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Observational assessment of safety in seroquel (OASIS): a specialist cohort event monitoring (SCEM) study in England

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Abstract

Background: This study was designed to monitor the short-term (up to 12 weeks) use and safety of quetiapine (Seroquel) extended release (XL) and quetiapine immediate release (IR) prescribed to patients with a clinical diagnosis of schizophrenia, and/or manic episodes associated with bipolar disorder by psychiatrists under normal conditions of use.

Methods: A Specialist Cohort Event Monitoring (SCEM) study was conducted in England February 2010–April 2013. This observational cohort study recruited patients prescribed quetiapine XL within the secondary care setting by psychiatrists. A reference cohort of quetiapine IR users was also recruited. Baseline and 12 week observational data were collected from psychiatrists who abstracted information from medical records onto bespoke questionnaires. Data were collected on demographics, indication, past medical history, prescribing information and events of interest. Summary descriptive statistics were calculated.

Results: The final cohort consisted of 869 eligible patients; 646 XL users and 223 IR users. The majority of XL and IR users were female (56.2% and 55.6%, respectively), with a median age of 40 (interquartile range [IQR]: 29, 49) and 39 (IQR: 28, 50) years, respectively. The most frequent indication for treatment was Manic episodes associated with Bipolar Affective disorder (53.4% XL and 49.8% IR). Median index dose was 200 mg/day (IQR: 100, 300) for XL users and 50 mg/day (IQR: 50, 100) for IR users, while median final maintenance dose was 400mg/day (IQR: 250, 600) and 300 mg/day (IQR: 100, 400), respectively. The most frequently reported event of interest in both cohorts was sedation ($n = 151$, 23.9% XL cohort and $n = 49$, 23.0% IR cohort).

Conclusion: Utilisation of quetiapine XL appeared to be in line with prescribing guidelines in terms of dose, and commonly reported events of interest were in concordance with the known safety profile. Overall, this SCEM study provided important information on the safety and utilisation of quetiapine XL in the secondary care setting in England.

Keywords: seroquel, quetiapine, safety, observational cohort

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Introduction

Prolonged-release quetiapine fumerate [quetiapine extended release (XL)] is an atypical antipsychotic, launched in the United Kingdom (UK) in September 2008 initially for the treatment of schizophrenia and/or manic episodes associated with bipolar disorder.[1] This delayed release formula is taken once daily and allows plasma concentrations to be maintained at high levels for a longer time, which enables less frequent dosing to maintain therapeutic drug concentrations. Thus it offers a more convenient dosage and administration regimen than the immediate release (IR) formulation, which is often given in two to three divided doses per day.

The recommended dose at start of therapy with quetiapine XL for schizophrenia and for manic episodes associated with bipolar disorder is 300 mg/day. Patients are then titrated within a target dose range of

150–800 mg/day depending on the indication and/or tolerance of the individual patient. Dose increases can be made at intervals as short as 1 day and in increments of up to 300 mg/day.[1] A slower rate of dose titration and lower target dose may be required in special populations such as elderly, or those with hepatic impairment or predisposed to hypotensive reactions.

The most commonly reported adverse drug reactions (ADRs) with quetiapine XL (incidence >5% and greater than placebo) in clinical trials include somnolence/sedation (including drowsiness), mild asthenia, tachycardia and orthostatic hypotension.[1] Suicidal ideation and suicidal behaviour are also common with quetiapine XL (between 1% and 10%).[1]

The clinical safety information available when a new medicine is marketed relates to a limited number of patients.[2] This also applies to new formulations of licensed medicines. Pre-marketing data will usually give little information on drug utilisation and safety post-marketing in real-world settings. Specialist cohort event monitoring (SCEM) offers the opportunity to collect exposure and outcome data on patients identified in other health care settings such as hospital and secondary care settings, through an active research network of clinicians, established collaboratively with an existing clinical research network.[3] The patient cohort can then be followed prospectively. This observational cohort study design offers the opportunity for the systematic collection and reporting of safety data on patients newly initiated on treatment with quetiapine (as the prolonged release formulation) in a mental health clinical practice setting. In addition, by collecting an internal reference cohort of quetiapine IR users it allows informal comparisons between the immediate release and prolonged release formulations of quetiapine.

The overall aim of the Observational Assessment of Safety in Seroquel (OASIS) study was to monitor the short-term (up to 12 weeks) use and safety of quetiapine XL and quetiapine IR prescribed to patients with a clinical diagnosis of schizophrenia, plus manic episodes associated with bipolar disorder by psychiatrists under normal conditions of use. A Risk Management Plan (RMP) is required when applying for marketing authorisation for a new medication. It includes information on a medication's known safety profile, important potential risks, identified risks and missing information as well as plans for studies to obtain further information on safety.[4] This study was requested as part of the UK RMP by the Medicines and Healthcare products Regulatory Agency (MHRA) and was one of the conditions for licensing of quetiapine XL in the UK. The study was subsequently included in the European Union (EU) RMP and its purpose was to provide further clarification of safety during titration and at higher doses of the prolonged release formulation.

