Results from a drug utilization study of extended release quetiapine fumarate prescribed by psychiatrists as treatment for major depressive disorder in selected countries in the European Union
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This multicenter, observational drug utilization (DU) study (NCT01594996) investigated the profile of patients and specialist providers who prescribed extended release quetiapine fumarate (quetiapine XR) for treatment of major depressive disorder (MDD) across five European countries (Germany, Italy, Romania, Spain, and Sweden). A DU data abstraction form captured information on the characteristics of physicians, patients, and drugs utilized in the medical management of depressive episodes in MDD, where the therapeutic regimen included quetiapine XR. Data were reported descriptively. This analysis included 811 patients. Psychiatric histories indicated a burden of severe MDD in these patients. Patient demographics were similar across countries; however, those in Sweden had a younger mean age. Physicians’ ratings of the therapeutic effect of prior treatment with antidepressants suggested the need for an add-on treatment for most patients. Overall, 15.7% of patients initiated quetiapine XR treatment as monotherapy. Presence of psychotic symptoms during depressive episodes predicted treatment with higher than recommended doses of quetiapine XR (odds ratio = 3.11; 95% confidence interval: 1.6–6.0). This analysis demonstrated similarities in DU across the countries analyzed, largely in accordance with the recommended dose of quetiapine XR as an adjunctive therapy to antidepressants in MDD (50–300 mg/day). Int Clin Psychopharmacol 33:59–65 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.

International Clinical Psychopharmacology, 2018, 33:59–65

Keywords: drug utilization, European Union, major depressive disorder, prescribing, extended release quetiapine

Introduction
In recent epidemiologic reviews of the global burden of disease, major depressive disorder (MDD) was ranked as the second leading cause of years lost to disability (YLDs) (Ferrari et al., 2013; Global Burden of Disease Study 2013 Collaborators, 2015), accounting for 8.2% of total YLDs (Ferrari et al., 2013). The impact on YLDs was greater for females than for males and in those aged 15–64 years compared with other age groups (Ferrari et al., 2013), however, the direct burden of MDD relative to other conditions varied by country and region (Global Burden of Disease Study 2013 Collaborators, 2015).

Key goals of treatment for patients with MDD are to reduce disease symptoms and improve functional impairment, quality of life, and lost work productivity. Treatment recommendations vary according to the type and severity of depression, previous treatment history, and presence of other coexisting psychiatric diagnoses. Therapy should be reviewed for patients with MDD who have not responded to antidepressant treatment or have experienced a partial response to acute treatment (4–8 weeks), require a switch to a new drug, or require augmentation (adjunctive/add-on) of the existing therapy (American Psychiatric Association, 2010).

The atypical antipsychotic extended release quetiapine fumarate (quetiapine XR) has been approved in the European Union (EU) since 2010 as an add-on treatment for patients with MDD who have a suboptimal response to prior antidepressant treatment with a single agent (European Medicines Agency, 2010). The recommended dose for quetiapine XR in MDD is 50–300 mg/day (AstraZeneca, 2017).

Postmarketing drug utilization (DU) studies are routinely performed to evaluate drug prescribing patterns in order to inform healthcare decision-making. This DU study
was conducted to characterize the profile of patients who are prescribed quetiapine XR for the treatment of MDD and investigate treatment practices surrounding the use of quetiapine XR in the selected countries that were broadly representative of the geographic regions in the EU.

**Methods**

**Study design and participants**

This was a multicenter, retrospective, observational study (D1443C000057; ClinicalTrials.gov identifier: NCT01594996) that investigated antidepressant DU across five European countries (Germany, Italy, Romania, Spain, and Sweden). The patient cohort consisted of individuals under specialist (psychiatric) care, who were prescribed quetiapine XR for major depressive episodes associated with MDD. The data collected on physicians’ practices included years in practice, practice setting, proportion of patients with MDD in the practice, and, for those with hospital privileges, the number of beds devoted to psychiatric care in those hospitals.

