Is there a potential of misuse for quetiapine? Literature review and analysis of the European Medicines Agency/EMA Adverse Drug Reactions' database

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Key words: quetiapine; olanzapine; drug misuse; European Medicines Agency; pharmacovigilance

ABSTRACT

Purpose/Background: A recent years' increase in both prescribing and availability of second generation antipsychotics (SGAs) has been observed. According to the literature, typically made up by case studies/series, quetiapine appears to be the most commonly misused SGA, with both intranasal and intravenous intake modalities having been described. Another SGA which has been anecdotally reported to be misused is olanzapine. For these molecules, both a previous history of drug misuse and being an inmate have been described as factors associated with misuse. Hence, whilst providing here an updated literature review of the topic, we aimed here at assessing all cases of quetiapine misuse/abuse/dependence/withdrawal as reported to the EMA's EudraVigilance (EV) database; this was carried out in comparison with the reference drug olanzapine.
Methods: All spontaneous, EMA database, reports relating to both quetiapine (2005-2016) and olanzapine (2004-2016) misuse/abuse/dependence/withdrawal issues were retrieved and a descriptive analysis was performed.
Results: From the EV database, 18,112 (8.64% of 209,571), and 4,178 (7.58% of 55,100) adverse drug reaction (ADR) reports of misuse/abuse/dependence/withdrawal were, respectively, associated with quetiapine and olanzapine. The resulting PRR values suggested that the misuse/abuse-; dependence-; and withdrawal-related ADRs were more frequently reported for quetiapine (respectively, 1.07; 1.01; and 5.25) in comparison with olanzapine.
Conclusions: Despite data collection limitations, present EV data may suggest that, at least in comparison with olanzapine, quetiapine misuse may be a cause for concern.

Key words: quetiapine; olanzapine; drug misuse; European Medicines Agency; pharmacovigilance

Introduction

The intentional misuse of prescribing medications [1] typically involves benzodiazepines; gabapentinoids [2]; opioids; anticholinergics [3]; a range of stimulants [4]; and the selective noradrenalin receptor inhibitors/SNRIs antidepressants [5]. Furthermore, the selective serotonin reuptake inhibitors/SSRIs have been reported to be associated with a risk of both an early and late onset [6] occurrence of withdrawal syndrome [7] (for a thorough review, see [8]). Conversely, there are only a few studies relating to the second generation antipsychotics' (SGA) potential of misuse and withdrawal. Currently, the most popular SGAs medications include aripiprazole, asenapine, clozapine, olanzapine, quetiapine and risperidone. Whilst being associated with a decreased risk of neuroleptic malignant syndrome and extrapyramidal symptoms, SGAs are considered safer than typical antipsychotics. Hence, a related SGAs' increase in prescribing, and hence availability, has recently been reported [9-10]. However, according to the updated (July 2017) PubMed/Medline/Embase literature review here carried out, only specific SGAs, e.g. quetiapine and olanzapine, have emerged as increasingly being misused [1; 3-4]; the following represents an overview of most significant related findings.

Quetiapine and olanzapine; overview of clinical pharmacological and misusing issues

When prescribed, quetiapine is administered in the 400-800 mg/day range for the treatment of schizophrenia; bipolar disorder; and as an add-on in major depression [11], with extensive off label use in anxiety and insomnia. Quetiapine may also be prescribed to treat withdrawal symptoms from abused substances (i.e., alcohol, cocaine, benzodiazepines, or opiates/opioids) whilst alleviating mood symptoms and anxiety [12-14]. However, quetiapine appears to be the most documented abusing SGA; it is anecdotally known as 'Susie Q'; 'Quell'; and 'baby heroin' [13-15], with 'Q ball' and 'Maq ball' being a combination with cocaine [14], or marijuana [16], respectively. Crushed quetiapine tablets can be self-administered through nasal insufflation [17-21], although both oral [13; 22; 23-26], and intravenous routes of administration [13; 19; 27] have been reported. Consistent with these anecdotal clinical observations, post-marketing surveillance reports indicate an increase in quetiapine availability on the black-market [13; 18; 25; 28-29]. Furthermore,

