

Evaluation of medical prescriptions and off-label use on board ships to improve healthcare quality

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Abstract. – OBJECTIVE: This study analyzed the appropriateness of drug therapies prescribed for a particular category of patients: the seafarers. We investigated an important problem of this area: the off-label use of drugs, which resulted to be a consequence of major shortcomings in the on-board pharmacies of ships. The off-label use of drugs is allowed, but can lead to some not negligible ethical and health problems, compromising the quality of provided healthcare.

MATERIALS AND METHODS: The analysis was performed on electronic health records of patients onboard ships without physicians, and assisted by the CIRM from 2011 to 2015. This work is divided into two phases: in the first one, we classified the diagnoses registered onboard on the basis of the ICD-10 classification proposed by the WHO. In the second phase, we evaluated the congruence of the pharmacological therapies prescribed by CIRM physicians, according to the MICROMEDEX Database, which provides comprehensive information about drugs and their use.

RESULTS: From the analysis emerged that prescribed drugs were not always corresponded to their primary indication of use. In particular, in 2011 off-label drug use was widely spread (more than 30%) in some ICD-10 classes. In the following years (2012-2015) a decrease of off-label use of drugs was noticed.

CONCLUSIONS: The results suggest that a standardization of onboard pharmacies is crucial, in order to have a complete on-board pharmacy that will allow preventing and counteracting any situation of health danger, which may occur onboard, ensuring high quality healthcare to seafarers all over the world.

Key Words

Prescriptions, Off-label, Ships, Health quality.

Introduction

The fundamental right to health comes both from a preventive activity and from the implementation of the right healthcare services. This right must be guaranteed to the whole population, in every place¹.

In this analysis we have investigated the pharmacological therapies prescribed for a particular category of workers, the seafarers. According to Oldenburg et al² and Caesar et al³, the ship is one of the most dangerous workplaces.

The International Labor Organization (ILO)⁴ has established that seafarers must get the same protection and the same access to medical care than ashore workers.

In 1992, the European Economic Community issued Directive 92/29/EEC on the minimum safety and health requirements for improved medical treatment on board vessels⁵, establishing that every vessel flying its flag, or registered under its plenary jurisdiction, must always carry specific medical supplies on board.

According to this Directive, each Member State must take the necessary measures to guarantee safety and medical assistance on board ships⁶⁻¹⁰.

The set of drugs and all the medical equipment onboard the ship constitutes the “on-board pharmacy”, currently called “medicine-chest”. That’s where we find all that may be necessary to prevent and cure any form of illness or accident that may occur on board. As a result, a well-organized and supplied medicine chest is the basis for providing medical assistance to seafarers.

In case of a disease or injury on board, the captain is suggested to contact the TMAS (Tele-medical Maritime Assistance Service). At this point, the TMAS physicians will try and give to the patient the best possible care¹¹.

Often telemedicine forces physicians to make decisions without specific medical investigations. Generally, the doctor does not remain in contact with the patient, but with the rest of the crew, making it a hard decision to take¹².

That is another reason why the doctor-patient relationship is more complex on board, and it is not always in accordance with the fundamental Ethical principles¹³.

The medical team that responds to requests for assistance must take into account the different provisions of medicines and medical devices available on board, which may vary, according to the nationality of the ship and the shipping company. Unfortunately, the lack of uniformity of the rules of various countries can create problems for patients embarked on ships with limited availability of drugs or other medical devices¹⁴.

The aim of this study was to evaluate the appropriateness of the drug therapies prescribed to sailors, embarked on merchant ships without a doctor onboard, and assisted by the International Radio Medical Centre (CIRM), the Italian TMAS, from 2011 to 2015.

This work is divided into two phases: in the first one, we classified the diagnoses registered on board on the basis of the International Statistical Classification of Diseases and Related Health Problems (10th Revision) of the World Health Organization (WHO)¹⁵.

In the second phase, we evaluated the congruence of the pharmacological therapies prescribed by CIRM physicians, according to the MICROMEDEX International Drug Information Database, which provides comprehensive information about drugs and their use and includes information on primary use of drugs, drug dosing and off-label uses¹⁶.

