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Analysis of Adverse Drug Reactions with Carbamazepine and Oxcarbazepine at a Tertiary Care Hospital

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Purpose: To describe adverse drug reactions (ADRs) to carbamazepine (CBZ) and oxcarbazepine (OXC), including severe cutaneous ADRs, at a tertiary care hospital over a 10-year period.
Materials and Methods: The frequency and clinical features of ADRs caused by CBZ and OXC were analyzed using the pharmacovigilance database and spontaneous ADR reporting data of Yonsei University Severance Hospital & Dental Hospital (Seoul, Korea) from January 1, 2010 to January 31, 2020.
Results: Among 10419 cases prescribed CBZ and OXC, 204 ADR cases were reported. The incidences of ADRs were 1.8% and 2.2% for CBZ and OXC respectively, with no significant difference (p=0.169). The most common clinical presentations were skin disorders. Female patients had relatively more frequent ADRs than male patients. Although mild skin ADRs were more frequent with OXC, nervous system disorders, general disorders, and hepatobiliary disorders occurred more often with CBZ. There were six reports of severe cutaneous adverse reactions to CBZ, while OXC had none. Both CBZ and OXC caused ADRs at daily doses lower than the recommended initial dose.
Conclusion: Due to lower incidence of severe ADRs with OXC than CBZ, we suggest OXC as a first-line prescription.

Key Words: Carbamazepine, oxcarbazepine, drug related adverse reactions, anticonvulsants

INTRODUCTION

Carbamazepine (CBZ) was first synthesized by Walter Schindler in 1953. In 1962, Blom saw its potential in the treatment of trigeminal neuralgia.[1] Since the U.S. Food and Drug Administration (FDA) approved CBZ tablets for epilepsy and trigeminal neuralgia more than 50 years ago, CBZ has become a first drug of choice to treat seizure disorders and neuropathic pain. It is also used as a second-line treatment for bipolar disorder.[2,3] CBZ is predominantly metabolized in the liver. At least 30 different metabolites have been identified, including carbamazepine-10,11-epoxide.[4] The metabolites of CBZ not only contribute to anti-convulsant and anti-neuralgic properties, but can also cause adverse reactions. The various types of adverse drug reactions (ADRs) of CBZ were first reported not long after approval of the drug:[5] a fair amount of severe skin reactions to CBZ, as well as mild ADRs, have been reported.[6]

Oxcarbazepine (OXC), the keto-analogue of CBZ, has been developed to help prevent side effects stemming from the metabolites of CBZ. The drug is primarily metabolized into 10-hydroxy-10,11-dihydrocarbamazepine, a therapeutically active metabolite.[7] Compared to CBZ, in a randomized double-blind crossover trial, the use of OXC achieved a reduction in the total

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number of seizures, increased alertness and concentration, and disappearance of allergic skin reactions associated with CBZ.[8] OXC is known to exhibit anti-epileptic activity comparable with CBZ when a 50% higher dose is applied. Despite the higher dose, the incidence and severity of adverse reactions are reportedly lower than those with CBZ.[9]

CBZ and OXC can cause similar adverse reactions, such as skin rash, central nervous system disorders, and digestive system disorders. They are also known to be causative drugs for severe cutaneous adverse reactions (SCARs), such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS).[6,10] Based on the individual case safety reports of SCARs in the Korean population from 1988 to 2013, CBZ is known to be the second most common causative drug for SCARs, including SJS, TEN, and DRESS.[11]

This study aimed to examine the frequency and clinical features of ADR caused by CBZ and OXC using the spontaneous ADR reporting database of Yonsei University Severance Hospital & Dental Hospital.

MATERIALS AND METHODS

Using the pharmacovigilance database and spontaneous ADR reporting data of Yonsei University Severance Hospital & Dental Hospital (Seoul, Korea) from January 1, 2010 to January 31, 2020, we selected the data and reports of patients with spontaneous reports of ADR associated with CBZ and OXC. The subjects were of ages 15 and over, and their diagnoses were classified. The clinical features of ADR reports were classified using the preferred terms of System Organ Class published by MedDRA®, Medical Dictionary for Drug Regulatory Activities, a standardized dictionary of medical terminology, developed under the auspices of the International Conference of Harmonisation (MedDRA MSSO, Brussels, Belgium): "Skin disorders," "Nervous system disorders," "Gastrointestinal disorders," "Blood and lymphatic system disorders," "General disorders and administration site conditions," and "Hepatobiliary disorders."