Central Ethics Committee approval was received in all five countries before the start of the study. A Scientific Advisory Board (SAB) for this study, comprising independent, external psychiatrists from each of the five participating European countries, provided scientific advice regarding the protocol and conduct of the study, and also advised on physician recruitment so that the selected population included in the study was representative of the distribution in each country. In addition, the SAB also provided country-specific context regarding psychiatric practice relevant to the study.

Study objectives were to document the characteristics of the patients, investigate clinical practices related to quetiapine XR use, and evaluate differences in DU between countries.

**Assessments**

At each center, patients initiating treatment with quetiapine XR within a 9-month period (3–12 months post-launch of quetiapine XR as a treatment for MDD in each country) were eligible for inclusion. During the first 3 months following launch of quetiapine XR in each country, physicians may not have been aware of the approval of quetiapine XR for an add-on treatment for MDD. Therefore, patients treated with quetiapine XR within the 3 months after launch were not included because they were not likely to be representative of the patients treated in subsequent periods.

The inception dates, defined as the date corresponding with 3 months post-launch of quetiapine XR, were as follows: Germany: 1 January 2011; Sweden: 1 April 2011; Spain: 1 May 2011; Romania: 1 August 2011; and Italy: 1 December 2011.

A drug utilization questionnaire (DUQ) was used to capture information on the characteristics of physicians, patients, and the drugs utilized in the medical management of depressive episodes in MDD where the therapeutic regimen included quetiapine XR. Investigators completed the physician section of the DUQ, and study monitors extracted data from these physician-completed questionnaires. Study monitors had direct access to medical records and other related information for patients who had provided informed consent. Patient DU data were extracted by monitors at each study site.

The DUQ was tested in a pilot study and modified on the basis of the pilot study findings and recommendations of the SAB.

**Statistical analysis**

Data obtained from the DUQ are reported descriptively according to individual country and overall. For continuous variables, the number of responses, mean, median, minimum, maximum, and SD were obtained. For discrete variables, the number and percentage of observed responses and proportion of each category represented are summarized. Two-sided 95% confidence intervals are provided for the proportion of patients prescribed a specified daily dose of quetiapine XR for each country and collectively overall.

Adverse event (AE), serious AE, and other safety data were not collected. Investigators were directed to report any AEs noted during routine medical practice, according to the standard spontaneous reporting procedures for marketed products in the country. As such, no safety analyses were conducted.

Exploratory analyses were performed using multivariate modelling to identify predictive factors for prescribing quetiapine XR as monotherapy.

**Results**

**Disposition**

In total, 103 sites screened 1119 patients, with recruitment of prescribers and patients lower than expected in Italy, Germany, and Spain, and much lower than expected in Sweden. Of these, 247 patients were not enrolled because of ineligibility (reasons included quetiapine XR not prescribed for MDD, quetiapine XR prescribed but not administered, and quetiapine XR treatment initiated beyond the inception period) and 58 patients for the lack of consent to participate (Fig. 1). Of the 814 patients enrolled, three were excluded from the analysis (data on quetiapine XR missing). Therefore, the final analysis population comprised 811 patients: Germany (n = 152); Italy (n = 105); Romania (n = 327); Spain (n = 196); and Sweden (n = 31).

**Physician and practice characteristics**

Seventy-six sites reported physician and practice details; of these, 75 sites recruited patients for the study (one site in Sweden did not enroll any patients): Germany (n = 15);
The mean length of time that the patient was seen by the investigator (time from when the patient was first seen by the investigator to the local inception date) was 2.2 years (SD: 1.26 years in practice was 24.6 (SD: 9.10).} of years in practice was 24.6 (SD: 9.10).

Physician assessment of the prior antidepressant treatment at the time of quetiapine XR initiation are presented in Table 3. Physicians’ Clinical Global Impression ratings of the therapeutic effect of prior antidepressant regimens before treatment with quetiapine XR were selective serotonin reuptake inhibitors (SSRIs) (24.3%), other atypical antidepressants [except serotonin–norepinephrine reuptake inhibitors (SNRIs)] (19.7%), and SNRIs (18.4%). The most common psychoactive drugs (other than antidepressants) prescribed for MDD before quetiapine XR included anxiolytics (29.1%) and other atypical antipsychotics (21.5%); this was apparent across all countries included in the analysis.

