ORIGINAL RESEARCH ARTICLE

A Post-Authorization Safety Study of Quetiapine as Antidepressant Treatment in Sweden: Nested Case–Control Analyses of Select Outcomes

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Abstract

Introduction This post-authorization safety study (PASS) was a commitment to the European Medicines Agency.

Objective This PASS investigated quetiapine as antidepressant treatment in Swedish registers with regard to the risk for all-cause mortality, self-harm and suicide, acute myocardial infarction, stroke, diabetes mellitus, extrapyramidal disorders, and somnolence.

Methods Users of quetiapine and antidepressants (2011−2014) who had changed treatment in the past year were included. Conditional logistic regression models were used to calculate odds ratios (ORs) and their 95% confidence intervals (CIs) for each outcome in nested case–control studies for quetiapine as combination therapy and monotherapy, monotherapy with antidepressants, and no medication, versus the use of combinations of antidepressants (reference group).

Results Overall, 7421 quetiapine users and 281,303 antidepressant users were included. For quetiapine in combination, risks were increased for all-cause mortality [adjusted OR (aOR) 1.31, 95% CI 1.12–1.54] compared with combinations of antidepressants; however, when stratified by age, only patients ≥ 65 years of age had an increased mortality, and, in a post hoc analysis excluding patients with Parkinson's disease, no mortality increase remained. Furthermore, the risk for self-harm and suicide was increased (aOR 1.53, 95% CI 1.31–1.79), but when stratified by age, the risk increase was found only among patients aged 18–64 years. Risks were also increased for stroke among patients ≥ 65 years of age (aOR 1.47, 95% CI 1.01–2.12), for extrapyramidal disorder (aOR 6.15, 95% CI 3.57–10.58), and for somnolence (aOR 2.41, 95% CI 1.42–4.11).

Conclusion Risks for all-cause mortality, self-harm and suicide, and stroke in older patients may be higher among patients treated with quetiapine and antidepressant combination therapy.

1 Introduction

Major depressive disorder (MDD) is an often disabling psychiatric condition that is characterized by one or more discrete depressive episodes of at least 2 weeks' duration involving changes in affect, cognition, and vegetative symptoms [1]. It affects about 6% of the population globally and occurs twice as often in women than in men [1–3]. Globally, MDD is the leading mental disorder associated with suicide and is also the second highest disease burden on society in terms of its treatment costs and effect on families and careers [4, 5].

More than 30% of patients with MDD do not achieve remission after the first two treatment trials [6, 7]. Several studies of add-on treatment with atypical antipsychotics, such as olanzapine, risperidone, quetiapine, and aripiprazole, have shown superior effects compared with placebo in patients with treatment-resistant MDD [8–10]. This has led to recommendations in clinical guidelines for the addition of certain atypical antipsychotics to antidepressants as second-line treatment in MDD [11]; however, in Sweden, quetiapine is the only atypical antipsychotic indicated for the treatment of MDD.

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Key Points

In this post-authorization safety study, quetiapine combination therapy compared with antidepressant combination therapy was associated with an elevated risk for all-cause mortality and stroke among patients aged ≥ 65 years, and for self-harm and suicide among patients aged 18–64 years.

Patients treated with quetiapine compared with antidepressants had a higher burden of disease and comorbidities, and a greater degree of alcohol abuse, substance abuse, anxiolytic and hypnotic use, suggesting selective prescribing to patients with a higher baseline risk profile.

No increased risks were observed for acute myocardial infarction and diabetes, and, in a post hoc analysis excluding patients with Parkinson's disease, no increased mortality in quetiapine-treated patients remained.

Quetiapine is an atypical dibenzothiazepine antipsychotic drug with antagonistic activity on dopamine, serotonin, histamine, and adrenergic receptors [12]. The extended-release (XR) formulation of quetiapine has demonstrated efficacy and safety compared with placebo in the treatment of MDD, both as monotherapy and as an add-on therapy to antidepressants [13, 14]. This formulation was approved as an add-on treatment for MDD by the European Medicines Agency in 2010 and the US FDA in 2009 [15, 16].

Clinical studies in patients with MDD reported that the most common adverse events (AEs) associated with quetiapine, either as monotherapy or as an add-on to antidepressants, were dry mouth, sedation, somnolence, headache, dizziness, weight gain, hyperlipidemia, hyperglycemia, and extrapyramidal effects [13, 14, 17]. In patients with schizophrenia, an elevated risk for cardiovascular mortality has been observed with high exposure to typical and atypical antipsychotics, including quetiapine, compared with low or moderate exposure [18, 19]. Among patients with bipolar disorder, the risk for developing diabetes was found to be elevated in quetiapine users compared with users of conventional antipsychotics [20]. However, the risk profile of patients with psychotic disorders may differ from that of other patients prescribed quetiapine, since many patients with psychotic disorders already have markedly elevated cardiometabolic risk factors at treatment baseline [21]. The AE profile of quetiapine when used as an antipsychotic or mood-stabilizing agent is well established, although the potential risks for the population of patients receiving quetiapine as an add-on to antidepressants may differ. This could be because of differing patient characteristics and possible differing pharmacological actions from quetiapine both in single-use

and in combination. Moreover, while some AEs may be of an acute nature, e.g. akathisia, others may be related to long-term exposure, e.g. metabolic effects.

