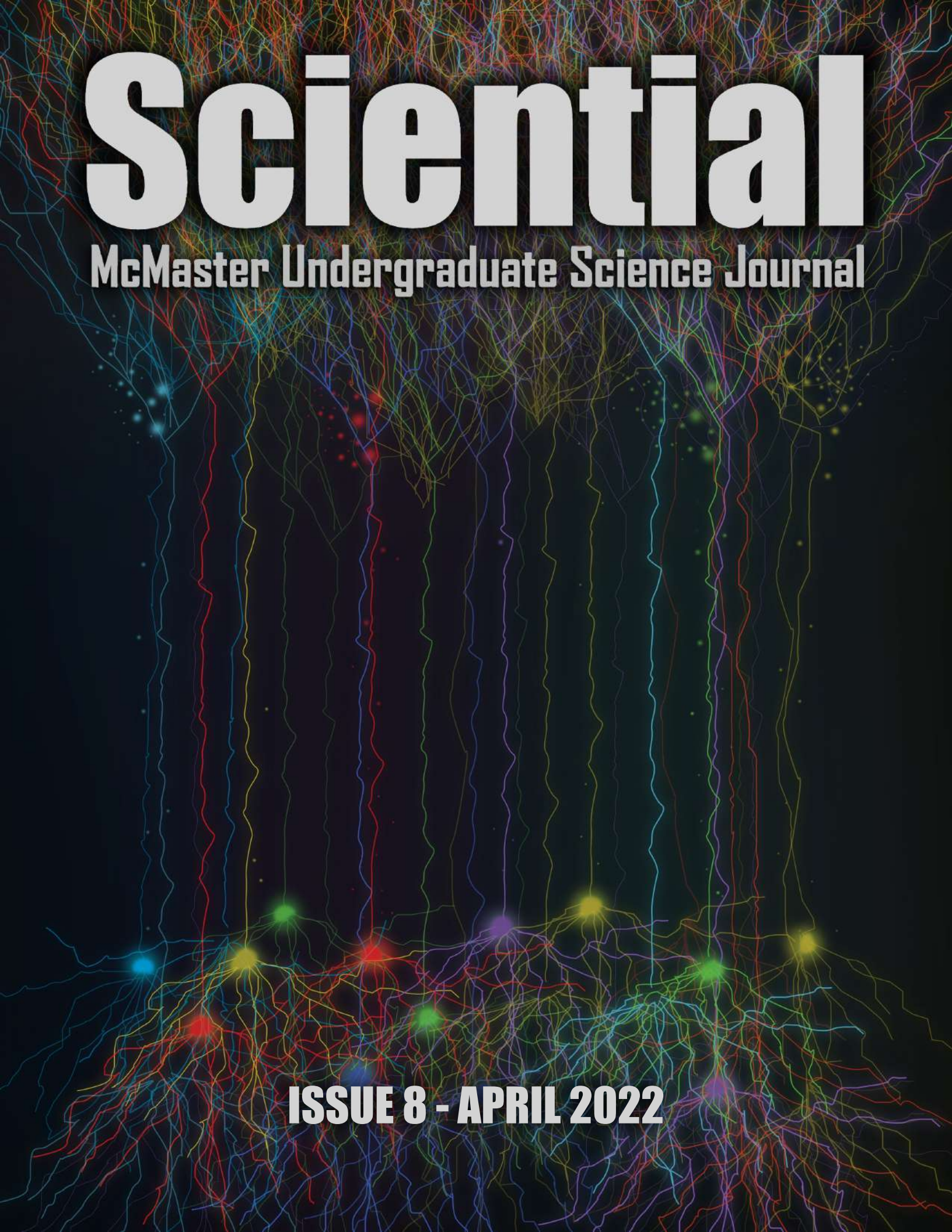
Sciential

McMaster Undergraduate Science Journal



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DEAR READER,

Welcome to Issue 8 of Sciential! As mentioned in the last few issues, the COVID-19 pandemic has made it difficult for people to gather and collaborate. It has also demonstrated and reinforced the importance of effective science communication and fostering a more scientifically literate world. Despite these conditions, at Sciential, we have committed ourselves to sustaining the collaboration that the journal generates and to continuing our responsibility of communicating science effectively.

Like all our issues, Issue 8 explores a variety of topics: the gender and sex differences of cardiovascular health; neuron potentiation; the feasibility of preventing aging; black hole thermodynamics; male body dysmorphia; non-small lung cell carcinomas; and the lack of accessibility in scientific lay summaries. We are excited to present to you the incredible work that undergraduate students at McMaster University have produced in these interesting research areas and disciplines.

We would also like to take a moment to congratulate and thank our incredible team for their unwavering commitment and phenomenal work on this issue. To our Senior Editors, Dalen Koncz and Lavanya Sinha, thank you for constantly upholding the standard of the journal and the work that we publish. A special thank you goes out to Angelina Lam and the rest of the Creative Board for their always extraordinary work ethic. Finally, to our editors, a thank you must be extended to recognize their dedication to ethical and proficient editing.

The upcoming school year will see a new executive team at Sciential! We are excited to announce the new Editors-in-Chief, Cynthia Chung and Mariyam Mohammed, and the new Senior Editors, Zahra Ridha and Samini Hewa. We strongly believe in the ability of these individuals to progress the journal and continue the amazing work that has been done here at Sciential since its inception.

As always, we would like to recognize Aiman Shahid and Alisa Nykolayeva, the founders of Sciential, our Senior Advisor Team, Dr. Kimberley Dej, Dr. Veronica Rodriguez Moncalvo, Dr. Katie Moisse, and Science Librarian, Abeer Siddiqui. Without these individuals, Sciential would not exist and neither would the incredible opportunities that it provides to all of McMaster University's students.

Being Editors-in-Chief in our graduating year was an experience that we are both so grateful and thankful for. We have met and collaborated with so many amazing people and we have learned so much along the way. Once again, we hope you enjoy Issue 8 of Sciential, McMaster's Undergraduate Science Journal!

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ORIGINAL RESEARCH OPEN ACCESS

Health in Bite Sized Pieces - Discovering Lack of Accessibility and Engagement in Lay Summaries

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SUMMARY

Lay summaries are a series of short paragraphs (100-350 words in total) that summarize all parts of a research manuscript (including introduction, methods, results, discussion, and conclusion) in a concise way that is accessible for lay audiences to comprehend. They are typically written by the authors of the manuscript. Lay summaries are essential for journalists, non-experts, and patients who wish to learn more about their health through the literature. This study observes how accessible and engaging lay summaries are in the field of medical sciences. Five lay summaries were collected and analyzed from four different journals and were graded based on a customized rubric. Hence, a total of 20 lay summaries were collected and analyzed. The average score in section four of the rubric for all journals—which assessed accessibility and engagement of these lay summaries—was 1.5 out of 5. These low scores can be detrimental because they can hinder reader comprehension. Implications of this study are that it will provide awareness such that authors consider writing more accessible and engaging lay summaries. A limitation of this study is the small sample size, which limits the results found to only the lay summaries analyzed.

ABSTRACT

The purpose of lay summaries is to summarize a research manuscript in a concise, accessible, and engaging manner for any reader to comprehend. This study seeks to analyze the amount of engagement and accessibility in lay summaries as part of medical research manuscripts. In this study, we analyzed a total of 20 lay summaries, five from each of the following journals: Elife, Multiple Sclerosis and Related Disorders Journal, Epilepsy and Behavior Case Reports (EBCR), and the Journal of Hepatology. One grader marked all the lay summaries using a customized rubric. The lowest average scores for all journals were 1.5 out of 5 in the accessibility and engagement section of the rubric. The average total scores between Elife and EBCR and Elife and the Journal of Hepatology were both significant and were 5.1 and 6.7 marks different, respectively. The results from this study indicate that the accessibility and engagement of lay summaries are not as adequate as they should be in the field of medicine. An implication of this study is that it will provide awareness and bring these undiscovered issues into light so that authors may consider writing lay summaries that meet the needs of their audience. A limitation to this study is the small sample size.

Keywords: Lay summary, engagement, accessibility, science communication, score

INTRODUCTION

Lay summaries are critical for conveying scientific research to the general public. They are a series of short paragraphs that are generally 250-300 words in total.[1] Lay summaries summarize all the parts of a research manuscript in a way that is accessible for any member of the public to comprehend, regardless of their scientific background.[1,2] Lay summaries differ from research abstracts in that they are designed to be engaging and accessible.[1] Accessibility refers to the ease that one can comprehend text, while engagement refers to how the writer interacts and keeps the audience interested throughout the piece. Although the origin of lay summaries is not entirely clear, Elife announced that its first lay summary was written in 2012 (Figure 1).[3] Elife is a scientific journal that houses peer-reviewed manuscripts.[4] In 2015, Elife staff brainstormed ways to engage the authors of manuscripts in creating lay summaries by running a pilot study of 100 authors who were offered to write lay summaries (Figure 1).[3] This pilot study was deemed successful as 79 out of the 100 authors submitted a lay summary.[3] By 2016, there was a pileup and rush to create lay summaries for Elife, possibly due to the increased awareness with re-

spect to the importance of lay summaries (Figure 1).[3] Consequently, Elife decided to select 60 manuscripts per month based on both topic and author enthusiasm to write a lay summary for Elife.[3] As of 2018, Elife has over 3,000 lay summaries published on their website (Figure 1).[5] There was no history found on the origin of lay summaries provided for Elsevier, which is a different scientific journal domain. However, despite the lack of history for Elsevier, it can be predicted that it follows a similar timeline to Elife's history. There was also no history found on the first lay summary or knowledge translation.

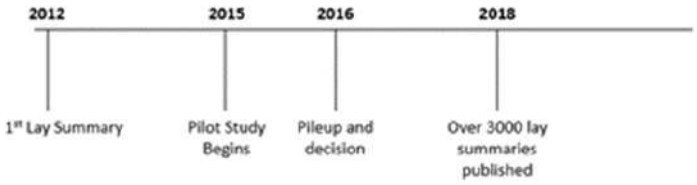


Figure 1. History of Elife Lay Summaries. The image above is a timeline depicting the dates to which the lay summaries evolved on Elife's website.[3]

Rationale Behind Lay Summaries

Funding is a big part of writing lay summaries because it allows for more lay summaries to be published as part of research manuscripts. The Canadian Institute of Health Research (CIHR) is involved in providing grants to research studies.[6] The CIHR mandates that there be a lay knowledge translation with every research proposal before funding can be provided.[6] Having a lay summary as a part of a research proposal aids funders in understanding the significance of the research.[7] This raises the question—should taxpayers who monetarily contribute to the research have access to the research manuscript free of charge? If not, this can be a major disadvantage to the consumer as they would not be able to reap the benefits of what they have contributed to. In November 2021, the 41st conference for the United Nations Educational, Scientific, and Cultural Organization (UNESCO) was held. In the conference, it was mentioned that science is more efficient in improving reliability and reproducibility when open, clear, collaborative practices among scientists are coupled with accessibility and accuracy.[8] These aspects go hand in hand to impact decisions and policy formation.[8] This was especially evident during the COVID-19 pandemic, when access to scientific knowledge was needed more than ever to form evidence-based decisions. One such example was choosing whether or not to get vaccinated.[8] Therefore, open access to science that is understandable for any audience can help propagate knowledge that can be essential for certain human rights.[8]

On a separate note, when authors write lay summaries to accompany their research, their papers gain more traction and visibility to the public.[9] A pilot study done by Elife has shown that only 42 out of the 300 readers of Elife lay summaries are considered lay audiences.[3] Of the 42, a small fraction of readers are patients, while the majority are retired individuals or educators.[3] The vast majority of lay audiences read lay summaries on the Elife website.[3] A possible diagnosis for this poor outreach to different audiences is that lay summaries are not physically accessible enough online for those who are in need. They are found exclusively on journal websites, which requires a specific and in-depth search string input to access. This can be justified from the feedback Elife received from participants, who stated that the lay summaries should have better online visibility, clarity in the content, and increased use of images and diagrams.[3] 89% of participants believed that other journals should also mandate lay summaries.[3]

Journal Guidelines and Nomenclature

Lay summaries help to address the questions of who/what/where/when/how/why for a given study in a way that is appropriate for any member of the public to understand.[1] One method this can be achieved is by having lay summaries use active voice rather than passive voice to ensure maximal comprehension.[1] Active voice is where the subject is carrying through with the verb, while passive voice is where the verb is being done on the subject.[10] For example, active voice is, "the researchers observed", whereas passive voice is, "it was observed by the researchers". Active voice is essential to use in science communication because it is the easiest to understand and allows the reader to be in tune with the actions of the author.[11] Elsevier notes that lay summaries should avoid jargon, run-on sentences, and awkward sentence structure.[1] Researchers have observed that jargon is a weak spot in scientific literature.[12] Even though some scientists attempt to use less jargon when writing for the public, their writing is still far from being understood by non-experts.[12] There should also be no grammatical errors to prevent distraction for the reader. Additionally, the use of positive language rather than negative language is strongly preferred. An example of this usage would be translating "no significant difference in cholesterol between groups" to "cholesterol remained constant for both groups", in which the latter is strongly preferred.[14] Since the use of positive language requires less words than negative language, positive language allows for a more direct message to the reader.[13] EBCR and the Journal of Hepatology had no guidelines for writing lay summaries, rather, their guidelines fell under Elsevier's guidelines as outlined above.

According to Elife, a lay summary should be approximately 350-400 words, whereas Elsevier recommends 200-300 words.[3] Elife guidelines suggest that language in a lay summary should be more active and

engaging rather than passive and formal.[3] Elife also indicates that lay summaries should not be viewed as creative writing pieces with imagery or poetry but rather as clear and concise.[3] Other key elements of Elife guidelines suggest that all sentences should be 35 words maximum, use verbs instead of nouns, and avoid using more than three common acronyms in total (ex. DNA).[5] Similar to Elsevier, Elife cautions authors of jargon use and complex terms that can be simplified (ex. novel versus new).[5] Elife also provides a skeleton template to follow, which includes a background (150 words), research question (75 words), important findings (100 words), who would benefit from findings, and future directions (75 words).[5] Additionally, Elife hires staff who create lay summaries based on the submission of author manuscripts.[5]

Although the different guidelines are set in place by these journals, there is no set system of quality control to monitor whether these suggestions are being incorporated. This contrasts the research manuscript, which undergoes multiple edits and reviews before publication. Arguably, the lay summary should undergo the same level of scrutiny since it is the first impression for readers who may not be well-versed in the field. If journals do decide to include a quality control system, it should be uniform across all journals so that the quality of lay summaries do not vary greatly from one journal to another.

Benefits and Importance of Lay Summaries - The Grand Scheme

Lay summaries are helpful for patients who wish to know more about their health.[14] Patient access to literature, facilitated through lay summaries, is the primary source of information that can aid them in being informed and managing their health.[14] Lay summaries can also be helpful for patients who wish to be involved in randomized controlled studies, as lay summaries help patients obtain a sense of the interventions in which they may participate.[15] Some of the journals have patients check off for, or rate their comprehension on "plain language summaries" to ensure proper science communication.[15]

Many journalists also use lay summaries to their advantage to decode complex studies and share it with the public.[9] When a research manuscript does not contain a lay summary, there can be misinformation when journalists or the public attempt to translate a study. For example, the media portrayed the use of ivermectin in treating COVID-19 as effective, but the original research had mixed results.[16] Important messages can get lost in this manner due to the complex nature of scientific language and methodology. Lay summaries are never about "dumbing it down" but rather combining professionalism, accessibility, and engagement all in one.[9] In addition, lay summaries can be of use for scientists who are experts in a certain area but non-experts in a different field. This would allow them to expand their research and expertise by allowing them to make connections between and upon other domains of science.[9] The pilot study conducted by Elife revealed that 93% of scientists who read digests in other fields found lay summaries useful.[5] The purpose of lay summaries should not be solely dedicated to those in a given field of research, but rather to obtain flexibility and reach out to other individuals with different educational backgrounds and interests.[17]

Lay summaries are typically located in areas that require subscription to the journal and cannot be shared on social media.[15] This makes lay summaries difficult to reach because it hinders the experience for patients who wish to seek information.[15] Researchers have also found that lay summaries have different titles such as "E-life digest", "patient summaries", "significance statement", lay summary, "plain language summary", "lay abstract", and "author summary".[15] This can be confusing for individuals who are attempting to find a lay summary as they are confronted with different names.[15]

Knowledge Gap

Many researchers who conduct research in the field of science communication have identified how to properly write a lay summary and recommendations to go about doing so. However, few have written about the current status of lay summaries that are currently published. Previous research that analyzed lay summaries specifically looked into their location within an online journal, whether there was free access, and who it was written by.[15] We will be expanding on their findings and assess lay summaries on their language choices, accessibility, and engagement. Our research addresses the question: how accessible and engaging are lay summaries in the field of medicine? We hypothesize that the lay summaries of the journal articles are not language accessible for the public and many articles will not meet the standards for proper lay summaries.

METHODS

For this study, the primary outcomes were to analyze accessibility and engagement in lay summaries. In order to observe these outcomes, we collected a series of 20 lay summaries. Five were from Elife, five were from Multiple Sclerosis and Related Disorders (MSRD), five were from Epilepsy Behavior Case Reports (EBCR) and five from the Journal of Hepatology. MSRD, EBCR, and the Journal of Hepatology had the same guidelines as Elsevier. Journals and lay summaries were chosen to be used based on whether their focus is in the field of medicine. After the lay summaries were collected, they were read and graded based on a custom designed rubric, as shown in Figure 2. One

researcher was responsible for grading all 20 lay summaries. Throughout the grading process, comments about spelling, grammar, and jargon were made, as denoted in Figure 2. Errors in the lay summaries were highlighted using the "add a comment" feature on a Microsoft Word document. An overall summary by the grader was included after grading the lay summary. After the individual sections were graded, a total score was calculated. Half points were given if a lay summary met half the criteria of one level, and half of the criteria of a higher level. In addition to using the rubric, the location and title of the lay summaries were noted. Microsoft Excel was used to tabulate the graphs by calculating the average, Q1, median, Q3, and range for each section of the rubric for each journal in Figures 3 and 4. Figure 4 was created using a boxplot for the total score of each journal. GraphPad was used to determine normality and significance. A one-way ANOVA was used to display significance while the Kolmogorov-Smirnov test was used to show normality for all four journals. The alpha value used was 0.05.

