sertraline 100mg/day was started again in another institution for recurring depression symptoms that started three months ago, although no improvement was recorded during 12 weeks of sertraline regimen, for which he applied to our hospital. Further query of medical history revealed no finding that favored bipolar disorder or any period implying hypomanic/manic symptoms. Initial mental state examination noted a depressive affect, worthlessness and incapability predominance in the content of thought, a plaintive tone of voice, decreased speech and appetite, and difficulty to get off and maintain to sleep. After admission, mirtazapine 15mg/day was added onto sertraline 100mg/day. At the end of day 2, patient was observed to have increased speech, elevated affect, and flight of ideas, upon which manic shift was determined and antidepressant treatment was discontinued. Treatment was re-arranged to valproic acid 1000mg/day and 300mg/day of quetiapine. Observing that manic symptoms disappeared thoroughly at the end of third week, the patient was discharged with the current treatment.

DISCUSSION

The cases presented in this mini-review and our case disclose developing of manic/hypomanic symptoms associated with mirtazapine treatment. One of the common points observed in these cases was that the diagnosis was major depression where it was used in antidepressant dose or in combination for depression, and the management did not cover mood stabilizers. In addition, there were also some additional risk factors, including the use of higher doses of antidepressants, organic etiology of depressive symptoms (post-stroke depression, advanced age, or atypical depression in adolescence), (9,17,18) or being triggered after trauma. No risk factor regarding manic/hypomanic shift was established when mirtazapine was initiated in combination with mood stabilizers. A recent study compared patients with bipolar disorders that were managed with either antidepressant monotherapy or combined antidepressant and mood

Table 1: Mirtazapine associated manic shift cases

	Patient Demographics	Diagnosis	Mirtazapine Dosage (mg/day)	Associated Treatment	Time to Manic Shift (days)	Active Symptoms	Intervention after Manic Shift and Its Efficacy
Manic Shift after Mirtazapine Monotherapy							
• Liu et al. 2009 (12)	66 yrs., female	Depression	30	Switch without cross-titration after fluoxetine therapy (20mg/day)	3	Mania	Mirtazapine was discontinued and switched to valproate and risperidone; symptoms relieved (within two weeks).
• Basavraj et al. 2011 (11)	42 yrs., female	Recurrent Depression	30	Switch after tapering of escitalopram (20mg/day)	14	Mania	Mirtazapine was discontinued and switched to lithium (900mg/day) and quetiapine (100mg/day); symptoms resolved (within two weeks).
• Habermeyer et al. 2010 (13)	51 yrs., male	Major Depression	45	None	5	Mixed Episode	Mirtazapine was discontinued and switched to lithium and olanzapine; symptoms relieved (within two weeks).
• Bhanji et al. 2002 (14)	43 yrs., female	Major Depression	60	Initiated after discontinuation of venlafaxine (225mg/day) and appropriate washout time. Combined with topiramate (400mg/day) after four weeks	7	Mania	Mirtazapine was reduced to 45mg/day and combined with lithium (600mg/day). Topiramate 400mg/day was continued.
Manic Episode After ≥30mg of Mirtazapine Added Onto SSRI Therapy							
• Ng 2002 (16)	48 yrs., female	Depression	30	Fluoxetine 40mg/day+ alprazolam 1mg/day	35	Mania	Fluoxetine and mirtazapine was discontinued and switched to valproate and clonazepam; manic symptoms gradually disappeared within three weeks. During subsequent 6-month follow-up showed depression managed with citalopram with no manic shift.
• Proost and Abraham 2004 (15)	35 yrs., female	Major Depression	45	Paroxetine 50mg/day	56	Hypomania	Spontaneous resolution after discontinuation of mirtazapine.
Manic/Hypomanic Shift after Therapy with <30mg/day of Mirtazapine							
• Soutullo et al. 1998 (17)	45 yrs., female	Major Depression	15	Sertraline 250mg/day	4	Hypomania	Resolution after discontinuation of mirtazapine.
• De Leon et al. 1999 (9)	68 yrs., male	Post-stroke Depression	15	Initiated after discontinuation of paroxetine 60 mg/day and appropriate washout time	3	Hypomania	Mirtazapine was discontinued and switched to carbamazepine and haloperidol.
• Goyal and Sinha 2008 (18)	15 yrs., female	Depression Episode	22.5	-	14	Mania	Mirtazapine was discontinued and switched to lithium and haloperidol, mania was resolved.
Manic Shift after Mirtazapine Discontinuance							
• MacCall and Callender 1999 (19)	65 yrs., female	Major Depression	30	-	2 days after 35-day course of mirtazapine therapy	Hypomania	Symptoms remitted after six months.
• Verma and Mohapatra 2014 (20)	54 yrs., male	Bipolar Disorder Type 1	15	Lithium 800mg/day	7 days after 6-month course of mirtazapine therapy	Mania	Remission after lithium 800mg/day and olanzapine 10mg/day.

stabilizer therapy, and reported that mood stabilizers were effective in preventing short- and long-term manic shifts (21). This again emphasize the importance of review of bipolar disorders during querying of past medical and family history.

