

Availability of Effective Evidence-Based Symptomatic Treatments for Cluster Headache in the EU Countries—A Survey of the European Headache Alliance and European Headache Federation

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Aims: To assess the reimbursement options and accessibility of three effective medicines for cluster headache (CH) (subcutaneous sumatriptan, oxygen, and zolmitriptan spray) across the European Union (EU). **Methods:** A brief survey investigating the availability of symptomatic treatments for CH was sent by email in January 2017 to at least one headache specialist for every single country in the EU. **Results:** The questionnaire was completed by 26 headache specialists (93% of the EU countries, representing 99.75% of the European population) and by 10 CH patients representative of patient organizations. Oxygen was reimbursable for 63% of the CH population. Oxygen device was reimbursable for 50% of the CH EU population. Subcutaneous sumatriptan was reimbursable for 66% and was accessible without restrictions for 45% of the CH EU population. Zolmitriptan spray was reimbursable for 23.7% and accessible without restrictions for 30.9% of the CH EU population. **Conclusion:** Only 47% of the EU population had unrestricted access to effective CH treatments, with unacceptable inequalities between eastern countries and the rest of Europe. Headache societies and patient associations should pressure European and national health authorities to improve the availability of effective symptomatic treatments for CH. *J Oral Facial Pain Headache* 2020;34:7–12. doi: 10.11607/ofph.2223

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Cluster headache (CH) is arguably the most severe pain condition that afflicts humans.¹ Patients have described the pain as “having a red hot poker forced through my eye,” an “agony,” and “a trip to hell you can’t control,” and they report that the intensity is so extreme it is unlike anything they have ever experienced.^{1,2} The severity of the pain has earned CH the nickname “suicide headache,” and a suicidal risk exists in this condition (in a recent survey, 55% of CH patients reported suicidal thoughts).² Treating cluster headache attacks can be tricky because the pain becomes extremely severe very quickly, and only a few evidence-based treatments can work.³ Fortunately, in the past 15 years, several clinical trials have been published, and effective symptomatic treatments have been established so that national and international guidelines on the symptomatic treatment of CH according to the principles of evidence-based medicine have been created.^{4–6} Indeed, treating CH in accordance with these guidelines is associated with better outcomes, and a wider distribution of these guidelines has been advocated as a tool to improve the quality of care of CH patients.⁶

For acute treatment, subcutaneous sumatriptan (SUMA sc), zolmitriptan nasal spray, and high-flow oxygen are the treatments with a level A recommendation.⁵ With SUMA sc and high-flow oxygen, almost 75% of the patients achieve a pain-free status within 20 minutes.^{7,8} These drugs should be considered as “life-preserving” due to the intense distress caused by CH.

A recent survey conducted by the International Headache Society (IHS) has revealed that oxygen for the treatment of CH attacks is not

universally reimbursed (unrestricted access to oxygen was found only in 40% of the countries participating in the survey).⁹

The aim of this study was to assess the reimbursement options and accessibility of three effective evidence-based therapies for CH (SUMA sc, oxygen, and zolmitriptan spray) across countries in the European Union (EU).

Materials and Methods

A brief survey including eight questions about accessibility and reimbursement of effective symptomatic treatments for CH was prepared by the Board of the European Headache Alliance (EHA) and sent via email to the European Headache Federation (EHF) country representatives and secretaries in January 2017. Because of the nature of the survey, no approval from a research ethics committee was required. Data were analyzed anonymously.

In total, 26 EU societies received the email questionnaire (Malta and Cyprus are not affiliated with the EHF).

A motivational email was sent every 2 weeks, and the survey was completed at the end of February 2017. For a complimentary point of view, in the countries where active CH patient associations exist (United Kingdom, Italy, Spain, Germany, France, the Netherlands, Belgium, Ireland, Austria, and Sweden), the survey was completed by CH patients collaborating with the EHA.

Availability of effective treatments was defined as one of three options:

- *Complete*: Both oxygen and SUMA sc were fully reimbursed and accessible.
- *Restricted*: Only one (oxygen or SUMA sc) was fully reimbursed and accessible.
- *Lacking*: Neither oxygen nor SUMA sc were fully reimbursed or accessible.

Zolmitriptan nasal spray was not included in rating the availability of symptomatic drugs for CH because it is less effective than SUMA sc and oxygen and because it has been registered in a limited number of EU countries due to a marketing choice of marketing approval (MA) holders.

For calculating the percentage of CH patients having access to the effective treatments in the EU, it was assumed that the prevalence of CH was the same in every country. For data about the EU populations, the authors referred to the 2015 data provided by Eurostat.