Content	Level 5 5 points	Level 4 4 points	Level 3 3 points	Level 2 2 points	Level 1 1 point	Criterion Score
Did you accurately summarize the study methods, results and conclusions?	You excelled at this task, providing information that was consistently on-point.	Your summary is mostly accurate but sometimes ambiguous.	Your summary is mostly accurate but incomplete, introducing the potential for confusion.	Your summary raises multiple questions or lacks focus and was difficult to unpack.	Your summary contains multiple inaccuracies.	/ 5
Did you accurately summarize the study rationale, implications and limitations?	You excelled at this task, providing information that was consistently on-point.	Your summary is mostly accurate but sometimes ambiguous.	Your summary is mostly accurate but incomplete, introducing the potential for confusion.	Your summary raises multiple questions or lacks focus and was difficult to unpack.	Your summary is off-point.	/ 5

Style	Level 5 5 points	Level 4 4 points	Level 3 3 points	Level 2 2 points	Level 1 1 point	Criterion Score
Is your writing clean, clear and logically organized?	Your writing is free of typos and grammatical errors and easy to follow, with smooth transitions that carry your reader from one thought to the next.	Your writing is clean and your sentences are strong, but the overall organization could be improved.	Your writing contains one typo, grammatical error, confusing sentence or awkward transition or it lacks some clarity in terms of sentence structure and organization.	Your writing contains more than one typo, grammatical error, confusing sentence or awkward transition.	Your writing has multiple mistakes or minimal flow.	/ 5
Is your writing tailored to its audience and purpose?	Your writing is a joy to read. You make complex concepts relatable and consider your audience from start to finish, in terms of the language you use and the organization of your thoughts.	Your writing is accessible and contains elements that will engage your audience.	Your writing is generally accessible and contains at least one element aimed at engaging your audience, but some parts fall flat.	Your writing is generally accessible but it lacks elements that will engage your audience and keep them reading from start to finish.	Your writing contains words or descriptions that are inaccessible to your audience or may bore them.	/ 5

Figure 2. Customized rubric based on a culmination of guidelines from a vast array of journals. The rubric shown above was created by Dr. Katie Moisse and used when grading the lay summaries. This is the same rubric used to grade student lay summaries in science communication courses in the Faculty of Science at McMaster University. The rubric is divided into two sections – content and style. There are two sub sections within both content and style which outline the accuracy in the content section, and engagement and accessibility in the style section.

RESULTS

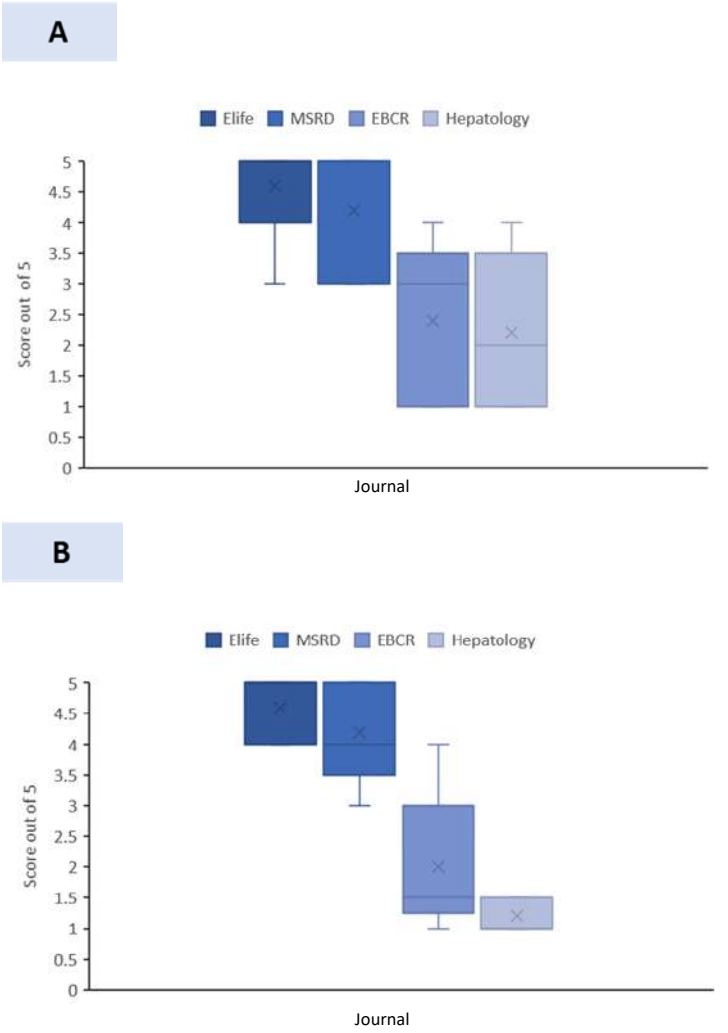
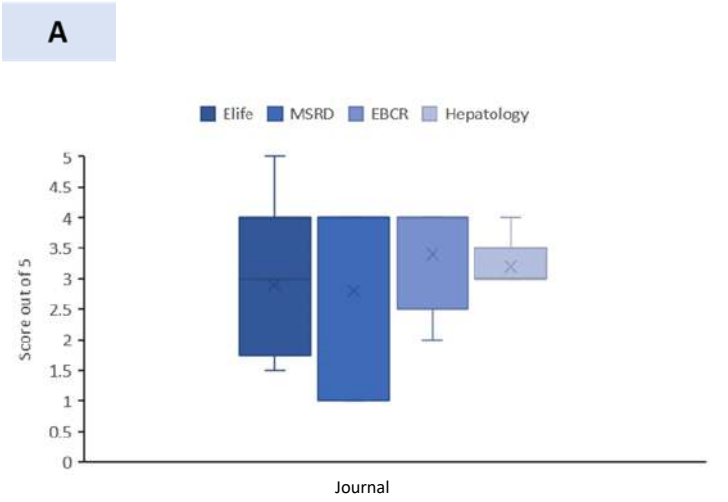


Figure 3. Scores out of 5 for section one and two of the rubric. The data in the graphs above was articulated by tallying the scores for each section of the rubric, then using Microsoft Excel to compute a boxplot. 5 lay summaries were selected from each journal. A. Section one: accuracy of methods, results and conclusions. B. Section two: accuracy of rational, implications, and limitations.



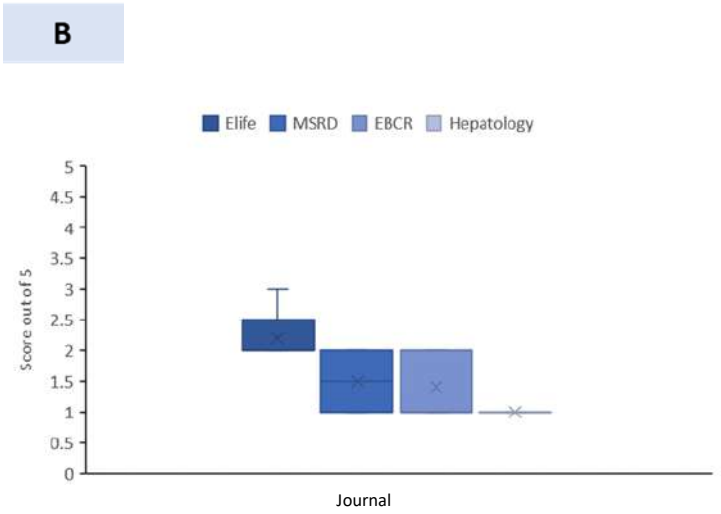


Figure 4. Scores out of 5 for sections three and four of the rubric. The data in the graphs above was articulated by tallying the scores for each section of the rubric, then using Microsoft Excel to compute a boxplot. Sample size used was 5 articles for each journal. Section three A was sentence structure, grammar and organization, and section four B was accessibility.

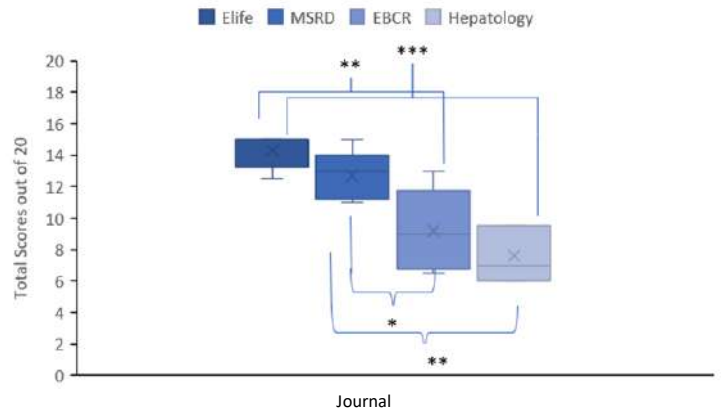


Figure 5. Total score out of 20 for each journal. The data shown above was found by totaling each lay summary from each journal. Microsoft Excel was used to tabulate the boxplot. Sample size used was 5 articles for each journal. The alpha value used was 0.05. The graph was noted with * if p-value < 0.05, ** if p-value < 0.01, and *** if p-value < 0.001. GraphPad was used to determine statistical significance.

In this study, we looked at four journals: Elife (n=5), (MSRD) (n=5), (EBCR) (n=5), and Journal of Hepatology (n=5). These were analyzed based on the rubric as outlined in the methods. In terms of the accuracy of methods, results and conclusions within section one of the rubric (Figure 3A), it appears that many lay summaries left out important sections such as the methods. Some of the results sections were also lacking. This is especially seen for EBCR and Journal of Hepatology since they both had low means of 2.4 out of 5 for EBCR and 2.2 out of 5 for Journal of Hepatology (Figure 3A). This section of the rubric had the same Q3 (5 out of 5), and the highest mean scores for Elife (4.6 out of 5) and MSRD (4.2 out of 5) (Figure 3A). Elife's mean score was higher than MSRD by 0.4 marks and nearly double EBCR and Journal of Hepatology. Two lay summaries out of the 20 analyzed were missing and or lacking results, while six were missing and or lacking the methods section.

For section two of the rubric, which outlined accuracy of rationale, implications, and limitations, more than half the articles from all journals were lacking information on implications. Out of all the articles, 11 were missing a comment about limitations. Elife and MSRD had the same Q3 (5 out of 5) (Figure 3B). The mean score for Elife and MSRD was 4.6 and 4.2 out of 5, respectively (Figure 3B). Q1 was greater by 0.5 marks for Elife than MSRD, 2.8 points greater for EBCR, and 3 points greater for the Journal of Hepatology (Figure 3B). The mean for EBCR and the Journal of Hepatology was 2 and 3 out of 5, respectively. Once again, the average scores for Elife and MSRD are nearly double EBCR and 1.4 fold greater than the Journal of Hepatology. Interestingly, the Q1 of MSRD (3.5 out of 5) and the Q3 of EBCR (3 out of 5) are similar (Figure 3B).

In terms of the language of lay summaries within section three of the rubric, Elife, MSRD, and EBCR had the same Q3 value of 4 out of 5 (Figure 4A). The mean scores for Elife, MSRD, EBCR and the Journal of Hepatology are 2.9, 2.8, 3.4, and 3.2, respectively. Here, EBCR has the highest mean while MSRD has the lowest mean. Many of the MSRD articles are filled with grammatical errors. Examples found in the lay summaries included missing commas, choppy sentence structure, run-on sentences, inappropriate capitalizations, repetition of words, and misuse of acronyms. Specifically, a lay summary done by Yoon & Cheong (2018) toggled between using dimethyl fumarate and its acronym (DMF) throughout the summary.[18] Notably, 70% of the lay summaries analyzed had at least one grammatical error. Another example of non-accessible grammar use is seen in the summary by Pommerich et al. (2018), where the authors use double negatives to mention the phrase, "not without limitations".[19]

Interestingly, the lay summaries published in MSRD exhibited more grammatical errors and sentence structure mistakes than the Elife journals. EBCR and the Journal of Hepatology had better grammar and sentence structure than Elife and MSRD (Figure 4A). Lay summary 7 by Thomsen et al. (2018) had the most jargon used in their lay summary.[20] Lay summary 9 by Roddam et al. (2019) had the most spelling and grammar errors, as well as poor sentence structure.[21] Lay summary 6 by Yoon & Cheong (2018) had the most sections missing in their lay summary and was lacking detail in these parts of their research manuscript.[18]

Interestingly, lay summaries 7, 9, and 6 mentioned above were all published in MSRD. Lay summary 2, written by Dahlén et al. (2021) had the best results as it had the fewest number of errors and the best sentence structure.[22] This lay summary was published on Elife.

In section four of the rubric, it appears that engagement and accessibility of lay summaries is a task that very few of the analyzed summaries have accomplished. For example, a summary from Roddam et al. (2019) in Elife used a rather causal tone such as "mental health problems" as opposed to difficulties in mental health.[21] Engagement was graded based on how the writer speaks to the reader in terms of tone, expression, and relatability. Many of the lay summaries contained a large amount of jargon in both journals. Many words and terms that have gone unexplained in these summaries include autoimmune, delirium, EEG, tissue scaffolding, and gastric ulcers, to name a few. The Elife journals had over double the jargon than the MSRD articles, but Elife's articles were more engaging. Hence, both journals had the same mean score of 1.5 out of 5 (Figure 4B). However, Elife and MSRD had half the amount of jargon in comparison to EBCR and the Journal of Hepatology (Figure 4B). The mean score for EBCR was 1.4 out of 5, and the mean score for the Journal of Hepatology was 1 out of 5 (Figure 4B). Jargon was found to take away from the summary by hindering the reader from full comprehension. The average score for all journals in section four of the rubric was 1.5 out of 5 (Figure 4B).

Overall, when comparing the average total scores between Elife and MSRD, Elife lay summaries had a higher average total score and higher score for each section of the rubric than MSRD (Figure 5). Elife's average total score was 14.3 out of 20, while MSRD's score was 12.7 out of 20 (Figure 5). Elife had an average of 1.6 more points than MSRD. The average overall score for Elife is significantly higher than EBCR by 1.55-fold (p-value < 0.01). Elife's average overall score was also significantly higher than the Journal of Hepatology, by 1.88-fold (p-value < 0.001) (Figure 5). The average overall score for MSRD is significantly higher than EBCR, by 1.2-fold (p-value < 0.05) and significantly higher than the Journal of Hepatology, by 1.67-fold (p-value < 0.01) (Figure 5). The average overall difference between Elife and EBCR, as well as Elife and the Journal of Hepatology are 5.1 and 6.7 marks, respectively (Figure 5).

Elife summaries were directly embedded in the online manuscript. Meanwhile, the MSRD, EBCR, and Journal of Hepatology lay summaries were harder to find as they were separated from its corresponding research manuscript and located on another website. The Journal of Hepatology uses the term "lay summaries", while Elife defines their lay summaries as Elife digests. MSRD and EBCR titled their lay summaries to be "100 word lay summaries".

DISCUSSION

The key findings from this study include how the scores for engagement and accessibility were 1.5 out of 5 overall. This justifies why there was a dip in the scores for section four of the rubric (Figure 4B), which was graded based on the component of engagement and accessibility. In section three of the rubric, EBCR has the highest mean (3.4) while MSRD has the lowest mean (2.8) (Figure 4A). This may be because the lay summaries for EBCR were very short, and thus there was less room for grammatical and structural errors. For Elife and MSRD, it appears that the accuracy in describing findings was better than the engagement and accessibility aspects of the rubric (Figure 3A and 3B). Engagement is an important aspect, because when absent, the reader does not feel compelled to continue to read. Knowledge retention also becomes limited.[23] In terms of accessibility, over 70% of the lay summaries used at least one jargon word that was not explained. This can lead to negative outcomes, because lay readers will not fully comprehend the science that is being portrayed. These findings contradict Elife and Elsevier's journal guidelines, which state that jargon and complex terms must be simplified.[5] As previously noted, when constructing a lay summary, it is best practice to avoid any form of jargon.[1] If this is not possible, then explaining the jargon is absolutely necessary. Seeing that lay summaries are geared to those who do not understand the field in which they read about, jargon is of little use to their audience. Cramm et al. (2017) mentions that the most important tip when writing a lay summary is to keep the audience in mind.[24]

Furthermore, over 30% of the lay summaries used passive voice which also added complexity to the science being portrayed to the reader (Figure 4A). This can be harmful to the audience because it forms a psychological barrier between the reader and the information being conveyed.[25] Another aspect of accessibility was the name and location of the lay summary on the website. The location of the Elife lay summaries were convenient and simple to find as they were embedded within the manuscript itself. Conversely, the lay summaries in MSRD, EBCR, and Journal of Hepatology were physically inaccessible, as they were difficult for patients to access (the lay summaries were on a separate webpage instead of grouped with their respective manuscript). Convenience is key for accessibility because without convenience, the summaries do not reach their intended audience. To add, the fact that Elife lay summaries were titled "Elife digests" and the Elsevier lay summaries were titled "100 word summaries" is potentially confusing for readers who may not be aware of the various names for a lay summary. In terms of sentence structure, over 50% of the sum-

maries had poor flow and sentence structure. This also impacts the accessibility of the summary for lay readers because choppy, unclear sentences can be distracting. This may lead the reader to spend extra time comprehending the piece.[26] From the findings, it appears that Elife lay summaries had significantly better overall scores than EBCR and Journal of Hepatology lay summaries (Figure 5). This could be because Elife hires staff who are trained to follow the guidelines for proper science communication in order to create lay summaries based on the authors' submission of their manuscripts.[5]

Other researchers found similar findings to our study in that the naming of the lay summary varied between journals.[15] These researchers found variations such as "plain language summaries", "author summaries", and "Elife digest".[15] Other studies have also discovered that lay summaries that have not been edited and revised to fit the intended audience received the least amount of understanding from the public.[17] Although researchers themselves may not realize that writing a lay piece is important (since 34% of scientists strongly disagree that lay summaries benefit the public), it does not mean that researchers should not create them at all.[17] A study done by Kirkpatrick et al. (2017) found that lay summaries that were edited by editors with a background in writing and science had significantly higher scores on the Flesch scale (p-value < 0.001).[17] This was compared to lay summaries written by authors with no edits or background in science communication. The Flesch reading score is calculated from a formula that takes total words, total sentences, and total syllables into a formula and assigns a score on a scale of 0 to 100. Higher scores indicate better simplicity and ease of understanding.[17] These results are similar to the findings of our study in that Elife had higher scores, likely because a trained team is responsible for creating the lay summaries.

Implications of this study are that it will provide awareness and bring these undiscovered issues into the light. In this way, authors may consider writing proper lay summaries. This may also be a turning point for journals to instill a system or quality control policy to ensure that the lay summaries published are within high standards. Limitations of this study include the fact that there was only one grader who graded all 20 of the lay summaries. This could pose a potential risk for bias in the marking. Additionally, the sample size for this study was relatively small (n=20), which reduces the generalizability of these findings. Future studies could also investigate impact factors and compare these impact factors for manuscripts with and without lay summaries. Flesch reading scores can also be calculated, which seeks to measure the ease of reading lay summaries.[17] Future studies can also evaluate how patients understand a poor lay summary with "spin" (misrepresentation of study results) versus the same lay summary without "spin".[27] This will allow researchers to see the relationship between "spin" and its impacts on reading comprehension. This study can bring awareness to authors such that they understand the need for science communication training in writing lay summaries. As demonstrated through Elife's better performance when writing lay summaries in comparison to the rest of the journals, scientists need formalized training in science communication to ensure that researchers are accurately and appropriately conveying important and impactful science.

CONCLUSION

This study sought to explore the accessibility and engagement of lay summaries within the field of medicine. The results indicate that accessibility and engagement of lay summaries are not as adequate as they should be in the field of science and medicine because the average score in section four of the rubric for all journals was 1.5 out of 5 (Figure 4B). Although the sample size was small, our findings are significant in that the average overall difference between Elife and EBCR, as well as Elife and the Journal of Hepatology, are 5.1 and 6.7 marks different, respectively (p-value < 0.01 and p-value < 0.001) (Figure 5). Implications of this study show that science communication training is needed to enhance lay summaries and encourage the publishing of lay summaries to meet the needs of patients, stakeholders, and the general population.

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The Potentiation of Cortical Pyramidal Neurons Due to the Gain of Function Mutation of Kv.4.2 Channels

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SUMMARY

Epilepsy is a disease characterized by recurrent seizures caused by abnormally high levels of activity in certain parts of the brain. High levels of activity in neurons, that is, increased neural firing rates, are commonly caused by specific genetic mutations. Several forms of therapies for epilepsy are available that broadly reduce the firing rates of neurons in the brain. These therapies are effective yet come with several side effects, such as dizziness. A targeted pharmacological intervention will reduce these side effects as it will not influence the brain in a broad manner and will aim to reduce the magnitude of the mutation's effect on the specific neurons involved in epilepsy. In 2014, a new mutation was discovered in a pair of twins suffering from seizures resistant to typical epilepsy medications. The way this mutation leads to seizures is still a mystery. This proposal aims to uncover the mechanism of action of this mutation, potentially leading to targeted pharmacological interventions to treat seizures caused by this mutation.

