Profiling patients using therapeutic fentanyl

HOT Scientific Article
HOT Trainee Wall
HOT Professional Tip
Greetings HOT members!

I hope that you all are doing well and safe, and ready for the upcoming Holiday season. This year is running very fast, and we are sure that you may be working hard to complete your pending tasks before the end of the year. The 2022-2023 Executive Committee (EC) also has been very busy in planning all the activities related to recruiting sponsors for our annual reception and mentoring luncheon next year and inviting candidates for officer elections for period 2022-2023. I would like to thank them, especially to our annual reception, awards and nominating committee chairs, for this outstanding effort in keeping our activities running, and also thank you for volunteering with us to participate in our ballot or sponsoring our events. We are a strong organization because of the effort from all of you as members and sponsors. Thank you very much for supporting us, as always.

Additionally, Toxenlaces editorial team would like to invite you again to send us news and accomplishments to be published in our newsletter. This activity can now be restarted, since most of us are back to the offices and labs. We would love to hear from you! We will start collecting these accomplishments in late November through our Toxenlaces editor-in-chief, Ms. Julia Rezende. Please keep an eye in your inbox since she will touch base with you all very soon.

For our current issue, we have the scientific article from Veronica Hernandez-Garcia et al., from Universidad de la Laguna in Spain, titled “Profiling patients using therapeutic fentanyl. Risk characterization and management proposals”. Also, we have the Trainee Wall, and our Toxenlaces Editor Assistant and undergraduate student from University of Sao Paulo, Rodrigo Goncalves Queijo, will talk to us about spheroids as a platform for toxicogenomic tests. We have also the HOT Professional Tip, related to deadline management, from Mr. José Francisco Delgado Jimenez and myself. We have as well an announcement from our Toxenlaces editors, inviting you to provide a short video to talk about your motivation to participate in HOT that will be posted in our social media. We would love to hear your story!

Finally, I would like to invite you to participate in our upcoming call for Travel Awards and Distinguished Toxicologist Award. Details about both types of awards can be located in our HOT website. Dr. Veronica Ramirez Alcantara will announce the beginning of document reception for these awards very soon. Feel free to contact her, or any of us in the EC, if you have any questions in how to apply to these awards.

Again, thank you very much for all your support this year. We hope to hear from you and celebrate your accomplishments together. We also hope that you enjoy this fall season and have a good time with your loved ones for the upcoming Holidays.

Best regards,

Teresa Palacios-Hernandez, Ph.D.
2022-2023 HOT President
HOT SPONSORSHIP CAMPAIGN

The Hispanic Organization of Toxicologists (HOT) is an all-inclusive Special Interest Group within the Society of Toxicology (SOT) comprised of professionals, predominantly of Hispanic origin, with expertise in scientific areas related to Toxicology. The HOT membership is diverse, with representatives from industry, academia, government, and commercial organizations within the United States (US) and numerous Ibero-America countries. It serves as a focal point for interaction, fellowship, networking, and professional development among Hispanic Toxicologists in the US and international Spanish and Portuguese-speaking scientific communities. The HOT operates in compliance with Section 501(c)(3) of the Internal Revenue Code, entailing HOT as a tax-exemption organization eligible to receive tax-deductible contributions.

Our annual success in this endeavor has always been due to the generous contributions of our dedicated sponsors. Your sponsorship will sustain HOT's activities during the annual meeting. It will also help increase the organization's visibility to SOT and HOT members, annual meeting attendees, and the international Spanish and Portuguese-speaking scientific communities.

There are two sponsorship opportunities on HOT for 2023 SOT Annual Meeting:
1. HOT Mentoring Activity and Luncheon
2. HOT Evening Reception
Any amount is welcome; for organizations, the recommended starting donation is $500.

Your sponsorship will be recognized during the HOT Evening Reception at the SOT Annual Meeting, on the HOT website, Facebook page, and our major media outlet, the Toxenlaces newsletter.

If you would like to sponsor any of these events of HOT at the 2023 SOT Annual Meeting, please send your payable check to the Society of Toxicology with notation of HOT-SIG and mail it to Society of Toxicology, 11190 Sunrise Valley Drive, Suite 300, Reston, VA 20191.

