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Dear readers,

We are excited to share the fifth issue of the Harvard Medical Student Review (HMSR), which features the diversity of perspectives that characterizes the medical and graduate student community. On the pages that follow, we hope you find this student-driven content compelling and educational. We believe that these scholarly, policy-focused, and visionary works underscore the importance of student contributions to the medical field, and we are honored to continue providing a forum for student voice.

This past year, we have continued to grow and expand in new directions. To further highlight student commentary on current events in healthcare and medicine, we recently launched an inaugural editorial contest, Perspectives. You can find the prize-winning entry contained herein, which we hope you also find engaging and thought-provoking.

Our ability to showcase this issue is only possible because of the consistent efforts of our large editorial team, including our Associate Editors who ensure the highest standards of scholarly excellence and our Arts Editors who help us visualize published content in illuminating ways. We also extend our gratitude to our ever-expanding board of faculty, strategic, and alumni advisors, as well as Gina Vild and the Office of Communications and External Relations for their continued benefaction and investment in the growth of the HMSR.

Sincerely,

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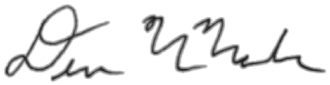

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The Harvard Medical Student Review (HMSR) is student-founded, student-managed, and student- administered under the guidance of faculty and staff. Its mission is to provide a platform for students to contribute to important issues facing health and medicine through a variety of formats, including scholarly articles, editorials, and original artwork. Contributions are invited from the Harvard medical, dental, and public health schools, the rest of Harvard University, and other medical schools.

The articles represent the views and opinions of the original authors and does not necessarily represent the views or opinions of the Harvard Medical Student Review or Harvard Medical School.

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VIEWPOINT
Reflective

All that Glitters: A Perspective on Peer Reviewed Publications

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As trainees and even as established clinicians, we are often gifted the following wisdom: pursue your passions, but make sure your passions are productive. The hidden meaning embedded in this term "productive" is that these passions should culminate in not just any form of scholarly material, but a peer reviewed paper. In an exploration of the origins and present state of peer review and its role for both the individual clinician and academic medicine at large, what follows is a discussion of the peer-reviewed publication as the "gold standard" of productivity, and what alternatives might be considered.

As trainees and even as established clinicians, we are often gifted the following wisdom: pursue your passions, but make sure your passions are productive. In the shadow of this encouragement is an implicit caveat – the kind of productivity these passions should inspire need not take the form of an oral presentation, nor a workshop, not a new tool, but a paper.

At the core of medicine is evolution – an anterograde inertia towards better. If research undergirds this ceaseless journey, then the peer-reviewed publication (PRP) is the gold standard. Certainly, the challenges of this system – delays in publication time, difficulty in detecting error, adequate power, availability of funding, and numerous sources of bias – have been described[1,2]. On the other hand, there are reasons for which the gold standard has gone untouched for so long. What follows is an exploration of the historical and current contexts that frame and reinforce the peer-reviewed publication as the mecca of academic medicine, and a reflection on whether we might make room for a second "first-line."

Publications: Past & Present Scholarship

Peer review in the sense that it functions today dates back to at least 1752 when the Royal Society of London established the so-called "Committee on Papers," which was formed for the explicit purposes of "refereeing" articles for publication in the scientific manuscript *Philosophical Transactions*.[3] One of the oldest and most established pillars of scientific integrity, the PRP persists as a cornerstone of academic medicine. The modern medical journal deliberately espouses this mission: selection of the "best research papers for their quality of work and the progression they bring" and maintenance of the "highest standards of editorial integrity" are listed right alongside the "improving lives" and the "betterment of public health" in the mission statements of some of today's most prominent journals.[4,5]

Through print, PRP's deliver innovation to a large audience simultaneously. Although one might argue that an oral presentation at a contemporary national meeting serves a similar purpose, referencing such a medium months or years later is more difficult. Moreover, at a time in history that did not boast modern conveniences like the internet or expedited travel, a written manuscript may have been the best,

if not the only, mechanism by which new information could be widely disseminated and preserved.

Aside from the public utility, a paper has individual advantages. For authors, a publication is the abstract pursuit of influence, the intrinsic desire to effect lasting change in their respective fields, made concrete. Of perhaps equal importance, it is also a means to an end in the ascent of the ivory tower. Although contemporary academic physicians in pursuit of tenure are considered for promotion based on a number of variables, productivity as measured by publications is the most consistent and significant factor. Though one might expect PRP's to be a focus of promotion for research and clinician-investigator tracks, one study found them to be a primary focus for even clinician-educators, albeit with fewer expected publications.[6]

Despite ongoing debate about the ability of peer review to neutrally assess a given study, the intensity of the process and its emphasis on "well-designed" scholarship places the product that emerges on a pedestal of objectivity. Although few would suggest that even the best of studies could yield truly objective data, a published, well-powered randomized control trial comes highly regarded and satisfies medicine's asymptotic pursuit of certainty better than any other form of scholarship. A PRP that survives the scrutiny of revision is therefore presumed to offer consumers the closest entity to an "answer" that we in our humanity can hope to generate; it is, we might say, the best we have.

More than One Winner: Future Directions

Historically, measures like impact factor and "number of times cited" have served as proxies of both dissemination and the contributory value of a given article or journal. And though widespread distribution is inherently valuable in perpetuating scholarship, there may be novel ways to quantify the same variables. Video platforms (e.g. YouTube, Vimeo) are accessed by millions of people everyday, and a video's number of views, shares, or comments are an objective measure of a product's reach. A suture skills tutorial which will be watched upwards of

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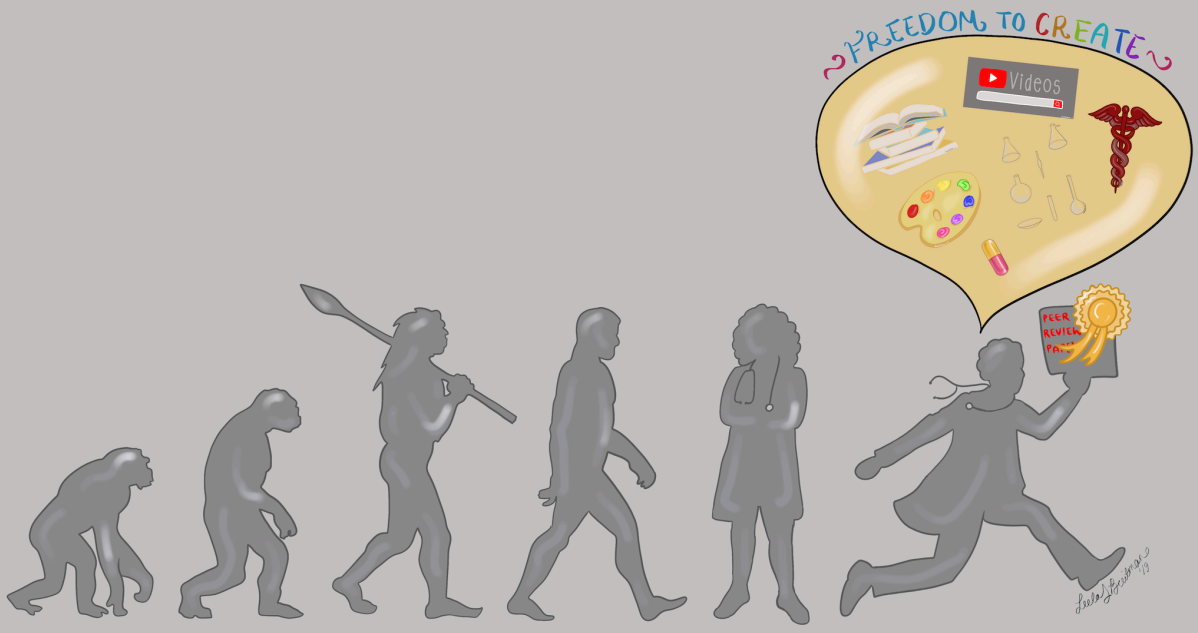

2 million times may have little to no influence on best practices the way a landmark trial cited over 2000 times will, but perhaps there is equal, albeit different, value in the extent to which it shapes its consumers' learning and patient-care landscapes.

