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Conference Report

Oro-Dental Pharmacovigilance in the Digital Age: Promoting Knowledge, Awareness, and Practice in Italy through a Smart Combined System—A Conference at the 30th National Congress of the Italian College of University Professors of Dental Disciplines

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Abstract: Adverse drug reactions (ADRs) represent a significant threat to patients' safety in dentistry, necessitating proactive measures for prevention and treatment. However, identifying ADRs of dental and oral interest can be challenging, and underreporting remains a persistent issue globally. This paper illustrates a smart system to help Italian healthcare personnel, including dentists, in identifying and reporting dental and oral ADRs. This educational program is within a larger multi-regional project financed by the Italian Agency of Drugs (AIFA). The proposed system comprises a free online questionnaire on ADRs of dental interest (including specific items about awareness and attitudes), and after the free consultation of an atlas of clinical images of dental and oral ADRs linked with a digital synopsis of drugs potentially related to ADRs. This section of the project was presented in April 2023 at the 30th National Congress of the Italian College of University Professors of Dental Disciplines, and the system appears to hold tremendous potential to improve the knowledge of healthcare professionals on oral and dental ADRs.

Keywords: adverse drug reactions; oral ADRs; digital system; dentistry pharmacovigilance; atlas; digital synopsis

1. Introduction

Adverse drug reactions (ADRs) are generally a critical problem, since many factors, such as those related to the patient, drug, differential diagnosis, and therapy management, should be critically considered. Edwards and Aronson define an "adverse drug reaction" as a harmful or unpleasant reaction resulting from drug use that poses future risks and requires prevention or specific treatments, dosage modification, or product suspension [1]. The term used by regulatory bodies and patient safety advocates is "drug-related adverse event", which includes harm caused by appropriate or inappropriate drug use (commonly known as adverse drug reactions or side effects) and administration errors. The prompt identification and reporting of ADRs are essential for patients' safety and regulatory decision making [2].

Furthermore, the systematic and comprehensive reporting of ADRs significantly contributes to the accumulation of crucial data that are essential to pharmacovigilance and regulatory authorities. This meticulous process involves the careful collection and analysis of ADR reports, which help to identify emerging safety concerns, patterns, and trends associated with specific drugs or drug classes.

By diligently documenting ADRs, regulatory agencies gain valuable insights into the potential risks and benefits of medications. This information allows them to assess the overall safety profile of drugs, enabling a thorough evaluation of their effectiveness and potential adverse effects. By evaluating these risks and benefits, regulatory bodies can make informed decisions regarding drug approvals, suspensions, or modifications of indications [3].

One of the key benefits of this approach is that it ensures that the medications on the market meet rigorous safety standards. By identifying emerging safety concerns early on, regulatory agencies can take appropriate measures to protect public health and safety. This proactive approach minimizes the potential harm caused by unsafe or ineffective drugs. Regulatory agencies can utilize this wealth of information to evaluate the risks and benefits of medications, ensuring that only drugs that provide maximum benefit and minimum harm are approved for market availability. By upholding stringent safety standards, patients can have confidence in the medications they receive, knowing that their well-being is the primary concern [4].

Healthcare professionals play a crucial role in the reporting of ADRs. However, under-reporting is a global problem, creating health, economic, and ethical burdens. Regulatory authorities usually support and empower healthcare professionals in this process by providing comprehensive education and training programs to enhance their awareness and understanding of the importance of ADR reporting. Clear communication channels and user-friendly reporting systems can also facilitate the reporting process, encouraging more healthcare professionals to actively participate and contribute to the accumulation of crucial ADR data [5,6].

ADRs in the field of dentistry can cause a wide range of oral manifestations involving both hard and soft tissues. These reactions can occur as a result of using various drugs during dental procedures or as side effects or reactions of systemic medications [7].

Regarding the manifestations of oral soft tissues, ADRs can take different forms depending on the type of drug involved. Some patients may experience tissue swelling, resulting in gum enlargement, when taking drugs such as anticonvulsants, calcium channel blockers, or immunomodulators [8]. Others may develop swelling of the oral mucosa, involving the lips, tongue, and rarely the uvula (Quincke's edema), following the use of drugs like ACE inhibitors, local anesthetics, and antibiotics [9]. The other common manifestations of ADRs include oral candidosis, a fungal infection characterized by white

and red patches or lesions on the oral mucosa, which can be favored using antibiotics, corticosteroids, or immunomodulators [10].

