

# Leucopenia Due to Quetiapine Abuse and Combination with Olanzapine: A Case Report

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## ÖZET

Ketiapin kötüye kullanımı ve olanzapin ile kombinasyonu sonucu gelişen lökopeni: Bir olgu sunumu

Ketiapin, kötüye kullanım potansiyeli taşıyan atipik bir antipsikotiktir. Olanzapin ise, yapıcı ketiapine benzeyen ve literatürde nadiren lökopeniye neden olduğu bildirilmiş bir atipik antipsikotiktir. Burada, yüksek doz ketiapin kötüye kullanımı ve eş zamanlı olanzapin kullanımı sonucu lökopeni gelişen, ketiapinin uzun salınımlı formuna geçiş yapılarak ilaç dozlarının düşürülmesi neticesinde kısa zamanda kan değerleri düzelen bir olgu sunulmuştur.

**Anahtar kelimeler:** Ketiapin kötüye kullanımı, olanzapin, lökopeni

## ABSTRACT

Leucopenia due to quetiapine abuse and combination with olanzapine: a case report

Quetiapine is an atypical antipsychotic that can be abused. Olanzapine is an another atypical antipsychotic that is similar to quetiapine in chemical structure and cases of leucopenia after olanzapine use have rarely been presented in the literature. In this report, we presented a case of high dose quetiapine abuse and olanzapine combination treatment leading to leucopenia. Blood levels returned to normal levels in a short period of time both by passing to extended release quetiapine and decreasing the daily dosage.

**Key words:** Quetiapine abuse, olanzapine, leucopenia

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## INTRODUCTION

Quetiapine is a dibenzothiazepine derivative and second generation antipsychotic (SGA) drug with an antagonistic effect through 5-HT<sub>2A</sub>, D<sub>1</sub>, D<sub>2</sub>, H<sub>1</sub>, alpha 1 and 2 receptors (1). Quetiapine was approved by the American Food and Drug Administration (FDA) for the treatment of manic/depressive episodes of schizophrenia and bipolar disorder. Although quetiapine is itself used in the treatment of substance and alcohol abuse and dependence (2,4), quetiapine abuse through oral, intranasal, and intravenous use has also been reported (5-10). Although the mechanism of quetiapine abuse is not yet fully understood, we believe quetiapine is abused because of its effects on the dopamine and serotonin receptors in the reward pathway of limbic system (5,6).

Another similarly-structured SGA commonly used in the treatment of bipolar disorder and schizophrenia is olanzapine. Olanzapine acts on the D<sub>1</sub>, D<sub>2</sub>, 5HT<sub>2A</sub>, 5HT<sub>2c</sub>, H<sub>1</sub>, alpha 1 and M<sub>1-5</sub> receptors (1). During olanzapine treatment, metabolic and endocrine side-

effects are encountered relatively frequently and thus less frequent side effects may be overlooked. One of these rare side effects is leucopenia. Treatment guideline published by the Canadian Society of Pharmacology and Therapeutics reported that although its mechanism is not exactly known, leucopenia developed at a rate of around one percent during olanzapine treatment. The literature contains case reports on leucopenia encountered during olanzapine use (11,12).

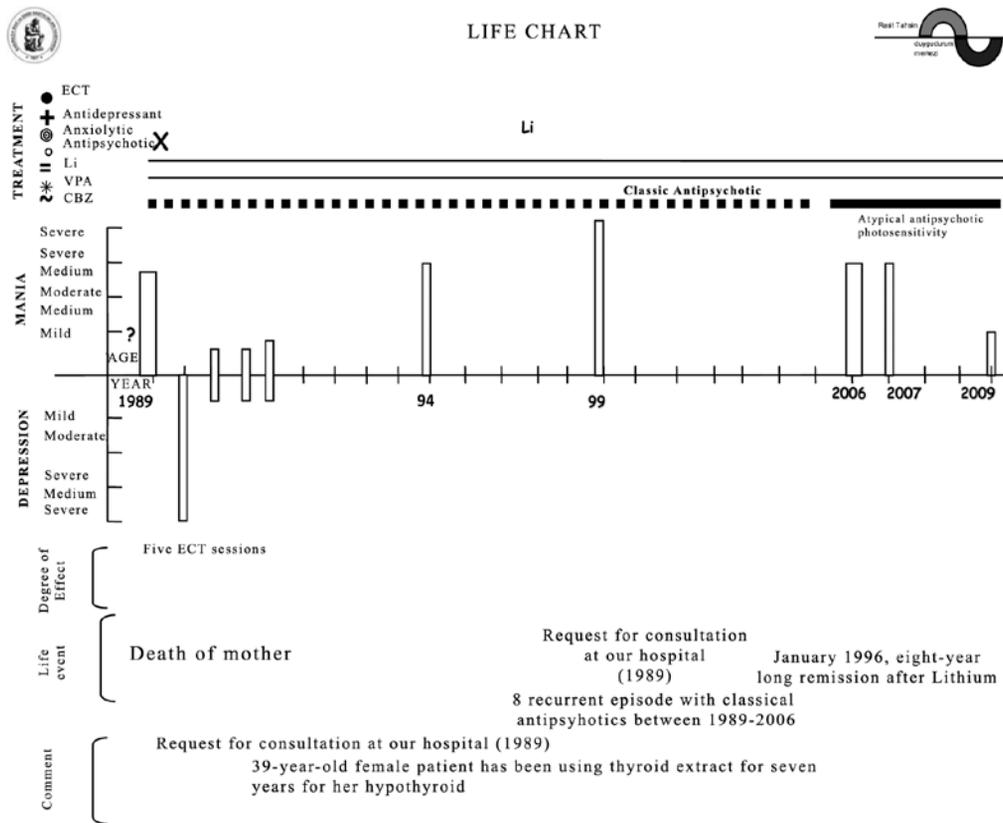
This article presents the hematological complications that developed in a patient diagnosed with bipolar I disorder and quetiapine abuse during quetiapine and olanzapine use, as well as the relevant literature.

