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TITLE:

Tapentadol: review of adverse drug reactions reported to Eudravigilance.

SHORT-TITLE:

Tapentadol-associated adverse drug reactions in Eudravigilance.

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Tapentadol; Adverse drug reactions; Eudravigilance; Individual case safety reports; Health professionals.

DISCLOSURES

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ABSTRACT

Background: Tapentadol is a novel opioid analgesic with a dual mode of action that was approved for acute and chronic pain. This drug has been associated with several adverse drug reactions (ADR), particularly involving Nervous System Disorders, Psychiatric Disorders, Gastrointestinal Disorders, and General Disorders and Administration Site Condition.

Objective: Since published studies on tapentadol suspected ADR are limited, the major aim of this study was to characterise suspected ADR reports related to the use of tapentadol, included in EudraVigilance (EV).

Methods: The data analysed was retrieved from EV - the European database of suspected ADR reports, between January 1st, 2017 and October 17th, 2019. The suspected ADR reports in which tapentadol was not the only reported drug of interest were excluded. We selected 865 cases from a total of 1467 reports identified.

Results: Within the selected suspected ADR reports, the majority referred to cases involving adults. A predominance of female suspected ADR reports (64.05%) was also observed. The five most frequent suspected ADR reported associated to tapentadol were nausea (9.36%), dizziness (9.25%), vomiting (4.86%), confusional state (4.62%) and headache (4.51%). Eight cases of serotonin syndrome were also reported. Almost 50% of the patients were shown to be completely recovered or were still recovering from these suspected ADR. About 47.57% of all cases were classified as serious suspected ADR. Fatal outcomes were shown to be rare (2.66%).

Conclusions: Pharmacovigilance databases are important tools to evaluate the safety and efficacy profiles of drugs, thus improving patients' safety and quality of life. The outcomes obtained with this study reveal that despite a complete or partial recovery was found among 49% of the total analysed suspected ADR cases, still around half of them were considered as serious suspected ADR. Therefore, the prescription of tapentadol still demands for caution and ongoing monitoring, in order to decrease its known and potential associated ADR.

Introduction

Prescriptions for opioids analgesics, aiming to manage moderate to severe pain, have globally increased. Therefore, one can expect that its increased use may lead to a visible rise in the number of adverse drug reactions (ADR) (1,2).

Tapentadol is a novel, centrally acting analgesic drug and has been suggested to be the first representative of a new class of opioids analgesics known as Mu-Opioid Receptor Agonist/Noradrenaline Reuptake Inhibition (MOR-NRI) (3,4). This drug was approved by the European Medicines Agency (EMA) in 2010 for both moderate to severe acute (somatic and visceral) and chronic pain conditions, including neuropathic pain and cancer pain (5). Tapentadol is an analgesic with a dual mode of action, being able to act as a Mu-Opioid Receptor (MOR) agonist and a Noradrenaline Reuptake Inhibitor (NRI), thus providing a strong analgesic effect by a synergic action and decreasing incidence of typical opioid-induced adverse effects (5–7).However, long-term opioid therapy may be associated with several adverse events, including Gastrointestinal Disorders, Nervous System Disorders (5), Psychiatric Disorders and General Disorders and Administration Site Conditions (6,8). One of the syndromes that may be associated to the use of tapentadol when prescribed concomitantly with other serotoninergic medicinal products due to the surplus of serotonin is serotonin syndrome, a potentially life-threatening syndrome (9–11). However, under treatment with tapentadol, this syndrome is unlikely to occur since tapentadol has no clinical relevant functional serotonin reuptake inhibition, remaining only a theoretical risk (5,11,12). The clinical features of serotonin syndrome include agitation, shivering, diaphoresis, mydriasis, tachycardia, hypertension, hyperthermia, diarrhea, tremor, and hyperreflexia (9).

The evaluation of tapentadol toxicity is then particularly relevant, concerning the public health impact of the current opioid epidemic (13).

ADR are among the leading causes of important morbidity and mortality worldwide. They arise as a serious public health concern, constituting both a clinical and economic

burden, as they may frequently lead to hospitalisation, surgery and lost productivity (2,14,15).

EMA defines ADR as “any noxious and unintended response to a medicine” (16). Many adverse reactions result from the use of drugs with unavoidably high toxicity, while others may be due to inadequate monitoring of therapies and doses (17).