Methods

Study design

OASIS was an observational, population-based cohort study that used SCEM methodology, conducted between February 2010 (first patient in) and April 2013 (end of data collection period). The study was designed to monitor the short-term (up to 12 weeks) safety and use of quetiapine XL initiated by psychiatrists in the secondary care setting in England. A reference (comparator) cohort of patients prescribed quetiapine IR was also recruited. Figure 1 outlines the study process.

Study sites

Psychiatrists were identified systematically from publicly available data sources, information provided by National Health Service (NHS) trusts, and existing research networks. All mental health NHS trusts in England were invited to participate ($n = 58$) and study facilitators were available to assist with study implementation. The aim was to recruit a representative sample of psychiatrists practicing within both rural and urban regions. In total, 407 psychiatrists across 49 NHS mental health trusts contributed patients to the study.

Psychiatrists were informed that they were participating in a study to monitor the use of a frequently prescribed oral atypical antipsychotic (quetiapine). The study was adopted by the UK Mental Health Research Network, who provides support to mental health research within the NHS, including access to researchers and mental health professionals. Psychiatrists were invited to participate in the study prior to study start and psychiatrist recruitment remained open throughout the study. Psychiatrists were required to register with the study co-ordinating centre in order to receive access to relevant study documentation. Remuneration, in line with the standard British Medical Association rate, was paid to

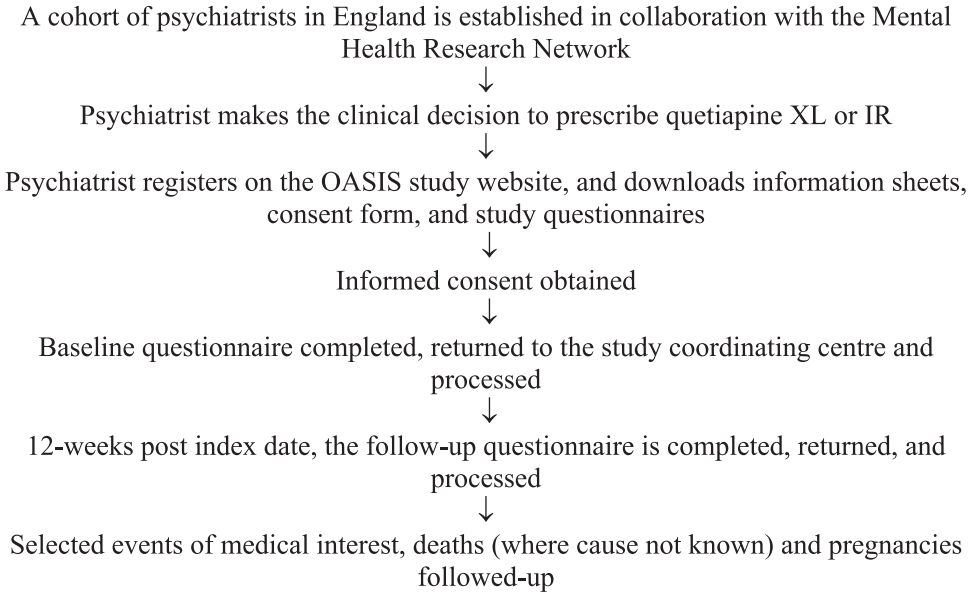

Figure 1. Process of OASIS SCEM study.
IR, immediate release; OASIS, Observational Assessment of Safety in Seroquel; SCEM, Specialist Cohort Event Monitoring; XL, extended release.

psychiatrists to cover time and administration costs incurred (either by themselves or associated staff).

Study subjects

Eligible patients were required to have a clinical diagnosis of schizophrenia or the manic phase of bipolar disorder during the study period. As patients with schizophrenic disorders are often not formally diagnosed with schizophrenia in the early stages of manifestation, an 'other indications' tick box was also included on the study questionnaire to allow these eligible patients to be captured. Patients must have presented within the secondary care setting for standard course of care, as in- or out-patients. Informed, written patient consent was required to participate.

Since this was an observational cohort study conducted in a naturalistic setting, open patient entry criteria were desirable to maximise external validity. Patients with co-morbidities were eligible for inclusion. Patients who switched treatment from IR to XL formulation were also eligible for inclusion.

The identification of the study population was through (non-probability) systematic sampling after the pharmacotherapeutic treatment decision had been made based on clinical need. This method was used since a probability sampling framework was not feasible and because participation within the study was not required as a condition of receiving treatment. This approach was intended to reduce conscious or unconscious selection bias on the part of the psychiatrist as to whom to invite to participate in the study, especially with regard to prognostic factors that may be related to prognosis. The patient was not asked to attend the psychiatrist more than usual or undergo any additional treatment.

Patients who presented with a primary diagnosis of bipolar depression or major depressive disorder were excluded, since these indications were not being investigated as part of this study. In addition, patients were excluded post-recruitment into the study if the initial survey questionnaire was not submitted within 3 months of the index date (the date of starting the relevant treatment).

