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## Frequency of ill-founded off-label prescribing in Dutch general practice

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### SUMMARY

**Purpose** The aim of this study is to quantify the extent of ill-founded off-label drug prescriptions in Dutch general practice. The study is based upon information on both the prescription itself and the patient's medical history.

**Methods** In total, 48 combinations of drugs and off-label indications were selected from a list of 477 known off-label combinations. These 48 combinations were considered as ill-founded since pharmacotherapeutic handbooks or clinical practice guidelines did not provide evidence for their efficacy and safety. They were considered to be relevant for investigation in general practice. We used a nationally representative information network of 85 general practices in the Netherlands. By using information on the patients' diagnoses and medication in the period before and after the prescription, we were able to exclude non-conclusively off-label prescriptions.

**Results** Twenty-one of the selected 48 off-label combinations did not occur in Dutch general practice. The drugs with the highest proportion of ill-founded off-label prescriptions were betahistine (26.7%), celecoxib (16.3%) and etoricoxib (12.5%). In total, 18.2% of the prescriptions, which were initially assessed as ill-founded off-label, were re-evaluated as on-label, after considering the patient's medical history.

**Conclusions** Ill-founded off-label prescribing in Dutch general practice is limited for 48 relevant combinations of drugs and off-label indications. In order to overcome limitations in registration databases, it is useful to look at as much information as possible—for example, co-medication and co-morbidity—when determining off-label prescribing. Studying ill-founded off-label prescribing should be performed on a day-to-day basis, especially for recently introduced drugs.

## INTRODUCTION

New drugs need to be authorized before market entrance.

To receive authorization, a favourable balance between beneficial and harmful effects has to be demonstrated.

Drugs are usually registered for a limited number of clinical diagnoses (indications) and for adult patients only. However, in daily practice, drugs are often used in situations that do not adhere to the authorization requirements. Such 'off-label prescribing' refers to the use of a drug that is not in line with the terms as formulated in the summary of product characteristics (SPC), that accompanies every registered product. A distinction should be made between well-founded and ill-founded (disputable) off-label prescriptions. In contrast to ill-founded, well-founded off-label prescriptions are recommended in clinical practice guidelines or pharmacotherapeutic handbooks. These recommendations are based on systematic examination of the published literature. The efficacy of ill-founded off-label prescription is often questionable and adverse drug reactions and unjustified health care costs may result. Earlier research shows that even off-label prescribed drugs (no distinction between ill- and well-founded) sometimes induce more adverse drug reactions than drugs prescribed on-label.<sup>1-3</sup> One important motive for physicians to prescribe off-label is the fact that the effectiveness of drugs is described in clinical guidelines, guidebooks and/or (new) scientific literature. However, motives that are based on experimental tendencies do also occur, such as the idea that the drug might be effective because of the registered indications or the supposed working mechanism, as well as good experiences observed by the professionals involved.<sup>4</sup> In 2005 the Dutch Medicines Evaluation Board and the Dutch Health Care Inspectorate stated that off-label prescribing should only be permitted if there is appropriate scientific evidence, that is, well-founded.<sup>5</sup> This statement was taken over in the Dutch Medicines Act, which came into force in July 2007.

For several groups of drugs or specific patient populations, the occurrence of off-label prescribing has been studied. Fairly large frequencies have been found,