Moreover, the story an author writes shapes the way it is told; that is, her intended impact guides the type of scholarship she will produce. An investigator seeking to demonstrate the noninferiority of a new therapy will conduct a trial and report her findings in traditional peer-reviewed form. A clinician-educator, by contrast, may seek to impart a skill rather than merely share information (i.e. how to conduct a large-group lecture), which may be best facilitated by a workshop, recorded video, or visit to another institution. In the case of the latter, the process of one-time "peer review" for submission in a journal may be less robust than the reiteration and revision that come from giving the same presentation repeatedly. This medium also has the potential to evolve and be adjusted more rapidly and organically than, for example, the findings of a years-long trial. This is not to say that educators or administrators cannot produce traditional peer-reviewed content; only that their particular narratives create the opportunity to disseminate content differently and in ways that are not only suited to their scholarship, but have unique benefits as well.

Finally, although the PRP provides the medical community with reassurance that we continue to evolve, we must question what sort of evolution it is that we seek. If, for example, we aim only to move the needle on best practices and novel therapies, the current paradigm is well suited. But if we aim to evolve individuals as well, there must be space for their ideas to not only flourish, but be affirmed and rewarded. The unspoken agreement that the PRP is the gold standard for faculty trickles down in whispers to trainees and, even if unintentionally, redirects them into "productive" tracks of thought. It encourages them to create in a way that answers a question rather than simply posing one. It puts that which is potentially novel at odds with that which is definitively high-yield.

The peer-reviewed publication is not going anywhere, and frankly we do not submit that it should. The gold standard remains a robust and reliable marker of progress, and a catalyst for innovation. But in considering the many ways to contribute meaningfully to this profession, it is apparent that other forms of innovation are not only acceptable relative to the PRP, but in some sense preferable and uniquely suited to perpetuate individuality and inquisition in scholarship. There is no regulation prohibiting any of us from pursuing these alternatives (e.g. a workshop video for trainee education or an oral presentation teaching participants how to use a new tool), only the inherent drive so many who seek careers in medicine have for success as defined by the worldly standards of the day. Rather than forcing these among us to weld a separate and, effectively, unequal accolades, let us foster a space that creates the freedom to… well, create. In doing so, we may unveil that not only gold glitters.

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Evidence-Based Policy Can Help Massachusetts Stay On Top Of Gun Violence

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The following essay provides an argument for the implementation of evidence-based gun control policies in Massachusetts. This argument is based on the disturbing trauma witnessed in the emergency room at Brigham & Women's Hospital, as well as the stagnant gun control rate over the last decade in our state. The argument is further supported by Dr. Hemenway's gun policy research and international policies that highlight the effectiveness of laws that strengthen background checks and limit gun ownership.

Our pagers rang "Code Trauma" when paramedics rushed a 15-year-old boy with a gunshot wound (GSW) to the chest into our emergency department. We urgently responded by running through the systematic algorithms of trauma care, but with each passing minute, his blood pressure dropped until his heart beat slowly gave way to the sound of silence. He hadn't graduated from high school or passed driving school yet, and now he laid in the bloody gurney of Trauma Bay 1. Time of death: 10:50 PM.

The amount of GSW victims we triaged that year felt surprising. Second to none in the United States, the state of Massachusetts is regularly noted as the nation's leader in gun violence prevention policy while boasting one of the lowest gun-related death rates per 100,000 people (1). Over the last two decades, the Commonwealth has passed the Gun Control Act of 1998 (2) focusing on gun licenses and firearm identification cards (FID), an assault weapons ban in 2004, and a comprehensive gun control bill in 2014 (3) touching on FID regulations, gun trafficking, mental health data sharing, suicide prevention, and broadened police discretion. More recently, Massachusetts became the first state to ban rapid-firing bump stocks in light of the 2017 Las Vegas shooting (4). These laws and regulations combined with low gun ownership rates are significantly responsible for the state's success.

However, coming face-to-face with a dying teenager afflicted by gun violence told us one thing: we can do better.

Well over the last decade, our state's progress in reducing the firearm mortality rate has stalled. The rate measured 3.4 deaths per 100,000 people in both 2005 and 2017 (5). These figures are relatively low when compared to other states, but they are distinctly high when compared to traditionally gun-avid countries like Australia (0.2 deaths per 100,000) and the United Kingdom (0.0 per 100,000) (6).

This impasse is partly a result of the Dickey amendment in 1996 that prevented the Centers for Disease Control & Prevention from advocating or promoting gun control, resulting in poor federal funding addressing the effectiveness of certain gun laws (7). But public outcry as a result of recent mass shootings has prompted universities and private institutions to allocate funds towards studying the effectiveness of gun policies—and it is working.

In 2017, David Hemenway and his group of researchers studied the association between U.S. firearm laws and firearm homicides. They analyzed gun control laws from varying cities, including all 50 U.S. states, and investigated the effects of firearm laws that curb firearm trafficking, strengthen background checks, improve child safety, ban military-style assault weapons, and restrict firearms in public places. Of these categories, the laws which strengthen background checks and permit-to-purchase regulations significantly decreased firearm homicide rates. The Task Force on Community Preventive Services and the National Academy of Sciences reached similar conclusions in the mid 2000s (6). It is clear from these studies that establishing effective gun laws that strengthen background checks and permit-to-purchase regulations could be the answer to advancing our gun violence prevention strategy.

Luckily, Massachusetts recently passed the "Red Flag" bill (8) in 2018, becoming the 4th state to enact a strong Extreme Risk Protection Order (ERPO). The Red Flag law provides an avenue for family and household members to petition the court to temporarily remove guns from people who pose a risk to themselves or others. The law works under the same premise as laws that strengthen background checks or regulate gun permits—that is, it helps remove firearms from the wrong hands. From Professor Hemenway's research and other studies (9), we know that the law's fundamental structure is likely to be an effective means of improving gun violence in Massachusetts.

Australia and the United Kingdom's remarkably low firearm mortality rates provide us with a similar message.

Since the 1980s, Australia has passed a series of laws to combat gun violence, including the National Firearms Agreement that banned semiautomatic rifles and shotguns, instituted a buyback of banned weapons, and more. Nevertheless, Australia's precipitous decline in firearm mortality rate is mostly attributed not to this agreement, but instead, to the country's earlier policies that regulated who has access to guns (10). In the United Kingdom, only police officers, members of the armed forces, or individuals with written permission from the Home Secretary are allowed to own a handgun (11). The general public in both countries have responded to heinous crimes through political group action, thereby significantly reducing firearm mortality through effective gun policies with the support of their legislative body—a feat the U.S. has yet to accomplish.

Although the Red-Flag law is poised to ignite a reduction in the gun death rate, public support mirroring that of countries like the United Kingdom, and more recently, New Zealand, is required to continue instituting effective gun control policy. Robustly supporting legislation that implements what we already know works—laws that strengthen background checks and limit gun ownership from people at high risk of committing a crime—will help Massachusetts further decrease its firearm mortality rate. Both successful international policies and recent gun research call for such a system. Massachusetts is leading the U.S. in firearm rules and regulations, but

Artist: Jonnell Small
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it can do better by centering conversations around research-based gun policy. An approach like so could ultimately prevent unnecessary deaths and allow more children to live out their dreams.