Patients were withdrawn automatically if the patient or psychiatrist provided informed written or verbal notification that they no longer wished to participate at any stage of the study.

Evaluable patients were those patients who provided consent and for whom analysable clinical data was provided in the data collection questionnaires. Evaluable patients for whom the 12-week questionnaire was returned with no clinical

information were included only within the drug utilisation analysis.

Ethics approval

Ethics approval for OASIS was granted by Southampton and Southwest Hampshire Research Ethics Committee (now South Central-Hampshire A) on 15 June 2009 (reference number 09/H0502/71).

Study size

The sample size was based on detecting at least a 2.5-fold increase in common events between subgroups of patients within the quetiapine XL cohort defined by dose ($\geq$600 mg and $<$600 mg), where the ratio of patients defined by these two categories was assumed to be 1:2, respectively. In order to achieve a 95% chance of observing a statistically significant 2.5-fold increase of risk from 3% to 7.5% between low dose and high dose users, with a power of 80%, a minimum total number of approximately 750 patients were required within each of the XL and IR quetiapine cohorts; approximately 250 patients in the $\geq$600 mg dose stratum and 500 patients in the $<$600 mg stratum. Thus, the intended total sample size was 1500.

However, lower than expected numbers of patients were prescribed high dose quetiapine, irrespective of formulation, and the low recruitment of quetiapine IR patients, led to the decision to end study recruitment without achieving the planned sample size. The study was therefore underpowered with regards to comparing high dose and low dose quetiapine users, consequently all analyses within this paper between the IR and XL cohorts are purely descriptive.

Data collection

Data was derived through secondary use of medical records; relevant data was extracted by psychiatrists and reported onto study specific questionnaires. The psychiatrists then submitted the completed forms to the study co-ordinating centre. Reported data was examined for clinical events of medical interest.

Study outcomes

Patients were observed from the start of treatment with quetiapine XL or IR for 12 weeks in order to allow for detection of outcomes associated with treatment initiation and the regimen of dose titration to maintenance dose. For eligible patients providing consent, the following information was requested from the psychiatrist at index date and at the end of the 12 weeks observation period *via* questionnaires: demographic variables, psychiatric history and indication-related variables, relevant prior medical history, exposure information, events during the observation period and treatment cessation information. Events of interest were clinical events collected *via* tick boxes on the questionnaire. For clarity of reporting of suicidal behaviour and self harm, such events have been classified according to the Columbia Classification Algorithm of Suicide Assessment (C-CASA).[5]

Statistical analysis

Data analysis consisted of summary tabulations and figures to describe the utilisation pattern of quetiapine XL and IR. Event frequencies were also summarised. Where specified, a category of unknown included missing and 'Don't know' responses. Categorical counts for pre-defined ranges and standard dispersion parameters were used to describe patient characteristics.

Results

The final cohort consisted of 869 eligible patients with baseline information (Figure 2), of which 845 patients also had information at 12 weeks. Figure 3 shows the distribution of consented patients throughout England and is presented overlaid with data provided by the Office for National Statistics, showing the use of specialist adult mental health services,[6] to illustrate distribution in relation to mental health service use.

Cohort characteristics stratified by quetiapine formulation are presented in Table 1 (n = 869 at baseline and n = 845 at 12 weeks). The most frequent indication for treatment with either formulation was manic episodes associated with bipolar affective disorder (53.4% XL and 49.8% IR). Examination of posology revealed 30 XL patients (4.6%) using high dose quetiapine ($\geq$600 mg/day) at index date and 616 XL patients (95.4%) using low dose ($<$600 mg/day) quetiapine at index date. In the IR cohort, 3 patients (1.3%) were using high dose at index date and 220 patients (98.7%) were using low dose. A total of 43.2% (n = 279) of XL patients were reported to

