Ital J Gender-Specific Med 2018; 4(1): 27-33

Gender differences and pharmacovigilance: analysis in the Italian population

Eleonora Castellana, Maria Rachele Chiappetta, Francesco Cattel

SC Farmacia Ospedaliera, AOU Città della Salute e della Scienza di Torino, Italy. *Received 7 January 2017; accepted 2 May 2018.*

Summary. *Introduction.* Adverse drug reactions (ADRs) are a major burden in healthcare. Scientific literature shows that women tend to have a higher risk of adverse drug reactions than men due to differences in pharmacokinetics, pharmacodynamics and drug use. *Materials and methods.* Data were obtained from the Italian National Pharmacovigilance Network and we focused our attention on ADRs in the period between 2001 and 2016. We identified: the most reported ATCs (Anatomic, Therapeutic, Chemical Classification), the severity of ADRs, age, outcome and sex. *Results*. During the observation period, 301,233 ADRs were reported, women have a higher risk of ADRs over the age of 2 and under the age of 11 years. Serious ADRs were more frequent in females than in males; on the contrary death events were more frequent in males than in females in all age groups. Women presented more ADRs when treated with thyroid hormones (81%-H03AA), aminoquinoline antimalarials (78%-P01BA), COX-inhibitor anti-inflammatory and anti-rheumatic drugs, (71%-M01AH), selective serotonin reuptake inhibitor antidepressants (68%-N06AB), benzodiazepine derivative anxiolytics (66%-N05BA), acetic acid derivative anti-inflammatory and anti-rheumatic drugs and related substances (59%-M01AB), broad-spectrum penicillins (58%-J01CA), penicillin associations including beta-lactamase inhibitors (57%-J01CR) and propionic acid derivative anti-inflammatory and anti-rheumatic drugs (57%-M01AE). Men had more ADRs when treated with protease inhibitors (61%-J05AE) and reverse transcriptase nucleoside inhibitors (70%-J05AF). *Conclusions.* ADRs are more frequent and more serious in women than in men, but death is more common in males.

Key word: pharmacovigilance, adverse drugs reactions, gender, women, men.

Differenze di genere e farmacovigilanza: analisi nella popolazione italiana

Riassunto. *Introduzione.* Le reazioni avverse a farmaci (ADRs) rappresentano un'importante voce di spesa del Servizio Sanitario Nazionale. Le donne, in letteratura, sono descritte come il genere più predisposto a manifestare un elevato rischio di reazioni avverse, rispetto al sesso maschile, a causa della differente farmacocinetica, farmacodinamica e differente utilizzo dei farmaci. *Materiali e metodi.* I dati ottenuti per l'analisi sono stati estrapolati dalla Rete Nazionale di Farmacovigilanza, focalizzando l'attenzione sulle ADRs avvenute nel periodo tra il 2001 e il 2016. I dati estrapolati sono: le classi ATC (classificazione anatomico, terapeutico, chimico) maggiormente segnalate, serietà delle ADRs, età, esito e sesso. *Risultati.* Durante il periodo di osservazione sono state raccolte 301.233 ADRs: il sesso femminile è stato soggetto ad un rischio più elevato di ADRs soprattutto dopo i primi 2 anni di vita e dopo gli 11 anni. Le reazioni avverse gravi sono state più frequenti nel sesso femminile rispetto a quello maschile. Le donne hanno presentato più ADRs se trattate con ormoni tiroidei (81%-H03AA), con i farmaci antimalarici (78%-P01BA), con i coxib antinfiammatori e antireumatici (71%-M01AH), con gli antidepressivi selettivi serotonina inibitori della ricaptazione (68%-N06AB), con i derivati ansiolitici delle benzodiazepine (66%-N05BA), con i farmaci antinfiammatori e antireumatici derivati dell'acido acetico e sostanze correlate (59%-M01AB), con le penicilline ad ampio spettro (58%-J01CA), con le associazioni di penicilline inclusi gli inibitori della beta-lattamasi (57%-J01CR) e i farmaci antinfiammatori e antireumatici derivati dell'acido propionico (57%-M01AE). Il sesso maschile ha invece visto più ADRs se trattato con farmaci inibitori della proteasi (61%-J05AE) e farmaci nucleosidici inibitori della trascrittasi inversa (70%-J05AF). *Conclusioni.* Le ADRs sono più frequenti e gravi nelle donne rispetto agli uomini, i quali, però, sono più soggetti a eventi di morte.