As part of a program of post-authorization safety studies in European databases to support the XR formulation of quetiapine in MDD, the aim of this study was to investigate the safety of quetiapine use in Sweden with regard to the risk for all-cause mortality, acute myocardial infarction (AMI), stroke, self-harm and suicide, diabetes mellitus, extrapyramidal disorders, and somnolence among patients prescribed quetiapine as an add-on treatment to antidepressants, compared with patients prescribed combinations of antidepressants.

2 Methods

2.1 Data Sources

In this retrospective, population-based study, patients were identified in the Prescribed Drug Register (PDR), which contains data on all prescriptions dispensed in retail pharmacies in Sweden from 1 July 2005 [22]. Linked patient data from three other Swedish registers were obtained, using the unique personal identification number assigned to all Swedish residents [23]: the National Patient Register (NPR), which contains diagnoses registered at all in- and outpatient specialized healthcare settings, as well as data on age, sex, and place of residence [24]; the Total Population Register, which contains information on dates of emigration and deaths for all residents in Sweden [25]; and the Cause of Death Register (CDR), which contains information on all deaths in Sweden, including main and contributory causes of death, based on death certificates [26].

2.2 Study Population

Patients aged ≥ 18 years at study entry who had a prescription filling for an antidepressant (AD) [excluding bupropion under the brand name of Zyban (GlaxoSmithKline AB, Solna, Sweden), prescribed for smoking cessation], or quetiapine, in 2011–2014, were identified from the PDR. Of these, patients who had a prescription filling for a different antidepressant in the last year (including fillings from 2010 for the earliest patients)—indicating a treatment change—were included in the study. The date of study entry (index date) was the date of the first treatment change (index dispensing, i.e. either add-on treatment or treatment switch). Patients who were not residing in Sweden in the year prior to study entry, who had a diagnosis [International Classification of Diseases, Tenth Revision (ICD-10)] of dementia or psychotic or bipolar disorder from 1 January 1997 to the index dispensing, who had been dispensed a mood

stabilizer (defined as lithium, carbamazepine, lamotrigine, or valproate) from 1 July 2005 to the index dispensing, and who had been dispensed any antipsychotic (excluding lithium) in the year prior to study entry were excluded from the study. Patients who experienced any event from the exclusion criteria during follow-up were censored on the date of the event, as were those who experienced 365 days without a prescription filling of any antidepressant or quetiapine. Thus, a dynamic study population was created so that each patient could contribute to multiple episodes of drug use by entering the population when the eligibility criteria were fulfilled and leaving the population when a new prescription filling had not occurred in 365 days. Patients were followed until study end (31 December 2014) or the first occurrence of a censoring event, emigration, or death. Figure 1 summarizes the study population selection.
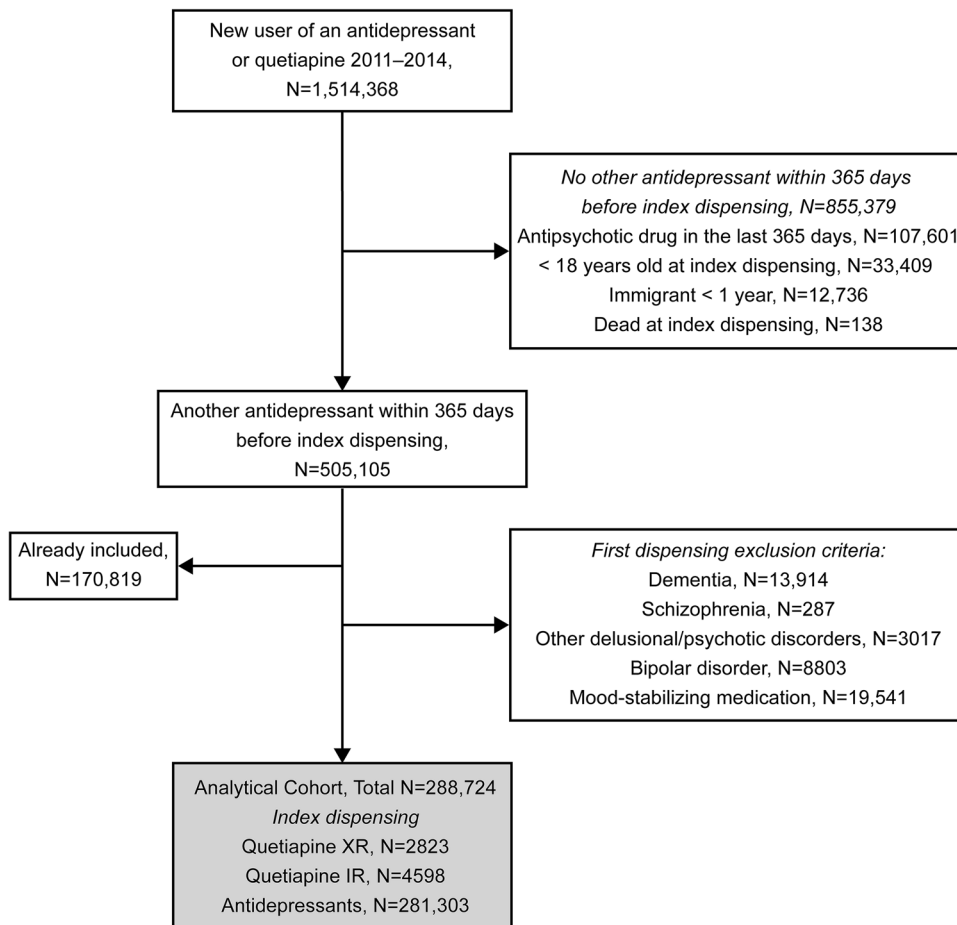
2.3 Cases and Controls