ABSTRACT

Kv4.2 channels are a type of K^+ channel responsible for the early repolarization phase in an action potential. In 2014, a gain of function (GOF) mutation in these channels was shown to lead to seizures. Since this mutation led to a more sustained K^+ current in the mutant neurons' repolarizing phase, it is unclear as to why it would lead to hyperexcitability rather than hypoexcitability. It has been shown that the transient silencing of glutamatergic neurons can lead to their potentiation, more specifically known as homeostatic potentiation. This proposal aims to test whether homeostatic potentiation of cortical pyramidal neurons of layer 2/3 is the underlying mechanism behind the seizures induced by this mutation. To examine this, three markers of potentiation will be investigated in pyramidal neurons of layer 2/3 in mice that are either wildtype (WT) or mutant for the Kv4.2 GOF mutation. These markers include the excitatory post-synaptic current (EPSC), spine density and the AMPA receptor density on the post-synaptic density (PSD), which should all increase after potentiation. The results of this research will reveal the mechanism behind this mutation's effects, potentially leading to the development of targeted pharmacological interventions for the form epilepsy induced by this mutation.

Keywords: GOF, Kv4.2; homeostatic potentiation, seizure, epilepsy, gain of function of kv4.2

INTRODUCTION

Epilepsy is a chronic condition characterized by recurrent seizures.[1] The majority of epilepsies originate from genetic mutations.[1] The bulk of known epilepsy mutations are monogenic mutations in different ion channels in the central nervous system (CNS).[1] These mutations often lead to neuronal hyperexcitability, leading to seizures.[1] Several unique mutations in K^+ channels have been identified as the cause of different types of epilepsy.[2] Most notably, voltage-gated K^+ channels are responsible for repolarization during the action potential (AP).[3] Hence, a loss of function (LOF) mutation in these channels will disrupt the repolarization event causing sustained depolarization, potentially leading to seizures.[4]

One subtype of K^+ channel is called Kv4.2.[5] These channels carry a transient potassium current, called the A-current.[5] The A-current is thought to be involved in the early phase of the neuron's repolarization.[6] The presence of Kv4.2 channels on the dendrites of pyramidal neurons in the CA1 region of the hippocampus of mice has been demonstrated.[7] These channels have been proven to prevent the axo-somatic backpropagation of action potentials and reduce the chance of the rapid firing of these neurons.[8]

Unexpectedly, in 2014, Lee and colleagues identified a gain of function (GOF) mutation in a Kv4.2 channel in identical twins with intractable seizures and autism.[9] Given that the Kv4.2 channels reduce the chance of rapid firing in these neurons, the discovery that a GOF mutation in the Kv4.2 channels leads to epileptic episodes, which are characterized by the rapid firing of the neurons, is quite counterintuitive.[8] They identified this mutation by performing whole-exome sequencing. They detected a *de novo* mutation in the *KCND2* gene[9] which codes for Kv4.2 channels.[10] The mutation led to the replacement of valine for methionine in the 404th position in the transmembrane S6 helix of the channel.[9] Lee and colleagues further studied this channel's kinetic properties by performing multiple voltage-clamp studies at membrane potentials ranging from -80 mV to +70 mV. These functional analyses revealed that the decay of K^+ current was significantly slower in the mutated channel compared to the wildtype (WT).[9] These results revealed that the Val404Met mutation significantly slows down the K^+ current inactivation leading to a sustained K^+ current.[9] There are currently two competing theories that attempt to explain these unexpected results.[2]

The first explanation relies on the discovery made by Paul and colleagues that the chandelier cells have high levels of expression of Kv4.2 channels.[11] Chandelier cells are interneurons that provide GABAergic input to the axon initial segment (AIS) of pyramidal neurons.[12] A GOF mutation in Kv4.2 channels in chandelier cells can lead to their hyperpolarization and reduce their GABAergic output to pyramidal neurons.[2] This can lead to abnormally high AP firing rates from the excitatory pyramidal neurons.[2] However, the pyramidal neurons also carry the same Kv4.2 GOF mutation as the chandelier cells. Consequently, the hyperpolarizing effects of this GOF mutation in the pyramidal neurons should, to some extent, counteract the reduction in the GABAergic input from the chandelier cells.

An alternative explanation relies on a phenomenon called homeostatic plasticity, which is the response of a neuron or a network of neurons to internal and external stressors to re-establish their baseline activity.[13] Studies show that the transient silencing of glutamatergic neurons can lead to compensatory responses that mimic long term potentiation (LTP).[14] For example, in 2013, Lambo and Turrigiano demonstrated that monocular deprivation of Long-Evans rats leads to the net potentiation of synapses deprived of the signal from the affected eye in area $V1_a$ and $V1_b$ of the primary visual cortex.[15] Interestingly, by blocking the trafficking of new AMPA receptors in these neurons, this effect was significantly reduced and even entirely disappeared in some cases.[15] This finding suggests that the mechanism underlying the homeostatic plasticity of glutamatergic neurons have some similarities to the process of LTP.[15] The cellular mechanism underlying this form of homeostatic plasticity may involve calcium-dependent sensors. These can sense the neuron's firing rate and adjust the trafficking of receptors to the synapse accordingly and change the protein expression profile of the neuron.[14] This is further evidence for the similarities between this form of homeostatic plasticity and LTP.[15]

The excitatory synapses onto the GABAergic neurons can also potentially undergo potentiation because of this mutation. This would reduce the effect of the potentiation of the cortical pyramidal neurons. However, it can be speculated that the potentiation of pyramidal neurons is having a higher influence due to the clinical presentation of this mutation. Since the mutation leads to generalized seizures, the potentiation of the GABAergic interneurons is either absent or outweighed by the potentiation of the cortical pyramidal neurons. This could partially be due to the fact that GABAergic interneurons make a small proportion of all the cortical neurons (10-15% in rodents).[16]

Considering the evidence, it can be expected that homeostatic plasticity is the underlying mechanism of the role of the GOF mutation in the Kv4.2 channels in epilepsy.[2] Since the GOF mutation itself would initially lead to hypoexcitability of the pyramidal neurons, a compensatory homeostatic response with LTP-like characteristics is possible. These synaptic changes could lead to hyperexcitability and uncontrollable firing of the pyramidal neurons, which could clinically present as seizures.

1.1 HYPOTHESIS

If the Kv4.2 channel GOF mutation strengthens the excitatory synapses on cortical pyramidal neurons, then the pyramidal neurons with this mutation should demonstrate significantly higher levels of synaptic potentiation compared to the wildtype pyramidal neurons.

1.2 MODEL ANIMAL

Since the Val404Met GOF mutation in Kv4.2 was recently discovered in humans in 2014, there are currently no model animals present with this specific point mutation. Also, because this mutation is a point mutation, a gene knockout technique cannot produce the desired model animal. Therefore, to perform the following experiments, mice with this specific mutation will be requested from a biotechnology company. Furthermore, Lee and colleagues demonstrated that the patients carrying these mutations were seizure free for the first two months of their lives.[9] Therefore, it can be expected that the effects of the mutations are amplified over early development. To study the role of development on the magnitude of the effects of this

mutation, all the following experiments will be done on 15 and 60-day old mice. It can be expected that the effects of the mutations will be significantly stronger in the 60-day old mice compared to WT and 15-day old mice. This prediction will be investigated by conducting all the following experiments on 15 and 60-day old mice. Therefore, there are four different animal models that will be studied per brain area.

1.3 AREA OF INTEREST

The cerebral cortex is a complex network of neurons with six distinct layers.[17] Layer II of the cortex contains small pyramidal neurons and layer III contains medium-sized pyramidal neurons that are vertically oriented.[17] Even though these two layers have discrete populations of cells, they are not easily distinguished in rodents based on their cytoarchitecture and are referred to as the pyramidal neurons of layer 2/3.[18] Due to these connections, an abnormal rapid firing in layer 2/3 can spread to other. Therefore, layer 2/3 pyramidal neurons are commonly studied for their role in seizures and their effects of monogenic mutations in pyramidal neurons. Consequently, all the following studies will be conducted in layer 2/3 of the cerebral cortex.

Since the specific locations of the start of the epileptic events caused by the Val404Met GOF are not yet identified, multiple areas of the brain must be investigated in this research. Brain slices will be taken from specific locations that are highly associated with epilepsy based on previous research. In 2005, Chabardès and colleagues showed that the anterior part of the cerebral cortex of the temporal lobe, which is also called the temporopolar cortex (Brodmann area 38), is a major site of epileptogenesis.[22] Therefore, temporal tissues for all the following studies will be collected from this area. The slices in the parietal lobe will be taken from the primary somatosensory cortex, since a study performed in 2017 by Niday and colleagues demonstrated that a dysfunction of KCNQ2 K^+ channels leads to hyperexcitability of layer 2/3 pyramidal neurons in this region.[21] The seizures that originate from the supplementary motor area (SMA) of the frontal lobe are common and have been the well documented.[23] Therefore, the frontal lobe slices will be taken from the SMA.

2.1 AIM 1

To measure EPSC amplitude in layer 2/3 pyramidal neurons with the Val404Met GOF mutation in Kv4.2 channels.

2.2.1 RATIONALE

A defining characteristic of the strengthening of synaptic function and potentiation of a neuron is an increase in the amplitude of excitatory postsynaptic current (EPSC).[24] The measurement of EPSCs is often used to evaluate whether a neuron has undergone potentiation.[20] A local pyramidal neuron and its glutamatergic target neurons can be identified by their morphological features by using infrared differential interference contrast microscopy.[21] Then the presynaptic neurons can be stimulated by a stimulating electrode and the response of the postsynaptic neurons can be recorded.

2.2.2 METHOD

A. Extracting the Tissue
   a. Both wild type (WT) and mutant animals will be kept in similar conditions. The experiment will be done on 15- and 60-day old animals.
   b. The animals will be anesthetized with diethyl ether and quickly decapitated. The brain tissue of animals will be removed. The brains will be fixed in a solution of paraformaldehyde in PBS. After fixation, 300 µm coronal sections of the layer 2/3 of the pyramidal neurons in the temporal, parietal and frontal cortex will be cut by using a vibratome. The thickness of these slices maintains the interconnected network of the neurons.[25] After slices are cut, they will be kept at 4°C in artificial cerebrospinal fluid (CSF) until they are needed for electrophysiological analysis.

B. Whole-Cell recording
   a. A local presynaptic pyramidal neuron in layer 2/3 and its postsynaptic targets will be identified in each slice based on their morphology. Since the slices are relatively thick, infrared differential interference contrast will be used to identify the target neurons.[21]
   b. A stimulating electrode will be inserted in the identified presynaptic neuron's membrane. The presynaptic neuron will be stimulated with suprathreshold pulses of current with a duration of 2-10 ms.[25] A whole-cell recording will be performed on the postsynaptic targets of the neuron. This involves positioning a small glass capillary tube onto the membrane of the postsynaptic cell, then applying suction until the membrane is ruptured. The capillary tube (i.e., electrode) will be connected to a signal amplifier, and the currents will be recorded on a computer. The recording solution of the electrode will mimic the intracellular solution of the neuron. Calcium chelators such as 1,2-bis(2-aminophenoxy) ethane-N,N,N',N'-tetraacetic acid will also be included in the recording solution to prevent the induction of LTP during the protocol.[26] The net-

work of neurons in layer 2/3 is highly interconnected with interneurons between the pyramidal neurons. The action of these interneurons can interfere with postsynaptic recordings because interneurons are indirectly excited by pyramidal cell stimulation, therefore reducing the probability of firing of the pyramidal neurons. This effect can mask the underlying EPSC. To prevent this, GABAergic transmission will be blocked by introducing a $GABA_A$ receptor antagonist called picrotoxin into the artificial CSF solution.[21]

c. To induce an AP in the presynaptic neuron, a depolarizing current will be injected into the presynaptic neuron. The EPSC in the postsynaptic neurons will be measured. This protocol will be repeated 100 times per prepared slice. A resting time of 1 second will be utilized between each recording to allow for neurons to return to their resting membrane potential. The maximum amplitude of each EPSC in all the neurons in each trial will be measured.
d. The maximum amplitude of EPSC in each trial in the WT and mutant animals will be averaged to calculate the mean EPSC. Since the aim of the experiment is to study the changes in mean EPSC as a result of two different variables (age and the allele) a two-way ANOVA will be utilized to determine if a significant difference in mean EPSC exists between the model animals. This analysis will be performed in each of the three brain regions independently.

2.2.3 EXPECTED RESULTS & LIMITATIONS

If the Val404Met GOF mutation in the Kv4.2 channels of pyramidal neurons in layers 2/3 contributes to the potentiation of postsynaptic pyramidal neurons, we would expect to see a larger mean EPSC amplitude in slices from mutant animals versus WT animals. In particular, the mean EPSC amplitude is expected to be highest in the 60-day old mutant mice.

Since slices from three distinct locations of the CNS will be collected, this study can reveal if the potentiation is localized to a specific area in the CNS. It has been shown before that there are subtle electrophysiological differences between different population of neurons.[27] However, the Kv4.2 channel seems to be widely expressed in all cortical pyramidal neurons.[28] Therefore, we do not expect to see a significant difference between the mean EPSC amplitude in different regions of the CNS within the same animal model

There are some potential limitations to this experiment. For instance, it is assumed that the presynaptic pyramidal neuron and all its postsynaptic targets can be identified by their unique morphology. Even though this was done before by Niday and colleagues in 2017, it is a difficult task due to the complexity of the network of neurons in layer 2/3. Moreover, it should be noted that the addition of a $GABA_A$ receptor antagonist removes the influence of the GABAergic input in the measurements taken in this experiment. The reason behind this step is to directly investigate the effect of this mutation on the glutamatergic neurons by eliminating some of the complexities that are present in a cortical network of neurons. Further studies can investigate the effect of this mutation in the inhibitory postsynaptic current (IPSC) induced by the GABAergic neurons to get a clear understanding of the influence of this mutation on the cortical networks of neurons.

3.1 AIM 2

To compare the dendritic spine density in layer 2/3 cortical pyramidal neurons in WT animals versus animals carrying the Val404Met GOF mutation in Kv4.2 channels.

3.2.1 RATIONALE

Dendritic spines are the main site of excitatory input onto a neuron.[29] It is expected that an increase in dendritic spine density will be observed due to potentiation. More dendritic spines will allow the neuron to receive more excitatory input, increasing its chance of firing in response to multiple stimuli.[30] For instance, in 2015, Watson and colleagues demonstrated that the density of dendritic spines significantly increased in hippocampal pyramidal neurons after LTP induction.[30] Therefore, dendritic spine density is a good marker of potentiation, and it will be assessed according to the following procedure.

3.2.2 METHOD

a. Both the WT and mutant animals will be kept in similar conditions. The experiment will be done in 15day old and 60-day old animals. The animals will be anesthetized with diethyl ether and quickly decapitated. The brain tissue of animals will be removed
b. The cerebrum of the animal will then be placed in a light-proof glass jar containing Golgi-Cox solution.[31] This is an ideal stain for visualizing dendritic spines.[31] The tissue will stay in the solution for 48 hours at 37°C in the dark.[31] 150 µm thick coronal brain sections will be taken from the three regions of interest. The tissues will be viewed under the 100x objective light microscope. The pyramidal neurons of layer 2/3 will be identified due to their morphology.
c. In each animal model 16 cortical pyramidal neurons will be randomly selected for further analysis.[32] The

total length of all the dendritic branches including the primary branches arising from the soma and the secondary subsequent branches of the neuron will be measured using the image processing program Image-J.[32]

d. Mushroom type spines (head larger than the neck), thin type spines (head smaller than neck) and stubby spines (no neck) will be counted.[32] This categorization ensures that other protrusions such as filopodia are not counted as stable spines. The number of spines will be counted by two different investigators and the average value of these two counts will be calculated.[33]
e. The mean number of spines per 10 µm will be calculated from each animal and each brain region by dividing the total number of spines per neuron by the total dendritic length. A two-way ANOVA will be performed to determine if there is a significant difference between the WT and mutant animals depending on two variables (age and allele). This analysis will be performed independently for each brain region.

3.3 EXPECTED RESULTS & LIMITATIONS

If the cortical pyramidal neurons in the mutant animal have undergone potentiation, then a higher density of dendritic spines can be expected in the mutant animal compared to the WT. Furthermore, the spine density is expected to be the highest in the 60-day old mutant mice.

The dendritic structures seem to vary between different cortical regions.[34] Therefore, differences between spine densities are expected if different regions of the CNS were compared to each other. That's why in this analysis the two-way ANOVA is performed in each region independently. Since the Kv4.2 channel is present on all cortical pyramidal neurons, it can be expected that all the three regions of interest will demonstrate the highest spine density in the mutant 60-day old mice.[28] A potential issue with this method is mischaracterizing protrusions that are not dendrites with functional, stable synapses. To combat this issue, only the thin, stubby, and mushroom-type protrusions will be counted.

4.1 AIM 3

To compare the AMPA receptor density in the PSD of the pyramidal neurons in layer 2/3 of the cortex of mutant animals vs WT animals.

4.2.1 RATIONALE

A common feature of potentiation of glutamatergic synapses is an increase in AMPA receptor density in the post synaptic density (PSD).[35] A higher density of AMPA receptors makes the postsynaptic neuron more responsive to presynaptic glutamatergic input.[35] This effect is partially responsible for the predicted results mentioned in Aim 1, as an increase in AMPA receptor density can increase the size of EPSC.[35] A method of quantifying the number of receptors in the PSD is called immunoelectron microscopy.[36] In this method, antibodies specific for a receptor can be coupled with secondary antibodies carrying electron-dense particles (such as gold particles) to reveal the targeted antigen's location.[36]

4.2.2 METHOD

A. Extracting the Tissue and Labeling

a. Both the WT and mutant animals will be kept in similar conditions. The experiment will be done in 15-day and 60-day old animals.
b. The animals will be anesthetized and intracranially perfused with paraformaldehyde, phosphate buffer and glutaraldehyde to preserve the tissue.[37] These tissue blocks will be dehydrated by the process of free-substitution with resin.[37]
c. Initially, 0.5 µm semi-thin sections will be cut from each region of interest and stained with toluidine blue (labels for acidic residues such as DNA) to orient the sample and identify the area of interest in each block.[36] Once the pyramidal cells of layer 2/3 are identified, 60 nm ultrathin sections will be cut and mounted on nickel grids.[37] Sections will be emersed in normal goat serum for 30 minutes to block nonspecific antibody binding.[37] The sections will be incubated with primary antibodies against common AMPA receptor subunits such as GluR1, GluR2 and GluR4 overnight.[37] Then the sections will be rinsed and incubated for one hour with secondary antibodies that are attached to gold particles.[37]

B. Electron microscopy

a. Electron microscopy will be started with low magnification to identify the pyramidal cells of the layer 2/3 based on their morphological futures. The synapses will be identified by the presence of presynaptic vesicles and postsynaptic density.[37]
b. The receptors will be quantified by counting the number of the gold particles which will appear as black dots located in the PSD.[37]
c. The area of PSD will be estimated by measuring the length of the PSD and multiplying it by the thickness of each section.[37]
d. By dividing the number of gold particles counted per area of PSD, the density of channels per section can be calculated.
e. A two-way ANOVA will be performed to determine if there is a significant difference between the spine density on neurons from WT and mu-

tant animals depending on age and allele. This analysis will be performed independently for each brain region.