The risk of harm can be minimised by ensuring the quality of prescription medications, and also that they are medically appropriate, effective and safe for patient use.

The rational use of medicines is essential to promote patient safety particularly through the assessment of its benefit-risk balance. Global drug safety depends on strong national pharmacovigilance systems that: i) monitor the development and quality of medicines, ii) report their harmful effects, and iii) provide accurate information for their safe use (18). The importance of suspected ADR voluntarily reported by health professionals and citizens (i.e. spontaneous reports) is to develop scientifically strong indicators of ADR and accurately identify rare, serious, unusual, or unexpected ADR as soon as possible after drug’s marketing launch (14,15).

Under the Directive 2010/84/EU, Members States had to create medicines web portals aiming to increase the level to transparency of pharmacovigilance processes and to facilitate the reporting of suspected ADR by both health professionals and citizens (19). These suspected ADR should then be forwarded to the EV - the official European database of suspected ADR reports. The EV provides data on suspected ADR for authorised medicines in the European Economic Area (EEA), covering EEA and non-EEA.

The aim of this study was to characterise suspected ADR reports associated to tapentadol in EudraVigilance (20) (EV) database from January 1st, 2017 to October 17th, 2019.

Methods and Statistical analysis

The analysed data were collected from suspected ADR reports referring to the use of tapentadol from EV, available at the general public access level, between January 1st, 2017 and October 17th, 2019.

Data format was then adjusted and combined in Microsoft Excel into one XLSX file. Further transformation was performed using R Studio software Version 1.2.5001 (21).

The EV database contained categorical variables, namely: “EU Local Number”, “Report Type”, “EV Gateway Receipt Date”, “Primary Source Qualification” (Non-Healthcare Professional, Healthcare Professional), “Primary Source Country for Regulatory Purposes“ (Non-EEA, EEA), “Patient Age Group” (0-1 month, 2 months-2 years, 3-11 years, 12–17 years, 18–64 years, 65-85 years, more than 85 years, and not specified), “Literature Reference“, “Patient Age Group” (as per reporter), “Parent Child Report”, “Patient Sex” (female, male, not specified), “Reaction List” (including reaction/ADR, duration, outcome and seriousness criteria), “Suspect/Interacting Drug List” (including drug, drug char, indication PT - action taken [duration - dose - route]), “Concomitant/Not Administered Drug List (including drug, drug char, indication PT - action taken [duration - dose - route])” and “Individual Case Safety Reports (ICSR) Form” (22).

The variables “Literature Reference“, “Patient Age Group” (as per reporter), “Parent Child Report”, “Concomitant/Not Administered Drug List (including Drug, Drug Char, Indication PT - Action taken [Duration - Dose - Route])” and “ICSR Form” were not included for analysis in our final database.

We first started by excluding suspected ADR reports where tapentadol was not the only reported drug of interest, as a single culprit drug cannot be pinpointed in such cases. Afterwards, we performed the statistical analysis by assessing the different reported suspected ADR in each selected individual report.

The analysed data is presented by the means of descriptive statistics with continuous variables being summarized by mean and standard deviation (SD), and categorical variables by counts and percentages. The unilateral Fisher´s exact test with Bonferroni

correction was used to compare suspected ADR proportions between patients' sex. A significance level of 0.05 was considered. The statistical analysis was performed in R software Version 1.2.5001 using R Studio interface (21).

Results

Suspected adverse reactions reporting rate

From January 1st, 2017 to October 17th, 2019, the total number of suspected ADR reports found for tapentadol was of 1467, from which 865 identified tapentadol as the only suspected drug. Our further analysis was based on those 865 suspected ADR reports.

As shown in Figure 1, the number of reports collected in the EV database increased over the analysed time period, as follows: 244 in 2017, 299 in 2018 and 322 until the October 17th, 2019.

Healthcare professionals were responsible for the reporting of 84% of the analysed reports and the EEA was found to be the major contributor, comprising 80% of the total reports. While within the EEA, 86% of the suspected ADR reports were submitted by healthcare professionals, in the non-EEA only 69.78% of the total reports were submitted by these professionals, as shown in Figure S1.

Among the 865 identified suspected ADR reports, 554 (64.05%) referred to female patients, 296 (34.22%) to male patients and 15 (1.73%) did not specify the sex of the patient. The ratio between the number of reports concerning female and male patients within the EEA and non-EEA was of, respectively, 2.13 and 1.14.