Additionally, cheilitis, the inflammation of the lips, presenting with redness, burning, and fissures, can occur following the use of various drugs such as ACE inhibitors, local anesthetics, aspirin, and others [11].

ADRs can also cause erythema multiforme, a mucocutaneous condition that leads to red, swollen, and vesicular lesions that can involve the entire oral mucosa. Antibiotics, anticonvulsants, antiretrovirals, and non-steroidal anti-inflammatory drugs (NSAIDs) are some of the medications that can cause this condition [12]. Another possible lesion is fixed drug eruption, which is characterized by the recurrence of a rash or lesion in the same location each time the drug is taken. Anesthetics, antibiotics, antiseptics, mouthwashes, and toothpaste are some of the commonly involved medications [13].

The other ADRs involving soft tissues include lupus-like lesions, presenting as skin rashes or ulcers that can appear in the oral cavity following the use of drugs such as beta-blockers, anticonvulsants, chlorpromazine, isoniazid, and others [9].

Contact oral lesions occur when the oral mucosa comes into contact with an irritating or allergenic substance present in certain medications, such as aspirin, trichloroacetic acid, potassium tablets, and others, causing inflammation, redness, swelling, and ulcers in the contact area [14].

Drug-induced lichenoid reactions are characterized by the development of lesions similar to lichen planus, a chronic inflammatory disease affecting the skin and mucous membranes. These lesions can occur in the mouth following the use of various drugs, such as ACE inhibitors, antibiotics, anticonvulsants, and others, and can cause symptoms like pain, itching, and sensitivity [15]. Superficial and transient mucosal pigmentations can be caused by medications such as amiodarone, antibiotics, chlorhexidine, and others [16].

ADRs can also affect the salivary glands, causing hyposalivation (reduced saliva flow), leading to a dry mouth, or they can cause secondary Sjogren's syndrome due to medications such as PD-1 immune checkpoint inhibitors [17]. Conversely, some patients may develop excessive salivation (sialorrhea), resulting in increased saliva or difficulty swallowing due to medications such as antipsychotics, general anesthetics, anticholinesterases, anxiolytics, anticonvulsants, and others [18].

Regarding the manifestations in hard tissues, ADRs can impact the dental elements and the underlying bone. Intrinsic and extrinsic dental pigmentation, which are characterized by tooth discoloration, can be a side effect of certain medications, such as antibiotics, chlorhexidine, and fluoride supplements [16]. Drug-induced bruxism, which refers to the involuntary grinding or clenching of teeth, can be triggered by medications such as anxiolytics, antidepressants, antipsychotics, and other drugs that affect serotonin and noradrenaline reuptake [18]. Lastly, jawbones can also be affected by ADRs due to the onset of osteonecrosis. The medication-related osteonecrosis of the jaw (MRONJ) is often associated with the use of drugs such as antiresorptive and antiangiogenic agents. This condition can cause the death of the jawbone tissue, resulting in pain and often in the exposure of the bone [19].

The aim of this conference report is to illustrate the contents of the speech at the National Congress, especially the literature and rationales related to the pharmacovigilance of oro-dental ADRs and the just-released smart system that may support all Italian healthcare providers, including physicians, dentists, and dental hygienists, in identifying and reporting ADRs related to oral medications in the current digital age. This speech was held in Catania at the 30th National Congress of the Italian College of University Professors of Dental Disciplines within the Day of National Interuniversity Consortium for Bio-Oncology (C.I.N.B.O.), named "Dentistry and Oral Medicine at the service of Special Care in Oncology. State of the art and Italian experiences".

2. Conference Section

Detecting ADRs in the oral cavity may be challenging for healthcare providers due to the wide range of potential symptoms and the difficulty in distinguishing ADRs from other medical conditions [20]. Therefore, healthcare providers should remain vigilant in monitoring patients for potential ADRs and report any suspected cases to drug-regulatory authorities (for Italy, AIFA-Italian Medicines Agency). Reporting ADRs, of course, is crucial for improving patients' safety and gaining a better understanding of the drug safety profiles, which could lead to changes in drug labeling and prescribing practices [21]. The evolution of global pharmacovigilance systems has been made possible through the collaborative efforts of various organizations and individuals, including healthcare professionals, patients, regulatory authorities, health authorities, academic organizations, pharmaceutical industries, the World Health Organization, and the International Conference on Harmonization [22].

