European Psychiatry 33 (2016) 61–67

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

Utilisation of extended release quetiapine (Seroquel XL™): Results from an observational cohort study in England

V. Osborne *, M. Davies, D. Layton, S.A.W. Shakir

Drug Safety Research Unit, Bursledon Hall, Blundell Lane, Southampton SO31 1AA, UK

ARTICLE INFO

Article history:
Received 22 September 2015
Received in revised form 17 December 2015
Accepted 18 December 2015
Available online

Keywords:
Mania and bipolar disorder
Schizophrenia and psychosis
Epidemiology
Psychopharmacology

ABSTRACT

Background: A post-authorisation safety study was carried out as part of the EU Risk Management Plan to examine the long-term (up to 12 months) use of quetiapine XL as prescribed in general practice in England.
Aim: To present a description of the drug utilisation characteristics of quetiapine XL.
Methods: An observational, population-based cohort design using the technique of Modified Prescription-Event Monitoring (M-PEM). Patients were identified from dispensed prescriptions issued by general practitioners (GPs) for quetiapine XL between September 2008 and February 2013. Questionnaires were sent to GPs 12 months following the 1st prescription for each individual patient, requesting drug utilisation information. Cohort accrual was extended to recruit additional elderly patients (special population of interest). Summary descriptive statistics were calculated.
Results: The final M-PEM cohort consisted of 13,276 patients; median age 43 years (IQR: 33, 55) and 59.0% females. Indications for prescribing included bipolar disorder ($n = 3820$), MDD ($n = 2844$), schizophrenia ($n = 2373$) and other (non-licensed) indications ($n = 3750$). Where specified, 59.3% (7869/13,276) were reported to have used quetiapine IR (immediate release formulation) previously at any time. The median start dose was highest for patients with schizophrenia (300 mg/day [IQR 150, 450]). The final elderly cohort consisted of 3127 patients and 28.5% had indications associated with dementia. The median start dose for elderly patients was highest for patients with schizophrenia or BD (both 100 mg/day [IQR 50, 300]).
Conclusions: The prevalence of off-label prescribing in terms of indication and high doses was common, as was use in special populations such as the very elderly. Whilst off-label use may be unavoidable in certain situations, GPs may need to re-evaluate prescribing in circumstances where there may be safety concerns. This study demonstrates the ongoing importance of observational studies such as M-PEM to gather real-world clinical data to support the post-marketing benefit:risk management of new medications, or existing medications for which license extensions have been approved.

1. Introduction

In the European Union (EU), Risk Management Plans (RMPs) became a regulatory requirement in 2005. Revised EU pharmacovigilance guidelines on RMPs came into force in 2012 and were subsequently revised in April 2014 [1]. At the time of authorisation, information on the long-term safety of a medicinal product can be relatively limited, so Post-Authorisation Safety Studies (PASS) may be included in the RMP to assess safety in populations/subpopulations after market launch [2]. Such studies may be requested as part of the RMP for new formulations of licensed medicines, such as the extended release version of quetiapine.

1.1. Seroquel XL™

Extended release quetiapine fumarate (Seroquel XL™; AstraZeneca), a once-daily atypical antipsychotic is licensed in the UK for the treatment of schizophrenia and manic episodes associated with bipolar disorder (BD) in adult patients (September 2008), the treatment of major depressive episodes in BD in adult patients (September 2009), for prevention of recurrence of manic, depressive, or mixed episodes in BD (January 2010), and as add-on treatment of major depressive episodes in patients with major depressive disorder (MDD) who have had sub-optimal response to

* Corresponding author. Tel./fax: +44 0 23 8040 8600.
E-mail address: vicki.osborne@dsru.org (V. Osborne).

http://dx.doi.org/10.1016/j.eurpsy.2015.12.004
0924-9338/

antidepressant (April 2010) [3]. Seroquel XL™ is the extended release version of immediate release quetiapine (Seroquel™), which has been licensed in the UK since 1997 [4]. Quetiapine XL was developed to provide more convenient and simpler administration for patients through once daily dosing, as opposed to the immediate release formulation [5]. This is achieved through the delayed release of the XL formulation, which allows plasma drug concentrations to be maintained at constant levels for a longer time period [6]. Faster dose titration and a different pharmacological and tolerability profile have been shown with quetiapine XL in comparison to the immediate release formulation [5,7].

The recommended dose at start of therapy with quetiapine XL for schizophrenia and for manic episodes associated with BD is 300 mg/day. For treatment of depressive episodes associated with BD and add-on treatment of MDD the recommended start dose is 50 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 [3]. Consideration should be given to slower rate of dose titration and lower target dose to special populations such as the elderly. Such patients should be started on 50 mg/day, with increasing increments of 50 mg/day depending on response and tolerance. For patients for whom an effective dose has been achieved with immediate release formulation, but switching is desired, then the patient may be switched to the XL formulation at an equivalent once daily dose [3].