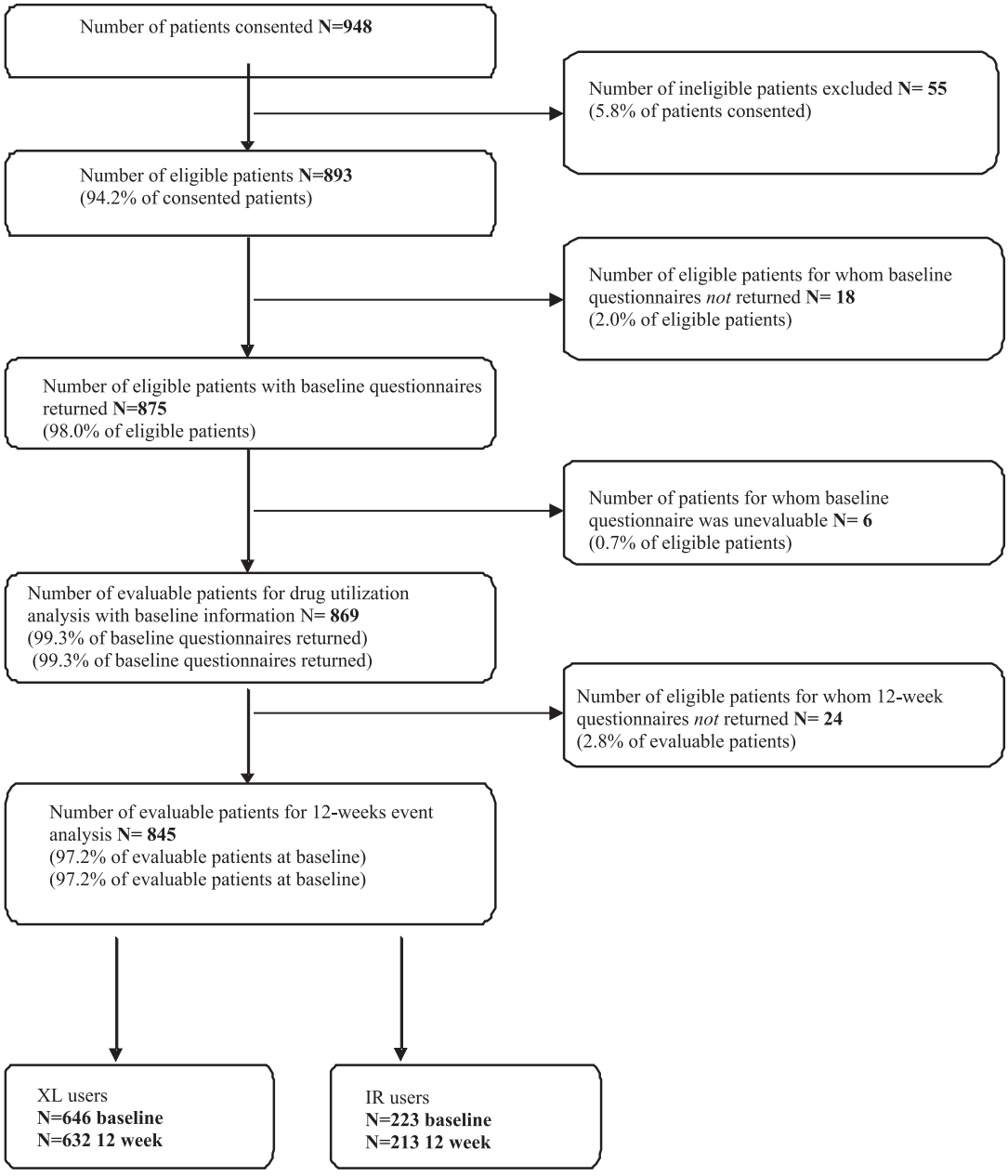

Figure 2. Flowchart of the number of patients recruited over the course of the study.

have been prescribed a maintenance dose of 600mg or more (high dose) during the 12 week observation period in contrast to 18.8% ($n = 42$) of IR users. There were 43 patients (6.7% XL cohort) who switched from quetiapine IR to quetiapine XL.

Prior history of suicide/self-injury was high in both cohorts (42.2% XL and 43.0% IR), as was depression (61.2% XL and 59.2% IR). Prior history of cardiac arrhythmias and myocardial infarction was low in both cohorts, though higher in the IR cohort (3.6 and 1.8%, respectively) compared with the XL cohort (1.7 and 0.9%, respectively).

Event frequencies are presented in Table 2 ($n = 845$ with 12 week data). The most frequently reported event of interest (unrelated to indication) in both the XL and IR cohorts was sedation ($n = 151$, 23.9% and $n = 49$, 23.0% respectively). Frequency of suicide/self-injury was 7% ($n = 44$)

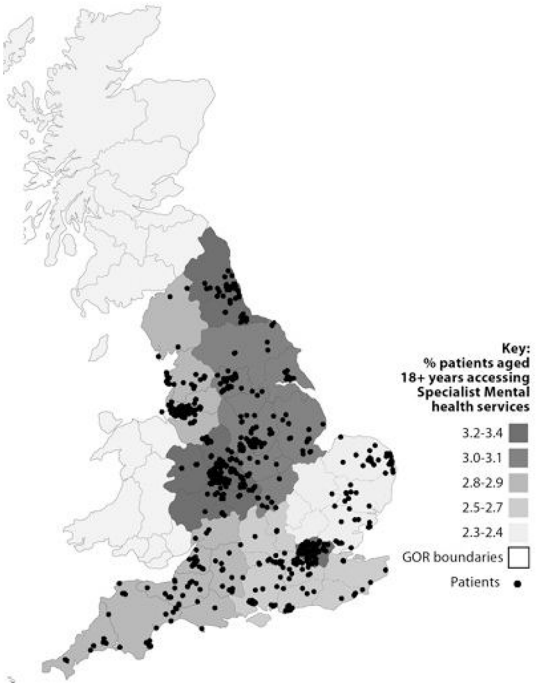

Figure 3. Distribution of consented patients throughout England, including patterns of specialist mental health service usage in England, 2010.[6]
GOR, government office regions.

in the XL cohort and 8.5% ($n = 18$) in the IR cohort.