quetiapine, either on its own or in combination with substances such as heroin and/or alcohol [30], is consistently associated with high rates of ambulance attendances, indicating rising community-level harms and greater harm relative to other atypical antipsychotics [31]. Indeed, quetiapine-related emergency department/ED visits increased in the USA by 90% between 2005 and 2011, from 35,581 ED to 67,497 attendances [32]. A 2005-2011 US, general population, National Poison Data System (NPDS) retrospective study on single substance quetiapine exposures [33] identified 3,116 cases of either misuse or abuse, which was more common in adolescents and with a moderate/major toxicity occurring in about 1 out of 4 cases. A more recent (e.g. 2003-2013) NPDS database retrospective analysis, identifying all cases of single-substance second-generation antipsychotic exposures coded as 'intentional abuse', was carried out [34]. During this 10-year period, some 2,118 cases of quetiapine, and 1,379 cases of remaining SGAs', abuse were identified. After quetiapine (representing 60.6% of all abuse cases during the study period), the next most frequently abused molecules were risperidone (530 cases, 15.2%) and olanzapine (246 cases, 7.0%). Among quetiapine cases, some 40.8% were treated and discharged, 10.3% admitted to critical care, and 7.2% admitted to a psychiatric facility.

Data from specific sub-populations provide further insights. Anecdotal reports indicate an increase in misusing levels in prison settings [13-14; 22; 35; 19], where recreational drugs are less readily available and quetiapine anxiolytic/sedative properties may be putatively helpful to cope with drug withdrawal [13]. McLarnon et al [36] examined quetiapine misuse among clients from a community-based methadone maintenance program, and found that 80% of participants reported a lifetime quetiapine use; of these, 21% reported taking quetiapine exclusively without a prescription. Malekshahi et al [37] screened some 429 addict inpatients and found that 73 (17%) reported levels of antipsychotic, and especially quetiapine (96% of cases), misuse which was carried out to enhance and/or counteract the remaining psychotropics' effects [17; 19; 21; 27; 38]. There may be no straightforward pharmacological explanations for non-medicinal quetiapine abuse. Overall, the recreational drugs' 'high' has been associated with increased levels of dopamine in the nucleus accumbens (NAc) shell/mesolimbic areas [15] and, similar to remaining antipsychotics, quetiapine blocks dopamine D2 receptors [16]. However, quetiapine, but not olanzapine, may

increase DA levels [39], preferentially in the NAc shell [40], with some data [41] suggesting as well a quetiapine-associated enhancement of cocaine reinforcing potency. Conversely, mechanisms like fast dissociation from dopamine receptors [12; 42-43]; and prefrontal dopamine release mediated by 5-HT_{1A} receptor activation and 5-HT_{2A} inhibition [44], putatively explaining some recreational effects, are shared by other, non-misusing, SGAs [45]. Hence, there may be other factors [46-47] or pharmacological effects which may be behind the molecule misusing potential. These effects may include: norquetiapine-related norepinephrine reuptake blockade [13]; $5HT_7$ antagonist properties [16]; and sigma receptors' activation [48-49]. Some pharmacokinetics' issues have been suggested to represent important issues as well in facilitating quetiapine misuse [50]. In fact, as quetiapine metabolism is mediated by the human cytochrome CYP3A4, a pharmacokinetic interaction may occur with a variety of drugs, including analgesics, anti-arrhythmia, antibiotics, anticonvulsants, antihistamines, antiparkinsonians, pump inhibitors, steroids, and triptans [50]. Furthermore, the high plasma concentrations of free testosterone in male subjects may contribute to higher CYP3A4 activity, which may be associated with a faster biotransformation of quetiapine, [50] and hence a possible tendency to increase its dosage, in males. Both quetiapine XR and IR formulations are generally well tolerated. However, with respect to the IR one, the XR formulation presents with a delayed (e.g. by approximately 3 hours) and blunted (e.g. by approximately 67%) serum peak, features that may contrast the occurrence of the drug-related 'rush', hence making it less attractive to abusers [28]. Furthermore, the XR formulation coating may make the crushed tablets' snorting quite problematic [29].

Olanzapine, at 5-20mg oral daily dosages, is prescribed to treat schizophrenia, bipolar disorder, and resistant depression [30]. Due to its relaxing/anxiolytic activity [54], olanzapine ('Lilly') has been anecdotally advised, at daily dosages of up to 50mg, as the 'ideal trip terminator/modulator' after a psychedelic drug binge. Valeriani et al [55] carried out a range of exploratory qualitative searches of 163 discussion fora/specialized websites, and found that misusers may ingest olanzapine to treat unwanted 'comedown' symptoms (depression, dysphoria, anxiety, and insomnia) from drug/alcohol intake [56], although olanzapine withdrawal symptoms have been described as well [37; 54]. More recently, it was assessed the prevalence of olanzapine misuse among adult patients

on methadone maintenance treatment attending the National Drug Treatment Centre (NDTC) in Dublin. Out of 92 participating clients, some 30% reported a lifetime history of non-medical use of olanzapine, with 9 people (10%) having reported daily dosages of 30 mg or higher and 3 people (3%) typically ingesting 100 mg. Although the most common reasons for self-administration were to cope with anxiety and sleeping disturbances, a quarter used olanzapine to 'get stoned' [57].