Parole chiave: farmacovigilanza, reazione avversa al farmaco, genere, donne, uomini.

Introduction

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. WHO established its Programme for International Drug Monitoring in response to the thalidomide disaster that came to light in 1961. The development of pharmacovigilance legislation is based on the observation that adverse drug reactions (ADRs) cause around 197,000 deaths per year in the European Union. An ADR is an 'noxious and unintended' response to a medicine that occurs during use[1].

Scientific literature shows that women tend to have a higher risk of adverse drug reactions and it has been reported that women are about 1.5-1.7 times more vulnerable to ADRs than men[2].

Differences between male and female subjects in physical (body-water space, muscle mass, organ blood flow, organ function) and physiological aspects (menopause, pregnancy and menstruation), as well as differences regarding pharmacodynamics and pharmacokinetics (bioavailability, distribution, metabolism, excretion) are purported and considered potential reasons for the difference in ADR risks. The clinical relevance of these gender-based differences to the occurrence of ADRs is not yet clear[3,4]. Historically, women of childbearing age were excluded from clinical trials after the thalidomide tragedy. In the aftermath of this event and in an attempt to protect all unborn life from unknown ADRs, all fertile women were banned from participation in clinical trials, regardless of whether they were pregnant[5]. Although the regulatory authorities have stressed the importance of including more women in clinical trials, women are still underrepresented in clinical research, especially in phase I and II trials[3,4].

The aim of this study was to investigate the gender-related differences in ADRs in the Italian population, on the basis of sex, during a 15-year observation period.

Materials and methods

Data were obtained from Italian National Network of Pharmacovigilance (INNP)[6] and we focused our attention on ADRs in the period between 2001 and 2016.

We analysed:

- gender;
- age, broken down into six groups (less than 1 month, from 1 month to less than 2 years, from 2 to 11 years, from 12 to 17 years, from 18 to 64 years and from 65 years);
- severity, non-serious and serious (congenital anomaly/deficit of the newborn, invalidity or severe permanent impairment, life-threatening event and death);
- outcome (improvement, still not recovered, recovered with consequences and recovered);
- ATC (Anatomic, Therapeutic, Chemical Classification) and drugs most reported.

Results

Gender and age

301,233 ADRs were collected during the observation period.

Table 1 shows that females have a higher risk of ADRs, especially over the age of 2 years. Between 1 month and 2 years of age, males are more susceptible to ADRs than females.

Non-serious adverse drug reactions

Males had "non-serious" adverse drugs reactions more often than females, up to the age of 2 years, whereas above this age, females were more susceptible than males (Table 2).

Serious adverse drug reactions

The results of the "Congenital anomaly/deficit of the newborn" analysis are not significant except in the 18-64 year group, in which women were more likely to experience ADRs than men. The "invalidity or serious permanent ADRs" were slightly higher amongst males up to 11 years of age, whereas after this age females were more often indicated. Moreover, "life-threatening ADRs" were more frequent amongst males up to 11 years, but were more common in females thereafter. On the contrary, death events were more frequent in males than in females in all age groups (Table 3).

Table 1. Distribution of age, gender and number of ADRs obtained from INNP between 2001 and 2016.

Age range	Females		Males		Not indicated		Total	
	n	%	n	%	n	%	n	%
Less than 1 month	158	36.4	181	41.7	95	21.9	434	0.10
From 1 month to less than 2 years	12,055	45.9	13,150	50.1	1053	4.0	26,258	8.70
From 2 to 11 years	10,141	53.8	8489	45.0	223	1.2	18,853	6.30
From 12 to 17 years	4797	59.5	3223	40.0	44	0.5	8064	2.70
From 18 to 64 years	78,186	58.1	55,295	41.1	1203	0.9	134,684	44.70
From 65 years	62,142	55.0	49,568	43.9	1230	1.1	112,940	37.50
TOTAL	167,479	55.6	129,906	43.1	3848	1.3	301,233	100.00

Table 2. Non-serious ADRs. Distribution of age, gender and number of ADRs obtained from INNP between 2001 and 2016.

