Quetiapine augmentation for depression: dosing pattern in routine practice

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This study investigated the dosing patterns of quetiapine augmentation (QA) for major depressive disorder (MDD) in routine practice. Between 1 January 2009 and 31 May 2013, patients with a diagnosis of MDD who were receiving QA in conjunction with an ongoing antidepressant were recruited into this study. The electronic medical records and clinical data for a total of 977 patients were reviewed up to a year. Almost half the patients maintained QA treatment for more than 3 months. The mean duration of QA was ~6 months, and the mean initial and maintenance doses were 23.6 and 40.7 mg/day, respectively (range = 12.5–400 mg/day). The most frequent adverse events observed were somnolence, followed by dry mouth and lethargy. Our results indicate that the actual doses of QA for MDD in routine practice should be lower than the doses used in placebo-controlled clinical trials and those recommended by a regulatory agency. Adequately powered and well-controlled prospective studies are needed to better understand the exact role of low doses of QA in the treatment of MDD, particularly in routine practice. *Int Clin Psychopharmacol* **30:54–58**

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Introduction

Quetiapine has been approved for the treatment of major depressive disorder (MDD) as augmentation therapy in 2009. The efficacy of quetiapine augmentation (QA) has been shown in identically designed (150, 300 mg/day, and placebo), two pivotal 6-week, placebo-controlled randomized clinical trials (RCTs) (Bauer *et al.*, 2009; El-Khalili *et al.*, 2010) and other additional RCTs. In such trials (McIntyre *et al.*, 2007; Chaput *et al.*, 2008; Garakani *et al.*, 2008; Bauer *et al.*, 2009; El-Khalili *et al.*, 2010), mixed efficacy of quetiapine has been observed across the doses (150 and 300 mg/day) in both pivotal trials (Bauer *et al.*, 2009; El-Khalili *et al.*, 2010). The primary endpoint was a mean change in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score from baseline. Significant superiority over placebo was observed in both strengths in one study (Bauer *et al.*, 2009), whereas it was only observed in quetiapine extended release (XR) 300 mg/day, but not in quetiapine XR 150 mg/day in the other study (El-Khalili *et al.*, 2010). Similarly, the remission rate was significantly higher in 150 mg/day quetiapine XR (36.1%) compared with placebo (23.8%), whereas it was numerically higher in 300 mg/day quetiapine XR (31.1%) compared with placebo in the later study (Bauer *et al.*, 2009); however, the remission rates were significantly higher with 300 mg/day quetiapine XR (46.2%) than placebo (24.5%), but not for 150 mg/day quetiapine XR (35.0%) in the former study (El-Khalili *et al.*, 2010). However, according to subsequent pooled studies (Bauer *et al.*, 2010), both doses proved to have superior efficacy compared with placebo in terms of MADRS score change as well as response and remission rates (Bauer *et al.*, 2010) irrespective of the ongoing antidepressant type (Bauer *et al.*, 2014). One of the crucial limitations of these two pivotal trials was that they used only two fixed doses, not reflecting real clinical practice where clinicians should adjust the dose to maintain patients with maximal efficacy along with minimal adverse events (AEs). It can be assumed that some patients with MDD in these studies may have received a dose of quetiapine XR that was either too high or too low; in fact, the minimal effective dose could not be found. Therefore, the proper dosing of QA for the treatment of MDD calls for further investigation.

According to a recent large study with prescription-claim data in routine practice (Jing *et al.*, 2013), the mean dose of QA at 2010 was 123 mg/day, which is lower than that recommended by the US FDA. In this context, previous studies investigating the use of atypical antipsychotics in routine practice have also clearly shown that prescribed doses for a particular drug may differ considerably from those recommended on the package insert label and results from RCTs (Hartung *et al.*, 2008).

RCTs are considered the gold standard for proving the efficacy of a drug; however, inherent pitfalls that do not

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properly incorporate busy real-world practice situations may limit the generalization of such results into routine practice (Marks *et al.*, 2009; Pae *et al.*, 2012). Hence, investigation of real-world practice relating to certain clinical issues would enable clinicians to address how to efficiently utilize certain medications under approved indications. Hence, the present investigation attempted to find the dosing trend of QA during the treatment of patients with MDD in routine practice.

