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Editorial

Exploring the Viability and Potential Impact of Launching a New Scientific Journal in the Current Academic Landscape

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Writing and publishing are essential for the growth and well-being of any society. Writing provides an outlet for creativity and self-expression, while publishing enables writers to establish an audience. Writers can share their stories, ideas, and perspectives with the world, which can shape opinions and provide valuable insights into a wide range of topics. Publishing extends the reach of writing by making it accessible to a broader readership. This allows writers to connect with a larger community of people who might never have heard of them or their work if it was not published. Publishing also provides an important platform for sharing knowledge and understanding between different cultures, societies and nations. It is through writing that ideas are shared, discussed, debated and explored in ways that would otherwise be impossible. The value of writing and publishing therefore lies in its ability to facilitate learning, dialogue and collaboration among individuals from different backgrounds. By providing a vehicle for disseminating information on a global scale, it has the potential to create positive social change.

Publishing research work is critical in the academic and scientific community, as it allows researchers to share their knowledge and results with other experts in the field. It also helps to validate the research by allowing peers to review and critique it. The publication also serves as a permanent record of the research that can be referenced by others. Ultimately, publishing research helps to advance knowledge and contributes to the understanding of important topics.

Utilizing scientific journals as an educational platform can significantly enhance learning and promote critical thinking in higher education. To achieve this, educators must understand the academic and social situations of their students, which is believed to enhance cognitive and critical thinking skills. Innovative science learning relationships often involve sustained cognitive apprenticeship with the online learning platform, which stimulates critical thinking, creativity, and problem-solving skills. To promote equity and academic excellence, institutions are encouraged to use all possible support systems, including virtual learning, to enhance teaching and learning experiences. Accessing online databases such as Gale, ProQuest, ISI Web of Science database, and the Social Sciences Citation Index is an excellent way to construct knowledge and develop critical thinking skills for students. Higher education institutions have also started utilizing big data to gain insight into student behavior and make informed decisions. Therefore, facilitation of using online educational platforms such as ZOOM, e-books & e-journals, open educational resources, and databases can provide an opportunity for further academic decision-making. This understanding provides a platform to critically analyze and discuss scientific research on teaching, which is essential for promoting critical thinking in higher education. For instance, the critical analysis was carried out using a self-devised framework to evaluate the effectiveness of a

novel online educational game. Delivery platforms are an essential aspect for game designers when designing educational games, thus making it a vital area of research in academic circles. This study expands research in a wide spectrum of academic areas besides adding to the existing knowledge on game design.

The importance of scientific biomedical journals cannot be overstated. Scientific biomedical journals are essential for providing the latest information and research in the field of medicine, enabling healthcare professionals to stay up-to-date on current developments in medical treatments and therapies. They are also essential for providing a platform for medical professionals to publish their original research and findings, which can lead to new treatments and advances in medicine. Additionally, they can help facilitate collaboration between different medical professionals as well as spread awareness about important breakthroughs in the field. Finally, scientific biomedical journals are also an invaluable resource for medical students who need access to detailed information about complex topics related to medicine that would otherwise not be available.

The current academic landscape is transforming, with pioneers exploring new uses of the digital medium, and this transformation can change the landscape of scholarly communication. However, to remain a viable and inclusive tool of urban research, academic research needs to explore new avenues. For instance, virtual worlds, such as Second Life (SL), have potential for large-scale educational purposes, but the barriers to their use need exploration. In terms of research synthesis, the landscape is also evolving, and there is a need to raise questions and open spaces for methodologists publishing in this field. Additionally, there is a need to explore the changing landscape of scientific publishing and consider high-profile operations as a viable alternative. The development of Open Access (OA) journals has shifted the landscape of scientific publishing significantly, and exploring the viability of this novel type of publishing can be useful. Within the broad landscape of scientific opportunity, chemical exploration has the potential for expansion, and exploring new phases for genomics research can be useful. The cultural science hypothesis can be explored using journals' specialisation to create the modern landscape in research. However, there is a need to consider the costs and benefits of this approach. In conclusion, exploring alternative positions and doing away with existing structures can transform the educational landscape.

Topics in Biomedical Research and Education publishes cutting-edge scientific research and reviews by globally recognized experts across a broad range of topics. These papers provide in-depth perspectives on the latest advances in basic, translational and clinical research, reflecting the diversity of this ever-changing field. In addition to promoting dialogue between scientists, clinicians and patients, the journal also takes pride in supporting the next generation of biomedical researchers by publishing cutting-edge papers by young investigators. Ultimately, the goal of the journal is to improve patient care by translation of scientific discoveries into clinical practice.

Biomedical research is an essential step in the advancement of medical knowledge and treatments. It helps to identify new causes of disease, devise new ways to prevent and treat illness, and develop more effective and safer medications. clinical research is a branch of biomedical research that involves studying new treatments in humans. These studies are essential in order to determine whether a new treatment is safe

and effective in people before it can be approved for use.

Educational materials play an important role in medical education and training, providing healthcare professionals with the latest evidence-based information to help them deliver the best possible care to their patients. By keeping up to date with the latest research and developments in their field, healthcare professionals can ensure that they are providing the best possible care to their patients.

Reviews by well-known experts in their field provide a valuable source of information for healthcare professionals. These reviews can highlight new research and developments in a particular field, and provide an expert opinion on the best way to treat a particular condition.

The journal also takes pride in highlighting research carried out by young researchers, providing opportunities for them to participate in the scientific discourse. By giving young researchers a platform to share their work, the journal helps to foster debate and discussion, and ultimately benefit patient care.

The editorial board of the journal is comprised of highly respected scientists and educators which ensures a high standard of quality of the published scientific work. Our dedicated team of reviewers ensures the highest standards of peer review for all submitted manuscripts.

As we move forward into an era of new medical discoveries and shifting paradigms, Topics in Biomedical Research and Education will continue to provide valuable insights and cutting-edge research to help address the pressing issues facing the healthcare industry. We invite all researchers, educators, and healthcare professionals to submit their original work for publication in this journal and become a part of the global scientific dialogue.

Letter to the Editor

SARS in Classical Greece? A glimpse in history

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Dear Editor,

Mystery in ancient Hellenic civilization represents a huge part of its history. Greek medico-philosophers tried through experience and in many occasions torturous observation to explain all about human physiology and medicine in its consummation. The Hippocratic School of Medicine marked the era by summarizing all available medical knowledge of the known world, as travel and medical review were among the fundamental methods to gain expertise. To propose a hypothesis that a case of a severe acute respiratory syndrome (SARS) was noted by Hippocrates and his followers is not far from possible. *(Figure 1)*

However, to add a virus from the family of Coronaviridae is something else. Nonetheless, some historical clues may allow such a narrative investigation. Caronaviruses were named after the Latin tern "corona" which means "crown", deriving from the ancient Greek verb "coroniao" (Greek: κορωνιάω) which describes the bending neck (flexion) movement, while "coronis" (Greek: κορωνίς) means the oval edge of something and in the case of humans the epicranium.[1] A single crown-like virion was directly visualized under the atomic force microscopy, specifying the family name.[2] There are still significant knowledge gaps in their epidemiology and transmission dynamics, while the spectrum of clinical features varies, presenting a heterogeneous cluster of symptoms, from mild to severe life threatening disease.

Since 2003 coronavirus SARS is identified, prompting a quest for novel types. The family was recognized in a diverse array in humans, domesticated animals and wildlife, especially in bat and bird species, which are believed to act as natural hosts. Bats were accused for the SARS-Cov-2 pandemic during 2019-2021. Recent molecular analyses demonstrated that coronaviruses are orders of magnitude older than previously suggested, exhibiting a past ancestor, common for all types of the family, who is likely far greater (millions of years) than it was believed.[3]

In ancient Greece the ceremonial religious sacrifice of cattle or sheep demanded the advent of bats for them to drink the animal's blood before the believers' practise "spondi" (Greek: σπονδή, an act of pouring a liquid as a sacrifice, or drinkin it in frenzy or ecstasy).[4]

Figure 1: *Hippocrates of Kos, Pieter Serwouters, Bonaventura Elzevier, Abraham Elzevier, 1628.*

Is there the possibility for a "miasmatic" cattle blood, which was infected by a bat virus? Looks like a fade case, but on the other hand all is possible.

Inside Corpus Hippocraticum various viral induced infections of the lower respiratory tract were noted, like bronchiolitis and bronchitis, usually presenting with cough accompanied by gastrointestinal disorders. In the report of the

"cough of Perinthos", a winter epidemic presented by the Hippocratics, dry or productive cough, rich in sputum production could be combined with pleurodynia, severe respiratory distress, orthopnoea, gastrointestinal disorders, arthralgia, voice irregularities and high fever waves, usually ending with pneumonia. Furthermore, an uncommon angina was described, characterized by intense respiratory distress with acute breathlessness and the felling of choking with peculiar rapid progression. The infected could pass away within the first day, or soon enough after the pathology's outset, "the sore throat angina, when not exhibit any event neither to the neck, not to the throat, but cause severe choking and wheezing, cause death the same day or the third day".[5]

Speculating for a Hippocratic SARS we only present a hypothesis with no firm strong clues. Exactly the same thing they all do when they exam the mysteries of the Hellenic antiquity!

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Case Report

Avulsion tibial tubercle fracture, resulting from a low energy trauma

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Abstract
This study aims to describe a rare tibial tubercle fracture (TTF) in an adolescent boy, associated with complete patellar ligament avulsion, resulting from low energy trauma. A 13-year-old boy, while walking home from school, experienced an abrupt twisting calf movement that injured his knee causing him to fell to the ground. Radiological examination revealed a TTF combined with high-riding patella. The fracture was promptly fixed with cannulated screws and transosseous sutures. A combined TTF and patellar ligament avulsion during mild activity in a healthy young individual is considered a rare phenomenon, and requires the same specialized surgical intervention as high-energy fractures, to avoid serious motion impairment.
Keywords: Adolescent knee trauma, high riding patella, patellar ligament avulsion, tibial tuberosity fracture

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Introduction

Avulsion fractures of the tibial tubercle (TTF) are rare and constitute less than 1% of all physeal injuries.[1] They mostly affect teenage boys, who are usually more energetic and competitive than girls and whose skeletons have not yet completed their growth at that young age. Typically, they occur during athletic activities, since physis undergoing developmental changes is more vulnerable to excessive loads exerted on it during sports.[2-6]

Reports on tibial tubercle fractures associate them with different levels of patellar ligament avulsion, that can be partial or complete. All cases presenting TTFs with simultaneous patellar ligament avulsion are attributed to high energy activity.[3-4]

To our knowledge, TTF cases with complete patellar ligament avulsion resulting from low-energy trauma are absent from the medical literature. How can mild physical activity of a young healthy male result in such a severe lesion?

Methods and Materials

A 13-year-old male with no medical history sustained an injury to his left knee, during his walk home from school after a sudden twist of his knee joint. He fell onto the ground and felt acute pain in his sprained knee. When trying to get up, he realized he could not use his injured leg or put any weight on it at all.

Physical examination revealed a sprained left radiocarpal joint and a large soft tissue swelling on the lower thigh, over the left knee. Palpation caused extreme tenderness, while the knee's range of motion was strongly reduced. Radiology demonstrated the TTF.

The detachment of the patellar ligament from its insertion site caused the proximal displacement of the quadriceps muscle and the uplifting of the patella towards the hip: a typical demonstration of high-riding patella.*(Figure 1)* Fragments of the fractured tibial tubercle were attached to the edge of the patellar ligament.