The safety outcomes included in the study were (1) all-cause mortality, identified by the date of death in the CDR; (2) AMI, defined as ICD-10 code I21; (3) stroke (ICD-10, I60–I69); (4) diabetes mellitus {ICD-10, E11, E13–E14, and/or prescription filling of any antidiabetic drug [anatomical therapeutic chemical (ATC) A10 antidiabetics)}; (5) self-harm and suicide (ICD-10: X60–X84, intentional self-harm; and Y10–Y34, events of undetermined intent); (6) extrapyramidal disorder [ICD-10: G21, secondary parkinsonism; G24, drug-induced dystonia, and/or prescription filling of trihexyphenidyl (ATC N04AA01) and biperiden (ATC N04AA02)]; and (7) somnolence (ICD-10, R40). In order to include incident outcome events only, patients with prior diagnoses or prescriptions for the outcomes were excluded from analyses, except for the self-harm and suicide outcome, where analyses were performed both on all patients and on patients without prior diagnoses of self-harm or suicidal behavior. Patients having any of the above outcomes were defined as cases.

Up to five controls were individually matched to each case, using incidence density sampling, with the matching criteria being age (± 5 years), sex, and calendar year of study entry. To be selected as a control, a patient had to be included in the study population and free of the outcome in question at the time the outcome occurred in the case. Cases hospitalized for more than 30 days immediately prior to a death identified in the CDR were excluded, along with their

Fig. 1 Flow of study population. *IR* immediate release, *XR* extended release

Flowchart:

New user of an antidepressant or quetiapine 2011–2014, N=1,514,368

→ *No other antidepressant within 365 days before index dispensing, N=855,379*
Antipsychotic drug in the last 365 days, N=107,601
< 18 years old at index dispensing, N=33,409
Immigrant < 1 year, N=12,736
Dead at index dispensing, N=138

Another antidepressant within 365 days before index dispensing, N=505,105

→ Already included, N=170,819

→ *First dispensing exclusion criteria:*
Dementia, N=13,914
Schizophrenia, N=287
Other delusional/psychotic discorders, N=3017
Bipolar disorder, N=8803
Mood-stabilizing medication, N=19,541

Analytical Cohort, Total N=288,724
Index dispensing
Quetiapine XR, N=2823
Quetiapine IR, N=4598
Antidepressants, N=281,303

controls, since medications given during hospitalization were not recorded in the PDR and were therefore unknown.

2.4 Exposures

The exposure to current pharmacologic treatment at the time of the outcome event was estimated according to the data on prescription filling, package size, and prescription dosage instructions from the PDR. Exposures were categorized as (1) quetiapine monotherapy; (2) combination therapy with quetiapine; (3) monotherapy with antidepressants; (4) no medication; and (5) users of antidepressants as combination therapy, which was set as the reference group.

2.5 Statistical Analyses

Conditional logistic regression models were used to estimate crude and adjusted odds ratios (aORs) and their 95% confidence intervals (CIs), to compare occurrence of the exposure between cases and controls for each of the seven outcomes. Because of the case-control design with incidence density sampling, the resulting odds ratios may be interpreted as relative risks (incidence rate ratios).

The analyses were adjusted for potential confounders that included comorbidities or comedications. The adjustments were performed with a predefined set of covariate variables for each outcome, and confounders were included in the analyses according to prespecified priorities [Table S1 of the electronic supplementary material (ESM)].

Two additional potential confounders were adjusted for in post hoc analyses: (1) severity of psychiatric illness measured as the number of hospital admissions for MDD in the past year and since 1997; and (2) severity of non-psychiatric illness measured as the number of hospital admissions for non-psychiatric conditions. Sensitivity analyses for selected outcomes were performed on patients stratified by age at outcome event: 18–64 years and ≥ 65 years. A post hoc analysis for all-cause mortality was performed by excluding patients with a diagnosis of Parkinson's disease or parkinsonism (ICD-10 G20, G21.9, G23.1, G23.8, G31.8) or those who were taking medication for Parkinson's disease (ATC N04) before the index date. A post hoc analysis for the self-harm and suicide outcome was performed on patients stratified by age groups: < 25 years, 25–39 years, 40–64 years, and ≥ 65 years.

Using a time-dependent exposure analysis (nested case–control study approach), data for medication at the date of an outcome are presented. An additional analysis was performed that included an intention-to-treat analysis (historical prospective cohort approach) for outcomes described on the basis of index medication (details available from the corresponding author).

All analyses were performed using SAS® version 9.4 (SAS Institute, Cary, NC, USA).