The neuro-pharmacological issues behind olanzapine misuse/self-medication potential may be associated, per se, with its anxiolytic/antipsychotic activity [16]; a 'reshuffling' in GABA(A) receptor subtypes over time [58]; and the rewarding glutamatergic stimulation of the ventral tegmental area dopaminergic neurons [55]. It is of further interest that both quetiapine [59] and olanzapine [60] present with different degrees of $5HT_{2C}$ and histamine/H1 antagonist properties [22; 60-61]. Finally, quetiapine, clozapine, and olanzapine are unique among SGAs, since they possess levels of anticholinergic activity, a pharmacological element which has been associated with a misusing potential [62]. However, olanzapine and clozapine are much more potent than quetiapine at inhibiting the muscarinic M1 receptors [60].

One could tentatively hypothesize that quetiapine and olanzapine are being misused in different ways and/or for different reasons. Both drugs may indeed be self-administered to cope with either anxiety/sleep disturbances and/or with remaining recreational drugs' withdrawal symptoms. However, whilst olanzapine may be ingested/misused to self-medicate the psychopathological issues associated with remaining recreational drugs' intake [55], quetiapine might possess peculiar levels of recreational value as well, which may increase its addictive liability levels [3].

According to the Prescription Cost Analysis (PCA) system [63], the total prescription items dispensed (any formulations) in England for quetiapine (2005-July 2016) and olanzapine (2004-July 2016) were respectively 21,171 and 23,025 thousands. In the same time frame, according to the Drug Analysis Profiles of the Yellow Card Scheme [64], some 2,344 ADRs were reported in the UK for quetiapine; out of these, 32 ADRs were classified as 'drug dependence/drug withdrawal/drug abuse'. In the case of olanzapine, the total number of ADRs reported was 3,452; out of these, 31 ADRs were classified as 'drug dependence/drug withdrawal/drug abuse'. Hence, at least in the UK and in comparison with olanzapine, quetiapine resulted to be: slightly less frequently prescribed;

and associated with a smaller total number of general, and hence a comparatively higher number, of abuse/dependence/withdrawal ADRs' reports. According to the 2015 Norwegian Prescription Database, antipsychotic-related, sales' figures, the pattern of quetiapine dispensing in Norway was likely to reflect a predominant off-label use of the molecule, although the paper however made no mention of olanzapine data [65]. Similarly, the national OPPIDUM French addictovigilance network has highlighted emerging behaviour of abuse, including prescribing opioids, pregabalin and quetiapine [66].

To better understand the issue of quetiapine abuse, as opposed to the reference drug olanzapine, we aimed here at analyzing the European Medicines Agency (EMA) EudraVigilance (EV) database [67], which collects electronic reports of suspected adverse drug reactions (ADRs) for all medicinal products authorized in the European Economic Area/EEA.

Methods

The EMA (e.g. the Agency responsible for the safety monitoring of medicines developed for use in the European Union-EU) EV database, focusing on case reports submitted, up to mid-July 2016, of quetiapine and olanzapine misuse-/abuse-/dependence- and withdrawal-related ADRs, was here assessed. The ADRs here considered were, per se, spontaneous, unsolicited, communications [68] reported by both Regulatory Authorities of the Member States where the reaction occurred, and/or by the Marketing Authorization Holders for those ADRs occurring outside the EEA.

Search periods for quetiapine and olanzapine differed, since they presented with different approval/commercial availability times; for a thorough description of the EV database refer to [2]. Within the standardized MedDRA Query (SMQ) 'drug abuse, dependence and withdrawal' section [69], we identified the following adverse reactions associated with quetiapine and olanzapine: 'dependence', 'drug abuse', 'drug dependence', 'drug withdrawal syndrome', 'intentional product misuse', 'substance abuse', 'substance dependence', and 'withdrawal syndrome'. 'Misuse' was here meant to be the 'intentional and inappropriate use of a product other than as prescribed or not in accordance with the authorized product information'. Conversely, 'abuse' was here defined as the 'intentional non-therapeutic use of a product for a perceived reward or desired non-therapeutic