Symptoms of skin disorders included rash, urticaria, erythema, and symptoms of fatal cutaneous reaction (e.g., EM, SJS, TEN, and DRESS). Symptoms of nervous system disorders included sleepiness, dizziness, memory impairment, headache, and tremor. Indigestion and vomiting were classified as gastrointestinal disorders. General disorders showed fever and weakness.

With the obtained data and reports, we analyzed the ADR incidences for each drug in connection with the reported daily dose. For CBZ, we also compared the stated ADR daily dose of immediate-release (IR) and controlled-release (CR) formulations.

This study protocol was approved by the Institutional Review Board of Yonsei University Dental Hospital (IRB No. 2-2020-0017).

Statistical analyses

From obtained reports, we calculated incidences according to the clinical features of ADRs for CBZ and OXC. The data were analyzed using Statistical Software for Social Sciences version 25 (IBM Corp., Armonk, NY, USA). Descriptive statistics and chi-square tests were used. Statistical significance was considered at $p<0.1$.

RESULTS

There were 9312 patients who have been prescribed either CBZ or OXC among a total of 10419 cases, of which 5094 (48.9%) were male and 5325 (51.1%) were female; the remaining 1107 were prescribed both. The age of the subjects ranged from 15 to 97, with a mean age of 46.6 years. The diagnoses of the patients were classified as "neuropathic pain," "episodic neurologic symptoms," "bipolar disorders," or others (Table 1).

The spontaneous ADR reporting system contained records of 204 ADR cases in 195 patients. There were 107 patients who experienced ADRs for CBZ only, 79 patients for OXC only, and nine for patients taking both drugs. 153 patients (75.0%) were reported to have one ADR clinical feature, while 39 patients (19.1%) and 11 patients (5.4%) had two and three ADR clinical features, respectively. Only 1 patient (0.5%) presented with four ADR clinical features. There was no statistically significant difference in ADR incidence for CBZ and OXC (CBZ: 1.8%, OXC: 2.2%, $p=0.169$). ADR incidence did not correlate with age ($p=0.495$). Female, however, showed higher ADR rates for both drugs ($p<0.001$) (Table 2).

The most common types of ADRs associated with the drugs

Table 1. Baseline Characteristics of the Patients

	CBZ	OXC	Total
Sex			
Male	3040 (29.2)	2054 (19.7)	5094 (48.9)
Female	3368 (32.3)	1957 (18.8)	5325 (51.1)
Age (yr)			
15–19	280 (2.7)	630 (6.0)	910 (8.7)
20–29	873 (8.4)	645 (6.2)	1518 (14.6)
30–39	966 (9.3)	634 (6.1)	1600 (15.4)
40–49	1030 (9.9)	642 (6.2)	1672 (16.0)
50–59	1180 (11.3)	612 (5.9)	1792 (17.2)
60–69	1038 (10.0)	506 (4.9)	1544 (14.8)
70 and over	1041 (10.0)	342 (3.3)	1383 (13.3)
Diagnosis			
Neuropathic pain	2582 (24.8)	886 (8.5)	3468 (33.3)
Episodic neurologic symptoms	2959 (28.4)	2964 (28.5)	5923 (56.8)
Bipolar disorders	410 (3.9)	44 (0.4)	454 (4.4)
Others	457 (4.4)	117 (1.1)	574 (5.5)
Total	6408 (61.5)	4011 (38.5)	10419 (100)

CBZ, carbamazepine; OXC, oxcarbazepine.
Data are presented as n (%).

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were mild skin disorders (non-SCAR), followed by nervous system disorders (Table 3). CBZ caused more ADRs related to the nervous system (p=0.087) and general (p=0.077) and hepatobiliary (p=0.091) disorders than did OXC (Fig. 1A). OXC was associated with a higher incidence of mild skin disorders (p=0.013) (Fig. 1B). Six patients reported SCARs, including EM, SJS, TEN, and DRESS, by CBZ. The symptoms started with skin rash and urticaria 14–30 days after taking the drug. Five of them had discontinued the drug right after the symptoms appeared. They were referred to the Departments of Allergy and Immunology and of Dermatology and Infectious Diseases and diagnosed with EM (F/70), SJS (F/74, F/37, F/67), TEN (F/44), and DRESS (M/74). After supportive care, all six experienced relief of symptoms. There were no reports of SCARs due to OXC.