We thank you in advance for your consideration and support. If you have questions about becoming HOT sponsor, please feel free to send an email to Alexandra Maria Moita Antunes, Ph.D., 2022-2023 HOT Sponsorship Subcommittee Chair, at alexandra.antunes@tecnico.ulisboa.pt, and Kelly Salinas, Ph.D., 2022-2023 HOT Treasurer, at ksalinas@srcinc.com.
Profiling patients using therapeutic fentanyl
Risk characterization and management proposals

BY VERÓNICA HERNÁNDEZ-GARCÍA, ARTURO HARDISSON-DE-LA-TORRE AND CARMEN RUBIO-ARMENDÁRIZ
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ABSTRACT
Despite the increasing surveillance of fentanyl medical prescriptions and pharmaceutical dispensing there is a global growing concern about the misuse of this analgesic and its risks. The objectives of this study were to characterize the patients and the therapeutical use and abuse of fentanyl to identify opportunities for the prevention and management of risks during fentanyl therapeutical use. Not only non-compliance with the recommendations of the analgesic ladder proposed by the WHO is observed in 20% of patients prescribed with fentanyl but 50% of the patients are maintained under fentanyl prescription for more than a year generating 45.8% of the patients admitting the need to consume a higher dose of fentanyl. While the Prescription Opioid Misuse Index (POMI) revealed that 8.3% of patients who use fentanyl have a higher risk of abuse, the Opioid Risk Tool (ORT) showed that 4.2% of therapeutic fentanyl users are at a moderate risk situation.
INTRODUCTION

Fentanyl (Figure 1) is a mu-opioid receptor agonist 50–100 times more powerful than morphine that is used in therapy for anaesthesia and severe pain management. The World Health Organization (WHO) Analgesic Ladder includes fentanyl in the third step (strong opioids) along with morphine or hydromorphone. These unique pharmacological effects of fentanyl have contributed to its widespread misuse (Volkow, 2021).

Despite the control and surveillance of fentanyl prescriptions and pharmaceutical dispensing, there is a global growing concern about the increasing use and misuse of this analgesic. Risks like tolerance, dependence, and other risk behaviors such as the consumption of illegal opioids stand out in fentanyl users. Inadvertent overuse, intentional misuse, and outbreaks of overdoses with fentanyl have been reported (Suzuki et al., 2017). Several factors (potency, rate of onset, lowered sensitivity to naloxone, and lowered cross tolerance to heroin) combine to make fentanyl more likely to cause opioid overdose deaths than other commonly abused opioids (Hill et al., 2020).

In 2016, fentanyl and its analogs were associated with nearly half of opioid overdose deaths in the United States (Han et al., 2019). In Canada, Alberta is one of the regions with the highest rates of fentanyl overdoses, generating a worrying mortality that has been recognized as "The Fentanyl Epidemic" (Fisher et al., 2018). In Europe, the use of (injected) fentanyl is a major contributor to the Estonian overdose death epidemic (Uusküla et al., 2020).

Numerous strategies and protocols have been designed to promote and guarantee the safe therapeutic use of this opioid and to prevent its misuse (Han et al., 2019). Interventions such as prescription drug monitoring programmes, increased law enforcement and abuse deterrent formulations have been followed by decreases in misuse of most opioid analgesics (Dart et al., 2021).

The Defined Daily Dose (DDD) was created by the WHO Collaborating Center for Drug Statistics Methodology as a technical unit of measurement. Defined as “the assumed average maintenance dose per day for a drug used for its primary indication in adults”, the DDD for fentanyl (Figure 2) has been set at 0.6 mg for nasal, 0.6 mg for the sublingual, buccal or mucosal routes, and 1.2 mg for the transdermal route every 24 h.

![Figure 1: Fentanyl molecule.](image-url)
The DDD does not necessarily correspond to the prescribed daily dose (PDD) defined as “the average dose prescribed according to a representative sample of prescriptions”. The discrepancies between the PDD and the DDD must be evaluated, and in the case of fentanyl, discrepancies could be used to detect and correct risk situations such as tolerance and dependence.

![Graph showing DDD (mg) for different routes of administration: NASAL 0.6 mg, SUBLINGUAL/ORAL 0.6 mg, TRANSDERMIC 1.2 mg.](image)

Figure 2: Fentanyl Defined Daily Dose (WHO, 2021).

In the management of the risks associated with the therapeutic use of fentanyl the follow-up of patients using opioids at Community Pharmacies has been crucial in preventing the misuse but also in characterizing patients at risk, identifying clinical tools for misuse detection and designing public health campaigns (Cochran et al., 2016; Hernández et al., 2020; Nielsen et al., 2020; Hernández et al., 2021; Hernández, 2022).

Based on this background, the objectives of this study were to characterize the patients and the therapeutical use and abuse of fentanyl as well as to identify opportunities for preventing and managing the risks during fentanyl therapeutical use.

**METHOD**

Observational, descriptive, cross-sectional, prospective study with analytical component on 24 patients (75% women and 25% men) who received fentanyl prescription. Patients were interviewed in a community pharmacy (Canary Islands, Spain) at the time of fentanyl dispensing. The risk of therapeutic fentanyl abuse was estimated using the Prescription Opioid Misuse Index (POMI) and the Opioid Risk Tool (ORT). The study is classified (code: VHG-TAP-2020-01) as a post-marketing study by the Spanish Medicines Agency (AEMPS).
RESULTS

Oncological pathologies (54.2%), musculoskeletal (41.7%) and aortic stenosis control (4.2%) generate most fentanyl prescriptions (Figure 3).