4.3 EXPECTED RESULTS & LIMITATIONS

If the GOF mutation in Kv4.2 K^+ channels induce potentiation in pyramidal cells of layer 2/3 of the cortex, it can be expected to see a significantly higher density of AMPA receptors in the PSD of mutant pyramidal neurons. Due to the ubiquitous expression of Kv4.2 channels on all pyramidal neurons, it can be expected that all brain regions demonstrate the result described above.

This investigation will be difficult due to the high complexity of the neural network in layer 2/3 of the cortex. Since the neurons have several connections, and since GABAergic interneurons are present in this area, it is essential to narrow down the targeted pyramidal cell's dendrite before conducting electron microscopy. To achieve this, the slices will be initially labelled with toluidine blue. This step is included in an immunogold labelling guideline by Zhaong and colleagues (2013). This label allows us to orient the samples appropriately, identify the region of interest based on morphology, and cut the surrounding tissue under the light microscope.

CONCLUSION

There are currently no experiments conducted to reveal why a GOF mutation in Kv4.2 channels can lead to the rapid firing of a neuron. This question can potentially be answered with this research. This understanding can significantly advance the field of neuroscience by providing a deeper insight in the field of homeostatic potentiation. The causes and effects of homeostatic plasticity are not well understood in the cortical pyramidal neurons, especially in the context of epilepsy. The findings of this research can propose the transient silencing of neurons with an increased K^+ current as a potential mechanism that induces homeostatic potentiation on cortical pyramidal neurons. Further research can build upon the findings of this study and investigate the effects of GOF mutations in voltage gated K^+ channels in other populations of neurons, especially the subcortical structures, since they are also often involved in localized seizures.[38] Furthermore, the findings of this research will shed light on the potential impact of homeostatic plasticity on the pathogenesis of epilepsy specifically and more broadly, on the activity rates of cortical networks of neurons.

With all the advancements of modern medicine, epilepsy is a highly manageable disease that responds well to treatments such as benzodiazepines. In fact, over 70 % of patients can become seizure-free with the appropriate treatment protocol.[1] However, some of these treatments do not specifically target the affected channels and neurons. Consequently, they lead to some side effects. For instance, benzodiazepines, which are a common treatment for the management of epilepsies, can also lead to side effects such as sedation, tolerance, and addiction, to name a few.[39] Side effects can be reduced if the specific neurons and channels involved in the pathogenesis of epilepsy are targeted for treatment.

Furthermore, the seizures induced as a result of this mutation were highly resistant to treatments such as benzodiazepines.[9] Hence, this research can provide the scientific community with a deeper understanding of the pathophysiology of the GOF mutation of the Kv4.2 channels. This knowledge can further be used to design specific pharmacological tools that target the Kv4.2 channels and reverse the mutations' effects. An example of a targeted epilepsy treatment is phenytoin. It targets voltage-gated sodium channels mostly in the motor cortex, which has been shown to be a very effective treatment for tonic-clonic seizures with less side effects than benzodiazepines.[40] Designing such targeted therapies is not possible without first understanding the pathology induced by the mutation.

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An Exploration of Black Hole Thermodynamics

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SUMMARY

Black hole thermodynamics concepts, and mathematical models are often utilized to better understand the characteristics of black holes. The fundamentals of black hole thermodynamics involve the four laws of black hole mechanics and the attributes of black holes, including black hole anatomy and surrounding spacetime. One struggle in black hole physics involves quantifying an entropic value to black holes while simultaneously obeying the second and third laws of thermodynamics. To obey these laws, the generalized second law of black hole mechanics can be applied to entropy and Hawking radiation calculations.[1] Stephen Hawking's findings from his revolutionary paper, *Particle Creation by Black Holes*, have changed the field of black hole physics and are worth investigating. Using the aforementioned content, derivations for the pertinent mathematic formulae can be summarized and analyzed. Conducting an in-depth exploration of black hole dynamics, entropy, and Hawking radiation will elucidate the complex nature of black holes.

ABSTRACT

Improvements in technology have enabled researchers to study interstellar phenomena at an exponential rate. Among some of the most enticing of such marvels are black holes. As a result of extensive research and exploration, the progression of black hole thermodynamics has yielded promising interdisciplinary results, particularly in the fields of math and physics. This paper will explore the fundamental concepts pertaining to black holes, and a brief outline of the scientific contributions made by notable theorists. These concepts will be followed by an in-depth discussion concerning the characteristics of black holes and black hole radiation. Derivations of formulae relevant to Hawking radiation, black hole entropy, and classical black hole dynamics will be summarized, as these are imperative to understanding the complex mechanisms that occur within a black hole. Furthermore, these formulae will be applied to pre-existing interstellar phenomena in order to understand the significance of the theoretical concepts related to black holes. Ultimately, the derived formulae will be put to the test using real black holes. A model will also be generated in a Python environment to visually exemplify Hawking radiation for a Schwarzschild black hole. Applications of this research have proven to enhance understanding in the fields of thermodynamics, astrophysics, quantum mechanics, and mathematics. The research and development towards the thermodynamic concepts related to black holes is imperative to elucidate the fundamental laws of physics that govern the forces that occur here on Earth.

Keywords: Black hole, Hawking radiation, entropy, classical dynamics, generalized second law

INTRODUCTION

Studying the thermodynamic properties of black holes has perplexed theoretical physicists for decades. However, Bekenstein has stated that there are many similarities between black hole physics and thermodynamics worth investigating.[2] Most black holes result from a star exhausting its thermonuclear fuel. Ultimately, the unstable core collapses on itself due to intense gravitational forces, resulting in an infinitesimally small volume and infinitely large point of central density called the singularity.[3,4] Alternatively, black holes can have non-stellar origins, perhaps forming from large quantities of interstellar gas that collapse into a supermassive black hole. These black holes are theorized to be at the centre of many observable galaxies, including the Milky Way.[5] An important feature of a black hole is the event horizon, a theoretical boundary that is located outside of the singularity. The event horizon has strong gravitational forces such that it prevents all particles from escaping a black hole. Exploring features of a black hole, such as the singularity and event horizon, will be crucial to developing a holistic understanding of black hole thermodynamics as each of these factors influence particle and spacetime

behaviour.

The Four Laws of Black Hole Mechanics

This paper will explore several intriguing phenomena that occur at the event horizon. In order to analyze the thermodynamic properties of black holes, the four laws of classical black hole mechanics must be considered. These laws will be the basis for the complex theories discussed subsequently, such as black hole entropy and Hawking radiation. First, the curvature and coordinates of a black hole and the surrounding spacetime will be formulated based on theories of the event horizon. These mathematical expressions signify relationships between black hole attributes and serve as the foundation for classical black hole dynamics.

In Newtonian physics, the escape velocity v from a body with mass M and radius r, with the standard gravitational constant G, is defined in the equation below.

$$v = \sqrt{\frac{2GM}{r}} \qquad \textit{(Eq. 1)}$$

For a black hole with a Schwarzschild radius r_s, the escape velocity must be greater than the speed of light c.[6] The Schwarzschild radius is the distance from the singularity of the black hole to the surface. Thus, the previous equation can be modified to:

$$c < v = \sqrt{\frac{2GM}{r_s}} \qquad \textit{(Eq. 2)}$$

One can define a spherically symmetric vacuum metric in Schwarzschild coordinates as equation 3.[7]

$$ds^2 = \left(1 - \frac{r_s}{r}\right) dt^2 - \left(1 - \frac{r_s}{r}\right)^{-1} dr^2 - r^2(d\theta^2 + sin^2\theta d\varphi) \qquad \textit{(Eq. 3)}$$

Although it is not derived here, this function plots a line element on the surface of a Schwarzschild black hole.[7] A line element is simply a line segment on any given surface. In this equation, r_s is the Schwarzschild radius, r is the distance of the line element from the singularity, ds is the distance of the line segment, and the angles θ and φ are the standard spherical coordinates for three-dimensional space.

Any infinitesimal distance on the surface of a Schwarzschild black hole can be modeled if the angle and radius of the line element is provided. Additionally, the outlined Schwarzschild coordinates require modification into Eddington-Finkelstein coordinates as time reaches infinity at the event horizon of a black hole. This is not accounted for in equation 3. Thus, all spacetime coordinates are singularized at that location because it is the final destination for any particle. Moreover, any particle that reaches the singularity of a black hole cannot escape, and will be trapped there for the duration of its spacetime continuum. Therefore, there are no points in spacetime beyond the singularity. The equation for Eddington-Finkelstein coordinates[8,9] can then be defined as

$$ds^2 = \left(1 - \frac{r_s}{r}\right) dv^2 - 2dvdr - dr^2 - r^2(d\theta^2 + sin^2\theta d\varphi) \qquad \textit{(Eq. 4)}$$

This entails that the curvature of the black hole diverges significantly towards its center at $r = 0$, the singularity.[10]

Before proceeding with the mathematical derivations, it is pertinent to first understand the different types of theoretical black holes. Stationary black holes are ones that remain at a certain point on a spacetime plane, but exhibit rotational motion and angular momentum, J.[11] Static black holes also remain at a fixed point, but do not rotate.[11] This distinction is important as some attributes, particularly Hawking radiation, are only observed in rotating, stationary black holes.[12]

The singularity theorems proposed by Penrose and Hawking explain the origin of singularities due to intense gravitational effects at the center of black holes.[13] Given the strength of gravity in a black hole, the singularity is a point at $r = 0$ where there is an infinite gravitational well; ultimately, no matter, light, or information can escape.[10] Penrose proposed the idea of the event horizon being analogous to a trapper surface.[14] This is a surface where all vectors are nullified. Essentially, any geometric object with magnitude and direction will cease to exist after entering this trapper surface. Thus, no movement of light can occur. The nullification of vectors is analogous to the entrapment of particles. The force of surface gravity is directed orthogonal to the trapper surface, in the downward direction toward the singularity.[14] This is because any particles or light rays traveling in the direction of a black hole will gradually shift their trajectory toward the singularity.[14] The convergence of exterior light rays in the direction of the singularity is defined as the null geodesic congruence.[15]

Geodesics are curvatures of the shortest path between two points on a surface.[15] Null geodesics are the same curves traced by massless particles, such as photons, where no time is associated with the distance as the particles move at the universal speed limit.[15] They are referred to as null geodesics because a photon has no time or age associated with it as it travels at the speed of light. Therefore, null geodesic congruence is the

curvature of a photon converging towards the singularity of a black hole. In order to model the convergence, ρ, of the event horizon, the area has to be defined as a fractional rate of change, δA

$$\rho = \frac{d}{d\lambda} ln\delta A \qquad \text{(Eq. 5)}$$

where λ is the affine parameter for the null geodesics.[4,16] An affine parameter is the boundary for an arc length of a null geodesic. The change in the convergence of the congruence can be written as

$$\frac{d}{d\lambda}\rho = \frac{1}{2}\rho^2 + \sigma^2 + R_{ab}k^a k^b \qquad \text{(Eq. 6)}$$

where σ is the shear tensor, and $R_{ab}k^a k^b$ is the affine parameter.[17] The shear tensor is defined as a set of multi-linear operations applied to an object falling towards the black hole; where, the surface gravity elicits a force of tension on the material.[17] This effect is not generally observable in everyday objects as the surface gravity on Earth is rather weak, compared to that of a black hole. Given that the surface of a black hole, or any spherical object, cannot fully converge past the singularity, the surface gravity would need to diverge at this point. Here, as $\Delta R_{ab}k^a k^b$ approaches 0 while still being greater than or equal to zero. The affine parameter will still be positive, as a negative will imply a decrease in surface gravity. However, the change in the affine parameter will decrease. Therefore, as the surface shrinks, the stress tensor on any material will approach a magnitude of infinity.[17] Essentially, the surface gravity on an object falling towards a black hole will increase exponentially as distance between the object and singularity decreases. However, once the object reaches the singularity, where surface gravity is theoretically infinite, the particle will start to diverge.[7] This is because the point of singularity is theoretically the end of the spacetime continuum. Ultimately, any massive object that becomes part of the black hole singularity will have its surface gravity elicited outwards.[17] This is because the singularity is the point where all mass is concentrated. Surface gravitational field vectors only act directed towards the outside of the singularity. This explains why surface gravity converges greatly as objects approach the singularity but diverge once they are integrated into the singularity.[7]

Particle Energy in a Black Hole

Now that the gravitational principles of an event horizon have been examined, the exploration of the energy that black holes generate by absorbing particles can be initiated. The first law of thermodynamics states that energy cannot be created or destroyed; hence, the energies of particles that are absorbed by a black hole must be fully utilized.[18] The energies absorbed can be rest energy, kinetic, gravitational, or other forms. Additionally, the energy utilized by a black hole can be expended in the form of Hawking radiation. Before Hawking radiation can be explored, the understanding of the extent of energy absorption by a black hole must be considered. This will involve the conversion of mass to energy, abiding by Einstein's general relativity principles.[19] One must first define the event horizon mathematically, before an interaction between it and a particle with mass m can be explored. The event horizon is often termed the Killing vector field ξ^μ, any vectors entering the field will theoretically become nonexistent on the spacetime continuum.[20] This is due to the impossibility of a particle from exiting the black hole after entry; thus, the Killing field terminates a particle's path entirely, leaving only the historical path. Now the conserved quantity of energy for a particle of mass m can be defined as

$$E = m\dot{x_\mu}\xi^\mu \qquad \text{(Eq. 7)}$$

where E is the particle energy at the Killing field and $\dot{x_\mu} = \frac{\xi^\mu}{|\xi|}$, the Killing field vectorized.[21] The energy expression above can then be simplified to

$$E = |\xi|m \qquad \text{(Eq. 8)}$$

where the distance between the particle and the singularity tends to the Schwarzschild radius, $r \to r_s$. The energy equation above indicates that the magnitude of a Killing field is applied to the mass of the particle to determine its energy. As this occurs, the energy expended by the black hole would equate to the mass m. The Killing vector $|\xi|$ is an indication of the particle's path approaching the singularity.[20] This suggests that it has a rest-mass energy consisting of kinetic energy and gravitational potential energy. The particle will possess kinetic energy at any given point while it approaches the Killing field, and the gravitational potential energy will be experienced as it falls closer to the center of a black hole.[20] A black hole's energy extraction capabilities elucidate its potential, given that it can convert all of the energy from any particle that enters the Killing field.

For the remaining sections of this paper, the convention $G = c = k = \hbar = 1$ will be used, as this will simplify the upcoming equations. Considering these variables are constants, and the exact values are not necessary to the further elucidation of formulae and concepts.

Zeroth Law

The zeroth law of black hole mechanics is a rather

straightforward one: the surface gravity κ of a stationary black hole is constant over the event horizon.[22] This coincides with the zeroth law of thermodynamics which states that *the temperature of a system in thermal equilibrium is constant*.[18] However, this law only applies to non-rotating, or static, black holes. Black holes that rotate are unable to maintain constant angular momentums, which can skew the surface gravity and make it non-uniform along the event horizon.[23]

First Law

The first law relates the change of mass of a black hole, dM, to the change in the black hole's area dA, angular momentum dJ, and charge dQ.[24] The variable κ represents surface gravity, ω represents angular velocity, and Φ represents electrostatic potential. The relationship is given by

$$dM = \frac{\kappa}{8\pi} dA + \Omega dJ + \Phi dQ \qquad \text{(Eq. 9)}$$

This shows the first law of black hole mechanics. It relates the change in a black hole's mass to other features of the black hole.[24] This principle is analogous to the first law of thermodynamics which is a relationship between the energy of a system and the heat and work present in the system.[18] By examining the terms in this equation, it can be theorized that surface gravity plays a role in the temperature of the black hole, given that it impacts the energy of the system. Essentially, the surface gravity κ will impact the energy of the black hole system and must be altered as well.[24] For example, if the black hole were to decrease in angular momentum and virtually stop spinning, the surface gravity would increase to compensate for that energy deficiency.[24] This relationship can be deduced from the equation above as all of these variables are included in the equation, and influential to the change in mass of the black hole. The other terms in the equation signify the changes in energy that can arise due to rotation, J, and electromagnetism, Q.[24]

Second Law

The second law states that *the area of the event horizon of each black hole does not decrease with time*.[22] This also implies that the area of the event horizon of a black hole formed by the merging of two black holes would be greater than the sum of the areas of the event horizons of the two black holes that formed it. The reason for this is that the surface area of a black hole, like the entropy of a system, can only increase. This is analogous to the second law of thermodynamics, that is *the entropy of any isolated system never decreases*.[18] However, the second law of black hole mechanics is more restrictive than the second law of thermodynamics. This is since in the latter, entropy can be transferred between systems by means of heat transfer and mass flow, but since black holes cannot bifurcate, area cannot be transferred between black holes.[25]

Third Law

The third law of black hole mechanics states "it is impossible by any procedure, no matter how idealized, to reduce κ to zero by a finite sequence of operations."[22] If one were to reduce the κ of a black hole by adding particles to it, the angular momentum would increase. κ will decrease as more particles are added. Simultaneously, the mass angular momentum of the black hole will approach the critical ratio $J/M^2 = 1$ for which $\kappa = 0$. This ratio is hypothetically possible; however, it would require an infinite amount of time. This implies that a black hole's surface gravity could never reach zero.[25] This is analogous to the third law of thermodynamics, where *the entropy change for any isothermal process involving perfect crystals approaches zero as temperature approaches absolute zero*.[18] A simplified mathematical proof can be done by re-examining the first law of black hole mechanics. If there is the inclusion of additional energy E, this energy would increase the angular momentum J of the black hole, thus, reducing the surface gravity κ.[26] A black hole that is able to achieve a surface gravity of zero is defined as an extreme black hole, for which the relation between mass, charge, angular momentum is

$$\kappa = \sqrt{M^2 - Q^2 - \frac{J^2}{M^2}}, \kappa \to 0 \qquad \text{(Eq. 10)}$$

An extreme black hole would also have a temperature of 0 K. However, this is not possible because of the minute amounts of entropy that must be present in a black hole and its surroundings and is purely theoretical.[27] If surface gravity κ does tend towards zero, it is the equivalent of stating that entropy of a system tending towards absolute zero is a well-defined constant, just as the third law of classical thermodynamics states. A well-defined constant means that entropy is not increasing, which is not possible in classical thermodynamics. This showcases the analogous nature of entropy and surface gravity principles in thermodynamics. This can be seen as a comparison between entropy and surface gravity because a black hole's surface gravity is impacted by its energy, not indifferent from entropy in a classical thermodynamic situation.