The majority of the suspected ADR reports included individuals above 18 years old, with only 2 referring to individuals under that age. A predominance of female suspected ADR reports was observed in every analysed age group. The data regarding the age of the patients according to the patients' sex are detailed in Figure S2.

The 865 selected suspected ADR reports contained 461 different suspected ADR, in a total of 1810 individual suspected ADR (1163 from female and 619 from male patients). From those 1810 individual suspected ADR identified, 47.57% were categorised as serious suspected ADR. Taking into consideration the total number of suspected ADR reports, 59.42% were shown to comprise at least one serious suspected ADR.

Suspected adverse reactions most commonly reported

The 5 most frequently reported suspected ADR within all the analysed reports were: nausea, dizziness, vomiting, confusional state and headache. Furthermore, these reactions have all occurred with a frequency above 4%, as shown in Table 1.

Suspected adverse reactions by sex

The most regularly reported suspected ADR within the selected reports were then separately analysed by patients' sex. The results are shown in Table 2 and Figure 3. The most commonly above-mentioned reported suspected ADR are associated with the following system organ classes: "Gastrointestinal Disorders", "Nervous System Disorders", "General Disorders and Administration Site Conditions" and "Psychiatric Disorders". Although the reports identifying serotonin syndrome as a tapentadol-associated suspected ADR were shown to present a low frequency (8 cases identified in total), it is of utmost importance to enhance this finding since it corresponds to a life-threatening situation.

To analyse if the reported suspected ADR differently affected female and male, we applied the Fisher exact test with Bonferroni correction to all the suspected ADR occurring with a frequency greater than 2%. For a significance level of 0.05, frequencies of dizziness and nausea were significantly higher in female, when compared to male. On the other hand, delirium and overdose were shown to be significantly higher in male (Table 3).

Outcomes of adverse reactions

Within all the identified suspected ADR in patients, 23 cases were reported with a fatal outcome, 275 did not recover, 5 recovered with sequelae and 885 (48.90%) recovered completely or were reported as recovering (74.5% of the reported suspected ADR revealed a known outcome). Subsequently, the remaining 34.36% reported suspected ADR were identified as having an unknown outcome (Figure 4). The reports displaying unknown outcomes were more commonly submitted by non-healthcare professionals than by healthcare professionals (37% *versus* 33.7%, respectively).

Within all the reports collected, the number of suspected ADR resulting in death was of 11 and 10, respectively for females and males (Figure 5). When considering the age group, the percentage of fatal outcomes was of 1.77% (18-64 years), 3.68% (65-85 years), 4% (over 85 years) and 1.64% (group not specified).

Discussion

This study revealed that the tapentadol suspected ADR have been slightly increasing over the analysed three years. This finding may be either multicausal, attributable to a better awareness in reporting suspected ADR and promote drug safety, due to population increased aging and consequent higher incidence of both moderate to severe acute and chronic pain, or to an increase in tapentadol prescription due to its action on the central nervous system, together with a dual mechanism of action and better tolerability (23,24).

Healthcare professionals were shown to be the main suspected ADR reporters, particularly within the EEA. This may be explained by an increased knowledge and awareness of drug safety use among healthcare professionals in developed countries (25).

The analysis of the suspected ADR reports revealed that practically all of them referred to adults (>18 years old). This finding may be due to a higher incidence of both moderate to severe acute and chronic pain in adults, compared to children and

adolescents, and the need to its treatment and control. The use of tapentadol in younger ages was shown to be residual, as only 2 reports were registered. Acute pain is common among infants, children, and adolescents (26); however, it is undertreated in both the clinical and community settings. Therefore, tapentadol may be regarded as a new treatment option in the management of moderate to severe acute pain in children and adolescents (27). Consequently, an increase in paediatric suspected ADR reports can be expected in the near future. The lack of paediatric reports observed within this study limits to draw further conclusions about the potential risk of tapentadol consumption in this age group.

The outcomes obtained in this study also revealed a predominance of suspected ADR reports with female. Although this phenomenon is considered common, it is not totally clear why female have an increased risk of developing suspected ADR. Some hypotheses have been suggested, including gender-related differences in pharmacokinetics, as well as immunological and hormonal factors (28). Furthermore, another possible factor may be female's greater readiness to report suspected ADR (29).

