

# Pattern of triptans use: a retrospective prescription study in Calabria, Italy

Damiana Scuteri<sup>1</sup>, Annagrazia Adornetto<sup>1</sup>, Laura Rombolà<sup>1</sup>, Maria Diana Naturale<sup>2</sup>, Adele Emanuela De Francesco<sup>3</sup>, Stefania Esposito<sup>3</sup>, Mariacristina Zito<sup>3</sup>, Luigi Antonio Morrone<sup>1</sup>, Giacinto Bagetta<sup>1,\*</sup>, Paolo Tonin<sup>4,#</sup>, Maria Tiziana Corasaniti<sup>2,5,#</sup>

1 Preclinical and Translational Pharmacology, Department of Pharmacy, Health Science and Nutrition, University of Calabria, Cosenza, Italy

2 School of Hospital Pharmacy, University "Magna Graecia" of Catanzaro, Catanzaro, Italy

3 Pharmacy Unit, "Mater Domini" University Hospital, Catanzaro, Italy

4 Regional Center for Serious Brain Injuries, S. Anna Institute, Crotona, Italy

5 Department of Health Sciences, University "Magna Graecia" of Catanzaro, Catanzaro, Italy

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## Abstract

Triptans are 5-hydroxytryptamine 1B/1D receptor agonists used in moderate to severe migraine attacks as first line when non-specific, symptomatic, nonsteroidal anti-inflammatory drugs are not effective. To gain insight in the treatment of migraine in the regional context, this retrospective (from January to August of the years 2017 and 2018) study aimed at monitoring the use of triptans approved by the regional health authority in Calabria. The data demonstrate that the overall treatment of migraine with triptans in the different provinces of Calabria falls in the average regional prescription/dispensation. Interestingly, Crotona showed a trend to an increased amount of defined daily dose/1000 inhabitants per day. The present analysis might stand for homogeneity of treatment of migraineurs in Calabria and highlights the need for better understanding the apparent differences in the local pattern of almotriptan use to improve the appropriateness.

**Key Words:** 5-HT 1B/1D receptor agonists; almotriptan; Calabria; DDD/1000 inhabitants per day; migraine; pharmacoepidemiology; pharmacology of migraine; prescriptions; treatment; triptans

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\*Correspondence to:

Giacinto Bagetta, MD,  
g.bagetta@unical.it or  
giacinto.bagetta@unical.it.

#Both authors contributed equally to this work.

orcid:

0000-0001-8540-6218  
(Giacinto Bagetta)

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## Introduction

Migraine represents a major public health matter reducing quality of life and impairing work productivity with social direct "out of pocket" and indirect costs (Charles, 2017). It accounts for over 90% cases of recurrent throbbing headache and is accompanied by a cluster of neurological disturbances (Scuteri et al., 2019). The acute therapy is intended to abort attacks and triptans represent the first line treatment in the moderate-severe attacks in which symptomatic nonsteroidal anti-inflammatory drugs (NSAIDs) do not prove efficacy (Martelletti and Giamberardino, 2019). Since clinical approval of the first triptan, i.e., sumatriptan, in the early 1990s several congeners (zolmitriptan, rizatriptan, naratriptan, eletriptan, almotriptan, and frovatriptan) have been developed with improved pharmacokinetics and enhanced efficacy and safety (Negro et al., 2018). These drugs are endowed with vasoconstrictor activity, their use not recommended by patients suffering from cardiocerebrovascular accidents (Negro et al., 2018). Another concern with triptans is the occurrence of medication-overuse headache (MOH). The European cross-sectional study Eurolight highlighted an overall undertreatment of migraine; in Italy the 14% of participants consulted a specialist and was treated with triptans (Katsarava et al., 2018). As assessed in a pharmacoepidemiology analysis

in France, a proportion of overuse is due to lack of appropriateness and to off-label prescriptions in patients aged over 65, not recommended for the use of triptans (Braunstein et al., 2015). An Italian study about triptan prescription in 2012 performed through the drug prescription databases on a sample of about 1 million people demonstrated that about 10% of triptan users potentially risks to develop MOH (Da Cas et al., 2015; Martelletti, 2015). The Calabrian landscape has never been explored. Therefore, the present pharmacoepidemiological retrospective study aimed at investigating the pattern of utilization of triptans approved by the regional health authority in each of the Calabrian provinces to increase awareness of the potential risk associated to triptans and to achieve the most effective use of these drugs limiting side effects.

