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Research Article

Analysis of primary outpatient data for off-label use of medicines in neurology

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Abstract

Introduction: The off-label use of medicines is a common practice that covers a wide range of therapeutic areas in both, adults and children. So far, the extent of off-label use among neurology patients in Bulgaria has not been studied. The aim of this study is to provide data on the off-label use in neurology patients in Bulgaria and to contribute to planning actions by the European Commission and EMA to provide a harmonized guideline and to regulate the off-label use of medicines within the European Union.

Materials and methods: The data on prescriptions of 360 neurology outpatients, treated in a 1 – year period, were recorded and provided for analyses. The Summaries of Product Characteristics, were used as reference documents for assessment of prescriptions.

Results: The results from this study show that most neurology patients (63%) were exposed to off-label use. Most of the medicines prescribed off-label (90%), were used for a therapeutic indication, other than the one listed in the authorized product information. Meloxicam is found to be the most commonly prescribed off-label medicine. Other medicines, like trasadone, pentoxyfylline and fupentixol / melitracen were prescribed less frequently, but deserve special attention, as they were found to be used off-label to a very large extent, some of them in 100% of prescriptions. Half of the top 10 medications, most commonly used off-label in neurology, were found to be non-steroidal anti-inflammatory drugs.

Conclusion: The results reveal a big gap between the authorized medicines and the real medical needs. Further studies based on a larger number of medical centers are needed to establish more accurate data on off-label prescribing in neurology patients on a national level.

Keywords

off-label use, neurology, pharmacovigilance

Introduction

Medicinal products regulation is the modern internationally accepted term to denote the set of activities, which the state exercises in various spheres of the pharmaceutical sector in order to provide the public with quality, efficiency and safety medicines (https://bda.bg/index.php?option=-com_content&view=article&id=53&Itemid=9&lang=bg).

In Europe, drug regulation was introduced with Directive 65/65/EEC in 1965, with one main purpose -to protect end users, i.e. patients (Edwards 2016).

Today, the world has recognized the need for regulation of medicinal products. Therefore, all processes from the development of the medicine, clinical trials and marketing authorization, to pricing, marketing, distribution, prescription and use, are regulated by law.

According to European Union (EU) drug legislation, only medicinal products with proven quality, efficacy and safety can be authorized and used for patient treatment (https://eur-lex.europa.eu/legal-content/en/ALL/?uri=-CELEX%3A32001L0083).

The terms of authorization (indications and posology) are specified in the Summary of product characteristics (SmPC). The SmPC is the official reference document to healthcare professionals for the way medicinal product should be used in real medical practice (https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/product-information/how-prepare-review-summary-product-characteristics#scientific-guidelines-with-smpc-recommendations-section).

However, medicines are not always used as per the terms specified in the SmPC. The intentional use of a medicinal products not in accordance with the SmPC is defined as off-label use. This refers to use for a different indication, different dosage, dosing frequency or duration, different method of administration or to use in a different patient group (e.g. children instead of adults) (https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices).

The off-label use or the use of an authorized medicinal product in an unauthorized way is a contradictory practice that questions drug regulation policies, especially when taking into account the prevalence of this type of practice.

According to some studies, the extent of the off-label use is up to 40% in adults and up to 90% in some pediatric patients (Gazarian et al. 2006). One of the reasons for the high prevalence in children is that there are not enough medicines authorized for use in children, but studies among adults are confirming that the off-label use is common practice between adults also.

In regards to medical areas, the off-label use could be found more often in some of them, such as pediatrics, oncology (including hematology), rheumatology, psychiatry, neurology, rare diseases etc. (Weda et al. 2017).

According to a study on off-label use in EU, published by European Commission in 2017, off-label use cannot be fully avoided. In the study several drivers that predispose the off-label use were identified (Weda et al. 2017):

- From a regulatory perspective – the market authorization process. There is limited drive to extend the marketing authorization, especially for products out of patent.
- From a healthcare system perspective – the high cost of on-label alternatives. Lack of authorization.
- From a healthcare professional's perspective – the lack of an alternative as well as lack of effectiveness of other products.
- From a patient's perspective –the safety and adherence are identified as important drivers.

The presence of so many drivers can explain why off-label use is a common practice, despite the numerous legislative initiatives in the field of drug regulation over the past two decades.

