

# Lorazepam-Quetiapine Doses in Manic and Mixed Episodes

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## Abstract

***Objective:** Little is known about lorazepam-quetiapine combination doses requirements for mania and mixed bipolar episodes despite frequent use. It was previously assumed that, by adding a benzodiazepine, antipsychotic dose could be lowered. The aim of the current study was to test this assumption and to evaluate dosage of lorazepam and quetiapine, when used together under routine clinical conditions for the treatment of manic or mixed episodes.*

***Methods:** Charts of all bipolar and schizoaffective adult inpatients, who had received quetiapine and lorazepam for a manic or mixed episode between 1999 and 2005 were retrospectively reviewed.*

***Results:** Seventy eight charts were analyzed. A positive linear relation was found between lorazepam dosage and respectively manic symptoms severity at entry and maximum quetiapine dosage. High quetiapine dosage during hospitalization predicts high quetiapine dosage at discharge whereas high lorazepam dosage does not.*

***Conclusions:** The present study confirms that, in natural settings, benzodiazepines were used frequently in association to quetiapine during the treatment of manic or mixed states. Lorazepam augmentation of quetiapine treatment does not lead to a reduction of the antipsychotic dose. Lorazepam dosage may rather be determined by the need of sedation, which declines at discharge (German J Psychiatry 2008; 11: 107-110).*

*Keywords:* Antipsychotic drugs, benzodiazepine, bipolar disorder, dosage, quetiapine, lorazepam

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## Introduction

Lorazepam, a short acting benzodiazepine (BZD) agent, is often used to control agitation (Chou et al., 1999) and to improve sleep (Nowlin-Finch et al., 1994). Not surprisingly, there exist several report and studies which indicate that lorazepam is useful in acute mania (Bradwejn et al., 1990; Chouinard, 1988; Curtin et al., 2004). Actual guidelines consider benzodiazepines, alone or in association with antipsychotic drugs, as an adjunct therapy of mood stabilizing agents in acute mania (Perlis, 2005).

Preliminary reports on classical antipsychotic agents suggested that BZD augmentation may facilitate reducing the antipsychotic dose, but this has not been tested in prospective trials under controlled conditions (Arana et al., 1986; Busch et al., 1989; Salzman et al., 1986; Santos et al., 1989). In a prospective controlled study, lorazepam 4mg/day was insufficient to produce an advantage when added to low

(5mg) or high (25mg) dose haloperidol in treatment of acute mania (Chou et al., 1999). Controlled studies on quetiapine efficacy in mania allowed prescription of benzodiazepines of up to 6 mg lorazepam or equivalent for no more than two weeks (Bowden et al., 2005; McIntyre et al., 2005; Sachs et al., 2004; Vieta et al., 2005; Yatham et al., 2004).

Little is known about dose requirements for acute mania and mixed episodes and its impact on concomitant antipsychotic prescription and dosage in naturalistic setting.

The aim of the current retrospective study was to evaluate the links between dosage of lorazepam and quetiapine, when used together under routine clinical conditions, in a sample of manic and mixed bipolar disorder (BPD) and schizoaffective bipolar disorder (SA) inpatients.

The present paper is the results of further analysis of a subsample of patients drawn from a previous study on quetiapine dosage in acute bipolar disorder episodes (Khazaal et al., 2007).

## Methods

Data are based on a systematic chart review of all adult inpatients with BPD or SA, who received a concomitant treatment of quetiapine and lorazepam for a manic or a mixed episode between December 1999 (introduction of quetiapine in Switzerland) and February 2005 in the mood and anxiety disorder treatment unit of the University Psychiatric Department of Lausanne. Medical charts included information on demographic and clinical characteristics, psychiatric diagnosis, number of previous hospitalization, medication, side effects and treatment response, clinical laboratory parameters and serum concentrations of mood-stabilizing agents, duration of hospitalization, seclusion and commitment procedures. Diagnosis was established according to ICD-10 criteria by psychiatry residents, who were supervised by a senior psychiatrist. Severity of the symptoms were systematically assessed at hospital admission and discharge using the Bech-Rafaelsen Mania Scale (MAS) (Bech, 2002) for manic episodes, the Montgomery Asberg depression rating scale (MADRS) (Montgomery et al., 1979) for depressive episodes and both scales for Mixed episodes. Evaluations were made by psychiatry residents, who attended bi-monthly to interrater trainings. The study protocol was approved by the local ethical committee and the institutional review board.