Age range	Females		Males		Not indicated		Total	
	n	%	n	%	n	%	n	%
Less than 1 month	69	46.3	75	50.3	5	3.4	149	0.10
From 1 month to less than 2 years	9858	46.4	10,601	49.9	771	3.6	21,230	11.80
From 2 to 11 years	7995	56.9	6000	42.7	46	0.3	14,041	7.80
From 12 to 17 years	3367	61.8	2064	37.9	16	0.3	5447	3.00
From 18 to 64 years	48,123	60.3	31,366	39.3	343	0.4	79,832	44.20
From 65 years	33,157	55.4	26,475	44.2	254	0.4	59,886	33.20
TOTAL	102,569	56.8	76,581	42.4	1435	0.8	180,585	100.00

Table 3. Congenital anomaly/deficit of the newborn ADRs.

Age range	Females		Males		Not indicated		Total	
	n	%	n	%	n	%	n	%
Congenital anomaly/deficit of the newborn ADRs								
Less than 1 month	13	41,9	9	29,0	9	29,0	31	32,00
From 1 month to less than 2 years	7	58,3	4	33,3	1	8,3	12	12,40
From 2 to 11 years	1	25,0	3	75,0	0	0	4	4,10
From 12 to 17 years	0	0	1	100	0	0	1	1,00
From 18 to 64 years	41	95,3	2	4,7	0	0	43	44,30
From 65 years	1	16,7	3	50,0	2	33,3	6	6,20
TOTAL	63	64,9	22	22,7	12	12,4	97	100,00
Invalidity or serious permanent ADRs								
Less than 1 month	0	0,0	2	100	0	0	2	0,10
From 1 month to less than 2 years	25	39,1	39	60,9	0	0	64	3,40
From 2 to 11 years	14	41,2	19	55,9	1	2,9	34	1,80
From 12 to 17 years	15	62,5	9	37,5	0	0	24	1,30
From 18 to 64 years	486	58,0	350	41,8	2	0,2	838	44,60
From 65 years	525	57,4	386	42,2	4	0,4	915	48,70
TOTAL	1065	56,7	805	42,9	7	0,4	1877	100,00
Danger of life ADRs								
Less than 1 month	4	57,1	3	42,9	0	0	7	0,10
From 1 month to less than 2 years	42	32,6	65	50,4	22	17,1	129	1,60
From 2 to 11 years	81	43,3	106	56,7	0	0	187	2,30
From 12 to 17 years	53	52,0	47	46,1	2	2,0	102	1,30
From 18 to 64 years	2221	56,1	1728	43,6	12	0,3	3961	49,40
From 65 years	2019	55,6	1581	43,5	31	0,9	3631	45,30
TOTAL	4420	55,1	3530	44	67	0,8	8017	100,00
Death ADRs								
Less than 1 month	4	66,7	1	16,7	1	16,7	6	0,20
From 1 month to less than 2 years	23	35,9	30	46,9	11	17,2	64	1,80
From 2 to 11 years	17	28,3	26	43,3	17	28,3	60	1,70
From 12 to 17 years	4	19,0	17	81,0	0	0	21	0,60
From 18 to 64 years	601	40,6	782	52,8	97	6,6	1480	41,60
From 65 years	883	45,8	911	47,2	135	7,0	1929	54,20
TOTAL	1532	43,0	1767	49,6	261	7,3	3560	100,00

Outcome of adverse drug reactions

As regards ADRs according to outcome, the adverse drug reaction data show that "improvement" is slightly higher in males up to 11 years of age, but higher in females after this date. A similar tendency is observed in the rate of "still not recovered" and "recovered with consequences" outcomes.

Over the age of 2 years, females have a higher "recovered" rate than males (Table 4).

Table 4. Outcome. Distribution according to age, gender and number of ADRs obtained from INNP between 2001 and 2016.