In neurology, off-label use is an integral and standard part of neurological practice (The Lancet Neurology 2008). Studies have shown, that medicines from different drug classes are used off-label to treat various neurological conditions: propranolol for migraine prophylaxis, isoflurane for the treatment of epileptic status, donepezil for treatment of fronto-temporal dementia, gabapentin for treatment of neuropathic pain and diabetic neuropathy, amitriptyline as a first line treatment for neuropathic pain, etc. (Mirsattari et. al. 2004; Demaagd 2008; Gupta et. al. 2014; Zhumadilov et. al. 2014; Mehta et. al. 2015; Birks et. al. 2018).

The aim of this study is to provide data on the off-label use in neurology patients in Bulgaria and to contribute to planning actions by the European Commission and EMA to provide harmonized guideline and to regulate the off-label use of medicines within the EU (https://ec.europa.eu/health/sites/health/files/files/committee/72meeting/pharm655.pdf).

Materials and methods

The design of the study is a nested, single center, retrospective, non-interventional study of data-base. We encountered considerable difficulties in collecting the data because many hospitals and medical centers refused to share information about physicians' prescriptions. Eventually, we collected the source data from the outpatient center of one of the largest private hospitals in Bulgaria.The data from the medical summaries of 360 randomly selected (30 patients/month for 12 months) neurology patients, was collected and recorded by the hospital's staff. During the period from January-December, 2016, all patients were treated by specialists in neurology. The source file obtained for analysis contained the following information: patient's age, gender, diagnoses, prescribed medicines (prescriptions), dosage and method of administration. For the purpose of this study, patient identification data (patient names, addresses, etc.) was not collected.

For assessment of prescriptions, the SmPCs published on the webpage of Bulgarian Drug Agency (public available information) were used as reference documents. Prescriptions, which were prescribed not in accordance with the terms laid down in the SmPC were considered off-label, as shown in Table 1. The SmPC used, was consistent with the trade name of the medicinal product.

Table 1. Determination of the off-label type.

Off-label type	Not in accordance with SmPC section
I – indication	4.1 Therapeutic indications
D – dosage	4.2 Dosage and Method of administration
M – method of administration	4.2 Dosage and Method of administration
A – age	4.2 Dosage and Method of administration and 4.4 Special warnings and precautions for use

Non-medicinal products, usually food supplements, were not subject to this assessment (e.g. oral vitamins, oral omega 3 fatty acids, etc.).

All prescriptions were assessed by two independent assessors, a clinical pharmacist and a pharmacovigilance expert, and all discrepancies were addressed to Bulgarian Drug Agency for final assessment.

Descriptive statistics, with absolute frequencies, means and standard deviation, were used to analyze the processed data. Statistical analysis was conducted using SPSS Statistics 19 (IBM, Armonk, NY, USA). Data were expressed as mean ± standard deviation. The differences in the mean values between groups were analyzed with the two-tailed Student t-test. Differences were considered significant when $p < 0.05$.

Results

Data from 358 neurology patients was processed. Incomplete or missing data was found in two patients and therefore, they were excluded from analyses. The patients were at a median age of 58.9 (range 18–88). Age was very poorly related to the total number of medications prescribed to patients (the older ones are prescribed a larger number) – Spearman's rank correlation coefficient – 0.236.

The same is valid for medicines prescribed off-label – Spearman's rank correlation coefficient – 0.124. Female gender was in slight predominance (55.6% vs. 44.4%), which is understandable due to the high age and more rapid reduction in men with increasing age.

The total number of prescriptions was 1082, which is median 3 medicines per patient. The mean number of prescriptions per patient was 3 (range 1–5). The mean number of off- label prescriptions per patient was 1 (range 0–4). The number of prescriptions between the two genders, did not differ to a significant extent ($p > 0.05$, Mann Whitney Test).

In relation to patients and prescriptions the results are presented in Table 2. Graphically the results are presented in Figure 1. Off-label patients were those who received at least one off-label prescription. Not assessed were those prescriptions which were for non-medicinal products.

Table 2. Off-label use with regard to patients and prescriptions.

Patients (n = 358)				Prescriptions (n = 1082)					
On-label		Off-label		On-label		Off-label		Not assessed	
No.	%	No.	%	No.	%	No.	%	No.	%
131	37	227	63	658	61	347	32	77	7

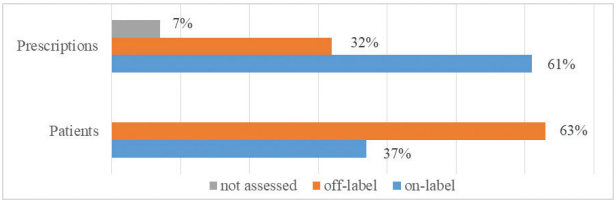

Figure 1. Off-label use with regard to patients and prescriptions.