Methods

Between 1 January 2009 and 31 May 2013, patients with a diagnosis of MDD who were receiving QA in conjunction with an ongoing antidepressant were recruited for this study. Depression was defined according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) using Clinical Modification codes F32.X (not including F33.X and F31.X). The strengths of quetiapine utilized in our clinical practice include XR and immediate release (IR) as follows: 25 and 100 mg = IR; 200, 300, and 400 mg = XR.

Data for all patients were collected from the electronic medical records (EMR) of a specialized depression outpatient clinic (OPC) at a university-affiliated hospital. A new prescription (index prescription point) of quetiapine was defined as the first prescription of this drug with the patient having had no previous prescriptions for QA. The follow-up visit to the OPC was verified using the prescription date and the actual days of prescription. Following data collection, each patient was tracked for up to 1 year after the index prescription point. Follow-up data collection was discontinued if the patient switched to another augmentation agent, did not receive further QA, and was observed to have poor compliance (on the basis of EMR description: less than 70% intake of immediate previous prescription pills), or had a gap between OPC visits of longer than 1 month. All data were collected independently by two investigators and subsequently verified and approved for data mining by the same investigators. EMRs were reviewed for the following clinical and demographic variables: age; sex; duration of QA; type of current episode (first onset or recurrence); mean initial and maintenance doses along with dose range of QA; presence of previous treatment strategy; type of current antidepressant; duration of illness; AEs; and continuation or discontinuation of quetiapine as of 3 months after QA initiation. The average daily dose of QA was calculated as the sum of the number of pills per day multiplied by dose and then divided by the sum of the number of days of prescription. Duration of QA was calculated using the total sum of prescription days.

The Bucheon St Mary's Hospital Institutional Review Board approved the study and all data were collected using data extraction forms with deidentified features of the patients (IRB approval number: HC13RISI0073).

Descriptive statistics are presented as mean (SDs) and numbers (percentage) for continuous and categorical variables, respectively. Statistical analysis was carried out using NCSS 2007 Power Analysis and Sample Size Software (NCSS; LLC, Kaysville, Utah, USA).

Results

On the basis of the selection criteria, the EMRs of 977 patients were reviewed, and their clinical and demographic data were collected (Table 1). The majority of patients were women (~60%), mean age 51 years. The most frequently used ongoing antidepressant agents were escitalopram, followed by paroxetine and venlafaxine. Approximately one-third of the patients had a history of different treatment strategies, such as antidepressant switching/combination therapy, for improvement of clinical outcomes. The mean duration of QA was ~6 months; the mean time to the first increase of the quetiapine dose was ~1 week and the mean initial and maintenance doses of quetiapine were 23.6 and 40.7 mg/day (range from 12.5 to 400 mg/day), respectively. Interestingly, almost half the patients still

Table 1 Clinical parameters in the present study ($n = 977$)

Clinical parameters	Values
Sex[a]	Female [588 (60.2)]
Age (years)	51.1 (17.4)[b]
Antidepressants[a]	
Escitalopram	200 (20.5)
Paroxetine	180 (18.4)
Venlafaxine	162 (16.6)
Sertraline	156 (16.0)
Duloxetine	124 (12.7)
Mirtazapine	61 (6.2)
Fluoxetine	49 (5.0)
Tianeptine	37 (3.8)
Bupropion	8 (0.8)
Recurrent episode	679 (69.5)[a]
Presence of past treatment strategies	340 (34.8)[a]
Switching	145 (42.6)
Combination	118 (34.7)
Augmentation	77 (22.6)
Duration of illness (days)	525.6 (872.3)[b]
Time to increasing the initial dose of quetiapine (days)	8.5 (3.5)[b]
Discontinuation of quetiapine 3 months after initiation	495 (50.7)[a]
Duration of treatment (days)	150.1 (141.4)[b]
Initial dose (mg/day)	23.6 (19.2)[b]
Maintaining dose (mg/day)	40.7 (38.9)[b]
Dose range	
Minimal dose	12.5
Maximal dose	400
Adverse events[a]	
Somnolence	386 (39.5)
Dry mouth	379 (38.8)
Lethargy	212 (21.7)
Concentration difficulty	136 (13.9)
Dizziness	126 (12.9)
Headache	121 (12.4)
Weight gain	109 (11.2)
Anxiety	102 (10.4)
Constipation	97 (9.9)
Dyspepsia	69 (7.1)