The five most frequent suspected ADR reported were nausea, dizziness, vomiting, confusional state and headache, which from these only confusional state is considered serious. These results are in accordance with the randomised clinical trial and the literature (5,30–33).

The analysis by gender demonstrated that nausea and dizziness were more prevalent in female than in male. In previous experimental settings, female have been shown to exhibit enhanced nausea, vomiting, headache, insomnia, loss of appetite, weight change, depression and dizziness (34).

This study identified 8 cases of serotonin syndrome, neither involving the coadministration of tapentadol with other serotonergic agents. However, in literature, causality assessment has not yet been proven between this syndrome and treatment

with tapentadol, being this only a theoretical risk (5). Nevertheless, this theoretical risk remains under close monitoring, as data continues to be collected on this topic (11). Most of the patients were shown to completely recover from the suspected ADR reported. Among all the reported suspected ADR, the occurrence of fatalities was rare (2,42%), and no statistically significant sex differences were observed: 1.99% fatalities were reported among female patients, while 3.38% were reported among male patients. Most of the fatal cases were reported in patients aged over 65 years old, which may be associated with age vulnerability and, eventually, due to the concomitant medication common in these age groups. Nevertheless, mortality data must be carefully interpreted, because a fatal outcome does not necessarily mean a causal relationship between the suspected drug and the fata event (35). Furthermore, it should be noted that 622 of the reported suspected ADR (34.36%) lacked information about the outcome source, thus precluding a reasonable evaluation.

The availability of the complete submitted reports, together with the assessment of further suspected ADR studies provided in EV, as well as in other databases, would be very beneficial to deepen our analyses and rise the knowledge on tapentadol suspected ADR, along with its implications in patients' health and wellbeing.

Conclusion

This descriptive study analysis has confirmed a favourable overall safety profile of tapentadol, albeit a few cases of the serotonin syndrome were identified. However, the majority of the patients were shown to completely recover from the suspected ADR reported. The prevalence of two of the most commonly reported suspected ADR (dizziness and nausea) was shown to be significantly higher in female, when compared to male. Fatal outcomes were shown to be rare. In sum, tapentadol prescription still demands caution and ongoing monitoring, in order to decrease the incidence of its associated suspected ADR.

Pharmacovigilance databases are important tools to evaluate the safety of drugs, as the information therein contained can help to identify rare, serious, unusual, or unexpected ADR immediately after their marketing launch. This feature is of significant importance for specific age groups that may be at increased risk of developing ADR, once it promotes patients' safety and wellbeing, thus allowing for a safer use of drugs in the future.

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Author contributions:

* Authors equally contributed to: paper's conceptualisation, data collection, processing and analysis, and paper's writing.

Disclosures

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Table 1. Tapentadol-reported suspected of ADR occurring with a frequency >2% in EudraVigilance database (01/01/2017–17/10/2019).

ADR	% of ADR reports	Number of suspected ADR reports	System Organ Class
Nausea	9.36%	81	Gastrointestinal Disorders
Dizziness	9.25%	80	Nervous system Disorders
Vomiting	4.86%	42	Gastrointestinal Disorders
Confusional state *	4.62%	40	Psychiatric Disorders
Headache	4.51%	39	Nervous system Disorders
Hyperhidrosis	3.82%	33	Skin and subcutaneous tissue disorders
Hallucination *	3.70%	32	Psychiatric Disorders
Somnolence	3.47%	30	Nervous system Disorders
Dyspnoea *	3.35%	29	Respiratory, thoracic and mediastinal disorders
Diarrhoea	3.01%	26	Gastrointestinal Disorders
Constipation	2.89%	25	Gastrointestinal Disorders
Anxiety	2.89%	25	Psychiatric Disorders
Tremor *	2.77%	24	Nervous system Disorders
Pruritus	2.77%	24	Skin and subcutaneous tissue disorders
Decreased appetite	2.77%	24	Metabolism and nutrition disorders
Malaise	2.66%	23	General disorders and administration site conditions
Drug ineffective	2.66%	23	General disorders and administration site conditions
Withdrawal syndrome *	2.54%	22	General disorders and administration site conditions

Drug dependence	2.54%	22	Psychiatric Disorders
Delirium	2.43%	21	Psychiatric Disorders
Overdose	2.08%	18	Injury, poisoning and procedural complications
Fatigue	2.08%	18	General disorders and administration site conditions

* Serious adverse events classified according to Channell & Schug, and US National Library of Medicine (ClinicalTrials.gov Identifier: NCT00421928 – Tapentadol)

Table 2. Tapentadol-reported suspected of ADR by patients' sex occurring with a frequency >2% in EudraVigilance database (01/01/2017–17/10/2019).