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REVIEW
Technology

Self-Tracking, Hacking, or Slacking? Health Justice in an Era of mHealth Technology

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As the doctor-patient relationship continues to evolve, there is increased enthusiasm for the role of mHealth technologies (smartphone apps or wearable sensors that monitor/log health-related functions) in the promotion of precision medicine. But numerous challenges have also emerged in the collection, transmission, and storage of personal health data. This paper addresses the ethical, legal, and public policy implications of mHealth use in the just allocation of health care resources. First, it utilizes Beauchamp and Childress' four principles of medical ethics (autonomy, beneficence, nonmaleficence, and justice) to weigh ethical considerations; next, it reviews privacy issues (e.g. informed consent, use of personal health information), and marketing influences, all of which raise legal concerns; and, finally, it looks at practical implementation of mHealth data/analysis, discussing evidence of current and future impacts upon health policy.

The doctor-patient relationship has undergone a substantial shift since the penning of the Hippocratic Oath; most notably, in its transition from a paternalistic decision-making model to a shared one. As the doctor-patient relationship continues to evolve, the medical profession must now determine how, and to what extent, it is prudent to incorporate mobile health technologies into healthcare. Mobile health (mHealth) technology refers to the use of smartphone apps or wearable sensors to monitor and log health-related functions and activities. Over the past decade, there has been increasing enthusiasm for the role of mHealth in promoting precision medicine, but numerous challenges have also emerged in the collection, transmission, and storage of personal health data. This paper addresses the ethical, legal, and public policy implications of mHealth use in the just allocation of health care resources. First, it utilizes Beauchamp and Childress' four principles of medical ethics (autonomy, beneficence, nonmaleficence, and justice) to weigh ethical considerations (Beauchamp & Childress, 2013); next, it reviews privacy issues (e.g. informed consent, use of personal health information), and marketing influences, all of which raise legal concerns; and, finally, it looks at practical implementation of mHealth data/analysis, discussing evidence of current and future impacts upon health policy.

In less than a decade, a steady stream of new smartphone applications and wearable mobile sensors allow users to monitor sleep, food intake, exercise, blood sugar, mood, and a host of other physiological states/behaviors. These technologies have helped advance a paradigm shift from total reliance on physician healthcare provision/responsibility to a more patient-engaged view that "My health is my responsibility, and I have the tools to manage it" (Sharon, 2017). Self-tracking for health is expected to play a key role in the move toward personalized healthcare, a model of preventive, targeted, patient-

participatory healthcare. mHealth is also being thought of as an avenue of ameliorating crises of public healthcare access/provision not only in industrialized nations, but in developing ones as well.

mHealth and telehealth have some overlap, but they are not the same; mHealth refers to mobile means of self-tracking (via apps or sensors), whereas telehealth refers to the broad use of technology for healthcare provision (e.g. doctor's appointment through video conference). There are thousands of health-related apps for smartphones and tablets that track information about food consumption, sleep patterns, blood chemistry, moods, menstrual cycles, heart rate, and stress levels, among other biological indicators. There are apps directed at managing various chronic conditions including those for diabetes, Crohn's disease, asthma, heart conditions, and pain; they act like digital journals, allowing users to log symptoms, the effectiveness of treatment and medications, and reactions to different foods and environments (Sharon, 2017). Analysis is typically offered in graph format, so users can visualize trends, such as when asthma symptoms peak, or what triggers high blood pressure. Mental well-being is another popular area for self-tracking; the Moodscope app, for example, allows users to score and track their daily moods and share these with a nominated buddy (Sharon, 2017). Some devices are designed to be worn directly on the body, automatically collecting data and wirelessly syncing it to the user's computer or smartphone. Currently, there are estimates of as many as 97,000 mobile health apps and 485 million wearable devices (Sharon, 2017).

Ethical Considerations

Self-monitoring applications have great potential to aid and modify people's lifestyle habits, and to encourage self-management of chronic conditions; uses which serve to increase patient autonomy. Interactive technological systems designed to change behavior of their users are known as persuasive technologies. Utilizing strategies from behavioral psychology, "nudging" applications use tactical choice patterns intended to facilitate or promote certain behaviors, while individuals retain freedom of self-determination (Paldan, Sauer, & Wagner, 2018). Accessed via smartphones or smartwatches, these technologies are marketed as empowerment strategies for taking charge of one's own health. Nudging practices have long been utilized within the advertising/marketing industry. And while they are met with criticism by some in the healthcare field, they are heartily embraced by others.

The use of technology for good, or medical beneficence, has been demonstrated in multiple studies reporting outcomes ranging from improved self-management of illness to improved access to care. In particular, rural residents report improved health care access, as barriers such as transportation, or provider distance, are mitigated (Francis, 2017). One specific example of mHealth beneficence is offered by Larry Smarr, a member of the Quantified Self movement, who discovered he had Crohn's disease before his doctors, due to his extensive self-tracking. He maintains that one cannot necessarily trust how one "feels"; certainty lies only in what can be measured (Sharon, 2017).

Issues of nonmaleficence arise through potential harms incurred as a result of patient/consumer actions taken due to lack of understanding, erroneous interpretation of presenting information, technology failures, or privacy and confidentiality breaches (Francis, 2017). (Privacy issues will be addressed in more detail in the section of the paper citing legal concerns.) There is also potential for harm in patient over-reliance on app use, in lieu of doctor visits or evidence-based treatments. Self-tracking exemplifies valuing "one's choices and the need to be responsible for them while, at the same time, relieving oneself of responsibility by delegating it to external technology" (Schüll, 2016).

Justice issues arise in the unequal opportunities those from lower socioeconomic groups must contend with in the access, and utilization, of such technologies. People require the financial resources to buy these (often expensive) devices, the time to fit their use into their daily routines (comprised of multiple jobs and tight schedules), and they need the knowledge and education to use these devices properly. Maintaining one's health through the adoption and maintenance of a healthy lifestyle requires

financial, personal, environmental and educational resources.

Individuals of higher socioeconomic means are therefore most likely to benefit from available "knowledge, efficacy, and resources in adopting innovative health-related behaviors" (Frantcis, 2017). A phenomenon referred to as the "digital divide" occurs when there is a divide in access to digital technology or information due to socio-economic demographic variances among groups. People age 65 and older, those who did not attend college, those living in households earning less than $30,000, and those in rural areas, have less access to smartphones and thus to self-monitoring applications (Francis, 2017).

Health and computer literacy also factor into health-related information searches, and self-monitoring behaviors. People of migrant background, low levels of education, low economic means, chronic illness, and older age have comparatively limited health literacy. These inequities serve to compound healthcare disparities through the "differential distribution of technologies that simultaneously enhance and impede literacy, motivation, and ability of different groups (and individuals) in the population" (Francis, 2017).

Corporate wellness programs offer lower health insurance premiums to employees based on activity measures (e.g. number of steps counted), or worker productivity through physiological indicators such as respiration or stress level measures. Employers promote programs to optimize employee health, improve productivity, and increase morale through friendly competition, but critics argue that the line between voluntary and compulsory participation is not always clear-cut, and those who do not participate (or succeed) in these initiatives are being penalized via more expensive premiums. Financial incentives, such as lower health insurance premiums offered to those using self-monitoring applications, can result in financial discrimination for those who are not able to use self-monitoring applications, thus exacerbating existing inequalities. Additionally, when construed as a choice, those who do not, or cannot, "choose" health-promoting activities risk scorn or stigmatization for added burdens placed on the public health system, and may incur penalizations or the withholding of treatments based on lifestyle (Sharon, 2017).

Legal Concerns

In addition to ethical issues surrounding mHealth use, there are legal concerns that have emerged regarding trust, privacy, and sharing of health data outside of clinical settings. Studies have shown that "members of the general public expressed little concern" (Ostherr et al., 2017) about sharing health data with the companies that sold the devices or apps they used, indicating that they rarely read the "terms and conditions" they signed or agreed to detailing how their data may be used by the company or shared with third-party affiliates (Ostherr et al., 2017). In contrast, interviews with researchers revealed significant resistance among potential research participants in sharing their user-generated health data (data captured through devices or software, e.g. via wearable heart rate monitors, step-counters, and sleep trackers) for purposes of scientific study.