## CASE REPORT

A 39-year-old female patient used mood stabilizer and typical antipsychotic drug until 2006 for the treatment of her bipolar I disorder that had first begun with a manic episode in 1989. She experienced eight episodes in total (four manic, three mixed, one depressive) during this period and underwent in-patient treatment three times

**Table 1: White blood cell count, hemoglobin thrombocyte, neutrophil percentage follow-up values**

Date	White Blood Cell Count (WBC)	Hemoglobin Values (HGB)	Thrombocyte Values (PLT)	Neutrophil Percentage	Drug Doses
August 21, 2009	2,200 10 <sup>3</sup> /μL	11.30 g/dl	148,000	56%	Olanzapine 20 mg/day Quetiapine 1200 mg/day Lithium 900 mg/day
October 22, 2009	3,900 10 <sup>3</sup> /μL	11.60 g/dl	155,000	69%	Olanzapine 20 mg/day Quetiapine 1200 mg/day Lithium 900 mg/day
November 25, 2009	2,900 10 <sup>3</sup> /μL	11.30 g/dl	148,000	60%	Olanzapine 20 mg/day Quetiapine 1800 mg/day Lithium 900 mg/day
December 23, 2009	4,090 10 <sup>3</sup> /μL	11.60 g/dl	124,000	64%	Olanzapine 20 mg/day Quetiapine XR 800 mg/day Lithium 900 mg/day
December 30, 2009	3,780 10 <sup>3</sup> /μL	11.50 g/dl	152,000	62%	Olanzapine 20 mg/day Quetiapine XR 800 mg/day Lithium 900 mg/day



**Figure 1: Translated into the Turkish from Post et al. (17).**

throughout her illness.

The psychiatric interview with and medical records of the patient showed that she had a history of hypothyroidism starting in 2002, and that her thyroid hormone treatment was ongoing. We learned that her lithium 900 mg/day, chlorpromazine 400 mg/day

treatment in 2006, when she had a manic episode, was changed to lithium 900 mg/day and quetiapine 800 mg/day, due to the development of photosensitivity. Since the desired control of manic symptoms could not be achieved, olanzapine 10 mg/day was added to the treatment and clinical improvement ensued. As her illness

progressed steadily, her treatment was set at olanzapine 30 mg/day, quetiapine 300 mg/day, and lithium 900 mg/day following a manic episode in 2007. The olanzapine dose was gradually lowered to 5 mg/day in the follow-up period and her follow-up care was continued with this treatment until June 10, 2009. The patient did not use the valproic acid recommended to her in the same year, on the grounds that it caused nausea. We found out that since her complaint of insomnia persisted, she increased the dose of quetiapine to 600 mg/day of her own initiative and eventually raised the dose up to 1200 mg/day. Due to a hypomanic episode that occurred during the patient's psychiatric evaluation on August 18, 2009, her treatment was continued as quetiapine 1200 mg/day, Lithium 900 mg/day, and olanzapine 20 mg/day and her episode was brought under control. One month later, during the patient's routine follow up, we found out that she had raised the quetiapine dose up to 1500 mg/day of her own accord. In an examination of the patient on November 5, 2009, propranolol 40 mg/day was added to her treatment for a tremor complaint (for the course of her illness, see Fig. 1)

At the request of the patient's sister, both women came to the outpatient unit on December 18, 2009. According to information provided by her sister, the patient had begun using eight to nine 200 mg quetiapine tablets a day and continued to do so, as she suffered complaints of sweating, unease, trembling hands and palpitation when she discontinued quetiapine. In the psychiatric examination, she said that she used quetiapine continuously because of the intense distress occurring when she did not use it, and had tried to quit it for the last three months. We also found out that she quarreled with her family frequently because she was using high-dose drug in disregard of her physician's recommendation, and that her family was making significant efforts to get her treated.

