

Reported adverse drug reactions in 2012

The practice of recording adverse drug reactions has been changed to include reactions reported by consumers, as well as those reported by health care professionals. However, the scope of reported adverse drug reactions in 2012 was very similar to that recorded in previous years.

In 2012, Fimea received 1,629 reports of adverse drug reactions, excluding vaccine adverse events. The total number of suspected adverse reactions was 4,710, which means approximately three adverse reactions per report. In 75% of the reported incidents, the described reactions were classified as severe. As in previous years, the largest number of reported reactions involved general symptoms and symptoms in the area where the drug was administered, as well as adverse reactions of the nervous system (figure 1).

Suspected reactions were reported for 444 medicinal substances, with the majority (71%) being reported by no more than three people. The number of medicinal substances reported at least 15 times was 25 (table 1). The most commonly reported drugs were the levonorgestrel-releasing intrauterine system (Mirena) and the teriparatide drug used to treat osteoporosis (Forteo), both for technical reasons (more information below).

Generally speaking, the reported adverse reactions do not warrant any conclusions as to the benefits or risks of a drug if they have not been weighed against the efficacy and safety of the drug. Similarly, the reports provide no grounds for drug comparison, nor does the number of reports indicate the actual occurrence of adverse reactions. The purpose of the reporting system is first and foremost to help identify unknown, rare, adverse drug reactions.

The Directive on human medicines came into force in July 2012. It contains detailed provisions on the obligations of the authorities and marketing authorisation holders regarding post-authorisation safety, such as the obligation to communicate any new adverse reactions on the basis of reported adverse drug reactions. It also states that reports of adverse reactions submitted by consumers will be processed in the same way as reports submitted by health care professionals. These changes were included in the national legislation in the Act amending the Medicines Act, which came into force on 1 June 2013. In 2012, a total of 108 reports were submitted by consumers. In most cases, the adverse effects described in these reports were previously known, and no new, frequently reported combinations of drugs and adverse reactions arose.

Figure 1. The organs and systems affected by adverse reactions reported in 2012, according to the MedDRA classification.

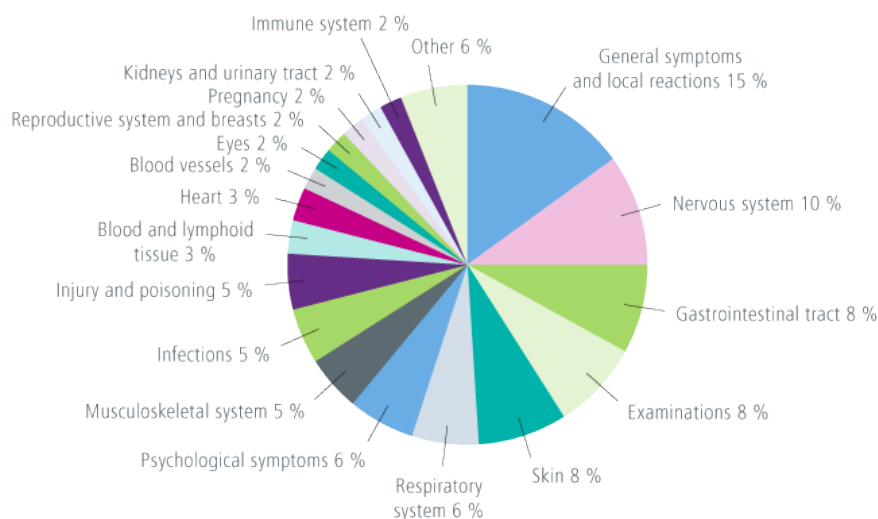


Table 1. Drugs most commonly reported for adverse reactions in 2012. New most commonly reported drugs compared to 2011 are marked with an asterisk (*).

Drug (trade names)	Number of reports
Levonorgestrel (Mirena)	53
Teriparatide (Forteo)*	52
Clozapine (Froidir, Leponex)	49
Pregabalin (Lyrica)	47
Rituximab (Mabthera)	41
Risperidone (Risperdal, Risperdal Consta)	33

Adalimumab (Humira)	30
Levodopa, carbidopa (Duodopa)	30
Infliximab (Remicade)	29
Denosumab (Prolia, Xgeva)*	28
Drospirenone, ethinyl estradiol (Yasmin, Yasminelle, Yaz)	23
Bevacizumab (Avastin)*	22
Capecitabine (Xeloda)	22
Olanzapine (Zypadhera, Zyprexa)	22
Sunitinib (Sutent)*	21
Tocilizumab (RoActemra)*	21
Docetaxel (Docetaxel Actavis, Taxotere)	19
Atorvastatin (Lipitor, Orbeos)	18
Dabigatran (Pradaxa)	17
Etanercept (Enbrel)	17
Quetiapine (Ketipinor, Seroquel)	16
Strontium ranelate (Protelos)*	16
Dienogest, estradiol valerate (Qlaira)*	15
Etoricoxib (Arcoxia)	15
Venlafaxine (Efexor depot)	15

Contraceptives

Since 2011, Mirena's marketing authorisation holder has classified all bleeding, including spotting, as a severe adverse reaction, which is therefore reported to Fimea (Kalliokoski 2012). Almost half (25) of the reported reactions (53) regarding Mirena were bleeding, or bleeding with another adverse reaction, and another significant reported reaction was pregnancy (14 reports, four involving ectopic pregnancy).