Efficient and efficacious pharmacovigilance requires a clear partnership among various stakeholders, such as national regulatory authorities and marketing authorization holders. However, the spontaneous reporting of ADRs remains the cornerstone of all pharmacovigilance systems, and the underreporting of ADRs is a significant public health problem worldwide [23–25].

Some studies have shown that healthcare professionals may not always report ADRs for various reasons, such as having a lack of knowledge or time [5,26]. The lack of knowledge regarding ADR reporting is an issue that needs to be principally addressed during healthcare professionals' training. A recent cross-sectional study revealed that, in Croatia, pharmacy students outperformed dentistry and medicine students significantly in terms of their knowledge. Among the participants, 92.2% of the pharmacy students, 21.8% of the dentistry students, and 70.8% of the medical students were aware of the importance of patient involvement in reporting ADRs. Nevertheless, the majority of the students expressed their belief that pharmacovigilance was inadequately covered in their study programs. This emphasizes the necessity of enhancing knowledge and awareness of pharmacovigilance among students aspiring to enter the healthcare profession, with the aim of improving their reporting practices in future clinical settings [27].

In Saudi Arabia, Bepari A. et al. conducted a study to assess the awareness, perspective, and basic practical skills related to the Saudi pharmacovigilance system among students of different healthcare professions using a questionnaire. Their practical pharmacovigilance skills were found to be inadequate [28].

Other studies have evaluated the knowledge and practice of reporting ADRs among dental students. The studies have shown that students had a moderate level of knowledge and inadequate practical experience, but had a positive attitude regarding pharmacovigilance [29–32]. This highlights the need to raise awareness among dental students about pharmacovigilance to improve the reporting of ADRs and increase the number of reported ADRs.

A cross-sectional study conducted at a university hospital in India assessed the knowledge, attitudes, and practices regarding pharmacovigilance and the reporting of ADRs among dental students using a questionnaire. The study findings indicated that the significant majority (64%) of the participants were unaware of the term "pharmacovigilance". The study also highlighted various barriers that contribute to the underreporting of ADRs. These barriers included the challenge of determining the occurrence of an ADR (52.0%), concerns about the accuracy of the report (37%), a lack of confidence in discussing ADRs with colleagues (29%), and the limited financial incentives (24%) associated with reporting [29]. Healthcare professionals and patients are encouraged to report ADRs, even if they are not sure that the drug caused the reaction [2].

A recent systematic review aimed to assess the effectiveness of various interventions implemented to improve ADR reporting by patients and healthcare professionals. The included studies utilized educational, technological, health policy, financial, and/or mixed interventions. The results indicated that financial measures and educational interventions involving face-to-face interactions significantly improved both the quality and

quantity of ADR reporting compared to that of interventions that did not involve direct interactions [33].

The development of new digital systems could be reconsidered as an additional strategy to facilitate ADR reporting, as reported in a narrative review that included various mobile applications used in the USA, France, Croatia, the United Kingdom, the Netherlands, India, and Poland for reporting ADRs. The development of these applications has led to an increase in the reporting of adverse drug events and has reduced barriers to ADR reporting, resulting in higher monthly reporting rates [34].

Educational interventions based on knowledge, attitude, and practice are another strategy that can reduce the underreporting of ADRs. Ganesan S. et al. conducted an educational intervention at the Jawaharlal Institute of Postgraduate Medical Education and Research to promote the spontaneous reporting of ADRs. A pre-intervention questionnaire and a post-intervention questionnaire were administered. After the educational intervention, the number of reported ADRs doubled compared to that during the pre-intervention period [35].

Despite the importance of pharmacovigilance in dentistry and the need to sensitize dentists to the identification and reporting of ADRs, there has not been a suggested tool that adequately directs and assists healthcare professionals in this relatively unknown process. However, there have been discussions on the rationale for pharmacovigilance in dental practice and the need for the vigilant, spontaneous reporting of adverse events by dental practitioners.

There is an urgent need to modernize pharmacovigilance education in healthcare curricula, including dental education, to optimize ADRs reporting by dentists [32,36]. Efficient and efficacious pharmacovigilance requires a clear partnership between various stakeholders, such as national regulatory authorities and marketing authorization holders. However, the spontaneous reporting of ADRs remains the cornerstone of all pharmacovigilance systems, and the underreporting of ADRs is a significant public health problem worldwide [23–25].