3 Results

3.1 Patient Characteristics of the Overall Study Population

Of 1,514,368 new users of antidepressants or quetiapine, the number fulfilling inclusion criteria and initiating treatment with quetiapine was 7421 (58.2% women), and 281,303 (66.5% women) for those initiating treatment with antidepressants (Fig. 1). Characteristics of the overall study population and the case–control sets are shown in Table 1. The mean age was lower for quetiapine users than antidepressant users (43 vs. 51 years).

A higher proportion of quetiapine users compared with antidepressant users had a history of alcohol and other substance-use disorder, a history of self-harm, a psychiatric diagnosis in specialized care, a diagnosis of MDD, a diagnosis of psychiatric disorders other than MDD, prescriptions written in specialized psychiatric care settings, and one or more hospitalizations, including an MDD diagnosis in the year prior to the index date (data not shown). Similar proportions of quetiapine users and antidepressant users had one or more hospitalizations for a non-psychiatric illness in the year prior to the index date and had prescriptions written in non-psychiatric care and other clinic settings (data not shown). A markedly lower proportion of prescriptions for quetiapine than for antidepressants were written in primary care settings (data not shown).

3.2 All-Cause Mortality

The risk of all-cause mortality was higher for current use of combination therapy with quetiapine and an antidepressant (aOR 1.31, 95% CI 1.12–1.54), but not for quetiapine monotherapy, compared with combination therapy with more than one antidepressant (Table 2). When stratified by age, the all-cause mortality was elevated only among patients ≥ 65 years of age (aOR 1.31, 95% CI 1.09–1.58) (Table 3). In a post hoc analysis excluding the 252 patients (71 cases, 181 controls) aged < 65 years with a diagnosis of Parkinson's disease or those who were taking medication for Parkinson's disease, no risk increase was seen among patients with quetiapine in combination therapy or monotherapy in either age group (18−64 years and ≥ 65 years) (Table S2 of the ESM).

3.3 AMI, Stroke, and Diabetes

No increased risk of AMI, stroke, or diabetes was observed for combination therapy or monotherapy use of quetiapine

Table 1 Descriptive characteristics of patients included in the overall study population and in the case–control analyses for study outcomes

| | Overall study cohort | | All-cause mortality | | AMI | | Stroke | | Diabetes mellitus | | Self-harm and suicide | | | | Extrapyramidal disorder | | Somnolence | |
| | | | | | | | | | | | All cases | | Incident cases[a] | | | | | |
	QTP	AD	Cases	Ctrl	Cases	Ctrl	Cases	Ctrl	Cases	Ctrl	Cases	Ctrl	Cases	Ctrl	Cases	Ctrl	Cases	Ctrl
N	7421	281,303	13,126	65,625	2018	10,090	2913	14,565	2941	14,705	5714	28,570	3918	19,590	523	2615	546	2730
Age at event[b], years [mean (SD)]	43.0 (17.9)	51.0 (19.5)	77.3 (14.7)	76.5 (14.4)	73.8 (13.4)	73.2 (13.3)	74.6 (13.8)	74.0 (13.7)	58.8 (15.2)	58.5 (15.2)	41.3 (18.2)	41.5 (17.9)	42.3 (18.7)	42.6 (18.4)	55.3 (21.1)	55.3 (20.8)	57.5 (21.9)	57.4 (21.6)
Women, %	58.2	66.5	60.1	60.1	56.7	56.7	64.5	64.5	59.0	59.0	60.4	60.4	59.0	59.0	59.1	59.1	57.3	57.3
Diagnoses of alcohol and substance abuse from 1997 to index date, %																		
Alcohol abuse	16.4	6.8	7.0	4.6	7.2	5.2	7.4	4.4	7.2	6.9	25.7	3.6	17.2	6.1	10.1	6.6	17.4	6.7
Substance abuse	16.5	5.3	2.9	1.2	5.4	3.4	5.6	3.1	5.3	4.6	21.6	2.4	14.1	4.5	12.0	5.3	18.3	5.0
Charlson comorbidity index on diagnoses from 1997 to index date, %																		
0	74.3	70.1	20.9	44.0	34.6	50.9	39.7	53.2	70.5	77.1	73.2	78.4	74.2	78.4	62.5	66.3	46.0	63.6
1–2	23.2	24.4	46.2	41.7	42.8	39.5	43.3	37.7	26.0	21.0	23.0	18.9	22.1	18.6	32.1	28.2	33.5	28.9
3–4	2.3	4.5	24.4	11.6	16.8	8.1	14.1	7.7	3.3	1.7	3.2	2.3	3.0	2.5	4.4	4.2	14.1	5.8
≥5	0.2	1.0	8.4	2.7	5.8	1.5	3.0	1.4	0.3	0.1	0.6	0.4	0.7	0.5	1.0	1.3	6.4	1.6
Number of non-psychiatric hospitalizations in the year before the index date, %																		
0	76.3	78.5	38.9	63.9	56.9	69.1	58.8	69.0	76.0	80.4	65.6	82.7	74.6	84.2	67.7	77.6	47.6	75.1
1	14.6	12.1	20.1	17.1	18.2	15.3	19.2	15.7	14.4	12.0	19.5	10.9	15.2	9.6	17.6	12.4	20.7	13.1
2	4.3	4.4	12.8	8.7	9.3	7.0	9.2	7.2	4.9	4.0	6.4	3.2	4.2	3.1	5.0	5.3	9.5	5.6
≥3	4.8	5.1	28.2	10.3	15.7	8.5	12.7	8.0	4.8	3.7	8.5	3.2	6.0	3.1	9.8	4.7	22.2	6.2
Number of hospitalizations for MDD in the year before the index date, %																		
0	89.3	97.5	97.6	97.8	97.6	97.4	97.7	97.8	97.1	97.4	86.8	96.7	89.6	97.7	92.4	96.7	91.9	97.3
1	8.1	2.1	1.8	1.8	1.7	2.2	1.9	1.8	2.2	2.2	9.5	2.7	8.0	1.9	5.7	2.7	5.3	2.4
2	1.8	0.3	0.4	0.3	0.5	0.4	0.4	0.3	0.5	0.2	2.7	0.5	2.0	0.3	1.3	0.6	2.0	0.3
≥3	0.7	0.1	0.2	0.1	0.1	0.1	0.0	0.1	0.2	0.1	1.0	0.1	0.5	0.1	0.6	0.1	0.7	0.0