The fracture was classified as type IIB according to Ogden classification due to the comminution of the tibial tubercle.[5]

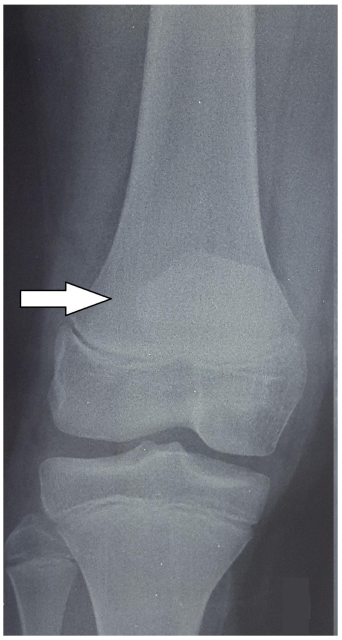

***Figure 1**. A. High riding patella (AP left knee radiograph) and B. High riding patella with avulsion tibial tubercle fracture (white arrow) (lateral left knee radiograph)*

The knee operation was scheduled within the next 8 hours. A 5 cm long longitudinal midline incision, was made over the area of the anterior tibial plateau,

revealing that the patellar ligament was completely torn and separated from its attachment point and the tubercle fragment was comminuted and displaced proximally.*(Figure 2)* Hemarthrosis was also present. With the use of C-arm fluoroscopy, the displaced TTF was fixed with two 4.0mm cannulated screws. The patellar tendon extensions around the tibial tubercle were additionally fixed with transosseous sutures (synthetic absorbable sutures, PDS 2). A long-leg cylindrical cast was placed on the boy's leg for 4 weeks. The fracture healing was confirmed by radiology 12 weeks after surgery.*(Figure 3)*

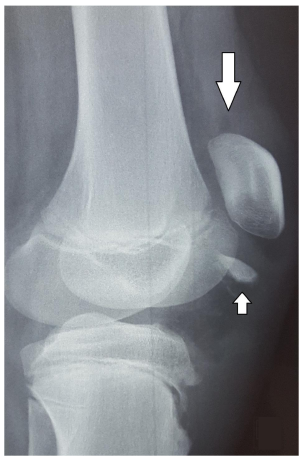

***Figure 2**. Raised patella and patellar ligament, with a fragment of the tibial tubercle (arrow) attached to its edge (intraoperative photograph)*

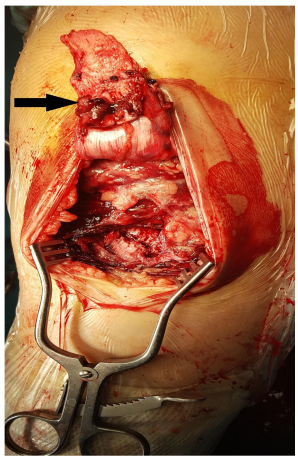

***Figure 3.** Osteosynthesis of TTF. A. AP and B. lateral radiograph of the left knee, 8 weeks after surgery*

Physical therapy was implemented to restore knee movement. The extension mechanism of the injured knee progressively improved, and the patient had complete recovery of the range of motion. Osteosynthesis material was removed 12 months after the operation.*(Figure 4)* The one-year follow-up confirmed full range of motion and no muscle atrophy, which enabled the boy's full return to high-impact activities.

Discussion

Avulsion TTF is a well-described injury in adolescent athletes, with an average onset age of 14.6 years old (range 13-16y).[2] Our case adds an innovative injury mechanism, namely low-energy trauma, to the very few published cases of tibial tubercle fractures with simultaneous patellar ligament avulsion.

Mayba in 1982, was the first to describe TTF with complete patellar ligament avulsion due to high-energy trauma.[4] Several studies noted that the most common mechanism was, in fact, high-energy jumping.[6] Sports and gym training put additional stress on bones and muscles. Young people participating in such activities, which especially involve running and jumping, have an increased risk of TTFs.[2] Violent active knee flexion against a tight quadriceps contraction (e.g. landing from a jump), or a violent quadriceps contraction against a fixed foot (e.g. jumping) are the usual causes of TTF.[6].

Documented causative factors for the patellar tendon avulsion as well as for TTF in adolescents include osteogenesis imperfect and Osgood- Schlatter disease, which often appears during puberty when bones, muscles, and tendons are growing at different rates.[7,9]

In our case the patient did not have any pre-existing radiographic or clinical signs of bone disease, and his injury was not the result of sports activity. TTF occurred after a rapid passive flexion and rotation of the knee against the contracting quadriceps: the boy was injured when he lost his balance while walking. It is astonishing how stumbling during a walk can cause such a severe injury to a young patient with no medical history.

We applied the Watson-Jones classification of TTFs, modified by Ogden according to the level of displacement and comminution of the fragment and found it to be type IIB.[6] In medical literature, type III TTFs are widely studied, while on the other hand a type II TTF with complete patellar tendon avulsion, resulting from low-energy trauma is an extraordinary phenomenon. Furthermore, a displaced avulsion of the entire ossification center of the tibial tubercle (usually ossified between 7 and 9 years of age) with comminution, imposed on a healthy 13-year-old patient should be considered as a medical rarity.[2,3,4,8,9]

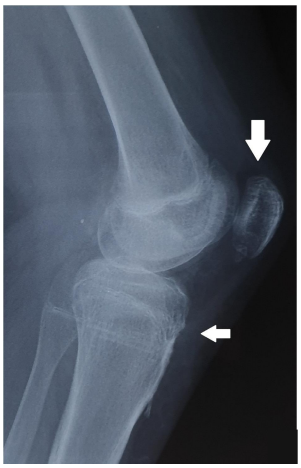

***Figure 4**. Healed fracture after the removal of the osteosynthesis material, 1 year postoperatively. A. AP and B. lateral left knee radiograph*

Surgery to treat TTFs is reserved for cases with comminution of the tibial tubercle. The immobilization period usually lasts between 3 and 6 weeks, after which

the range of motion is gradually restored.[2,3,4,7] Our case received the same surgical treatment, followed by leg immobilization within the suggested time limits and resulted in full recovery of knee function. We, therefore, suggest that type IIB TTF combined with patellar ligament avulsion should be treated with specialized open surgery for TTF repair to avoid grave consequences in the patient's quality of life.

It seems that low energy activity in adolescents, even in cases having no additional risk factors, can traumatize the knee joint more severely than is reported in the literature.

Conflicts of Interest Statement
The Authors declare that there is no conflict of interest.

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Case Report

Rhabdomyolysis and acute kidney injury requiring dialysis after norfloxacin-rosuvastatin co-administration

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Abstract

Aims: The increasing use of electronic gadgets from medical students raises awareness for related health disorders such as visual complaints. A 67-year-old male presented at the Emergency Department, because of severe, gradually deteriorating weakness and muscle pain for the past fifteen days. He had been on norfloxacin for the last three weeks due to a recently diagnosed acute prostatitis. He was also receiving rosuvastatin as chronic treatment for dyslipidemia. Extended proximal muscle wasting was the only pathological finding after a thorough clinical examination, while the lab tests confirmed excessive acute rhabdomyolysis with consequent acute kidney injury, requiring hemodialysis. During hospitalization extensive work up was not able to establish any specific diagnosis for the underlying disease. The aforementioned incident was eventually attributed to the co-administration of norfloxacin and rosuvastatin. Discontinuation of both drugs resulted in gradual alleviation of the symptoms, supporting our clinical hypothesis. However, the patient underwent multiple hemodialysis sessions for three months, before finally restoring his previous kidney function.

Introduction

Statin-induced myopathy is a well-described side effect of statins, usually occurring with atorvastatin or simvastatin during the first few weeks of treatment or after increasing the administered dose.[1,2] Temporary withdrawal of the drug or dose reduction is highly advisable in those cases.[2] However, when a patient has been uneventfully taking a statin for a longer period and such an effect is suddenly presented, it is more than often correlated with other causes of myositis, or with a recent, concurrent use of another drug. Antifungals, macrolides, fibrates, and cyclosporine are known to interfere with the metabolism of statins in more than one possible way, thus leading to the accumulation of the drug, followed by an increase in statin-related adverse effects.[2-5] Although not commonly reported, fluoroquinolones may also have such effects, when co-administrated with statins.[6-8] Awareness of such interactions seems to be of great significance, since quinolones are often enough prescribed for common infections to outpatients. Therefore, they could provoke effects that could easily go unnoticed.

Case Presentation

A man in his late 60s presented to the hospital, due to severe weakness and pain in his lower extremities. The patient reported muscle weakness, which started almost two weeks ago, while his daily routine remained the same as always, with no excess in physical effort. He also stated that his weakness got worse in time and muscle pain was recently added to the symptoms. One week prior to the symptoms' onset, he was diagnosed with acute prostatitis and had started treatment with norfloxacin (400mg per tab). Patient's medical history included diabetes mellitus, ischemic heart disease, thrombocytopenia and anemia related to myelodysplastic syndrome, and dyslipidemia. Chronic medication included aspirin (100mg), vildagliptin/ metformin (50/850mg), bisoprolol (2.5 mg), ramipril (5mg) and rosuvastatin (40mg). He was an active swimmer, non-smoker, with no known allergies, and reported alcohol consumption only occasionally. Clinical examination revealed severe symmetrical, proximal muscle weakness and tenderness concerning bilateral shoulder girdle muscles, quadriceps, and hip muscles (muscle strength grading 3/5). The biceps, brachioradialis, and triceps reflexes were decreased, while the patellar and achilles reflexes were absent. No prominent signs of arthritis, skin rash, or indications of nerve damage were present.

Investigation. Routine laboratory tests revealed a significant elevation of creatine kinase levels (CPK 31000 U/l), an increase in the liver function enzymes (aspartate aminotransferase 1027 U/l - reference levels <37, alanine transferase 421 U/l - reference levels <41), as well as increased levels of blood urea nitrogen and creatinine (BUN 104 mg/dl, cre 7.5 mg/dl). Aerial blood gases were indicative of mild metabolic acidosis, as a result of the acute kidney injury. The kidney dysfunction was mainly attributed to the rhabdomyolysis and myoglobinuria, since clinical presentation, history, urinary analysis and kidney ultrasound excluded other causes such as hypoperfusion, glomerular disease, and urinary outflow obstruction.

Differential Diagnosis. The sudden onset and deterioration of symptoms are compatible with all forms of acquired myopathy. Hypomagnesemia and hypo- or hyperkalemia are some of the most prominent candidates for myopathy,9 but they were easily excluded as the cause. Infectious or endocrine disorders, such as HIV infection, Cushing's disease or thyroid abnormalities were also excluded. Autoimmune

and inflammatory myopathies are also included in the differential diagnosis; tests for myositis-specific autoantibodies (c-ANCA, p-ANCA, anti-PR3, anti-MPO) were negative, while serum aldolase levels were between normal limits.[10]

A myopathy mediated by anti-HMG-CoA reductase antibodies was another considerable possibility, but was rejected, since the patient had already improved in a few days after discontinuation of the norfloxacin and rosuvastatin, without any specific treatment.[11-14] Statin-induced myopathy incited by the recently co-administered fluoroquinolone was the most prevalent scenario for this clinical case, as an exclusion diagnosis.

Treatment, Outcome and Follow-up. Intravenous crystalloid fluids were administered, in order to ameliorate the kidney injury. During hospitalization and a few days after the discontinuation of norfloxacin and rosuvastatin, the creatine kinase levels gradually became normal and the patient regained his physical strength. Liver function enzymes also improved. However, the patient remained hospitalized due to persistent oliguric kidney injury and dysfunction, since the serum creatinine levels deteriorated, before finally reaching a plateau in four to six days. *(Figure 1)*

Because of the oliguria and persistent metabolic acidosis despite the administration of sodium bicarbonate intravenously, the patient entered into hemodialysis sessions.

After being successfully mobilized, he was discharged from the hospital and continued hemodialysis sessions in an outpatient facility. Three months later, his kidney function was finally getting back to normal and he had also returned to his daily activities without any restrictions. At the time, he was still on most of his chronic medication with the exception of rosuvastatin. Almost five months after hospitalization he started treatment with atorvastatin (20mg per day), while he continued receiving the rest of his chronic medication with no modifications.

At a follow-up of one year, he is free of symptoms with normal physical activity and normal laboratory test evaluation.