A total of 128 (19.8%) patients in the XL cohort and 40 (17.9%) patients in the IR cohort stopped treatment during the study period. The most frequently reported reason for stopping XL treatment was sedation ($n = 29$, 22.7% of patients who stopped treatment), whilst within the IR cohort, the most frequently reported reason for stopping was 'side-effects' (preferred term MedDRA adverse drug reaction) in seven patients (17.5%) who stopped treatment.

Discussion

The SCEM study design provided a framework suitable to evaluate the safety and utilisation of quetiapine XL in the secondary care setting in England. Examination of demographics and indications revealed that age, sex and indication distribution was similar between the IR and XL cohorts. In comparison with clinical trials, the XL cohort included in this study were slightly older (40 years *versus* 34–37 years) and a higher proportion were female (56.2%) than in trials (29.7–45%).[7,8] The OASIS study also included patients who were excluded from clinical trials, such as those over 65 years of age and those who had previously used certain antiepileptics and antipsychotics in the 28 days prior to starting quetiapine XL.[7,8] Consequently, the OASIS study provides information on real-world patients who differ from clinical trial patients.

Examination of past medical history indicated a potentially lower frequency of prior cardiovascular events for the XL cohort compared with the IR cohort. This may suggest that the XL formulation is being prescribed to groups of patients who may be less susceptible to adverse events of cardiovascular origin, though it cannot be confirmed as we did not collect information from specialists regarding prescribing decisions specifically based on past medical history of other conditions. However, the antipsychotic related cardiovascular effects are well known.

The possibility of channelling (patients are more likely to be prescribed a specific drug than another based on particular characteristics) may introduce important bias in that baseline characteristics of the XL user population is different to the IR population. This phenomenon has been reported historically for a number of newly marketed new entity drugs (for example, COX-2 selective inhibitors)[9,10] but appears equally likely for new formulations of existing treatments. In examining the event profiles between the two formulation sub-cohorts, the frequency of selected cardiovascular and related outcomes appears to differ and be lower for XL users (albeit event count is low) than IR users, and one explanation is that the XL formulation users are simply different in terms of baseline risk.

The start and maintenance doses for both XL and IR users within the OASIS study shows marked variability of dosing between and within formulations. These observations suggest that practitioners are choosing dosage regimen based on clinical need, and titrating treatment to achieve the minimum effective dose as per the prescribing guidelines.[1] In looking at between-formulation differences, patients using quetiapine XL were generally prescribed higher doses at index and at the end of the study period, compared with patients using quetiapine IR. One possible explanation for this is that treatment was initiated on the IR formulation and titrated up before switching to the XL formulation, though the overall proportion of switchers was low (6.7%). High

Table 1. Cohort characteristics, stratified by quetiapine formulation.

Characteristics	XL users *n* = 646	IR users *n* = 223
Age at start of treatment (years), *n* (%):		
18–24	99 (15.3)	36 (16.1)
25–29	64 (9.9)	32 (14.4)
30–34	86 (13.3)	24 (10.8)
35–39	70 (10.8)	22 (9.9)
40–44	92 (14.2)	24 (10.8)
45–49	73 (11.3)	23 (10.3)
50–54	67 (10.4)	22 (9.9)
55–59	40 (6.2)	10 (4.5)
60–64	38 (5.9)	12 (5.4)
⩾65	14 (2.2)	17 (7.6)
Not known	3 (0.5)	1 (0.4)
Median age (IQR)	40 (29, 49)	39 (28, 50)
Sex, *n* (%):		
Males	281 (43.5)	97 (43.5)
Females	363 (56.2)	124 (55.6)
Not known	2 (0.3)	1 (0.4)
Start dose, *n* (%)		
High dose (⩾600 mg/day)	30 (4.6)	3 (1.3)
Low dose (<600 mg/day)	616 (95.4)	220 (98.7)
Median (IQR)	200 (100, 300)	50 (50, 100)
Final maintenance dose		
Median (IQR)	400 (250, 600)	300 (100, 400)
Indication, *n* (%):		
Schizophrenia	258 (39.9)	89 (39.9)
Manic episodes associated with bipolar affective disorder	345 (53.4)	111 (49.8)
Other Indications*	43 (6.7)	23 (10.3)
Prior history of events (ever), *n* (%):		
Suicide/self-injury	274 (42.2)	96 (43.0)
Depression	396 (61.2)	132 (59.2)

(Continued)

Table 1. (Continued)