Results

At the end of the study period, the questionnaire was completed by 26 headache specialists representing 92% of the EU countries and 99.75% of the EU population (the authors were unable to find a physician and/or CH patient to complete the survey in Malta or Cyprus). In 22 countries, the questionnaire was completed by the EHF country representative, and in the remaining 4, it was completed by other EHF specialists indicated by one of the authors (D.M.), who at the time was the EHF President. Ten CH patients representing 72% of the EU population also completed the questionnaire. Six of them were the president/coordinator of their national association, and 4 were delegated by their associations. The answers provided by the headache specialists and CH patients were coherent in every country.

The questionnaire included two questions about the availability of SUMA nasal spray that were not included in the final analysis because 8 of 10 expert patients released unsolicited comments about its infrequent use by CH patients due to its partial effectiveness.

Oxygen and Equipment For Its Use

Oxygen was fully reimbursed or with minor restrictions in 12 EU countries, representing 63% of the EU population (Austria, Belgium, Denmark, Finland, France, Germany, Luxembourg, the Netherlands, Slovenia, Spain, Sweden, and the United Kingdom), and was not reimbursed in 10 countries, representing 20% of the EU population (Bulgaria, Croatia, Czech Republic, Estonia, Greece, Latvia, Lithuania, Poland, Romania, and Slovakia). In the remaining 4 (Hungary, Ireland, Italy, and Portugal), major restrictions were reported (Table 1).

Oxygen mask device was fully reimbursed in 11 EU (Austria, Denmark, Finland, France, Germany, Luxembourg, the Netherlands, Slovenia, Spain, Sweden, and the United Kingdom) countries, representing 50% of the EU population, and was not reimbursed for 34% of the EU CH sufferers.

Subcutaneous Sumatriptan

SUMA sc was fully reimbursed or with minor restrictions in 16 EU countries (Austria, Belgium, Czech Republic, Denmark, Finland, France, Greece, Italy, Luxembourg, the Netherlands, Portugal, Slovenia, Slovakia, Spain, Sweden, and the United Kingdom), representing 66% of the EU population. Limited access to the drug was reported in 13 countries, representing 55% of the EU population (Table 2), caused mainly by the difficulties in obtaining a prescription due to physicians' budget restrictions and lack of supply to pharmacies.

Table 1 Reimbursement of Oxygen and Equipment for Its Use in the European Union (EU) Countries

EU countries		No. of countries (%)	% of EU population
In your country, is oxygen for cluster headache reimbursed by the national public health system or private health insurance companies?			
Yes (or minor restrictions) ^a	Austria, Belgium, Denmark, Finland, France, Germany, Luxembourg, the Netherlands, Slovenia, Spain, Sweden, United Kingdom	12 (46)	63
Yes, with restrictions ^b	Hungary, Ireland, Italy, Portugal	4 (15)	17
No	Bulgaria, Croatia, Czech Republic, Estonia, Greece, Latvia, Lithuania, Poland, Romania, Slovakia	10 (39)	20
In your country, is the device for using the oxygen (mask and others) for cluster headache reimbursed by the national public health system or private health insurance companies?			
Yes (or minor restrictions)	Austria, Denmark, Finland, France, Germany, Luxembourg, the Netherlands, Slovenia, Spain, Sweden, United Kingdom	11 (42)	50
Yes, with restrictions ^c	Belgium, Portugal, Italy	3 (12)	16
No	Bulgaria, Croatia, Czechia, Estonia, Greece, Hungary, Ireland, Latvia, Lithuania, Poland, Romania, Slovakia	12 (46)	34

^aThe need for a specialist's request considered as a minor restriction if not otherwise specified.

^bLimited reimbursement (Hungary); only for those presenting contraindications to triptans (Italy); depending on regional basis (Portugal); activation of a complex long-term condition needed and not automatically covered by private health insurance (Ireland).

^cOnly nasal cannula (Belgium).

Table 2 Reimbursement and Accessibility of Subcutaneous Sumatriptan in the European Union (EU) Countries

EU countries		No. of countries (%)	% of EU population
In your country, are sumatriptan injections for cluster headache reimbursed by the national public health system or private health insurance companies?			
Yes (or minor restrictions) ^a	Austria, Belgium, Czech Republic, Denmark, Finland, France, Greece, Italy, Luxembourg, the Netherlands, Portugal, Slovenia, Slovakia, Spain, Sweden, United Kingdom	16 (61)	66
Yes, with restrictions ^b	Germany, Hungary	2 (9)	19
No	Bulgaria, Croatia, Estonia, Ireland, Latvia, Lithuania, Poland, Romania	8 (30)	15
In your country, is sumatriptan injection for cluster headache easily accessible to patients?			
Yes it is easily accessible	Austria, Belgium, Czech Republic, Denmark, Finland, France, Luxembourg, the Netherlands, Slovenia, Slovakia, Spain, Sweden, United Kingdom	13 (50)	45
No ^c	Bulgaria, Croatia, Estonia, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Portugal, Romania	13 (50)	55

^aThe need for a specialist's request considered as a minor restriction if not otherwise specified.