for example, 17% of prescriptions for hospitalized elderly<sup>6</sup> and 32% of prescriptions for patients with dermatological diseases.<sup>7</sup> Other topics studied were for antipsychotics,<sup>8</sup> pregnant women,<sup>9</sup> children<sup>10,11</sup> and drugs used in oncology.<sup>12</sup> Two studies carried out in the Netherlands showed that the same magnitude can be expected in general practice: 11–72% for new introduced drugs and 21–58% for antidepressants in children and adolescents.<sup>13–15</sup> When off-label prescribing is studied, researchers do not very often make a distinction between well-founded and ill-founded off-label prescribing. Accordingly, we wanted to quantify the occurrence of ill-founded off-label prescribing for a broad range of drugs. Because 75–80% of all prescribed drugs in the Netherlands are prescribed by GPs, we wanted to focus on general practice. We wonder if GPs, being generalists, know the exact indications of all prescribed drugs. One important aspect here is the understanding that in the Netherlands, the GP acts as a gatekeeper to the health care system. All Dutch inhabitants are registered with a general practice and the GP is the first person consulted when health problems arise. Moreover, after a patient referral, a visit to an Accident and Emergency department, or after a hospital admission, the GP is informed about the medical findings (e.g. diagnosis and laboratory results) and interventions.

## METHODS

### Data

Data were used from the Netherlands Information Network of General Practice (LINH), an information network of a representative sample of general practices in the Netherlands.<sup>16</sup> We assessed the occurrence of ill-founded prescribing in 2004. In order to examine the medical

context, we also used patients' medical information from 2003. In total, 78 general practices with a total patient population of 319 843 persons were included in our analysis. Participating GPs routinely register all patient contacts in electronic medical records.

Subjects of registration are diagnoses, prescriptions, and referrals to other health care professionals. Diagnoses are coded according to the ICPC-1,<sup>17</sup> and drugs according to the ATC-classification.<sup>18</sup> In 2004, an ICPC-code was assigned to almost 100% of all patient contacts, and to 72.4% of all prescriptions.

### Definitions

Off-label prescribing was defined as 'a prescription for an indication different from the indications stated in the Dutch SPC'. Off-label prescribing due to age, dose, route of administration or contra-indications were not evaluated. Oncological indications were excluded,

since these were hardly ever prescribed by GPs. An off-label combination was defined as a combination of a drug with an off-label indication for this specific drug.

An ill-founded off-label prescription was defined as an off-label prescription which is not recommended in pharmacotherapeutic handbooks or clinical practice guidelines.

### Relevant ill-founded off-label combinations

In order to determine which combinations of drugs and off-label indications were suitable for study in general practice, we made an inventory of known off-label combinations described in international literature,

pharmacotherapeutic handbooks and Dutch clinical practice guidelines. Moreover, we asked innovative pharmaceutical companies, the Netherlands Pharmacovigilance Centre (LAREB), the Royal Dutch Pharmaceutical Society and the Dutch Association of Health Care Insurers to report cases of undesirable off-label use. From the inventory we made a selection of combinations of drugs and ill-founded off-label indications using the following criteria:

- the indication is not included in the Dutch SPC;
- off-label use for this indication is not recommended in pharmacotherapeutic handbooks (the 2005 editions of Dutch Physicians Desk Reference, the pharmacotherapeutic handbook of the Dutch pharmacists and the United States Pharmacopeia—Drug Information, Volume I);
- off-label use for this indication is not recommended in Dutch clinical practice guidelines, largely developed by the Dutch College of General Practitioners and the Dutch Institute of Health Care Improvement;
- the indication is likely to occur in general practice, since the expected overall prevalence of the indication in a general practice population is more than 1 per 1000 persons;
- the combination of drug and off-label indication can be operationalized using the International Classification for Primary Care (ICPC) and the Anatomical Therapeutic Chemical (ATC) classification.

The inventory resulted in 477 off-label combinations, of which 48 met the above criteria of ill-founded off-label combinations (Table 1, columns 1 and 2).

### Analysis

The drugs included in our analysis could be assigned to a maximum of two ATC-codes. For off-label indications, we sometimes had to use a wider range of ICPC codes.

Borderline personality disorder, for example, does not have a unique ICPC-code. Therefore, it was classified as personality disorder—a broader definition (Table 1, columns 3 and 4).

When such broader disease categories were used, we also verified that no other disease within that broader category was an approved indication for the examined drug (Table 1, column 5).