Hawking Radiation

In Stephen Hawking's paper *Particle Creation by Black Holes,* he demonstrates that at the event horizon of a black hole, particles are emitted while their antiparticles are trapped in the horizon.[28] These antiparti-

cles are ultimately consumed by the black hole, thus decreasing the black hole's mass.[28] This has introduced many interesting notions about the entropy of a black hole. This emission of particles can be perceived as a photon near the horizon that splits into two waves, one with positive frequency, and the other with negative frequency. The wave with negative frequency enters the black hole and decreases the system's mass.[29] Hawking realized that black holes emit particles such as neutrinos and photons. These emitted particles are analogous to radiation emitted from a black body. Black body radiation is the thermal equilibrium radiation emitted from a body dependent on the temperature of that body. However, black hole temperature will be dependent on surface gravity, κ, given by equation below.[25]

$$T = \frac{\kappa}{2\pi} \approx 10^{-6}\left(\frac{M_{\odot}}{M}\right) \quad \textit{(Eq. 11)}$$

where T represents the temperature, κ represents the black hole's surface gravity, M_o is the solar mass, and M is the mass of the black hole. In Hawking's case, T is an analogue to the radiated particles. He also found that temperature is approximately equal to the solar mass over one million times the black hole's mass, in units Kelvin.[3] Hawking made this discovery by first considering the collapse of a Schwarzschild black hole in spacetime.[28] Next, he considered the quantum field in spacetime as time approaches infinity.[25] The calculations showed that as time approached infinity, the particles corresponding to the emissions from a black body at the Hawking temperature are given by:

$$T = \frac{\kappa}{2\pi} \quad \textit{(Eq. 12)}$$

Given that energy is lost due to Hawking radiation, the black hole must progressively lose mass. The time at which a black hole fully evaporates is proportional to M^3 and is approximately equal to:

$$t = 10^{-17}M^3 \quad \textit{(Eq. 13)}$$

This implies that a 10^{15} gram black hole would have a lifetime of about 10^{17} seconds, or approximately 3.17 billion years, while a black hole of solar mass would have a lifetime of 10^{54} times the age of the universe.[18]

The Generalized Second Law

There is great difficulty when applying the second law of thermodynamics to a black hole using classical mechanics. This was explained simply to Jacob Bekenstein during his graduate studies by his advisor John Archibald Wheeler as, "if I drop a teacup into a black hole, I conceal from all the world the increase in entropy".[30] Wheeler had thought that the matter, in this case a teacup, would disappear into a space time singularity and lose all the entropy associated with it.[25] However, Bekenstein worked around this problem and postulated the generalized second law of black hole mechanics in the equations below:

$$S' \equiv S + S_{bh} \quad \textit{(Eq. 14)}$$

$$S' \equiv S + \frac{A}{4} \quad \textit{(Eq. 15)}$$

Bekenstein defined S' as the *generalized* entropy, S as the ordinary entropy outside a black hole, and S_{bh} to be the black hole entropy.[24] When considering the generalized second law, the second law of thermodynamics is not violated as the ordinary entropy is replaced with the general entropy.

However, Bekenstein identified flaws in the generalized second law. If a box with entropy S and energy E is slowly lowered towards a black hole adiabatically, its entropy will be absorbed by the black hole fully, while the energy can be recovered as work.[31] From the second law of thermodynamics, the energy in the box can be expressed as work which means this arbitrary action acts as a Carnot cycle with 100% efficiency.[25] A Carnot cycle is the most efficient engine possible in thermodynamics and is purely theoretical. Quite apparently, this is a violation of the second and third laws of thermodynamics. However, Bekenstein proposed that if the box was lowered in a quasi-static manner, a slow enough process that maintains thermal equilibrium, the box will not get close enough to the horizon to incur the aforementioned phenomenon, meaning the generalized second law is still valid.[25]

A problem arose with the generalized second law after the discovery of Hawking radiation. To compensate for the lost energy from Hawking radiation, according to the conservation of energy and mass-energy equivalence, the black hole must lose mass.[25] However, this violates the ordinary second law of black hole mechanics, since this implies that entropy is also lost, which cannot occur in the closed black hole system.[25] But, according to the black hole entropy equation, the generalized black hole entropy would not decrease from Hawking radiation.[25] This implies that the generalized second law of classical thermodynamics holds for this scenario, but the second law of black hole mechanics does not.[25]

Black Hole Entropy

As described by Bekenstein, entropy is one of the most "abused" terms in physics.[32] By this he refers to the fact that several different measures of entropy have

been developed and utilized. However, complications still arise when applying different measures of entropy to a black hole.[32] This is because they are unrefined areas of knowledge. Some researchers even predict that it is favourable to ill-refer the entropic value of a black hole "entropy" as a more accurate description is "entropy-like quantity." This is because the exact location of a black hole's features, such as microstates and charge, are unknown.[33] Nevertheless, in order to define an entropic value of a black hole, one must look at entropy as a measure of disorder or unknown information.[32]

The first approach for a black hole entropy calculation was given by Hawking and Gibbons in 1977.[34] This calculation was analogous to the entropy term in the first law of black hole mechanics. However, this classical approximation of black hole entropy was flawed since the entropy grew too fast for the energy to be a defined value.[25] An alternative approach called entanglement entropy was then developed. This entropic calculation involves computing the trace of the density matrix multiplied by the logarithm of the density matrix as given below

$$S = -Tr\rho ln\rho \qquad \textit{(Eq. 16)}$$

where ρ is the density matrix, and S is defined as von Neumann entropy.[35] This computation alone will output a value that diverges. However, if a short distance cut-off—a regularization of the short-distance behaviour of the quantum field—is inserted, the entropy value becomes dependent on the surface area of the event horizon.[35] This is a natural approach to conclude that a black hole's entropy is proportional to its surface area. However, this formula is also dependent on the short distance cut-off which has not been explored thoroughly at this point in time.[25] The most successful calculation of a black hole's entropy is one derived from principles in the field of string theory, which is outside the scope of this exploration.[25]

In summary, assigning an entropic value to a black hole is a rather complex task. Due to varying definitions of entropy and the strange nature of black holes, this problem continues to perplex physicists and does not have a definite solution. Nonetheless, physicists such as Bekenstein have laid a foundation for the entropic value of a black hole and the understanding of this concept will only increase with time.

Black Hole Modeling

Now that the various aspects of black hole mechanics have been explored, they can be model using Python. The specific aspects that will be analyzed and modeled in this section are black hole surface gravity, entropy, temperature, and lifetime. Surface gravity is a geometric concept that has been discussed heavily in this paper.[22] Entropy and temperature closely relate to Hawking radiation and the generalized second law.[36] Lifetime is a good indicator of the evaporation process for a supermassive Schwarzschild black hole, and an interesting attribute worth exploration.[37] Note, each equation is only dependent on the mass of the black hole. All equations used for the following models are provided in the appendix. Although derivations will not be provided in this paper, the equations stem from concepts pertaining to Hawking radiation. Thus, the purpose of this section is to understand and illustrate the relationships between the mass and the various attributes being explored.

Five different black holes were included in this modeling exercise, each was significantly different in mass. These black holes vary in mass but are arbitrary in terms of astronomical location. In this exploration the blackholes at the center of the Milky Way, Andromeda, Sombrero galaxy, the Phoenix Cluster and Messier 87 were compared. Plotting these phenomena on the same graph allows for meaningful relationships with respect to the measured quantities to be derived. The values for each body were found from Georgia State University's online black hole mass database, consisting of approximated interstellar quantities.[38]

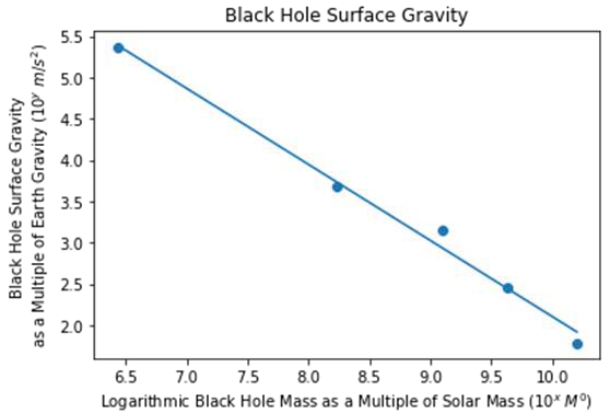

Figure 1. **The surface gravity of five different black holes as a function of solar mass multiples.**

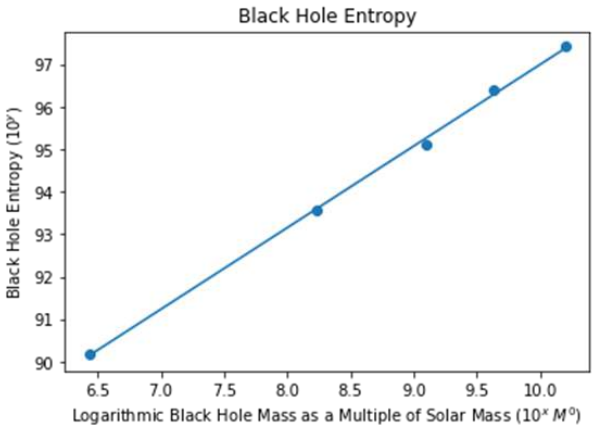

Figure 2. **The entropy of five different black holes as a function of solar mass multiples.**

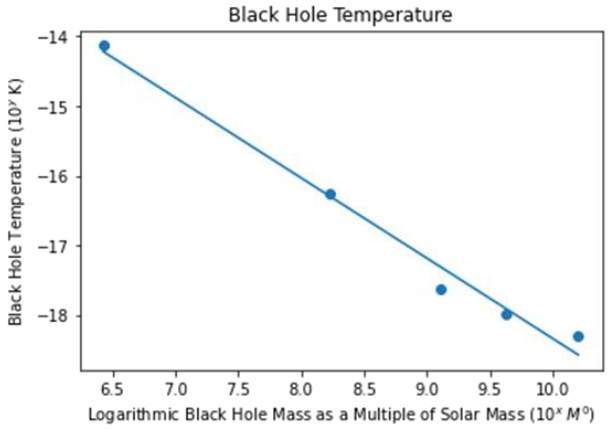

Figure 3. **The temperature of five different black holes as a function of solar mass multiples.**

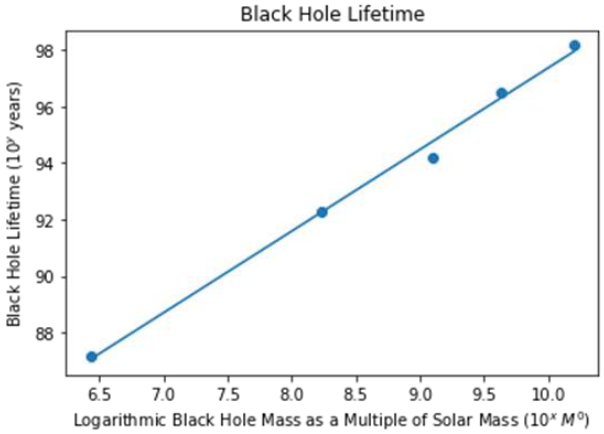

Figure 4. **The lifetime of five different black holes as a function of solar mass multiples.**

Although equations grant the ability to understand relationships, illustrations such as the plots above enable the visualization of the connections between select variables from these functions. The main trends that can be observed from the graphs above are the increase in entropy and lifetime, and the decrease in temperature and surface gravity with increasing solar mass.

Decreases in surface gravity are expected as this relationship was proven earlier in the Third Law section. As the mass and energy of a black hole increases, the surface gravity must decrease to compensate for that increase. The lifetime of a black hole increased as well, which is to be expected as the evaporation of a larger black body will take longer. The most interesting relationship exists between the entropy and the temperature. Conventional thermodynamic theory suggests that increased temperature leads to increases in entropy due to greater sums of kinetic energy distributed in a system, leading to greater degrees of disorder or randomness in the system.[18] However, the opposite appears to be true for a black hole. In order to understand this, the relationship between entropy and temperature as defined by black hole mechanics must be examined. Entropy of a black hole is proportional to the number of Planck-length-sized squares that can be accommodated in the cross-sectional area.[39] Planck length is defined as $l_P \approx 1.62 \times 10^{-35}\ m$

Given that the Planck length is a very small quantity, and how massive black holes generally are, the entropy of a black hole can reach astronomical levels. As black holes get exponentially larger, the entropy will tend towards enormous values.[32] This definition is referred to as the Bekenstein bound and was employed by Stephen Hawking when exploring the temperature for singularities of black holes.[33] Hence, it allows the separation of temperature and energy analysis from conventional thermodynamic theory. The thermal energy inside a black hole is very small as the particles are incredibly dense; hence, they are unable to move and contact one another. Rather, the particles are directed in a very linear path towards the singularity, which prevents them from interacting with one another.[24] Inability to generate movement in a random manner leads to a temperature of nearly absolute zero. As black holes absorb more matter and increase in size, the entropy will increase drastically but the temperature will continue to decrease and approach absolute zero.[25] Essentially, the temperature of a black hole follows the conventional theory of thermodynamics. But, defining the entropy is more difficult as supplemental concepts must be brought in to understand this almost paradoxical relation, and negative correlation between the two variables.

CONCLUSION

This exploration of the literature has elucidated the thermodynamic properties of black holes and provided meaningful insights on the interstellar phenomena. Mathematical equations pertaining to various black hole characteristics and using Python have been summarized and used to model important black hole features. Additionally, the discussion of relevant theories such as classical black hole dynamics, entropy, and Hawking radiation proved fruitful in the exploration of black hole activity. This review summarized the anatomy and geometry of black holes, in addition to the effects they have on the surrounding spacetime. Additionally, the event horizon, singularity, generalized second law and its connection to black hole entropy were important topics thoroughly explored in the liter-

ature. Hawking radiation and the non-zero temperature were abundant concepts in the academic literature, thus, explained in this paper. Modeling assisted in contextualizing and illustrating many of these sophisticated concepts; thus, enabling the interpretation of meaningful relationships between black hole characteristics. This was a complex undertaking, but worthwhile given the incredible discoveries made about an obscure cosmological occurrence.

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ARTICLE INFORMATION

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APPENDIX

Surface Gravity:

$$\kappa = \frac{1}{M}\frac{c^4}{4G^2}$$

Entropy:

$$S = M^2\frac{4\pi G}{\hbar c}$$

Temperature:

$$T = \frac{1}{M}\frac{\hbar c^3}{8\pi k_B G}$$

Lifetime:

$$t = M^3\frac{5120\pi G^2}{\hbar c^4}$$

ACADEMIC REVIEW OPEN ACCESS

Non-Small Cell Lung Carcinoma–A Brief Review and Discussion

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SUMMARY

Non-small cell lung carcinoma (NSCLC) is amongst the most commonly diagnosed cancers and grows throughout the tissues of the lung. This report aims to understand the epidemiology, detection methods, and most effective treatment modalities used in stage three-A NSCLC. NSCLC is an advanced type of lung cancer that grows at a slower rate in comparison to others located in lung tissues. NSCLC can be correlated to smoking cigarettes or e-cigarettes and has displayed patterns of familial aggregation. Detection methods such as low-dose spiral computed tomography provide detailed three-dimensional pictures of the chest cavity without exposing the patient to harsh radiation. Radiotherapy gives positive outlook to non-operable patients, specifically high-dose rate brachytherapy. The effects of this treatment have been explored with cell survival curves. Chemotherapy is also an effective treatment, and the chemical structure of the common drug cisplatin has been explored. Understanding the epidemiology, detection methods, and available treatment modalities help to design effective treatment and prevention plans for stage three-A NSCLC.

ABSTRACT

Lung cancer is the development of cancerous cells within the lung tissue and/or the airway that has potential to further spread. The diagnosis of lung cancer is a multifaceted issue requiring innovative approaches, detection technologies and treatments. Understanding lung cancer's epidemiology provides insight into lung cancer's high prevalence. As most are diagnosed at further developed stages, recognizing the associated factors will provide a better understanding of how to approach treatment.[1] Genetic components such as germline mutations and over expression of epidermal growth factor have been analyzed. Advancements in traditional computed tomography (CT) scanning has contributed to an increased survival rate due to the ability to locate tumours in the most discrete locations.[2] Early detection can occur using a spiral CT scan allowing physicians to perceive the lung cavity from multiple perspectives.[3] Early identification of lung cancer is critical in determining the survival of the patient. Treatments for lung cancer that are declared most effective are radiotherapy, chemotherapy, or chemoradiotherapy.[4] Brachytherapy is an emerging form of radiation therapy that provides radiation in the closest proximity. Cisplatin is the standardized agent, analyzed for its efficiency in the treatment of various stages of lung cancer.[5] This discussion will explore the epidemiology, detection methods, and one of many available treatment methods to understand therapies and prevention mechanisms for stage three-A NSCLC.

Keywords: Lung cancer, non-small cell, smoking, brachytherapy, low-dose spiral CT, cisplatin

INTRODUCTION

The development of cancer involves genetic mutations leading to the growth of tumourous masses. Tumour growth is known to be a fast-acting process. As tumours grow and begin to spread, they pose a threat to neighbouring tissues and organs. Based on the 2020 Canadian cancer statistics regarding Canadian cancer patients, the diagnosis of lung cancer is most common.[6] In addition, lung cancer has been seen to be the leading cause of the death of Canadian cancer patients.[6] The high mortality rate associated with lung cancer is reflective of its low survival rate and high diagnosis rate. A reason as to why the reported survival rate is so low may be due to the delay in detecting the cancerous cells. It has been reported that about 50% of Canadians diagnosed with lung cancer have progressed to stage three or four before detection.[6] This report will specifically focus on non-small cell lung carcinoma (NSCLC), which is the most commonly diagnosed type of lung cancer

NSCLC is a type of lung cancer that grows at a slower pace than others located in the tissues of the lung.[7,8] The major subtypes of NSCLC are squamous cell carci-

noma, large cell carcinoma, and adenocarcinoma.[8] Some common symptoms associated with the diagnosis of NSCLC are shortness of breath, chest pain, and fatigue.[7,8] When first diagnosed, NSCLC can be classified under a spectrum of five stages, which assist in gauging the first line of action. These stages have been identified as values spanning from zero to four; where stage zero indicates extremely early detection and stage four is extremely late. If a patient is diagnosed with stage zero NSCLC, it is due to the discovery of cancerous cells along the lining of the air sacs or airway of the lung; little to no spread has occurred at this stage.[9] On the other hand, a patient diagnosed with stage four NSCLC has cancerous cells in various locations in the body (lymph nodes, adrenal gland, brain, liver). This can be classified as distant metastasis.[10] It is known that patients diagnosed with stage four have a very low survival rate.[9] This report includes a brief discussion on the diagnosis of NSCLC in stage three-A. Specifically, the socioeconomic and genetic factors associated with epidemiology, spiral computed tomography scanning as a detection method, brachytherapy as a radiotherapy option with a reference to cell survival curves, and the use of cisplatin as a chemotherapeutic agent have been discussed.

1. EPIDEMIOLOGY

The frequency of lung cancer diagnosis is a battle the Canadian population has been fighting for several decades. Lung cancer is currently the leading cause of cancer death in Canada, causing approximately 83,300 deaths in 2020.[11] The most common types of lung cancer consist of small cell lung cancer, lung nodules, NSCLC, and mesothelioma.[12]Additionally, rarer forms of lung cancer are seen not to initially develop in the chest cavity but, in other locations of the body known as metastatic cancer development.[12] The Canadian Cancer Society released a report including the 2020 estimated lung cancer statistics that reports the number of new cases and deaths in the Canadian population, along with an estimated five-year survival percentage. They estimated that 15,000 males would be diagnosed, and 11,000 male lung cancer patients would pass away.[13] Further, 14,800 female cases were estimated along with 10,200 female lung cancer related deaths.[13] They estimated the five-year survival rate for males to be 15% in comparison to 22% for females.[13] As previously mentioned, the Canadian population experienced 83,300 deaths due to lung cancer in 2020, a value of approximately 60,000 deaths greater than initially projected.[13] What are the factors that contribute to a mortality rate so substantially different than projected? This review will study both the socioeconomic and genetic factors associated with the diagnosis and mortality of lung cancer amongst the Canadian population.