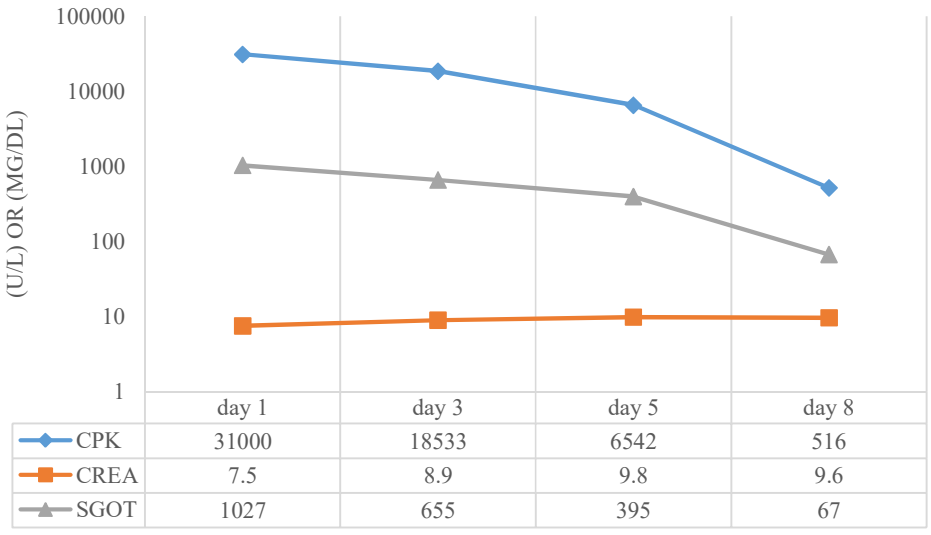

Figure 1. Variation in creatine kinase [CPK], serum creatinine, and aspartate aminotransferase [SGOT] levels during our patient's hospitalization.

Discussion

Statins are considered the cornerstone of drug therapy for dyslipidemia, while they are also crucial in the primary and secondary prevention of cardiovascular events.[15] The lipid-lowering mechanism of statins is well known; they act as HMG-CoA reductase inhibitors, thus limiting cholesterol synthesis in the liver.[16] On the other hand, the mechanism of statin-induced myopathy is vague and indefinite. It has been proposed that the reduction in the cholesterol levels, which statins provoke, may have a negative impact on the myocyte cell membrane stabilization, as well as on mitochondrial activity, not only disrupting the function of the muscle cell but also making it more prone to apoptosis.[1-4] In addition, it was postulated that the lipophilicity of the drug might play a crucial role in muscle cell damage, since lipophilic statins may permeate the cell membrane, reach the cytoplasm and instigate

myotoxicity more easily when compared to hydrophilic agents (e.g. rosuvastatin).[1-4] The aforesaid theory, however, seems to be rejected by some meta-analyses.[17] Most studies implicate a link between the likelihood of statin-related myotoxicity and co-prescribed drugs, which interfere with statin metabolism.[2-4] Several similar case reports shed light on the possible mechanisms of the interaction between statins and fluoroquinolones;[6-8] the current theories usually pertain to the inhibition of the CYP metabolic pathway by quinolones.[8,18] Any restriction of CYP activity leads to the accumulation and toxic levels of CYP substrates, such as statins.

In our case, the most possible scenario was that norfloxacin slowed down or even blocked the metabolism of rosuvastatin, which is primarily metabolized to N-desmethylrosuvastatin by CYP2C9; nevertheless, norfloxacin is not a common inhibitor of CYP2C9.[19,20] Moreover, according to on-topic studies, it is unlikely that either stimulation or inhibition of the said metabolic pathway could provoke effects of such clinical severity.[21,22,23] Pharmacogenetics may be the key to why our patient had such an extreme response to the co-administration of these two drugs.[2,4,22]

Conclusion

Statins are commonly prescribed drugs and statin-associated myopathy is a well-described medical condition. Physicians should be aware of this side effect. Co-administration of statins and other medicine seems to enhance the likelihood of developing myopathy, via inhibition of the statins' CYP-mediated metabolism. The severity of symptoms may vary from mild myalgias to significant rhabdomyolysis. Patients prescribed statins should be informed by their physician about the possible side effects of the drug, in order to seek medical assistance immediately if need be.

Conflict of Interest

The authors declare no conflict of interest.

Patient Consent Form

Written consent form obtained

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Review Article

Medical Students and Computer Vision Syndrome. A review

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Abstract

Aims: The increasing use of electronic gadgets from medical students raises awareness for related health disorders such as visual complaints. The aim of this review is to examine the association between medical students and computer vision syndrome (CVS).

Methods: A research of the current literature was undertaken in PubMed using the terms: "medical students AND computer vision syndrome" in order to find related published articles referred to medical students. Studies written in English language and referred only to medical students were included.

Results: Thirteen articles were found eligible and were included in the study. Additional sources of scientific associations were also taken into consideration. The majority of medical students suffered from visual and ocular problems. The most common symptoms were among other dryness, blurred vision including extra-ocular complaints such as headache, muscular pain and sleep disorders. The screen time varied and in some cases seemed to relate with the used device. Moreover, a considerable number of medical students had previous ocular disorders and most of them wore glasses.

Conclusion: The prevalence of CVS should raise awareness. Rational use of screen time and the adoption of ergonomic practices should be encouraged in order to medical students revealed from such complaints.

KeyWords: medical students, computer vision syndrome, visual problems

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Introduction

Electronic devices have a major role in our everyday lives. Undoubtedly, they have facilitated many aspects of our daily habits. Nevertheless, their extreme and careless use should raise awareness since they can potentially become harmful to our health, especially to our eyes. According to the American Optometric Association[1] the vision and eye-related complaints due to the extensive use of electronic gadgets such as smartphones, tables and computers describe the computer vision syndrome (CVS)[1]. It is well-known that medical students spend a lot of time in front of digital screens for their academic tasks. Sometimes, the increased screen time may lead to a variety of ocular complaints.

The aim of this review is to examine the current literature concerning the association between medical students and CVS.

Methods and Materials

An advanced literature search was conducted in PubMed, using the following term: "medical students AND computer vision syndrome". The resulting literature was consisted of 28 articles and was carefully screened by a single investigator. Only studies written in English were included. Additional search filters such as text availability, article type and publication date, were not applied. Further references from the initial articles with useful information related to the aim of the review were also screened. Current data from the official website of the American Optometric Association were also included. Studies referred to only medical students were included. Hence, a total of 14 references were included.

Results

The literature retrieved six studies which examined the association between medical students and CVS. The data are categorized in Table 1. Wang et al.[2] in their cross-sectional, web-based survey compared Chinese medical students who attended classroom lectures and students from a Bachelor of Medicine and Bachelor of Surgery (MBBS) who took online courses. The results revealed that the occurrence of CVS was greater among MBBS students with a male predominance. The most common symptoms in MBBS students were dryness and the sense of a foreign body, 72.97% and 62.16% respectively, whereas in Chinese students the most common feeling was heavy eyelids (53.97%). Furthermore, the majority of MBBS students spent 7 to 9 hours per day in front of a screen and the most used devices were phones and computers. On the other hand, most of the Chinese students spent only 2 to 4 hours per day using mainly their phones.

Another cross-sectional survey[3] from Paraguay revealed that 82.5% of the participants were suffering from CVS. 138 of them spent up to 4 hours using their notebooks and the statistical difference was significant

(p=0.049). Moreover, the results retrieved that 141 (61.8%) medical students had previous ocular disorders and most of them (59.2%) wore eye glasses. Patil et al.[4] in their study described a male predominance in CVS (80.23% in males whereas 75.87% in females) even though it was not statistically significant. CVS deteriorates the sleep quality of the medical students (75.5%, p<0.001) concerning sleep duration and latency.

Table 1. Relation between medical students and CVS

Researchers	Type of study	Origin of study	No of MS	Gender of MS	Prevalence of CVS	Symptoms	Screen time	Previous visual problems/use of glasses or lenses
Wang et al. [2] (2021)	cross-sectional, observational, web-based survey	Indian (70.27%), Indonesian (12.16%), Sri Lankan (6.76%), Pakistan (6.76%), others (4.05%).	137/171responders (83 Chinese students & 88 MBBS students)	females: 33.33% of Chinese & 47.30% of MBBS responders	50.79% Chinese students 74.32% MBBS students	Chinese students: heavy eyelids (53.97%), dryness (50.79%), feeling of a foreign body (46.03%), colored halos around objects (7.94%) MBBS students: dryness (72.97%), feeling of a foreign body (62.16%), heavy eyelids (58.11%), colored halos around objects (2.70%)	Chinese students: >12h: 1.59% 10-12h: 4.76% 7-9h: 22.22% 5-6h: 20.63% 2-4h: 46.03% <2h: 4.76% MBBS students: >12h: 5.41% 10-12h: 22.97% 7-9h: 43.24% 5-6h: 22.97% 2-4h: 5.41% <2h: 0	NA
Coronel-Ocampos et al. [3] (2022)	cross-sectional survey	Paraguay	228	163 (71.5%) females 65 (28.5%) males	188 (82.5%)	NA	MS with CVS notebook: ≤ 4 h 50 (75.8%) ≥ 4 h 138 (85.2%) smartphone ≤ 4 h 21 (84.0%) ≥ 4 h 167 (82.3%) tablet ≤ 4 h 158 (85.4%) ≥ 4 h 30 (69.8%) PC/Laptop ≤ 4 h 154 (83.2%) ≥ 4 h 34 (79.1%)	141 (61.8%) previous ocular disease 135 (59.2%) lenses with frame 7 (3.1%) contact lenses
Patil et al. [4] (2019)	cross-sectional, analytical study	India	463/500 responders	177 (38.2%) males 286 (61.8%) females	359 (77.5%) boys (80.23%) girls (75.87%)	poor sleep quality 75.49%	≤2 h: 156 (33.69%) >2 h: 307 (66.31%)	NA
Kharel & Khatri [5] (2018)	descriptive cross-sectional survey	Nepal	236/299 responders	76.2% males 23.8% females	71.6% 63.7% males 36.2% females	headache (50%) dry eyes (45%).	2-3 h/d: 37.2%	Myopia: most common refractive error (31.2%) prevalence of orthoptic problem: 17.5%
Almousa et al. [6] (2022)	observational descriptive cross-sectional study	Saudi Arabia	300	124 (41.3%) males 176 (58.7%) females	94%	musculoskeletal pain (84.3%) headache (71.1%) dry eyes (68%) burning eye sensation (66%) eye redness (50.7%) blurred vision (47%) pain in/around the eyes (45%) watery eyes (35.7%) double vision (18.3%)	total hours of studying h/d:* pre-COVID19: 5.1 ± 2.1 (1–15), 5 (4–6) during COVID-19: 6.4 ± 2.7 (1–20), 6 (5–8)	161 (53.7%) corrective lens: • 151 (93.8%) eye glasses • 10 (6.2%) contact lens
Iqbal et al.[7] (2021)	cross-sectional case-control study	Egypt	733	217 (39.0%) males 340 (61.0%) females	557 (76%)	visual blur 40.9%) headache (46.8%) dry eyes, eye strain/fatigue, eye redness, double vision, refocusing difficulties, near vision difficulties, unclear objects, insomnia, depression, neck & joint pains, inability to hold objects, difficulty to write	total daily 5.3 ± 1.9 screen-time 176 (31.6%) day 381 (68.4%) night	84 (15.1%) previous DED diagnosis 332 (59.6%) refractive errors/wearing 29 (5.2%) contact lenses

*mean ± SD [range], median (IQR)

Abbreviations: No = number; MS = medical students; CVS = computer vision syndrome; h = hour; h/d = hours per day; NA = not available; MBBS = Bachelor of Medicine and Bachelor of Surgery; DED = dry eye disease

The male predominance of CVS was also noticed in a descriptive, cross-sectional study[5]. Headache and dryness were noticed and myopia was the most common refractive disorder. Almousa et al.[6] described a 94% prevalence of CVS among the enrolled medical students. The researchers reported visual and extra-ocular disorders such as musculoskeletal pain (84.3%) and headache (71.1%) and underlined that during COVID-19 pandemic the symptoms were more frequent and severe than the pre-pandemic era. Moreover, during the pandemic the screen time was also increased.