1.2. Modified Prescription-Event Monitoring (M-PEM) Studies

M-PEM studies provide active surveillance of targeted medicines on a national scale in England [8]. M-PEM studies systematically collect information on baseline characteristics of patients in relation to pre-specified risks, physician prescribing and decision-making behaviours, and can quantify the incidence and prevalence of risks of adverse events after treatment initiation. As such, M-PEM is recognised as a tool to conduct real-world PASS that not only align with risk management objectives to gather additional safety monitoring information or assess a pattern of drug utilization, but also satisfy key regulatory requirements for marketing authorization holder (MAH) RMP needs. For example, M-PEM studies can gather data on potential off-label use (which occurs when a drug is prescribed for an indication, a route of administration or to a group that is not included in the approved product information document for that drug).

This post-marketing M-PEM study was carried out by the DSRU as requested by the Medicines and Healthcare Regulatory Agency (MHRA) in the UK as a post approval commitment by the MAH for quetiapine XL. It was incorporated into the EU RMP for the product. The overall aim of the M-PEM study was to examine the safety and long-term (up to 12 months) use of quetiapine XL as prescribed in general practice in England. There was no requirement to perform a comparative study with other antipsychotics. This paper presents the results of one of the study objectives: to provide a description of the drug utilisation characteristics of quetiapine XL.

2. Methods

2.1. Study design

M-PEM uses an observational, population-based cohort design for post-marketing surveillance. It offers the opportunity to systematically collect information at the patient level for the whole cohort, defined according to a single common exposure (the study drug), and identify subgroups defined by particular prognostic characteristics. The methodology has been published in detail elsewhere [8] but is outlined briefly below.

2.2. Identification of patients

Patients were identified from dispensed National Health Service (NHS) prescriptions for quetiapine XL, written by general practitioners (GPs) in England between September 2008 and February 2013. These prescription data were supplied in confidence to the DSRU by the NHS Business Services Authority (NHSBSA). Data provided in confidence by the NHSBSA include prescription date, drug name, patient and prescribing physician names and addresses.

At least twelve months after the first identified quetiapine XL prescription was issued for each patient, the prescribing GP was sent a postal questionnaire. All patients were included where a returned questionnaire was received that confirmed that quetiapine XL had been prescribed. Patients were included in the study regardless of the indication for prescribing, dose or frequency of administration of quetiapine XL.

The M-PEM study sample size was based on achieving a final evaluable cohort of at least 10,000 patients. Following the extension of the range of indications, a regulatory requirement was that the evaluable cohort was also to be comprised of a minimum of 1000 patients with bipolar disorder (BD) and a minimum of 1000 patients with major depressive disorder (MDD). For each of these indication groups, at least 500 were to be elderly patients aged 65 years and above (elderly cohort). Accordingly, data collection was extended in 2011 and 2012 to selectively capture data for these elderly patients to facilitate attainment of each of the minimum target numbers.

2.3. Data collection

The M-PEM questionnaire requested information on how quetiapine XL was prescribed in the real-world setting. GPs were asked to summarise relevant information recorded in the patient's medical charts as part of routine clinical care. This included the indication for prescribing, the start dose, the maintenance dose and date the maintenance dose was reached. Information on who initiated treatment (psychiatrist or GP) was requested. GPs were also asked to provide information on the pre-quetiapine XL exposure baseline risk status of patients; this included particular focus on specific conditions of interest (raised blood glucose, new onset or worsening of Type II diabetes mellitus, metabolic syndrome, blood dyscrasias [neutropenia and agranulocytosis], extrapyramidal symptoms/sedation [including drowsiness]). This information was requested for the three months time period prior to starting quetiapine XL, which was chosen to capture information on recent and acute changes in patient health as well as known relevant long-term conditions. Information on medications used in the 30 days prior to starting treatment with quetiapine XL was also requested. This time period was chosen to identify possible concomitant prescribing of medications associated with drug-drug interactions. Specifically, the GP was asked if the patient had used immediate release quetiapine, other atypical antipsychotics, other psychoactive drugs (e.g. drugs which act on the central nervous system) or CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, nelfinavir, ritonavir, aprepitant, diltiazem, verapamil, erythromycin, fluconazole, fosamprenavir, grapefruit juice) during this period.

2.4. Analysis

Data analysis consisted of summary tabulations and figures to describe the utilization pattern of quetiapine XL. Total counts and proportions expressed as percentage of total responses were provided. Categorical counts for pre-defined ranges and standard dispersion parameters were used to describe patient characteristics. Prevalence ratios were also calculated. Where possible, data were

also stratified by the indication as relevant. A Kaplan-Meier survival estimate was used to examine person–time on treatment.