We selected all patients who had one of the 48 potentially ill-founded off-label combinations of drug and indication in 2004. For each selected patient, all medical information available in the database was examined for the years 2004 and 2003. This included diagnoses (including co-morbidity), referrals, reasons for referrals, other prescriptions and indications for other prescriptions. As such, we were able to review the character of the prescription in a broader context and to deselect prescriptions that were off-label at first sight, but after reviewing were not conclusively off-label.

There can be plausible explanations why a combination of a drug and indication at first sight seems to be off-label: (a) the disease for which the drug was given is present, but was not registered at the moment of prescription, (b) at the moment of prescription, the disease was not yet diagnosed and registered, but some time later it was, (c) at the moment of prescription, the GP registers the (off-label) chronic disease of the patient, instead of the (on-label) complaint for which the drug is meant and (d) the GP makes a mistake when entering the codes in the electronic medical record.

Using the numbers before and after deselection, a range could be defined around the true number of ill-founded off-label prescriptions. These were related to the total number of prescriptions of the drug concerned and the total number of prescriptions with the relevant indication. Data were analysed using SPSS for Windows, Rel. 12.0.1. (Chicago: SPSS Inc., 2003).

## RESULTS

The database included 319 843 patients, who received a total of 2678 off-label prescriptions for the selected 48 combinations of drugs and ill-founded off-label indications in 2004. After studying additional medical information on these patients, 487 prescriptions (18.2%) were excluded because there was reason to assume that the prescription may not have been off-label.

Most prescriptions were excluded because the patient received a different drug for one of the approved indications of the examined drug (8.1%).

Consequently, 2191 prescriptions could be considered as convincingly ill-founded off-label.

Table 2, shows that, after excluding non-conclusive off-label prescriptions, only 25 of the examined 48 combinations of drugs and off-label indications were found in the database. We summarize the main results here. For 21 combinations, no prescriptions were found in the initial search (see Table 1). Four drugs had more than 100 off-label prescriptions. The proportions of ill-founded off-label prescriptions among all prescriptions for a particular drug, varied from less than 1% for several drugs, to 26.7% for betahistine. For the COX-2 inhibitors celecoxib and etoricoxib, 16.3 and 12.5% respectively were prescribed for back symptoms in 2004. Olanzapine and risperidone were prescribed for three ill-founded off-label indications: ADHD, aggression in children and adolescents and antisocial personality disorder. Of all prescriptions of olanzapine, 5.1% was prescribed off-label for these off-label indications, and of all prescriptions of risperidone, 10.0%.

## DISCUSSION

This study assessed the occurrence of ill-founded off-label prescribing in the Netherlands by GPs. Forty-eight combinations of drugs and ill-founded off-label indications were included in this study. In a patient population of 319 843 patients, 2191 prescriptions were found with one of these combinations. In these cases there is no evidence to justify a good balance between effectiveness and safety. Because no ICPC code was assigned to 27.6% of all prescriptions, we do not want to make an estimate of the frequency of ill-founded off-label prescribing in the total practice population. Besides, our research concerned only a selection of all possible ill-founded off-label combinations.

The number of 2191 prescriptions (as above) suggests that the occurrence of ill-founded off-label prescribing by general practitioners in the Netherlands is limited, with a few

exceptions. In other studies, researchers found percentages of 20 or more (ill- and well-founded together).<sup>6-15</sup> However, some remarks should be made here. As previously mentioned, we made a selection of combinations of drugs and ill-founded off-label indications that can be expected in a general practice database and, as such, this study does not comprise the full range of ill-founded off-label combinations. The possibilities for off-label prescribing are almost inexhaustible. Moreover, the current study only measured indication-related off-label use.

Off-label use related to age, dosage, duration of time, route of administration and presence of contraindications were not examined.