![Figure 3: Pathologies generating therapeutic prescription of fentanyl.](image)

Three out of four patients receive a prescription for fentanyl (strong opioid) after having exhausted the previous WHO analgesic Ladder (Step 1: non-opioids e.g., acetaminophen; Step 2: mild opioids e.g., codeine). However, in 20% of these users there is a therapeutic jump from step 1 to step 3 without having received the prescription of mild opioids (step 2). 50% of the patients maintain the prescription of fentanyl for more than a year. WHO analgesic ladder jumps, and chronic prescription are identified as hazards and potential risks both for the patient and the community and are evidences of a lack of follow-up of therapeutic fentanyl by the health system.

6.3% of patients who use fentanyl receive a Prescribed Daily Dose (PDD) that exceeds the Defined Daily Dose (DDD) because of the combined prescription of more than one pharmaceutical form of fentanyl. The identification during fentanyl dispensing at the community pharmacy of patients receiving PDD > DDD would not only prevent negative health outcomes but reenforce the commitment of all health care systems with a solid pharmacotherapeutic follow-up.

92% of fentanyl patients are polymedicated (45.8% take between 10 and 20 different drugs and 33.3% consume 5-10 drugs). In addition, 58% of patients receive fentanyl combined with benzodiazepines (BZD) and antidepressants, 20.8% with antiepileptics and antitussives, 16.7% with other opioids, and 12.5% with antipsychotics. These interactions expose patients to higher risks and suggest that polyprescription must be strictly monitored in fentanyl users (Figure 4). The FDA has warned patients and their caregivers about the serious risks (dizziness or light-headedness, extreme sleepiness, slowed or difficult breathing, coma, and death) of taking opioids along with BZD or other central nervous system (CNS) depressant medicines, including alcohol. Serious risks include unusual.

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Analyzing predictive behaviors of abuse, we observed 45.8% of the patients admitted feeling the need to consume more fentanyl than the dose currently prescribed. The Prescription Opioid Misuse Index (POMI) (Figure 5) revealed that 8.3% of patients who use fentanyl have a higher risk of abuse. The Opioid Risk Tool (ORT) showed that 4.2% of therapeutic fentanyl users are at a moderate risk situation. These percentages are considered significant and should be the target of health care programs.

Figure 4: Frequent treatments combined with therapeutic fentanyl; potential drug interactions.

Figure 5: Prescription Opioid Misuse Index (POMI) results among therapeutic fentanyl patients.
CONCLUSIONS

Although the main cause for fentanyl prescription continues to be the treatment of cancer pain, the use of fentanyl in the management of chronic non-cancer pain reaches similar rates. Non-compliance with the recommendations of the WHO analgesic ladder is observed in 20% of patients who are prescribed with fentanyl. The chronic prescription of therapeutic fentanyl in treatments of more than one year is a risk which suggests the need to review prescription protocols. The evaluation of patients using tests such as the POMI and the ORT at different care levels where fentanyl is prescribed and dispensed would be used to identify and treat patients at risk for fentanyl abuse/dependence. It is recommended to monitor and reassess the risk benefit of the combined use of fentanyl with other drugs with potential interactions such as BZDs and antidepressants.

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References


Spheroids as a platform for toxicogenomics tests

BY RODRIGO G. QUEIJO

My name is Rodrigo Gonçalves Queijo, an undergraduate student at the School of Pharmaceutical Sciences at the University of São Paulo (USP) in São Paulo, Brazil. During my first year, I became part of the Skin Biology and Melanoma group and got an internship focused on standardizing a three-dimensional model of melanoma spheroids to study tumor heterogeneity, with an emphasis on oxidative metabolism.
What is going on?

2D X 3D: THE FUTURE OF NEW METHODS THAT CAN GENERATE VALUABLE RESULTS

The two-dimensional (2D) monolayer models, widely disseminated and used on current literature and research, allow analyzing the expression of genes and proteins, and serve as an initial model for functional tests (1,2). However, the 2D models are not able to reconstruct the complex and heterotypic in vivo cellular microenvironment (3,4). In contrast, three-dimensional (3D) organotypic culture promotes physiological parameters of organs and tumors, and allows to mimic the architecture of the parental tissue, which is important for understanding the role of the microenvironment, transcriptional plasticity and therapeutic agents for targeted therapy in heterogeneity (5,6,7).

A type of 3D culture is the 3D multicellular spheroid-type culture model. This model is based in the property of homotypic cell-cell adhesion and can be created by 1) hanging drop, 2) cultivation on non-adherent surfaces and, more recently, 3) by magnetic levitation. The similarity of spheroids with avascularized tumor nodules boosted their application in tests with chemotherapeutic agents, because several trials showed that while monolayer tumor cells were sensitive to the action of various chemotherapeutics, when cultivated in a spheroid model, the tumor cells were resistant. On the other hand, some drugs were effective only when the cells were in a 3D environment (8,9).