Materials and Methods

The analysis was carried out on 17,844 clinical records of patients assisted by the CIRM from 1st January 2011 to 31st December 2015. For each case assisted by the Centre, a digitalized medical file was established and updated following every contact with the ship. Out of 17,844 clinical records, 632 were excluded from the study for the

following reasons: medical care for personnel embarked on aircrafts, other cases of on-board advice on the management of the on-board pharmacy or advice on the maintenance of good hygiene conditions on board the ship.

The study is divided into two phases: in the first step, the diagnosed diseases, signed by the competent CIRM physicians, have been categorized based on the International Statistical Classification of Diseases and Related Health Problems (10th Revision) of the World Health Organization (WHO)¹⁵. This standard is used worldwide for general epidemiology, health management and clinical analysis. In the second step, we evaluated the congruence of pharmacological therapy prescribed in the 17,212 clinical records that were the subject of the study, according to the Micromedex International Drug Information Database (MICROMEDEX). This database includes information on primary use of drug, drug dosing and off-label uses, and it also gives information about chemical, pharmaceutical, and related biological substances used in clinical patient care, covers teratogenicity, toxicology, alternative medicine, pharmaceutical information and also drug reviews, guidelines, clinical reviews, and information from package inserts and drug texts¹⁶. The demographic data of people assisted and receiving pharmacological therapy prescriptions were assessed. Analysis did not consider either the rank of people who received pharmacological prescription or the flag of the ship where they worked.

This survey is a part of the project called “Healthy Protection and Safety on Board Ships” (“Healthy Ship”). It is a project of disease prevention and health protection approved by the CIRM Foundation Ethical Committee¹⁷⁻²¹.

Statistical Analysis

Microsoft Excel and OriginPro 9.1 (OriginLab) software were used to process data and to analyze results. Data are expressed in the text as means \pm SD.

Results

Figure 1 summarizes the number of patients assisted by the CIRM from 2011 to 2015, the total number of requests for assistance received, and the number of excluded cases.

The cases taken into consideration almost totally concern male patients (16,784 cases, 97.5%),

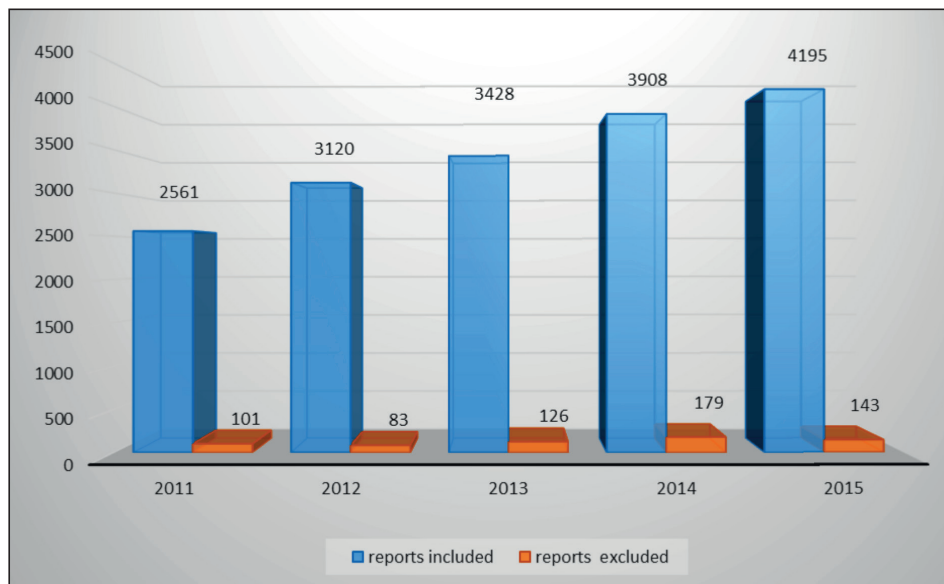


Figure 1. Number of patients on board ship assisted by CIRM from 2011 to 2015 and cases included and excluded for the present analysis.

who are part of the ship crew, regardless the role and flag they belong to. In contrast, only 428 cases (2.5%) were ascribed to female patients. The ratio recorded between male and female patients was therefore about 40:1.