effect including, but not limited to, getting high/euphoria'. The term 'addiction', typically replaced by 'dependence' [70], is the 'overwhelming desire to take a drug for non-therapeutic purposes together with the inability to control or stop its use despite harmful consequences'. Finally, 'withdrawal' is here defined as: 'a substance-specific syndrome which follows cessation or reduction in the intake of a psychoactive substance previously regularly used' [71]. ADRs' numbers differed from those referring to case reports, since different reporters/senders could have independently flagged the same ADR to EMA. Each individual patient in the database has a code (EV local number) for identification. Hence, the number of individual patients was unequivocally identified. To more properly compare quetiapine with olanzapine, the proportional reporting ratio (PRR) approach was here considered, and defined as: 'the ratio between the frequency with which a specific adverse event is reported for the drug of interest (relative to all adverse events reported for the drug) and the frequency with which the same adverse event is reported for the drug(s) in the comparison group (relative to all adverse events for drugs in the comparison group' [72]). Being a measure of disproportionality, a PRR greater than 1 suggests that the adverse event is more commonly reported for individuals taking the drug of interest relative to the comparison drug(s) (see also [2]). The PRR is computed as follows:

$$\frac{W/W+X}{Y/Y+Z}$$

(where: W=number of quetiapine cases relating to the chosen adverse event(s); X=number of quetiapine cases involving any other adverse events; Y=number of olanzapine cases relating to the chosen adverse event(s); and Z=number of olanzapine cases involving any other adverse events (for a thorough description of both the PRR approach and the ethical issues relating to the EV database data storage, please refer to [2]).

Results

Quetiapine ADRs

Over the period 07/2005–07/2016, EMA received 209,571 ADRs reports relating to quetiapine (see Table 2); of these, 18,112 reports were relating to misuse/abuse/dependence/withdrawal issues,

corresponding to 884 patients, and 8.64% of all ADRs recorded. Most (87.21%) patients were in the 18-64 years old age-range, whilst 2.1% were in the 9-18 years old age-range. The number of reports increased consistently year-per-year, with a peak in 2009 (85,169 reports) and a decrease in 2014 (6,180 reports), reaching 2,062 by July 2016 (see Fig. 1). Using the SMQ terms, most frequently reported ADRs were classified as 'drug abuse' (52.21%), 'drug dependence' (26.43%), and 'substance abuse' (7.6%). In the sample, male adults were more represented (F/M ratio=0.96), however an overall female majority (F/M ratio: 1.22) was identified in the total number of ADRs' reports. The index drugs reported to be mostly misused in combination with quetiapine included antidepressants (identified in n=415/884, e.g. 46.9% of cases, with citalopram, trazodone and sertraline being those most typically reported); benzodiazepines (identified in n=392; 44.3%); and opiates/opioids (identified in n=383; 43.3%). The precise quetiapine dosage associated with the ADRs of interest was reported in only a minority of cases (e.g. 259 out of 884 patients). In 106 cases, quetiapine resulted to be prescribed in the dosage-range of 25-200 mg, whilst in 43 cases the dosages ingested exceeded the daily maximum therapeutic amount of 800 mg, with 19 grams being the highest level being reported. Although information on the formulations of quetiapine (e.g. extended/XR vs immediate-release/IR) associated with the above ADRs were available for only a minority of reports (e.g. n=2,265), the IR preparations were here involved on most cases (n=2,122; 93.7%). Finally, 22 cases of quetiapine nasal insufflation, and 18 cases of parenteral/intravenous intake, were here described.

Olanzapine ADRs

Over the period 09/2004–07/2016, EMA received 55,100 ADR reports relating to olanzapine (see Table 2). Of these, 4,178 were relating to misuse/abuse/dependence/withdrawal issues, corresponding to 237 patients and 7.58% of all ADRs recorded. Most (71.6%) patients were in the 18-64 years old age-range, whilst 2.15% were in the 9-18 years old age-range. The number of reports showed a peak in 2012 (ADRs number: 1,158; see Fig. 2). Using the SMQ terms, most frequently reported ADRs were classified as 'drug abuse' (55.43%) and 'drug dependence' (29.94%). Most subjects involved were male adults (F/M ratio: 0.96), and the same gender distribution was

seen as well in all ADRs' reports (F/M ratio: 0.84). Index drugs reported to be mostly misused in combination with olanzapine included antidepressants (identified in n=114, e.g. 48.1% of cases, with sertraline, fluoxetine and trazodone being those most typically reported); benzodiazepines (identified in n=104; 43.9%); and opiates/opioids (identified in n=82; 35.9%).