Data came from a large, nationwide general practice network. Information about patient contacts is registered in an electronic information system that mainly takes place during patient contacts. Because a large majority of the general practices in the Netherlands have a computerized patient registration system (Electronic Patient Record), GPs who participate in the LINH network should not be very different from GPs who do not participate in LINH. In addition, research showed that there were only small differences in medical practice between GPs participating in LINH and non-participating GPs.<sup>19</sup> In contrast to previous studies, which studied all the prescriptions outside the SPC, this study focused especially on off-label indications that are not documented as well founded. In addition, we used all patients' medical information available in the database, to control for limitations in the database and mistakes that could have been made by GPs when adding information at any point in time. As a result, we demonstrated that for 81.8% of all potentially ill-founded off-label prescriptions, the drug was actually prescribed for an ill-founded off-label indication. For the other 18.2%, the prescription might have been prescribed on-label. The only other study that explicitly looked at ill-founded off-label prescribing was performed in the USA among office-based physicians.<sup>20</sup> The authors found that about 15% of all prescriptions was ill-founded off-label. For specific drugs, the percentages were higher than in our study. This may partly be due to the fact that they applied different methods, used data from 2001, had a different patient population (including patients treated [table 2] by physicians working in ambulatory secondary care services) and was performed in a country with a different health care system to the Netherlands.

The combinations of drugs and ill-founded off-label indications observed most frequently were betahistine for dizziness (not Ménière), celecoxib for back symptoms, etoricoxib for back symptoms and amitriptyline for headache (not migraine). For each of the studied diagnoses, the percentage of off-label prescriptions of all prescriptions was <6%. The only exception was dizziness, for which betahistine was prescribed in 32.5% of all prescriptions. This drug is strictly approved for 'the syndrome of Ménière'. It is hard to distinguish between the various forms of dizziness.<sup>21</sup> The Dutch Physicians Desk Reference states that before prescribing a drug for dizziness, the physician needs to reach a precise diagnosis and to prescribe approved drugs only.<sup>22</sup> Apparently, many GPs do not know the strict indication for betahistine or they doubt the diagnosis that they made. The latter is confirmed by the fact that over 300 (24.4%) of the off-label prescriptions for betahistine were excluded by applying the selection criteria. These are the prescriptions of patients who received a diagnosis both for Ménière and dizziness. Betahistine does not have severe adverse drug reactions, aside from increased risk of respiratory problems in asthma patients. Drugs that do have more serious adverse reactions are antipsychotic drugs, including the atypical antipsychotic drugs olanzapine and risperidone.<sup>23-24</sup> Of all prescriptions of olanzapine, 5.1% was prescribed off-label for personality disorders or behaviour problems, and of all prescriptions of risperidone, 10.0% was prescribed off-label for these indications. In other studies higher frequencies were found.<sup>25-26</sup> In the Netherlands, COX-2 inhibitors are known for their frequent off-label prescribing.<sup>27,28</sup> The reasons why GPs prescribe COX-2 inhibitors off-label are— the supposed smaller amount of adverse effects (stomach problems), user-friendliness, and the continuation of earlier prescriptions by the medical specialist. Besides, GPs think the

drug is beneficial for a broader range of indications than those for which it is in fact registered.

<sup>28</sup> Some years ago, concern arose about the safety of COX-2 inhibitors, as their use may increase the risk of cardiovascular events, especially myocardial infarctions.

<sup>29</sup> Based on this example of recently introduced, potentially hazardous drugs, we think it is worthwhile to assess the frequency in general practice on a routine basis.

One final observation is that although different studies have shown drugs off-label prescribed for obesity,<sup>30</sup> we did not find these combinations, apart from fluoxetine and obesity (only four prescriptions in 2004). We are therefore inclined to conclude that Dutch GPs do not prescribe ill-founded drugs for obesity, although we cannot rule out that when a drug is given for obesity, GPs register a code for a chronic disease that is closely related to obesity (like diabetic mellitus, hypertension and heart failure), instead of obesity.