## Materials and Methods

### Design of the study

This retrospective survey was carried out in collaboration with the Calabrian Pharmacovigilance Territorial Service of the health district of Catanzaro (Calabria, Italy). Since in Italy triptans are reimbursed by the National Health System, data dealing with their prescriptions were obtained from the regional drug reimbursement and prescription database. Accordingly, over the counter purchased triptans, though

residual, are not available in the present study. In particular, prescriptions of triptans (Anatomical Therapeutic Chemical Code, ATC, N02CC: N02CC01 Sumatriptan; N02CC03 Zolmitriptan; N02CC04 Rizatriptan; N02CC05 Almotriptan; N02CC06 Eletriptan; N02CC07 Frovatriptan) provided by the Regional Health Service through Territorial Pharmacy and by direct distribution for the period ranging from January to August of the years 2017 and 2018 were taken into consideration. The study was carried out using retrospectively collected and anonymized data. In Italy, such studies do not require ethical approval by an Ethics Committee as determined by the Italian Drug Agency note 20 March 2008 (GU Serie Generale n° 76 31/3/2008). The need for written informed consent was waived owing to the retrospective nature of the study.

### Data analysis

Drug quantities were expressed as defined daily dose (DDD)/1000 inhabitants per day using the ATC/DDD Index of the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology. DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults and only one DDD is assigned per ATC code and route of administration. Regional data were extracted and a comparison of the results from each province was calculated through Microsoft Office Excel (2010) spreadsheet (Microsoft, Milan, Italy). Intra-regional variability was expressed as quartiles and two-tailed *P* values were evaluated statistically for difference considering *P* < 0.05 significant. Means for DDD/1000 inhabitants per day related to triptans were assessed and evaluated statistically for difference through Mann-Whitney *U* test. Statistical analyses were performed using GraphPad Prism® 6.0 (Graphpad software Incorporated, San Diego, CA, USA). Ethics approval was not required for this study being neither an interventional nor an observational human trial; on the other hand, the analysis on pharmacoutilization was carried out on anonymized data.

## Results

### DDD/1000 inhabitants per day for antimigraine medications in Calabria

The results retrieved from the drug prescription database show that the DDD/1000 inhabitants per day were homogeneous between January–August 2017 and January–August 2018 (Table 1). In particular, all the values for prescriptions of triptans (N02CC: N02CC01 Sumatriptan; N02CC03 Zolmitriptan; N02CC04 Rizatriptan; N02CC05 Almotriptan; N02CC06 Eletriptan; N02CC07 Frovatriptan) provided by the Regional Health Service through Territorial Pharmacy and by direct distribution for the period ranging from January to August of the years 2017 and 2018 were reported in Table 1. All the Calabrian provinces presented mean values for triptans use in line with the values referred to the whole region, apart from Crotona which showed a trend to an increased amount of DDD/1000 inhabitants per day that, however, does not reach statistical significance (Mann-Whitney *U* test) (Table 1).

### DDD/1000 inhabitants per day for Almotriptan

This pharmacoepidemiological retrospective study highlighted that, in the time period considered, the triptan most prescribed in Calabria was almotriptan. It ranked first in all the areas apart from Cosenza and Vibo Valentia, without statistically significant differences with the prescription values of the whole Calabria region (two-tailed *P* values = 0.4798 and 0.4684 for 2017 and 2018, respectively). Values of DDD/1000 inhabitants per day for this drug were the highest in Crotona both in January–August 2017 and in January–August 2018 [1.84 (29.53%) and 1.75 (27.17%); Figure 1A and B]. The least prescribed drug was zolmitriptan.