The physicians’ ratings of patients’ prior antidepressant therapy at the time of quetiapine XR initiation were categorized as ‘minimal improvement’ in 22.5% or ‘unchanged or worse’ in 32.4% of patients. Physician assessment of the prior antidepressant therapy at the time of quetiapine XR initiation were categorized as ‘minimal improvement’ in 22.5% or ‘unchanged or worse’ in 32.4% of patients.

Patients’ psychiatric histories were similar across the five countries. The mean time interval from diagnosis of MDD to start of quetiapine XR treatment was 4.7 (SD: 7.33) years, with the shortest interval recorded in Romania [8.3 (SD: 10.65) years] (Table 2). At the time of initiating quetiapine XR treatment, the majority of patients (68.4%) with data available had previously experienced at least three depressive episodes. In the population included in the analysis, the most common psychiatric comorbidity was anxiety (range: 17.8–80.0% of patients). All patients in the study had been hospitalized for MDD at least once, but no clear trend in the number of hospitalizations for MDD was observed [35.3% (n = 85/241) of patients had one hospitalization for MDD, 25.3% (n = 61/241) of patients had two hospitalizations for MDD, and 39.4% (n = 95/241) of patients had three or more hospitalizations for MDD].

Overall, 187 (29.8%) out of 628 patients with data available experienced psychotic symptoms during a depressive episode. A greater proportion of patients in Romania (42.0%) experienced psychotic symptoms during any depressive episode compared with the other countries (range: 11.5–33.0%).

Medications used by patients for the treatment of MDD in the 12 months before initiation of treatment with quetiapine XR are shown in Table 3. Overall, the three most common subclasses of antidepressants prescribed before quetiapine XR were selective serotonin reuptake inhibitors (SSRIs) (24.3%), other atypical antidepressants [except serotonin–norepinephrine reuptake inhibitors (SNRIs)] (19.7%), and SNRIs (18.4%). The most common psychoactive drugs (other than antidepressants) prescribed for MDD before quetiapine XR included anxiolytics (29.1%) and other atypical antipsychotics (21.5%); this was apparent across all countries included in the analysis.

The physicians’ ratings of patients’ prior antidepressant therapy at the time of quetiapine XR initiation were presented in Table 3. Physicians’ Clinical Global Impression ratings of the therapeutic effect of prior antidepressant regimens before treatment with quetiapine XR were categorized as ‘minimal improvement’ in 22.5% or ‘unchanged or worse’ in 32.4% of patients. Physician assessment of the prior antidepressant therapy at the time of quetiapine XR initiation were presented in Table 3. Physicians’ Clinical Global Impression ratings of the therapeutic effect of prior antidepressant regimens before treatment with quetiapine XR were categorized as ‘minimal improvement’ in 22.5% or ‘unchanged or worse’ in 32.4% of patients.
treatment was rated as ‘unchanged or worse’ in 96.6% of patients in Italy but only in 10.7% of patients in Germany.

### Treatment patterns

Table 4 presents quetiapine XR treatment patterns and DU indices by country. Overall, similarities in DU were

