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Original article

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

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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

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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