2.5. Ethical considerations

This study was conducted in accordance with national and international guidelines [9,10]. In addition, under Section 251 of the NHS Act 2006, the DSRU have received support from the Ethics and Confidentiality Committee of the National Information Governance Board to gain access to and process patient identifiable information without consent for the purposes of medical research [11].

3. Results

3.1. Cohort characteristics

In total, of the 34,326 questionnaires posted to prescribing GPs for individual patients, 19,185 (55.9%) were returned and of these 4569 (23.8%) were excluded. The most frequent reasons for exclusion were patient not registered (where the patient had either moved or was a temporary patient and so was no longer registered; $n = 1976$), no record of drug (where the GP could not find the prescribing record on their computer system; $n = 1609$) and blank questionnaire returned (no clinical information provided; $n = 512$). Thus useful clinical information was available on a cohort of 14,616 evaluable patients. Of these, 13,276 patients contributed to main M-PEM cohort (Fig. 1). An additional 1340 eligible elderly patients were identified through the extension to the study to specifically capture patients aged 65 years and above (elderly cohort). This resulted in a pooled evaluable elderly cohort of 3127 patients. The final M-PEM cohort was evaluated separately to the elderly cohort.

The characteristics of the main M-PEM cohort are displayed in Table 1 and the characteristics of the elderly cohort are displayed in Table 2. Seventy-eight patients were aged less than 18 years old in the main M-PEM cohort.

In terms of any prior use of quetiapine, 59.3% ($n = 7869$) of the main M-PEM cohort were reported to have used quetiapine IR (immediate release formulation) previously at any time and 63.4% ($n = 1982$) of patients within the elderly cohort were reported to have used quetiapine IR previously at any time.

3.2. Treatment initiation

3.2.1. Main M-PEM cohort

The most frequent indication for prescribing was BD ($n = 3820$, 29.9% where indication specified). In total, 28.3% of patients in the cohort were prescribed quetiapine XL for non-licensed indications. The most frequently reported non-licensed indications were psychotic disorder ($n = 692$, 11.8% of non-licensed indications) and depression ($n = 668$, 11.4% of non-licensed indications). Of note, depression which is considered non-licensed is depression other than MDD.

The initiating practitioner was specified for 12,603 patients, of which the most frequent type was a psychiatrist ($n = 12,097$, 94.9% where type specified).

3.2.2. Elderly cohort

The most common indication for prescribing in the elderly cohort was other (non-licensed) indications ($n = 1493$, 51.4% where indication specified). More than one indication verbatim term could be reported for patients with non-licensed indications and, in total, 2334 indication terms were reported. The most frequently reported of these verbatim indications was dementia in 560 patients (24.0% of all verbatim non-licensed indication terms [$n = 2334$]).

In total, 861 subjects (57.7% of patients with non-licensed indications) were reported to have indications associated with dementia at start date. The corresponding prevalence in the elderly cohort was 28.5% ($n = 892$); the additional 31 patients having concomitant indications of schizophrenia ($n = 7$), BD ($n = 7$) and MDD ($n = 17$).

The initiating practitioner was specified for 2818 elderly patients, of which the most frequent type was a psychiatrist ($n = 2436$, 86.4% where type specified).

3.3. Dose

3.3.1. Main M-PEM cohort

Where dose at start was specified ($n = 12,028$), the median dose on starting quetiapine was 200 mg/day (IQR 50, 300). After stratification by indication, the median start dose was highest for patients with schizophrenia (300 mg/day [IQR 150, 450]),