Data generated from wearable technologies and mobile apps may serve to uncover new indicators of health and illness outside of traditional clinical settings. On the flip side, there is also potential risk involved when data that emerges is subsequently shared, or utilized, in ways that may not serve user/participant best interests. Questions surrounding who benefits from big health data are further entangled with uncertainties about data ownership, sharing, trust, and privacy (Ostherr et al., 2017). Contemporary practices of health datafication within and outside clinical settings pose new "challenges to traditional understandings of agency and ownership of medical data" (Health Information Law Project, 2015; Ostherr et al., 2017).

Special privacy and confidentiality issues, such as those involving family planning services and treatment for sexually transmitted diseases can raise important mHealth implications. Hospitals need to be sensitive to the special issues raised in the use of personal health records (PHR) by their patients and families, such as what might be added to a personal health record, how, and by whom, that can be occasioned by the link between a patient's electronic health record (EHR) and PHR (Petersen & DeMuro,

2015). How might social media sites interface with an individual's EHR or PHR? Although a topic of debate in the United States, it is generally accepted that "an individual's medical record is owned by the provider who retains the record, not the individual whose medical information resides in the record" (Petersen & DeMuro, 2015). As providers move to EHRs, the location of information from an individual's EHR might be in more disparate locations, but providers still take the position that they own a patient's medical record. This ownership, however, does not take all rights away from patients as they are still covered by privacy protections included in the Health Insurance Portability and Accountability Act of 1996 (Petersen & DeMuro, 2015). Patient-generated health data (PGHD) is health-related data created, recorded, or gathered from patients (or designees) from multiple sources, including patient registries, research networks, social media, remote sensors, smart wearable devices, and mHealth apps. Patients may believe that they are in control of their PGHD, when in fact, due to the multiple venues utilized, each with its own privacy/exclusion criteria, this may not be the case.

Medical contexts, or traditional clinical settings are sites where formal doctor–patient interaction is governed by health law such as the Health Information Portability and Accountability Act of 1996 (HIPAA) and the U.S. Food and Drug Administration (FDA) which governs the use of medical devices, including some digital health tools (Ostherr et al., 2017). When considering how user-generated health data travels through social and information networks, regulatory boundaries between the non-clinical and the clinical must be defined; specifically, boundaries between consumer-facing software applications and devices (which do not require FDA approval and are not governed by HIPAA), and clinical-facing apps and devices (regulated by FDA and HIPAA). Although the proliferation of PGHD may seem a natural extension of consumer reliance on technology and online information-sharing, healthcare is not like other service industries; it is a unique realm comprised of "histories, demands, and stakes that do not…apply to rideshare networks, real estate tourism, or romantic match-making services" (Ostherr et al., 2017). This problematic boundary-blurring manifests as the "net of surveillance" is extended; beginning with user self-surveillance, who in turn invite peers to participate in monitoring practices (via sharing personal data on social media and other digital platforms), which results in data being potentially used for other purposes (e.g. marketing, potentially discriminatory, etc.). Marketing practices are already noticeable in the "gamification" of self-tracking, where self-trackers can compare their data against others'; intrusive surveillance practices are thus normalized, at the expense of unsuspecting participants having fun (Sharon, 2017).

Large corporations that manufacture self-tracking devices like Nike and Fitbit transform the data their users generate into commercial value by sharing this information with various third parties. Some view these practices as free "digital labor", forms of unpaid labor that people carry out online under the guise of fun and leisure that end up being highly profitable for these corporations (Sharon, 2017). News about the amount of data shared or sold by health technology companies and by platforms like Facebook, the lack of transparency about some of these activities, and the possible malicious uses by third-parties of these data have sparked a "techlash" reflecting public unease about many technologies central to mHealth research and clinical care (Schairer, Rubanovich, & Bloss, 2018).

Health-related device and software companies operating outside of hospitals, clinics, and other HIPAA-protected zones "face few restrictions on their exploitation of users' data" as consumers must agree to the "terms and conditions" to activate and use the app. In many cases, these lengthy, complexly written terms of use permit the parent company to sell users' health data to third parties, such as marketers, advertisers, and other types of data brokers (Ostherr et al., 2017). Paradoxically, some users are more willing to share their health data on an app than with their healthcare provider. This may result from the device's sociotechnical infrastructure; the social networking capacity that enables users to share their health data is often a key feature in product design and a central marketing component for many health-related apps on mobile devices. While

users seem generally aware that consenting to a company's terms of use constitutes a legal contract, very few report reading those agreements before consenting to them; "research suggests that the concept of privacy itself is undergoing change in the public consciousness, and the legal system has not kept pace" (Ostherr et al., 2017).

The person who generates data only controls the data until he/she posts such data on a social media site; once posted, the social media sites take the position that the data is theirs and they can use it as they wish (incorporated in the legalese of consent). Due to the many complications created by a social media site owning an individual's data, in 2012 the European Union (EU) introduced the "right to be forgotten", implemented by requirements that search engines, like Google, remove links to personal information at the request of the individual (Petersen & DeMuro, 2015).

Questions related to provider licensure pose another potential barrier to the routine use of mHealth. When a patient has her radiograph read, many current US state laws require that it be read by a physician licensed in the state where the patient is located and had the radiograph (Petersen & DeMuro, 2015). If, for example, a patient resides in New York and has an mHealth device that continues to monitor aspects of her health while the patient crosses three states, does the patient's physician need to be licensed in each of the other three states where data is transmitted? Some states issue a telemedicine license to facilitate practice across state lines when the physician holds an unrestricted license in another state (Petersen & DeMuro, 2015). But for practitioners without a telemedicine license, mHealth transmissions/readings across state lines and out of a provider's state/s of licensure can pose potential liability issues.

mHealth tools pose challenges for the process of obtaining meaningful informed consent from users. The risks are wide ranging; insurance discrimination based on data from mHealth technologies integrated into workplace wellness programs, invasion of privacy of family members/bystanders with collection of data in home environments, "compromising community safety (as in military presence recently revealed by the Strava app), and political manipulation through profiling based on health data" (Schairer et al., 2018). The unique obstacle for mHealth with respect to informed consent is that users, whether research participants, patients, or "lifeloggers" (people digitally recording all aspects of their lives), are nearly always required to agree to terms of use of the under-regulated commercial entities supplying mHealth devices and services (Schairer et al., 2018). Typical terms of use for commercially developed apps and devices include lengthy legalese covering the release or selling of personal identifiable data; such complicated terms of agreement do not comply with principles of informed consent (Schairer et al., 2018). In medical settings, institutional review boards (IRBs) require clear and explicit language stating risks, such as risks to privacy, and how patient confidentiality will be protected. But "there is a challenge in reconciling IRB-approved informed consent documents with the terms of use set forth by commercial entities" (Schairer et al., 2018).

Collaborative private and public initiatives are well underway; examples include one between Apple and leading research centers using the "ResearchKit" platform (which allows clinicians to develop apps for carrying out medical studies on iPhones), Google's "Baseline Study" in partnership with Duke and Stanford Universities, or the Institute for Systems Biology's "Hundred Person Wellness Project" (Sharon, 2017). Research scientists and policy-makers must remember to exercise caution around data neutrality. Algorithms and big data are not necessarily objective; study designs, meanings, and interpretations are at the hands of human beings, which means they cannot be completely free of bias and embedded value judgments. Ideals of wellness, health, and even happiness may be configured in ways that perpetuate normative stereotypes, influencing mHealth users to think about their own behaviors in accordance with predetermined (societal) standards, rather than evidence-based medical ones (Sharon, 2017).