| Country | Germany (N=152) | Italy (N=105) | Romania (N=327) | Spain (N=196) | Sweden (N=31) | Total (N=811) |
|---------|----------------|--------------|-----------------|--------------|--------------|---------------|
| **Age at start of treatment with quetiapine XR (years)** | | | | | | |
| Mean (SD) | 52.7 (14.26) | 51.4 (14.16) | 52.6 (11.13) | 48.6 (14.33) | 43.0 (12.93) | 51.1 (13.21) |
| Median | 52.1 | 50.6 | 53.4 | 47.9 | 41.9 | 51.6 |
| **Sex [n [%]]** | | | | | | |
| Male | 66 (66.0) | 27 (25.7) | 72 (22.0) | 64 (32.7) | 7 (22.6) | 236 (29.1) |
| Female | 86 (56.6) | 78 (74.3) | 255 (78.0) | 132 (67.3) | 24 (77.4) | 575 (70.9) |
| **Two most commonly recorded psychiatric disorders in each country in addition to MDD [n [%]]** | | | | | | |
| Anxiety | 84 (52.9) | 173 (52.9) | 123 (62.8) | 16 (51.6) | 423 (52.2) |
| Alcohol abuse | 31 (20.4) | – | – | – | 75 (9.2) |
| Other Axis I disorder | 54 (35.5) | – | – | 11 (35.5) | 174 (21.5) |
| Other Axis II disorder | 18 (17.1) | – | – | 57 (29.1) | – | 133 (16.4) |
| **Time interval from MDD diagnosis to start of quetiapine XR treatment (years)^[a,c]** | | | | | | |
| Mean (SD) | 4.8 (9.58) | 8.3 (10.65) | 2.9 (4.27) | 4.6 (6.43) | 5.1 (9.22) | 4.7 (7.33) |
| 95% CI | 2.2–7.5 | 6.0–10.7 | 2.3–3.9 | 3.9–5.8 | 0.9–9.3 | 4.0–5.3 |
| Median | 1.8 | 3.9 | 0.9 | 1.9 | 1.9 | 1.4 |
| Minimum, maximum | 0.0, 56.2 | 0.0, 48.3 | 0.0, 33.8 | 0.0, 77.1 | 0.0, 105.0 | 1.0, 56.2 |
| **Depressive episodes experienced in lifetime [n [%]]^[d]** | | | | | | |
| 0 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.6) | 0 (0.0) | 1 (0.1) |
| 1 | 12 (16.0) | 10 (11.8) | 30 (16.5) | 42 (25.4) | 2 (11.1) | 96 (18.5) |
| 2 | 10 (13.3) | 8 (9.4) | 24 (13.2) | 24 (15.1) | 1 (5.6) | 67 (12.9) |
| ≥3 | 53 (70.7) | 67 (78.8) | 128 (70.3) | 92 (57.9) | 15 (83.3) | 355 (88.4) |
| Unknown | 77 | 20 | 145 | 37 | 13 | 292 |
| **Hospitalizations for MDD [n [%]]^[e]** | | | | | | |
| 0 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 1 | 36 (37.1) | 16 (50.0) | 22 (24.4) | 8 (57.1) | 3 (37.5) | 85 (35.3) |
| 2 | 31 (32.0) | 15 (51.5) | 15 (51.5) | 20 (22.6) | 1 (5.6) | 61 (25.3) |
| ≥3 | 30 (30.9) | 11 (34.4) | 48 (53.3) | 2 (14.3) | 4 (50.0) | 95 (39.4) |
| Unknown | 55 | 237 | 182 | 23 | 570 | |

**Cl**, confidence interval; MDD, major depressive disorder; XR, extended release.

^[a]Start of quetiapine XR treatment was before MDD diagnosis for three patients.

^[b]Observed number of cases [n [%]] were: Germany, 52 (34.2); Italy, 84 (80.0); Romania, 196 (59.9); Spain, 172 (87.8); Sweden, 21 (67.7); and total 525 (64.7).

^[c]Percentages calculated excluding patients with ‘unknown’ history.

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**Table 2 Patients’ demographics and psychiatric medical history at start of treatment with quetiapine XR, by country**

| Country | Germany (N=152) | Italy (N=105) | Romania (N=327) | Spain (N=196) | Sweden (N=31) | Total (N=811) |
|---------|----------------|--------------|-----------------|--------------|--------------|---------------|
| **Practice location** | | | | | | |
| Urban center | 11 (73.3) | 14 (100.0) | 20 (100.0) | 14 (87.5) | 7 (83.6) | 66 (86.8) |
| Suburban | 1 (6.7) | 0 (0.0) | 0 (0.0) | 1 (6.3) | 2 (18.2) | 4 (5.3) |
| Rural | 3 (20.0) | 0 (0.0) | 0 (0.0) | 1 (6.3) | 2 (18.2) | 6 (7.9) |
| **Practice setting** | | | | | | |
| General hospital | 2 (13.3) | 3 (21.4) | 1 (5.0) | 1 (6.3) | 3 (27.3) | 10 (13.2) |
| University hospital | 5 (33.3) | 10 (71.4) | 5 (25.0) | 2 (12.5) | 2 (18.2) | 24 (31.6) |
| Mental health center | 2 (13.3) | 1 (7.1) | 2 (10.0) | 7 (43.8) | 1 (9.1) | 13 (17.1) |
| Other open care | 0 (0.0) | 0 (0.0) | 4 (20.0) | 1 (6.3) | 2 (18.2) | 7 (9.2) |
| **Hospital facilities** | | | | | | |
| Private office | 5 (33.3) | 0 (0.0) | 8 (40.0) | 3 (18.6) | 2 (18.2) | 18 (23.7) |
| Mixed | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (12.5) | 1 (8.1) | 3 (3.8) |
| Other | 1 (6.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.3) |