Female Patient			Male Patient		
Suspected ADR	**% of female suspected ADR reports**	**Number of suspected ADR reports**	**Suspected ADR**	**% of male suspected ADR reports**	**Number of suspected ADR reports**
Nausea	12.64%	70	**Confusional state**	6.08%	18
Dizziness	11.73%	65	**Somnolence**	4.73%	14
Vomiting	5.96%	33	**Dizziness**	4.39%	13
Headache	5.23%	29	**Overdose**	4.39%	13
Hyperhidrosis	4.15%	23	**Delirium**	3.72%	11
Hallucination	4.15%	23	**Drug dependence**	3.72%	11
Dyspnoea	3.43%	19	**Nausea**	3.72%	11
Constipation	3.43%	19	**Dyspnoea**	3.38%	10
Confusional state	3.43%	19	**Headache**	3.38%	10
Drug ineffective	3.25%	18	**Hyperhidrosis**	3.38%	10
Decreased appetite	3.25%	18	**Tremor**	3.38%	10
Diarrhoea	3.07%	17	**Withdrawal syndrome**	3.38%	10
Somnolence	2.89%	16	**Anxiety**	3.04%	9
Pruritus	2.89%	16	**Diarrhoea**	3.04%	9
Malaise	2.71%	15	**Hallucination**	3.04%	9
Tremor	2.53%	14	**Urinary retention**	3.04%	9
Asthenia	2.53%	14	**Vomiting**	3.04%	9
Dry Mouth	2.35%	13	**Malaise**	2.70%	8
Anxiety	2.35%	13	**Pruritus**	2.70%	8
Withdrawal syndrome	2.17%	12	**Fatigue**	2.36%	7
Insomnia	2.17%	12	**Urticaria**	2.36%	7
Abdominal Pain Upper	2.17%	12	**Agitation**	2.03%	6
…	…	…	**Constipation**	2.03%	6
Overdose*	0.90%	5	**Decreased appetite**	2.03%	6
Urinary retention*	0.72%	4	**Muscle spasms**	2.03%	6
Delirium*	0.54%	3	**…**	…	…

* Suspected ADR included in the table, as they have shown to be statistically significant for Tapentadol's use concerning patients' sex.

Table 3. Unilateral p-values obtained using Fisher's exact test with Bonferroni correction for comparison of suspected ADR displaying a >2% frequency between patients' sex.

Patients' Sex	Suspected ADR	p-value
Female>Male	Dizziness	0.004
	Nausea	<0.001
Male>Female	Delirium	0.021
	Overdose	0.027

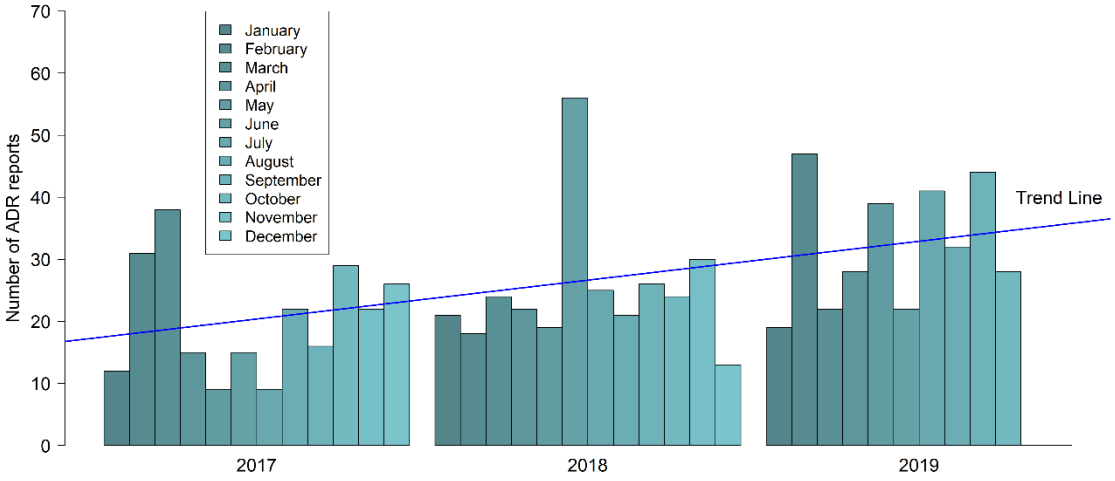


Figure 1 – Number of suspected ADR reports collected between January 1st, 2017 and October 17th, 2019.