In the examinations, the patient was found to have low leucocyte, neutrophil, hemoglobin, hematocrit, thrombocyte, basophil and eosinophil values and internal medicine consultation was requested. She was transferred to the extended release (XR) form of quetiapine, the dosage was lowered to 1200 mg/day, and olanzapine 20 mg/day, lithium 1200 mg/day treatment was continued. In an examination five days later, quetiapine XR was lowered to the dose of 800 mg/day and one week later to 400 mg/day. In an examination one week later, we observed an improvement in all low values in the

patient's hemogram table (Table 1). As a result of the patient's internal medicine consultation, we reached the medical opinion that low values in the patient's blood table were related to the high dose of drugs used and monthly hemogram follow-up was recommended. We found out that the patient did not want to come to interviews on the grounds that the quetiapine dose had been lowered, and she continued to use quetiapine 800 mg/day.

## DISCUSSION

In recent years, several cases have been reported of quetiapine use meeting substance abuse criteria (5-10). Despite reports that quetiapine may have the potential for dependence, a case of quetiapine dependence has not yet been reported. In our case as well, quetiapine use does not meet the dependence criteria in DSM-IV-TR (13), but it does meet DSM-IV-TR abuse criteria: 'repetitive substance use resulting in not being able to hold the main responsibilities expected at work, school or home' and 'continuous substance use in spite of continuous or repetitive social or interpersonal problems caused or aggravated by the effects of the substance'. The patient's other symptoms such as development of tolerance, increase to a high dose, unwillingness to discontinue use, fighting attempts to discontinuation, and severing her connection with the treatment team suggest the dependence potential of the patient (13). At the same time, another striking point is that when quetiapine used in patient treatment is changed from the quetiapine immediate release (IR) form to the quetiapine extended release (XR) form, the dose can be lowered from 1500 mg/day to 800 mg/day, half of the previous amount. This may be related with the stable plasma concentration fluctuations of quetiapine XR, and thus side effects, are experienced less with it(14). Daily doses of quetiapine abuse vary between 800 and 2400 mg/day in the literature. In our case, the highest observed quetiapine udosage was 1800 mg/day. Moreover, we believe that beyond the oral use of quetiapine, intranasal and intravenous abuse is not as rare as thought. Although intranasal and intravenous substance use is preferred by the people with a diagnosis of addiction because of the early onset of the effect, some claim that the intranasal and intravenous use of quetiapine does not induce more euphoria, but is preferred as it ensures better quality sleep (8). The fact that the patient used

olanzapine, which comes from the same group as quetiapine, may have made it easier for her to tolerate withdrawal symptoms. However, another significant feature of the case is the development of leucopenia during treatment with high-dose of olanzapine and quetiapine (1,11), two antipsychotics similar in chemical structure to clozapine. In the literature, there are reports of leucopenia-neutropenia being encountered during use of both olanzapine and quetiapine (11,15, and 16). Some articles report that the hematologic complications encountered with quetiapine resolve immediately after discontinuation of the drug, but severe fatal hematologic complications are also seen during olanzapine use (12). The emergence mechanism of leucopenia is thought to be related to bone marrow suppression (12,16). In our case, while no hematologic side effects were observed in the period during which the patient used only quetiapine, development of leucopenia was observed during an increase of quetiapine to a high dose and concurrent high-doses of olanzapine. After the quetiapine dose was lowered (from 1600 mg/day to 800 mg/day), however, the leucocyte count rose from 2,200  $10^3/\mu\text{L}$  to 3,780  $10^3/\mu\text{L}$ . Given that the patient had no history of disease or general medical condition and that no hematologic

complication occurred during low-dose quetiapine monotherapy, leucopenia may be considered to have arisen from the high-dose combination of olanzapine and quetiapine. Thus when drugs from the same group are used in combination, it must be remembered that these drugs may together carry a greater risk of side effects. Two features make this case report important – the potential risk for abuse of quetiapine and occurrence of leucopenia during combination treatment with quetiapine and olanzapine – and therefore a contribution to the literature.

## CONCLUSION

It is necessary to follow up on drug side effects closely through clinical examinations and laboratory tests, particularly in patients with multiple drug use. Beside this, it must be considered to follow up the patient closely for abuse or dependence when medicine with a risk of dependence are used for treatment purposes, to check for the existence of comorbid general medical conditions, and to provide follow-up care for the patient concurrently with other specialty areas when required.

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