In the cross-sectional, case control study of Iqbal et al.[7] CVS was reported in 76% of medical students and the most frequent complaints were blurred vision and headache. The severity of the syndrome seemed to be affected by refractive errors, increased screen time and close eye-screen distance.

Discussion

According to American Optometric Association (AOA)[1] the most common symptoms of computer vision syndrome (CVS) include eyestrain, dryness, headache, blurred vision and musculoskeletal complaints such as neck and shoulder pain. Previous vision problems, poor lighting and posture, short eye to screen distance or the combination of these factors can lead to CVS. Eye examination confirms the diagnosis.

Ergonomic practices are essential in order to relieve or even prevent the symptoms of CVS. AOA[1] suggests the location of the computer screen to be 15 to 20 degrees below the eye level and 20 to 28 inches away from the eyes. Mowatt et al.[8] found that visual symptoms were less frequent when the electronic device was below the eye level. Avoidance of glare with the appropriate computer position, the use of glare screen filters and the balance of light between computer screen and the surrounding are helpful.[1,9] Furthermore, comfortable seating position and blinking are recommended.[1] Another useful practice is the 20-20-20 rule. In other words, everyone should take a 20 second break to view something that is 20 feet away every 20 minutes. Some secondary preventive measures can be artificial tears, however, ethical issues arise.[9]

The literature supported that CVS, also known as digital eye strain, has a high prevalence in medical students. This disorder affects other groups of students, for instance engineering students. Logaraj et al.[10] claimed that engineering students were at higher risk of developing CVS than medical students since they spent more hours per day in front of a screen. It should be underlined that COVID-19 pandemic played an important role in the development of CVS. Screen time increased during the pandemic[11] given that in person teaching was replaced with distance learning. The extended screen time use during pandemic increased the prevalence of ocular complaints.[12,13] Alamri et al.[14] in their cross-sectional study compared the use of electronic devices before and during COVID-19 pandemic. The results revealed a significant increase in their use. Most students (49%) of their cross-sectional study used electronic devices for virtual classes and 20% of the responders had multiple symptoms of ocular complaints due to extended screen time. Moreover, Wang et al.[2] reached similar results. They observed that MBBS students during COVID-19 pandemic spent a lot of hours in front of screens due to the virtual classes and the incidence and severity of CVS's symptoms were more profound compared with students who took classroom lectures. These findings were confirmed by Almusa et al.[6] who observed that 38% of the enrolled students had more severe symptoms, and 48% experienced more frequent symptoms during the pandemic due to the extended use of digital devices. Consequently, COVID-19 pandemic led to extensive use of digital devices exacerbating symptoms of CVS or previous ocular problems.

Our study is an up-to-date review concerning the association between CVS and medical students. The limitation of this study is that we excluded studies referred to other kinds of students along with medical students, for instance "health profession students" that included medical, nursing and pharmacy students, in order to have a homogeneous sample.

Conclusion

Take all the above into consideration, it is profound that CVS due its high prevalence is a worldwide health issue that requires awareness. Medical students should be informed about its symptoms and guided about daily measures that can be taken in order to minimize the complaints accompanying CVS. Hence, ergonomic practices are of paramount importance.

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Review Article

The interrelationship between Covid-19 and heart failure

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Abstract

Infections from the novel coronavirus (severe acute respiratory syndrome-Coronavirus 2, SARS-CoV2) and the associated disease (coronavirus disease 19, COVID-19) have heart failure (HF) as a risk factor and complication. As an independent predictor of poor prognosis, the presence of chronic HF may lead to increased morbidity and mortality in patients with COVID-19. This is achieved through multiple pathophysiologic mechanisms (inflammation, endothelial dysfunction, dysregulated coagulation), causing functional status deterioration in patients with chronic HF, combined with thrombotic and arrhythmic complications. De-novo HF in patients with COVID-19 is another frequent complication, often associated with right ventricular dysfunction. Beyond the acute manifestations of COVID-19, the long-term consequences of SARS-CoV-2 infection on the heart should not be neglected. Myocardial injury may be identified in a significant proportion of recovered individuals, with uncertain prognostic implications. Finally, vaccination against SARS-CoV2 is of great importance in patients with HF since it may lead to reduced morbidity and mortality.

KeyWords: Covid-19 , heart failure

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Introduction

The emergence of the severe acute respiratory syndrome-Coronavirus 2 (SARS-CoV-2) with the associated disease (coronavirus disease 19, COVID-19) has led to a pandemic with increased morbidity and mortality, along with a significant worldwide healthcare burden. The main manifestation of COVID-19 includes pneumonia and acute respiratory distress syndrome. However, extrapulmonary manifestations are not uncommon, and are associated with disease severity and a poor prognosis. Additionally, many risk factors have been related to disease progression, such as heart failure (HF). The aim of this mini-review is to describe the importance of the interaction between HF and COVID-19.

COVID-19 in heart failure patients

Individuals with comorbidities are frequently faced with an increased risk of severe COVID-19 course and mortality, such as those with cardiovascular disease. In this particular patient subpopulation, mortality could even be 4-fold higher compared to the general population.[1] More specifically, congestive HF is an independent prognostic factor of in-hospital mortality .[2] Such patients have impaired immunity, are frail, and have limited ability to overcome the hemodynamic consequences of severe infections. It has been shown that, in HF patients, monocytes secrete pro-inflammatory cytokines compared to healthy individuals.[3] When this is combined with the hyperinflammatory reaction to COVID-19, optimal cardiac function and cardiac output are required, which are not feasible in failing hearts.

In patients with chronic HF, SARS-CoV-2 infection and COVID-19 can lead to acute decompensation of functional status, due to multiple mechanisms. Initially, the secretion of pro-inflammatory cytokines and the mobilization of macrophages and granulocytes leads to a cytokine storm that may exacerbate the preexisting injury.[4-5] Endothelial dysfunction and generalized endotheliitis are cardinal features of COVID-19 pathophysiology, which can have detrimental consequences for patients with HF.[6]

The increased metabolic demands could potentially lead to cardiac dysfunction and either de novo HF or acute decompensation of chronic HF. At the same time, in septic conditions, coagulation abnormalities and platelet activation could have a hazardous effect.[5-7] The thrombotic complications of COVID-19 are well-known, and their non-negligible incidence may lead to the need for anticoagulation in hospitalized patients.[8] Acute kidney injury represents an additional aggravating factor during COVID-19, which could promote volume overload and HF decompensation.[9] Lastly, the use of various medications for COVID-19 management has been associated with proarrhythmic effects, such as QT interval prolongation, ventricular arrhythmogenesis, and sudden cardiac death.

Patients with HF with a left ventricular assist device (LVAD) represent a unique subgroup, characterized by a different inflammatory profile with disrupted cellular immunity and a higher proinflammatory cytokine burden.[10-11] However, there is no certain proof that this leads to an increased risk of SARS-CoV-2 infection. The optimal preload and afterload in such patients are critical in order to maintain cardiac output in infectious

conditions. In case of hemodynamic abnormalities, many complications, such as right HF and device thrombosis, may ensue.[12] Early case reports with coexisting COVID-19 and LVAD mentioned described the presence of persisting hypoxia and right heart failure, with multiorgan failure as the end result (13). The management of such patients should include their placement in a prone position, along with optimal medical therapy.

Heart failure as a COVID-19 manifestation

Among patients hospitalized for COVID-19, the incidence of de novo HF may reach 33% in patients who required admission to an intensive care unit (14). In a Spanish cohort of 3080 patients hospitalized for COVID-19, the incidence of acute HF was 2.5%, and its development was associated with high rates of mortality that approached 50%. It should be stressed that 78% of patients with acute HF did not have a history of chronic HF.[15] Pathophysiologic mechanisms such as inflammation and thrombosis are able to promote the development of HF. Beyond those, the activation of the sympathetic nervous system, along with SARS-CoV-2-induced myocardial damage and myocarditis are equally important in cardiac dysfunction development.

Right ventricular dysfunction is a common phenomenon in COVID-19 due to the close relationship between the right ventricle and pulmonary circulation. Therefore, right HF contributes to swift hemodynamic destabilization, the incidence of arrhythmias and sudden cardiac death. Right ventricular dilatation is a frequent finding in autopsy studies of patients with severe COVID-19.[16] Subsequently, echocardiographic studies identified a significant proportion of right ventricular dilatation (12-15%) and dysfunction (16-35%), along with increased pulmonary artery systolic pressure, even in subjects without known cardiac disease.[17-19] Right ventricular remodeling in such patients was associated with a 2-fold increase in mortality. Furthermore, many patients with severe COVID-19 require positive pressure ventilation, which affects preload, afterload, and ventricular coupling, negatively impacting right ventricular function.

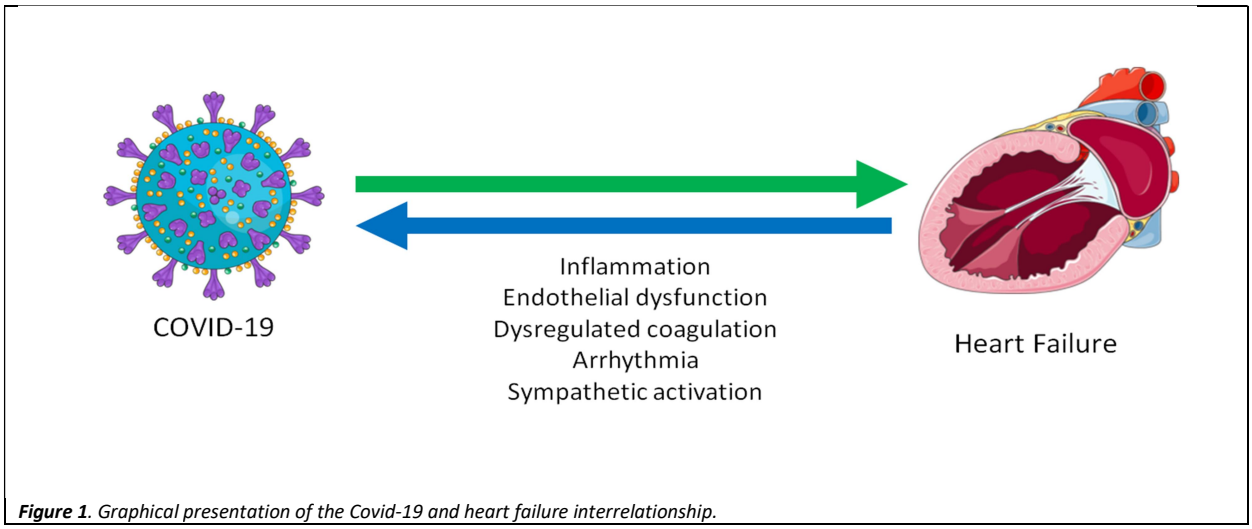

***Figure 1**. Graphical presentation of the Covid-19 and heart failure interrelationship.*

Long-term cardiac consequences of COVID-19

The long-term influence of SARS-CoV-2 and COVID-19 in various organ systems is a matter of extensive scientific investigation, since patients report persistent symptoms such as fatigue, dyspnea, and palpitations several months after the acute phase of the disease.[20] Concerning cardiac complications, subacute myocarditis and prolonged inflammation are factors that aid HF development.[21] Furthermore, endothelial dysfunction may be evident months after SARS-CoV-2 infection.[6] In this context, the use of cardiac magnetic resonance imaging can provide useful data regarding the presence and the degree of injury, even in patients with mild symptoms during the acute phase of COVID-19. According to study results, it appears that cardiac involvement two months after the infection is evident in a significant proportion of patients, especially those with persisting symptomology.[22] In a study of athletes after COVID-19, persisting myocarditis was noted in 15% and previous myocardial injury in 31%.[23] The echocardiography study is also useful, as it can reveal the presence of diastolic dysfunction, abnormal left ventricular myocardial deformation, and pericardial effusion.[24-26] The importance of those findings has not been explored, however. Nonetheless, it should be stated that persistent myocardial injury and ensuing

fibrosis are independent factors for chronic HF development.[27] Therefore, prompt recognition and continuous follow-up of those patients, along with the initiation of cardioprotective medication (renin-angiotensin-aldosterone system blockers, sodium-glucose cotransporter 2 inhibitors) may lead to positive outcomes.