Data are represented as [a]*n* (%) by the property of the variables; [b]mean (SD).

maintained QA without termination 3 months after initiation. The most frequent AEs were somnolence, followed by dry mouth and lethargy. Other frequent AEs included difficulty in concentration, dizziness, headache, weight gain, anxiety, constipation, and dyspepsia. No patient had been on any medications to relieve extrapyramidal symptoms.

Discussion

The present findings indicate that the actual doses of QA in routine practice should be much lower than those recommended by a regulatory authority and the findings from RCTs. In line with our findings, a recent large claim-base study using data from 2006 through 2010 ($n = 8026$) (Jing *et al.*, 2013) found that the mean daily doses of QA (129, 139, 137, 136, and 123 mg/day in 2006, 2007, 2008, 2009, and 2010, respectively) were consistently lower than those recommended by the US FDA (150–300 mg/day) and results from previous RCTs. In addition, the proportion of patients receiving QA at less than 150 mg/day was ~71% in 2010, whereas the proportion receiving quetiapine at higher than 300 mg/day was only 5% in 2010. This trend was also replicated in our previous study that investigated the dosing trend of aripiprazole augmentation (AA) in routine practice, where the maintenance dose of AA was 4.4 mg/day significantly lower than those recommended by the US FDA (10–15 mg/day) and results from previous RCTs (Pae *et al.*, 2014).

Although the two RCTs evaluating QA utilized fixed doses of 150 and 300 mg/day (Bauer *et al.*, 2009; El-Khalili *et al.*, 2010), the efficacy findings did not support more beneficial effects of a higher dose of QA versus a lower dose (Bauer *et al.*, 2009; El-Khalili *et al.*, 2010; Han *et al.*, 2013). Similarly, there has been an increase in recent studies reporting the beneficial effects of lower doses of AA for the treatment of MDD particularly in Asian regions (Lin *et al.*, 2011; Pae *et al.*, 2011; Chen *et al.*, 2012; Han and Pae, 2013; Kamijima *et al.*, 2013; Pae and Patkar, 2013; Pae *et al.*, 2013; Patkar and Pae, 2013). In fact, the first large RCT of AA for an Asian population (Kamijima *et al.*, 2013) has also found that a lower dose (3 mg/day) of AA should be more useful than a higher dose (mean dose = 9.8 mg/day) in terms of the risk and benefit aspect; however, such beneficial effects of lower dose of AA were not replicated in Western population studies (Mischoulon *et al.*, 2012). Similarly, the efficacy of quetiapine XR of 50 mg/day as monotherapy was also proven in a three-dose arm study (Weisler *et al.*, 2009) and it was also different from placebo in the change in the MADRS total score from baseline by day 4. Such positive results with lower doses of quetiapine XR call for further investigations on the clear role of low-dose QA (e.g. < 150 mg) for the treatment of MDD. In fact, quetiapine XR doses of 100 and 200 mg/day were not tested in such previous trials.