The precise olanzapine dosage associated with the ADRs of interest was reported in only a minority of cases (e.g. 115 out of 237 patients); in 19 cases (16.5%) olanzapine resulted to be prescribed at a dosage below 5 mg. Conversely, in 37 cases (32.2%) the dosage ingested exceeded indeed the daily maximum therapeutic amount of 20 mg, with 11 grams being the highest level reported. Finally, 1 case of olanzapine nasal insufflation, and 7 cases of parenteral/intravenous intake were here described.

Quetiapine versus olanzapine; PRR Computation

The 'quetiapine versus olanzapine' PRR values were calculated whilst considering the most represented ADRs' categories (e.g. a) intentional product misuse; drug abuse; and substance abuse; b) drug dependence; and substance dependence; and c) withdrawal syndrome; and drug withdrawal). The resulting PRR values suggested that the misuse/abuse-; dependence-; and withdrawal-related ADRs were more frequently reported for quetiapine (respectively, 1.07; 1.01; and 5.25) in comparison with olanzapine (see Table 1).

Related Fatalities

In the 884-patient quetiapine misuse/abuse/dependence/withdrawal group (18,112 ADRs), 368 (45.2%; 2,979 ADRs) fatalities were identified, but only in 5 cases the drug was reported on its own. Conversely, in the 237-patient olanzapine misuse/abuse/dependence/withdrawal group (4,178 ADRs), 79 (34.6%; 687 ADRs) fatalities were identified, and only in 1 case olanzapine was reported on its own. For both quetiapine and olanzapine, most fatalities involved female adults; had occurred in non-EEA countries; and had been reported by pharmaceutical companies.

In association with both quetiapine and olanzapine fatalities, antidepressants, opiates/opioids, and benzodiazepines were the concomitant drugs most typically identified. A range of recreational substances (e.g. alcohol, amphetamines, cannabis, and ketamine) was at times identified as well.

Discussion

To the best of our knowledge, this is the first study aimed at systematically identifying and analyzing quetiapine-, as opposed to olanzapine-, misuse/abuse/dependence/withdrawal issues. Present, large scale, data have been extracted from a pharmacovigilance database, such as the EMA's EV that, together with the World Health Organization's Drug Monitoring Program [73], is considered a worldwide reference standard.

Although the observation period for olanzapine was longer, the selected misuse/abuse/dependence/withdrawal-related ADR reports were more represented in the quetiapine, in comparison with the olanzapine, group; respectively: n=18,112 vs n=4,178. These ADRs showed a peak in 2009 and 2012, respectively, for quetiapine and olanzapine. A consistent proportion of reports were being filed here by the pharmaceutical companies manufacturing the branded products. However, in recent years the generic formulations of both molecules have gradually/partially replaced worldwide the branded formulations; this may somehow explain the recent years' observed reduction in related ADRs' levels. It is of note that most related literature papers, so far, have been based on small case series/single case studies [19; 26; 54]. Conversely, current findings refer to much larger (e.g. 884 vs 237) numbers of patients respectively presenting with either quetiapine or olanzapine misuse/abuse/dependence/withdrawal issues, tentatively suggesting different (e.g. quetiapine higher than olanzapine) addictive liability levels of these molecules. This is consistent with the resulting PRR values, indicating that the misuse/abuse-; and dependence-related ADRs were here more frequently reported (e.g. respectively: 1.07; and 1.01) for quetiapine in comparison with olanzapine. Furthermore, a range of idiosyncratic (e.g. insufflation; parenteral/intravenous) intake modalities were more frequently identified in the quetiapine (n=40) vs olanzapine (n=8) groups. Consistent with previous literature findings [51], the XR formulations were here represented in only a minimal proportion (e.g. 6.3%) of cases.

Overall, most quetiapine and olanzapine ADRs' misuse/abuse/dependence/withdrawal reports involved adult (18-64 years old) males. Although gender distribution issues for bipolar disorder are somehow unclear [74], the finding is consistent with males being more represented both in substance misuse [75]; and schizophrenia [76] disorders. Considering the putative recreational value of these molecules, it is a reason of concern that for both quetiapine and olanzapine some 2% of the abuse/misuse/dependence/withdrawal ADRs involved children/adolescents.