Age range	Females		Males		Not indicated		Total	
	n	%	n	%	n	%	n	%
Improvement								
Less than 1 month	34	54.8	24	38.7	4	6.5	62	0.10
From 1 month to less than 2 years	1041	46.3	1193	53.0	15	0.7	2249	3.00
From 2 to 11 years	1667	48.5	1752	51.0	17	0.5	3436	4.60
From 12 to 17 years	941	57.2	700	42.6	3	0.2	1644	2.20
From 18 to 64 years	20,517	57.1	15,338	42.7	107	0.3	35,962	47.90
From 65 years	17,158	54.1	14,437	45.5	101	0.3	31,696	42.20
TOTAL	41,358	55.1	33,444	44.6	247	0.3	75,049	100.00
Not still recovered								
Less than 1 month	6	40.0	9	60.0	0	0,0	15	0.10
From 1 month to less than 2 years	221	44.0	276	55.0	5	1,0	502	3.10
From 2 to 11 years	328	45.1	398	54.7	2	0,3	728	4.50
From 12 to 17 years	201	54.0	168	45.2	3	0,8	372	2.30
From 18 to 64 years	4643	56.9	3489	42.7	30	0,4	8162	49.90
From 65 years	3555	54.1	2999	45.6	20	0,3	6574	40.20
TOTAL	8954	54.8	7339	44.9	60	0,4	16,353	100.00
Recovered with consequences								
Less than 1 month	1	20.0	4	80.0	0	0	5	0,10
From 1 month to less than 2 years	65	43.9	82	55.4	1	0.7	148	3.00
From 2 to 11 years	53	46.9	60	53.1	0	0	113	2.30
From 12 to 17 years	49	58.3	35	41.7	0	0	84	1.70
From 18 to 64 years	1307	57.1	972	42.5	10	0.4	2289	46.90
From 65 years	1173	52.4	1053	47.1	12	0.5	2238	45.90
TOTAL	2648	54.3	2206	45.2	23	0.5	4877	100.00
Recovered								
Less than 1 month	82	43.2	96	50.5	12	6.3	190	0.10
From 1 month to less than 2 years	9586	46.2	10,328	49.7	846	4.1	20,760	14.50
From 2 to 11 years	6384	59.6	4289	40.0	45	0.4	10,718	7.50
From 12 to 17 years	2727	63.9	1530	35.8	13	0.3	4270	3.00
From 18 to 64 years	35,843	60.6	23,019	38.9	246	0.4	59,108	41.20
From 65 years	27,502	56.8	20,707	42.8	215	0.4	48,424	33.80
TOTAL	82,124	57.2	59,969	41.8	1377	1.0	143,470	100.00

ATC

There was a significant difference for ATC reports (Figure 1 and Table 5): female subjects experienced more ADRs than male subjects, except for protease inhibitors (J05AE) and reverse transcriptase nucleoside inhibitors (J05AF). In this case, adverse drug reactions are more common in men than in women (61% and 70% respectively).

ADRs were more frequently reported in females for certain classes of drugs, such as thyroid hormones (81%-H03AA), antimalarial aminoquinolines (78%-P01BA),

