tract infection might increase clozapine levels and contribute to side effects. Our case demonstrated a clear association between the emergence of negative myoclonus and remarkable elevations in clozapine plasma concentration. Furthermore, these changes are correlated with leukocytosis and C-reactive protein level in response to UTI.

In conclusion, during treatment with clozapine, clinicians must be aware of the potential for increase in the clozapine level when patients are affected by a range of infections. Therefore, particular attention must be devoted to signs of clozapine toxicity, especially with adverse effects developing in a dose-dependent manner such as myoclonic movement including negative myoclonus.

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Olanzapine and Quetiapine Use During Breastfeeding
Excretion Into Breast Milk and Safe Breastfeeding Strategy

To the Editors:

Treating mental disorders with modern antipsychotic drugs in breastfeeding women often presents as a medical dilemma. Although the benefits of breastfeeding are well known,[1] the safety of such antipsychotic medications in breastfeeding is not thoroughly documented.[2] Despite the lack of information on the safety profiles of modern antipsychotic drugs in breastfeeding women, in situations where pharmacotherapy is required, these drugs are often prescribed during lactation. Therefore, measuring excretion of these drugs into breast milk and deliberating strategies to minimize infant exposure are warranted.

Here, we present a 33-year-old female patient (86 kg, first pregnancy) with a diagnosis of bipolar disorder type I, giving birth to twin babies at term after an uneventful pregnancy, maintained via in vitro fertilization. She started breastfeeding her infants after birth, and sodium valproate was initiated 2 days after delivery because she had a history of intolerable medication-free follow-up. While under the sodium valproate treatment with blood levels within the therapeutic range, the patient entered into manic phase at the 18th to 20th days postpartum. For management of her psychotic and manic symptoms, she was put on 15 mg/d of olanzapine and 200 mg/d of quetiapine in addition to her ongoing treatment with sodium valproate because both drugs have been reported to be acceptable for breastfeeding.[2–4] Although the medical condition of the patient had improved, she desired to continue breastfeeding while taking her medications. On this request, she was offered to follow once-daily treatment regimen and let daily breastfeeding to start only after 8 hours of every night at bedtime (q.h.s.) medication regimen. Seven days after the initiation of olanzapine and quetiapine treatment, upon obtaining the patient's and her husband's written informed consent, milk samples were started to be collected for measuring excretion of olanzapine and quetiapine into the breast milk.

The patient was given single daily doses of olanzapine (15 mg) and quetiapine (200 mg) at 11 P.M. and the babies were fed with formula throughout the night. At 7 A.M., she had been asked to pump and discard her milk accumulated throughout the night, and then with upcoming fresh milk, she breastfed her infants as needed by the babies until she takes her next dose at 11 P.M. Three breast milk samples were collected and saved by the

TABLE 1. Breast Milk Drug Concentrations, AUC Calculations, and Infant Exposure for Olanzapine and Quetiapine

Parameter	Olanzapine	Quetiapine
Breast milk drug concentration, ng/mL		
11 P.M.	7.6 (4.8–12.3)*	0.9 (0.5–1.1)†
4 A.M.	12.7 (9.5–17.2)	10.7 (8.3–14.5)†
8 A.M.	10.0 (9.2–17.2)	3.7 (3.3–7.7)†
AUC_{24h}, ng.h/mL	212.4 (193.3–334.2)	102.3 (78.5–145.5)
AUC_{bf}, ng.h/mL	137.7 (119.9–233.1)‡	40.1 (34.3–70.1)‡
Infant exposure to AUC_{24h}, %	63.5 (59.0–67.9)	45.2 (38.2–50.8)
Absolute infant dose, μg/kg per day	1.29 (1.12–2.19)	0.38 (0.32–0.66)
Relative infant dose, %	0.74 (0.64–1.25)	0.02 (0.01–0.03)

Data are presented as median (25th–75th quartile).

*$P < 0.001$ when compared with 4 A.M. and 8 A.M.

†$P < 0.001$ when compared with every other time point within group.