Management of patients with heart failure during the COVID-19 pandemic

The implementation of social distancing measures and the prohibition of movements could indirectly affect patients with chronic HF.[28] The limited accessibility to healthcare facilities and the fear of contracting SARS-CoV-2 infection are deterring factors for patients with HF regarding the programmed follow-up visits. The lack of close surveillance may have deleterious consequences on their prognosis. Therefore, informing HF patients about the need for frequent medical evaluation, including visits to specialized centers, is warranted even during the pandemic.

The establishment of remote monitoring may be an acceptable alternative, since a greater attendance could be achieved, without increasing the rates of hospitalization or mortality. Despite the fact that a thorough clinical examination cannot be conducted remotely, the detection of certain features of congestion (lower limb edema, jugular vein distention) in conjunction with registration of body weight and vital signs could adequately guide the attending physician toward the optimal management of the patient. Remote pulmonary artery pressure monitoring is another alternative for the physicians of patients with HF. The management of those patients according to this parameter has led to significantly lower rates of hospitalization for chronic HF decompensation due to the constant optimization of medical therapy.[29].

SARS-CoV-2 vaccination in heart failure patients

As previously mentioned, the presence of HF, especially in the elderly or frail individuals, is a potent risk factor for poor prognosis in COVID-19, leading to multiple complications and the need for intensive care unit admission with mechanical support of respiratory and cardiac function. On this basis, vaccination against SARS-CoV-2 in patients with HF is indicated, similarly to influenza and pneumococcal vaccination.[30] Large clinical studies of vaccines against SARS-CoV-2 included patients with HF and confirmed their efficacy and safety in this patient population.[31-34] Vaccination should be conducted imminently, ideally in a stable, compensated HF state.[30]. Iron replenishment in cases of coexisting iron deficiency could potentially improve the vaccine's efficacy.[30] Following vaccination, the measurement of antibodies is not essential, and the patients should strictly follow preventive strategies (hand hygiene, wearing a face mask, and keeping their distance).[30] Vaccination against SARS-CoV-2 should be performed in immune-compromised patients, such as those after heart transplantation, despite the uncertain immune response.[35]. Those patients, apart from the meticulous compliance with the preventive strategies mentioned above, may benefit from additional vaccine doses.

Attending physicians should be aware of the rare complications such as thromboembolism and myocarditis, without however discouraging vaccination of HF patients for this reason.[30] The development of local hematomas is another complication which more commonly affects subjects with thrombocytopenia or on antithrombotic treatment.[30] However, a serious allergic reaction to vaccine components remains the only contraindication to vaccination, whose prevalence is not more common in patients with HF.[36]

Conclusion

The presence of chronic heart failure is an independent indicator of poor prognosis in patients with COVID-19, as shown by the high morbidity and mortality rates in this subgroup. Through multiple pathophysiologic mechanisms, COVID-19 could lead to acute decompensation of chronic HF, along with thrombotic and arrhythmic complications. A de novo heart failure development in COVID-19 patients is frequently observed, and depends on right ventricular dysfunction. Long-term cardiac consequences of SARS-CoV-2 are of considerable clinical and scientific interest, as they are noted in a significant proportion of convalescent patients. At the same time, since patients with heart failure are in need of frequent monitoring, the implementation of social distancing measures could have detrimental effects on their prognosis, warranting the need for remote monitoring. Finally, vaccination against SARS-CoV-2 is vital in patients with heart failure, as it can lead to reduced morbidity and mortality rates.

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Review Article

CDK4/6 inhibitors and SSRIs/SNRIs: A brief review of their safety profiles focusing on potential drug interactions

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Abstract

Currently, the mainstay of treatment for advanced and metastatic hormone receptor positive (HR+), Human Epidermal Receptor -2 (HER-2) negative breast cancer includes the combination of CDK4/6 inhibitors (ribociclib, palbociclib, and abemaciclib) with endocrine therapy. However, interpatient variability has been associated with increased toxicity or questionable therapeutic responses. Indeed, several factors such as concomitant medications and pharmacogenetics may significantly affect the absorption, distribution, metabolism and elimination of CDK4/6 inhibitors, resulting in subtherapeutic or toxic plasma levels. Traditionally, depressive symptoms have been highly associated with cancer patients, and thus antidepressant therapy (typically SSRIs or SNRIs) is frequently co-initiated early in the course of cancer treatment. This brief review aims to compile and present existing data regarding the safety profiles as well as drug-drug interactions that may result from the co-administration of CDK4/6 inhibitors with SSRIs/SNRIs. Increased awareness by medical oncologists warrants a safer and more effective clinical use of CDK4/6 inhibitors.

Keywords: CDK4/6 inhibitors, breast cancer, SSRIs, SNRIs, personalized medicine

Introduction

Breast cancer (BC) is the most frequent cancer in women, representing 12.2% of the newly diagnosed cancers in 2020, while it ranks as the second most common malignancy overall.[1] The most common subtype of breast cancer is Hormone Receptor (estrogen receptor and/or progesterone receptor) positive (HR+), HER2 (human epidermal growth factor receptor 2) negative (HER2-) breast cancer, representing the 72.6% of all diagnosed cases.[2]

The high impact that the alterations of cell cycle regulators have on tumor progression, as well as the various limitations of chemotherapy, led to the development of targeted therapies, which have been proven to be efficacious when added to hormonal therapy.[3-5] Given that cyclin-dependent kinases (CDKs) hold a key role on the cell cycle progression, they constitute a milestone for the development of targeted therapies [3]. This review focuses on CDK4/6 inhibitors, which prevent the cell cycle transition from G1 to S phase and have been recently incorporated into global practice guidelines.[4,6]

Palbociclib was the first representative of this class of targeted therapies that received regulatory approval by the U.S. Food and Drug Administration on 2015 (IBRANCE®, Pfizer Inc.), followed by European's Medicines Agency in 2016.[7-8] Following this, ribociclib (KISQALI®, Novartis Pharmaceuticals Corp.) and abemaciclib (VERZENIO™, Eli Lilly and Company) similarly gained market authorization in 2017 and 2018 respectively.[9-12] A meta-analysis incorporating 8 randomized controlled trials (RCTs) demonstrated that the adjunction of CDK4/6 inhibitors to endocrine therapy significantly improved progression-free survival (PFS) compared to endocrine therapy alone, in patients with metastatic HR+/HER2− breast cancer, irrespectively of their menopausal status and the metastatic site.[13]

Despite the advances in BC treatment, disease diagnosis and treatment are still considered a traumatic experience for the majority of the patients. Multiple studies have demonstrated the increased psychological burden of patients with BC.[14-16] More specifically, women from the very beginning of their diagnosis and during their treatment experience anxiety, depression, fear of death and difficulty in sleeping.[17] Hence, it is common clinical practice to apply psychological interventions, in order to alleviate the burden of these symptoms and improve the quality of life of BC patients.[18] Consequently, antidepressant therapies, mainly selective serotonin reuptake inhibitors (SSRIs)

and serotonin-norepinephrine reuptake inhibitors (SNRIs), are usually prescribed for these cases.[14] However, one major issue emerging from the co-administration of oral drugs, is the increased possibility for drug-drug interactions (DDIs), leading to increased toxicity or sub therapeutic drug levels and thus a negative impact on patient's safety and on the efficacy of the treatment, respectively.[19]

Herein, we try to summarize existing data regarding the possible DDIs between CDK4/6 inhibitors and SSRIs/SNRIs, aiming to serve as a tool for physicians for the optimal therapeutic management of BC patients facing emotional distress.

Methods and Materials

In this brief narrative review, we tried to address the subject of drug interactions between CDK4/6 inhibitors and two commonly prescribed classes of anti-depressants (SSRIs and SNRIs), from two main perspectives. The first one relates to the pharmacokinetic profiles of the medications under discussion. The prediction of DDIs is often based on their pharmacokinetics and predominantly their hepatic metabolism by cytochrome P-450 enzymes. For example, enzymatic inhibition of an isoform i.e. CYP3A4 by drug A, will result in decreased metabolism and thus increased toxicity of drug B, in case that the latest is a substrate for CYP3A4. Similarly, decreased plasma concentrations and thus reduced efficacy of drug B, will result in case of co-administration with an inducer of CYP3A4 (drug A). Moreover, when two co-administered drugs are metabolized by the same isoform, only the one with the highest affinity will be accommodated within the catalytic site of the metabolizing enzyme. Therefore, it will prevent the binding and metabolism of the other drug, leading to increased toxicity. The second perspective relies to the assessment of the hypothesis that the prediction of a pharmacokinetic DDI is clinically significant. This consideration critically driven our conclusions based on current literature, summaries of product characteristics (SPCs) and recent safety data.

CDK4/6 inhibitors: Ribociclib, Palbociclib, Abemaciclib

Mechanism of action. The mechanism of action of CDK4/6 enzyme inhibitors is based on preventing the transition of the cell cycle from G1 to S phase. This can be better comprehended by examining the physiological role of CDK4/6 in cell cycle, as seen *in Figure 1*. Normally, growth signals detected at G1 phase induce the cyclin D expression, which subsequently binds to CDK4/6 enzymes.[3] This CDK-Cyclin D complex leads to the phosphorylation of Retinoblastoma (Rb) protein, and therefore to Rb inactivation. The Rb protein is a negative regulator of the cell cycle, as it attaches to E2F transcription factors, inhibiting, in this way, transition from G phase to S phase. By phosphorylating Rb protein, E2F are released, leading to the expression of genes that are essential for cell cycle progression to S phase. In summary, the role of CDK4/6 inhibitors is the prevention of the Rb protein hyper-phosphorylation, the interruption of the cell cycle and, finally, cancer cell uncontrollable proliferation.[20]

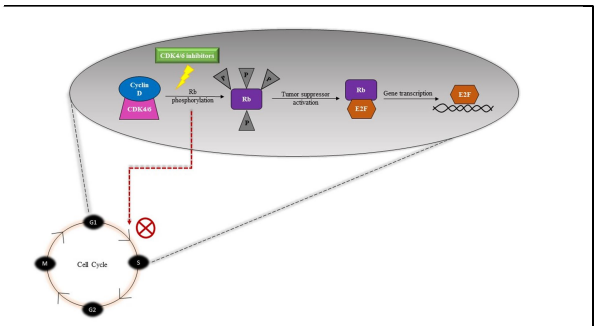

Figure 1. CDK4/6 inhibitors: Main mechanism of action. CDK4/6 inhibitors prevent the transition of the mitotic cell cycle from G1 to S phase. Normally, growth signals at G1 phase induce the cyclin D expression, which subsequently binds to CDK4/6 kinases. This complex leads to the phosphorylation and inactivation of Retinoblastoma (Rb) protein. The latest is a negative regulator of the cell cycle, as it attaches to E2F transcription factors, inhibiting transition from G phase to S phase. By inactivating Rb protein, E2F are released, leading to the expression of genes that are essential for cell cycle progression to S phase. CDK4/6 inhibitors prevent the Rb protein phosphorylation and overall cancer cell uncontrollable proliferation.

Toxicology Profile. CDK4/6 inhibitors (ribociclib, palbociclib and abemaciclib) share common and different pharmacodynamic and pharmacokinetic features. Despite being slight, those differences translate into different types and frequencies of toxicities, that can play a crucial role when selecting the appropriate agent for a patient. In general, CDK4/6 inhibitors demonstrate similar mechanisms of toxicity towards highly proliferative tissues, such as bone marrow suppression and gastrointestinal adverse events.[21-23] However, there are some differences between these three medications regarding the severity and incidence of hematological and gastrointestinal disorders. More specifically, myelosuppression (mainly anemia, leukopenia and neutropenia) is frequently observed with ribociclib and palbociclib, whereas diarrhea, nausea and vomiting are often associated with abemaciclib. The management of the aforementioned hematologic toxicities include dose adjustments or the use of erythropoietin and granulocyte colony-stimulating factors (G-CSFs) in case of symptomatic anemia (Hb<10 g/dl) and neutropenia, respectively.