Characteristics	XL users *n* = 646	IR users *n* = 223
Somnolence	103 (15.9)	43 (19.3)
Sedation	122 (18.9)	42 (18.8)
Hypertension	59 (9.1)	21 (9.5)
Cardiac arrhythmias	11 (1.7)	8 (3.6)
Myocardial infarction	6 (0.9)	4 (1.8)
Medication use in 28 days prior to index by ATC class, *n* (%)		
N05A Antipsychotics	341 (52.8)	104 (46.6)
N05B Anxiolytics	5 (0.8)	3 (1.3)
N06A Antidepressants	241 (37.3)	99 (44.4)
N05C Hypnotics and sedatives	97 (15.0)	28 (12.6)
N02A Opioids	20 (3.1)	17 (7.6)
Concomitant medication use by ATC class, *n* (%)		
N05A Antipsychotics	131 (20.3)	46 (20.6)
N05B Anxiolytics	2 (0.3)	3 (1.3)
N06A Antidepressants	130 (20.1)	35 (15.7)
N05C Hypnotics and sedatives	97 (15.0)	21 (9.4)
N02A Opioids	16 (2.5)	7 (3.1)

*Other indications were those that could not be grouped into the schizophrenia or manic episodes in bipolar affective disorder categories, but were also not indicative of an exclusion criterion.
ATC, anatomical therapeutic chemical; IQR, interquartile range; IR, immediate release; XL, extended release.

dose prescribing was still low overall and, since the recommended starting doses of quetiapine XL are higher than quetiapine IR, this suggests that psychiatrists are adhering to prescribing guidelines.

For both formulations, the most common events of interest reported were sedation, somnolence, depression and suicide/self-injury. However, it should be noted that a prior medical history of these events was also very common within the cohorts. Somnolence, otherwise known as drowsiness or sleepiness, and sedation are well known common side effects of atypical antipsychotic drugs.[1,11] Patients treated with quetiapine are more likely to experience somnolence within the first 2 weeks of treatment, and this generally resolves over time.[12] Additional risk factors for somnolence include concomitant medication such as anxiolytics, hypnotics and opioid analgesics plus alcohol intake.[13] In clinical studies, patients experienced a higher level of sedation 1 h after dosing of IR compared with XL, although no significance in sedation was found after 7 or 14 h post-dosing.[13,14] The summary of product characteristics lists somnolence/sedation as very common (⩾10%),[1] which is in concordance with the frequency found in this study for the XL cohort. Previous placebo-controlled clinical trials have shown the incidence of somnolence and sedation combined to be 25% in schizophrenia patients treated with Seroquel XL over 6 weeks at doses ranging from 300 to 800 mg/day, and 50% in a 3-week trial in bipolar disorder, with doses ranging from 400 to 800 mg/day.[11] It is also widely accepted that quetiapine is more sedative than other second generation antipsychotics; a

Table 2. Count and percentage of events of interest, stratified by quetiapine formulation.

Event	XL user *n* = 632		IR user *n* = 213		Total *n* = 845	
	n	%	*n*	%	*n*	%
Sedation	151	23.9	49	23.0	200	23.7
Somnolence	122	19.3	44	20.7	166	19.6
Depression	80	12.7	29	13.6	109	12.9
Suicide/self-injury	44	7.0	18	8.5	62	7.3
Suicide/self-injury: Suicidal ideation	13	2.0	8	3.6	21	3.3
Suicide/self-injury: Suicidal behaviour	7	1.1	4	1.8	11	1.7
Suicide/self-injury: Self-injurious behaviour, with no suicidal intent	12	1.9	2	0.9	14	2.2
Suicide/self-injury: Non classifiable	12	1.9	4	1.8	16	2.5
Akathisia	20	3.2	7	3.3	27	3.2
Parkinsonism	12	1.9	7	3.3	19	2.2
Hypotension	7	1.1	8	3.7	15	1.8
Hyperglycaemia/diabetes mellitus	9	1.4	4	1.9	13	1.5
Cardiac arrhythmias	5	0.8	7	3.3	12	1.4
Hypertension	3	0.5	7	3.3	10	1.2
Dyslipidaemia	4	0.6	4	1.9	8	0.9
Convulsions	3	0.5	3	1.4	6	0.7
Hypothyroidism	5	0.8	1	0.5	6	0.7
Angio-oedema	2	0.3	3	1.4	5	0.6
Acute dystonia	3	0.5	1	0.5	4	0.5
Allergic/atopic conditions	3	0.5	1	0.5	4	0.5
Syncope	2	0.3	1	0.5	3	0.4
Hyperprolactinaemia	3	0.5	0	0.0	3	0.4
Hepatic impairment	1	0.2	2	0.9	3	0.4
Hyperthyroidism	2	0.3	0	0.0	2	0.2
Renal impairment (stage 1–2 CKD)	2	0.3	0	0.0	2	0.2
Tardive dyskinesia	1	0.2	0	0.0	1	0.1
Neuroleptic malignant syndrome	1	0.2	0	0.0	1	0.1
Myocardial infarction	0	0.0	1	0.5	1	0.1
Renal failure	1	0.2	0	0.0	1	0.1
Renal Impairment (stage 3–4 CKD)	0	0.0	1	0.5	1	0.1

(Continued)

Table 2. (Continued)

Event	XL user *n* = 632		IR user *n* = 213		Total *n* = 845	
	n	%	*n*	%	*n*	%
Malignancies	1	0.2	0	0.0	1	0.1
Severe cutaneous ADRs	1	0.2	0	0.0	1	0.1
Haemopoetic disorder	1	0.2	0	0.0	1	0.1
Agranulocytosis	1	0.2	0	0.0	1	0.1

ADR, adverse drug reaction; CKD, chronic kidney disease; IR, immediate release; XL, extended release.