| Country | Germany (N=152) | Italy (N=105) | Romania (N=327) | Spain (N=196) | Sweden (N=31) | Total (N=811) |
|---------|----------------|--------------|-----------------|--------------|--------------|---------------|
| **Length of time patient was seen by investigator (years)^[b]** | | | | | | |
| Mean (SD) | 1.0 (2.47) | 2.0 (3.71) | 1.8 (3.39) | 4.4 (6.75) | 0.4 (1.26) | 2.2 (4.50) |
| Median | 52.1 | 50.6 | 53.4 | 47.9 | 41.9 | 51.6 |

XR, extended release.

^[a]One site in Sweden (site 100) reported physician and practice characteristics but did not enroll any patients.

^[b]Time from when a patient was first seen by the investigator to the inception date for each country.
Table 3 MDD medications prescribed 12 months before initiation of quetiapine XR, and Clinical Global Impression of antidepressant treatment before quetiapine XR treatment, by country

| Country | Germany (N = 152) | Italy (N = 105) | Romania (N = 327) | Spain (N = 196) | Sweden (N = 31) | Total (N = 811) |
|---------|------------------|----------------|------------------|----------------|----------------|----------------|
| Prior MDD medication* | | | | | | |
| Antidepressant drugs | | | | | | |
| Tricyclic antidepressant | 27 (17.8) | 6 (5.7) | 6 (1.8) | 18 (9.2) | 1 (3.2) | 58 (7.2) |
| SSRIs | 37 (24.3) | 10 (9.5) | 64 (19.6) | 203.9 (155.0) | 50 (25.5) | 197 (24.3) |
| Other atypical antidepressant (except SNRIs) | 40 (26.3) | 6 (5.7) | 59 (18.0) | 50 (25.5) | 5 (16.1) | 160 (19.7) |
| SNRIs | 27 (17.8) | 12 (11.4) | 50 (15.3) | 51 (26.0) | 9 (29.0) | 149 (18.4) |
| Other psychoactive drugs | | | | | | |
| Conventional antipsychotics | 17 (11.2) | 4 (3.8) | 14 (4.3) | 7 (3.6) | 0 (0) | 42 (5.2) |
| Atypical antipsychotics | 84 (55.6) | 26 (24.8) | 58 (17.7) | 31 (15.8) | 5 (16.1) | 174 (21.5) |
| Mood stabilizers | 10 (6.6) | 6 (5.7) | 34 (10.4) | 19 (9.7) | 0 (0) | 69 (8.5) |
| Anxiolytics | 28 (17.1) | 17 (16.2) | 102 (31.2) | 90 (45.8) | 1 (3.2) | 236 (29.1) |
| Sedatives/hypnotics | 14 (9.2) | 3 (2.9) | 43 (13.1) | 24 (12.2) | 0 (0.0) | 84 (10.4) |

Clinical Global Impression of antidepressant treatment before quetiapine XR – therapeutic effect
| | Marked vast improvement | Moderate improvement | Minimal improvement | Unchanged or worse |
| | 30 (20.8) | 61 (50.0) | 30 (24.6) | 13 (10.7) |

| Country | Germany (N = 152) | Italy (N = 105) | Romania (N = 327) | Spain (N = 196) | Sweden (N = 31) | Total (N = 811) |
|---------|------------------|----------------|------------------|----------------|----------------|----------------|
| Modal daily dose prescribed (mg)* | | | | | | |
| Mean (SD) | 140.0 (129.29) | 158.3 (133.81) | 192.4 (124.04) | 128.6 (115.89) | 135.9 (90.55) | 160.5 (126.11) |
| 95% CI | 119.2–160.7 | 132.4–184.2 | 178.9–205.8 | 112.2–144.9 | 102.3–168.7 | 151.9–169.2 |
| Median | 100.0 | 100.0 | 200.0 | 50.0 | 100.0 | 150.0 |
| Minimum, maximum | 25, 800 | 25, 800 | 25, 800 | 50, 900 | 50, 900 | 25, 900 |