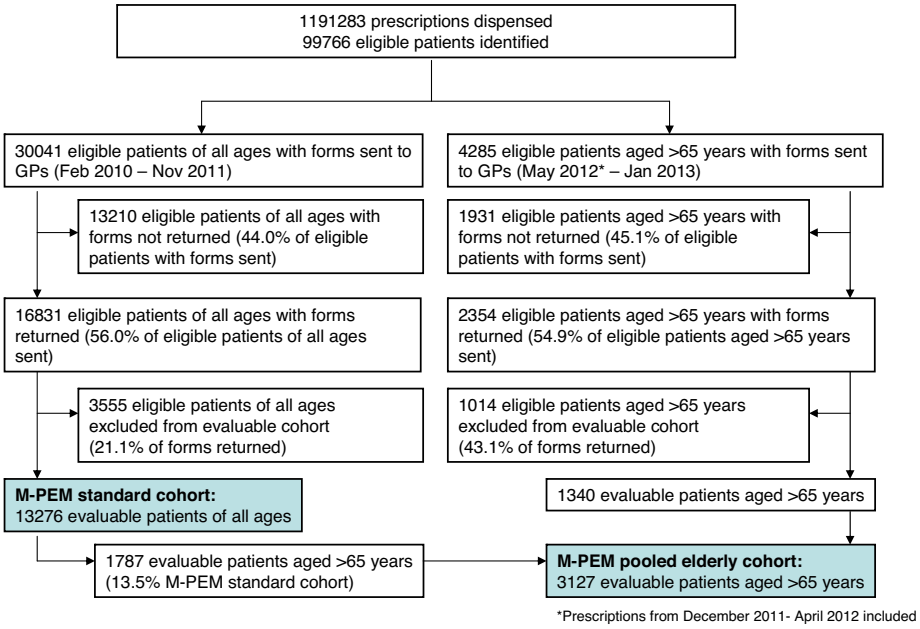

Fig. 1. Flow chart defining evaluable cohort.

Table 1
Cohort characteristics of main M-PEM cohort.

Characteristics	Total cohort $n = 13276$	Indication: schizophrenia $n = 2373$	Indication: bipolar disorder $n = 3820$	Indication: major depressive disorder $n = 2844$	Indication: non-licensed indications $n = 3750$
Age at start of treatment (years)					
Median age (IQR)	43 (33, 55)	42 (32, 53)	43 (34, 53)	44 (35, 54)	44 (32, 64)
Sex, n (% specifed)					
Males	5447 (41.0)	1283 (54.1)	1236 (32.4)	1075 (37.8)	1644 (43.7)
Females	7828 (59.0)	1088 (45.9)	2574 (67.6)	1769 (62.2)	2117 (56.3)
Initiating practitioner, n (% specified)					
Psychiatrist	12097 (94.9)	2218 (96.6)	3622 (97.1)	2652 (95.4)	3278 (91.5)
General practitioner (GP)	506 (4.0)	60 (2.6)	91 (2.4)	109 (3.9)	228 (6.4)
Other	140 (1.1)	17 (0.7)	19 (0.5)	20 (0.7)	76 (2.1)
Medications used in 30 days prior, n (% specified)					
Other atypical antipsychotic	2460 (24.4)	708 (39.2)	702 (23.8)	450 (19.8)	563 (19.3)
Other psychoactive drug	5915 (62.8)	784 (52.0)	1878 (66.6)	1618 (73.3)	1553 (56.8)
CYP3A4 inhibitor	595 (8.6)	89 (7.3)	186 (9.1)	1553 (56.8)	152 (7.8)
Morbidities reported within 3 months prior to start[a]*, n (% specified)*					
Extrapyramidal symptoms	303 (3.1)	103 (6.1)	66 (2.3)	54 (2.4)	73 (2.6)
Somnolence/sedation	1456 (15.4)	248 (15.0)	547 (20.0)	296 (14.0)	337 (12.3)
Depression	4411 (43.2)	446 (26.0)	1351 (44.6)	1542 (64.0)	1014 (35.0)
Type 2 Diabetes Mellitus	612 (5.8)	145 (7.8)	168 (5.4)	132 (5.6)	156 (5.1)

[a] Only selected morbidities were requested on the questionnaire, the top four are presented here.

whilst patients treated for MDD or other indications had the lowest observed median start doses (both 100 mg/day [IQR 50, 300]).

The final maintenance dose at the end of the 12-month observation period where specified ($n = 9180$) was also examined and, for the whole cohort, the median maintenance dose was higher than at start dose (300 mg/day [QR 100, 600]). Again, after stratification by indication median maintenance dose in the schizophrenia group was the highest of all groups (400 mg/day [IQR 300, 600]).

A high proportion of patients with schizophrenia were commenced on start doses in excess of 300 mg/day ($n = 741$, 34.7% where specified). Additionally, a high proportion of patients with BD were commenced on start doses in excess of 300 mg/day ($n = 836$, 23.9% where specified). Over half of patients with MDD ($n = 1616$, 61.1%) were commenced at doses in excess of 50 mg/day. In terms of maintenance dose, the proportions in the M-PEM cohort prescribed in excess of 800 mg/day for schizophrenia or BD were much lower ($n = 15$, 1.1% and $n = 9$, 0.4% respectively), whilst a high proportion of those treated for MDD were maintained at doses in excess of the recommended 300 mg/day ($n = 468$, 28.4%).

The time from start dose to maintenance dose was calculated as the time from the start date to the maintenance dose date within the 12-month observation period, where both dates were provided by the GP. Within this period, 5576 (61.7% of 9,043 at start) patients were recorded as achieving maintenance dose in the M-PEM cohort. The median time from start dose date to maintenance dose date for the whole cohort was 72 days (IQR 14, 236). Approximately 16% of patients achieved maintenance dose within the first 10 days; this occurring most frequently for those treated for schizophrenia ($n = 304$, 19.44% of indication schizophrenia where dose data specified).