Cochrane review compared quetiapine with other antipsychotics for use in schizophrenia and identified that quetiapine was more sedating than ziprasidone ($n = 754$, two randomised controlled trials, relative risk = 2.2 confidence interval 1.35–3.63).[15] In a small study conducted in patients with stable bipolar I disorder, the acute sedative effects of risperidone and quetiapine were compared. Patients self-reported that they were significantly sleepier whilst receiving quetiapine treatment compared with risperidone.[16]

Depression was also frequently reported; the frequency of depression reported in the XL cohort was 12.7%. A study that aimed to prospectively measure the link between depressive symptoms and functional outcomes in the long-term treatment of people with schizophrenia assessed patients at enrolment and again at 12 months.[17] This study found approximately one-third (39.4%) of the participants with schizophrenia were concurrently depressed at enrolment. The depressed group were significantly more likely to have an earlier age at onset of their illness, schizoaffective disorder diagnosis, psychiatric hospitalisation in the previous year, and a comorbid diagnosis of personality disorder (primarily personality disorder not otherwise specified). During the 6 months prior to enrolment, the depressed subjects were less likely to be treated with typical antipsychotics and were more likely to be treated with antidepressants, anti-anxiety agents, mood stabilizers and hypnotics.[17]

In the XL cohort, frequency of suicide/self-injury was 7%, which is in concordance with the summary of product characteristics as this event is listed as common (frequency $\geq 1\%$ and $< 10\%$).[1] The possible association between antipsychotic medication use and suicidal ideation/attempt has been investigated extensively and there are numerous publications in the literature. Amongst patients with schizophrenia or major depression, a lifetime risk of suicide has been estimated to be 5% and 3.4%, respectively.[18,19] In contrast, the lifetime rate of suicide attempts in a sample of patients with bipolar I, bipolar II, or schizoaffective disorder (bipolar type) has been estimated to be much higher, and determined to be 25.6%.[20] Within studies of both bipolar disorder and schizophrenia, patients with a history of suicidal behaviours or depression are more likely to have poorer long-term functional outcome and a more difficult course of illness, including further suicidal behaviours.[17,21] Warnings of a possible risk of suicidal ideation and behaviour have been inserted in the product label of quetiapine XL and other antipsychotic and antidepressant medication. However, undertaking an assessment of any causal relationship between a drug and a suicidal event is complicated by the high background rate of such events in the treated populations and the high prevalence of known risk factors for suicidal behaviour. It is for this reason that drug relatedness assessments were not undertaken for these events within OASIS.

Potential episodes of suicidal behaviour were identified and all available information was reviewed for each identified eligible case. Within the XL cohort, 20 events (3.1%) were classified as suicidal events (suicidal ideation or behaviour) according to C-CASA. Within the IR cohort, 12 (5.4%) were classified as suicidal events.

Overall, the OASIS study provided data on real-life use of quetiapine XL in the immediate post marketing period. Utilisation appeared to be in line with prescribing guidelines in terms of dose, and the frequency of events of interest

reported was consisted with the product label. Comparison of prior medical history between the XL and IR cohorts revealed potential channelling of quetiapine XL towards those without a history of cardiac events, suggesting that the XL user population may be different to the IR user population. However, the most commonly reported events of interest occurred at similar frequency within the two indication cohorts.

Limitations

It is important to note that patients being treated for the depressed phase in their bipolar illness were excluded from the OASIS study. Therefore this may impact on the rates of depression and suicidal ideation/behaviours seen in the cohort.

A recognised limitation of the study is the selection bias introduced by the lower than anticipated levels of recruitment, particularly within the IR cohort. It was originally anticipated that recruitment of patients prescribed the IR formula would be greater than those prescribed the XL formulation in the early years of the study; however, the converse was observed. Moreover, recruitment of XL patients remained greater than IR patients throughout the study. The lower than planned recruitment limited the analysis that could be performed and any inferences thereof.

Patients were required to give informed consent to participate in the OASIS study. One issue with conducting such a study in the psychiatric population is the ability of the patient to give informed consent. An individual's autonomy is essential to giving genuinely informed consent. Within psychiatric patients, this autonomy may be limited since the patient's clinical state may render them unable to exercise free judgement, or it may interfere with the thought processes required to comprehend the nature of the research proposed.[22] Studies have shown that patients with schizophrenia or schizoaffective disorder have a lower decision-making capacity when compared with medically ill and non-ill patients.[23] Cognitive capacity, physical functioning and a diagnosis of mental illness have been shown to have the greatest impact on decision-making capacity.[16] Patients approached to participate in the OASIS study were those newly initiated on quetiapine. It is possible therefore that patients would have not been stable on their medication, with their illness controlled, at the time that informed consent was sought. Reports from psychiatrists indicated that this posed problems with seeking informed consent from patients and that potential participants were lost due to being unable to give informed consent at the time of quetiapine initiation.