Statistical analyses were carried out using SPSS for Windows (version 11.0). An initial exploratory analysis involved calculation of means, standard deviation and median for age, MAS, MADRS, lorazepam and quetiapine dosages (respectively highest doses per patient and per hospitalisation), lithium and valproate serum concentrations as well as number of previous hospitalizations.

Lorazepam dosages were classified as high (>13 mg/day) and low ( $\leq$  13 mg/day), with regard to the median lorazepam dose (13 mg), whereas quetiapine dosages were classified as low ( $\leq$  800 mg/day) and high (> 800 mg/day), in consideration to the usually studied quetiapine range ( $\leq$  800 mg).

In order to assess potential links between use of high vs. low lorazepam dosage and relevant clinical variables, preliminary screening with Pearson correlations and Bonferroni correction for quantitative variables and Chi-squares tests for categorical variables were completed. Variables identified by these means were then included in a multiple regression. A logistic regression was carried out to assess the quetiapine discharge dosage in relation to quetiapine and lorazepam doses given during the hospitalization. For all analyses a significance level of  $p \leq 0.05$  was used.

**Table 1: Sociodemographic and clinical characteristics**

Patients (n)	39
Female (n, %)	17 (43.6%)
Age, years (mean $\pm$ SD.)	36.8 $\pm$ 10.5
Numbers of previous hospitalization (mean $\pm$ SD)	15.7 $\pm$ 16.7
Hospitalizations for manic or mixed episode (n)	78
Bipolar I (n)	40
Schizoaffective, bipolar type (n)	38
Actual comorbidity with a substance dependence (n, %)	17 (34%)
Number of hospitalizations during the studied period (mean $\pm$ SD.)	3.6 $\pm$ 3
Manic episode (n, %)	48 (61.5%)
Mixed episode (n, %)	30 (38.5%)
Presence of psychotic symptoms (n, %)	32 (41.0%)
Duration in days (mean $\pm$ SD; median)	30.5 $\pm$ 30.3; 20
Compulsory hospitalization (n, %)	27 (34.6%)
Seclusion during the hospitalization (n, %)	33 (42.3%)
Entry MAS score for mania (mean $\pm$ SD)	18.2 $\pm$ 6
Entry MAS score for mixed episode (mean $\pm$ SD)	21.9 $\pm$ 7.8
Entry MADRS score for mixed episode (mean $\pm$ SD)	21.9 $\pm$ 6.6
Discharge MAS score for mania (mean $\pm$ SD)	6.0 $\pm$ 4.3
Discharge MAS score for mixed episodes (mean $\pm$ SD)	8.8 $\pm$ 3.4
Discharge MADRS score for mixed episodes (mean $\pm$ SD)	10.2 $\pm$ 3.9
Maximum quetiapine dosage in manic episode (mean $\pm$ SD; median)	655 $\pm$ 385; 600
Maximum quetiapine dosage in mixed episode (mean $\pm$ SD; median)	1044 $\pm$ 500; 1000
Dosage of Quetiapine at discharge (mean $\pm$ SD; median)	516 $\pm$ 450; 400
Maximum lorazepam dosage in mg/day (mean $\pm$ SD; median)	14.5 $\pm$ 10.9; 13
Discharge lorazepam dosage (mean $\pm$ SD; median)	4.2 $\pm$ 4.3; 3
Lithium (n)	18
Lithium concentrations in meq/l (mean $\pm$ SD)	0.73 $\pm$ 0.20
Valproate (n)	45
Valproate concentrations in mg/dl (mean $\pm$ SD)	62.4 $\pm$ 21
Concomitant treatment with an other antipsychotic drug (n)	12
Concomitant treatment with an antidepressant (n)	7
Concomitant treatment with topiramate (n)	9
Concomitant treatment with methadone (n)	2

## Results

The sample population comprised thirty nine patients. During the studied period the included patients totaled 78 hospitalizations: 48 for mania and 30 for mixed episodes.