In an attempt to facilitate research, recent changes to the Common Rule have expanded exemptions for informed consent. But expanding exemptions may become problematic for mHealth research

as the public becomes more concerned about privacy issues related to consumer devices and apps (Schairer et al., 2018). Some have proposed opt-out consent in situations where "the potential benefits of mHealth research for collective health" may be deemed significant enough to outweigh individual autonomy (Schairer et al., 2018), or establishment of a "health data commons", a system of governance that would allow individuals to lend their health data to research as part of a collective that would set its own terms for data use (wherein participants use democratic means to negotiate the terms of consent) (Schairer et al., 2018). All these approaches are ways to reinvent informed consent, which begs the question, Should we be experimenting with informed consent (for medical/research purposes)? And, if so, how do we define vulnerable populations in the context of mHealth users?

Health Public Policy

Public policy supports greater use of PGHD (Petersen & DeMuro, 2015). The Office of the National Coordinator for Health Information Technology has indicated that bringing patient-reported data into certified electronic health records is a high priority and expected to "stimulate greater patient engagement in stage 3 of the meaningful use electronic health record incentive program" (Petersen & DeMuro, 2015). The FDA has also acknowledged the need to use patient-generated information in pharmacovigilance. The growing use of self-tracking devices means that a significant amount of data can be generated beyond the clinic by patients themselves, thus "reconfiguring them as knowledge producers, not just knowledge recipients" (Sharon, 2017). In this way, citizens and patients are effectively helping to improve population health, by actively contributing to medical decision-making and research in ways that were previously inconceivable (Sharon, 2017).

Federal Agencies such as the Agency for Healthcare Research and Quality, the National Institute of Health, and the Department of Health and Human Services Office of Minority Health, fund grants for research in mHealth. It is not yet clear which agencies will ultimately have oversight for specific components of this evolving field; nor is it known the extent of US regulation and guidance. The complexity of the issues, along with legislation pertaining to various aspects of the mHealth continuum, highlight an increasing need to adequately sort out these regulations (Bloomrosen, 2014). There are also evolving tensions between government regulators and the private sector business community to balance the needs for patient safety with the desire to promote technological innovation.

As the field of medicine embraces big data, a "truism has taken hold: more data equals more knowledge equals better health outcomes" (Ostherr et al., 2017). But if more data consists of erroneous data, then more is not better—for research, treatment, nor health outcome purposes. Are data generated from mHealth technologies as reliable as data obtained through gold standard equipment and technologies? Studies conducted so far have yielded mixed results. mHealth app accuracy can be negatively impacted by patient movements and positional variability, differences in smartphone technologies, variations in app software (e.g. algorithm), and environmental effects (e.g. uncontrolled ambient lighting) (Li et al., 2019). One study comparing iPhone app-based heart rate measurements with in-hospital electrocardiograms and pulse oximetry measurements showed that only one app measured heart rate with comparable accuracy to pulse oximetry, while three other apps did not perform as well (Coppetti et al., 2017). It was also found that contact (fingertip-based) PPG apps performed better than non-contact PPG apps (PPG refers to photoplethysmography, a photoelectric technique for detecting changes in blood volume, using smart-phone camera technology (Elgendi et al., 2019), with "differences of 20 bpm or more in 20%" (Coppetti et al., 2017) of non-contact app transmissions. Another study comparing the diagnostic accuracy of a smartphone PPG app for atrial fibrillation (AF) against the gold standard 12-lead ECG, found the FibriCheck app accurately detected AF in 192 of 196 subjects, a 98% similarity (Proesmans et al., 2019). Discrepancies in PPG app data results serve an important reminder; people should not be overly reliant on such apps as standalone monitoring devices. The more serious the

medical condition being monitored by app or remote sensor, the greater the need for clinical and empirical substantiation of data/transmission equivalency to that of gold standard medical equipment.

In-depth examination and synthesis of what works and what does not will require rigorous, ongoing assessment. While there is growing literature that documents the promise of mHealth, the current evidence base is not yet sufficient to adequately inform public policy. Due to evolving, overlapping, and increasingly blurred boundaries of the healthcare, information technology and telecommunications industries, "public policy challenges especially those related to cybersecurity, privacy, and standards and interoperability must be considered" (Bloomrosen, 2014). There are some encouraging mHealth results from a report by the MEASURE Evaluation project, a project funded by the U.S. Agency for International Development (USAID) that works to strengthen health information systems in developing countries, which indicate that "mobile technologies have helped to improve training and service quality of healthcare workers; lower the cost of services by reducing redundancy and duplication; and enhance access to reliable data to facilitate decision making" (MEASURE Evaluation of mHealth, 2018).

Utilizing mHealth technologies for the just allocation of healthcare, by reaching underserved populations, is certainly an exciting prospect, but it is still too early to tell whether this technology will yield the improvements projected. Not only do privacy/data use issues need to be addressed from a legal perspective, and technology accessibility and literacy levels addressed from a socioeconomic perspective, but there remain cultural sensitivity issues (e.g. distrust

of medical practices) carrying over from in-person medical relationships to technology-enabled ones. Efforts are being made to foster increased trust/receptivity to mHealth technology use through local churches and community centers. In one such collaborative effort in Minnesota, academic medical hospitals are working closely with five predominately African-American churches to recruit congregants into a pilot study investigating mHealth technology use in the promotion of cardiovascular health (Brewer et al., 2018).

mHealth researchers and policy developers must be cognizant that most apps are developed for the general population, and not focused on the health needs of underserved communities (Anderson-Lewis, Darville, Mercado, Howell, & Di Maggio, 2018). As a result, research regarding the use of mHealth interventions for the populations that may need it the most remains sparse. Positive results are reported for the text4baby program dedicated to improving maternal and child health outcomes among low-income, minority, and underserved women. The program applies "culturally tailored health messages and uses in depth strategies to survey and identify the optimal methods for delivery of service and care among the target population" (Anderson-Lewis et al., 2018). Such lessons of cultural tailoring are important for mHealth projects currently underway. Mobile phones and other portable health information technologies offer unprecedented opportunities to improve the health of the U.S. population and reach traditionally underserved populations. As this paper demonstrates, there remain numerous ethical, legal, and public policy challenges yet to be adequately addressed. But there are many reasons to remain optimistic about the potential for mHealth to improve healthcare access across demographics (socioeconomic, ethnic, cultural, age, gender) and terrains (urban, remote, resource- or access-poor). mHealth technology is indeed well positioned to help bridge some of the gap in healthcare provision; in so doing, it can improve equity and the just allocation of health care resources across the United States, and globally.

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REVIEW
Science

The Neural Underpinnings of Sacral Neuromodulation Therapy for Functional Gastrointestinal Disorders

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Sacral Neuromodulation (SNM) is an established nerve stimulation treatment for Functional Gastrointestinal Disorders (FGIDs) such as Faecal Incontinence (FI), Slow Transit Constipation (STC) and ileus. SNM may involve the surgical placement of electrodes against the sacral roots of the spinal cord to alter the physiological function of the target organs. It can also be performed by using Transcutaneous Electrical Nerve Stimulation (TENS) which is a non-invasive and cost-effective SNM technique consisting of placing electrodes on the intact skin instead of implantation. However, despite the increasing application of this therapy, the neural underpinnings of SNM are poorly understood. One of the consequences of this poor understanding is that currently SNM is administrated on a trial-and-error basis and there are no standard guidelines on the optimal therapeutic parameters. Evolving studies aim at exploring the neural mechanisms of SNM for FGIDs by either focusing on the extrinsic innervation of the gut or probing the relationship between the gut and the central nervous system (CNS). Recent studies have revealed that various brain regions could be involved in the process. Moreover, detecting meaningful electrical changes over the somatosensory cortex of SNM treated patients indicates that C-afferent fibers might be the most likely target nerves of SNM. Nevertheless, a deeper understanding of the underlying neural function of SNM is essential to improve identification of the most effective stimulation techniques and parameters for FGIDs which can subsequently influence the decision of clinicians for permanent implantation of electrodes.