‡$P < 0.001$ when compared with AUC_{24h}.

patient at 4 A.M., 8 A.M., and 11 P.M. (before taking her medications) for 27 days within a 48-day period. Drug levels were measured via liquid chromatography–mass spectrometry with 0.04- and 0.06-ng/mL limits of quantitation for olanzapine and quetiapine, respectively. Drug levels at 7 A.M. were estimated using linear equation where the variables are hours and drug levels at 4 and 8 A.M. Area under the drug concentration curves (AUCs) were calculated for 24 hours (AUC_{24h}; from 11 P.M. to 11 P.M.) and for breastfeeding period (AUC_{bf}; from 7 A.M. to 11 P.M.) using the linear trapezoidal rule. Daily infant exposure to AUC_{24h} (%) was calculated with the formula: $[AUC_{bf}/AUC_{24h}] \times 100$. For daily absolute infant dose calculation, the following formula was used: $C \times 0.15$, where C is the breast milk drug concentration derived from $AUC_{bf}/16$ (daily breastfeeding duration in hours), and 0.15 (liter per kilogram) is the average breast milk consumption of an ordinary infant per day.[5] Relative infant dose (%) was calculated from the formula: [absolute infant dose (microgram per kilogram per day)/maternal dose (milligram per kilogram per day)] × 100. Because the distribution of drug concentration data was not normal, nonparametric statistical tests were used. All data are presented as median (25th–75th percentile). Bonferroni-corrected Wilcoxon signed rank test was used for repeated within-group drug concentration comparisons per time point. The Wilcoxon signed rank test was also used for the AUC_{24h} versus AUC_{bf} comparisons. A P value of less than 0.05 was considered to indicate statistical significance. Analyses were performed with Statistical Package for the Social Sciences 20 (IBM Corporation, USA) and Excel 14 (Microsoft Corporation, USA).

The breast milk concentrations of olanzapine and quetiapine at the 3 predetermined regular sampling times and their pharmacokinetic parameters are presented in Table 1. The daily median breast milk concentrations of olanzapine and quetiapine were 10.2 (7.5–14.3) ng/mL and 3.7 (1.1–9.5) ng/mL, respectively. Olanzapine drug concentration at 11 P.M. was significantly lower when compared with the concentrations at 4 A.M. and 8 A.M. ($P < 0.001$). Quetiapine drug concentrations were also significantly different at each time point when compared via the repeated within-group Wilcoxon signed rank tests ($P < 0.001$). The AUC_{bf} was significantly lower when compared with AUC_{24h} for both olanzapine and quetiapine ($P < 0.001$). The median infant exposure to AUC_{24h} was 63.5% for olanzapine and 45.2% for quetiapine (Table 1). The relative infant doses were 0.74% for olanzapine and 0.02% for quetiapine. Previously described breastfeeding strategy with q.h.s. medication schedule and the milk accumulated in the following 8 hours being discarded have continued for 15 months while the mother was on antipsychotic medication. Development of the infants was monitored monthly and recorded as normal by the Department of Pediatrics, Infant Unit at the Dokuz Eylul University in Izmir, Turkey, with no adverse effect being noted by the family or pediatricians.

Reported findings are based on 3 times daily sampling of breast milk for 27 days within a 48-day period. Although more frequent sampling would enable more precise pharmacokinetic profiles, given practical reasons associated with bipolar diagnosis and challenges of early motherhood to twin babies, this could not be possible. Although 27 days of measurement offer a long period of follow-up in determining steady drug levels, 3 times daily sampling of breast milk only might be considered as a limitation of the present work.[6] Likewise, lack of quantifiable clinical outcome data may be considered as a limitation, especially in the light of previously reported olanzapine-associated adverse effects/events in breastfed babies.[7,8] Future studies involving more frequent sampling times, measurement of plasma drug concentrations of the mother and the baby, as well as quantifiable infantile growth–related clinical outcomes would shed further light on the matter.

In this case report, we report on the pharmacokinetic analysis of breast milk levels and excretion of olanzapine and quetiapine into the breast milk for 27 days, which is the longest duration of breast milk measurement reported so far. Our findings on the excretion of olanzapine and quetiapine into milk and infant doses were comparable with the previous reports.[9–17] Relative infant doses of olanzapine and quetiapine were found to be much less than the generally accepted safety threshold, which was 10% of the maternal dose.[5] Promoted breastfeeding strategy with q.h.s. medication regimen and discard of subsequent 8 hours of milk accumulation was found to be promising because it significantly reduced the infant's exposure to the drugs excreted into breast milk. This strategy may offer effective treatment of mother's mental situation with modern antipsychotic medications during lactation without interruption of mother's milk and as such without compromising infants' physical and psychological development and health. Future work on women who need pharmacologic treatment with antipsychotic medications while lactating would help to confirm or refute the clinical usefulness of this approach.