The most frequently reported combined oral contraceptives were the drospirenone-ethinyl estradiol tablets (Yaz, Yasmin, Yasminelle; 23 reports). Pregnancy was the reported adverse reaction in 13 cases. Nine incidents of a deep vein thrombosis and/or pulmonary embolism were reported, and one cerebral infarction. Drospirenone-ethinyl estradiol tablets are the most commonly prescribed contraceptive in Finland, which is why the number of reported reactions most probably reflects the popularity of the drug, as well as the severity of the reported adverse reactions. For some time, an increased risk of venous thromboembolism has been a known adverse reaction associated with combined oral contraceptives, and is now being re-assessed by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC).

15 reports concerning the sequential dienogest-estradiol tablet Qlaira have been submitted. In nine cases, pregnancy was reported as the adverse reaction, and a deep vein thrombosis and/or pulmonary embolism was reported in two cases.

Osteoporosis medication

As many as 49 of the 52 reported adverse reactions to teriparatide (Forsteo) originated in the so-called patient assistance programme. In some of these cases, it was not clear whether the adverse reactions were suspected to be a consequence of the teriparatide medication. The reported symptoms included various effects on specific organs, the most commonly reported ones being various types of arrhythmia. Palpitations and tachycardia are expected side effects of teriparatide, in other words those that are mentioned in the summary of product characteristics. Under the European Medicines Agency's coordination, efforts are being made to draw up more detailed instructions on how to provide the authorities with information on adverse effects that accumulate during various patient assistance programmes.

Denosumab (Prolia, Xgeva) is used to treat osteoporosis and prevent pathological fractures in patients with bone metastases. It was the suspected drug in 28 reports, seven of which involved hypocalcaemia and six osteonecrosis of the jaw, both known adverse effects of denosumab.

Sixteen reports of strontium ranelate (Protelos) were submitted, six of which described various skin conditions, most commonly a rash. In one reported case, the patient was believed to have toxic epidermal necrolysis and drug reaction/rash with eosinophilia and systemic symptoms (DRESS). In five reported cases, the patient was diagnosed with deep vein thrombosis and/or pulmonary embolism. All of the above are expected adverse reactions to strontium ranelate.

Antipsychotic drugs and antidepressants

49 incidents of suspected adverse drug reactions to the antipsychotic drug clozapine (e.g. Froidir, Leponex) were reported. In 21 cases, the patient had developed agranulocytosis or leukopenia/neutropenia, and some had consequently developed an infection, or even sepsis. Notably, in some cases the adverse reactions had occurred several years after use of the drug. The other main group of adverse reactions to clozapine included various changes in ECG, most typically prolonged QT intervals, as mentioned in the SPC.

Risperidone (e.g. Risperdal) was the suspected drug in 33 reports, 24 of which mentioned reactions to the long-acting injection (Risperdal Consta). Highly diverse reactions were reported: in seven cases, the patient had developed various extrapyramidal symptoms, such as akathisia and tardive dyskinesia. In three cases, elevated prolactin levels and dysmenorrhea were reported.

22 reports of olanzapine (e.g. Zyprexa) were submitted, seven of which exclusively involved the long-acting injection (Zypadhera). Various psychological or nervous-system related symptoms were described, such as drowsiness, confusion or anxiety, all of which are common side

effects of olanzapine.

Quetiapine (Seroquel, Seroquel Prolong) was reported 16 times, and in six cases a number of suspected drugs were reported, usually another antipsychotic. In three cases the patient had developed leukopenia/neutropenia, in two cases tachycardia and in two cases tardive dyskinesia.

The antidepressant venlafaxine (e.g. Efexor) was reported 15 times. A range of different adverse reactions were reported, the most common ones being various withdrawal symptoms. In four cases, withdrawal symptoms were reported when the dose was gradually decreased to discontinue use altogether.