1. Introduction

Sacral Neuromodulation (SNM) was first used clinically in the early 1980s to treat patients with urinary incontinence and retention (9). SNM involves the surgical placement of electrodes against sacral roots of the spinal cord to modulate the

physiological function of the target organs through nerve stimulation (Fig.1). It can also be performed using Transcutaneous Electrical Nerve Stimulation (TENS) which is a non-invasive and cost-effective neuromodulation technique consisting of placement of electrodes on the intact surface of the skin. TENS is an ideal alternative to electrode implantation as similar results can be achieved while avoiding infection and other complications associated with the surgical procedure (16).

TENS therapy was initially introduced to manage painful conditions. Hence, it was not extensively used to treat non-painful conditions such as functional gastrointestinal disorders (FGIDs). In 1995 Matzel & colleagues used SNM for the first time to treat Faecal Incontinence (FI) (11,15). Since then, SNM has been evaluated and used by clinicians to manage FI, chronic constipation and ileus. It has specially become a first line therapy for FI with a success rate of 74-86% (4,11,15).

Nevertheless, despite the increasing application of this treatment, the neural underpinnings of SNM are poorly understood specially with respect to FGIDs (9,11,15). The main paradox about SNM's physiological function is that not only it can treat a wide range of disorders, but it is beneficial for disorders with divergent symptoms. It is intuitively difficult to fathom how SNM can benefit both FI and chronic constipation which are disorders with contrasting pathophysiology.

An increasing number of studies have explored SNM's underlying mechanism of action in both clinical settings and animal models (8,9,11,12). Some postulate that SNM modulates the balance between afferent and efferent nerve tone whereas others have demonstrated a central cortical effect (10,11). However, most data on the neural function of SNM are derived from the field of urology (10,15). The activation of afferent inhibitory pathway is generally accepted as the underlying neural mechanism of SNM in urinary incontinence and idiopathic detrusor instability. Studies have also revealed that stimulation of afferent fibres in the pudendal nerves inhibits the overactive bladder (17,22).

Although research on the outcomes of SNM for urinary tract ailments can provide insights into the workings of SNM for FGIDs, it is not enough to identify its neural mechanisms for such disorders. Over the past two decades, several hypotheses have been advanced to explain the beneficial effects of SNM for FGIDs. These can be classified into two main research focus areas of extrinsic innervation of the gut and the central nervous system.

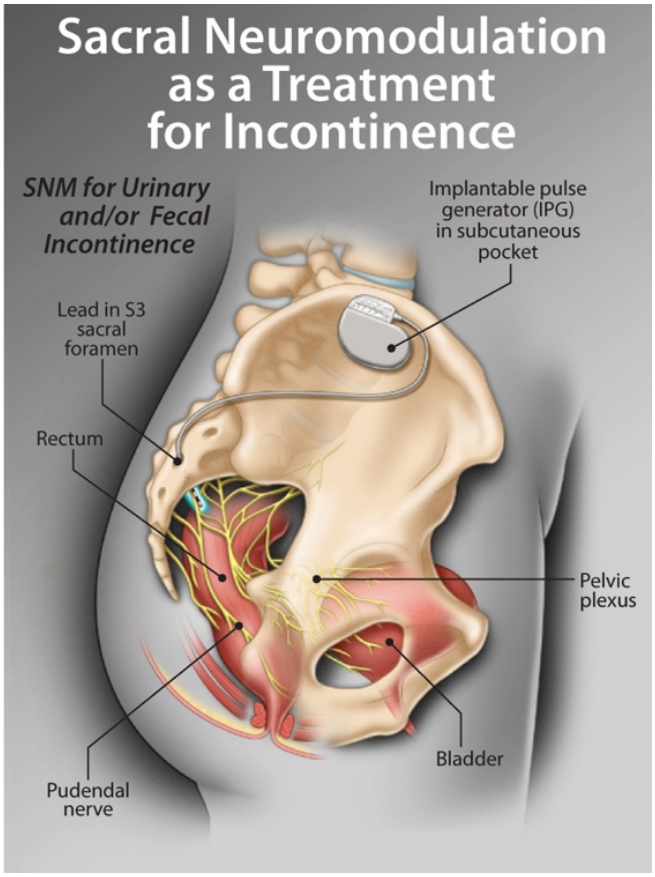


Figure 1: Implanted sacral nerve stimulator for treatment of faecal and urinary incontinence [Figure from Elterman & Van Asseldonk, 7].

2. Extrinsic Innervation of The Gut

2.1 Hypothesis 1: Somato-visceral Reflex

There is much evidence that somato-visceral reflexes mediate colonic activity (5,10, 25). Therefore, several studies on the effect of SNM on both FI and chronic constipation have relied on this hypothesis (5,10,24,25). For instance, a colorectal electromyographic activity experiment by Vitton et al., (2008) demonstrated that stimulation of sacral dorsal roots in cats inhibits the colonic spike potential frequency. This effect faded away by administrating a

noradrenergic blocker and sectioning the sympathetic efferent fibres indicating that the sympathetic system was involved in the process (25).

Clinical studies on FI patients have provided support for this hypothesis; though the existence of a somato-visceral reflex in humans is not as clear as in animals (10). Studies by Michelsen et al., (2010) on the postprandial effects of SNM in FI patients revealed a significant increase in retrograde transport in the descending colon and a modest increase in total colonic transit time in patients who received SNM therapy. This implies the existence of a sympathetic inhibition reflex that is activated to improve continence (20).

However, other studies on FI patients have reported varying results. For instance, in a study by Uludag et al., (2006) anal resting and squeeze pressure as well as segmental and total colonic transit time in FI patients did not show any significant difference after SNM. Moreover, studies on patients with slow-transit constipation provide evidence for a contrasting neural mechanism (24). Dinning et al., (2006) reported that SNM can induce colonic propulsive activity which is triggered by parasympathetic system rather than sympathetic in constipated patients. Additionally, a study on mucosal blood flow revealed that SNM can increase blood flow to the colonic mucosa which is achieved by enhancing parasympathetic activity (10).

A possible explanation for such discrepancies is that SNM modulates both sympathetic and parasympathetic systems and the observed effects are the net result of this dual activation. In addition to somatic afferent fibres, parasympathetic efferent fibres could also be activated to achieve the balance between afferent and efferent nerve tone. Somato-visceral dual activation hypothesis has been convincingly evaluated for urinary tract disorders (9,23). However, future research is required to determine if SNM for FGIDs results in this dual activation.

2.2 Hypothesis 2: Modulation of the Perception of Afferent Signalling

This hypothesis suggests that SNM inhibits the activity of C-afferent fibres that form the ascending limb of the defecation reflex. SNM blocks the transfer of sensory signals to the brain stem and results in reduced defecation. Anatomically, the fibres originating from S2-S4 spinal segments comprise of the pelvic nerves, the pudendal nerve (somatic fibres) and afferent sensory fibres innervating the colon, rectum and anal sphincters. Therefore, SNM may potentially stimulate both somatic and autonomic efferent and afferent fibres. However, there is much evidence that the afferent sensory fibres are the most likely neural targets of SNM (8,10,11,21). This hypothesis is strongly supported by data that detected the cerebral effects of SNM over the somatosensory cortex (8,9,10,11,15).

Additional supporting evidence for this hypothesis comes from decades of TENS studies on painful conditions demonstrating that neuromodulation blocks incoming afferent information in peripheral nerves. Impulses generated in afferents by TENS travel towards the sensory receptors and collide with impulses generated during activation of sensory receptor cells by natural stimuli that are travelling to the CNS. Therefore, afferent information is extinguished during TENS therapy (16). Moreover, high intensity TENS activates small-diameter myelinated afferents that have higher thresholds of activation. TENS-induced activity in these afferents leads to excitation of inhibitory interneurons preventing the transmission of nociceptive information to the CNS (16).