Gastrointestinal (GI) toxicities, such as nausea, vomiting and diarrhea are easily manageable with conventional methods, including antidiarrheal medication or by dose adjustments.[24-27] Of note, prophylactic use of loperamide is often recommended from the initiation of treatment, in order to avoid abemaciclib-associated diarrhea.[28]

Furthermore, the use of ribociclib has been linked with QT interval prolongation and risk of Torsades de Pointes (TdP). Therefore, co-administration of medications that induce QT prolongation should be avoided. In any case, the recommendations suggest that the patient should be monitored closely by ECG, in order to capture any significant electrophysiological differences from baseline.[23] On the other hand, abemaciclib and palbociclib use has not been linked with QT prolongation; however concomitant use of medications that prolong QT is also discouraged.[21,22] Finally, post-authorization safety data suggest additional monitoring due to the increased risk of thromboembolic events (venous and arterial thromboembolism) with CDK4/6 inhibitors.[29]

SSRIs and SNRIs

Mechanism of action. SSRIs increase serotonin's concentration in the synaptic cleft by blocking its reabsorption by the presynaptic neuron in a highly selective manner. They demonstrate a 20-1500-fold higher selectivity for serotonin than norepinephrine, while no presynaptic release of serotonin or norepinephrine is stimulated.[30] On the other hand, SNRIs inhibit reuptake of both major neurotransmitters of depression, norepinephrine and serotonin. They demonstrate low to no binding affinity for other neurotransmitter receptors, such as adrenergic, muscarinic, dopamine, histamine H1 receptors and postsynaptic serotonin receptors.[31] *(Figure 2)*

Toxicology Profile. Regarding the SSRI and SNRI-induced toxicity, these agents are mainly associated with neuromuscular, autonomic and mental status symptoms.[32] Serotonin receptors are mainly located in the central nervous system (CNS), but they are also detected in platelets and the GI tract.[33] Consequently, GI adverse events, such as nausea, vomiting, and diarrhea are quite common. Risk of GI bleeding, most likely due to the reduction of blood serotonin uptake by platelets, should also be taken under consideration.[33-34] Owed to their anticholinergic activity, SNRI treatment can also cause dry mouth, whereas increased heart rate and increased blood pressure might also occur.[34-35]

On the contrary, SSRIs do not generally affect blood pressure; however, the risk of orthostatic hypotension in high doses and/or in the elderly, has been reported.[34-36] Moreover, even though the exact mechanism is still under discussion, SSRIs tend to reduce basal heart rate, in a dose-dependent manner.[36]

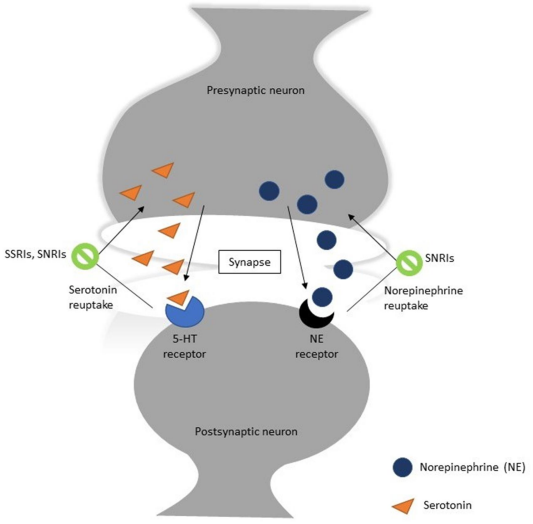

Figure 2. *Mechanism of action of SSRIs and SNRIs.*

Among SSRIs, the QT interval prolongation is demonstrated most significantly by citalopram and escitalopram.[34-35] Another adverse event of these antidepressant classes is sexual dysfunction, often persistent even after treatment discontinuation.[34,38] Finally, serotonin syndrome-caused by excessive stimulation of serotonin receptors- may lead to potentially life-threatening circumstances. This syndrome manifests with a variety of signs and symptoms from tachycardia, fever and agitation at mild and moderate cases to acidosis, hypertension, malignant hyperthermia, rhabdomyolysis, coma and clonus, in severe cases.[33].

Pharmacokinetic and Pharmacodynamic Interactions between CDK4/6 inhibitors and SSRIs/SNRIs

The pharmacokinetic profiles of CDK4/6 inhibitors, SSRIs and SNRIs are summarized in Table 1, 2 and 3 respectively. All three CDK 4/6 inhibitors are subject to hepatic metabolism by the isoform CYP3A4 [39], which represents the dominant biotransformation enzyme for the majority of the drugs. Hence, concomitant medications should be thoroughly monitored for their CYP3A4 inhibitory/induction potential. In addition, drugs that have been identified as CYP3A4 substrates, may require a dose reduction (especially those with a narrow therapeutic index-NTI), since CDK 4/6 inhibitors, mainly ribociclib, display an inhibitory potential on CYP3A4. Previous articles have published extensive lists including

the drugs that are major or sensitive CYP3A4 substrates or have a NTI.[3,39]

***Table 1**. PK parameters of CDK4/6 inhibitors: Palbociclib, Ribociclib and Abemaciclib*

	Palbociclib	Ribociclib	Abemaciclib	References
Indication	HR-positive HER2-negative mBC			[41-43]
	1st line: in combination with AI 2nd line: in combination with Fulvestrat i.m after prior ET → d1, d15, d29	1st line postmenopausal: in combination with AI 1st line premenopausal: in combination with ET 2nd line: in combination with Fulvestrat i.m → d1, d15, d29	Adjuvant (high risk early BC): in combination with AI 1st line: in combination with AI 2nd line: in combination with Fulvestrat i.m→ d1, d15, d29 1st line as monotherapy in adult patients with advanced or metastatic HR+ HER2- BC	
	Pre/perimenopausal women: LHRH-agonist for OFS			
PK parameter				
Bioavailability	46%	66%	45%	[41-45]
Route of Administration	Oral	Oral	Oral	[41-43]
Dosage	125 mg QD 3/1	600 mg QD 3/1	150 mg BID with ET or 200 mg BID as monotherapy	[41-43]
Dose adjustments	100 mg QD 3/1 75 mg QD 3/1	400 mg QD 3/1 200 mg QD 3/1	150 mg BID 100 mg BID 50 mg BID	[41-43]
Dosage form	Caps: 75, 100, 125 mg Tabs: 75, 100, 125 mg	Tabs: 200 mg	Tabs: 50, 100, 150 mg	[41-43]
Human protein binding	85%	70%	96.3%	[41-43]
Plasma distribution volume	2800L	1090L	690-750L	[41-45]
Metabolism	Weak, time dependent CYP3A4 inhibitor SULT2A1	Potent dose-depentent CYP3A4 inhibitor (600mg) moderate CYP3A4 inhibitor (400mg) CYP1A2 CYP2E1	CYP3A4 inhibitor	[41-45]
Active metabolites	M17 (CYP3A4) M22 (UGT) → NCS	M1 (NCS), M4 (major metabolite formed by CYP3A4, NCS pharmacological activity), M13 (NCS)	M2 (CYP3A4) → major M18 (CYP3A4) M20 (CYP3A4)	[41-44, 46]
Major elimination route	Hepatic (sulphonation, oxidation)	Hepatic (oxidation)	Hepatic	[41-43]
Excretion	74% faeces 17% urine	69.1% faeces 22.6% urine	81% faeces 3% urine	[41-45]
Half-life time ($t_{1/2}$)	28.8 h	29.7 to 54.7 h	18.3 h	[3, 41-44]
Substrates (inhibition)	P-gp (BBB) BCRP (BBB)	P-gp (intestine) BCRP (intestine)	P-gp (BBB) BCRP (BBB)	[3, 41-43]
Food effect	Caps with food Tabs with/without food	Tabs with/without food	Tabs with/without food	[41-44]

mBC: metastatic breast cancer; AI: Aromatase inhibitor; ET: endocrine therapy; i.m.: intramuscular; LHRH-agonist: luteining hormone-releasing hormone agonist; OFS: Ovarian function suppression; 3/1: 3-weeks-on/1-week-off; BID: twice daily; SULT: sulfotransferase; P-gp: P-glycoprotein; BCRP: breast cancer resistance protein; Caps: capsules; Tabs: tablets; M22: palbociclib glucuronide; M17: lactam palbociclib; M1: secondary glucuronide; M4: LEQ803; N-demethylation; M13: CCI284; N-hydroxylation; M2: N-desethylabemaciclib; M18: hydroxy-N-desethylabemaciclib; M20: hydroxyabemaciclib; GI: gastrointestinal; BBB: blood brain barrier.

In terms of protein binding, abemaciclib displays the highest binding affinity to human plasma proteins, and thus a lower Vd, compared to ribociclib and palbociclib. Since, only the unbound (free) percentage of a drug is pharmacologically active, competitive displacements between co-administered, highly protein-bound drugs, may result in meaningful increases in the free concentration of the displaced drug. Therefore, despite that no such DDI studies exist, one should take into consideration the possibility of altered distribution, in case that abemaciclib is co-administered with another drug that is also highly protein-bound. Furthermore, as shown in *Table 1*, ribociclib, palbociclib and abemaciclib are substrates of the membrane transporters P-gp and

BCRP. There is also evidence that CDK4/6 inhibitors exert an inhibitory effect on drug efflux pumps.[3] Consequently, DDIs may result from a) the competition with other drugs that are also substrates for these transporters and b) the increased plasma concentrations of drugs, due to transporters' inhibition by CDK4/6 inhibitors. However, there are currently no specific guidelines for the management of such DDIs, so appropriate monitoring is suggested.

Table 2 *Legend: PK parameters of SSRIs*

SSRIs							
PK parameter	**Escitalopram**	**Citalopram**	**Fluoxetine**	**Sertraline**	**Paroxetine**	**Fluvoxamine**	**Vortioxetine**
Main indication	OCD, MDD, PD, SAD, GAD	MDD	MDD, OCD, bulimia nervosa	OCD, MDD, PD, PTSD, SAD, PMDD	OCD, PD, GAD, PTSD, MDD	OCD, MDD	MDD
Most common adverse event	Nausea, Gastrointestinal disorders, Headache, Sleep abnormalities, Sexual dysfunction						
PK parameter							
Bioavailability	80%	80%	90%	44%	30-60%	53% (2-fold higher in men)	75%
Route of Administration	Oral	Oral	Oral	Oral	Oral	Oral	Oral
Dose for MDD	10 mg QD (initial) 20 mg QD (maximum)	40 mg QD	20-60 mg QD	50 mg QD (initial) 200 mg QD (maximum)	20mg QD (initial) 50mg QD (maximum)	50-100 mg QD (initial) 100 mg QD (recommended) 300 mg QD (maximum)	10 mg QD (initial) 20 mg QD (maximum)
Dosage Form	Tabs: 10, 15, 20 mg	Tabs: 10, 20, 40 mg, Oral sol: 2mg/mL	Caps: 20 mg, Oral sol: 20mg/5mL	Tabs: 25,50,100 mg, Oral sol: 20mg/mL	Tabs: 10, 20, 30, 40 mg, Oral suspension: 10mg/5mL	Tabs: 25, 50, 100 mg Extended-release caps: 100, 150 mg	Tabs: 5, 10, 15, 20 mg
Human protein binding	56%	80%	95%	98%	93%	80%	98-99%
Plasma distribution volume	12-26 L/kg	12 L/kg	20-40 L / kg	25 L / kg	3.06 L/kg	25 L/kg	2,600 L/kg
Metabolism (inhibition)	CYP2C19 CYP3A4 CYP2D6 (moderate)	CYP2C19 CYP3A4 CYP2D6 (moderate)	CYP2D6 (potent) CYP2C19 (moderate) CYP3A4 (weak)	CYP3A4 CYP2C19 CYP2D6	CYP2D6 (moderate) CYP3A4 (weak)	CYP1A2 (potent) CYP3A4 (moderate) CYP2C9 (moderate) CYP2C19 (moderate)	CYP2D6 (potent) CYP3A4/5 (weak) CYP2C9 (weak)
Major elimination route	Hepatic	Renal	Renal	Hepatic	Hepatic	Hepatic	Hepatic
Excretion	Urine	Urine	Urine	Faeces	Urine 64% Faeces 36%	Urine 85%	Urine 2/3 Faeces 1/3
Half-life time ($t_{1/2}$)	27-33 h	35 h	4-6 d	26 h	21 h	15.6 h	66 h
Substrates	P-gp	ABCB1	P-gp	P-gp	P-gp	P-gp	P-gp (poor)
References	[47-49]	[49,50]	[49,52]	[51,53,54]	[51,55,56]	[51,57, 58]	[59]