The age of assisted patients, regardless of gender, was between 18 and 64 years (Mean 38.5 ± 11.6 years). As per female gender patients, they were people involved in cruise ships, guests of merchant ships (supernumerary) and migrants.

The number of medical assistance requests received by the CIRM increases every year and the number of patients assisted in 2015 was almost twice that of patients assisted in 2011 (Figure 1). Regarding the 632 cases not taken into consideration in this analysis, we talk of medical care for people on aircrafts, or requests that do not involve the underwriting of a diagnosis and related pharmacological therapy (Figure 1).

Table I summarizes the diagnosis, classified according to the International Classification of Diseases (ICD)-10. The diseases of the digestive system (class XI ICD-10) were the ones with the highest incidence, covering 18.28% of patients (3,261 cases) followed by injury, poisoning and certain other consequences of external causes (class XIX ICD-10), covering 17.97% of patients (3,207 cases). These are followed by diseases of the skin and subcutaneous tissue (class XII ICD-10) covering 9.47% of patients (1,690 cases) and

diseases of the genitourinary system (class XIV ICD-10) covering 8.94% of patients (1,595 cases) (Table I). Then, we have diseases of the musculoskeletal system and connective tissue (class XIII ICD-10) covering 7.22% of patients (1,288 cases) and diseases of the circulatory system (class IX ICD-10) covering 6.66% of patients (1,189 cases).

For each class of diagnosed disease, we analyzed the prescribed pharmacologic therapies, and compared them with the primary use indications of drugs reported in the IBM Micromedex database (Figure 2).

Some prescriptions were consistent (CON) with the indication of primary use, others were not consistent (NC); in some prescriptions, doctors associated two or more medicines. In some of these, the prescription was consistent with the indication of primary use (ACC), sometimes only one of the drugs was consistent (ACN), and in other cases none of the prescribed medications were consistent (ANN).

In 2011, the off-label use of drugs has been widespread (over 30%) in some classes of diseases, particularly in ICD-10 categories from III to IX. The maximum inconsistency occurred in class V, where no prescription was found to be congruent (Figure 2).

In 2012, the prescription of drugs that did not comply with primary use guidelines mostly decreased, but remained higher than 20% in classes

Table I. The number of diagnoses (and their percentage) identified on the basis of the ICD-10 classification system (ICD-10 World Health Organization Version: 2016). IX- Diseases of the circulatory system; XI- Diseases of the digestive system; XII- Diseases of the skin and subcutaneous tissue; XIII- Diseases of the musculoskeletal system and connective tissue; XIX- Injury, poisoning and certain other consequences of external causes.

International Statistical Classification of Diseases and Health Related Problems, 10th Revision ICD-10	2011 NUMBER OF CASES/ PERCENT	2012 NUMBER OF CASES/ PERCENT	2013 NUMBER OF CASES/ PERCENT	2014 NUMBER OF CASES/ PERCENT	2015 NUMBER OF CASES/ PERCENT	TOTAL NUMBER OF CASES/ PERCENT
T IX- Diseases of the circulatory system	232 8.72%	226 7.06%	205 5.77%	258 6.31%	268 6.18%	1189 6.66%
XI -Diseases of the digestive system	481 18.07%	634 19.79%	640 18.01%	718 17.57%	788 18.17%	3261 18.28%
XII- Diseases of the skin and subcutaneous tissue	222 8.34%	291 9.09%	323 9.09%	381 9.32%	473 10.90%	1690 9.47%
XIII- Diseases of the musculo-skeletal system and connective tissue	152 5.71%	217 6.77%	244 6.87%	337 8.25%	338 7.79%	1288 7.22%
XIV- Diseases of the genito-urinary system	252 9.47%	322 10.05%	301 8.47%	342 8.37%	378 8.71%	1595 8.94%
XIX- Injury, poisoning and certain other consequences of external causes	482 18.11%	581 18.14%	657 18.49%	716 17.52%	771 17.77%	3207 17.97%
Cases Excluded	101 3.79%	83 2.59%	126 3.55%	179 4.38%	143 3.30%	632 3.54%
Total Cases	2662	3203	3554	4087	4338	17844

II, IV, VI, and XIV. It is important to notice that the prescriptions of drugs in association have decreased substantially, compared to the previous year (Figure 2).