Prescriptions that have been identified as off-label, have been further analyzed in order to determine the type of off-label use. Most of the off-label medicines were prescribed for different, than the specified therapeutic indication in accordance with their SmPC. Final results are presented in Figure 2.

The most frequent uses were oral (77%), intramuscular (12%), topical (11%) and subcutaneous (0.1%). The distribution in the analyzed different groups of prescriptions are presented in Table 3.

The most commonly prescribed off-label medicines are presented in Table 4. Meloxicam for parenteral use, was the most commonly prescribed off-label medicine, and was prescribed off-label with regard to indication in 96% of prescriptions. It was found that, another medicine with same generic composition (different trade name) was prescribed less frequently and to a much lesser extend off-label (33%).

The second most common off-label medicine, salicylic acid/ diethylamine/ myrtecaine cream was also prescribed off-label with regard to indication in 96% of prescriptions. Among the rest, we will highlight trasadone, pentoxyfylline and fupentixol / melitracen which were prescribed off-label to a very large extent.

Diagnoses (n = 84), for which medicines were most commonly prescribed off-label are presented in Table 5. Off-label treatment was considered a treatment where at least one medicine was prescribed off-label. We highlight four critical diagnoses for which treatments were 50% or more off-label: disorders of the autonomic nervous system, polyneuropathy, damage to the ulnar nerve and disorders of vestibular function.

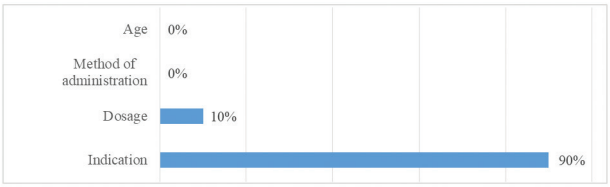

Figure 2. Type of off-label use.

Table 3. Distribution with regard to method of administration.

Method of administration	Prescriptions					
	On-label		Off-label		Not assessed	
	No.	%	No.	%	No.	%
Oral	503	76	265	77	67	87
Intramuscular	89	14	40	11	0	0
Topical	65	10	42	12	10	13
Subcutaneous	1	0.2	0	0	0	0

Table 4. Top 10 off-label prescribed medicines.

	Trade name	Active substance	Pharm. form	Strength	Drug class	Off label prescriptions		On-label prescriptions	
						No.	%	No.	%
1	**Movalis**	Meloxicam	Solution for inj.	15mg / 1.5 ml	Non-steroidal anti-inflammatory drug	26	96	1	4
2	**Algesalsuractiv**	Salicylic acid/ Diethylamine/ Myrtecaine	Cream	1g / 100g and 10g/100g	Non-steroidal anti-inflammatory drug	23	96	1	4
3	**Aspirin Protect**	Acetylsalicylic acid	Tablets	100mg	Non-steroidal anti-inflammatory drug	22	50	22	50
4	**Triticco**	Trasadone	Tablets	150 mg	Antidepressant	16	100	0	0
5	**Vasonit**	Pentoxifylline	Tablets	600mg	Hemorrheologic agent	16	100	0	0
6	**Agapurin SR**	Pentoxifylline	Tablets	400 mg	Hemorrheologic agent	15	88	2	12
7	**Trombex**	Acetylsalicylic acid	Tablets	75 mg	Non-steroidal anti-inflammatory drug	13	46	15	54
8	**Deanxit**	Flupentixol/ Melitracen	Tablets	0,5 mg	Antipsychotic/ tricyclic antidepressant	10	83	2	17
9	**Magnesium**	Magnesium	Tablets	500 mg	Mineral supplement	10	71	4	29
10	**Melbek**	Meloxicam	Solution for inj.	15mg / 1.5 ml	Non-steroidal anti-inflammatory drug	10	33	20	67

Table 5. Diagnoses most commonly associated with the off-label use of medicines.