The socio demographic and clinical characteristics of the patients and the episodes are shown on Table 1.

When quetiapine was introduced during the hospitalization, a rapid titration scheme (200 mg at day 1, 400 mg at day 2) was initially used, and the dosage thereafter adjusted every 2-7 days, in order to optimize efficacy and tolerability.

Among the patients who had already been under quetiapine treatment at admission, the dosage was increased during the hospitalization to a dosage above than 800 mg in 12 cases (dosage range: 50 – 2100 mg/day). Lorazepam was mostly prescribed in association to quetiapine since the beginning of the treatment of a manic or a mixed episode. Lorazepam doses were adapted during the stay in most cases (69/78) every 2-5 days (dosage range: 2-80 mg/day).

Treatment response was defined as a  $\geq 50\%$  MAS respectively MADRS reduction. At discharge, 81.8% of patients with mixed states and 70.7% of patients with mania were considered responders with regard to the MAS. Likewise, 77.8% of patients with mixed states and 85.7% of patients with depressive state were considered responders with regard to the MADRS scores.

A positive linear relation was found between lorazepam dosage and respectively MAS entry score ( $p < 0.0005$ ) and maximum quetiapine dosage ( $p = 0.01$ ). Whereas this relation was negative between lorazepam dosage and presence of quetiapine before hospitalization ( $p = 0.003$ ), no statistical significant relation was found between lorazepam dosage, MADRS or episode type.

By logistic regression, the estimated odds ratio between quetiapine dosage at discharge and quetiapine dosage during the hospitalization was 3.4. Thus, patients classified in the high quetiapine dosage group during the hospitalization were roughly 3.4 times more likely to remain in the same group at discharge than those in the low quetiapine dosage group ( $p < 0.0005$ ), whereas high lorazepam dosage during hospitalization did not predict high quetiapine dosage at discharge ( $p = 0.8$ ).

## Discussion

In contradiction to preliminary reports suggesting that BZD augmentation may facilitate reducing the classical antipsychotic dose (Arana et al., 1986; Busch et al., 1989; Salzman et al., 1986; Santos et al., 1989), the present study found a positive linear relationship between quetiapine and lorazepam dosage. Furthermore, lorazepam dosage was not associated with MADRS scores but with MAS scores reflecting severity of manic symptoms. Higher lorazepam dosage seems to be used in order to control rapidly irritability, agitation, impul-

siveness, and aggression that characterize the hyper-aroused state of manic and mixed episodes (Vieta et al., 2005). At discharge, most patients with mania were considered responders with regard to the MAS, which probably means, that the treatment strategy used was helpful for most patients.

One can hypothesize that the simultaneous increase in both quetiapine and lorazepam dosages reflects parallel action as well as different length of action on the core symptoms of mania and mixed states. In addition, the fact that patients treated by quetiapine before hospitalization require lower lorazepam dosage during the hospitalization may lead to consider that they are easier to treat, possibly because quetiapine is already acting.

High quetiapine dosage during hospitalization predicts high quetiapine dosage at discharge whereas high lorazepam dosage does not. Lorazepam dosage may rather be determined by the need of sedation, which declines at discharge. A question should arise: Why clinicians have used lorazepam, which has sedative properties, in association with quetiapine, a drug that has antipsychotic properties, but also relatively strong sedating effects? It is probably due to clinician expectation to reduce antipsychotic dosage and side effects in relation to quetiapine. An additive sedative effect will probably also be expected. In the present naturalistic study, lorazepam was concomitantly prescribed with quetiapine since the beginning of the treatment of the episode. Doses of both quetiapine and lorazepam were then adapted to clinical response. Expectations related to this strategy seem not to be supported by the present study. Lorazepam augmentation of quetiapine treatment does not lead to a reduction of the antipsychotic dose.

Some limitations have to be considered when interpreting the results of the present study. Especially, it used an open label retrospective design, and the observation period was limited to the hospitalization period. Further studies with prospective comparison of respectively high and low lorazepam and quetiapine dosage is needed in order to determine with more precision adequate dosages and their relation to admission as well as discharge symptoms.

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