The number of off-label prescriptions lowers also in 2013, remaining higher than 20% only in class IV and higher than 15% in classes III and IX (Figure 2).

In 2014 the reduction continues, and the percentage of off-label use remains about 15% only in classes IV, VI, XIII and XIV (Figure 2).

Finally, in 2015, the off-label use was about 5% only in some classes such as I, III, V, X, and XIII (Figure 2).

In Figure 3 we can observe the trend of off-label drug utilization over the years (2011-2015) in the main categories of diseases that we have highlighted in the previous paragraphs, and which are shown in Figure 2.

Analyzing the global trend, although in some classes of diseases we have a greater off-label use of drugs, we can notice that the off-label use

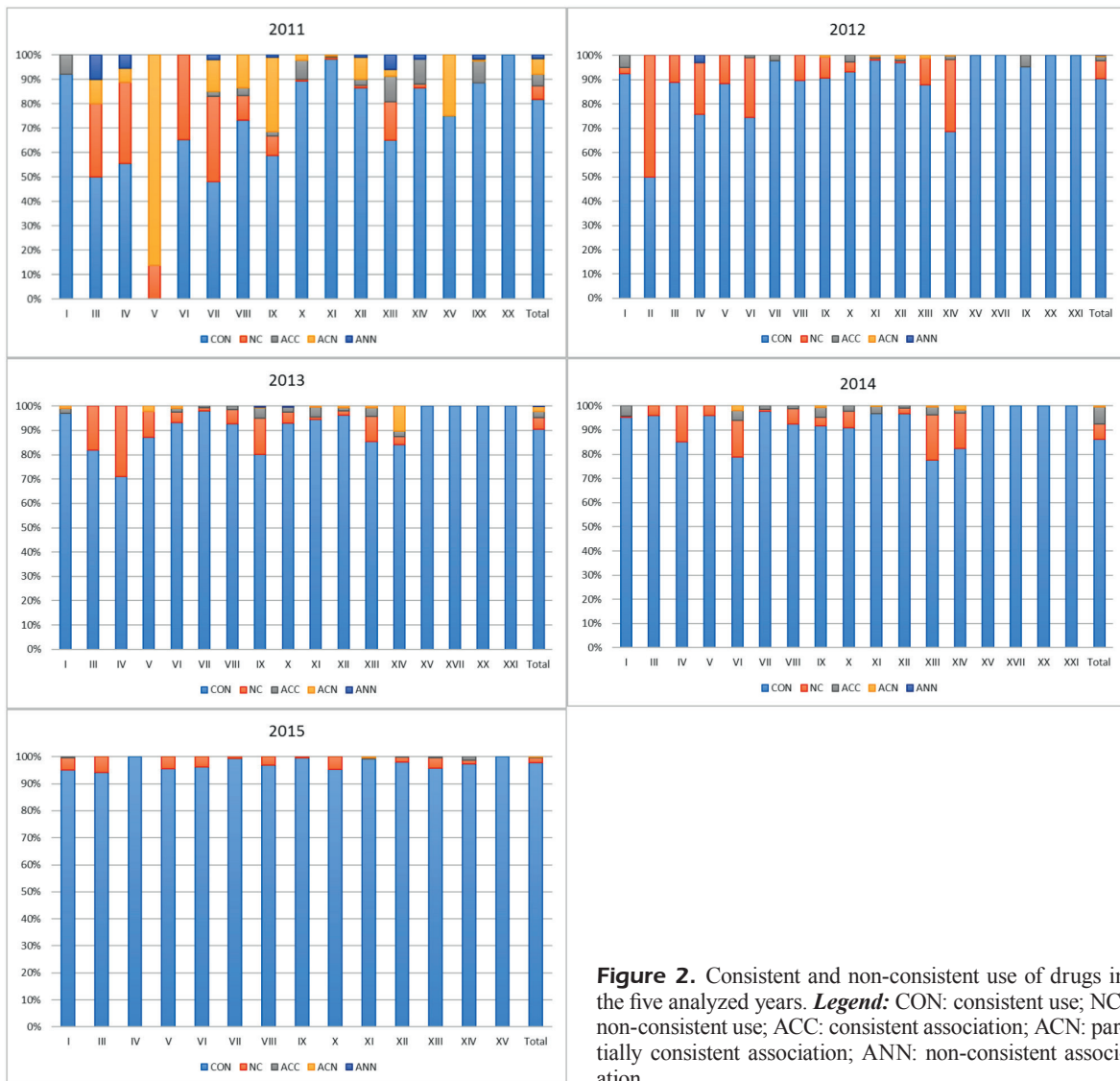


Figure 2. Consistent and non-consistent use of drugs in the five analyzed years. **Legend:** CON: consistent use; NC: non-consistent use; ACC: consistent association; ACN: partially consistent association; ANN: non-consistent association.

of drugs involves only less than 10% of the total cases considered, and it lowers over the years.

In Class III we observed a high use of off-label drugs in the first years, alone or in association; starting from 2012 the drugs were no longer associated, but the off-label utilization was still high; it lowers under 10% starting from 2014, but at the end of the study it remains over the 5% (Figure 3).

Class IV starts from a very high percentage of off-label use, and it keeps high up to 2013, then lowers down to zero in 2015 (Figure 3-XIII).

Class V and IX (and similarly happens for class VII, not shown in Figure 3) start with a very high use of association between drugs, and one of them was off-label; these associations were no

longer used after the first year, while the use of drugs not complaining for their marketing authorization (NCMA) slightly lowers over the years (Figure 3).

Class VI starts with a percentage of NCMA drugs about 35% that lowers to 1.7% in 2013. The percentage rises again in 2014 up to 15% than lowers up to 3.7% in 2015 (Figure 3-XI).

In Class XIII the percentage of NCMA is over 10% from 2011 to 2014, reaching its maximum in 2014 (18.5%) than lowers to 3.7% in 2015 (Figure 3-XIII).

Class XIV has a very erratic trend, with a generally low percentage (lower than 3%) of NCMA drugs, but in 2012 and 2014 the use rises respectively to 29.8% and 14.7% (Figure 3-XIV).