While this hypothesis elucidates how SNM might aid FI patients, it provides little explanation for the beneficial effects of SNM for constipation. If SNM blocks the C-fibres in the ascending limb of the defecation reflex, then how are constipation symptoms improved through SNM therapy where colonic propulsive motility is enhanced? This question requires further investigation.

2.3 Hypothesis 3: Modulation of External Anal Sphincter Activity

Modification of the activity of external anal sphincter (EAS) could be one of the reasons that SNM boosts faecal continence. This hypothesis maintains that SNM activates somatic large afferent fibres that enhance EAS activity leading to improved

continence. Nevertheless, it was magnetic stimulation studies that gave rise to this hypothesis not SNM.

Harris et al., (2008) demonstrated that chronic lumbosacral magnetic stimulation increased the amplitude of cortico-anal electromyographic response which implies that a supraspinal mode of action is responsible for increasing EAS squeeze pressure in FI patients. However, results from this study could not be replicated in patients who were treated by SNM. Additionally, anorectal manometry failed to identify any significant change in the EAS activity after chronic SNM therapy in FI patients. Yet, several studies recording cortical activities, detected the activation of motor cortex during SNM administration which is consistent with this hypothesis (10,13).

Apart from lack of substantial evidence that SNM modulates EAS activity, this hypothesis is not enough to explain how SNM works for such a wide range of FGIDs. If more supporting data is gathered, this hypothesis can at best help in understanding how SNM enhances EAS activity in FI.

3. Central Nervous System: Brain and Spinal Effects of SNM

Recently with the advancement of brain imaging techniques, a clear effect of SNM on the CNS has been detected (1,9-11,18). Although research on central effects of SNM for FGIDs is deficient, there is strong electrophysiological evidence from TENS studies on both painful and other non-painful conditions for the central effects of SNM. Evolving animal and human data reveal specific changes in cortical activation following SNM treatment specially over the somatosensory cortex using Electroencephalogram (EEG), PET scan or MRI (8).

For instance, a series of pain studies by Garisson & Foreman (1994, 1996, 2002) on anesthetized cats using microelectrodes to record extracellular action potentials found that TENS reduced activity in 65% of spontaneously active spinal dorsal horn cells. These results were reproduced in several other animal studies (16). They later postulated that the mechanism of action of TENS includes inducing activity in small-diameter cutaneous and muscle afferents. This activity excites central transmission neurons in ascending neuronal tracts which synapse in regions of the brain that are part of the descending pain-inhibitory pathways and form a feedback loop to the spinal cord to prevent further transmission of noxious information (16).

One of the most comprehensive studies on the cerebral effects of SNM for FGIDs was performed by Giani et al., (2011) who evaluated the cortical effects of SNM (percutaneous insertion of a temporary electrode into the sacral nerve root at S3) after pudendal nerve stimulation administrated to both FI and constipated patients. Electrical cortical responses were recorded before and after chronic SNM therapy using a mere two electrode EEG. Evaluation of the latency of the somatosensory evoked potentials (SEP) induced by pudendal nerve stimulation took place before and one month after SNM therapy (9). Results demonstrated a significant decrease in the latency before the first positive electric deflection (P40) over the somatosensory cortex in patients of both groups who were successfully treated with SNM as well as in the first negative deflection (N50) in FI patients (9,15). These results indicate that SNM mainly targets afferent sensory fibres. Moreover, it implies that measurement of P40 and/or N50 SEPs using a non-invasive EEG test may help to predict the outcome of SNM which subsequently influences the decision of clinicians for permanent implantation of electrodes.

Using PET scan and MRI, Lundby et al., (2011) inferred that the afferent projections of colorectum are the target of SNM in FI patients. They measured local increase of regional cerebral blood flow (rCBF) caused by increased neural activity through analyzing changes in the uptake of a radiolabeled tracer of blood flow. The initial stimulation of sacral nerves through an implant activated a region on the contralateral frontal cortex but after chronic stimulation this activation was shifted to ipsilateral caudate nucleus which is a region of the brain involved in learning and reward processing (Fig.2). A similar cerebral effect has also been observed in vagus nerve stimulation (18).

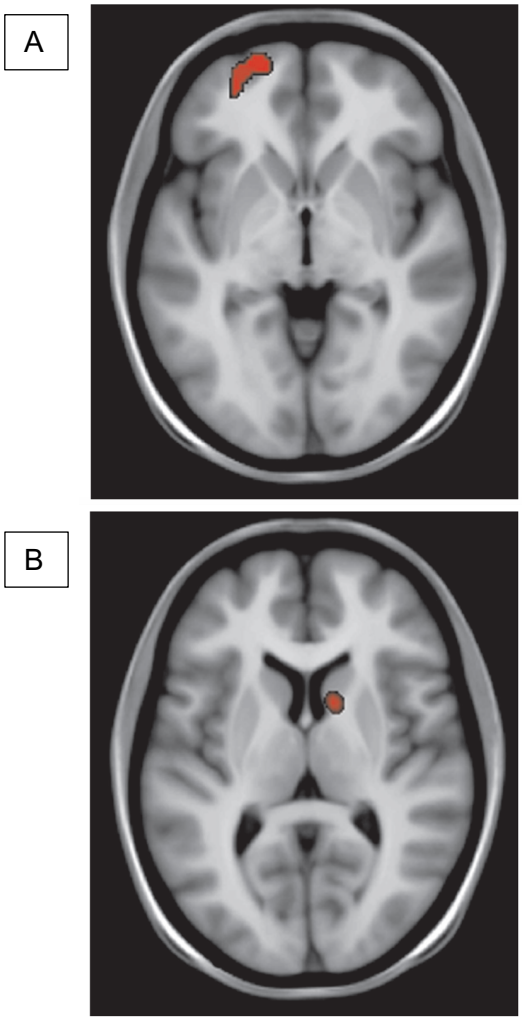


Figure 2. Changes in regional cerebral blood flow (rCBF) tested via PET/MRI co-registration. (A) The red region shows initial activation of the contralateral frontal cortex 30 minutes after onset of sacral nerve stimulation. (B) Red shows activation of the ipsilateral caudate nucleus after 2 weeks of sacral nerve stimulation. Statistical significance was at $P < 0.05$. [Figures from Lundby et al.,18].

To establish optimal stimulation parameters, Evers et al., (2014) conducted an animal experiment in which anal canal SEPs were recorded using a flexible multi-electrode array inserted in the brain of anesthetized rats. For SNM stimulation, a needle electrode was placed in the first sacral foramen and a wide frequency range of 0.1 to 100 Hz and various durations were applied. Results revealed that the magnitude of evoked potentials over the somatosensory cortex depended significantly on SNM stimulation frequency. Even a short burst could result in a long-term potentiation in the somatosensory cortex. However, to produce this effect, a critical burst duration of at least 3 minutes was required (8).

The effect of stimulation frequency and amplitude on SNM's outcome has also been studied in humans. Duelund et al. (2013), examined different pulse combinations for 4 weeks on FI patients and more than half of the patients preferred higher frequency stimulation of 31 Hz to increase total number of spontaneous bowel movements per week (6).

Remarkably, various clinical TENS studies on constipation, FI and ileus suggest a wide range of optimal stimulation parameters for the same disorder (6,16). As pointed out by Devane et al., (2015), the optimal stimulation parameters are so highly variable in the literature that it is impossible to establish any standard guidelines. On the other hand, in most human studies higher frequencies and longer durations provided better results while in animal studies the trend is towards lower frequencies (8). This casts doubt on the transferability of results from animal models to humans. However, different methodological issues may be partly responsible for this observed discrepancy. For example, in most animal studies only a brief time period is examined in contrast to the chronic nature of SNM therapy in humans (8,10).