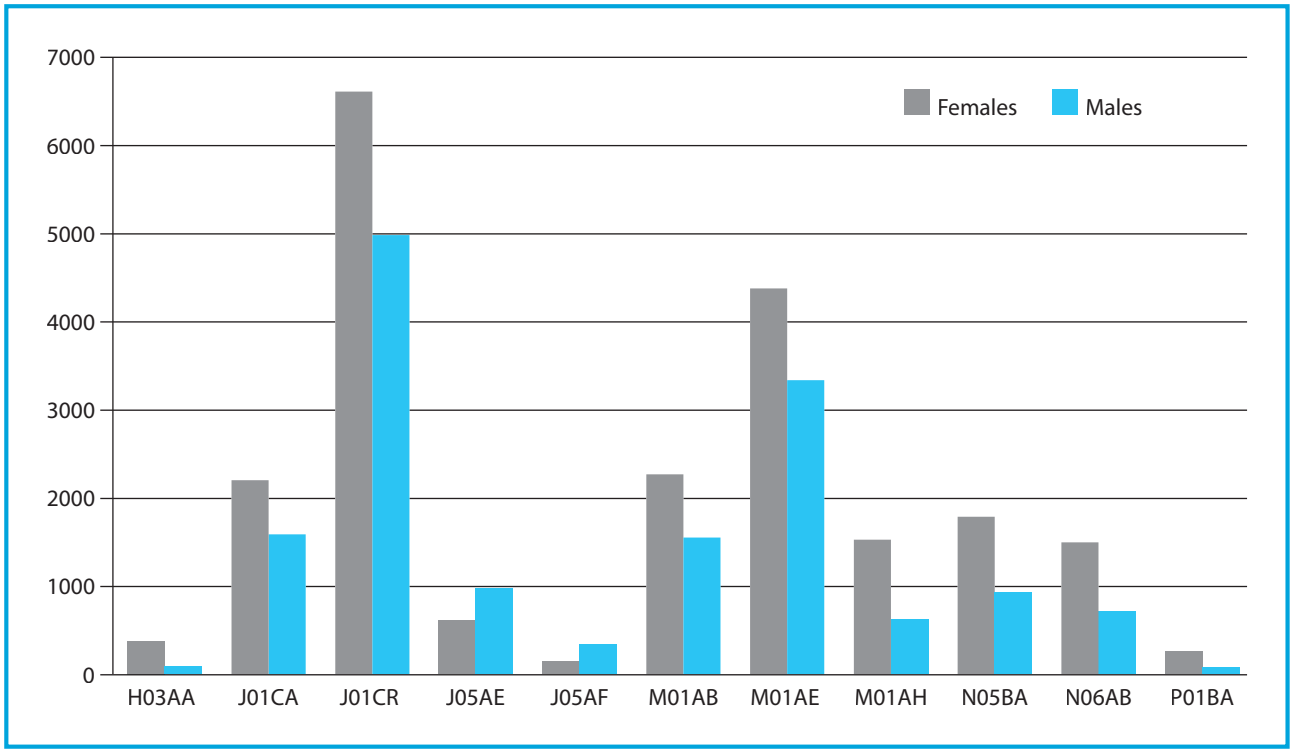

Figure 1. Major gender toxicity report for ATC.

Table 5. Major number of ADRs reported for ATC.

ATC	Females (n)	Males (n)	Total (n)	Females (%)	Males (%)
H03AA	377	87	464	81	19
J01CA	2211	1590	3801	58	42
J01CR	6609	4985	11594	57	43
J05AE	614	976	1590	39	61
J05AF	146	336	482	30	70
M01AB	2270	1557	3827	59	41
M01AE	4381	3340	7721	57	43
M01AH	1525	627	2152	71	29
N05BA	1788	929	2717	66	34
N06AB	1500	709	2209	68	32
P01BA	262	75	337	78	22

Table 6. Drugs most reported in relationship with ATC.

ATC	Description	Drugs most reported
H03AA	Thyroid hormones	Levothyroxine
J01CA	Broad-spectrum penicillins	Amoxicillin
J01CR	Penicillin associations, including beta-lactamase inhibitors	Amoxicillin and clavulanate
J05AE	Protease inhibitors	Ritonavir and telaprevir
J05AF	Reverse transcriptase nucleoside inhibitors	Zidovudine and lamivudine
M01AB	Anti-inflammatory and anti-rheumatic acetic acid derivatives and related substances	Diclofenac
M01AE	Anti-inflammatory and anti-rheumatic propionic acid derivatives	Ibuprofen and ketoprofen
M01AH	Anti-inflammatory and anti-rheumatic COX inhibitors	Celecoxib and etoricoxib
N05BA	Benzodiazepine derivative anxiolytics	Lorazepam and alprazolam
N06AB	Selective serotonin reuptake inhibitor antidepressants	Citalopram, paroxetine and escitalopram
P01BA	Aminoquinolines antimalarials	Hydroxychloroquine

COX inhibitor anti-inflammatory and anti-rheumatic drugs (71%-M01AH), selective serotonin reuptake inhibitor antidepressants (68%-N06AB), benzodiazepine derivative anxiolytics (66%-N05BA), anti-inflammatory and anti-rheumatic acetic acid derivatives and related substances (59%-M01AB), broad-spectrum penicillins (58%-J01CA), penicillin associations including beta-lactamase inhibitors (57%-J01CR) and propionic acid derivative anti-inflammatory and anti-rheumatic drugs (57%-M01AE). The relationship between ATC and the drugs that caused major toxicity is shown in Table 6.

Discussion

As stated by The Italian Medicines Agency (AIFA), "compared to the past, current scientific knowledge has allowed us to identify, differences in genetic, anatomical, physiological, hormonal features as well as in habits, lifestyles, sports, nutrition, social factors and cultural rights, between men and women". In 2012, AIFA pharmacovigilance data also showed that most of the adverse reactions in women are caused by overdose or polydrug use, events that are related to a drug dosage calculated using a male model of 70 kg. These differences therefore support the importance of encouraging the development of "gender-specific medicine"[7].

In Italy, the AIFA encourages doctors and hospital pharmacists to report ADRs.

In our study, most reactions were more common in women, but men have more adverse drugs reactions before the age of 2 years and over the age of 11 years; most ADRs occurred in the 18 to 64 years age group. One possible explanation is that patients in this age group use a greater number of medicines[8].

Most of the ADRs were not severe and had a positive outcome. Although the female population had a higher prevalence of ADRs, and serious ADRs, death was more commonly reported in the male population.