^bDifficulties in obtaining a prescription depend on regional basis (Germany); very limited reimbursement/high cost (Hungary).

^cConsidered unsafe (Portugal); difficulty in obtaining a prescription (Italy, Germany); lack of supply of the pharmacy (Greece, Italy); elevated cost (Hungary).

Zolmitriptan Nasal Spray

Zolmitriptan nasal spray was fully reimbursed or with minor restrictions in eight EU countries (Austria, Finland, Luxembourg, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom), representing 23.7% of the EU population, and was not reimbursed or was reimbursed with major restrictions in the remaining 18 countries. In more than 50% of the EU countries, zolmitriptan nasal spray is not registered or marketed (Table 3).

Availability of Effective Treatments for CH in the EU Countries

The availability of effective treatments for CH was rated as complete for 11 EU countries, representing 46.8% of the EU population (Austria, Belgium, Denmark,

Finland, France, Luxembourg, the Netherlands, Slovenia, Spain, Sweden, and the United Kingdom); restricted for 6 countries, representing 35.2% of the EU population (Czech Republic, Germany, Greece, Italy, Portugal, and Slovakia); and lacking for 9 EU countries, representing 18% of the EU population (Bulgaria, Croatia, Estonia, Hungary, Ireland, Latvia, Lithuania, Poland, and Romania) (Fig 1).

Discussion

Drug availability is a complex and global problem. This study explores the availability and reimbursement statuses of three effective therapies for CH based on the declarations of CH specialists and CH

Table 3 Reimbursement and Accessibility of Zolmitriptan Nasal Spray in the European Union (EU) Countries

EU countries		No. of countries (%)	% of EU population
In your country, is zolmitriptan nasal spray for cluster headache reimbursed by the national public health system or private health insurance companies?			
Yes (or minor restrictions) ^a	Austria, Finland, Luxembourg, the Netherlands, Portugal, Spain, Sweden, United Kingdom	8 (34)	23.7
Yes, with restrictions ^b	Germany	1 (4)	16
No	Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, France, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Romania, Slovenia, Slovakia	17 (62)	60.3
In your country, is zolmitriptan nasal spray for cluster headache easily accessible to patients?			
Yes, it is easily accessible	Austria, Finland, Luxembourg, the Netherlands, Portugal, Spain, Sweden, United Kingdom	8 (34)	30.9
No ^c	Belgium, Bulgaria, Croatia, Czechia, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Poland, Romania, Slovenia, Slovakia	18 (66)	69.1

^aThe need for a specialist's request considered as a minor restriction if not otherwise specified.

^bDifficulties in obtaining a prescription depend on regional basis (Germany).

^cIn more than 50% of the EU countries, zolmitriptan nasal spray is not registered or marketed.

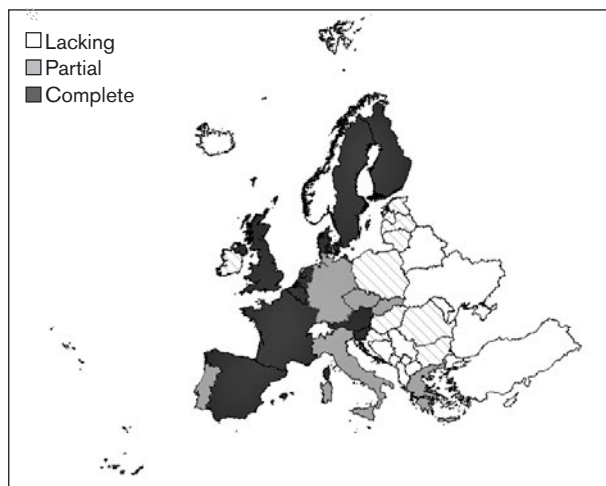


Fig 1 Availability of effective symptomatic treatments for cluster headache in the European Union countries.

patients in a broad set of European countries. The description of the marketing status, reimbursement, and context regarding drug shortages showed that the reasons for the lack of availability differ between European regions and countries. Based on this survey, only 47% of the EU population has unrestricted access to effective CH treatments, with unacceptable inequalities between eastern countries and the rest of Europe.