Use of quetiapine XR as monotherapy at initiation of treatment [n (%)]
| Use of quetiapine XR as monotherapy at initiation of treatment | Yes | No |
|-------------------------------------------------------------|-----|----|
| 30 (20%) | 28 (18.5) | 68 (65.7) |

Use of quetiapine XR as monotherapy over course of treatment [n (%)]
| Use of quetiapine XR as monotherapy over course of treatment | Yes | No |
|-------------------------------------------------------------|-----|----|
| 24 (15.8) | 16 (8.2) | 8 (25.8) |

Dose outside recommended limits
| Dose outside recommended limits | (high) | (low) |
|--------------------------------|-------|------|
| 128 (84.2) | 128 (84.2) | 128 (84.2) |

Discontinue quetiapine XR during study observation period [n (%)]
| Discontinue quetiapine XR during study observation period | Yes | No |
|----------------------------------------------------------|-----|----|
| 19 (12.5) | 19 (12.5) |

Duration of quetiapine XR use during study period (months)
| Duration of quetiapine XR use during study period | Mean (SD) | Median |
|--------------------------------------------------|-----------|--------|
| 4.2 (2.64) | 4.4 | 5.2 |

CI, confidence interval; MDD, major depressive disorder; OR, odds ratio; XR, extended release.

*Twelve months before initiation of quetiapine XR.

Table 4 Quetiapine XR treatment patterns and drug utilization indices, by country

| Country | Germany (N = 152) | Italy (N = 105) | Romania (N = 327) | Spain (N = 196) | Sweden (N = 31) | Total (N = 811) |
|---------|------------------|----------------|------------------|----------------|----------------|----------------|
| Initial daily dose of quetiapine XR (mg) Mean (SD) | 205 (144.9) | 144.9 (102.3) | 189.9 (159.9) | 144.9 (102.3) | 195.2 (96.05) | 193.1 (129.45) |
| 95% CI | 181.9 (137.30) | 183.6 (147.53) | 212.3 (131.16) | 174.4 (110.00) | 195.2 (96.05) | 193.1 (129.45) |
| Median | 159.9–203.9 | 155.0–212.1 | 198.0–226.6 | 158.9–189.9 | 159.9–230.4 | 184.1–202.0 |
| Minimum, maximum | 25, 800 | 25, 600 | 25, 800 | 25, 900 | 25, 900 | 25, 900 |

Drug utilization of quetiapine XR in the EU

*References: Brody et al.

observed. The starting doses exceeded recommendations in the majority of patients, and maintenance doses were higher than recommended in a small proportion of patients, which differed across countries. The mean initial daily dose of quetiapine XR was 160.5 mg (SD: 126.11) and ranged from 25 to 900 mg. The mean daily dose of quetiapine XR prescribed during the study observation period was 193.1 mg (SD: 129.45), ranging from 174.4 mg (SD: 110.00) in Spain to 212.3 mg (SD: 131.16) in Romania. On the basis of a sensitivity analysis (correcting for prescription strength for 1-day overlap of more than one quetiapine XR prescription),
the proportion of patients who received doses of quetiapine XR above the recommended limit was similar in Sweden, Germany, and Italy (ranging between 11.8 and 13.3%) but different for Romania (16.5%) and Spain (7.1%) (Table 4).

Patients who experienced psychotic symptoms during depressive episodes had a 3.1-fold greater likelihood of receiving a higher than recommended dose of quetiapine XR [odds ratio (OR) = 3.11; 95% CI: 1.6–6.0] compared with those who did not experience psychotic symptoms.