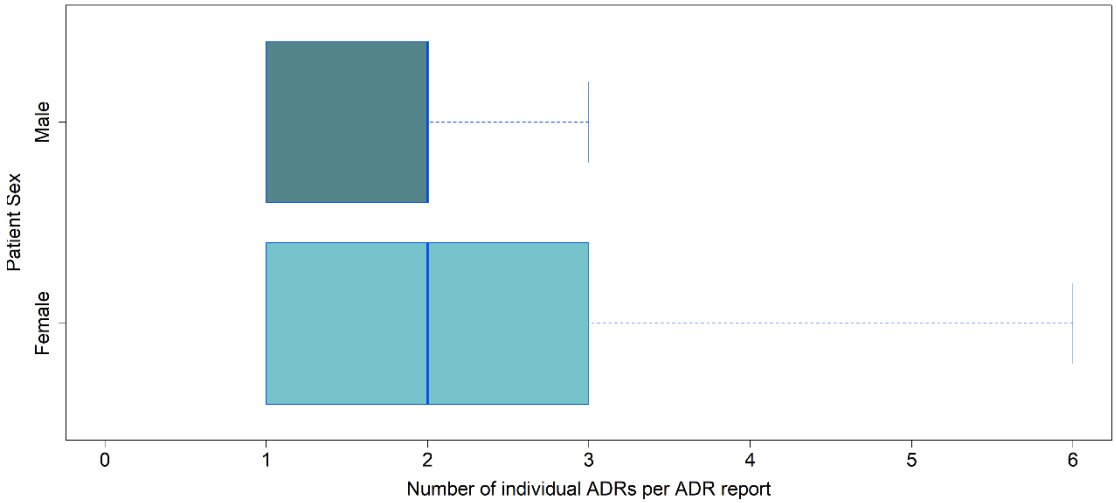


Figure 2 – Comparison between the number of suspected ADR per report considering patients' sex (outliers were removed).

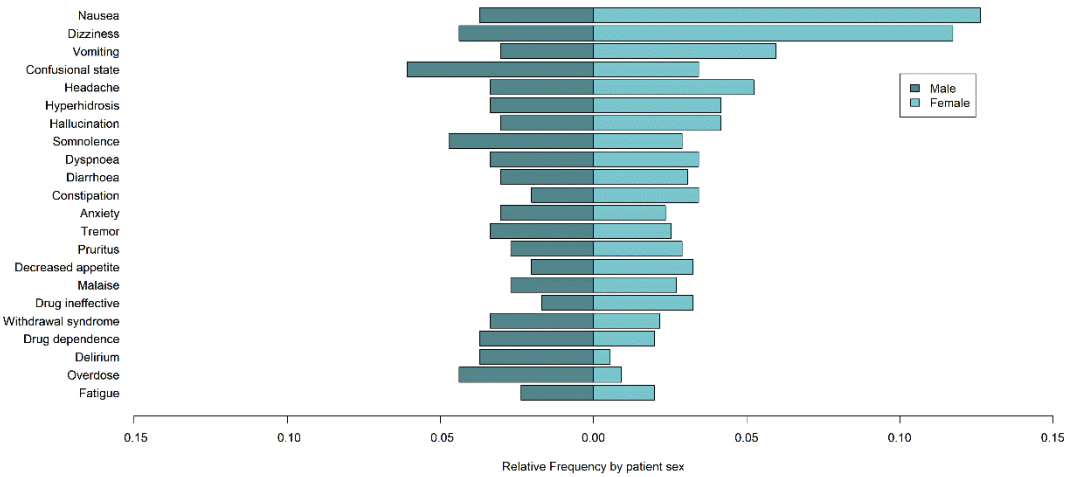
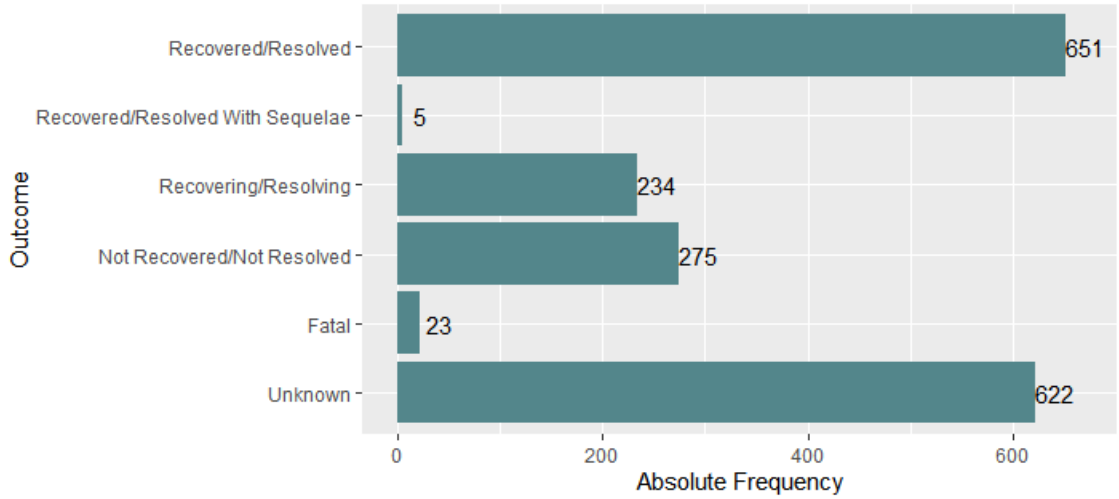