No successful treatment is available for many of the examined off-label indications. Kos et al.<sup>31</sup> showed that dissatisfaction with available drug therapy is one of the incentives for off-label use. Examples here are chronic headache, dizziness, obesity and alopecia androgenetica in women. Research on new therapies or research on off-label therapies for such indications should be stimulated.

## CONCLUSION

This study shows that ill-founded off-label prescribing in Dutch general practice is limited to 48 relevant combinations of drugs and off-label indications. An important exception to this rule is betahistine for dizziness. We know from other studies that GPs lack knowledge about the on- or off-label status of a drug at the moment of prescribing. Supporting GPs by the inclusion of a reporting system in their electronic patient registration, that gives a message if an ill-founded drug is prescribed, can prevent them from prescribing drugs for undesired off-label indications.

Other exceptions are COX-2 inhibitors, prescribed for back symptoms. Especially for recently introduced drugs, registration networks like LINH are highly suitable for monitoring ill-founded off-label prescribing on a day-to-day basis. For many of the examined off-label indications, no good, successful treatment is available. Therefore, research on therapies for such indications (including off-label therapies) should be stimulated.

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#### TABLES AND ANNEXE

##### KEY POINTS

- The examination of 48 combinations of drugs and ill-founded off-label indications in Dutch general practice, showed that combinations with betahistine, celecoxib and etoricoxib occurred most frequently. Overall, on the basis of these 48 examined ill-founded off-label combinations, it appears that off-label prescribing of medication not recommended in clinical practice guidelines or handbooks, is limited in Dutch general practice.
- In evaluating the on- or off-label status of a prescription, it is useful to examine all available patient information, for example, co-medication and co-morbidity, in order to decide whether an off-label prescription is conclusively off-label. In this study, over 18 per cent of all prescriptions of the 48 combinations of drugs and ill-founded off-label indications examined was re-evaluated as on-label, upon examination of the patient's medical history.
- The prevalence of off-label prescribing can be assessed in general practice information networks. Such information networks are useful to monitor ill-founded off-label prescriptions on a day-to-day basis, especially for recently introduced drugs.

Table 1. Overview of the examined combinations of drugs and off-label indications, ICPC-1 codes, descriptions of the applied off-label indications and codes of the approved on-label indications in 2005; a distinction is made between combinations for which prescriptions were found in the LINH general practice database and combinations for which no prescriptions were found