1.1 Socioeconomic Factors

The World Health Organization (WHO) predicts that the presence of lung cancer on an international spectrum will continue to increase with time due to the significant use of tobacco.[1] Tobacco is seen as one of the primary risk factors associated with the development of lung cancer and many other pulmonary carcinomas as a result of smoking cigarettes.[1] It is often the NSCLC subtype, adenocarcinoma, that has a strong cigarette smoking correlation. The population of tobacco cigarette smoking individuals may be on the decline, but in more recent times there has been a rise in the electronic cigarette (e-cigarette) smoking population, ultimately increasing the risk of developing this deadly disease.[14] Moreover, those who are exposed to second-hand smoke (environmental smoke) are also at a high risk of developing lung cancer.[10] There is no quantity of second-hand smoke that is deemed safe to be around.[10] Second-hand smoke is the primary associated risk factor for the diagnosis of lung cancer in non-smoking individuals.[10] There is a correlation between individuals who smoke and lung cancer diagnosis, although there are other associated risk factors that must be considered. Family history can also contribute to the development of lung cancer. Figure 1 shows a plot of former and current smokers along with the percentage of participants who had quit. An increase in the quitter percentage is apparent through the years of 1999 to 2015 but a decline is observed after 2015.[14] Additionally, the decrease in quitter percentage implies an increase in the current smokers observed in the 2017 data. The study did not clearly dictate the reasons behind why this had occurred, although participants switching to another source of nicotine such as e-cigarettes is a likely observation.[14] This theory is likely as e-cigarettes became more prevalent in Canada between the years of 2015 to 2017 along with Bill S-5 being amended in 2018 permitting for e-cigarettes to contain nicotine.[15]

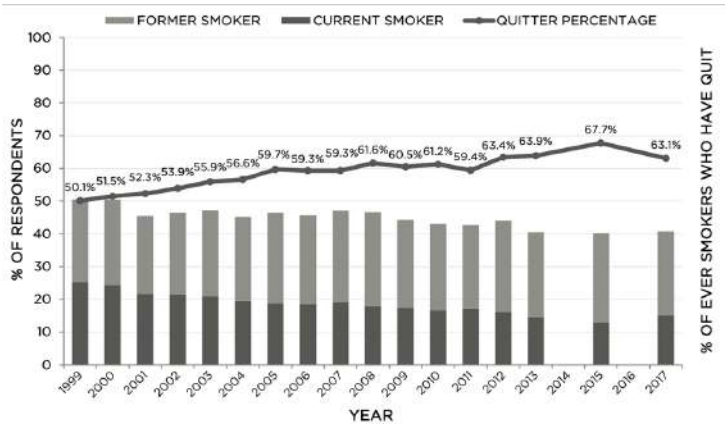

Figure 1. Results of a study conducted by the Centre of Population Health Impact analyzing smoking trends from 1999 to 2017. The percentage of participants who have a history of smoking is

represented by the bars displayed along the x-axis. Dark grey bars represent current smokers and light grey bars represent former smokers. The scatter plot shows the trend of quitter percentage over the years.

1.2 Genetic Factors

Genetic susceptibility to lung cancer remains predominantly elusive, however, there have been various reports on germline mutations associated with lung cancer susceptibility. [16] Particularly in the epidermal growth factor receptor (EGFR) and erb-b2 receptor tyrosine kinase 2 (ERBB2). [16] EGFR is expressed at normal epithelial, neurogenic, and mesenchymal tissue and is a transmembrane receptor tyrosine kinase protein. [17] When EGFR binds to a ligand, it phosphorylates in the intracellular domain, which leads to downstream signal transduction[17]. The over-expression of this gene is associated with NSCLC and is shown to reduce survival and facilitate poor chemosensitivity. [17] In NSCLC, intracellular EGFR overexpression is observed in 43-89% of cases. [17] There has also been evidence that NSCLC shows familial aggregation after tobacco smoking adjustments. [18] There have been linkages to families with aggregation of lung cancer to a region on chromosome 6q23-25. [18] The risk increases 1.51-fold for individuals with first degree relatives that smoke compared to those without a family history of smoking. [19]

2. METHOD OF DETECTION

In modern-day medicine, the primary focus lies in a detection modem that prioritizes the safety of the patient while still ensuring that they are receiving the highest quality of care. A CT scan provides the physician with highly detailed images of the focus area in order to identify the potential presence of a tumour in both two-dimensional slices and three-dimensional images of the whole organ or cavity. [20]

2.1 Methods Behind CT Scanning

As previously mentioned, both sliced and whole images of the desired area are produced by the CT scanner. With each rotation, the CT develops a two-dimensional image using mathematical techniques. [21] The process to produce these images is facilitated by a rotating x-ray source as shown in Figure 2. The source will rotate in a circular motion around the circumference of the x-ray tube where the patient lays. The x-ray source could possibly be an element of either barium, iodine or gold composed in an aqueous solution. [22] Located in front of the x-ray source is a bowtie filter. This works to alter the incoming frequency of the source by adjusting the angle it is distributed on the patient to create a balance within the exposed photon flux on the detector array. [22] The bowtie filter can be modified in many shapes and sizes depending on the type of image that is desired to be produced. [23] The CT scanner uses fan-beam geometry to emit the radiation allowing for a distributed flux upon the detector array. [23] The linear detector array moves in a circular motion in a 180° displacement of the x-ray source to develop an image as the x-ray source flows through the patient. [24] This setup allows for clear images or slides of the patient to be developed on the technician's computer.

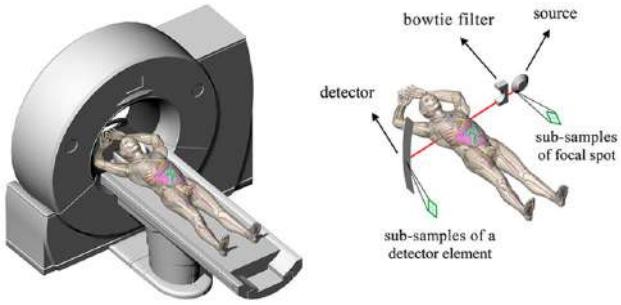

Figure 2. Shown on the left is what the CT scanner looks like on the outside while the image on the right side shows the mechanisms located within the scanner to facilitate the development of the images.[25]

2.2 Low-Dose Spiral CT Scanning

In terms of lung cancer detection, an emerging type of computed tomography (CT) scanning known as low-dose spiral scans has been praised for its ability to provide detailed images of intended locations while emitting far less radiation to the patient. [26] As tumours in the lung can sometimes be difficult to detect, the use of a low-dose spiral CT scanner makes the detection of cancers a far less challenging task. [27] A low-dose spiral CT scan continuously rotates around the patient in a helix shape to develop three-dimensional images of the chest cavity, allowing the physician to observe many different perspectives. [24] Some benefits to using this method include less radiation exposure to the patient and a greater ability to detect tumours in early developmental stages. [28] The low-dose CT scanner provides a lower amount of radiation emission, an average value of 2 mSv in comparison to traditional CT scanning, an average value of 7 mSv. [28] Traditional CT scanning emits approximately three and a half times the amount of radiation putting the patient at greater risk. The traditional CT radiation emittance value is equivalent to two full years of background radiation exposure emitted to the patient at one given time. [29] Although the dose of radiation received from this low-dose CT scanning is higher than traditional chest x-ray scanning, the benefits of undergoing this detection technique outweigh the cons tremendously. [28] The advantages of this scanning technology can be seen in a study conducted by Henschke et al. (1999) which included 1,000 participants who had all declared they are currently smokers. The study concluded with an 85% detection rate for stage one lung cancer discovered using a low-dose spiral CT scan. [30] Low dose CT scanning allows for clear imaging, preventing the need

for multiple scans during the detection process which ultimately reduces radiation exposure.

3. TREATMENT METHODS

In today's day and age, the appropriate technology has been developed to attack cancers that have previously been labeled as incurable. With the knowledge scientists hold today, innovative approaches to treating and potentially curing these kinds of cancers have developed promising solutions. The use of radiotherapy alongside chemotherapy is called chemoradiotherapy and has been known for its effective and safe treatment against cancer.[31] The chemotherapy treatment helps to weaken the cancerous cells, making the radiation therapy the patient is receiving much more effective. Some suggest chemoradiotherapy is one of the most promising treatment plans for those diagnosed with lung cancer, specifically NSCLC.

3.1 Radiotherapy

Radiotherapy is a form of cancer treatment that exposes doses of radiation to the cancerous site specifically the tumour. This impacts the growth of cancerous cells making it challenging for cell reproduction. When deciding between different radiotherapeutic approaches to NSCLC, many options present themselves with unique benefits and disadvantages. Brachytherapy is a radiotherapeutic approach that begins with placing a small-sized seed of radioactive matter either locally or directly into the targeted location.[31] The placement is done surgically using a bronchoscope that is put into the mouth and into the bronchi, where the tumour site is located to ensure the radioactive material is as close as possible.[32] The use of a bronchoscope is best for this procedure as it is a thin, flexible device that is equipped with a camera and light fixture, providing medical staff with the ability to see inside the lungs.[33]

A physician may choose HDR-B therapy as it is one of the most effective radiotherapeutic option.[31] This is because the radioactive material travels a small distance to get to the desired site, posing little risk to the neighbouring organs.[31] Most frequently, iridium-192 is used as the radioisotope in this procedure, which has a negative beta decay model (Equation 1).[34] Negative beta decay is present when a neutron transforms into a proton (e), initiating the release of a gamma-ray photon (γ) and an electron antineutrino (υ_e).[35]

$$_{77}^{192}Ir \rightarrow {}_{78}^{192}Pt + \gamma + \upsilon_e + {}_{-1}^{0}e \qquad (1)$$

HBR-B is seen as a valuable asset to the treatment of NSCLC as it provides treatment with the greatest, strongest force. This gives an optimistic outlook for many of these patients having such short life expectancies due to an inoperable tumour. HBR-B is seen as a promising solution due to its short-ranged gamma rays which allow for an increased amount of accuracy.[36] HBR-B's accuracy helps to target the maximum dosage towards the desired region, putting surrounding tissues at less of a risk.[36] HBR-B has been frequently chosen over low-dose-rate brachytherapy by physicians because of its high efficiency and safety rankings. Most often, HBR-B is not the sole treatment option. HBR-B is used simultaneously with external beam radiotherapy (EBT) to provide the patient with a boost in their treatment timeline.[37] Together, both EBT and HBR-B are strong primary treatment plans with a tolerable toxicity emittance for patients diagnosed with NSCLC that are ineligible for surgery. One limitation of pursuing this treatment is its restricted access.[38] Few cancer treatment centers are equipped with the technology to pursue a treatment like this one making physicians think twice about selecting HBR-B.[37]

3.2 Cell Survival Analysis During HBR-B Treatment

Normal tissue and cancerous tissue react very differently to radiation therapy. Radiation therapy damages DNA to the point where a cell cannot divide or multiply, and because tumours grow faster than normal cells, they are the first to be damaged.[39] However, there is a point where normal cells are destroyed much faster than cancerous cells. To define this point, we can utilize a linear-quadratic model and determine the surviving fraction of cells after an absorbed dose, given in Gray (Gy). The ratio of surviving cells is given by the dosage (D) proportional to two coefficients, alpha (α) and beta (β), where α is proportional to D, and β is proportional to (D^2). Our model assumes that normal cells have an α/β ratio of 3, shown in Equation 2, and cancerous cells have an α/β ratio of 10, shown in Equation 3.

$$n(t) = -0.2473t - 0.0824t^2 \qquad (2)$$

$$c(t) = -0.4t - 0.04t^2 \qquad (3)$$

Figure 3 models the relationship of surviving cells versus dose of radiation therapy in Gy. The equal survival ratio, where normal and cancerous cells are equally damaged, occurs at 3.601Gy. At this dose, the ratio of surviving cells is -1.96. It is extremely important that radiation dosages do not surpass this, as normal cells will be destroyed faster than cancerous cells.

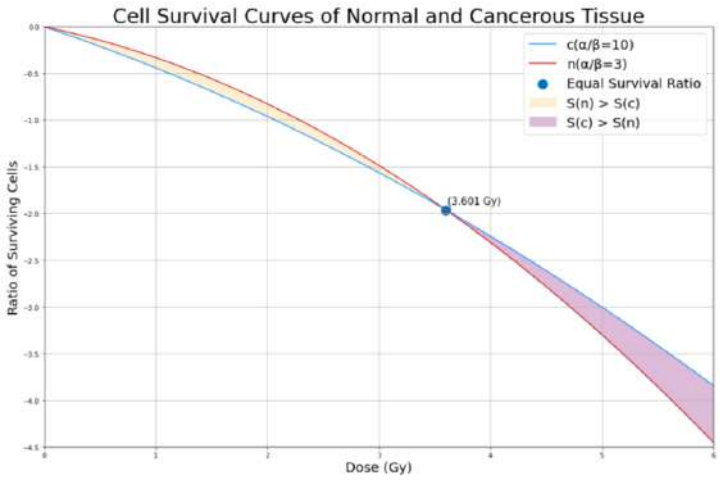

Figure 3. Cell survival curves for normal tissue and cancerous tissue utilizing Equation 2 and 3. The equal survival ration occurs at 3.601Gy. Radiation doses greater than 3.601Gy will destroy more normal tissue than cancerous tissue. This graph was developed using Python 3.

From this model we were able to determine the optimal dose, where there is the greatest amount of surviving normal tissue and least amount of cancerous tissue. The optimal dose is 1.8Gy and can be displayed by number of treatments to determine when cancerous cells are destroyed. Figure 4 assumes a starting point of 10^8 cells and shows the number of surviving cells decrease as number of treatments increase. Normal tissue persists as the greater number of surviving cells until treatment seven, where cancerous cells have a higher survival rate. At this point, normal tissues are depleted at greater quantities than cancerous tissues and the treatment becomes toxic.

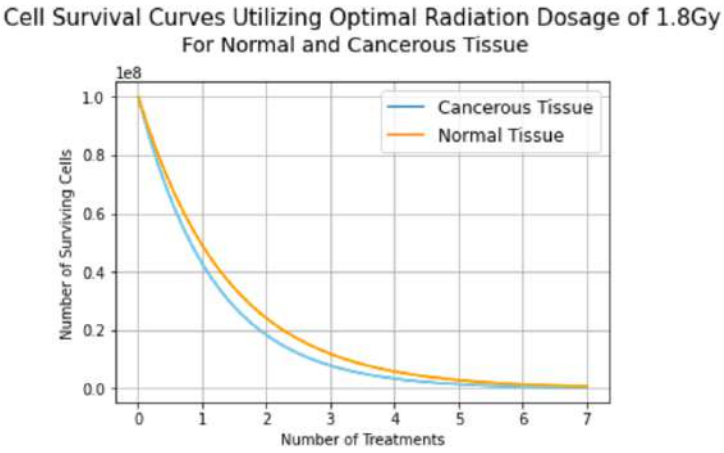

Figure 4. Normal and cancerous tissue undergoing radiation therapy of 1.8Gy displayed over a number of treatments. This model assumes a starting point of 10^8 cells. This graph was developed using Python 3.

3.3 Chemotherapy

Chemotherapy is often used in combination with other techniques such as surgery and radiation to treat stage three-A NSCLC. The chemotherapeutic drug this review is focusing on is cisplatin, often combined with an alternate drug such as gemcitabine or paclitaxel to reduce drug toxicity and drug resistance.[5,40] For stage three-A NSCLC patients, chemotherapy and surgery are used if they cannot be given radiation. Stage-three-B and three-C patients may be given chemotherapy if they are too unwell to undergo chemoradiotherapy or radiation therapy.[40] Cisplatin is considered an irritant and causes inflammation to the vein it is administered in.[5] It also may have harsh side effects such as nausea, vomiting, kidney toxicity, low blood count, ototoxicity, and blood culture abnormalities.[5] Cisplatin can be used to treat carcinomas, germ cell tumours, lymphomas, and sarcomas.[5] Cisplatin is composed of a doubly charged platinum ion surrounded by four ligands as seen in Figure 5.[5] The chloride ligands on the right form leaving groups, allowing the ion to form bonds with DNA bases, and the ligands on the left form stronger interactions with the platinum ion.[5] Carboplatin is a less toxic, yet very similar drug to cisplatin.[41] It differs from cisplatin by containing bidentate dicarboxylate ligand instead of the chloride ligands.[5] This reduces DNA reactivity and induces slower kinetics.[5]

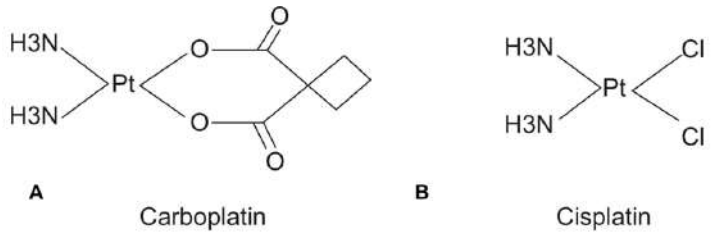

Figure 5. Showing the chemical structure of (A) carboplatin with bidentate dicarboxylate ligands and (B) cisplatin with chloride ligands.[41]

Cisplatin applies cytotoxic effects by forming DNA adducts including mono, inter, and intrastrand cisplatin DNA cross-links that affect the cell cycle at S, G1, or G2-M phase.[42] It becomes active once it enters the cell, and the chloride atoms on the right ligands are displaced by H_2O molecules.[5] The products of this displacement are electrophiles which bind to the N7 reactive center on purine residues.[5] This causes DNA damage and the 1,2-intrastrand crosslink, which is primarily responsible for stimulating this bondage, resulting in apoptosis by preventing the cell from repairing and replicating itself.[42] The adducts between 1,2-intrastrand and purine residues represent 90% of all adducts.[5] The increased metabolic activity and mitochondrial malfunction prompts cancerous cells to display high oxygen species reactivity.[5] Oxidative stress is the most prominent mechanism for cisplatin toxicity

and can cause damage to cellular proteins, lipids, and DNA, which lead to fatal lesions.[5] The mitochondria becomes damaged, mostly from the oxidative stress due to cisplatin losing its sulfhydryl group and taking in calcium, which reduces membrane potential.[5] Resistance of cancer cells to cisplatin chemotherapy after the first round of therapy is mediated by microRNAs creating a resistivity and sensitivity to the drug.[44] The stimulation of nuclear factor erythroid 2-related factor 2 (Nrf2) protects cancer cells from cytotoxic impacts by translocating to the nucleus, binding to antioxidant response element, and upregulating antioxidant and detoxifying enzymes.[43] Researchers are continuously looking for strategies to inhibit cisplatin resistance. This includes altering drug delivery platforms and exploring nano- and microcarriers.[43]

CONCLUSION

With extensive research and advancements through epidemiological lenses, detection methods, and treatment modalities, we can efficiently design treatment and prevention plans that benefit the general population. Lung cancer epidemiology includes determinants, distribution, incidence rates and frequency of this disease. The study of the associated epidemiology of lung cancer provides an understanding behind the factors which contribute to its high incidence and mortality rates observed today on an international scale. It is critical to acknowledge the trends this disease currently possesses in addition to predisposing risks and other causes, in an attempt to decrease future incidence. It has been concluded that there is a contributing genetic component alongside the diagnosis of lung cancer within a family.[18] With this, it becomes challenging to develop a sole cure for a disease that has associated mutations which are very unpredictable. Further, it has been concluded that the 6q23-25 chromosome has been studied for its linkages between lung cancer diagnosis within the family tree making it a crucial factor to analyze in determining the genetic susceptibility for lung cancer.[18]

Lung cancer begins with localized tumour growth that can become metastatic as the severity of cancer increases. With this, it is extremely important to ensure that the first approach in the detection process is as clear and informative as possible to prevent the development of a worsened condition and ultimately, further spread. An effective imaging technique is spiral CT scanning, where both two-dimensional and three-dimensional images are produced, providing physicians with multiple perspectives of both the whole chest cavity and individual cross sections.[24] In the present day, this imaging technique has come to be extremely common as it allows for conclusions to be developed in a timely manner, preventing delay in the treatment process.