Figure 3 – Relative frequency of suspected ADR occurring with a frequency >2% by patients' sex.



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460 Figure 4 – Outcomes' source of the suspected ADR reported between January 1st,

461 2017 and October 17th, 2019.

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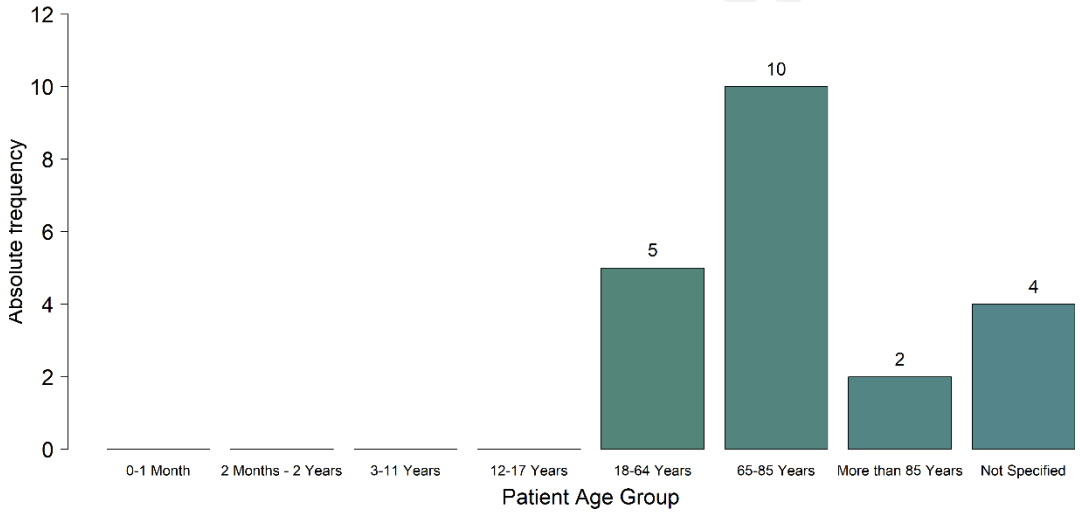