Drugs	Off-label indications	Applied off-label indication codes (ICPC-codes)	ICPC description of applied off-label codes	ICPC-codes of approved on-label indications
<b>Combinations for which prescriptions were found in LINH</b>				
Cimetidine	Warts in children	S03 (age < 25)	Warts in children	D84, D85, D86, D87
Hydroxyethylrutosides	Diabetes mellitus (incl. diabetic microangiopathy)	T90	Diabetes mellitus	K06, K94, K95
Verapamil	Prophylaxis of migraine	N89	Migraine	K74, K75, K76, K78, K79, K85, K86, K87
Lisinopril	Prophylaxis of migraine	N89	Migraine	K85, K86, K75, K77, T90
Finasteride	Alopecia androgenetica in women	S23 (females)	Hair loss/alopecia (females)	No selection criteria used since the drug is off-label for females
Estrogens	Stress incontinence	U04	Urine-incontinence (not enuresis)	Wide range of indications, not exactly covered: Chapter W, Chapter X, L95
Oxybutynin	Gastro-intestinal disorders (spasms)	Chapter D	Tractus digestivus	U02, U04, U05, U13
Desmopressin	Nocturia due to prostate complaints	Chapter U, Y06, Y85; age ≥ 25, male	Urinary tract (not other symptoms/complaints urine), symptoms/complaints of prostate, benign prostate hypertrophy	T01, T99, P12 (age < 25)
Meloxicam	Neuropathic pain	Chapter N	Nervous system	L84, L88, L89, L90, L91
Celecoxib	Backache (no rheumatoid arthritis)	L02, L03, L86	Back symptoms/complaints, low-backache with or without radiation	L84, L88, L89, L90, L91
Etoricoxib	Backache (no rheumatoid arthritis)	L02, L03, 86	Back symptoms/complaints, low-backache with or without radiation	L84, L88, L89, L90, L91, T92
Methysergide	Tension headache	N02	Tension headache	N89, N90, D11
Valproate sodium	Schizophrenia	P72	Schizophrenia	N88
Carbamazepine	Gambling addiction	P80	Personality-/character disorder	N86, N88, N92, P15, P73, T01, T99, U02
Lamotrigine	Borderline syndrome	P80	Personality/character disorder	N89
Topiramate	Bipolar disorder	Chapter P	Mental problems	N88, N89
Gabapentin	Bipolar disorder	Chapter P	Mental problems	N88 <sup>a</sup>
Gabapentin	Restless legs syndrome	N04	Restless legs	N88 <sup>a</sup>
Olanzapine	ADHD <sup>†</sup>	P21	Overactive child/hyperkinetic syndrome	P72, P73
Olanzapine	Antisocial personality disorder	P80	Personality/character disorder	P72, P73
Risperidone	ADHD <sup>†</sup>	P21	Overactive child/hyperkinetic syndrome	P70, P72, P73
Risperidone	Aggression in children and adolescents <sup>†</sup>	P22, P23; age ≤ 30	Other concerns behaviour child or adolescent	P70, P72, P73
Risperidone	Antisocial personality disorder	P80	Personality/character disorder	P70, P72, P73
Amitriptyline	Chronic headache (not migraine)	N01	Headache (not tension headache, migraine or symptoms/complaints sinuses)	P12, P76
Fluoxetine	Obesity	T82, T83	Obesity (QI > 30) or overweight (QI ≤ 30)	P76, P79, T06
Naltrexone	Gambling addiction	P80	Personality/character disorder	P15, S02
Betahistine	Dizziness (not Ménière)	N17	Vertigo/dizziness (not Ménière)	H82
<b>Combinations for which no prescriptions were found in LINH</b>				
Cimetidine	Obesity	T82, T83	Obesity (QI > 30) or overweight (QI ≤ 30)	D03, D84-86
Metformin	Obesity	T82, T83	Obesity (QI > 30) or overweight (QI ≤ 30)	T90
Acarbose	Obesity	T82, T83	Obesity (QI > 30) or overweight (QI ≤ 30)	T90
Topiramate	Obesity	T82, T83	Obesity (QI > 30) or overweight (QI ≤ 30)	N88, N89
Bromocriptine	Obesity	T82, T83	Obesity (QI > 30) or overweight (QI ≤ 30)	N87, W19, X21, Y7, Y10, Y16, T29, T73, T99
Fluvoxamine	Obesity	T82, T83	Obesity (QI > 30) or overweight (QI ≤ 30)	P76, P79
Sertraline	Obesity	T82, T83	Obesity (QI > 30) or overweight (QI ≤ 30)	P74, P76

Table 1. (Continued)