Thyroid hormones (levothyroxine), aminoquinoline antimalarials (hydroxychloroquine), COX inhibitor anti-inflammatory and anti-rheumatic drugs (celecoxib and etoricoxib), selective serotonin reuptake inhibitor antidepressants (citalopram, paroxetine and escitalopram) and benzodiazepine derivative anxiolytics (lorazepam and alprazolam), were the medicines for which more ADRs were observed in women than in men. It should be pointed out that, statistically, women take more drugs than men[9] and that the incidence of conditions, such as thyroid and autoimmune diseases and depression are more frequent in women[10].

Men are more vulnerable to protease inhibitor drugs (ritonavir and telaprevir) and reverse transcriptase nucleoside inhibitors (zidovudine and lamivudine); in this case, men are subject to a greater number of HIV (Human Immunodeficiency Virus) diagnoses[11].

Conclusions

These data suggest that ADRs are more frequent and severe in women than in men, but that death occurs more often in males.

It should be pointed out that women take more drugs than men and that some classes of drugs are used more by one sex than the other, depending on the medical conditions, which are often gender-dependent.

These data indicate the need to include women in clinical studies and the importance of monitoring ADRs to ensure greater medicinal product safety.

Key messages

- Scientific literature shows that women tend to have a higher risk of adverse drug reactions than men due to differences in pharmacokinetics, pharmacodynamics and drug use.
- Our study focused our attention on ADRs in the period between 2001 and 2016. Data were obtained from the Italian National Pharmacovigilance Network.
- During the observation period, 301,233 ADRs were reported: women have a higher risk of ADRs over the age of 2 and under the age of 11 years. On the contrary death events were more frequent in males than in females in all age groups. These data suggest that ADRs are more frequent and severe in women than in men, but that death occurs more often in males.
- It should be pointed out that women take more drugs than men and that some classes of drugs are used more by one sex than the other, depending on the medical conditions, which are often gender-dependent.
- These data indicate the need to include women in clinical studies and the importance of monitoring ADRs to ensure greater medicinal product safety.

Reference

1. World Health Organization (WHO). Pharmacovigilance. Available from: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en (updated December 2017).
2. Rademaker M. Do women have more adverse drug reactions? Am J Clin Dermatol 2001; 2 (6): 349-51.
3. Zopf Y, Rabe C, Neubert A, Gabmann KG, Rascher W, Hahn EG, Dormann H. Women encounter ADRs more often than do men. Eur J Clin Pharmacol 2008; 64: 999-1004.
4. Fattinger K, Roos M, Vergeres P, Holenstein C, Kind B, Masche U, Stocker DN, Braunschweig S, Kullak-Ublick GA, Galeazzi RL, Follath F, Gasser T, Meier PJ. Epidemiology of drug exposure and adverse drug reactions in two Swiss departments of internal medicine. Br J Clin Pharmacol 2000; 49: 158-67.
5. Sabine Oertelt-Prigione. Gender differences and clinical trial design. Clin Invest 2011; 1 (2): 187-90.
6. Italian Medicines Agency (AIFA). Farmacovigilanza. Available from http://www.agenziafarmaco.gov.it/content/farmacovigilanza (updated June 2018).
7. Loddo G, Cottonaro S, Daga F, Bellini P. Gender medicine: a new approach for healthcare. Programma scienziati in azienda - XIV edizione Baveno, 16 settembre 2013-19 luglio 2014. Available from: http://www.istud.it/up_media/pwscienziati13/gender_medicine.pdf.
8. Singh H, Dulhani N, Kumar BN, Singh P, Tewari P, Nayak K. A pharmacovigilance study in Medicine department of tertiary care hospital in Chhattisgarh (Jagdalpur), India. J Young Pharm 2010; 2 (1): 95-100.
9. National Institute of Statistics. Available from: http://dati.istat.it (updated April 2018).
10. AIFA & ISS. L'uso dei farmaci in Italia. Rapporto nazionale anno 2011. Available from: http://www.epicentro.iss.it/farmaci/pdf/OsMed/OSMED%202011.pdf.
11. European Centre for Disease Prevention and Control. HIV/AIDS surveillance in Europe 2017. Available from: https://ecdc.europa.eu/en/infectious-diseases-public-health/hiv-infection-and-aids/surveillance-and-disease-data/annual.

Conflict of interest statement: the Authors declare no financial disclosures related to the content of this article.

Acknowledgments: Special thanks to Dr Danila Turco.

Correspondence to:
Eleonora Castellana
SC Farmacia Ospedaliera
AOU Città della Salute e della Scienza di Torino
Corso Bramante 88
10126 Torino, Italy
email: ecastellana@cittadellasalute.to.it