Another remarkable point is that manic episode may develop during treatment with mirtazapine at low doses used for hypnotic-sedative effect, as we just reported in our case. Previous reports defining the rate of manic episode as 0.25 (22), and no observing of manic shift compared to other antidepressants (42.1% for fluoxetine, 30.6% for bupropion, 30.6% for venlafaxine, and 18.8% for nefazodone) in rapid cycling bipolar disorder in a 2008 study (23) may lead to trivialization of this association. This might be attributed to masking of manic/hypomanic symptoms by the hypnotic/sedative effects of mirtazapine.

The most important contribution of our case report to the literature is that it suggests the potential of lower doses mirtazapine therapy to lead to manic shift relatively earlier than that in previous case reports. It is also noteworthy that in the absence of any evidence for bipolar disorder, the symptoms can be quickly controlled by mood stabilizers.

We hope that this case report and its management

provides a guidance to physicians who will encounter the same clinical problem in the future.

Contribution Categories		Author Initials
Category 1	Concept/Design	M.D., A.G., H.G., M.S.A., S.B., Y.T.T., M.A.C., K.N.O.
	Literature review	M.D., A.G., H.G., M.S.A., S.B., Y.T.T., M.A.C., K.N.O.
	Data analysis/Interpretation	M.D., A.G., H.G., M.S.A., S.B., Y.T.T., M.A.C., K.N.O.
	Case follow-up (if applicable)	M.D., M.S.A., K.N.O.
Category 2	Drafting manuscript	M.D., A.G., H.G., M.S.A., S.B., Y.T.T., M.A.C., K.N.O.
	Critical revision of manuscript	M.D., A.G., H.G., M.S.A., S.B., Y.T.T., M.A.C., K.N.O.
Category 3	Final approval and accountability	M.D., A.G., H.G., M.S.A., S.B., Y.T.T., M.A.C., K.N.O.
Other	Technical or material support	M.D., A.G., H.G., M.S.A., S.B., Y.T.T., M.A.C., K.N.O.
	Supervision	M.D., A.G., H.G., M.S.A., S.B., Y.T.T., M.A.C., K.N.O.
	Securing funding (if applicable)	N/A

Informed Consent: Written consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

REFERENCES

- de Boer T. The effects of mirtazapine on central noradrenergic and serotonergic neurotransmission. *Int Clin Psychopharmacol* 1995; 10(Spull.4):19-23.
- Wichniak A, Wierzbicka A, Jernajczyk W. Sleep and antidepressant treatment. *Curr Pharm Des* 2012; 18:5802-5817. **[CrossRef]**
- Allain N, Leven C, Falissard B, Allain JS, Batail JM, Polard E, Montastruc F, Drapier D, Naudet F. Manic switches induced by antidepressants: an umbrella review comparing randomized controlled trials and observational studies. *Acta Psychiatr Scand* 2017; 135:106-116. **[CrossRef]**
- Koszevska I, Rybakowski JK. Antidepressant-induced mood conversions in bipolar disorder: a retrospective study of tricyclic versus non-tricyclic antidepressant drugs. *Neuropsychobiology* 2009; 59:12-16. **[CrossRef]**
- Post RM, Altshuler LL, Leverich GS, Frye MA, Nolen WA, Kupka RW, Suppes T, McElroy S, Keck PE, Denicoff KD, Grunze H, Walden J, Kitchen CM, Mintz J. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. *Br J Psychiatry* 2006; 189:124-131. **[CrossRef]**
- Pacchiarotti I, Bond DJ, Baldessarini RJ, Nolen WA, Grunze H, Licht RW, Post RM, Berk M, Goodwin GM, Sachs GS, Tondo L, Findling RL, Youngstrom EA, Tohen M, Undurraga J, González-Pinto A, Goldberg JF, Yildiz A, Altshuler LL, Calabrese JR, Mitchell PB, Thase ME, Koukopoulos A, Colom F, Frye MA, Malhi GS, Fountoulakis KN, Vázquez G, Perlis RH, Ketter TA, Cassidy F, Akiskal H, Azorin JM, Valentí M, Mazzei DH, Lafer B, Kato T, Mazzarini L, Martínez-Aran A, Parker G, Souery D, Ozerdem A, McElroy SL, Girardi P, Bauer M, Yatham LN, Zarate CA, Nierenberg AA, Birmaher B, Kanba S, El-Mallakh RS, Serretti A, Rihmer Z, Young AH, Kotzalidis GD, MacQueen GM, Bowden CL, Ghaemi SN, Lopez-Jaramillo C, Rybakowski J, Ha K, Perugi G, Kasper S, Amsterdam JD, Hirschfeld RM, Kapczynski F, Vieta E. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiatry* 2013; 170:1249-1262. **[CrossRef]**