Drugs	Off-label indications	Applied off-label indication codes (ICPC-codes)	ICPC description of applied off-label codes	ICPC-codes of approved on-label indications
Pentoxifylline	Diabetic neuropathy	T90 AND N94	Diabetes mellitus AND other peripheral neuritis/neuropathy	K92
Buspirone	(Diabetic) neuropathy	N94	Other peripheral neuritis/neuropathy	P01, P74
Atenolol	Chronic weariness syndrome after Pfeiffer	A04 AND A75	Weakness/tiredness AND infectious mononucleosis	K04, K78-80, K74-K76, K85, K86
Clonidine	Nicotine addiction	P17	Tobacco abuse	N89, X11
Carbamazepine	Migraine	N89	Migraine	N86, N88, N92, P15, P73, T01, T99, U02
Gabapentin	Migraine	N89	Migraine	N88*
Gabapentin	Migraine	N89	Migraine	N88*
Gabapentin	Withdrawal signs for alcohol or drugs	P15, P19	Chronic alcohol abuse or drug abuse	N88*
Olanzapine	Aggression in children and adolescents <sup>†</sup>	P22, P23; age ≤ 30	Other concerns behaviour child or adolescent	P72, P73
Olanzapine	Obsessive disorder	P79	Other neurosis	P72, P73
Quetiapine	Obsessive disorder	P79	Other neurosis	P72, P73
Imipramine	Stress incontinence	U04	Urine-incontinence	P76, P12
Montelukast	Urticaria	S98	Urticaria	R96, R97
Cyproheptadine	Anorexia nervosa	T06	Anorexia nervosa/bulimia	A12, A85, R97, S12, S87, S88, S98

\*By now, also approved for N94, S70 and T90.

<sup>†</sup>By now, also included in the guideline on ADHD for children and adolescents, in case of behaviour problems and aggression.

Table 2. Quantification of the off-label prescriptions, practice population of 338 118 persons

Drugs	Applied off-label indications	Number of off-label prescriptions	Number of off-label prescriptions deselected (not conclusively off-label)	Number of conclusively off-label prescriptions	Percentage off-label prescriptions with regard to the total number of prescriptions of the drug concerned	Percentage off-label prescriptions with regard to the total number of prescriptions with the indication concerned
Cimetidine	Warts in children	3	0	3	0.3	0.4
Hydroxyethyl-rutosides	Diabetes mellitus (incl. diabetic microangiopathy)	3	2	1	0.5	0.002
Verapamil	Migraine	22	12	10	0.5	0.1
Lisinopril	Migraine	7	4	3	0.1	0.03
Finasteride	Alopecia androgenetica in women	10	0	10	1.1	5.2
Estrogens	Urine-incontinence	59	39	20	0.5	0.7
Oxybutynin	Tractus digestivus	20	13	7	0.9	0.01
Desmopressin	Urinary tract (incl. nocturia due to prostate complaints)	20	0	20	2.8	0.2
Meloxicam	Nervous system (incl. neuropathic pain)	46	3	43	1.8	0.1
Celecoxib	Back symptoms	399	19	380	16.3	1.5
Etoricoxib	Back symptoms	274	24	250	12.5	1.0
Methysergide	Tension headache	2	0	2	15.4	0.1
Carbamazepine	Personality disorder (incl. gambling addiction)	5	0	5	0.3	0.3
Valproate sodium	Schizophrenia	11	0	11	0.5	1.1
Lamotrigine	Personality disorder (incl. borderline syndrome)	1	1	0	0.0	0.0
Topiramate	Mental problems (including bipolar disorder)	1	1	0	0.0	0.0
Gabapentin	Mental problems (including bipolar disorder)	40	0	40	3.4	0.03
Gabapentin	Restless legs	19	0	19	1.6	1.5
Olanzapine	Overactive child (incl. ADHD)	2	0	2	0.1	0.2
Olanzapine*	Personality disorder (incl. antisocial)	76	6	70	5.0	3.7
Risperidone	Overactive child (incl. ADHD)	49	1	48	3.7	4.6
Risperidone	Other concerns behaviour child and adolescent (incl. aggression)	23	0	23	1.8	7.3
Risperidone	Personality disorder (incl. antisocial)	57	0	57	4.4	2.9
Amitriptyline	Headache (not migraine)	260	46	214	3.0	4.3
Fluoxetine	Obesity/overweight	14	10	4	0.1	0.8
Naltrexone	Personality disorder (incl. gambling addiction)	3	0	3	5.5	0.2
Betahistine	Dizziness (not Ménière)	1252	306	946	26.7	32.5

\*One outlier with 103 prescriptions of olanzapine was excluded.