3.3.2. Elderly cohort

In the elderly cohort, where dose at start was specified ($n = 2735$), the median dose on starting quetiapine was 50 mg/day (IQR 50, 100). When data were stratified by indication, the

Table 2
Cohort characteristics of elderly cohort.

Characteristics	Total cohort $n = 3127$	Indication: schizophrenia $n = 357$	Indication: bipolar disorder $n = 529$	Indication: major depressive disorder $n = 526$	Indication: non-licensed indications $n = 1493$
Age at start of treatment (years)					
Median age (IQR)	77 (69, 84)	71 (67, 77)	70 (67, 76)	73 (68, 80)	81 (74, 86)
Sex, n (% specified)					
Males	1187 (38.0)	115 (32.2)	173 (32.7)	205 (39.0)	607 (40.7)
Females	1940 (62.0)	242 (67.8)	356 (67.3)	321 (61.0)	886 (59.3)
Initiating practitioner, n (% specified)					
Psychiatrist	2436 (86.4)	314 (92.6)	490 (95.3)	437 (87.4)	1128 (81.7)
General Practitioner (GP)	283 (10.0)	24 (7.1)	18 (3.5)	52 (10.4)	180 (13.0)
Other	99 (3.5)	1 (0.3)	6 (1.2)	11 (2.2)	73 (5.3)
Medications used in 30 days prior, n (% specified)					
Other atypical antipsychotic	376 (16.7)	101 (37.1)	88 (22.1)	68 (16.7)	111 (9.8)
Other psychoactive drug	1092 (52.7)	115 (49.6)	245 (64.8)	268 (69.3)	446 (43.1)
CYP3A4 inhibitor	151 (9.1)	20 (10.5)	34 (11.5)	30 (10.4)	65 (7.7)
Morbidities reported within 3 months prior to start[a]*, n (% specified)*					
Extrapyramidal symptoms	134 (6.1)	22 (8.4)	17 (4.3)	29 (7.4)	62 (5.6)
Somnolence/sedation	274 (12.9)	32 (13.1)	52 (13.7)	42 (11.6)	140 (12.8)
Depression	715 (31.6)	56 (21.6)	173 (41.6)	272 (62.1)	207 (18.6)
Type 2 Diabetes Mellitus	262 (10.9)	47 (16.4)	70 (15.7)	40 (9.3)	100 (8.3)

[a] Only selected morbidities were requested on the questionnaire, the top four are presented here.

median start dose tended to be highest for patients with schizophrenia or BD (both 100 mg/day [IQR 50, 300]), whilst patients treated for MDD or non-licensed indications had lower observed median start doses (both 50 mg/day [IQR 50, 100]).

The final maintenance dose at the end of the 12-month observation period where specified in the elderly cohort (n = 1620) was also examined and for the whole cohort the median maintenance dose was slightly higher than at start dose (100 mg/day [IQR 50, 200]). Again, after stratification by indication median maintenance dose was the highest for schizophrenia and BD groups (200 mg/day [IQR 100, 400] and 200 mg/day [IQR 100, 300]).

The median time from start dose to maintenance dose for the elderly cohort was 63 days (IQR 13, 227), which was shorter than in the main M-PEM cohort.

3.4. General health characteristics

3.4.1. Main M-PEM cohort

The most frequently reported pre-existing condition, irrespective of indication, within the three months prior to starting quetiapine XL was depression (n = 4411 patients, 43.2% where specified). Depression was also the most frequently reported pre-existing morbidity for each of the three licensed indications. Depression was 2.46 times more frequent in those treated for MDD than schizophrenia (Prevalence ratio [PR] 2.46 [95% CI 2.26, 2.68]) and also significantly higher than those treated for BD (PR 1.43 [95% CI 1.36, 1.51]) and non-licensed indications (PR 1.83 [95%CI 1.73, 1.94]).

3.4.2. Elderly cohort

The most frequently reported morbidity in the three months prior to start date was depression in 715 patients (31.6% where response provided), followed by somnolence/sedation in 274 patients (12.9% where response provided). After stratification by indication group, depression remained the most frequently reported morbidity in the three months prior to start date, for each of the three licensed indications and also for patients with non-licensed indications; the highest prevalence was in the MDD group.

3.5. Prior medication use

3.5.1. Main M-PEM cohort

The most frequently reported medication used, irrespective of indication, in the 30 days prior to starting treatment was "Other psychoactive drug" (other than atypical antipsychotics) in 5915 patients (62.8% where response provided n = 9416); this was also the most frequently reported prior therapeutic agent within each indication. However, the prevalence of such reported use in the month prior to start date was more common in patients with MDD, compared to those treated for schizophrenia (73.3% vs. 52.0%; PR 1.41 [95% CI 1.34, 1.49]). The same pattern was observed for BD (73.3% vs. 66.6%; PR 1.10 [95% CI 1.06, 1.14]) and non-licensed indications (73.3% vs. 56.8%; PR 1.29 [95% CI 1.24, 1.34]).