As most of the lung cancer cases diagnosed are late stages, it is extremely crucial that treatment plans are developed for each unique patient situation.[1] Both radiotherapy and chemotherapy have been seen as effective treatment options. Although, the most effective treatment is known as a combination between both radiotherapy and chemotherapy, a term coined chemoradiotherapy[4]. Brachytherapy is known to be the most precise in issuing radiation to the desired location within the body.[1] Inserting radioactive material near or embedded into the cancerous site prevents any unnecessary exposure to neighbouring tissues and organs.[31] Chemotherapy has been acknowledged for its abilities in the treatment of lung cancer, specifically the use of the drug cisplatin that can tremendously limit the reproduction of cancerous cells.[40] Many medical advancements have been made throughout this past century involving both treatment plans and associated technology which have contributed to lower incidence rates. Although, there still lie many unanswered questions about the most effective treatment guidelines that apply to every patient.

Lung cancer holds a significant risk to those with a history of smoking both traditional and electronic cigarettes. Knowing this, the importance of a treatment which is less harmful to neighbouring organs and tissues such as HBR-B is critical in mitigating the associated treatment impacts. Moreover, the use of cisplatin is most effective as a treatment when combined with radiotherapy. Further research into pharmacotherapeutic approaches to the treatment of lung cancer are strongly encouraged. Despite the complexity lung cancer holds, medical advancements in the long-term care and treatment of this disease have been very effective and will continue to decrease the observed incidence and mortality rates.

APPENDIX

Using the Keywords, Lung Cancer, Non-Small Cell, Smoking, Brachytherapy, Low-dose Spiral CT, Cisplatin, the authors were able to locate articles to compose this piece. National Center for Biotechnology Information's MeSH database was the primary database for our search. Through this database the selection of many subheadings also helped to refine our search. Each manuscript used in this piece was read by both authors to validate its relevance to this topic and strength in the science community. Taking an interdisciplinary approach to this review was of primary focus. Incorporating the disciplines of Life Science, Physics, Chemistry, Epidemiology and Mathematics to strengthen our understanding of NSCLC was our primary goal.

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Cardiovascular Health—Why We Need an Intersectional Sex and Gender Approach

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SUMMARY

The lack of education at the undergraduate level into sex and gender dimensions in research is appalling. Having learned about how something as foundational as terminology has been misappropriated in literature across journals and institutions in our HTHSCI 2T03: Sex and Gender course at McMaster University, we endeavoured to dive deeper into why sex and gender exclusion is problematic. We found that cardiovascular health research, in particular, is victim to the misappropriation of terminology, gender bias in study enrolment, and hegemonic masculine attitudes; and that these issues directly affect subpopulations with cardiovascular conditions. The lack of a sex and gender lens in cardiovascular research leads to an inadequate understanding of how disease risk and development is different within different genders and sexes. This contributes to a lesser standard of care for women and LGBTQ+ peoples, consequently resulting in a greater burden of disease. Therefore, more research should be conducted with a sex and gender lens in order to build a stronger understanding of disease manifestation using targeted research questions and a focus on intersecting social and biological identities.

ABSTRACT

A sex and gender perspective in research involves an appreciation for the intersectionality between sex, gender, and other social factors (i.e. sexuality, socioeconomic status, race/ethnicity, etc.) with the risk and development of disease. This piece argues for the greater adoption of a sex and gender perspective in cardiovascular (CV) research. The lack of appreciation for the impact of sex and gender in disease has led to an underrepresentation of women and LGBTQ+ populations in studies and an underappreciation for both the biological and psychosocial impacts of sex and gender on pathogenesis.[1,2] As a result of this insufficient understanding, these populations have faced a greater disease burden, poorer outcomes, and inequitable health interventions.[3] The incorporation of a sex and gender lens in CV research will serve to lessen the burden of disease on these underserved populations through developing a greater understanding of the unique differences in the risk and progression of disease. Accordingly, this opinion piece hopes to illustrate the need for a sex and gender perspective in CV research in order to urge researchers, journal publishers, and supporting bodies to include sex and gender as a priority in future research.

Keywords: Cardiovascular health, sex and gender, sex inclusion, social determinants of health, health equity, study bias

INTRODUCTION

Defining the terms 'sex' and 'gender' and the intersectional perspective

One would instinctively assume that the terms 'sex' and 'gender' have unique meanings. However, in the scientific world, high-ranking journals are often guilty of conflating these terms despite experts and scholars openly demarking them.[4] The misuse of these terms by articles published in prestigious journals perpetuates the erroneous narrative that sex and gender dimensions are inconsequential and unnecessary to include with purpose and accuracy. In this piece, we explore how sex and gender are two unjustifiably overlooked social determinants of health that are important for biomedical research today. For the purposes of this paper, sex refers to a set of physical, chromosomal, genetic, and physiological attributes used to define an individual as male, female, or intersex, whereas gender encompasses sexuality, socioeconomic status, race/ethnicity, among other underrecognized factors.[5,6] This complexity justifies the use of an intersectional approach between sex, gender, and health such that research acknowledges the nuances that inform best practices in healthcare worldwide.[6,7] It is important to have a clear definition of what is meant by a "sex and

gender perspective". For the purposes of this opinion piece, we argue that for CV health studies, both in humans and cell or tissue cultures, researchers and editors should (1) define how sex is determined in the study, and (2) outline the rationale for including or excluding a gender analysis of their results on populations with varying socio-economic status, culture, and gender identity. It is widely acknowledged that many studies will not be "designed" to analyse sex and/or gender differences, which is why this piece argues for the greater adoption of the international Sex and Gender Equity in Research (SAGER) guidelines which emphasize the need for researchers to consider whether or not sex and gender dimensions are appropriate for analysis.[8] With this definition of a "sex and gender perspective" it is important for researchers to differentiate between the variables sex and gender. The reason for this is two-fold. First, the use of common definitions will "improve the ability to conduct meta-analyses of published and archived data".[8] Second, by being aware of the differences between sex and gender, researchers will better explain the methods in which the sex of participants was defined, which is only of benefit for study validity. Encouraging researchers to outline the methods by which they have disaggregated sex data is one of the most strongly urged SAGER guidelines because it will guide researchers to better understand ways to innovate and apply their results to the males, females, and intersex participants in their study. This is most clearly seen in the scientific field where a historical neglect for sex and gender-based analyses have both hindered innovation and led to problematic outcomes. In engineering, the lack of consideration of physiological and anatomical differences between the sexes resulted in higher risk for whiplash injuries among female car occupants compared to men.[9,10] Regarding innovation, understanding inherent sex-based differences will provide a framework for further exploration across intersecting gender identities to better meet the needs of society.[8] While the impact of having a "sex and gender perspective" on the scientific field is variable depending on the types of studies being conducted and their intended outcomes, the inclusion of the SAGER guidelines will certainly improve one aspect of health research, that is, cardiovascular health. This will be examined closely in the following paragraphs.

Historical Context

To date, there has been an alarming underrepresentation of women and LGBTQ+ peoples in cardiovascular disease (CVD) research.[7] The interplay between sex, gender, and health in cardiovascular systems provides an immense gap in our knowledge which has led to a greater CVD burden and poorer health outcomes in both women and LGBTQ+ individuals compared to biological men.[3] To rectify these inequities, there must be an equitable emphasis on research into the role of both sex and gender differences on the development of disease in order to reduce risk and improve treatment and prevention of these diseases in understudied populations.

Acknowledging sex and gender dimensions in biomedical research that uses sex as a variable is essential for any study to be reproducible – a cornerstone of the scientific method. However, researchers, funders, and editors have historically failed to treat the gendered aspects of health research as a priority.[12] The legal inclusion of female-identifying and racial/ethnic minority participants in research began with the National Institutes of Health Revitalization Act of 1993 in the United States.[13] In 2016, the international SAGER guidelines were established.[12] However, these efforts have not sufficiently addressed the widespread exclusion of sex and gender dimensions in research because of the historical view of male bodies as the "norm".[14] Male patients dominate medical textbooks and literature regarding CV pathologies and are therefore seen as the standard reference point.[15] Thus, it seems as though researchers are hesitant to prioritize the gendered aspects of health due to a historical misunderstanding of its definition and the normalization of men as a physiological standard.

ARGUMENTS

A clear indication of this hesitancy is the persistence of implicit gender bias, especially involving the enrolment in CV studies and the subsequent reporting of gender-related data.[3,14,16] A study by Wilson et al., investigating 96 CV publications at Ontario Universities, discovered that females were underrepresented (<40% of sample) or excluded 63% of the time (Fig. 1).[14] Furthermore, despite heart disease being of similar prominence in females and males, two-thirds of heart disease clinical research focuses solely on males.[14,17] The effects of this underrepresentation are worsened by the failure of researchers to disclose gender-related data; only 9% of male-only studies' titles indicate the population and only 10% provide a justification for their unequal male-to-female inclusion.[14] This underrepresentation of women in research can result in adverse consequences, as observed between 1997 - 2001, and again in 2005, when 80% of prescription pharmaceuticals were withdrawn from the US market for being significantly more harmful to women than men. These are just a few examples of when a sex and gender-based analysis would have provided sufficient information to guide dosing and applicability of drugs in men and women prior to approval.[8] Neglecting the effects of prescription drugs on women is a product of the aforementioned view of biological men as the standard in clinical testing where, as accounted by Wilson et al., 66% of Ontarian studies between 2010-2018 describe male bodies as a pathological reference

point.[14] The implications of the underrepresentation of women in studies is especially damaging in the context of cardiovascular drug clinical trials: the exclusion of women from these trials results in a lack of appreciation for differences between male and female body composition and drug pharmacokinetics (PK) when developing drug dosage recommendations which may lead to sex differences in drug efficacy and safety.[18] For example, women tend to have a higher body fat percentage, lower body weight, plasma volume, and organ size than men which leads to a faster and longer onset of lipophilic drugs.[18] It was found that some antiarrhythmic drugs are able to achieve a much higher peak plasma level in women accompanied by a higher rate of adverse drug reactions (ADRs) in females.[18] Additionally, with anticoagulant drugs, it was found that the lower glomerular filtration rate in females results in slower drug clearance and up to a 24 times longer drug half-life in women.[19] While there is an established difference in the PK and metabolism of drugs between males and females, the clinical relevance of this is unclear due mainly to the fact that women are not represented in clinical trials which assess the safety and efficacy of these drugs.[19] Consequently, by ensuring equitable representation of women in clinical trials and other studies, we promote the proactive discovery of potential ADRs rather than the reactive treatment of these effects in the general public.

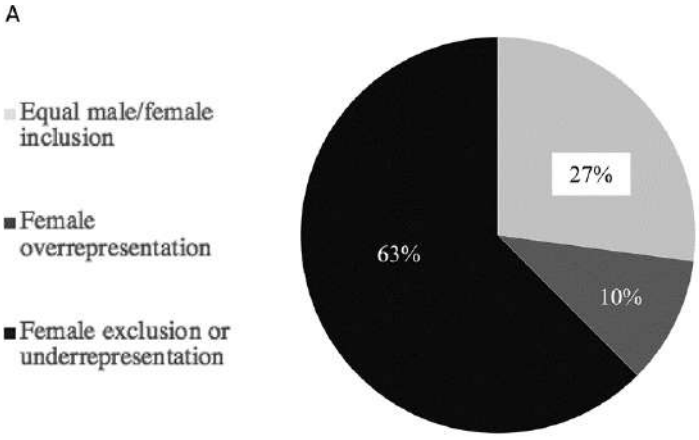

Figure 1. **Female inclusion in NSERC-funded CV research at Ontario universities (2010-2018).[12]**

The harmful normalization of the male body standard has directly labelled women as a "vulnerable population" in the scientific community.[14] One reason for this is the pervasive notion in CV research that the female anatomy is overly complex.[11] This notion, that CV health is significantly different or complex in women was founded on two observations: hormonal fluctuations and contraceptive use.[18] The menstrual cycle is an established factor in blood pressure research, yet researchers are often dissuaded from including women due to the perceived experimental challenges with controlling for this factor, especially in population-based studies.[18] As a study by Chapman et al. points out, oral contraceptive pills significantly influence vascular health, yet they are not being reported with transparency or with any emphasis in studies that investigate sex as a biological variable in CV health research.[18] The supposed complexity that these factors present researchers with is leading to the question of whether or not to include women in large-scale studies.[18] This is problematic, because, as Wilson et al. attests, only 40% of NSERC-funded single-sex studies in CV health acknowledged the limited generalizability of results from participants of the same sex, mostly men.[14] Not acknowledging the issues with excluding women due to this presumptive "complexity" is detrimental to the scientific integrity, linguistic precision, and authorial accountability of CV research.[4] Despite international guidelines mandating the equal inclusion of women and marginalized groups in research, this statistic shows how the "male norm" has and continues to influence the generalizability of CV research and further promotes a damaging sex bias.

Furthermore, adopting a sex and gender perspective in CV research will help lessen the burden of disease in underrepresented populations by promoting a holistic understanding of the interplay between sex, gender and other sociocultural factors in CVD. While biological sex is well-understood in CVD research, the underrepresentation of females, intersex, and transgender peoples limits the translation of research into universal treatments.[1,19] This issue is exacerbated when considering the intersection of CVD and race/ethnicity, through which the psychosocial impact of gender perception strongly determines the prominence of risk factors in different populations.[2,17] Certain gender identities are highly predisposed to psychosocial stress through traumatic experiences leading to the adoption of CVD risk-modifying behaviours, including drug and alcohol consumption among others.[1,20] This is emulated with institutionalized and societal gender roles through which women and LGBTQ+ individuals experience disadvantages in socioeconomic status, employment and access/utilization of healthcare.[1,17]

CONCLUSION

Prioritizing a sex and gender perspective in CV research is an essential step towards health equity. By adopting an intersectional approach to CV research, we will ensure that overlooked intersecting identities are more equitably represented in the literature, fostering more informed decisions regarding CVD prevention and treatment. As such, we call on leaders in the research community to evoke changes in order to spark a paradigm shift in CV research. Fig. 2 highlights a continuum of awareness that should be examined more closely by ethics boards and publishing groups,

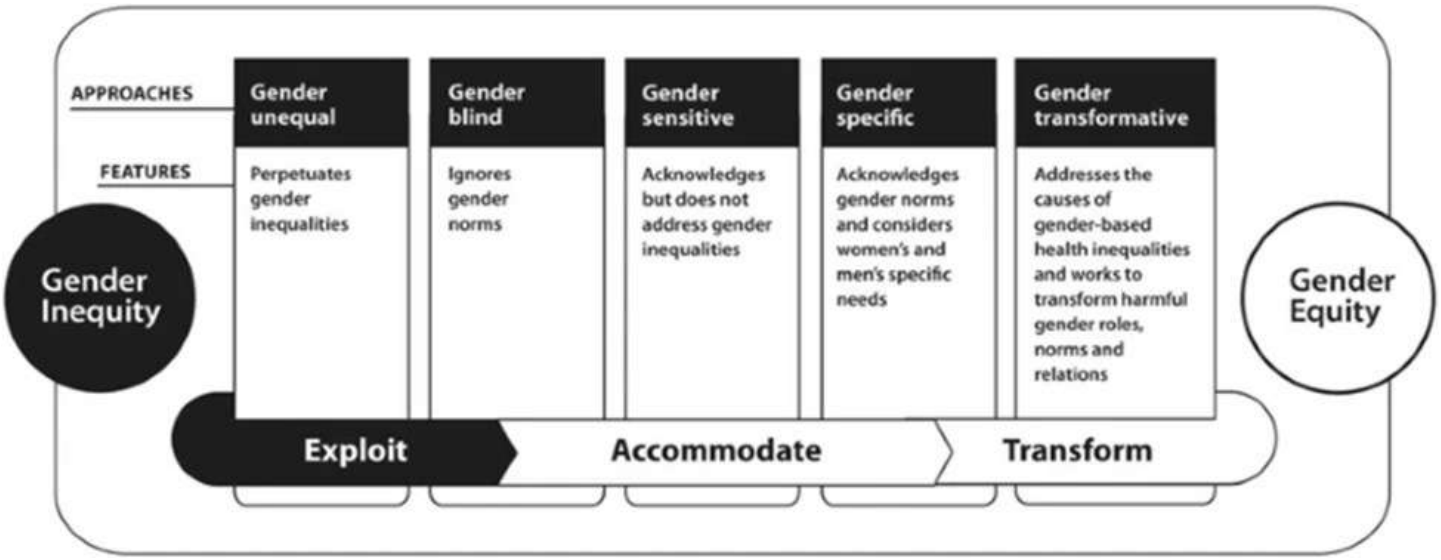

Fig. 2. Proposed continuum of approaches for integrating sex and gender.[21]

made by Greaves. We call on researchers to consider sex and gender dimensions while forming research questions and ensure that these dimensions are acknowledged and evaluated, even briefly. Additionally, we call on funding agencies to incentivize the incorporation of a sex and gender lens in research, as exemplified by the Tri-Council Policy Statement guidelines, and reaffirm their commitments to the SAGER international guidelines. Ultimately, we hope that through the consideration of sex and gender in CVD we can push towards improving the health outcomes from CVD in all sex and gender populations.

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To look like Superman: Male body dysmorphia

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SUMMARY

Body dysmorphia (BD) is a severe mental condition where an individual has obsessive thoughts pertaining to their appearance. These individuals tend to see flaws in their appearance that are otherwise unnoticeable to the general eye. BD can get in the way of one's ability to live a normal life. Specifically, males tend to suffer from a specific subtype of BD called muscle dysmorphia (MD), where one fixates in achieving a muscular appearance. With the surge in social media use, various novel media outlets have become the biggest influence in our lives, specifically surrounding appearance. The notion of men experiencing body issues has not been typically and openly expressed by the media, which has resulted in the condition being under-diagnosed and under-represented. Today, ordinary males feel pressure to obtain potentially unreachable standards for a body by taking part in excessive workout routines grounded in weightlifting, consuming large amounts of protein and weight-gaining supplements, and possibly abusing anabolic steroids. Currently, there remains a lack of studies and existing literature on this topic, making it challenging to determine concrete data surrounding the prevalence of males experiencing this disorder and the effective treatment options.

ABSTRACT

Body dysmorphic disorder (BDD) is a psychiatric illness characterized by obsessive thoughts in relation to one's appearance. Body dysmorphia continues to gain attention in the media, academia, and scientific community. This mental health condition can happen to any gender and is evaluated to be a chronic and long-term condition. Although research and developed models have attempted to understand the etiology of BDD, there is limited amount of research regarding the illness in relation to men. This highlights the need to bring awareness surrounding this topic by expressing thought provoking questions, as without treatment, BDD will progressively worsen as one ages. In this piece, we present thoughts on why this area is under-represented, and briefly describe what body dysmorphia is and the main area of distress in men. Moreover, we discuss why men are fixated on achieving the "ideal male image", what this image appears to be, the possible body dysmorphia-inducing factors, and the overarching need to conduct more research on this topic.