Pregabalin

Therapeutic indications of pregabalin (Lyrica) include the treatment of neuropathic pain, generalised anxiety disorder and epilepsy. It was the suspected drug in 47 reports. Of all reports, 26 cited drug poisoning incidents which resulted in the patient's death. These were not, however, individual cases that had originally been reported separately; rather, they were based on two literature and lecture sources. These and a later review discuss the growing misuse of pregabalin (Joukanen 2011) and fatal poisonings in general (Vuori 2012). Pregabalin was linked to 12 fatal poisoning cases in 2009, and to 15 cases in 2010 (Vuori 2012).

TNF alpha and interleukin inhibitors

Rituximab (Mabthera) was the suspected drug in 41 reports. Rheumatoid arthritis was the therapeutic indication in 24 reports and cancer in eight. The most commonly reported side effects were those listed in the SPC. In 13 cases, the patient had developed an infection, such as pneumonia, which often coincided with other adverse reactions. Two cases of progressive multifocal leukoencephalopathy (PML) were reported; in one case the patient died. In eight reports, various symptoms or allergic reactions associated with the infusion were described. In five cases, the reported adverse reactions were leukopenia/neutropenia and/or thrombocytopenia.

In previous years, other biological medicines have also been among the most frequently reported drugs in terms of adverse reactions. Drugs reported 15 times or more included adalimumab (Humira), infliximab (Remicade), tocilizumab (Roactemra) and etanercept (Enbrel). Reports related to adalimumab, tocilizumab and etanercept usually involved infections. The most commonly reported adverse reactions to infliximab were allergic reactions and reactions to the infusion.

Cancer drugs

Adverse reactions to the vascular endothelial growth factor (VEGF) inhibitor bevacizumab (Avastin) were reported 22 times. This drug is also used intraocularly, to treat macular degeneration. In five cases, the occurrence of intraocular inflammation, or endophthalmitis, was reported in connection with this treatment. In three cases involving cancer treatment, gastrointestinal perforation was reported, and in four cases the cancer had spread.

Capecitabine (e.g. Xeloda) is used in the treatment of cancers such as colon, rectal and breast cancer. It was the suspected drug in 22 reports, the most commonly reported reaction being diarrhoea, which usually occurred in conjunction with other adverse reactions. Two occurrences of myocardial infarction or coronary artery spasm were reported.

Sunitinib (Sutent) is used to treat cancer, such as metastatic kidney cancer. It was the suspected drug in 21 reports, which described a range of different adverse reactions. In four cases, the patient had developed hypothyroidism in addition to other adverse reactions.

In 2011, delayed infusion site reactions were reported in connection with the administration of Docetaxel Actavis. These were discussed in the European Medicines Agency's Pharmacovigilance Working Party. The cause of the local reactions remained unclear. In 2012, 19 reports of docetaxel were submitted, seven of which described various hypersensitivity symptoms such as dyspnoea and redness. In ten cases, reactions in the Docetaxel Actavis infusion site were reported. To investigate this phenomenon, a survey was sent to all care units using docetaxel in late 2012, and the case is still pending.

Other drugs

Duodopa is an enterally administered levodopa/carbidopa gel used for the treatment of advanced Parkinson's disease. Of the 30 reports submitted, most described problems were associated with the administration of the drug or the progress of the disease and the related complications, such as pneumonia. Problems associated with the intestinal catheter, such as blockage or infection, were described in 11 reports.

The lipid-lowering drug atorvastatin (Lipitor, Orbeos) was reported in 18 cases, nine of which involved muscle or joint pain, usually coinciding with other miscellaneous adverse reactions. Three reports were submitted by the drug users, two of which cited muscle problems.

Adverse reactions to the anticoagulant dabigatran (Praxada) were mentioned in 17 reports, ten of which described bleeding, most commonly in the gastrointestinal tract.

The anti-inflammatory drug etoricoxib (Arcoxia) was reported 15 times, the majority of the causes being hypersensitivity symptoms or skin reactions. These included anaphylaxis and the Stevens-Johnson syndrome.

Risks and benefits of drugs continuously assessed

All reports are reviewed and recorded in Fimea's adverse drug reaction database. Reactions classified as severe will also be sent to the European Medicines Agency for inclusion in its adverse reaction database. This database is continuously observed to identify new side effects. This is the most important role of the adverse reaction record. While an individual report may not result in any action, the risks and benefits of drugs are being continuously assessed in the light of information received from a number of sources.

In 2013, the black triangle, which will appear in the summary of product characteristics and package leaflets, is intended to encourage

people to report any adverse reactions and to focus attention on new drugs and previously unidentified side effects).

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LITERATURE

Kalliokoski A. Haittavuosi 2011. Sic! 2012; 2(2): 50–4.

Joukanen S. Pregabaliinin väärinkäyttö on lisääntynyt. Suom Lääkäril 2011; 9: 756-9.

Vuori E, et al. Myrkytyskuolemien määrä on kääntynyt laskuun. Suom Lääkäril 2012; 22: 1735-41. |