This new digital approach promises to provide tools that can assist clinicians in the suspected diagnosis and reporting of drug adverse events in dentistry, with the objective of raising awareness among dentists about ADR reporting.

During this lecture, “Clinical Practice Regarding Special Care in Cancer Patients”, the authors addressed strategies for the prevention and management of complications and ADRs affecting the hard and soft tissues of patients undergoing oncological treatments. Often, these conditions are not highlighted or reported to the appropriate authorities, resulting in the underreporting of ADRs in the oral cavity and a simultaneous reduction in the patient’s quality of life.

As reported in a recent study conducted in Denmark, which analyzed oral adverse drug reactions (OADR) in the Danish Medicines Agency’s database from January 2009 to July 2019, it was found that 48% of OADRs were classified as “serious”. The most common reported symptoms were orofacial swellings (1041 cases), the medication-related osteonecrosis of the jaw (MRONJ) (607 cases), and para- or hypoesthesia (329 cases). Out of a total of 343 cases, 480 OADRs were associated with biological or biosimilar drugs, with 73% of them involving the MRONJ. Physicians reported 44% of the OADRs, followed by dentists with 19% and citizens with 10%. Therefore, it is crucial to educate all healthcare professionals so that they can recognize and report suspected ADRs systematically, reliably, and consistently to ensure patients’ safety [37].

In response to this demand, the University Hospital of Palermo, Policlinico P. Giaccone, applied a proposal by the name “ADR in Dentistry in the Digital Age: From Reporting to Specialist Consultation with One Click” in a multi-regional AIFA call. The proposal was financed by AIFA.

The aim of this project is to raise awareness about ADRs in dentistry (ADRs) and promote their reporting. The project is being implemented across regions such as Sicily, Campania, and Piedmont, but dissemination will be conducted in all national territories.

The initial phase of the project was approved by the local Ethical Committee (approval number 06/2023) and involved the creation of a questionnaire in Italian (https://docs.google.com/forms/d/e/1FAIpQLSc4LmdXbvxpPqi1SkhIy9c34DbObSDMzSIwbpigT-VQyNszPA/viewform, accessed on 5 August 2023) that aimed to investigate the awareness of dentists, physicians, and dental hygienists regarding the reporting of ADRs in the oral cavity; the questionnaire campaign will last until the 30 October 2023. Upon completing the questionnaire, users will find a link to access an atlas (Figure 1), which is always available online for free, which collects all ADRs in the dental field and an interconnected digital synopsis of drugs related to adverse reactions in dentistry (Figure 2) both in Italian language. It is accessible via the following link: https://giuseppinacampisi.it/introduzione-al-progetto-aifa-per-odontoiatria/, accessed on 5 August 2023.

Figure 1. A screenshot of the atlas of adverse drug reactions in the oral cavity extracted from the website and translated into English to comply with the editorial guidelines of this journal. The official website is exclusively in Italian, as the project was funded by the Italian drug regulatory agency for the use of Italian healthcare personnel.

The online digital atlas of ADRs is a web-based platform that provides healthcare professionals with information on the signs and symptoms of oro-dental ADRs, along with interactive links to the synopsis of the drugs that cause ADRs. The atlas on oro-dental ADRs is a valuable tool for healthcare professionals to identify ADRs promptly. The platform is updated regularly to ensure that healthcare professionals have access to the latest information on ADRs, and it allows them to directly report through the link to the AIFA website. To date, no tools in the literature have been published to assist healthcare professionals in identifying and recognizing ADRs using images and brief descriptions. This tool serves as a bridge between the educational and digital aspects, both of which are beneficial in increasing ADR reporting [34,37].

The authors expect that it can be a valuable initiative to raise awareness and provide a smart tool to support healthcare professionals in the field of ADRs in dentistry. This project has the potential to improve patients' safety and contribute to the overall advancement of dentistry. The use of the online atlas and synopsis can facilitate the recognition and reporting of suspected ADRs by healthcare professionals, thus improving the management and prevention of adverse events.