	Diagnosis	Off-label treatments		On-label treatments	
		No.	%	No.	%
1	Other peripheral vertigo	32	42	44	58
2	Damage of the intervertebral discs in the lumbar spine and the other parts of the spine with radiculopathy	27	20	108	80
3	Non-insulin-dependent diabetes mellitus with polyneuropathy	21	37	36	63
4	Radiculopathy	15	29	37	71
5	Other disorders of vestibular function	14	50	14	50
6	Polyneuropathy, unspecified	13	65	7	35
7	Damage to the ulnar nerve	13	50	13	50
8	Damage of the intervertebral discs in the cervical section with radiculopathy	13	18	59	82
9	Other disorders of the autonomic nervous system	13	68	6	32
10	Consequences of cerebral infarction	10	12	73	88

Discussion

Neurology, as a therapeutic area, is ranked second in regard to off-label prescriptions in adults (Weda et al. 2017). The results of this study showed, that one-third (32%) of prescriptions were off-label and most of the patients (63%) were exposed to off-label use of medicines. These findings confirm that the off-label use is common practice in neurology, but complete comparison with other studies is difficult to be done. Most of the off-label studies in neurology, have been conducted between hospital patients and variations are observed due to methodology used and the population studied (Perearnau et al. 2006; Koopman et al. 2010; Steinhoff et al. 2012; Weda et al. 2017).

According to some of the studies, non-steroidal anti-inflammatory drugs (NSAIDs) arecommonly used off-label (Loder and Biondi 2004; Neubert et. al. 2010). In this study, we found that NSAIDs are half of the medicines most commonly prescribed off-label in neurology, shown in Table 4. Two of them, Movalis and Melbek have same generic composition (meloxicam), but different off-label extent (96% and 33%). Both products were prescribed off-label mainly in regard to indication. The reason might be, that in most cases, the diagnosisis too general (e.g. damage to the intervertebral discs). In this case, the diagnosis does not reflect, whether this is due to degenerative disorders of the intervertebral discs, spinal trauma, tumors, or inflammatory diseases of the spine (e.g. rheumatoid arthritis or ankylosing spondylitis) for which Movalis is actually approved. The same applies to Melbek which, compared to Movalis, is authorized for treatment of osteoarthritis as well.

The second most commonly off-label prescribed medicine, salicylic acid/ diethylamine/ myrtecaine cream, was found to be off-label in 96% of prescriptions as per the valid SmPC at the study period. The main reason was that it was approved for local treatment of pain in the muscles and ligaments, but was mainly prescribed in neurology to treat nerve pain. However, this ranking has changed completely with the entry into force of the new SmPC from 2019, which adds nerve pain treatment as a new indication for this medicinal product. This change in the SmPC practically has removed the product from the list of most commonly prescribed off-label medicines (Table 4).

This is a good example of the important role of the marketing authorization holder (MAH) which, by its action can significantly reduce the off-label use. Unfortunately, under current EU legislation, MAHs are not required to take any action, even if the product is used completely not in accordance with the terms laid down in the SmPC (https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=-CELEX:32004R0726).

Prescribed less frequently, trasadone, pentoxyfylline- and fupentixol / melitracen, deserve special attention, as were prescribed off-label to a very large extent, some of them in 100% of prescriptions. Trasadone is approved for treatment of depressive disorders, but was prescribed for another therapeutic indication (vertigo, Meniere's disease, consequences of stroke, etc.) and in another dosage, than the one listed in the SmPC. Pentoxyfylline is approved for treatment of peripheral arterial circulatory disorders and functional disorders of the inner ear caused by circulatory disorders, but was prescribed for another therapeutic indication (polyneuropathy, consequences of stroke, etc.). Fupentixol / melitracen is approved for treatment of de-

pressive disorders, but was prescribed for another therapeutic indication (vertigo, headache, etc.).

Most of the off-label medicines, were found to be used for different therapeutic indication than the one approved in the authorized product information (90%). This shows a big gap between the available authorized medicines and real medical needs.

This study also revealed some critical diagnoses where treatment was 50% or more off-label (Table 5). This is significant for Bulgarian Society of Neurology, which provides recommendations and published guidelines for treatment of these medical conditions.

Conclusion

Off-label prescriptions are a significant part of the treatment of neurological patients and greater responsibility should be assumed with this regard.

The example with the updated SmPC has shown the important role of the MAH and this can be a good guide for the Competent Health Authorities in their efforts to regulate the off-label use.

We must also pay attention to professional medical associations, that need to be proactive in recognizing pharmacotherapy guidelines and providing national consensus for on-label treatments with authorized medicines.

Although the study is limited to one center, a relatively small sample size and outpatient data only, it reveals many different aspects of the off-label use among neurology patients. Further studies based on a larger number of medical centers are needed to establish more accurate data on off-label prescribing in neurology patients on a national level.

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