The daily doses of the drugs, compared to the initial daily dose in patients without ADRs, were analyzed. At daily doses lower than the recommended initial dose (400 mg/day for CBZ IR and CR formulation, 600 mg/day for OXC), all drugs were found to cause ADRs (Fig. 2).

Table 2. Comparison of the Number of Patients with or without ADR

	ADR		Total	*p* value
	Yes	No		
Drug				0.169
CBZ	116 (1.8)	6292 (98.2)	6408 (100)	
OXC	88 (2.2)	3923 (97.8)	4011 (100)	
Age (yr)				0.495
15–19	13 (1.4)	897 (98.6)	910 (100)	
20–29	37 (2.4)	1481 (97.6)	1518 (100)	
30–39	26 (1.6)	1574 (98.4)	1600 (100)	
40–49	35 (2.1)	1637 (97.9)	1672 (100)	
50–59	34 (1.9)	1758 (98.1)	1792 (100)	
60–69	35 (2.3)	1509 (97.7)	1544 (100)	
70 and over	24 (1.7)	1359 (98.3)	1383 (100)	
Sex				<0.001
Male	63 (1.2)	5030 (98.8)	5093 (100)	
Female	141 (2.6)	5185 (97.4)	5326 (100)	
Total	204 (2.0)	10215 (98.0)	10419 (100)	

ADR, adverse drug reaction; CBZ, carbamazepine; OXC, oxcarbazepine.
Data are presented as n (%).

DISCUSSION

OXC is indicated in both monotherapy and adjunctive therapy for the treatment of partial seizures with or without secondary generalization in adults and children above 4 years (USA) or 6 years (Europe) of age. However, in this study, we chose subjects older than 15 years, since CBZ is more rapidly metabolized to carbamazepine-10,11-epoxide in children below age 15.[12] Thus, over the age of 15 years, the result of our study showed no significant relationship between age and ADR incidence.

Gender differences in ADRs have been reported mainly for gastrointestinal disorders.[13] In males, electrolyte disturbances are known to be more frequent,[14] while female commonly present with more gastrointestinal and cutaneous allergic reactions. Female generally have a lower lean body mass, reduced hepatic clearance, and lower activity of cytochrome P450 (CYP) enzymes; thereby, female tend to metabolize drugs at lower rates than male.[15] Female also show higher rates of consultation and complaints, as well as better compliance with drugs.[16]

Our results revealed no significant differences in overall ADR incidences between CBZ and OXC. However, nervous system disorders, general disorders, and hepatobiliary disorders occurred mostly with CBZ. Since OXC was developed by altering the structure of CBZ with the intent to avoid metabolites causing side effects, the mechanism of action of OXC mainly involves blockade of sodium channels, but differs from CBZ by modulating different types of calcium channels. In contrast to CBZ, which is oxidized by the cytochrome P-450 system, OXC undergoes reductive metabolism at its keto moiety to form the monohydroxy derivative, which is glucuronidated and excreted in the urine. The involvement of the hepatic cytochrome P-450-dependent enzymes in the metabolism of OXC is minimal.[17]

The fact that there was no report of SCAR directly for OXC, while CBZ had six cases, is notable. Fortunately, all patients with SCARs to CBZ received treatment after proper specialist

Table 3. Clinical Features of ADRs Caused by CBZ and OXC

	Skin		Nervous system	Gastro-intestinal	Blood and lymphatic system	General disorders	Hepato-biliary	Others	Patient demographic
	Mild (non-SCAR)	Severe* (SCAR)							
Drug									
CBZ	59 (0.92)	6 (0.09)	42 (0.66)	11 (0.17)	10 (0.16)	14 (0.22)	8 (0.12)	17 (0.27)	6408 (100)
OXC	58 (1.45)	0 (0.00)	16 (0.40)	6 (0.15)	9 (0.22)	3 (0.07)	1 (0.02)	8 (0.20)	4011 (100)
p value	0.013	0.053	0.087	0.785	0.427	0.077	0.091	0.503	
Total	117 (1.12)	6 (0.06)	58 (0.56)	17 (0.16)	19 (0.18)	16 (0.15)	9 (0.09)	25 (0.24)	10419 (100)

ADR, adverse drug reaction; SCAR, severe cutaneous adverse drug reaction; CBZ, carbamazepine; OXC, oxcarbazepine.
Data are presented as n (%).
*Severe skin disorders include erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reactions with eosinophilia and systemic symptoms.