Misuse/abuse/dependence/withdrawal ADRs were here associated, in 1 case out of 6, with supra-therapeutic, or even extraordinarily high, dosages for quetiapine and this occurred even more frequently (eg. 1 case out of 3) for olanzapine. Conversely, however, these ADRs were frequently (e.g. quetiapine: 41%; olanzapine: 16%) reported as well for sub-therapeutic dosages (e.g. up to 200 mg for quetiapine and up to 5 mg for olanzapine). In everyday clinical practice, and this is especially true for quetiapine, these small dosages are frequently prescribed for a range of issues such as insomnia, inner restlessness, and anxiety [12-13]. Thus, the current finding of a potential for both molecules to be associated with misuse/withdrawal issues in such a low dosage-range might be considered of clinical relevance.

Apart from benzodiazepines and opiates/opioids, antidepressants (mostly SSRIs and trazodone) were those drugs most frequently identified in combination with both quetiapine and olanzapine. Indeed, this may suggest the comorbid presence of depression with substance misuse conditions. On the other hand, trazodone prescribing has been advised for the treatment of alcohol-, drug- and benzodiazepine-dependent patients [77]. Although the use of SSRIs for the treatment of addictions is quite controversial [78], it is of interest that, similarly to remaining psychotropics, SSRIs have indeed been associated with the occurrence of a proper withdrawal syndrome [79], and this may have overlapped with the quetiapine and olanzapine withdrawal reporting levels here identified. The quetiapine vs olanzapine withdrawal PRR value (5.25) resulted here to be particularly high. This finding seems to be consistent with a range of literature reports, suggesting both levels of tolerance [26], and the occurrence of a discontinuation/withdrawal syndrome (e.g. craving, insomnia, nausea, sweating, headache, diarrhea, vomiting, dizziness and irritability) following the abrupt cessation of quetiapine intake [13; 25; 61]. Other reports describe as well both

a ‘rebound’ (e.g. rebound psychosis and rebound insomnia; [80]); and a proper ‘withdrawal’ syndrome (e.g. tachycardia, insomnia, anxiety, and dysphoria [60]) after discontinuing or switching from olanzapine to another drug. Quetiapine IR preparations, here most typically represented, are short-acting, and therefore more likely to produce a physiological withdrawal reaction than the longer-acting olanzapine. This can occur in people who are taking it as prescribed, as well as those who are 'misusing’ it. This may contribute to explaining the substantial withdrawal PRR difference here observed between quetiapine and olanzapine.
Unfortunately, however, the EV database did not provide here further details of clinical interest, including: medication dosage prescribed prior to discontinuation; range/intensity of withdrawal symptoms; time-frame of the clinical presentation of withdrawal; and the possible concurrence of psychopathological conditions.

Fatalities

In the EV database 368 quetiapine- and 79 olanzapine-related fatalities were respectively identified. Although this finding is in itself interesting, to be able to calculate properly the related ‘fatal toxicity index’ [81] the total number of patients exposed to either quetiapine or olanzapine may be needed. Furthermore, most fatalities were here the result of a polydrug intake, including opiates/opioids, and this may well have increased the levels of risk [82; 83].
Quetiapine fatalities have already been described [13; 22-26; 29; 84-85]. Finally, Vance and McIntyre [86] described 28 cases involving olanzapine examined at the San Diego County Medical Examiner’s Office during the time-frame 2004–2007, and in only 6 cases olanzapine was identified on its own.

Limitations

Case reports of suspected ADRs alone are rarely sufficient to confirm that a certain effect in a patient has been caused by a specific medicine. The fact that a suspected adverse reaction has been reported does not necessarily mean that the medicine has caused the observed effect, as this could have also been caused by the disease being treated, another illness, or it could be associated

with another medicinal product taken by the patient at the same time. The number of case reports for a particular medicinal product depends *inter alia* on its availability on the market and its extent of use, the nature of the reaction, as well as the public awareness of a safety concern. Hence, comparing the number of case reports between medicines may give a misleading picture of their safety profile. Furthermore, spontaneous reports were likely to reflect here issues relating to prescribed drugs only, whilst these molecules are widely available from rogue websites and, in some countries, over the counter as well [87]. One could argue that there may be major issues in using worldwide, spontaneously reported, adverse effects' data. Furthermore, the comparison here considered between quetiapine and olanzapine may be difficult, since it assumes that these drugs have similar levels of adverse effects other than the misuse/withdrawal effects, whilst the two molecules present with different profiles of adverse effects/AEs [16]. Indeed, consistent with UK prescription data [63] there were here many more ADRs reported for quetiapine than for olanzapine, but it is unclear if this was due to different global prescribing rates. Unfortunately, however, these prescribing figures are not available due to the wide differences in both availability and collection of prescription data around the world. Present data focus on misuse/abuse/dependence and withdrawal, but these are not the same issues. Indeed, the occurrence of a withdrawal syndrome is not an indication, per se, of an index drug possessing a misuse/recreational value. Several ADRs relating to the same patient were here identified. This may have happened because of a range of different sources reporting the same ADR but also because a number of different ADRs may have been reported for the same patient. Report duplications may occur e.g. where a healthcare professional reported the same suspected ADR to both the national regulator and the Marketing Authorization Holder, and both eventually reported the index ADR to the EV. Furthermore, due to the nature of spontaneous reports, not all data fields are provided for all reports. In particular, the subjects' possible psychiatric/drug misuse history was not available, and the abuse/dependence diagnosis was not made in accordance with international classification standards. Furthermore, a PRR exceeding 1 could also reflect sampling variation in the data, reporting errors, biased reporting, multiple reports of the same case or the same patient, or a number of other causes. Spontaneous reports reflect the information as provided to EV by the