Overall, 127 (15.7%) patients initiated quetiapine XR as monotherapy at a mean dose of 176.6 mg (SD: 130.4); of these, 102 (12.6%) patients remained on quetiapine XR as monotherapy during the course of the study observation period. More patients received quetiapine XR as monotherapy in Sweden and Italy than in the other three countries. A total of 684 (84.3%) patients used quetiapine XR treatment as an add-on to an antidepressant at initiation, at a mean dose of 157.6 mg (SD: 125.2).

Mean adherence to treatment, as assessed by the investigator, was 89.6% (SD: 18.47) overall and ranged from 70.8% (SD: 21.99) in Sweden to 99.3% (SD: 4.09) in Romania.

### Exploratory modelling of predictive factors for use of quetiapine XR monotherapy

A multivariate logistic regression model to identify predictive factors for quetiapine XR monotherapy was based on 692 patients and included 98 patients who were receiving quetiapine XR monotherapy at initiation of treatment. Age and prior medication were statistically significant factors in the initiation of monotherapy. Patients in older age groups (≥40 years) were less likely to be initiated on monotherapy, as indicated by ORs of less than 1.0 compared with the reference age group (patients aged <40 years) (Table 5). Although not statistically significant, patients receiving prior treatment with either tricyclic antidepressants or other antidepressants, including SSRIs and SNRIs, were more likely to be initiated on monotherapy compared with the reference group.

Other factors that were not statistically different, but appeared to be possibly predictive of use of quetiapine XR monotherapy, included the following: patients from Italy and Sweden versus other countries; the interaction of prior medication and country (a greater number of patients receiving no therapy or prior medication with tricyclics or all other psychoactive medications in Italy and Sweden initiated monotherapy than patients in those countries receiving prior medication with SSRIs and SNRIs); patients from general and university hospitals versus other locations (Table 5).

### Discussion

This retrospective, observational DU study was designed to evaluate the characteristics of patients under specialist (psychiatric) care who were prescribed quetiapine XR for the treatment of major episodes associated with MDD. Findings suggest that there were similarities in demographic characteristics of the patients across the five European countries included in the analysis. The psychiatric histories noting multiple previous depressive episodes and hospitalizations indicated that patients had severe MDD at initiation of quetiapine XR treatment. Physicians’ ratings of the therapeutic effect of prior antidepressant therapy in categories of ‘minimal improvement’ or ‘unchanged or worse’ suggested a need for an add-on treatment for the majority of patients.

Overall, similarities in DU were observed and found to be largely in accordance with the recommended dose of quetiapine XR (50–300 mg/day) (AstraZeneca, 2017). Some differences in DU indices were apparent across countries. Although the majority of patients (80.1%) were treated with doses of quetiapine XR within recommended limits, the proportion of patients who received doses of quetiapine XR above the highest recommended dose (300 mg/day) was shown to vary by country. Exploratory modelling of this outcome suggests that presence of psychotic symptoms during depressive

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**Table 5 Factors predictive of quetiapine XR use as monotherapy**

| Final model | OR estimate | 95% CI | P-value |
|-------------|-------------|-------|---------|
| **Age at initiation of quetiapine XR treatment (years)** | | | |
| < 40 | Reference | Reference | Reference |
| ≥ 40 to <52 | 0.44 | 0.3, 0.7 | 0.002 |
| ≥ 52 to <65 | 0.60 | 0.4, 1.0* | 0.043 |
| ≥ 65 | -0.33 | -0.2, 0.7 | 0.003 |
| **Presence of prior medications** | | | |
| Subgroups 2, 4, or 4A | 0.32 | 0.0, 3.3 | NS |
| Subgroups 2, 4, or 4A and subgroups 1, 3, or 5 | 7.19 | 0.5, 102.7 | NS |
| Subgroups 1, 3, or 5 or no prior medications | Reference | Reference | Reference |
| **Physician practice setting** | | | |
| General/university | 0.74 | 0.5, 1.1 | NS |
| All others | 0.81 | 0.3, 2.4 | NS |
| **Interaction factor (prior medications × country)** | | | |
| Subgroups 2, 4, or 4A and all other countries | 2.52 | 0.2, 28.0 | NS |
| Subgroups 2, 4, or 4A and subgroups 1, 3, or 5 and all other countries | 0.07 | 0.0, 1.0* | NS |
| Subgroups 1, 3, or 5 or no prior medications and Sweden | Reference | Reference | Reference |

Prior medications are defined according to the following subgroups: (1) tricyclic antidepressants; (2) SSRIs; (3) monoamine oxidase inhibitors; (4) other atypical antidepressants, except SNRIs; (4A) SNRIs; (5) N06CAxx antidepressants in combination with psycholeptics or N05Xxx drugs.