Keywords: Male, body dysmorphia, muscle dysmorphia, image, media

INTRODUCTION

The opinion of an ideal human physique has become a staple primarily in North American cultures and Western societies.[1] For decades, the focus of body image and related studies on self-esteem and appearance has been on women.[2] Our culture has slowly progressed and become more comfortable with discussing unrealistic body and beauty expectations; however, most of these conversations and studies in this area of research are focused on the female population.[3,4,5] We strongly believe the media does not place as much emphasis on males compared to females, possibly because vanity and appearance are immediate attributes given to women and is often used to judge or select women compared to men. Despite this highly debatable topic of conversation, we believe that men are becoming increasingly concerned with body appearance, as body image is not just a woman's problem.[2]

Thoughts surrounding physical appearance has invaded the minds of every individual at least once in their life, as it is an intrinsic desire to want to look good to gain praise, attention, and be viewed as attractive. Conversely, we strongly believe the surge in obsession over physical appearance is the result of pressure inflicted by social media. The surge in social media use, the constant documentation of ourselves through selfies, and the ability to "edit" a photo has increased the pressure to look a certain way, in addition to questioning how we physically view ourselves. The accessibility of mobile apps that allows one to place a filter to alter the face and body has resulted in skewed perceptions of one's physical appearance while changing the standards of beauty significantly.

Moreover, social platforms have allowed for continuously changing opinions of masculinity and desired body shapes and features. This puts pressure on men to try and fit the ever-changing views on the ideal male body. Consequently, this affects men's desire to look good under society's standards, to be perceived as attractive, and to validate themselves through popular slang that labels a man's body (such as "six pack abs", "dad body", and "fat"). Society places increasing value, worth, and importance on physical appearance that can be modified or "fixed" through excessive diet, exercise, and plastic/cosmetic surgery. We believe that with increasing media usage, we are creating an environment where eating disorders flourish and body dysmorphia becomes the "norm". Additionally, men are hesitant to reveal feelings of embarrassment and shame. We believe that men also fear being viewed as "weak", "weird" or "delicate" if they are diagnosed with a psychiatric disorder, such as body dysmorphia (body dysmorphic disorder).[3] Consequently, it is no surprise that we are living in a society where males feel the need to keep their feelings of unhappiness and lack of confidence hidden. This brings forth the fact that body dysmorphia is not restricted by gender nor age; hence, it is an area that requires more attention and research with regards to the male population. Moreover, if a so-called "ever-increasing" and "accepting" society is emerging, men deserve the right to access treatment without the repercussions of shame. Boys who struggle with body image issues are viewed as "less of a man" and their thoughts are deemed as socially inacceptable.[6,7] Today, society fails to recognize the growing needs surrounding young males and body issues, despite the limited number of studies that do exist in this area continuing to acknowledge that men struggle in this regard.[8]

Issues such as eating disorders and body and muscle morphia being rare topics of conversation may be the reason why male body issues are under-diagnosed and under-represented. This is due to a number of factors, including limited research and evidence, the uncertainty of inconsistent diagnostic tools, and the old-age view that it is taboo for men to be concerned with appearance of sharing feelings. While more studies have begun to include or solely involve the male population, very few tend to encompass adolescent boys (similar to studies that look at adolescent girls) and younger adult men, proving there is a significant gap. Therefore, with the rise and popularity of social media and the availability of different platforms, research is needed to gather more concrete results on the possible impacts of these forms of media on body image and the male population. This piece helps to inform readers on body dysmorphia, its possible cause, a subtype of the disorder known as muscle dysmorphia, as well as discussing the ideal male image men often try to attain.

DISCUSSION

What is Body Dysmorphia and What are the Main Areas of Concern with Males?

Body dysmorphia, also known as Body Dysmorphic Disorder (BDD) or Dysmorphophobia, is a psychiatric illness (disorder) that was brought into light in 1997; therefore, is a relatively new condition.[9,10,11] It has been estimated that BDD affects 2.4% of the population, with symptoms beginning in pubescent years.[9] This disorder is characterized by compulsive thoughts pertaining to an individual's body, as they view one or more aspects of their physical appearance as flawed when in reality the imperfection(s) is/are often unnoticeable to others.[9,11] The obsession with an individual's perception of their "flawed" feature(s) results in daily acts such as mirror checking, skin pulling, excessive grooming, and experiencing strong feelings of mental stress due to constant comparison.[9] These preoccupied behaviours induce distress and/or impairment. This further causes social isolation, difficulty in occupational performance, or other areas of normal daily performance.[9,11]

The main areas of concern for men with BDD are body weight, height, and muscle mass (also known as muscle dysmorphia) being the biggest insecurities.[11] Furthermore, issues regarding one's skin (acne and/or scarring), hair (including thinning), body hair (which may be excessive), nose (size and/or structure), and genitals (penis size) are other major concerns.[9,11] The physical features that men are often apprehensive about are often related to the degree to which it is visible or controllable. Men are also apprehensive of features that are a symbol of masculinity.

An excessive desire to appear a certain way by either losing weight, gaining body mass, or fixing the "defected" feature(s) makes individuals susceptible to psychological, environmental, and biological risks.[1] The strong desire to attain the ideal body has been linked with heart and renal failure, dehydration, and the abuse of illegal substances (for example, anabolic

steroids). These desires, by extension, also cause threatening side effects such as extreme dieting, addiction to/dependency on exercise, and illnesses such depression and/or anxiety.[1]

Muscle Dysmorphia: The Main Distress in Males

Muscle Dysmorphia (MD) is a newly recognized subtype of body dysmorphia that is more prevalent in males.[11] MD is based on compulsive distress surrounding the perception of a lack of muscular size and leanness.[1] MD is characterized by an individual's obsessive thoughts and behaviour to increase their body mass to appear muscular. This involves gaining weight without gaining fat.[1,2] Thoughts include a hatred for their current body shape and a strong desire to change it through increased muscle mass. This causes affected men to follow excessive workout routines involving weightlifting, eating large amounts of protein and carbohydrates, taking weight-gaining supplements, as well as anabolic steroids.[2]

An individual who suffers from MD does not perceive themselves as lean or muscular. Instead, they view themselves as smaller than they appear despite being significantly more "built" compared to the average individual.[2] These men possess and display a number of psychological and behavioural symptoms, including relinquishing attendance to social events, occupational obligations or recreational activities in order to maintain a strict workout regime.[2] It also involves rearranging their daily lives to ensure that lifting weights and exercising are always prioritized.[2] Other symptoms include continuous training despite injury.[2] In addition, they actively avoid situations or events where their bodies will be exposed. If they are forced to remove clothing and reveal their bodies, they experience extremely high levels of anxiety.[2]

MD is said to have originated in bodybuilding groups.[12] In fact, common groups that experience MD are competitive natural and non-natural body builders, weight trainers who are trying to attain a specific physique, and college football players.[1] Compared to the average weightlifter, men who suffer from MD dwell upon their appearance through "mirror checking", taking part in social comparisons (for example, by camouflaging with other muscular men), and experience greater body dissatisfaction. All of these factors manifest through dysfunctional eating patterns, heightened used of anabolic steroids, and mood, anxiety and/or eating disorders.[2] It has been estimated that 5-10% of weightlifters experience MD.[13]

Although there are a limited number of studies in the area of muscle dysmorphia and more generally in males, some have been able to provide insights regarding participants diagnosed with MD.[10]

An important question to ask is whether certain male age groups experience more symptoms relating to body appearance than others (i.e., younger vs. older men) and are there differences in the types of body concerns they have based on age? It was found that symptoms of MD begin to show at 19 years of age; however, this can range anywhere from 16-18 years old.[9,10] Specifically, researchers found that individuals with MD spend more than three hours a day contemplating on how to become more muscular, believe that they have little power over their weightlifting routines, justified a reason for exercise and diet regimes to interfere with their daily lives, and have an avoidance for social activities due to insecurities regarding their muscular appearance.[10,14,15]

Looking like Superman: Achieving this Vision, the Ultimate Goal

A popular question on this topic is: Does having more muscle mean you are more of a man?

Muscle mass is a primary dimorphic characteristic between the sexes.[1] For many decades, the male figure has become a defining feature in classifying gender and separating the two groups.[1] Specifically, men with a mesomorphic body shape (the traditional "V-body shape") have been portrayed as the ideal.[1] The desire for men to achieve this vision stems from the fact that men are habitually judged by their muscularity and their ability to represent signs of power.[1] In particular, researchers have connected "the muscular physique" to power, authority, strength, sexual chivalry, and self-esteem.[1] Therefore, any man appearing as physically weak, small, or faint are immediately associated with femininity, hence the feeling of inadequacy.[1] Therefore, men have acknowledged that the only way to prevent this is by maintaining a muscular body to demonstrate their masculinity.[1] Society must address how cultural factors and other variables relate to the "ideal male" body, simply because men are naturally more muscular. Based on this idea, men may feel the need to consistently appear leaner/more muscular to represent their dominance. Therefore, the value that society has placed on muscularity may provide a justification as to why MD is becoming more common in men and emerging as a psychiatric condition.

The Etiology of Body & Muscle Dysmorphia Disorder

The exact cause of body and muscle dysmorphia is a complex and partially answered question.[1] Researchers have tried to create models that are able to define key traits and characteristics to better analyse the disorder.[1] It has been argued that these disorders originate as a result of sociocultural factors—describing

men that encounter pressures to appear a certain way to meet societal norms set by the media—and cultural factors, as well as family and friends who have a strong influence.[1] However, according to Grieve, the 3 most significant attributes that induce MD are an irregular and unhappy view of one's own body, as well as possession of a specific ideal body image.[2] In addition to these defining attributes, feelings of perfectionism, low self-esteem, and standards of beauty set by the media have all been identified as underlying causes that lead to the development of body and muscle dysmorphia.[1] Reasons that may account for one's strong fixation on achieving and preserving a muscular physique include fear of powerlessness, feelings of insecurity, childhood bullying, or attempts to compensate for illnesses that make them appear smaller in size.[1] Therefore, these individuals begin a fitness journey rooted in self-control, ambition, aspirations, commitment, and self-achievement.[1]

However, it is important to mention that not all men who follow a rigorous diet and prioritizes regular exercise suffer from body or muscle dysmorphia.[1] Instead, it is specific attributes, such as a fixation on muscle tone and healthy (non-fat) weight gain, that are key indicators of men who suffer from this illness.

The Influence of the Media

The media is a broad term encompassing various types of platforms that have become a major influence in our lives. Various outlets, such as magazines, billboards, the radio, movies, television shows, video games, and action figures have conveyed increasingly impossible body standards. Although pressures from family members, peers, school, athletics, and health professionals influence the perception of oneself, the mass media has become the leading source of pressures related to physical attractiveness.[2] Traditionally, males have been assumed to be sheltered against the effects of media pressure because the body shapes depicted in media in the past have typically described as "average".[2] However, in the past two decades, male models used in the media (particularly billboards, movies, and television shows) have toward a hypermeromorphic (muscular) shape.[2] This transition has increased pressure on ordinary males to obtain unreachable standards as a physique.[2] For example, the number of fitness magazines targeted for men (including the inclusion of unclothed men in such campaigns) have become the norm.[2] Therefore, there is an increased opportunity for men to be influenced by these muscular models, the same way females have been influenced by skinny women.[2]

In general, the media creates a social comparison through advertisements. As the number of specific male body types in posters increases, the opportunity and likelihood for such comparison increase amongst the general public.[2] A social theory coined by Festinger (a cognitive psychologist who discovered the social comparison and cognitive dissonance theories) states that people evaluate themselves based on a comparison to others.[2,17] Therefore, if the media constantly portrays men as muscular, this body type becomes a standard that men use for comparison. Consequently, men will be more likely to view their own bodies negatively.[2] As such, males are becoming increasingly affected by media standards, resulting in a heightened chance of developing BDD or MD.

CONCLUSION

This opinion piece brings forth thoughts on why this area is underrepresented, briefly describes body dysmorphia, and discusses the main areas that cause distress in men. Moreover, it discusses why men are fixated on achieving the "ideal male image", the possible influences of body dysmorphia, as well as the increasing need to conduct more research on this topic.

Today, research on body and muscle dysmorphia continues to grow in Western and non-Western societies, as the issue of these disorders are becoming more frequent in the population and amongst males. The existing literature have a limited understanding of individuals who suffer from this disorder, and fail to recognize the well-known and obvious features of BD and MD. Furthermore, there is a limited comprehension of these disorders, including diagnosis and categorizing its subtypes, the frequency of the illness (particularly beyond Western societies like in North America, Britain and Australia), its causes, and the effective treatment.[10] The lack of studies on this topic has made it challenging to determine supporting data.

We believe body and beauty standards for both men and women will never fade. Society will always place importance on one's physical appearance. However, it is important that we discuss these challenges as a society, particularly in a manner that allows one to express their true feelings. Women have suffered and worked harder to counter the current cultural standards to achieve inclusive beauty. Despite these steps towards the right direction, we must also recognize that men are newer candidates to this struggle. To conclude, acknowledging this issue is the first step in realizing that this is a problem that men face, and it is through research and helpful conversations that we can make a positive change.

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ence, insightful reflection, and the unfortunate reality that not enough discussion has been expressed in the realms of academia, media platforms, and mainstream culture.

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Stopping Aging: Dream or Reality?

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SUMMARY

As people get older, their bodies start to break down. This can greatly reduce people's quality of life. However, some people claim that there are ways to stop the aging process. The question is whether this is true or not. The methods proposed for stopping aging are good diet and exercise, taking medications to reduce the effects of aging, and replenishing good cells in the body to allow for repair. These are all great solutions and do have the potential to slow down the aging process. Yet, they are not enough to stop it altogether. Nonetheless, these techniques should still be implemented in society while research continues in this field to improve anti-aging mechanisms in the future.

ABSTRACT

Aging is a reality and is associated with the progressive physiological breakdown of the body. This can cause many health problems such as heart disease, cerebrovascular disease, diabetes, etc. However, some claim that the aging process can be stopped. Proposed mechanisms for stopping aging include good nutrition and exercise, pharmacological interventions, and stem cell therapy. These have shown good prospects for slowing down the aging process but not for stopping it altogether. It may also not be possible to stop aging for a long time, considering that it is polygenic and complex in nature. This piece provides clarification for the current state of modern science in terms of its ability to stop aging, as well as an outlook for what to expect in the future.

Keywords: Anti-aging, lifespan, stem cells, telomerase, exercise, drugs

INTRODUCTION

Aging is defined as the "progressive accumulation of changes with time that is associated with or responsible for the ever-increasing susceptibility to disease and death".[1] These changes deteriorate many different body systems. Most notably, aging progressively deteriorates the cardiovascular system leading to conditions such as hypertension and atherosclerosis, which increase the risk of heart disease and cerebrovascular disease.[2] In fact, heart disease is the leading cause of death in the world and thus the biggest complication of aging.

Overtime, the life expectancy of people around the world has increased but this has been primarily due to better management of symptoms of diseases and their pathophysiology.[3] The root of these problems have not been tackled as effectively. However, with emerging research, it is claimed that certain techniques can stop the aging process, but this sounds rather too good to be true and warrants a thorough analysis.[4]

NUTRITION AND EXERCISE

The end of a DNA strand is called the telomere, and it is made up of thousands of repeating nucleotides.[5] Due to the nature of DNA replication, a small amount of the telomere is cut in each cell replication cycle. This telomere serves to protect the functional DNA. However, when the telomere is depleted, portions of genes start to be lost. This has been linked to the pathogenesis of several diseases.[5] However, there is an enzyme called telomerase that can elongate telomeres. Research shows that good nutrition and exercise can increase telomerase activity in the body.[5] This includes a calorie-limited and balanced diet, along with regular low- to mid-intensity endurance training.[5] With that being said, this primarily slows down the pathogenesis of diseases and the aging process still continues.

PHARMACOLOGICAL INTERVENTIONS

There are some drugs that have gained interest by researchers, as anti-aging mechanisms. Many of these

focus on calorie restriction as this has shown a large potential for slowing down the aging process.[4] For instance, there are four proposed pathways that are active during calorie restriction and are associated with increased life expectancy. These pathways include the activation of AMP protein kinase, activation of sirtuins, inhibition of insulin-like growth factors-1, as well as the inhibition of the mammalian target of rapamycin.[4] These pathways can be pharmacologically stimulated through the use of the drugs metformin, resveratrol, pegvisomant, and rapamycin, respectively. These mimic the effects of calorie restriction within the body, to harness its anti-aging properties.[4] There is also research to show that hormonal replacement can be used as an anti-aging mechanism. This is because hormone levels generally decrease with age which can lead to cardiovascular disease, thromboembolic events, etc.[6] As such, replenishing hormones to optimal levels can reduce the effects of aging. Furthermore, there is also research to show that the gut microbiota is key for maintaining optimal functioning of the immune system.[7] With age, the gut microbiota becomes remodelled with more pro-inflammatory constituents. This can result in the exacerbation of many auto-inflammatory diseases such as atherosclerosis.[7] Pharmacological interventions can re-establish a healthy gut microbiota and reduce the impacts of age-related diseases.[4] Likewise, there is research pointing towards the potential of vitamin D as an anti-aging supplement.[4] Vitamin D deficiency is common in elderly people and is associated with neurogenerative diseases such as Alzheimer's disease, as well as reduced muscle mass.[8,9] Supplementing vitamin D can reduce the risk and effects of these diseases, and thus act as an anti-aging mechanism.[4] However, the fact still remains that all these mechanisms are still limited in the sense that they can only slow down the aging process, rather than suspending it.

STEM CELL THERAPY

Stem cells are cells that are able to divide and differentiate into specific cells.[10] This is vital for maintaining the body's functional cells, as well as for repair. For example if someone has a bone fracture, periosteal stem cells and bone marrow mesenchymal stem cells are involved in the healing process.[11] However, the regenerative properties of stem cells generally decrease with age resulting in the progressive deterioration of body systems, and a reduced ability to withstand injury.[10] As such, stem cell therapy can be used to replenish healthy stem cells within the body and this can act as an anti-aging mechanism. This has the greatest potential to arrest aging but the process of generating stem cells is still error prone and can lead to the development of cancer.

CONCLUSION

Overall, there are many promising techniques to slow down the aging process but few that are viable for stopping it altogether. On top of that, aging is polygenic in nature which means that there are many factors at play in its progression.[12] Targeting all of these at the same time is unrealistic which means that some form of aging will persist despite treatment. As such, the concept of stopping aging still seems like a distant dream rather than a currently attainable goal.

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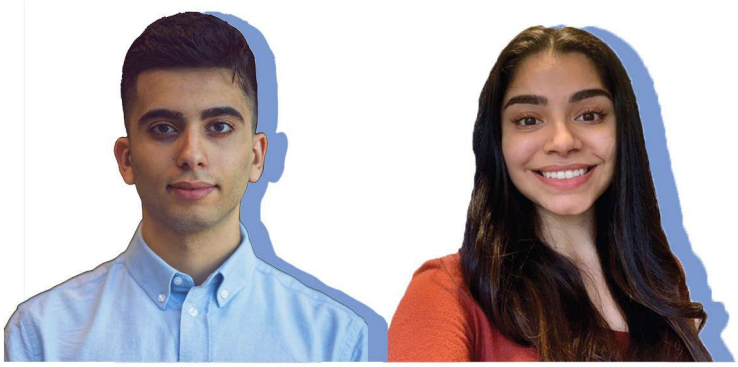

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