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Quetiapine Treatment for Self-Mutilation in Chorea-Acanthocytosis
A Case Report

To the Editors:

Neuroacanthocytosis is a rare hereditary disorder presenting with orofaciolingual dyskinesia, involuntary choreiform movements, and acanthocytosis.[1] Limb and orobuccal chorea as well as frequent lip and tongue mutilation are also seen in neuroacanthocytosis.[2] In this report, successful treatment with quetiapine in a case of chorea-acanthocytosis (a subtype of neuroacanthocytosis) with prominent self-mutilating orobuccal and finger-biting behavior is presented.

A 29-year-old male patient, unemployed due to disability, single, and living with his family in a rural region, was evaluated during his hospitalization in the inpatient unit of the Department of Neurology at the Hacettepe University Faculty of Medicine. His symptoms included skin picking, involuntary biting of lips and intraoral region, hitting the floor with his head, as well as general involuntary movements of the body.

No complications of delivery or problems during his early childhood were reported. When he was 6 years old, his parents recognized slowness of speech and retardation when giving answers to questions. During primary school years, sudden jerks of his shoulders were noticed. No medical help was sought for the abnormal movements, which was assumed by his family to be tics. The abnormal movements got worse in time and they interfered with the performance of simple daily activities. When he was 23 years old, involuntary mouth and tongue movements started. A particular diagnosis could not be made upon evaluation in a hospital. Nevertheless, anticholinergic treatment with biperiden was initiated, which did not lead to any benefit. For the next 6 years, involuntary movements gradually increased and became disabling, particularly with additional biting of fingers, lips, and intraoral region; fidgetiness; pounding his head; and severe skin picking. In an attempt to avoid self-mutilation, he devised an apparatus made of a short plastic hose to bite on when he had the urge to chew his fingers. The patient did not have any known history of seizures; none of his family members had any known history of any movement disorders. Consanguinity was not reported for his parents.

With these complaints, he was evaluated at the outpatient unit of the Department of Neurology at Hacettepe University Faculty of Medicine and 6 mg/d of pimozide was initiated to ameliorate involuntary choreiform and dyskinetic movements. One month later, he was hospitalized. After the clinical evaluation of laboratory (acanthocytes in peripheral blood sample) and magnetic resonance findings (severe atrophy in nucleus caudatus), a diagnosis of chorea-acanthocytosis was established. Chorein Western blot testing was not readily available at the time of his evaluation.

Subsequently, pimozide was lowered to 3 mg/d because of lack of response in 2 days and 5 mg/d of haloperidol was initiated. Because there was no adequate response in the following month after the addition of haloperidol, the Department of Psychiatry examined the patient for minor depressive symptoms and self-mutilation. Twenty milligrams per day of paroxetine was initiated for the depressive symptoms, haloperidol was discontinued, and 50 mg/d of quetiapine was introduced and gradually increased to 600 mg/d in 3 days for the control of self-mutilation. A week after increasing quetiapine to 600 mg/d, self-mutilating behavior decreased substantially. Long-standing chronic wounds in his mouth, lips, and fingers started to heal. His sleep duration increased to 8 hours from 2 hours. Biperiden treatment, which he had increased to 20 mg/d on his own, was tapered to 6 mg/d. His choreiform movements persisted, yet he was discharged with near total remission in self-mutilating behavior.

The patient was reevaluated at 3 months, when he had tapered quetiapine to 300 mg/d, and at 12 months, when he had tapered quetiapine to 50 mg/d, because of sedation. At both visits, the self-mutilating behaviors had reemerged.

Self-mutilating behavior in chorea-acanthocytosis contributes to the morbidity of the illness significantly. Managing this cluster of symptoms is pharmacologically challenging. To our knowledge, no publication exists, besides the anecdotal use of typical antipsychotics, regarding the pharmacological management of self-mutilating behavior in chorea-acanthocytosis.

Disruptions to key frontostriatal loops, secondary to pathology in the striatum and pallidum, seem to predispose individuals to major neuropsychiatric syndromes including obsessive-compulsive disorder and