AD antidepressant, *AMI* acute myocardial infarction, *Ctrl* controls, *MDD* major depressive disorder, *QTP* quetiapine, *SD* standard deviation

[a] Excluding patients with a history of self-harm prior to the index date

[b] For cases and controls, age at the event of the case is presented

compared with combination therapy with antidepressants (Table 2). However, when stratified by age, a higher risk for stroke was identified (aOR 1.47, 95% CI 1.01–2.12) with combination therapy with quetiapine in the older (≥ 65 years) age group (Table 3). An additional, post hoc analysis showed ORs that were somewhat higher for ischemic stroke than for stroke due to bleeding, with a statistically higher risk for ischemic stroke in users of combination therapy with quetiapine and users of monotherapy with AD (Table S3 of the ESM).

3.4 Self-Harm and Suicide

The risk was higher for self-harm and suicide among current users of combination therapy with quetiapine (aOR 1.53, 95% CI 1.31–1.79) compared with combination therapy with antidepressants (Table 2). The risk was also elevated among patients without a prior history of self-harm (aOR 1.52, 95% CI 1.26–1.84). When stratified by age group, the risk was increased for monotherapy or combination therapy with quetiapine in the 18–64 years age group only (Table 3).

3.5 Extrapyramidal Disorder and Somnolence

The risks were higher for extrapyramidal disorder (aOR 6.15, 95% CI 3.57–10.58) and somnolence (aOR 2.41, 95% CI 1.42–4.11) among current users of combination therapy with quetiapine compared with combination therapy with antidepressants; however, numbers were small in most groups (Table 2).

4 Discussion

In this study, patients with second-line combination therapy of quetiapine with antidepressants were found to have an increased risk for all-cause mortality and stroke (if ≥ 65 years of age), suicide and self-harm, extrapyramidal disorder, and somnolence compared with patients with combinations of antidepressants. In general, patients prescribed quetiapine had differing characteristics before study entry regarding various aspects of psychiatric morbidity compared with those prescribed antidepressants. This suggests that results could be interpreted considering the phenomenon of 'channeling', (i.e. selective prescribing in populations who do not adequately respond to earlier approved drugs and/or do not tolerate them) [27–29].

4.1 All-Cause Mortality

Use of atypical antipsychotics, including quetiapine, has been associated with an increased mortality risk compared with psychiatric non-users [30]. While all-cause mortality was associated with quetiapine in combination with antidepressants in the present study among patients aged 65 years and above, the association did not remain in the post hoc analysis that excluded patients with Parkinson's disease. Hence, the risk increase may be due to the known increased mortality associated with Parkinson's disease [31]. Antipsychotic use has also been associated with a doubled mortality risk among patients with Parkinson's disease in a retrospective study in which quetiapine was the most commonly prescribed atypical antipsychotic, with an associated hazard ratio for death of 2.16 [32]. In the present study, a substantial number of patients aged > 65 years using quetiapine had a diagnosis of, or had been prescribed medication for, Parkinson's disease prior to the index date compared with those treated with antidepressants (40% vs. 6%). It is unclear whether these patients were prescribed quetiapine for MDD, a common comorbidity in patients with Parkinson's disease, or for psychotic symptoms associated with Parkinson's disease. Although not licensed for this purpose, quetiapine is recommended in several guidelines as a treatment for psychotic symptoms in Parkinson's disease [33–35]. However, the results from this study support the notion that quetiapine should be used with caution in elderly patients with Parkinson's disease, regardless of the reason for treatment.

4.2 Self-Harm and Suicide

Quetiapine in combination with antidepressants was associated with an increased risk for self-harm and suicide when compared with the use of combinations of antidepressants, both among patients with and without a history of self-harm. This is in contrast to a previous study where add-on use of quetiapine was shown to decrease suicidality among patients with unipolar depression [36]. A pooled analysis of randomized clinical trials in patients with MDD reported no increased incidence of treatment-emergent suicidality in patients treated with quetiapine who were not already considered to be at high suicide risk at baseline [37]. In the present study, one could speculate that the association seen may be due to confounding by higher rates of psychiatric morbidity among patients prescribed quetiapine compared with those prescribed antidepressants, including a history of psychiatric diagnosis, alcohol abuse, substance abuse, and anxiolytic and hypnotic use, which we may not have been able to fully control for. Of special consideration may be a reported off-label use of quetiapine in patients with borderline personality disorder, a patient group with high rates of self-harm and suicide attempts [38].