We may speculate on the discrepancy in the use of QA between routine practice and existing RCTs. Our findings may reflect the carefulness of clinicians to minimize the potential AEs associated with QA. In this context, a series of meta-analysis have consistently shown the safety and tolerability issues of QA (Nelson and Papakostas, 2009; Wen *et al.*, 2014). For instance, the odds ratio of QA for discontinuation because of AEs was 4.85, which is markedly higher than those of other individual atypical antipsychotic and the whole antipsychotics together (aripiprazole = 2.38, olanzapine = 3.85, risperidone = 1.55, and whole antipsychotics = 3.32) (Wen *et al.*, 2014). Indeed, the discontinuation rate of QA (20.9%) for any reason was also markedly higher than those from other antipsychotics (AA = 12.1%, risperidone augmentation = 16.3) (Nelson and Papakostas, 2009; Kamijima *et al.*, 2013). Although the dosages of 50, 150, and 300 mg/day of quetiapine XR were generally tolerated in clinical trials, the overall incidence of AEs and discontinuation rates had a trend toward a higher proportion in the quetiapine XR treatment groups in a dose-dependent manner compared with placebo treatment groups (Bauer *et al.*, 2010; Bauer *et al.*, 2014). In addition, quetiapine has been well-known to increase the risk of metabolic syndrome and weight gain; a recent meta-analysis has proven that the use of antipsychotics in patients with MDD was a significant moderator for increased prevalence of metabolic syndrome (prevalence rate in MDD = 30.5%) (Vancampfort *et al.*, 2013). In fact, with low doses of quetiapine, even when prescribed as a sedative for insomnia, metabolic AEs can occur and should be considered in the overall benefit to risk analysis (Coe and Hong, 2012). In routine practice, comorbidity issues associated with drug–drug interactions increasing AEs may have also influenced the prescription pattern of QA. From another perspective, it should be reasonable to assume that low-dose QA was used to treat specific symptoms of MDD, such as sleep disturbance, agitation, irritability, or anxiety, as proposed in previous studies (Maglione *et al.*, 2011; Carney, 2013; Jing *et al.*, 2013). Prescription patterns of clinicians in the effectiveness and safety of QA in clinical practice may differ because of the heterogeneity of patient populations (age, concomitant drug, duration of illness, family history and comorbid psychiatric symptoms, etc.) from those expected from clinical trials as evidenced from the existing literature (Martin *et al.*, 2005). Because of the different genetic backgrounds of Asian and Western populations on CYP3A4 (e.g. 1B allele), ethnic differences potentially leading to different plasma levels with the same dose must be considered when investigating the metabolism of quetiapine (Chowbay *et al.*, 2005). Currently, QA is partly approved for the treatment of MDD even in Asian populations. Thus, more data collected from routine practices in Asian and Western countries will help to identify whether there may be actual differences in the prescription of quetiapine for the treatment of MDD and

may prompt the establishment of a minimal effective dose of QA for MDD.

This retrospective study has clear limitations such as the follow-up period, inherent shortcomings of EMR, association between the doses and clinical severity. This study was not designed prospectively; thus, the exact reasons for different QA dose titration patterns during the follow-up period could not be identified. Other limitations are the lower validity of a retrospective study, potential bias caused by the investigator, underlying cost issues, the failure to assess the degree of treatment resistance, and the difficulty in dose assessment in the EMR. In addition, quetiapine XR has differential pharmacokinetic effects; that is, sustained drug exposure with once-daily dosing, a faster dose titration, and different tolerability profiles such as a lower intensity of sedation than quetiapine IR. In fact, these differences may also affect the dosing pattern of clinicians as reported in some studies (Eriksson *et al.*, 2012). Thus, mixed use of IR and XR formulations may be another shortcoming of the present study. One-third of the patients had been trialed on a switching, combination, and augmentation strategy based on our EMR; however, we could not define whether these populations were exactly treatment resistant or not because of the inherent pitfall of EMR study. Finally, these data are based on information from only one university-based hospital and only on the basis of OPC treatment; thus, we cannot generalize the present findings to all types of clinical practice.

Conclusion

The current findings suggest that the actual doses of QA used in routine clinical practice may be on the much lower end of the spectrum relative to US FDA recommendations and that the dosing patterns differ from those in RCTs. This discrepancy should be addressed in future well-designed and adequately powered pragmatic clinical studies.

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Conflicts of interest

There are no conflicts of interest.

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