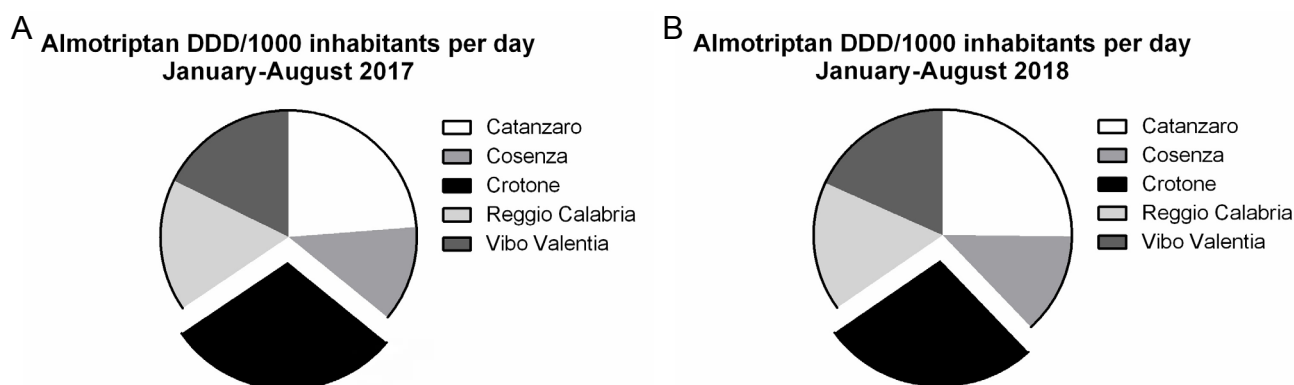
## Discussion

Migraine is a complex neurological disorder responsible for short-term health loss, relative to the acute peak of the disease known as ictal disability, and which can evolve from episodic to chronic with the possible development of MOH

**Table 1** Values of DDD/1000 inhabitants per day for antimigraine medications in Calabria and provinces

	Calabria Region		Catanzaro		Cosenza		Crotona		Reggio Calabria		Vibo Valentia	
	Jan.–Aug. 2017	Jan.–Aug. 2018	Jan.–Aug. 2017	Jan.–Aug. 2018	Jan.–Aug. 2017	Jan.–Aug. 2018	Jan.–Aug. 2017	Jan.–Aug. 2018	Jan.–Aug. 2017	Jan.–Aug. 2018	Jan.–Aug. 2017	Jan.–Aug. 2018
N02CC05 Almotriptan	1.10	1.15	1.48	1.62	0.76	0.83	1.84	1.75	1.05	1.07	1.10	1.17
N02CC04 Rizatriptan	1.04	1.02	0.94	0.99	0.94	0.95	1.61	1.55	1.01	0.92	1.14	1.21
N02CC01 Sumatriptan	0.94	0.89	0.67	0.74	0.94	0.88	1.27	1.12	1.02	0.88	0.92	1.00
N02CC07 Frovatriptan	0.74	0.75	0.55	0.55	0.97	0.95	0.45	0.60	0.68	0.72	0.63	0.61
N02CC06 Eletriptan	0.60	0.67	0.65	0.70	0.54	0.63	0.49	0.62	0.65	0.67	0.68	0.84
N02CC03 Zolmitriptan	0.19	0.22	0.14	0.11	0.20	0.21	0.26	0.28	0.17	0.28	0.27	0.30
Mean	0.77	0.78	0.74	0.78	0.73	0.74	0.99	0.99	0.76	0.76	0.79	0.85

Aug.: August; DDD: defined daily dose; Jan.: January.



**Figure 1** DDD/1000 inhabitants per day for almotriptan in all the Calabrian provinces from January to August 2017 (A) and 2018 (B). The province presenting the highest amount of prescriptions/dispensations of almotriptan is Crotone: DDD/1000 inhabitants per day January–August 2017 = 1.84 (29.53%) (A) and DDD/1000 inhabitants per day January–August 2018 = 1.75 (27.17%) (B). First quartile (25% percentile) 2017 = 0.90; third quartile (75% percentile) 2017 = 1.66. First quartile 2018 = 0.95; third quartile 2018 = 1.68. DDD: Defined daily dose.