Reasons for Unavailability

The European drug market is regulated at the European and the national levels. Regulations and policies applied at country levels are prone to have an impact on patients' access to effective drugs. Regional variability is also sometimes observed regarding the ability to get a prescription, like in

Germany. The reasons for drug restrictions and unavailability are then heterogenous. With the notable exception of Ireland, the availability of treatments for CH might be reflected by the per capita health expenditure of each member state, making it difficult to identify a plan of action for a change. In contrast, for zolmitriptan, availability appears to be a result of marketing choices from the MA holders. In some countries, the drug is reimbursed by a health system or private insurance, whereas in others, the MA holders have decided to go on the market without any reimbursement. In addition to marketing and reimbursement restrictions, some drugs are impacted by shortages, in particular sumatriptan. Reasons for drug shortages are multifactorial (lack of active substances, quality problems, etc), but may also result from strategic factors.¹⁰ This strengthens the hypothesis that the causes of the unequal availability of CH drugs goes beyond well-known variability between health insurance systems and also involves uncontrollable factors, such as economic and strategic choices from marketing holders.

Previous Experiences

This is the very first study focused on treatments for CH in the EU countries, but some studies of interest have been conducted on triptans. In 2003, Folino-Gallo et al observed 83% to 140% price differences between oral triptans in eight European Union countries, suggesting that patients' access to the most cost-effective triptans was varying between countries.¹¹ In a more general way, other works have demonstrated the lack of availability of analgesics in Europe, in particular for opioid drugs¹²⁻¹⁴ (corresponding to the N02A subgroup of the Anatomical Therapeutic Chemical Classification System).¹⁵

As observed in the present study, lack of availability of analgesics was traditionally reported to be higher in southern European countries compared to countries in northern Europe. This distribution decline could also be seen between western and eastern European countries, the latter of which are reported to be far more concerned by insufficient accessibility of analgesics. However, in the case of opioid analgesics, the underlying cause is very different due to the abuse liability and subsequent regulatory measures applied to opioids. These regulations were originally implemented to prevent the diversion of medicinal opioids (nonmedical use, illicit markets), but have a great impact on the medical availability of opioids and consequently on the medical consumption of these substances. During the last decades, the WHO and the International Narcotics Control Board (INCB), in charge of the implementation of the international UN drug treaties, have produced several reports highlighting the lack of opioid availability and the need to improve medical use of opioids.^{16,17} In France, in the late 1990s, the under-utilization of opioids was pointed out by international organizations.¹⁸ This contributed to raising the awareness of the authorities and led to the implementation of three consecutive national strategic plans to improve pain management since 1998.¹⁸ Substantial changes were implemented in the framework regulation in the early 2000s. For the first time, the legislation recognized the right for all patients to have access to pain management.¹⁹ Later, the obligation for health care professionals to manage and relieve the patient's pain was also defined. Following these actions, the context of use changed extensively within a couple years. The example of Spain is another illustration of such changes.²⁰ Even if specific CH drugs were not concerned, this experience is very illustrative of the potential for change after raising awareness of multiple stakeholders at a global level in the context of inadequate access to effective analgesics.

Impact on Patients

In addition to the observed inequity in drug availability, the relation between these restrictions and the actual level of use has been demonstrated for a wide range of drug classes. In addition, the impact of these restrictions on adherence and quality of life has been specifically shown for triptans²⁰ and is expected to be all the more important for CH patients due to the particular nature of this disease.

Strengths and Limitations

This survey benefits from extensive coverage, with 93% of the EU countries included, representing 99.75% of the European population. Accuracy of the information provided is enhanced by the collection of

information through an expert panel and by the absence of any observed discordance when different sources (physicians and CH patients) were used for the same country. To the best of the present authors' knowledge, this is the very first study investigating the availability of effective evidence-based symptomatic treatments for CH in the EU countries.

Perspectives

Based on these results, opportunities for promoting the access to effective CH drugs in Europe may be identified. While national particularities and choices of marketing holder appear difficult to control, there may be a role for the patient associations. It could be expected that, in the countries where patient associations are traditionally active, there may be greater attention paid to patient needs. A potential proposal is to create a network of patient associations with representatives from every EU country for a lobbying action.²¹

Conclusions

Based on this survey, only 47% of the EU population had unrestricted access to CH effective treatments, with unacceptable inequalities between eastern countries and the rest of Europe. Headache societies and patient associations should pressure European and national health authorities to improve the availability of effective symptomatic treatments for CH.

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