7. Benazzi F. Antidepressant-associated hypomania in outpatient depression: a 203-case study in private practice. *J Affect Disord* 1997; 46:73-77. **[CrossRef]**
8. Boerlin HL, Gitlin MJ, Zoellner LA, Hammen CL. Bipolar depression and antidepressant-induced mania: a naturalistic study. *J Clin Psychiatry* 1998; 59:374-379. **[CrossRef]**
9. De León OA, Fumaga KM, Kaltsounis J. Mirtazapine-induced mania in a case of poststroke depression. *J Neuropsychiatry Clin Neurosci* 1999; 11:115-116. **[CrossRef]**
10. Wichniak A, Jarkiewicz M, Okruszek Ł, Wierzbicka A, Holka-Pokorska J, Rybakowski J. Low risk for switch to mania during treatment with sleep promoting antidepressants. *Pharmacopsychiatry* 2015; 48:83-88. **[CrossRef]**
11. Basavraj V, Nanjundappa GB, Chandra PS. Mirtazapine induced mania in a woman with major depression in the absence of features of bipolarity. *Aust N Z J Psychiatry* 2011; 45:901-902. **[CrossRef]**
12. Liu CC, Liang KY, Liao S-C. Antidepressant-associated mania: soon after switch from fluoxetine to mirtazapine in an elderly woman with mixed depressive features. *J Psychopharmacol* 2009; 23:220-222. **[CrossRef]**
13. Habermeyer B, Bayer U, Müller-Spahn F. Mania associated with mirtazapine treatment and mixed depression. *Pharmacopsychiatry* 2010; 43:37-38. **[CrossRef]**
14. Bhanji NH, Margolese HC, Saint-Laurent M, Chouinard G. Dysphoric mania induced by high-dose mirtazapine: a case for 'norepinephrine syndrome'? *Int Clin Psychopharmacol* 2002; 17:319-322. **[CrossRef]**
15. Prost E, Abraham G. Mirtazapine-induced shopping spree. *Can J Psychiatry* 2004; 49:495. **[CrossRef]**
16. Ng B. Mania associated with mirtazapine augmentation of fluoxetine. *Depress Anxiety* 2002; 15:46-47. **[CrossRef]**
17. Soutullo CA, McElroy SL, Keck PE Jr. Hypomania associated with mirtazapine augmentation of sertraline. *J Clin Psychiatry* 1998; 59:320. **[CrossRef]**
18. Goyal N, Sinha VK. Mirtazapine-induced manic switch in adolescent unipolar depression. *Aust N Z J Psychiatry* 2008; 42:1070-1071.
19. MacCall C, Callender J. Mirtazapine withdrawal causing hypomania. *Br J Psychiatry* 1999; 175:390. **[CrossRef]**
20. Verma JK, Mohapatra S. Mirtazapine withdrawal-induced mania. *J Pharmacol Pharmacother* 2015; 6:214-215. **[CrossRef]**
21. Viktorin A, Lichtenstein P, Thase ME, Larsson H, Lundholm C, Magnusson PKE, Landén M. The risk of switch to mania in patients with bipolar disorder during treatment with an antidepressant alone and in combination with a mood stabilizer. *Focus (Am Psychiatr Publ)* 2015; 13:68-74. **[CrossRef]**
22. Montgomery SA. SAT-7-5 Safety of mirtazapine: a review. *Eur Neuropsychopharmacol* 1995; 5:263-264. **[CrossRef]**
23. Gao K, Kemp DE, Ganocy SJ, Muzina DJ, Xia G, Findling RL, Calabrese JR. Treatment-emergent mania/hypomania during antidepressant monotherapy in patients with rapid cycling bipolar disorder. *Bipolar Disord* 2008; 10:907-915. **[CrossRef]**