4.3 AMI, Stroke, and Diabetes

Quetiapine, as well as many other psychotropic drugs, has been associated with an increased risk for metabolic

Table 2 Case–control analysis for the association between study outcomes and treatment with quetiapine or ADs at the time of an event

	Cases [n (%)]	Controls [n (%)]	Conditional logistic regression	
			Crude OR (95% CI)	Adjusted OR (95% CI)
All-cause mortality				
Combination therapy with quetiapine	231 (1.8)	853 (1.3)	1.23 (1.06–1.43)	1.31 (1.12–1.54)
Monotherapy with quetiapine	56 (0.4)	195 (0.3)	1.30 (0.96–1.76)	1.37 (0.99–1.89)
Combination therapy with ADs	4637 (35.3)	21,041 (32.1)	1 (Ref)	1 (Ref)
Monotherapy with AD	6078 (46.3)	32,672 (49.8)	0.84 (0.80–0.88)	0.88 (0.84–0.92)
No AD	2124 (16.2)	10,864 (16.6)	0.88 (0.83–0.93)	0.96 (0.90–1.02)
AMI				
Combination therapy with quetiapine	29 (1.4)	139 (1.4)	0.99 (0.65–1.48)	0.98 (0.64–1.51)
Monotherapy with quetiapine	6 (0.3)	27 (0.3)	1.05 (0.43–2.54)	1.31 (0.54–3.20)
Combination therapy with ADs	632 (31.3)	2983 (29.6)	1 (Ref)	1 (Ref)
Monotherapy with AD	980 (48.6)	5139 (50.9)	0.90 (0.80–1.00)	0.93 (0.83–1.05)
No AD	371 (18.4)	1802 (17.9)	0.97 (0.84–1.12)	1.01 (0.87–1.18)
Stroke				
Combination therapy with quetiapine	51 (1.8)	190 (1.3)	1.23 (0.89–1.68)	1.26 (0.91–1.74)
Monotherapy with quetiapine	10 (0.3)	43 (0.3)	1.07 (0.53–2.14)	1.21 (0.60–2.45)
Combination therapy with ADs	946 (32.5)	4338 (29.8)	1 (Ref)	1 (Ref)
Monotherapy with AD	1419 (48.7)	7405 (50.8)	0.87 (0.80–0.96)	0.89 (0.81–0.98)
No medication	487 (16.7)	2589 (17.8)	0.85 (0.75–0.97)	0.90 (0.80–1.02)
Diabetes mellitus				
Combination therapy with quetiapine	46 (1.6)	221 (1.5)	0.86 (0.62–1.19)	0.87 (0.62–1.22)
Monotherapy with quetiapine	11 (0.4)	54 (0.4)	0.84 (0.44–1.61)	0.86 (0.45–1.66)
Combination therapy with ADs	1441 (49.0)	7684 (52.3)	1 (Ref)	1 (Ref)
Monotherapy with AD	877 (29.8)	3646 (24.8)	0.77 (0.70–0.84)	0.78 (0.71–0.86)
No AD	566 (19.2)	3100 (21.1)	0.74 (0.66–0.84)	0.76 (0.68–0.86)
Self-harm and suicide				
All cases				
Combination therapy with quetiapine	404 (7.1)	642 (2.2)	2.37 (2.07–2.71)	1.53 (1.31–1.79)
Monotherapy with quetiapine	70 (1.2)	207 (0.7)	1.27 (0.96–1.67)	0.71 (0.52–0.99)
Combination therapy with ADs	1848 (32.3)	7115 (24.9)	1 (Ref)	1 (Ref)
Monotherapy with AD	2403 (42.1)	14,103 (49.4)	0.63 (0.59–0.68)	0.66 (0.61–0.71)
No AD	989 (17.3)	6503 (22.8)	0.55 (0.50–0.60)	0.52 (0.47–0.58)
Incident cases[a]				
Combination therapy with quetiapine	223 (5.7)	423 (2.2)	1.93 (1.62–2.30)	1.52 (1.26–1.84)
Monotherapy with quetiapine	39 (1.0)	101 (0.5)	1.37 (0.94–2.00)	1.02 (0.68–1.53)
Combination therapy with ADs	1310 (33.4)	4895 (25.0)	1 (Ref)	1 (Ref)
Monotherapy with AD	1665 (42.5)	9670 (49.4)	0.62 (0.57–0.67)	0.64 (0.59–0.70)
No AD	681 (17.4)	4501 (23.0)	0.53 (0.47–0.59)	0.52 (0.47–0.58)
Extrapyramidal disorders				
Combination therapy with quetiapine	51 (9.8)	46 (1.8)	5.61 (3.53–8.90)	6.15 (3.57–10.58)
Monotherapy with quetiapine	16 (3.1)	8 (0.3)	9.23 (3.84–22.17)	13.51 (4.98–36.65)
Combination therapy with ADs	129 (24.7)	627 (24.0)	1 (Ref)	1 (Ref)
Monotherapy with AD	246 (47.0)	1342 (51.3)	0.88 (0.69–1.11)	1.05 (0.81–1.37)
No AD	81 (15.5)	592 (22.6)	0.66 (0.49–0.91)	0.70 (0.49–0.99)
Somnolence				
Combination therapy with quetiapine	25 (4.6)	45 (1.6)	2.45 (1.45–4.13)	2.41 (1.42–4.11)
Monotherapy with quetiapine	5 (0.9)	15 (0.5)	1.48 (0.52–4.17)	1.52 (0.53–4.33)
Combination therapy with ADs	268 (49.1)	1387 (50.8)	1 (Ref)	1 (Ref)
Monotherapy with AD	153 (28.0)	680 (24.9)	0.85 (0.68–1.06)	0.86 (0.69–1.07)
No AD	95 (17.4)	603 (22.1)	0.69 (0.51–0.92)	0.70 (0.52–0.93)