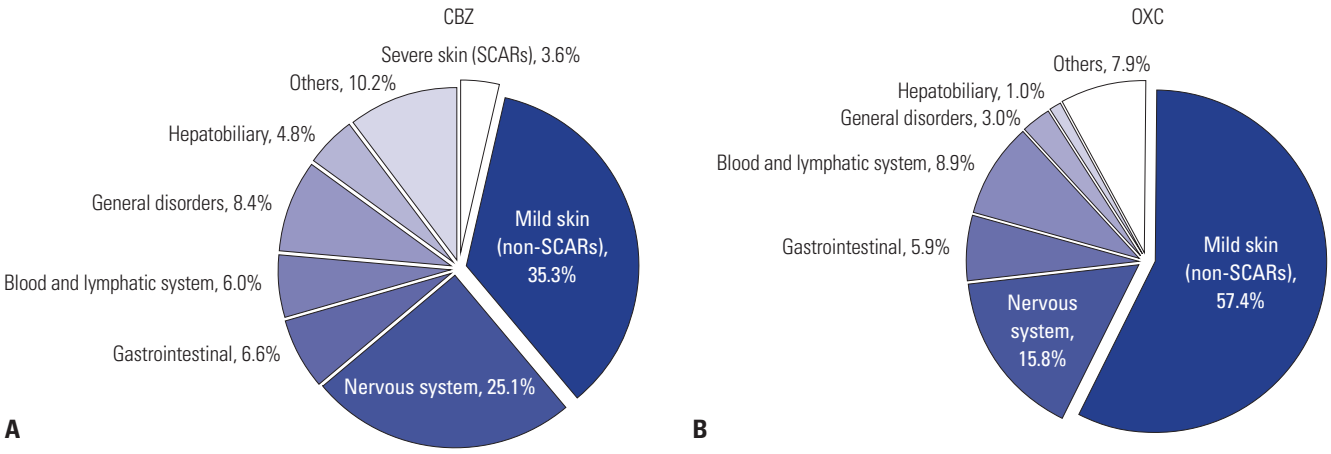

Fig. 1. The ratio of clinical features of ADRs to CBZ (A) and OXC (B). SCARs, severe cutaneous adverse reactions; ADR, adverse drug reaction; CBZ, carbamazepine; OXC, oxcarbazepine.

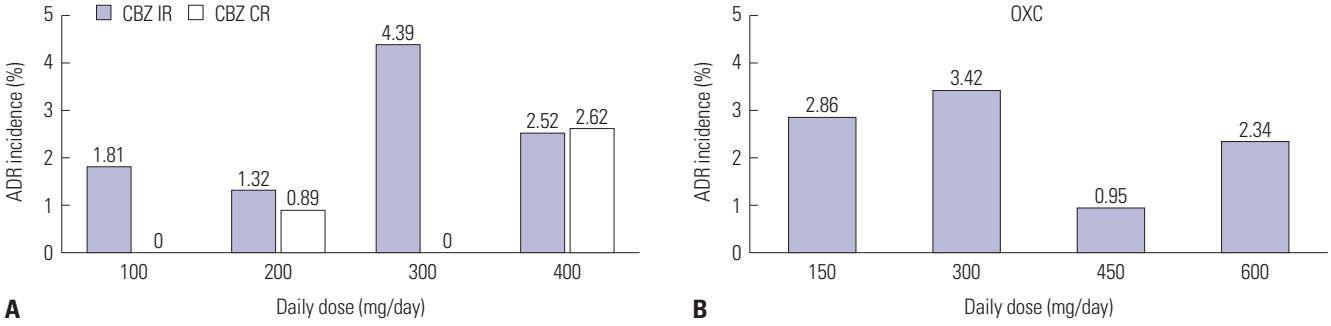

Fig. 2. Incidence of ADRs to CBZ (A) and OXC (B) according to initial daily dose. ADR, adverse drug reaction; CBZ, carbamazepine; IR, immediate-release; CR, controlled-release; OXC, oxcarbazepine.