Conclusion

The OASIS study provided important information on the safety and utilisation of quetiapine XL in the secondary care setting in England. Utilisation appeared to be in line with prescribing guidelines in terms of dose. Somnolence and sedation were the most commonly reported events, which is in line with the known safety profile.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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References

1. Seroquel XL. Summary of product characteristics, AstraZeneca UK Limited: UK, https://www.medicines.org.uk/emc/product/6363/smpc (accessed 07 July 2020).

2. Rawlins MD and Jefferys DB. United Kingdom product licence applications involving new active substances, 1987-1989: their fate after appeals. *Br J Clin Pharmacol* 1993; 35: 599–602.
3. Osborne V and Shakir SAW. Event monitoring in the UK. In: *Pharmacoepidemiology*. Hoboken, NJ: Wiley-Blackwell, 2019.
4. European Medicines Agency. Risk-management plans, https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pharmacovigilance/risk-management/risk-management-plans (2018, accessed 25 June 2020).
5. Posner K, Oquendo MA, Gould M, *et al.* Columbia classification algorithm of suicide assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry* 2007; 164: 1035–1043.
6. Health Management and Policy Alert. *Patterns of specialist mental health service usage in England*. Office for National Statistics, 2010.
7. Peuskens J, Trivedi J, Malyarov S, *et al.* Prevention of schizophrenia relapse with extended release quetiapine fumarate dosed once daily. *Psychiatry Edgmont* 2007; 4: 34–50.
8. Kahn RS, Schulz SC, Palazov VD, *et al.* Efficacy and tolerability of once-daily extended release quetiapine fumarate in acute schizophrenia: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2007; 68: 832–842.
9. Layton D, Souverein PC, Heerdink ER, *et al.* Evaluation of risk profiles for gastrointestinal and cardiovascular adverse effects in nonselective NSAID and COX-2 inhibitor users: a cohort study using pharmacy dispensing data in The Netherlands. *Drug Saf* 2008; 31: 143–158.
10. Leufkens HG, Urquhart J, Stricker BH, *et al.* Channelling of controlled release formulation of ketoprofen (Oscorel) in patients with history of gastrointestinal problems. *J Epidemiol Community Health* 1992; 46: 428–432.
11. Seroquel XR (quetiapine fumarate) extended-release tablets - US prescribing information: AstraZeneca Pharmaceuticals LP; UK, https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022047s011s016s017s019s022lbl.pdf (2009, accessed 07 July 2020).
12. BMJ Publishing Group Ltd and Royal Pharmaceutical Society. *British National Formulary*. 2013.
13. Datto C, Berggren L, Patel JB, *et al.* Self-reported sedation profile of immediate-release quetiapine fumarate compared with extended-release quetiapine fumarate during dose initiation: a randomized, double-blind, crossover study in healthy adult subjects. *Clin Ther* 2009; 31: 492–502.
14. Bui K, Earley W and Nyberg S. Pharmacokinetic profile of the extended-release formulation of quetiapine fumarate (quetiapine XR): clinical implications. *Curr Med Res Opin* 2013; 29: 813–825.
15. Asmal L, Flegar SJ, Wang J, *et al.* Quetiapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev* 2013; 11: CD006625.
16. Harvey PD, Hassman H, Mao L, *et al.* Cognitive functioning and acute sedative effects of risperidone and quetiapine in patients with stable bipolar I disorder: a randomized, double-blind, crossover study. *J Clin Psychiatry* 2007; 68: 1186–1194.
17. Conley RR, Ascher-Svanum H, Zhu B, *et al.* The burden of depressive symptoms in the long-term treatment of patients with schizophrenia. *Schizophr Res* 2007; 90: 186–197.
18. Blair-West GW, Cantor CH, Mellsop GW, *et al.* Lifetime suicide risk in major depression: sex and age determinants. *J Affect Disord* 1999; 55: 171–178.
19. Hor K and Taylor M. Suicide and schizophrenia: a systematic review of rates and risk factors. *J Psychopharmacol* 2010; 24(Suppl. 4): 81–90.
20. Dalton EJ, Cate-Carter TD, Mundo E, *et al.* Suicide risk in bipolar patients: the role of co-morbid substance use disorders. *Bipolar Disord* 2003; 5: 58–61.
21. Leverich GS, Altshuler LL, Frye MA, *et al.* Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley foundation bipolar network. *J Clin Psychiatry* 2003; 64: 506–515.
22. Dyer AR and Bloch S. Informed consent and the psychiatric patient. *J Med Ethics* 1987; 13: 12–16.
23. Candilis PJ, Fletcher KE, Geppert CMA, *et al.* A direct comparison of research decision-making capacity: schizophrenia/schizoaffective, medically ill, and non-ill subjects. *Schizophr Res* 2008; 99: 350–358.