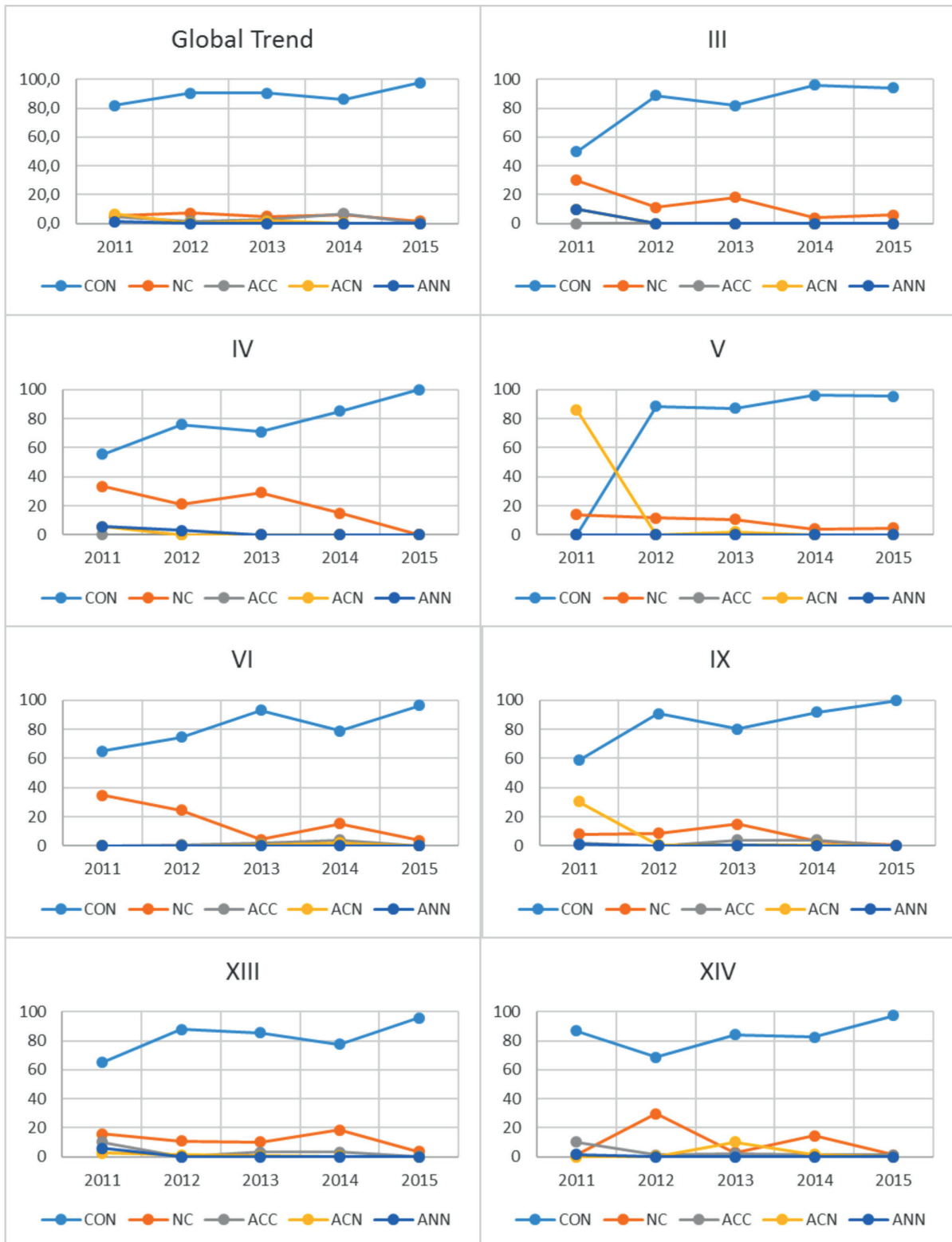


Figure 3. Time-trend of consistent and non-consistent use of drugs in the five analyzed years, for the classes of disease with a greater non-consistent use. **Legend:** III: Diseases of the blood and blood-forming organs; IV: Endocrine, nutritional and metabolic diseases; V: Mental and behavioural disorders; VI: Diseases of the nervous system; IX: Diseases of the circulatory system; XIII Diseases of the musculoskeletal system and connective tissue; XIV: Diseases of the genitourinary system; CON: consistent use. NC: non consistent use. ACC: consistent association. ACN: partially consistent association. ANN: non consistent association.

Discussion

The prevention of medication errors (MEs) and adverse drug events (ADEs) are internationally recognized as important healthcare priorities¹⁸. It is necessary that medical ethics acknowledge that medicine, society and medical jurisprudence have changed and doctors must be given new rules in order to protect both patients' rights and dignity of the profession¹⁹.

On board ships health problems can have serious consequences; the risk is even higher in vessels involved in long route travels and without a physician onboard. In these circumstances everyone on board knows that the health and life of each one may depend on the quickness and suitability of the applied intervention, as well as the availability of medications needed for the inconvenience that may occur.

On board ships, pharmacological treatment can be complicated for several reasons. First of all, with the exception of cruise ships or some passenger ships, most commercial vessels have neither a doctor on board nor qualified health personnel. Consequently, the treatment of diseases or accidents is responsibility of the captain, who can be assisted by TMAS¹⁹.