source/reporter. Finally, EMA has to ensure that the protection of privacy and integrity of individuals is guaranteed. Hence, certain data elements (e.g. country specific information, nationally authorized products) were here not disclosed.

Conclusions

Despite data collection limitations, and although further studies are clearly needed, both the literature and current EMA data may tentatively suggest that, at least in comparison with olanzapine, quetiapine misuse may be a cause for concern. Whether quetiapine misuse is occurring on a large scale cannot be confirmed from here but, as the EV reports were submitted spontaneously, present figures may only underestimate the magnitude of the problem. Further prospective studies should be encouraged to better assess quetiapine/SGAs' addictive liability levels. Overall, there is the need for increased awareness and education regarding medication abuse, an issue being facilitated by wide online levels of medicines' availability [87]. Healthcare professionals should be vigilant when prescribing any psychotropics, including both antidepressants [88] and antipsychotics, and particularly to inmates and/or to patients with a substance misuse history. Owing to the possibility of diversion, the increasing off-label use of quetiapine should be reduced; the amount of drug prescribed per individual prescription limited; and, if any related misuse issues are being identified, physicians should consider medication tapering [11; 53].

Acknowledgements

We acknowledge the support offered by EMA in providing access to the EV database. The views expressed here are those of the authors and do not necessarily reflect the EMA officers' views. We thank dr Paolo Alcini, Head of Data Standardisation and Analytics-EMA, for assistance with the analysis of our data and his comments on the manuscript. In contributing to this paper, FS was supported in part by grants of the European Commission (Drug Prevention and Information Programme 2014–16, contract no. JUST/2013/DPIP/AG/4823, EU-MADNESS project). Further financial support was provided to FS by the EU Commission-targeted call on cross border law enforcement cooperation in the field of drug trafficking, DG Justice/DG Migrations and Home

Affairs (JUST/2013/ISEC/DRUGS/AG/6429) Project EPS/NPS (Enhancing Police Skills concerning Novel Psychoactive Substances).

Conflicts of interest

Prof. Schifano and Dr. Chiappini declare no conflicts of interest with respect to the content of this manuscript; however, Prof. Schifano is a member of the EMA Psychiatry Advisory Board.

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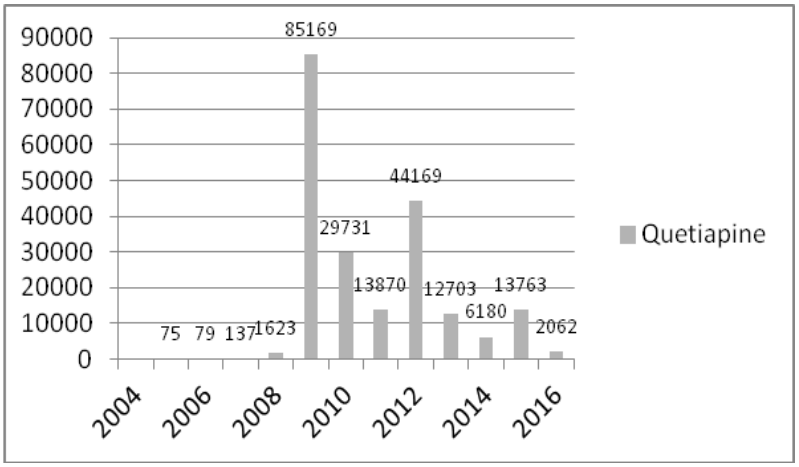

Figure 1: **Number of quetiapine misuse/abuse-; dependence-; and withdrawal-related adverse drug reactions (ADRs) during the 2005-2016 time-frame**