Adjusted ORs and their 95% CIs were estimated with conditional logistic regression models, including all prespecified covariates, using combination therapy with ADs as the reference category

AD antidepressant, *AMI* acute myocardial infarction, *CI* confidence interval, *OR* odds ratio, *Ref* reference

[a]Excluding patients with a history of self-harm prior to the index date

Table 3 Association between selected study outcomes and treatment with quetiapine or ADs at the time of an event, stratified by age

	Age 18–64 years Adjusted OR (95% CI)	Age ≥ 65 years Adjusted OR (95% CI)
All-cause mortality		
Combination therapy with quetiapine	1.20 (0.87–1.66)	1.31 (1.09–1.58)
Monotherapy with quetiapine	1.17 (0.65–2.11)	1.37 (0.93–2.01)
Combination therapy with ADs	1 (Ref)	1 (Ref)
Monotherapy with AD	0.66 (0.58–0.75)	0.91 (0.87–0.96)
No medication	0.77 (0.66–0.90)	0.98 (0.92–1.05)
AMI		
Monotherapy or combination therapy with quetiapine[a]	0.64 (0.28–1.44)	1.28 (0.82–2.00)
Combination therapy with ADs	1 (Ref)	1 (Ref)
Monotherapy with AD	0.83 (0.65–1.08)	0.96 (0.84–1.09)
No AD	0.80 (0.59–1.08)	1.10 (0.93–1.32)
Stroke		
Combination therapy with quetiapine	0.78 (0.39–1.56)	1.47 (1.01–2.12)
Monotherapy with quetiapine	1.56 (0.53–4.55)	0.98 (0.37–2.61)
Combination therapy with ADs	1 (Ref)	1 (Ref)
Monotherapy with AD	0.99 (0.79–1.24)	0.87 (0.78–0.96)
No AD	0.94 (0.72–1.23)	0.90 (0.78–1.04)
Diabetes mellitus		
Monotherapy or combination therapy with quetiapine[a]	1.01 (0.72–1.41)	0.46 (0.22–0.98)
Combination therapy with ADs	1 (Ref)	1 (Ref)
Monotherapy with AD	0.77 (0.68–0.87)	0.79 (0.68–0.93)
No AD	0.71 (0.61–0.83)	0.85 (0.69–1.04)
Self-harm and suicide		
All cases		
Monotherapy or combination therapy with quetiapine[a]	1.34 (1.15–1.56)	1.22 (0.71–2.08)
Combination therapy with ADs	1 (Ref)	1 (Ref)
Monotherapy with AD	0.66 (0.61–0.72)	0.65 (0.53–0.79)
No AD	0.50 (0.45–0.56)	0.75 (0.58–0.99)
Incident cases[b]		
Monotherapy or combination therapy with quetiapine[a]	1.38 (1.15–1.66)	0.85 (0.48–1.52)
Combination therapy with ADs	1 (Ref)	1 (Ref)
Monotherapy with AD	0.61 (0.55–0.67)	0.59 (0.48–0.73)
No AD	0.48 (0.43–0.54)	0.71 (0.53–0.94)

Adjusted ORs and their 95% CIs were estimated with conditional logistic regression models, including all prespecified covariates, using combination therapy with ADs as the reference category

AD antidepressant, *AMI* acute myocardial infarction, *CI* confidence interval, *OR* odds ratio, *Ref* reference

[a]Quetiapine exposure had to be collapsed due to a small number of events

[b]Excluding patients with a history of self-harm prior to the index date

outcomes—as does, importantly, having psychiatric diagnoses such as anxiety and depression [39, 40]. The relative risks for AMI and stroke were similar in the overall study population, although in the age-stratified analysis, the risk for stroke was higher for use of quetiapine in combination with antidepressants among patients aged ≥ 65 years. This is in line with an observational study showing an increased risk for stroke among elderly patients treated with quetiapine compared with non-users [41], and a study where atypical antipsychotic drugs were also associated with an increased risk of stroke, particularly in elderly patients and those with dementia [42]. However, the results from the present study should be interpreted with caution because the lower boundary of the CI for this finding was very close to 1, few events were reported, and the aOR was not increased for patients aged ≥ 65 years receiving quetiapine as monotherapy. In addition, the fact that none of the other analyses showed any significant increases may indicate that this is not a major risk with quetiapine treatment in this population.