3.5.2. Elderly cohort

Overall, the most frequently reported medication prior to start date was "other psychoactive drug" in 1092 patients (52.7% where response provided). After stratification by indication group, other psychoactive drug was still the most frequently reported medication prior to start date within each licensed indication group, with the highest prevalence in the MDD indication group (69.3% where response provided). However, for patients with non-licensed indications, the most frequently reported medication in the 30 days prior to start date was quetiapine IR (n = 564, 44.6% where response provided).

4. Discussion

4.1. General discussion

4.1.1. Main M-PEM cohort

The final M-PEM cohort consisted of 13,276 patients. The most frequent indication for prescribing was BD (29.9% where indication specified). This proportion is consistent with results obtained in another cohort study conducted in the US, in which 32.4% (n = 25,245) of a cohort of all antipsychotic users (n = 77,946 in total) had an indication of BD [12]. In the M-PEM study, a further 2373 patients (18.6% where specified) had an indication of schizophrenia. This was slightly higher than the proportion of patients with a diagnosis of schizophrenia seen amongst the US cohort of antipsychotic users, which included 14.3% of patients with schizophrenia (n = 11,170) [12]. In terms of demographics, within the M-PEM cohort, 7828 (59.0% of cohort) were females and 5447 (41.0% of cohort) males. At start date, the median age of the M-PEM cohort was 43 years (IQR 33, 55); this is also consistent with the US cohort study by Yood et al., in which 60.1% of the antipsychotic users were female (n = 46,817) and the median age was found to be 45 years [12]. As such, the characteristics of patients being prescribed quetiapine XL in England would appear to be similar to antipsychotic users in the US. The study by Yood et al. used data from three sources of electronic healthcare databases in the US which contained pharmacy data and claims records for diagnoses [12]. There are several key differences between this US based study and the M-PEM study based in the UK including methodology, data source and healthcare structure. Therefore these data cannot be directly compared and should be interpreted with caution.

Quetiapine XL is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group [3]. In this study, there were 78 patients in the cohort aged less than 18 years, indicating a very low percentage of such patients ($< 1\%$) were being prescribed quetiapine XL.

As expected in this M-PEM study, the most frequent initiating practitioner specified was a psychiatrist (94.9% where type specified); this is consistent with recommendations included within the UK National Institute for Health and Care Excellence (NICE) guidelines for schizophrenia and BD, recommending that patients with first presentation of psychotic symptoms or suspected BD be referred to secondary care for further evaluation [13,14].

A high proportion of patients with schizophrenia, BD or MDD were commenced on start doses in excess of the Summary of Product Characteristics (SPC) upper recommended start dose. In terms of maintenance dose, the proportions in the M-PEM cohort prescribed in excess of that recommended within the SPC for schizophrenia or BD were much lower, whilst a high proportion of those treated for MDD were maintained at doses in excess of the recommended 300 mg/day.

The Royal College of Psychiatrists consensus statement on high-dose antipsychotic use states that there is no evidence to justify using doses higher than those recommended and that high doses should only be used after other evidence-based strategies have failed [15]. One explanation for the common prescribing of high doses is for the treatment of patients with longer psychiatric disease duration at the start date; in such patients higher doses may be required to stabilise and/or maintain the condition. Another explanation is that almost all initiation in this study was by specialist psychiatrists who would have experience of dealing with such patients and therefore experience with prescribing high doses.

The proportion of patients prescribed quetiapine XL who had one or more characteristics/conditions/co-prescribed medications that were contraindications or warnings for use was examined. Of

conditions considered a special warning or precaution for use, the most frequently reported was somnolence/sedation in 15.4% where specified. Within the SPC, quetiapine is associated with somnolence shortly after starting treatment and thus patients are advised to exercise caution until familiarity with the medication is reached [16].

4.1.2. Elderly cohort

In terms of age, a special population of interest were those patients aged 65 years and over (elderly cohort). As expected, start dose and maintenance doses were generally much lower in elderly patients than that reported for the main M-PEM cohort, which suggests practitioners are following prescribing recommendations and guidelines as quetiapine should be used with caution in the elderly, especially during the initial dosing period.