Unfortunately even the most recent international recommendations give the captain the ultimate responsibility for choices or treatment¹⁸. This is a rather questionable principle, which does not take into account the limited medical knowledge of a ship captain.

The second problem is the limited availability of medicinal products on board ships. Every vessel, even small ships and those covering short distances, should have a minimum supply of medicinal products and medication items that constitute the so-called ship "medicine chest"¹⁹. The World Health Organization (WHO)²⁰, the European Union⁵ and the main maritime countries have regulated the contents of the medicine chest of their ships⁵⁻⁹.

However, the above-mentioned can be very different in terms of number and types of medicinal products and other supplies, potentially limiting the possibility of prescribing the most common and effective treatments. Hence, the often off-label use of drugs may depend on the lack of availability of the most indicated medicinal products on board.

The results showed that the prescription did not always correspond to the primary indication of use reported in Micromedex Database. The important

off-label use that we have seen in some of the above-mentioned years was eventually due to the shortage of some medicines on board. The off-label use of drugs is legal, but can lead to some not negligible ethical and health problems²², and therefore, should be limited to the extent of possible.

Often, some specific drugs are not included in the medicine chest, and this happens especially for some categories of diseases, such as those considered "less dangerous"; these shortcomings are usually caused by the poor knowledge of legislature about the actual health conditions found on board. These shortcomings explain partially why we have found an important "off-label" use of drugs in different classes of diseases; due to these lacks, physicians are forced to prescribe alternative drugs, other than those of first choice, or those they would ordinarily prescribe²¹. This could represent a problem that could potentially limit the quality of prescribed therapies. As a matter of fact, although the "off label" use of drugs is noticeable in medical practice, clear scientific evidence exists for potential side effects for human health, especially of some medicinal classes. Regarding the medical treatment and assistance provided to a ship, the TMAS doctor should pay attention not only to the diagnosis, but also to the prognosis. Telemedicine implies that the doctor should make decisions without a clinical examination, often without any additional and specific medical investigations, and by maintaining a communication with other people who are in direct contact with the patient. Regarding the patient's medical history, the doctor usually has to rely on the patient's colleagues; this may make it harder to make a decision¹¹. When the patient is on board, the doctor-patient relationship is more difficult to regulate in strict compliance with fundamental ethical principles¹².

For all these reasons, we believe that it is necessary to improve maritime healthcare acting on the composition of the medical chests, in order to make revisions based on the actual incidence of onboard illnesses, which will lead to the creation of a complete on-board pharmacy able to prevent and counteract any situation of health danger, which may occur onboard.

Conclusions

The lack of some drugs in the medicine chest, and the legal and practical issues concerning the procurement of specific medicines

in different countries, can be a major obstacle to the prescription of effective treatments for a seafarer. The latter also performs a particularly dangerous profession²³, which therefore requires a higher consideration in terms of quality of healthcare provided.

From collected data, off-label prescriptions are necessary because doctors have a limited choice of drugs onboard. The prescription of a medicine for a use that is not included in the product authorization is not illegal, but is associated with a number of clinical, safety and ethical issues. Introducing a more equipped medical chest could reduce the off-label prescription of drugs, and all the issues related to it²².

It is necessary to improve maritime occupational healthcare by improving national and cross-national collaborative health research²⁴ and acting in terms of prevention and proper care. In order to achieve this, it is necessary to act on the composition of medical chest. A revision of the laws regulating the medical chest, based on the actual incidence of onboard illnesses needs to be taken in consideration. This will allow doctors to choose the most appropriate and effective therapies for each patient. After all, proper use of medicines is a topic of medical assistance¹².

Regular exchange of information between doctors and patients and supervision of prescriptions by competent international authorities will contribute to a rational therapeutic use of the various classes of drugs. Based on the survey carried out in this study, it should be taken in consideration by national and supranational institutions, in order to provide higher quality medical care to seafarers.

Ethical approval and consent to participate

C.I.R.M. Foundation Ethics Committee.

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Conflict of Interest

The authors declare that they have no competing interests.

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