MDD: Major depressive disorder; OCD: Obsessive-compulsive disorder; PD: Panic disorder; PTSD: Post-traumatic stress disorder; SAD: Social anxiety disorder; PMDD: Premenstrual dysphoric disorder; GAD: Generalized anxiety disorder; PE: Premature ejaculation; h: hours; d: days;

Among SSRIs, fluoxetine, sertraline and paroxetine are the ones that are weak inhibitors of CYP3A4. *(Table 2)* Therefore, in terms of metabolism, they are considered relatively safe candidates, compared to other SSRIs that are moderate or potent CYP3A4 inhibitors. However, all three of them are highly bound to plasma proteins, and therefore, as stated above, caution is recommended when co-administered with abemaciclib (in the latest case, paroxetine, may offer a safer option due to the lowest affinity with plasma proteins, compared to sertaline and fluoxetine). Moreover, all of them are substrates for drug efflux proteins, and thus co-administration with drugs that

inhibit P-gp activity, like CDK4/6 inhibitors, may lead to increased bioavailability and therefore risk of toxicity. Another interesting point that could influence the SSRI selection, relates to their half-lives. More specifically, fluoxetine has a long half-life, prolonging the time to reach steady-state plasma concentrations. This should be taken under consideration in cases that require a more rapid therapeutic outcome. To sum up, fluoxetine, sertraline and paroxetine seem to be a good combination with CDK4/6 inhibitors, with paroxetine offering the safest option in case of abemaciclib. On the other hand, duloxetine is the only SNRI that is not metabolized by CYP3A4, being a reasonable candidate for co-administration with CDK4/6 inhibitors. As mentioned above, although there is insufficient data regarding the significance of such interactions, co-administration with abemaciclib should be monitored, due to high binding of duloxetine with human plasma proteins and potential need for dose titrations. Similarly, the effect on P-gp cannot be predicted, since both CDK4/6 inhibitors and duloxetine exhibit inhibitory potential on this transporter.

Table 3. *PK parameters of SNRIs*

SNRIs					
PK parameter	**Venlafaxine (prolonged release)**	**Venlafaxine (immediate release)**	**Desvenlafaxine (ODV)**	**Duloxetine**	**Levomilnacipran**
Main indication	MDD, GAD, SAD, PD, agoraphobia		MDD	MDD, GAD, diabetic peripheral neuropathy	MDD
Most common adverse events	Nausea, Dry mouth, Headache, Hyperhidrosis, Gastrointestinal disorders			Nausea, Headache, Dry mouth, Somnolence, Dizziness	Suicidal thoughts, Nausea, constipation, hyperhidrosis, insomnia
PK parameter					
Bioavailability	40-45%	40-45% (slower absorption rate)	~80%	~50% (range 32-80%)	92%
Route of Administration	Oral		Oral	Oral	Oral
Dosage form	Caps: 37.5, 75, 150 mg	Tabs: 37.5, 50, 75 mg	Caps: 25, 37.5, 50, 75, 150 mg	Caps: 30, 60 mg	Caps: 20, 40, 80, 120 mg
Dose for MDD	37.5 mg QD (initial) 75 mg QD (recommended) 225 mg QD (maximum)	75 mg QD (recommended) 375 mg QD (maximum)	50 mg QD (recommended) 200 mg (maximum)	60 mg QD (recommended) 120 mg (maximum)	20 mg QD (initial) 40 mg (recommended) 120 mg QD (maximum)
Human protein binding	27%		30%	96%	22%
Plasma distribution volume	4.4±1.6 L/kg		200-300 L/kg	1620–1800 L/kg	387-473 L/kg
Metabolism	CYP2D6 (potent) CYP3A4 (weak)		CYP3A4 (weak) CYP2D6 (weak) CYP2C9	CYP1A2 CYP2D6	CYP3A4 (potent) CYP2C8 CYP2C19 CYP2D6 CYP2J2
Major elimination route	Hepatic		Hepatic	Hepatic	Renal
Excretion	Urine 87%		Urine 69%	Urine 72%	Urine 58%
Half-life time ($t_{1/2}$)		5±2 h	9-11 h	~12 h (8-17 h)	~12h
Substrates	P-gp BCRP		Not P-gp substrate *in vitro*	Dose-dependent P-gp inhibition	P-gp
Food effect	With food	With/without food	With/without food	Without food (delays absorption)	With/without food
References	[60, 61]			[31,62,63]	[64]

ODV: O-desmethylvenlafaxin; BCRP: breast-cancer resistance protein

Another major concern is associated with the pharmacodynamic interactions between the drug classes under discussion and mainly their effect on QTc interval. Among all SSRIs and SNRIs citalopram and escitalopram present a known risk of TdP.[40] Additionally, co-administration of CDK4/6 inhibitors (especially ribociclib) with other drugs that prolong QTc is discouraged and/or there are clear recommendations for close monitoring in case that the concomitant medication cannot be discontinued or replaced. Consequently, citalopram and escitalopram may not provide a safe option, especially with ribociclib. Moreover, it should be noted that a thorough medication history should be obtained throughout the course of treatment with CDK4/6 inhibitors, for the identification of other drugs that may have an additive effect in QTc prolongation.

Conclusions

DDIs and their potential impact on drug safety and/or efficacy should be a matter of great significance, especially when treating cancer patients. Despite that our knowledge on clinically meaningful drug interactions is limited, due to the lack of dedicated clinical trials, we tried to summarize and elucidate current evidence on the safe co-administration and potential DDIs between CDK4/6 inhibitors and two major classes of anti-depressants (SSRIs and SNRIs). Sertraline and paroxetine (SSRIs) and duloxetine (SNRI) seem to display relatively safer profiles compared to other SSRIs and SNRIs, when co-administered with CDK4/6 inhibitors.

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Review Article

The Role of Epidemiology in Health Technology Assessment and Reimbursement of New Medicines: A Review

Short title: Epidemiology and health technology assessment

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Abstract

Objectives. After a medicinal product has been licensed, national health technology assessments (HTAs) are performed to ensure patients have affordable access to new treatments. However, little is known about the role of epidemiology in this phase. Therefore, the aim of this review is to summarize the impact of epidemiology on the HTA process, up until the final determination of the new drug reimbursement prices.

Material and Methods. A literature review was conducted to identify the criteria, data sources, and reimbursement procedures used by various international and European HTA bodies.

Results. Epidemiology is a vital component of both economic and clinical assessments of innovative drugs. It plays a crucial role in several stages of the HTA process, including: a) determining which health technologies will be assessed, b) providing information on the disease burden and unmet medical needs, and c) uncovering the economic worth of the product and projecting the financial effects of launching it in the market. d) ascertaining the conclusive confidential reimbursement amount by means of negotiation. The HTA process utilizes epidemiological data, obtained primarily from national representative databases containing real-world data, which is often hard to access, particularly in certain countries.

Conclusion. Epidemiology serves as the foundation for the economic and clinical evaluation of cutting-edge medicines during the HTA phase. To guarantee the dependability of the evaluation, epidemiological information sourced from national representative databases should be employed.

Keywords: epidemiology; reimbursement; health technology assessment; innovative drugs; real world data

Introduction

The etymology of 'Epidemiology' derives from the Greek words epi (upon), demos (the people), and logos (study of what befalls a population).[1] The field investigates the frequency of disease occurrence in a population (descriptive epidemiology) and the underlying determinants (risk factors) impacting this frequency (analytical epidemiology).[2,3] These determinants encompass natural, biological, social, cultural, and behavioral factors. Epidemiology is a fundamental science of public health that seeks to control health issues and prevent diseases.[2,3] It provides comprehensive details about disease and health events, such as diagnosis, at-risk individuals, place and time of occurrence, causes, risk factors, transmission, consequences for the population, and the likelihood of risk escalation or mitigation.[4]

The importance of epidemiology in shaping health and public policy through evidence-based healthcare policymaking is becoming an increasing evident.[5] At each stage of the healthcare policy-making process, epidemiology plays a significant role.[6] In terms of assessing population health, epidemiology can aid in identifying the actual health requirements or dangers of a group, assessing the overall impact of health issues and their socioeconomic implications on society, and identifying disparities in health. Additionally, epidemiology can aid in assessing the effectiveness of interventions. When it comes to shaping healthcare policies and putting them into action, one can offer guidance in establishing objectives for preventing illnesses, simulate the effects of different interventions on the general health of the population, and furnish an impartial foundation for selecting which options are most worth pursuing, all of which are critical for effective implementation. Additionally, with respect to assessing the effectiveness of policies, it can aid in devising a systematized means of tracking health issues and identifying areas, where healthcare services may be deficient, allowing for better planning and the enhancement of present initiatives.[6]

In the pursuit of pharmaceutical and biological products, epidemiological investigation plays a crucial role. From the initial stages of research and development to authorization and post-marketing activities, epidemiology is an integral part of drug development, characterized by considerable expenses and time investment.[7]

The pharmaceutical industry employs epidemiologic research to identify medical needs that are not met and

to gain insight into the burden of a targeted disease, which is manifested through mortality and morbidity rates, among other indicators. Companies also gather post-marketing safety data deemed necessary by regulatory authorities. In addition, epidemiological data is used by pharmaceutical firms to stimulate regulatory approval, particularly for rare conditions that are typically investigated through single-arm trials. In such cases, data from those trials are compared to information contained in existing databases (known as "historical controls") in order to derive a measure of the relative efficacy of the new product.[8-10] Nevertheless, once a medicine has been licensed, national health technology assessments (HTAs) are conducted to ensure that patients have affordable access to the new drugs.

Our aim in this narrative review is to present the role of epidemiology in the HTA and reimbursement of a new medicinal product, as no published work has explored this topic yet to our knowledge.

Material and Methods

To investigate the criteria, data sources, and reimbursement processes used by various international and European HTA bodies, a literature review was carried out. Relevant published material was scrutinized in both the PubMed database and Google Scholar using the keywords "health assessment technology AND epidemiology role AND/OR epidemiology effect AND/OR reimbursement procedures." A standardized data extraction form was used to extract data using these keywords, and the study followed the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines. A total of 1272 results were initially found, but after carefully selecting and applying exclusion criteria, 36 references were ultimately included in the review.

Results and discussion

The HTA process serves as an important determinant for reimbursement decisions, aiding in the efficient allocation of healthcare resources. Its primary objective is to produce greater value for money spent by evaluating efficacy systematically and transparently, safety and economic data in a biased-free and strong manner.[11] Numerous European countries employ HTA procedures in approving innovative drug therapies.[12-14] In accordance with the foundational model of the European Network of HTA (EUnetHTA), the process evaluates nine domains *(Table 1)* with the first four pertaining to clinical evaluation primarily based on global data like disease burden, allowing for a rapid assessment of new drug effectiveness.[15] The remaining five focus more on non-clinical evaluation, assessing issues such as economic, social, ethical and legal aspects associated with national frameworks.[15]

Table 1. *Parameters for evaluation according to the basic model of the European Network of HTA (EUnetHTA)*

- ❒ The health problem and current use of technology (CURRENT)
- ❒ Description and technical characteristics of technology (TECHNICAL)
- ❒ Safety (SAFETY)
- ❒ Clinical effectiveness (EFFECTIVENESS)
- ❒ Costs and economic evaluation (ECONOMIC)
- ❒ Ethical analysis (ETHICS)
- ❒ Organizational aspects (ORGANISATIONAL)
- ❒ Patients and Social aspects (SOCIAL)

  Legal aspects (LEGAL

The role of epidemiology is vital in the entire process of HTA, beginning with horizon scanning and prioritization, extending to the support of unmet medical needs, clinical and economic evaluations, and the formation of managed entry agreements that ultimately determine the reimbursement price of innovative medicines.