Approximately half of the elderly cohort had non-licensed indications reported. The overall prevalence of indications associated with dementia (irrespective of indication group) in the elderly cohort was 28.5%. Of the elderly cohort who had indications associated with dementia, 57.7% were patients within the non-licensed indication group (i.e. they had no licensed indication reported at all). A recent study in the Lancet suggested that the prevalence of dementia in the UK in 2011 was 6.5% [17]. There are few published UK data on the level of use of antipsychotic medication among older people in general or people with dementia in particular. The NHS Information Centre for Health and Social Care completed an analysis using the IMS Disease Analyzer database based on a sample of 1,098,627 patients for a 12-month period from 1 April 2007 to 31 March 2008. This yielded 192,190 people (17.5%) over the age of 65 with a record of dementia, of whom 10,255 (5.3%) received a prescription for an antipsychotic [18]. However this may be an underestimate since a formal diagnosis is often not confirmed. A pharmacy led programme reviewing antipsychotic prescribing for people with dementia in the UK found that approximately 15% of patients with dementia were receiving low dose antipsychotics [19]. Taken together, these data suggest that the prevalence of dementia being treated with antipsychotic medication is high, however it is beyond the scope of this study to make any inferences on the benefit: risk balance where such uncertainty regarding the data remains.

The National Institute for health and Care Excellence (NICE) in the UK has published information on the use of antipsychotics in people with dementia. Whilst this document summarises evidence, it is not formal NICE guidance [20]. The NICE formal guidelines on dementia state that people with Alzheimer's disease, vascular dementia, dementia with Lewy bodies (DLB) or mixed dementias with mild-to-moderate non-cognitive symptoms should not be prescribed antipsychotic drugs [21]. However, the guidelines state that people with these conditions with severe non-cognitive symptoms (psychosis and/or agitated behaviour causing significant distress) may be offered treatment with an antipsychotic drug where certain conditions are met [21]. This contradicts the licenses for antipsychotic drugs in the UK, including quetiapine XL, since they are not licensed for use in dementia [22].

4.2. Strengths and limitations

One of the major strengths of M-PEM methodology is that it is non interventional and does not influence prescribing practices. There are also no exclusion criteria i.e. all patients prescribed and dispensed the study drug are eligible for inclusion.

However the response rate for returned questionnaires within this study was 55.9% (19,185 returned, 34,326 sent). As such, non-response bias is a potential limitation of the study. This study did not assess the impact of non-response bias but this response rate is comparable to response rates reported elsewhere for GP postal surveys [23] and higher than the reporting rates of suspected ADRs in the Yellow Card Scheme [24,25]. Another limitation is that underreporting is possible in M-PEM studies, as for any other observational study. Also, exposure in this study is based on dispensed prescription data. These data are more accurate than exposure data based solely on written prescriptions, however patient compliance may still be an issue.

4.3. Conclusions

This M-PEM study informed on aspects of drug utilisation such as determinants of prescribing and cohort characteristics. Quetiapine XL was mostly initiated by psychiatrists and the majority of patients had indications in accordance with prescribing recommendations. Significant between-patient variability in terms of start and maintenance dose was observed, however such differences are expected as part of good clinical practice in individualising therapy. The prevalence of off-label prescribing in terms of indication and high doses was common, as was use in special populations such as the very elderly. However, evidence suggests such prescribing is frequent in the treatment of mental health conditions. Whilst off-label use may be unavoidable in certain situations, GPs may need to re-evaluate prescribing in circumstances where there may be safety concerns. This study demonstrates the ongoing importance of observational studies such as M-PEM to gather real-world clinical data to support the post-marketing benefit:risk management of new medications, or existing medications for which license extensions have been approved.

Author contributions

Vicki Osborne assisted in analysing data, interpreting the results of the study, drafting and revising the paper. Deborah Layton researched background information, designed the M-PEM study, monitored data collection for the study, wrote the statistical analysis plan, assisted in analysing data, interpreting the results of the study and drafting and revising the paper. Miranda Davies and Saad Shakir assisted in designing the M-PEM study, monitoring data collection for the study, interpreting the results of the study and revising the paper.

Disclosure of interest

The Drug Safety Research Unit is an independent charity (No. 327206), which works in association with the University of Portsmouth. It receives unconditional donations from pharmaceutical companies. The companies have no control on the conduct or the publication of the studies conducted by the DSRU. The Unit has received such funds from the manufacturer of Seroquel XL™ (AstraZeneca). Saad Shakir has received money for providing training and advice in pharmacovigilance to pharmaceutical companies. Deborah Layton has received money for development of an educational module on ADR reporting for the Royal Pharmaceutical Society and as a guest lecturer to undergraduate pharmacy students. Vicki Osborne has received money as a guest lecturer to postgraduate pharmacovigilance students. Miranda Davies declares that she has no competing interest.

Acknowledgments

We would like to thank all the staff at the DSRU who contributed to this study. We would like to thank the help of Mr Shayne Freemantle for his assistance with data management and IT support. We thank the GPs who have participated in this study, and without whose general support M-PEM would not be

possible. We also thank the NHS Business Services Authority (NHSBSA) for their important participation.