referral. Management should begin with the withdrawal of the suspected drug, as early withdrawal of drugs with a short elimination half- life is associated with better outcomes of patients with severe drug eruptions. In the one case of the SJS patient, changing the drug right after the occurrence of the severe ADR did not eradicate the symptoms. In cases of acute skin failure, patient management must be undertaken in specialized intensive care units or in burn units.[18] The prompt decision of the clinician is necessary for a favorable prognosis.

According to the ADR reports in this study, there was a difference in daily doses between IR and CR tablets of CBZ in relation to ADRs. For CBZ CR, most of the ADR cases were reported at 400 mg/day, while CBZ IR had a number of reports at 100, 200, and 300 mg/day. OXC mainly showed ADRs at a dose of 150, 300, and 600 mg/day. This might arise as a result of use instructions provided to patients at Yonsei University Severance Hospital & Dental Hospital. The CBZ medications we use consist of 200 mg tablets of CBZ CR formulation and 200 mg and 400 mg tablets of CBZ IR formulation. For OXC, 300 mg and 600 mg OXC IR formulations are available. The recommended initial doses of CBZ and OXC are 200 mg twice daily (400 mg/day) and 300 mg twice daily (600 mg/day), respectively. Although the accuracy of tablet splitting is controversial,[19-21] IR formulation can be halved, while CR formulation is not recommended to be modified. Since the halved CBZ IR and OXC already showed a considerable number of ADR reports, we recommend starting from a lower dose to prevent possible ADR events. Also, clinicians should consider administering half-dose tablets of CBZ and OXC.

This study was based on spontaneous reports of clinicians prescribing the drugs. All spontaneous reporting systems are affected by under-reporting.[22] Considering the purpose of the system, most reports were intended to document that the doctor had to change or withdraw the medication due to ADR symptoms. We should keep in mind that the incidence might not include mild symptoms that the patient could endure during treatment.

As CBZ and OXC are commonly used in clinics, clinicians should be aware of the likelihood of ADRs with respect to these drugs. Although OXC had more reports of mild skin reactions, SCARs only occurred with CBZ. Furthermore, other types of ADRs, such as nervous system disorders, general disorders, and hepatobiliary disorders, showed higher incidences with CBZ. OXC has been proven to have anti-epileptic efficacy comparable with CBZ[8,9] and also has FDA approved indications for children. Based on this limited study, we recommend OXC as a first-line prescription of anti-epileptic drugs. Given the significant number of ADR reports at daily doses below the recom-

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mendation, initial doses of CBZ and OXC should be set even lower. Even in cases of severe ADRs, fast and proper management by clinicians can prevent serious outcomes.

AUTHOR CONTRIBUTIONS

Conceptualization: Alec Hyungtack Kim and Seong Taek Kim. Data curation: Jung Eun Lee and Soo Hyun Kim. Formal analysis: Jung Eun Lee. Funding acquisition: Seong Taek Kim. Investigation: Jung Eun Lee and Soo Hyun Kim. Methodology: Jung Eun Lee. Project administration: Jung Eun Lee. Resources: Soo Hyun Kim. Software: Jung Eun Lee and Kang Ryul Min. Supervision: Alec Hyungtack Kim and Seong Taek Kim. Validation: Seong Taek Kim. Visualization: Jung Eun Lee and Seong Taek Kim. Writing—original draft: Jung Eun Lee. Writing—review & editing: Kang Ryul Min, Alec Hyungtack Kim, and Seong Taek Kim. Approval of final manuscript: all authors.