CI, confidence interval; MAOI, monoamine oxidase inhibitors; OR, odds ratio; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; XR, extended release.

*Value of 1.0 due to data rounding.
episodes was associated with a statistically significantly higher likelihood of receiving a dose of quetiapine XR that exceeded the recommended dose range.

The results from this study indicate that prescribing patterns of quetiapine XR for the treatment of MDD are similar across Europe, although some differences in demographic characteristics – for example, patient age, and treatment patterns (e.g. use of monotherapy) were observed between Sweden and other countries.

A greater proportion of patients in Sweden and Italy were observed to have initiated quetiapine XR as monotherapy compared with the other countries analyzed. Exploratory modelling of factors that were predictive of quetiapine XR monotherapy use included the following: (i) age less than 40 years; (ii) no prior antidepressant therapy or prior medication with tricyclic antidepressants; (iii) the interaction of prior medication and country, such as a greater number of patients in Italy and Sweden receiving no therapy, prior medication with tricycles, or all other psychoactive medications initiated quetiapine XR monotherapy, compared with patients in those countries receiving prior medication with SSRIs and SNRIs; and (iv) patients from general and university hospitals. From these data, no clear trend is apparent to identify which patients may be prescribed monotherapy. The pattern of quetiapine XR use as monotherapy may reflect psychiatrists’ prior experience of prescribing quetiapine XR as monotherapy for bipolar depression.

One limitation of this analysis was that the recruitment of prescribers and patients was lower than expected in Italy, Germany, and Spain, and much lower than expected in Sweden. Commonly reported barriers to recruitment included the following: lack of interest in noninterventional research on the part of psychiatrists in some countries; unreliable projections of potentially eligible patients; treatment with quetiapine XR outside of the study inception period; and lack of patient consent. A further limitation of the study is the DUQ structure, which precludes identification of the exact number of hospitalizations that occurred before quetiapine XR initiation.

**Conclusion**

This analysis demonstrated similarities in DU across the countries analyzed that were largely in accordance with the recommended dose of quetiapine XR as an adjunctive therapy to antidepressants in MDD (50–300 mg/day).

The findings from this study indicate that quetiapine XR is prescribed for MDD at doses that are similar in patients across Europe. Some differences in treatment patterns were seen between Sweden and the other countries, such as patient age and use of quetiapine XR as monotherapy. Together, these findings provide robust evidence for the use of quetiapine XR as a treatment of depressive episodes in MDD in specialist care settings across these five EU countries.

**Acknowledgements**

The authors thank the patients and investigators involved in this study.

This study was sponsored by AstraZeneca. Study delivery was provided by Quintiles. Medical writing support, funded by AstraZeneca, was provided by Karleen Nicholson, PhD, on behalf of Complete Medical Communications.

AstraZeneca was responsible for development of the study protocol, data collection, and oversight of the Contract Research Organization (CRO) responsible for study delivery and the creation of the draft Study Report. EU Regulatory Agency oversight of the protocol and progress was required. A Scientific Advisory Board comprised a psychiatrist from each of the five countries who provided scientific advice on the proposed data collection, and provided scientific advice regarding its conduct. Quintiles conducted the study with AstraZeneca oversight. CMC assisted in the drafting of this manuscript.

**Conflicts of interest**

R.S. Brody and H. Wray are employees of AstraZeneca and own AstraZeneca stock. A. Thuresson is an employee of AstraZeneca. C.L. Liss is a former employee of AstraZeneca. K. Kastango and A. Fabre are employees of QuintilesIMS. A. Bryant is a former employee of QuintilesIMS.

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