The prioritization and selection of health technologies to be assessed by HTA bodies are pivotal for public health. To ensure transparency, comprehension and practicality in the decision-making process, both theoretical and practical approaches have been published.[8,16] These prioritize criteria including epidemiologic indicators, such as prevalence, incidence and disease-adjusted life expectancy to identify the disease burden and unmet medical needs for the prioritization of health technologies by HTA bodies, according to literature reviews.[16-18] HTA bodies utilize various criteria to prioritize, including clinical outcomes, such as final or surrogate clinical endpoints and health-related quality of life outcomes, the presence or absence of alternative therapies, innovative value in terms of added therapeutic benefits, cost-effectiveness assessments along with budgetary impacts, and other forms of evidence, such as its placement in therapeutic protocols or potential benefits for specific sub-populations. Additionally, ethical considerations related to human dignity and necessity are also taken into account.[8, 17]

Two primary factors for prioritization in Sweden are the severity of the illness and the availability of

treatment.[17] More severe illnesses are given priority through Willingness to Pay (WTP). In Italy and Germany, "disease frequency" and "burden of disease" are explicitly or implicitly used for priority setting by HTA bodies.[19] In Canada, the disease burden and current alternatives are key criteria for prioritizing HTAs. [16]

The evaluation of a new health technology by HTA entities heavily relies on the concept of Unmet Medical Need (UMN). Recent research has classified UMN definitions into three categories: *(a) those solely influenced by the availability of other treatments, (b) those considering the disease's severity or burden in addition to alternative treatments, and (c) those encompassing three aspects – alternative treatment availability, disease severity/burden, and patient population size*.[8]

The size of patients' population depends directly on the prevalence and the incidence of the disease and usually larger population means larger UMN. However, even for small populations, an UMN might exist, especially when treatment alternatives are completely lacking and the disease is life threatening (i.e., orphan medicines).[8]

The impact of living with illness, disability, and premature death is measured by the burden of disease (BoD), which is a component of UMN.[20] BoD is quantified by the disability-adjusted life years (DALY), which reflects the difference between a life lived in perfect health and the current health status. This is measured by the number of healthy life years lost due to illness (Years Lived with Disability, YLDs) and premature death (Years of Life Lost, YLLs).[20-22] In essence, BoD combines mortality and morbidity into a single, comprehensive metric. [22]

To determine YLLs, the number of deaths from a particular disease or injury in a reference year is multiplied by the remaining life expectancy at the age of death within each age and sex group. YLDs, on the other hand, are calculated by multiplying the prevalence or incidence of a disease by the severity of disability associated with it, the duration of the disease, and its severity distribution.[20] This requires extensive epidemiological modeling and may draw on various data sources, such as patient-reported outcomes, expert opinions, and literature research. Accurate mortality data is essential for YLL estimation, whereas YLD estimation is a more complex process.[20]

It has been demonstrated from the aforementioned points that epidemiology plays a significant part in bolstering the UMN's belief that a novel medicinal product will be sufficient. Upon examination of the assessment standards employed by European HTA organizations, we have come to comprehend that the concept of burden of disease is evaluated in either an implicit or explicit manner, with unmet medical needs being one of the interpretations alongside severity and prevalence (i.e., rarity) of the disease.

Formal criteria for determining medical need vary across countries. In France, the presence of alternative therapies and disease severity are defining factors. In Germany, disease severity is included in the clinical benefit assessment. In England, unmet clinical need and availability of alternative therapies are important factors, with disease severity particularly relevant for life-extending medications for patients with limited life expectancy.[17]

In Italy, the Netherlands, Spain, and Poland, the evaluation process generally considers the severity and prevalence of the disease, as well as the availability of treatments, whether explicitly or not.[17] In Greece, the clinical benefit is a major evaluation criterion and its determination considers the severity and burden of the disease.[23] In Australia, epidemiology holds significant weight in the evaluation process and, within the context of social values, makes allowances for rare cases, where patients have no other treatment options, and their condition is expected to lead to premature death.[18]

Epidemiology plays an important role in supporting the economic value of a product across various economic domains.

Assessment of cost-effectiveness outcomes. During the HTA process, a new drug undergoes assessment of its economic value through data analysis of cost-effectiveness. This involves a comparison of two or more interventions in terms of monetary cost (€) and physical effectiveness (e.g., life years gained, reduction of blood pressure in mmHg). The resulting Incremental Cost Effectiveness Ratio (ICER) reflects the additional cost required for a patient treated with the new drug to achieve an additional level of effectiveness compared to the standard of care or an alternative therapy. This ratio is based on the calculation of the cost per unit of effectiveness gained (e.g., life year, quality adjusted life year, event avoided).[24-26] In order to establish the cost-effectiveness of a new treatment, it must be determined that the calculated ICER falls below a predetermined threshold, known as the willingness to pay (WTP) threshold. The World Health Organization (WHO) recommends a WTP threshold of 1 to 3 times the gross domestic product (GDP) per capita of the relevant country.[25,27] However, there is evidence based literature demonstrating that this WTP threshold is extremely higher for orphan drugs and end of life treatments.[28] A mounting collection of literature suggests that the WTP threshold for orphan drugs and end of life treatments is notably high. Berdud et al, research, for instance,

indicates that the proposed incremental cost-effectiveness threshold (CET) for orphan drugs is reasonably adjusted to £39.1K per QALY at the orphan population cut-off. Additionally, for ultra-orphan drugs, the adjusted CET is estimated to be even higher at £937.1K.[29]

The three criteria used to classify a drug as an orphan and assess its cost-effectiveness at a higher WTP threshold include: *(a) Treating patients with short life expectancy, usually under 24 months, (b) Providing evidence that the new treatment offers a prolongation of life of at least three months compared to the current NHS standard, and (c) Being licensed for a small patient population*.

These criteria highlight the significance of epidemiological evidence in evaluating the cost-effectiveness of medicinal products, as it is utilized to classify drugs as orphan and trigger higher WTP thresholds. NICE (National Institute for Health & Care Excellence) recognizes that the rarity of the disease plays a key role in the evaluation of orphan drugs, and it has been decided that there is an intention to pay more for rare and serious diseases.[17]

Budget Impact Analysis. Apart from cost-effectiveness analysis, budget impact analysis is usually assessed by the HTA bodies to determine the impact that the reimbursement of the new product might have on the budget of the payer for a pre-defined time horizon.[31] The framework facilitates a comparison of two scenarios. The first pertains to the current state of the market, while the second envisions the future market situation after the introduction of a new treatment. This comparison captures the percentages of newly diagnosed and existing eligible patients that the new treatment is expected to attract from the existing options. The budget impact analysis measures the ramifications of this adoption on the healthcare system. It appraises its impact on a specific target population using various epidemiological indicators, such as mortality, disease prevalence, percentage of diagnosed and treated patients, and possible side effects. Furthermore, it takes into account the data on resources used and the unit costs of any other related healthcare services. Ultimately, the total cost of each scenario is evaluated and compared to determine the fiscal implications of adopting the new treatment.[32] Budget impact analysis relies heavily on epidemiology as it provides essential indicators such as prevalence, incidence, and mortality rates which help to determine the number of eligible patients for new treatments. Other important factors include the expected number of patients to be treated and the average survival time after diagnosis, also play a critical role. To accurately estimate the eligible population over the next 5 years, projections for epidemiological indicators must be used. These projections are based on historical data and assist in determining the patterns of these indicators.

The value of epidemiology in negotiation and reimbursement. Negotiation is the final stage of the process before the final decision for reimbursement or not of the new medicinal product. The main task of the Negotiation Committee is to negotiate prices of medicines that have received a positive recommendation by the HTA Committee and inform back the HTA Committee about the agreement concluded with manufacturers (if any). The agreements are divided into financial and outcome-based agreements. Financial based agreements are related to the total cost of the new treatment either per patient or for the entire target population and the outcome-based agreements relates to the effectiveness of new treatment in daily clinical practice.[33] Epidemiology plays a dominant role in the negotiation process. The appropriate population size for the approved indication of a new drug can influence the negotiation strategy. This means different price for different population groups. The bigger the target group, the bigger discounts the drug companies ask for, and vice versa. This applies both to price-volume contracts, which are the most used financial-based contracts, and to contracts with a ceiling on medical costs (closed budgets). Therefore, knowledge of the epidemiological indicators of the disease, such as incidence, prevalence and mortality, contributes greatly to the correct calculation of the target population. Thus, given the treatment plan and recommended daily dose for the appropriate patient, the expected number of units to be sold can be estimated. This is considered as an important parameter because the deal price depends on this expected amount.[34] In performance-based contracts, particularly conditional maintenance contracts and performance-based contracts, reimbursement applies only to those patients who respond to treatment or subsets of patients. This response is measured by epidemiological indicators per patient, such as impact on mortality and survival, impact on morbidity (symptoms or worsening), safety data and, achievement of therapeutic milestones over time periods.[34]

Sources of epidemiological data for pricing and reimbursement. Epidemiological evidence certainly plays a key role in the reimbursement process. Ideally, the data needed to assess disease epidemiology should be collected from nationally representative systems with factual data that are sure to be reliable sources. Instead, incidence estimates are usually derived from

multiple real-world data sources based on what is currently available to describe the epidemiology of the disease. Real-world data is categorized into data extracted from primary sources and data extracted from secondary sources. Primary sources are classified as prospective and retrospective studies that are designed and implemented to fulfill a predefined research objective. Secondary sources include characterized databases with patient-level data developed for other purposes (e.g., medical records, electronic medical records, benefit data, laboratory/biomarker data).[35-36] Another source of real-world data might be face-to-face interviews with key opinion leaders or advisory boards. It goes without saying, that the last is the less robust method for extraction of epidemiologic estimates, but still is an option in absence of any data from other sources. In case that a specific epidemiologic indicator is available from more than one sources, with none of these being a nationally representative database, a systematic review and meta-analysis should be conducted to obtain a pooled figure after considering the quality of each available study. Finally, only high-quality studies should be taken into account to obtain a robust pooled estimation for the epidemiological data.

It is widely accepted that epidemiology is the cornerstone of the new drug development and reimbursement process, and epidemiologic data are usually obtained from real data sources. However, there are difficulties in obtaining reliable epidemiological data. First, although it is generally accepted that data collected from national health databases would be more representative and reliable, such databases are almost non-existent in most countries. Second, even when such databases are available (i.e., electronic prescribing systems, patient registries, etc.), access is limited. Third, even when national health databases exist, they are characterized by poor quality due to the lack of a standardized methodology for actual data entry and analysis.[34] There is an urgent need to develop disease-specific registries in each country. The development and appropriate use of treatment protocols by healthcare professionals could also help to reflect daily clinical practice and produce high-quality real-world data. Real-time visibility and access to all stakeholders (i.e., MAHs, regulators, public health decision makers, patient organizations) is another important tool for improvement.[35] Digitization could definitely help develop efficient, high capacity and fast database systems. The quality, quantity and validity of RWE are of the greatest importance, because they can contribute to the development of constructive and transparent discussions that lead to transparent and comprehensive decisions about the rational allocation of medical resources not only for curative therapy, but also for prevention.

Conclusions

Epidemiology plays a central role in health technology assessment and the substitution of new drugs. It is used internationally in the stages of the evaluation and reimbursement process for new medicines, from the priority of the products to be evaluated to the final confidential price of those products. Access to National Health Service databases is necessary to obtain representative and reliable epidemiological data to facilitate the HTA process. Their development and use require excellent planning, dedicated well-trained staff and budget, and good cooperation between all stakeholders.

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