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REFERENCES

1. Blom S. Trigeminal neuralgia: its treatment with a new anticonvulsant drug (G-32883). Lancet 1962;1:839-40.
2. Hirschfeld RMA, Bowden CL, Gitlin MJ, Keck PE, Suppes T, Thase ME, et al. Practice guideline for the treatment of patients with bipolar disorder. 2nd ed. In: American Psychiatric Association practice guidelines for the treatment of psychiatric disorders: compendium 2002. Arlington (VA): American Psychiatric Association; 2002. p.547-634.
3. Ghaemi SN, Berv DA, Klugman J, Rosenquist KJ, Hsu DJ. Oxcarbazepine treatment of bipolar disorder. J Clin Psychiatry 2003;64:943-45.
4. Lertratanangkoon K, Horning MG. Metabolism of carbamazepine. Drug Metab Dispos 1982;10:1-10.
5. Gayford JJ, Redpath TH. The side-effects of carbamazepine. Proc R Soc Med 1969;62:615-6.
6. Kim HK, Kim DY, Bae EK, Kim DW. Adverse skin reactions with antiepileptic drugs using Korea adverse event reporting system database, 2008-2017. J Korean Med Sci 2020;35:e17.
7. Breton H, Cociglio M, Bressolle F, Peyriere H, Blayac JP, Hillaire-Buys D. Liquid chromatography-electrospray mass spectrometry determination of carbamazepine, oxcarbazepine and eight of their metabolites in human plasma. J Chromatogr B Analyt Technol Biomed Life Sci 2005;828:80-90.
8. Houtkooper MA, Lammertsma A, Meyer JW, Goedhart DM, Meinardi H, van Oorschot CA, et al. Oxcarbazepine (GP 47.680): a possible alternative to carbamazepine? Epilepsia 1987;28:693-8.
9. Dam M, Ekberg R, Løyning Y, Waltimo O, Jakobsen K. A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy. Epilepsy Res 1989;3:70-6.
10. Yang CY, Dao RL, Lee TJ, Lu CW, Yang CH, Hung SI, et al. Severe cutaneous adverse reactions to antiepileptic drugs in Asians. Neurology 2011;77:2025-33.
11. Kang MG, Sohn KH, Kang DY, Park HK, Yang MS, Lee JY, et al. Analysis of individual case safety reports of severe cutaneous adverse reactions in Korea. Yonsei Med J 2019;60:208-15.
12. Korinthenberg R, Haug C, Hannak D. The metabolization of carbamazepine to CBZ-10,11-epoxide in children from the newborn age to adolescence. Neuropediatrics 1994;25:214-6.
13. Yu YM, Shin WG, Lee JY, Choi SA, Jo YH, Youn SJ, et al. Patterns of adverse drug reactions in different age groups: analysis of spontaneous reports by community pharmacists. PLoS One 2015;10:e0132916.
14. Domecq C, Naranjo CA, Ruiz I, Busto U. Sex-related variations in the frequency and characteristics of adverse drug reactions. Int J Clin Pharmacol Ther Toxicol 1980;18:362-6.
15. Rademaker M. Do women have more adverse drug reactions? Am J Clin Dermatol 2001;2:349-51.
16. Montastruc JL, Lapeyre-Mestre M, Bagheri H, Fooladi A. Gender differences in adverse drug reactions: analysis of spontaneous reports to a Regional Pharmacovigilance Centre in France. Fundam Clin Pharmacol 2002;16:343-6.
17. Schmidt D, Elger CE. What is the evidence that oxcarbazepine and carbamazepine are distinctly different antiepileptic drugs? Epilepsy Behav 2004;5:627-35.
18. Roujeau JC. Treatment of severe drug eruptions. J Dermatol 1999;26:718-22.
19. McDevitt JT, Gurst AH, Chen Y. Accuracy of tablet splitting. Pharmacotherapy 1998;18:193-7.
20. Verrue C, Mehuys E, Boussery K, Remon JP, Petrovic M. Tablet-splitting: a common yet not so innocent practice. J Adv Nurs 2011;67:26-32.
21. Quinzler R, Gasse C, Schneider A, Kaufmann-Kolle P, Szecsenyi J, Haefeli WE. The frequency of inappropriate tablet splitting in primary care. Eur J Clin Pharmacol 2006;62:1065-73.
22. Thiessard F, Roux E, Miremont-Salamé G, Fourrier-Réglat A, Haramburu F, Tubert-Bitter P, et al. Trends in spontaneous adverse drug reaction reports to the French pharmacovigilance system (1986-2001). Drug Saf 2005;28:731-40.