References

[1] European Medicines Agency. Guideline on good pharmacovigilance practices (GVP): module V – risk management systems (Rev 1); 2014.
[2] European Medicines Agency. Guideline on good pharmacovigilance practices (GVP): module VIII – post-authorisation safety studies (Rev 1); 2013.
[3] AstraZeneca UK Limited. Seroquel XL 50 mg, 150 mg, 200 mg, 300 mg, 400 mg prolonged-release tablets: summary of product characteristics; 2014 [Ref type: pamphlet].
[4] AstraZeneca UK Limited. SEROQUEL 25 mg, 100 mg, 150 mg, 200 mg, 300 mg film-coated tablets; 2014 [Ref type: pamphlet].
[5] Peuskens J, Trivedi J, Malyarov S, Brecher M, Svensson O, Miller F, et al. Prevention of schizophrenia relapse with extended release quetiapine fumarate dosed once daily: a randomized, placebo-controlled trial in clinically stable patients. Psychiatry 2007;4(11):34–50.
[6] Bui K, Earley W, Nyberg S. Pharmacokinetic profile of the extended-release formulation of quetiapine fumarate (quetiapine XR): clinical implications. Curr Med Res Opin 2013;29(7):813–25.
[7] Hallinen T, Soini E, Granstrom O, Leinonen E, Koponen H, Hanninen K. Differential use of extended and immediate release quetiapine: a retrospective registry study of Finnish inpatients with schizophrenia spectrum and bipolar disorders. BMJ Open 2012;2:e000915.
[8] Layton D, Hazell L, Shakir SA. Modified prescription-event monitoring studies: a tool for pharmacovigilance and risk management. Drug Saf 2011;34:e1–9.
[9] CIOMS/WHO. International guidelines for biomedical research involving human subjects. Geneva: CIOMS; 2002 [Available from: URL: http://www.cioms.ch/publications/layout_guide2002.pdf].
[10] Royal College of Physicians. Guidelines on the practice of ethics committees in medical research involving human subjects, 3rd ed, London: Royal College of Physicians of London; 1996.
[11] Health Research Authority. Advisory Group advice and approval decisions. Prescription-event monitoring, CAG ref: ECC 5-07(b)/2009. HRA; 2013 [Available from: URL: http://www.hra.nhs.uk/about-the-hra/our-committees/section-251/cag-advice-and-approval-decisions/].
[12] Yood MU, DeLorenze G, Quesenberry Jr CP, Oliveria SA, Tsai AL, Willey VJ, et al. The incidence of diabetes in atypical antipsychotic users differs according to agent–results from a multisite epidemiologic study. Pharmacoepidemiol Drug Saf 2009;18(9):791–9.
[13] NICE. Schizophrenia – core interventions in the treatment and management of schizophrenia in adults in primary and secondary care; 2009 [Report nº.: clinical guideline 82].
[14] NICE. Bipolar disorder – the management of bipolar disorder in adults, children and adolescents in primary and secondary care; 2006 [Report nº.: clinical guideline 38].
[15] Royal College of Psychiatrists. Consensus statement on high-dose antipsychotic medication; 2006 [Report nº.: council report CR138].
[16] AstraZeneca. Seroquel XL: UK summary of product characteristics; 2010.
[17] Banerjee S. Good news on dementia prevalence – we can make a difference. Lancet 2013;382:1384–6.
[18] Health IMS. The use of medicines in dementia care. London: IMS; 2009.
[19] Child A, Clarke A, Fox C, Maidment I. A pharmacy led program to review antipsychotic prescribing for people with dementia. BMC Psychiatry 2012;12:155.
[20] National Institute for health and Care Excellence. Low-dose antipsychotics in people with dementia. NICE; 2015 [Available from: URL: http://www.nice.org.uk/advice/ktt7/resources/lowdose-antipsychotics-in-people-with-dementia-1632175200709].
[21] National Institute for health and Care Excellence. Dementia: supporting people with dementia and their carers in health and social care. NICE; 2015 [Available from: URL: http://www.nice.org.uk/guidance/cg42/resources/guidance-dementia-pdf].
[22] Joint Formulary Committee. British National Formulary (BNF) 69. Pharmaceutical Press; 2015.
[23] McAvoy B, Kaner E. General practice postal surveys: a questionnaire too far? BMJ 1996;313(7059):732–3.
[24] Heeley E, Riley J, Layton D, Wilton L, Shakir S. Prescription-event monitoring and reporting of adverse drug reactions. Lancet 2001;358(9296):1872–3.
[25] Martin R, Kapoor K, Wilton L, Mann R. Underreporting of suspected adverse drug reactions to newly marketed (''black triangle'') drugs in general practice: observational study. BMJ 1998;317(7151):119–20.