4.4 Extrapyramidal Disorder and Somnolence

In accordance with the pharmacological profile of quetiapine [43], elevated risks for extrapyramidal disorders and somnolence were observed with quetiapine use compared with the use of combinations of antidepressants. The risk increase regarding somnolence was observed even though many antidepressants, most notably mirtazapine, are associated with an increased risk compared with placebo [44]. However, the inference drawn from these analyses may be limited due to the fact that AEs may not be consistently registered in the PDR, although, in the case of extrapyramidal disorders, the analyzed outcome also included prescriptions of biperiden and trihexyphenidyl.

4.5 Strengths and Limitations

Strengths of this study include the use of nationwide Swedish registers as data sources, which in general have high quality and completeness [22, 24], and which provided an initial study population with sufficient power to perform nested case–control analyses while adjusting for several potential confounders. Because the controls were randomly sampled from the eligible controls in the study population, the sampling probability as a control was proportional to the amount of person-time that patient had spent at risk of disease, and since there was matching on time from inclusion into the study population until the outcome, the follow-up time was similar for cases and controls [45]. Although little precision is typically gained by selecting more than four controls to each case, there can be some gain and, especially for rare exposures, a higher number of controls also help to increase the chance of catching exposures to better estimate the true exposure among all the potential controls [45]. Accordingly, because we found that we could achieve a higher number of controls than four to nearly all cases, we chose to do so.

The method of comparing second-line users of quetiapine with patients with other second-line antidepressant treatment was intended to emulate the treatment setting in which quetiapine is likely to be prescribed, and also to create comparison groups, taking into account the inherent risks for several adverse outcomes associated with both psychiatric diagnoses and with antidepressant therapy in general [39, 40], risks that generally increase among difficult-to-treat patients [46].

Limitations of this study include the main indication for treatment not being available in the PDR; hence, the inclusion of patients with non-psychiatric indications for antidepressant use, such as neuropathic pain, fibromyalgia, or premenstrual syndrome, could not be avoided. Reasons for drug switch or discontinuation were unknown, and could be due a number of reasons, such as poor response, adverse effects, poor adherence, remission, or interactions with other prescribed drugs, including non-psychiatric drugs. Drug dispensing information in the PDR was not available for treatments administered only during hospital admissions, and the NPR does not include visits or diagnoses from primary care, therefore this information was not available for adjustment in the study. Socioeconomic and smoking data were also unavailable, and such risk factors may have been unevenly distributed in the exposure groups. Considering the higher rate of substance-use disorders among patients with quetiapine, and the suspected channeling bias of quetiapine towards patients with greater psychiatric morbidity, it is likely that these factors could have affected the risks of mortality, AMI, and stroke, especially among quetiapine users. Thus, residual confounding is likely to remain in the analysis, suggested by the differing characteristics between patient groups. Extrapyramidal disorder and somnolence outcomes may have been underreported because the main underlying reason for the medical encounter (e.g. depressive episode) is most likely to be the one recorded as a diagnosis rather than an AE. Although the validity of recorded diagnoses in the NPR is generally high, no validations of any diagnoses were performed. In addition, hospitalizations for MDD were incorporated as measures for severity as there are no agreed-upon constructs for assessment of severity of MDD.

Patients' actual use of the filled prescriptions was unknown, but was likely to have been less than optimal, since high rates of non-adherence to antidepressant medication have been reported [47]. Finally, to ensure that the study was adequately powered, this study included patients using both the immediate-release (IR) and ER quetiapine formulations. The IR quetiapine formulation is indicated for schizophrenia and manic and depressive episodes of bipolar I disorder, and is more frequently prescribed, whereas the XR formulation is additionally indicated as add-on treatment for MDD [15]. Consequently, the patient populations and their associated comorbidities may have differed between the two formulations. However, results reported in the original reports from analyses restricted to the use of the XR formulation were consistent with the results in the present study (data not shown). The proportion of cases and controls found to use quetiapine in monotherapy in the present study was comparable with what was found in a drug utilization study of quetiapine XR use for MDD across five European countries, including Sweden [48].

The results from this study are representative of the outpatient population of antidepressant users, although not of inpatient users, in Sweden. Although the results may be generalizable to other patient populations prescribed antidepressants in other countries, they may vary due to differing treatment practices, reimbursement systems for medication costs, and organization of health care, and, more specifically, psychiatric care, in each country.

5 Conclusions

The risk for self-harm and suicide was increased for monotherapy or combination therapy of quetiapine and antidepressants in the 18–64 years age group only. This could possibly be explained by selective prescribing of these treatments to patients at high risk for these outcomes. When quetiapine was used in combination with antidepressants, a higher risk for stroke and all-cause mortality was found in the older age group (≥ 65 years), although the increased mortality did not remain when patients with Parkinson's disease were excluded. No significant associations were found between quetiapine use (either as monotherapy or in combination) and AMI or diabetes.

Compliance with Ethical Standards

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