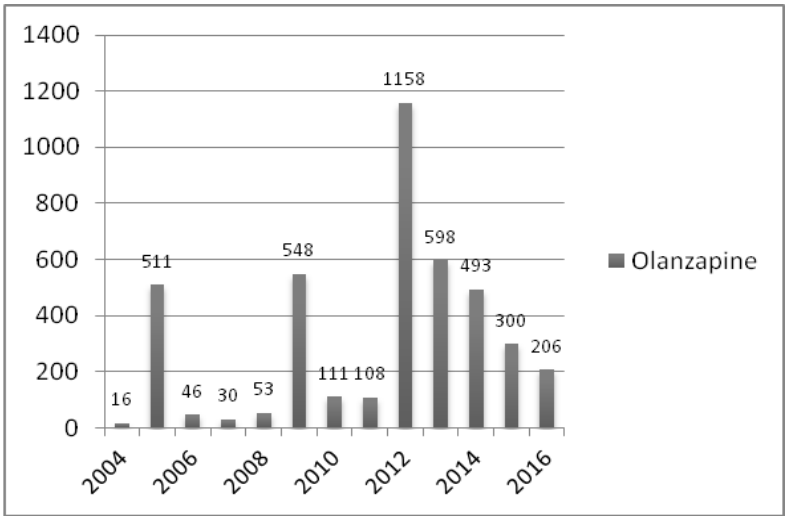

Figure 2: Number of olanzapine misuse/abuse-; dependence-; and withdrawal-related adverse drug reactions (ADRs); 2004-2016

Quetiapine ADRs	**No of ADRs**	**Proportion of Quetiapine ADRs**	***Quetiapine vs Olanzapine PRR***
Drug abuse (A1)+ Substance abuse (A2)+ Intentional product misuse (A3)	9,457+1,378+395=11,230	11,230/209,571=0.0535	**1.07**
Drug dependence (A4)+ Dependence (A5) + Substance dependence (A6)	4,788+48+997=5,833	5,833/209,571=0.0278	**1.01**
Withdrawal syndrome (A7)+ Drug withdrawal syndrome (A8)	246+636=882	882/209,571=0.0042	**5.25**
Other Adverse Events (B)	191,626	191,626/209,571=0.9143	
Total (A1+A2+A3+A4+A5+A6+A7+A8+B)	209,571	209,571/209,571=1	
Olanzapine ADRs	**No of ADRs**	**Proportion of Olanzapine ADRs**	
Drug abuse (C1)+ Substance abuse (C2)+ Intentional product misuse (C3)	2,316+324+106=2,746	2,746/55,100=0.0498	
Drug dependence (C4)+ Dependence (C5) + Substance dependence (C6)	1,251+7+129=1,387	1,387/55,100=0.0251	
Withdrawal syndrome (C7)+ Drug withdrawal syndrome (C8)	35+10=45	45/55,100=0.0008	
Other Adverse Events Olanzapine (D)	49,868	49,868/55,100=0.9050	
Total (C1+C2+C3+C4+C5+C6+C7+C8+D)	55,100	55,100/55,100= 1	

Table 1: Quetiapine and olanzapine misuse/abuse-; dependence-; and withdrawal-related ADRs' frequency whilst considering all drug adverse events reported

	QUETIAPINE ADRs	OLANZAPINE ADRs
Time-frame considered	07/2005–07/2016	09/2004–07/2016
Total number of ADRs	209,571	55,100
Misuse-abuse-/dependence-/ withdrawal-related ADRs	18,112	4,178
Number of unique patients being reported to the database	884	237
Age range most typically represented	18-64 yy (87.21%)	18-64 yy (71.6%)
ADRs most typically represented	drug abuse (52.21%), drug dependence (26.43%), substance abuse (7.6%)	drug abuse (55.93%), drug dependence (29.94%)
Gender most typically represented	Male (F/M ratio=0.96)	Male (F/M ratio=0.96)
Concomitant drugs most typically represented	Antidepressants (in n=415/884, 46.9% of cases, with citalopram, trazodone and sertraline being those most typically reported); benzodiazepines (in n=392; 44.3%); opiates/opioids (in n=383; 43.3%)	Antidepressants (in n=114/288, 48.1% of cases, with sertraline, fluoxetine and trazodone being those most typically reported); benzodiazepines (in n=104; 43.9%); and opiates/opioids (in n=82; 35.9%)
Fatalities	368 patients	79 patients

Table 2: Overview of data relating to quetiapine and olanzapine ADRs as reported to the EV database