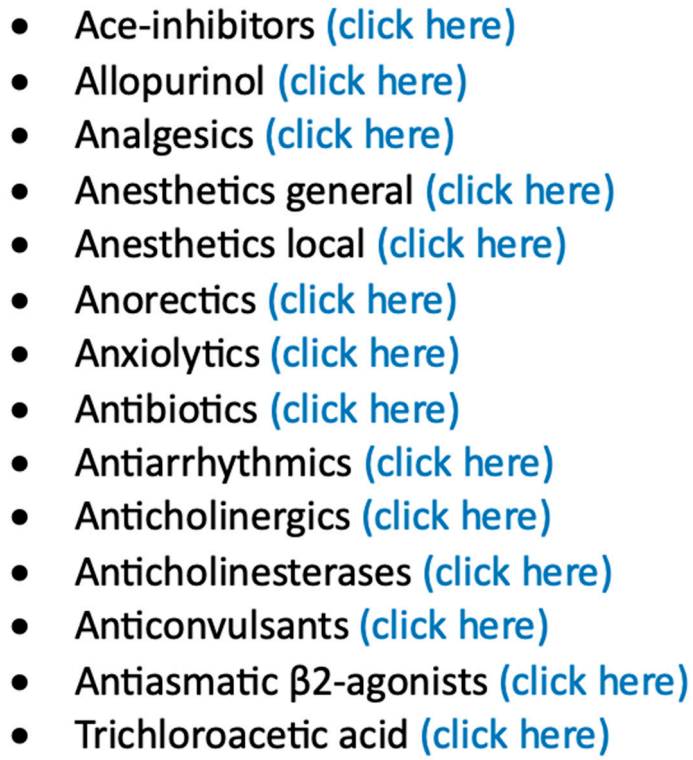

Figure 2. A screenshot of digital synopsis of drugs related to adverse reactions in the oral cavity extracted from the website and translated into English to comply with the editorial guidelines of this journal. The official website is exclusively in Italian, as the project was funded by the Italian drug regulatory agency for the use of Italian healthcare personnel.

Furthermore, the availability of a smart tool specifically dedicated to dentistry can have a significant impact on the education and professional development of future dentists. Dental students, residents, and practitioners can access the online atlas and synopsis to deepen their understanding of ADRs and develop strategies to prevent or mitigate them. This promotes a culture of continuous learning and improvement within the dental community, ultimately leading to better patient care and safety.

Dental students can utilize the online atlas and synopsis as a practical guide to learn about the specific aspects of ADRs that may occur in a dental context. This allows them to gain in-depth knowledge during the early stages of their education, preparing them to effectively handle real-life situations during clinical practice.

On the other hand, dental residents, dental hygienists, and physicians can use the online atlas and synopsis as tools for updating and furthering their knowledge. They can consult these resources to stay up to date with the latest information on ADRs and recommended management strategies. This enables them to improve or maintain a high level of competence and adopt an evidence-based approach in their daily practice.

Moreover, the online atlas and synopsis may serve, in the next future, as interactive platforms where dental students and oral health professionals can share experiences and clinical cases related to ADRs. This facilitates the exchange of knowledge and best practices within the dental community, encouraging pharmacovigilance, collaboration, and innovation in the management of oro-dental ADRs.

3. Concluding Remarks

Pharmacovigilance plays a critical role in ensuring patients' safety, and the project "ADR in Dentistry in the Digital Age: From Reporting to Specialist Consultation with One Click" could be a significant advancement in promoting the identification and reporting of

oro-dental ADRs. This project and its products represent, to the best of our knowledge, the first tools dedicated to the recognition and reporting of oro-dental ADRs.

By recognizing the barriers to ADR reporting and actively working to overcome them, regulatory authorities can foster a culture of transparency and collaboration. This collaborative approach encourages open dialogue and information sharing between healthcare professionals and regulatory agencies. Best practices, case studies, and lessons learned can be shared to enhance collective knowledge and improve the overall quality of ADR reporting.

Ultimately, improving ADR reporting among healthcare professionals is essential for effective pharmacovigilance. It requires a multifaceted approach, including education, streamlined reporting processes, and a supportive regulatory framework. By enhancing the reporting infrastructure and empowering healthcare professionals, we can ensure the timely and comprehensive collection of ADR data, leading to improved patient safety metrics and the overall well-being of society.

The next step will be the standardization of ADR reporting practices among dental healthcare professionals in order to facilitate effective analysis of data and comparison of ADRs and to improve the quality of healthcare services.

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