MY PROJECT PROPOSAL

In my project, the 3D spheroid model was chosen to evaluate the heterogeneity and resistance of melanoma. Melanoma is a complex disease, with great aggressiveness and high mortality rates linked to metastatic capacity, evasion of immune system and chemoresistance (10,11). Although there are target-directed therapies with the objective of inhibiting some proliferation and/or differentiation pathways, the studies show a long-term development of resistance to treatment from the selection of intrinsically resistant or acquired resistance cells (12,13). Therefore, the use of 3D culture that allows the creation of a complex tumor microenvironment, composed of non-cancerous stromal cells and non-cellular components, are certainly becoming an important tool for analysis and elucidation of mechanisms of action and drugs and understanding of resistance phenomena.

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References
GET TO KNOW OUR MEMBERS

MAKE A SHORT VIDEO (1MIN) EXPLAINING:

WHAT YOU DO

HOW YOU MEET HOT

WHAT CHANGED IN YOUR LIFE BEING A HOT MEMBER

*VIDEOS WILL BE POSTED ON HOT’S FACEBOOK

Send your video to Toxenlaces
Editors:
Julia (juliarezende@usp.br)
Rodrigo (rodrigogoncalvesqueljo@usp.br)
We would like to meet you!
Deadline management

Tips and strategies to keep your tasks on track!

BY JOSE FRANCISCO DELGADO AND TERESA PALACIOS

Every single time in our career and personal lives, we need to deal with deadlines. Deadline establishment is very important to manage our tasks. However, it is very common to miss some of them especially when busy times come. From our experience, we think that we all may struggle to set realistic deadlines for challenging tasks or projects, and the reason, according to several sources, is because of our Human nature (nobody is perfect).
Some difficulties we also find to establish reasonable deadlines and meet them, may be caused by inexperience with a specific task or project, some disorganization, misunderstandings or miscommunication, and last-minute conflicts (professional or personal ones). Also, it is common to see that some urgent deadlines may overlap, then our agendas become chaotic.

However, managing deadlines become less difficult when we get more experience in the project or task performed, we learn to establish priorities and we try to organize our tasks to avoid us being drowned on them. It is a matter of time to start understanding the assigned task(s) so we would be able to estimate on better basis the required time to complete them, and then we will have more mental peace to work in harmony and meet our established goals.

Then, please see below some of our suggestions for a better deadline management:

- According to several sources, the recommendation for an adequate deadline management when there are multiple projects in our queue is by learning to prioritize overlapping or competing deadlines for each of them.
- You should try to get informed about the scope of each project and potential challenges that may cause delays, by taking a closer look at how you use/obtain resources for each of these projects. Then, try to finish the most complicated ones as top priority.
- The key of an adequate deadline management and get additional support for completion, is to keep always an open communication with your supervisor, since your supervisor may be able to give you a better overview of potential risks, expectations for task completion, available resources, etc., that will help you to complete your tasks in the proposed deadlines.
- Always it is good to use a work management platform, for better planning and task scheduling, but most important, to avoid forgetting important dates and missing deadlines for simple mistakes. Calendars in your computer or phone are always very helpful.

### Links of interest

1. [https://www.wrike.com/blog/top-tips-for-deadline-management/#:~:text=Deadline%20management%20is%20a%20process%20efficiently%20managing%20your%20available%20resources](https://www.wrike.com/blog/top-tips-for-deadline-management/#:~:text=Deadline%20management%20is%20a%20process%20efficiently%20managing%20your%20available%20resources)
2. [https://hygger.io/blog/11-tips-manage-time-improve-deadline-management-skills/](https://hygger.io/blog/11-tips-manage-time-improve-deadline-management-skills/)

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If your Hispanic Organization is planning a Toxicology meeting or if you are organizing a Toxicology event intended for a primarily Hispanic audience and want to promote it in the upcoming *Toxenlaces* issues, send an email to Alexandra Maria Moita Antunes (Councilor for Sister Organizations) at alexandra.antunes@tecnico.ulisboa.pt.
HOT wants you to be part of the organization! To make it available to everyone, HOT accepts applications from non-SOT members to become HOT members. Yes, that is right! You only have to have the desire to collaborate with and be part of our great organization.

Your HOT membership provides you with valuable resources throughout your scientific career as for networking through the largest Hispanic toxicologist community, giving you opportunity for Travel Awards or serving as a mentor to the young Hispanic toxicologists; besides you receive the Toxenlaces newsletter!

Download the application by clicking on the following link: Non-SOT Member Application.

So, what are you waiting for? **We are looking forward to receiving your application today!**