(Martelletti, 2015). Inappropriate management of migraine has been a matter of the utmost importance throughout the last decades, as already shown in the FRAMIG 2000 study (Lucas et al., 2005), and in Italy a lot of the patients of a survey conducted from September 2006 to March 2007 resulted unsatisfied with the acute treatment (Cevoli et al., 2009). The current context is not more encouraging, as supported by the Eurolight study demonstrating undertreatment of migraine and showing that in Italy the 14% of people consulted a specialist and received triptans as treatment (Katsarava et al., 2018). Unmet medical needs concern the 38.2% of triptan users identified in a real-world analysis conducted from 2012 to 2015 using the database created by ReS (Fondazione Ricerca e Salute – Research and Health Foundation) and CINECA (Interuniversity Consortium) (Piccinni et al., 2019). The lack of awareness of the optimal handling of migraine sufferers can also lead to overuse within underdiagnosis and undertreatment. The latter evidence is supported by a recent study carried out in Austria, underlining a low rate of triptans, but with fluctuation and potential overuse (Zebenholzer et al., 2018). Our pharmacoepidemiological study assessed the pattern of triptans utilization in Calabria region for the first time. The DDD/1000 inhabitants per day for triptans prescriptions resulted homogeneous between 2017 and 2018 in the time period object of study and there was no intra-regional significant variability except for the province of Crotona presenting a trend to an increased value of DDD/1000 inhabitants per day, with the most used drug represented by almotriptan. The latter triptan ranked the first place also in the whole region. This finding could be due to the favourable pharmacokinetic profile of almotriptan, one of the newest in the class. In fact, it presents 70% oral bioavailability, which is much higher than the bioavailability of the other triptans ranging from 14% of sumatriptan to 50% of eletriptan (Dahlof et al., 2002). Naratriptan is endowed with 63% to 74% oral bioavailability, but almotriptan does not show variability between males and females and oral absorption is not influenced by food (Dahlof et al., 2002). The Tmax values (and the consequent rapidity of action) go

from 2–3 hours of sumatriptan, naratriptan and frovatriptan to 1.5–2 hours of almotriptan and zolmitriptan and to 1–1.5 hours of rizatriptan, but frovatriptan is characterized by the longest half-life of 26 hours (Dahlof et al., 2002). A double-blind, randomized, multicenter, cross-over study in twelve centers across Italy compared almotriptan with frovatriptan demonstrating a similar effectiveness profile (Bartolini et al., 2011). For almotriptan the main elimination is renal, requiring particular attention in patients suffering from renal failure, and it is mainly metabolized by monoamine oxidase-A but also by different isoforms of cytochrome P450 not producing clinically relevant interactions with other drugs in spite of this metabolism; however, a dose reduction whether administered concurrently with potent CYP3A4 inhibitors might be recommended (Negro et al., 2013). The clearance of this drug resulted reduced by moclobemide and verapamil (Negro et al., 2013). Thanks to its metabolism it is characterized by limited variability of clinical response due to the individual genomic background (Negro et al., 2013). The pharmacodynamic profile of almotriptan defines it as agonist of 5-hydroxytryptamine (5-HT) 1B/1D receptor subtypes responsible for vasoconstrictor and antinociceptive activity, respectively, with high affinity selectivity for human 5-HT1B, 5-HT1D, 5-HT1F receptors and low affinity for the other serotonergic receptors (see Negro et al., 2013). In preparations of isolated vessels almotriptan presented: higher potency and efficacy in contracting meningeal arteries; comparable efficacy to sumatriptan on extracranial vessels; lower activity on coronary arteries linked to risk of serious side effects (see Sandrini et al., 2007). An optimal choice of the triptan should be tailored to the features of the patient and of the migraine attacks. Thus, studies able to distinguish triptan users according to their characteristics and comorbidities and to define them as occasional or regular users and overusers are needed to better understand the highlighted variability of treatment in the local context. Furthermore, trials head-to-head comparing the available triptans in the over 65 patients are pivotal to deepen the knowledge of cardiocerebrovascular side effects in this fragile population. Prescription databases should

also be used to assess specificity and sensitivity of treatment response through the approach of precision medicine, as previously reported for the Danish national pharmacy database (Hansen et al., 2019). The development of educational programs for the diagnosis of migraine and the awareness of the appropriate prescription of antimigraine medications is an indispensable tool to improve the management of migraine sufferers and to increase the effectiveness of the treatment reducing attack-related disability and side effects, particularly in the populations at increased risk. This is a fundamental approach in order to reduce chronification of migraine episodes and overuse of drugs with consequent MOH.

**Author contributions:** MTC, LAM, PT, and GB conceived the study. DS participated in the design of the study, collected the results, analyzed the literature, and wrote the manuscript. AA, LR, AEDF, SE, MZ and MDN participated in the literature retrieval. All authors read and approved the final manuscript.

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**Reporting statement:** This study followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.

**Biostatistics statement:** The statistical methods of this study were reviewed by the biostatistician of University of Calabria.

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