463 Figure 5 – Number of fatal outcomes of suspected ADR per age group.

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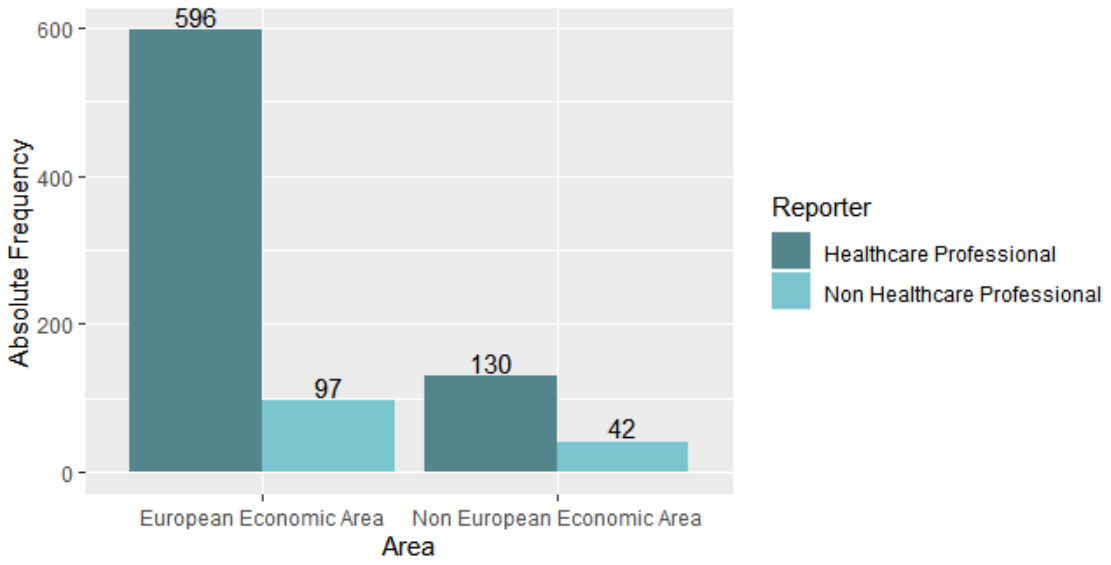

Figure S1 – Number of suspected ADR reports per geographic origin and professional qualification.

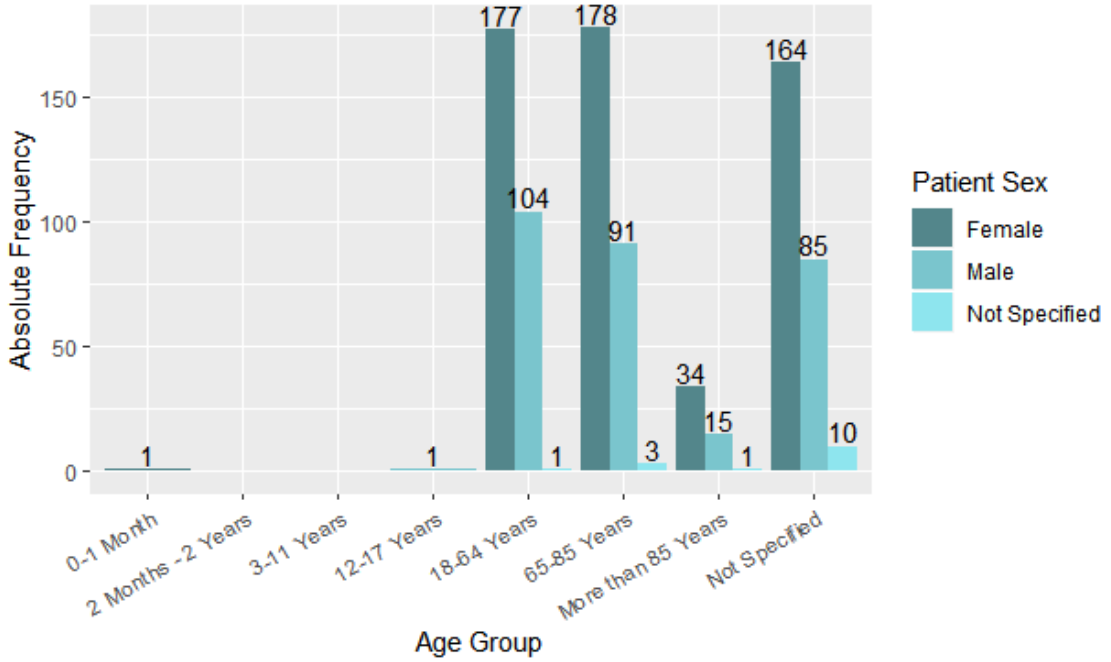

Figure S2 – Number of suspected ADR reports per age group and patients' sex.