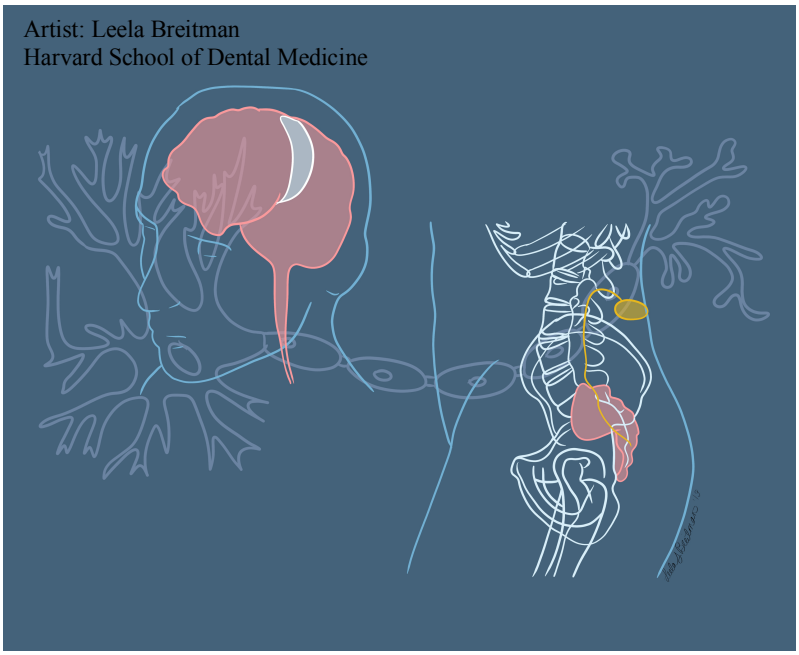
Another line of research on central effects of SNM is focused on the expression of a protein product of proto-oncogene c-Fos which is expressed in response to direct stimulation by neurotransmitters and has been long used to label activated neurons in the CNS. It is known that electrical stimulation of the pelvic nerves induces c-Fos expression in dorsal horn neurons of the spinal cord (14). Ishigooka et al., (2002) investigated the effect of SNM on c-Fos expression within the spinal cord in rats with or without lower urinary tract irritation who underwent SNM and c-Fos immunohistochemistry of the spinal segments. Results revealed that the animals treated by SNM had a significantly higher c-Fos positive cells in L6 and S1 spinal segments (14). However, to my knowledge, no such studies have been conducted on SNM for FGIDs.

Despite the increasing body of research, there is not yet sufficient information neither about the central effects of SNM on the clinical outcome for FGIDs nor the most effective parameters to be

administrated. One of the consequences of this poor understanding is that currently SNM is applied to the GI patients on a trial-and-error basis. The excruciating process may involve going through a test period of 2-4 weeks (or longer) of surgical temporary electrode implantation to evaluate the potential benefits of SNM therapy before implanting permanent electrodes (8,10,11).

Oddly enough, the optimal stimulation parameters used for urinary tract disorders have been directly transferred to gastroenterology without adaptation which indicates lack of sufficient research in the field (8). In addition, the gap in knowledge about underlying neural mechanisms of SNM has led to the uncertainty of whether sensory or motor results are the best predictor for treatment success (11,15). Although most clinical studies have been focused on the cortical representation of the anal sphincter pathway and somatosensory cortex excitability, animal studies suggest the involvement of multiple brain structures such as dorsal brainstem and caudate nucleus (15,18). Such observations are more consistent with results obtained from studies on patients with urinary incontinence (1,9,11).

More importantly, results of the effect of SNM on somatosensory cortex seem conflicting (11,15, 22). While some studies show increased cortical excitability (13), others reported a significant reduction in excitability of the somatosensory and anal sphincter motor cortex after chronic SNM treatment (8,20). In-depth investigation of the central neural mechanisms of SNM for FGIDs is essential to improve identification of the most effective stimulation parameters and to determine which patients are the best candidates for different available SNM treatment options including temporary and permanent implants, TENS therapy or combinatory treatments (4,8,11,15,22).



4. Concluding Remarks

Review of the literature shows that neuromodulation for pain management is more comprehensively researched compared to non-painful conditions. Since SNM initially emerged to treat urinary tract disorders (6,10), FGIDs have received even less attention among the non-painful conditions. However, without fuller understanding of the neurophysiology of SNM, this treatment remains empirical for FGIDs (4). The evolving body of literature on central and peripheral mechanisms of SNM point to the afferent sensory nerves to be the target fibres within the nerve root (10,16). This is currently the most convincing hypothesis of SNM mechanism with supporting evidence from a wider range of studies (4). Efficacy of SNM at voltages at the sensory but sub-motor threshold (4) and clear changes over the somatosensory cortex following SNM administration in both humans and animal models (3,4,8,9,10,11,15) add to the credibility of this hypothesis. Nevertheless, sub-sensory stimulation as low as 50% of the sensory threshold can still be as effective as stimulation at the sensory threshold (6).

Furthermore, at present it is not yet fully understood why in some studies patients manifest increased cortical excitability after SNM treatment (13, 15) while the opposite effect is observed in others (9, 15, 22). One of the reasons for such disparate results might be due to uncertainty about the optimal sensory response to SNM which makes it difficult to reliably compare data from different

groups of researchers (4). This area of SNM research requires serious investigation as it can shed light on not only the central pathways activated by SNM but also on the optimal sensory responses. On the other hand, the conflicting data regarding cortex excitability can be explained by time effect. Reduction in excitability of cortico-anal and somatosensory cortex are reported after chronic SNM treatment while increase in excitability is observed after acute SNM therapy (15).

Although SNM seems to rely on different neural mechanisms for various disorders, there are similarities in the way SNM modulates the underlying neural pathways. The group of nerve fibres that SNM targets and the regions of the brain that it activates resemble each other in disparate conditions. Furthermore, the spinal and supraspinal neural pathways for defecation considerably overlap with those of lower urinary tract (10). This might mean that SNM follows one general neural mechanism that regulates sensory responses depending on the optimal response required to achieve overall homeostasis.

It is known that afferent nerves are critical for sending signals of sensation, fullness or discomfort to the brain to initiate a "response reflex". Such response reflex could be the micturition, the defecation or the withdrawal reflex. The main afferents involved in both micturition and defecation reflexes connect with interneurons in the sacral spinal cord (16). The interneurons in turn synapse with efferent parasympathetic neurons to form spinal reflexes. However, spinal reflexes are modulated by several centres in the brain (10,15,16).

Therefore, it is plausible that SNM modulates response reflexes of any kind by altering the afferent signalling depending on the status quo activity of the afferent nerve fibers innervating the target organ. If any of the response reflexes are excessively active, SNM decreases the afferent signalling to inhibit the reflex and if the reflex is hypoactive, SNM increases the activity of afferent fibres to enhance afferent signalling. This hypothesis could explain the contradictory results obtained from different cortical studies while being consistent with how TENS for pain management modulates the transmission of signals evoked by noxious stimuli. Further research is required to test this proposition.

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REVIEW
Science

Stem Cells To Cure Sickle Cell Anemia

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Sickle cell anemia (SCA) is one of the most prevalent genetic disorders in the world and the most common congenital anemia in the United States. The severity of SCA spans from mild clinical cases, managed by careful living, to severe cases involving bone crises, infection, stroke, and multi-organ failure. Hematopoietic stem cell transplantation (HSCT) is the most widely known and effective method to cure the disease and is used today in only severe cases due to risks of graft rejection and fatal infections. The use of stem cells for the cure of sickle cell disease from the early days of transplantation to the most recent breakthroughs in stem cell therapy, gene therapy and genome-editing will be examined in this review.

Introduction

In 1904, Grenadian dental student, Walter Clement Noel, was admitted to Chicago Presbyterian Hospital with complaints of fatigue and bodily pain. He was first examined by a cardiology resident by the name of Ernest Irons who contacted his attending physician, James B. Herrick when he inspected Noel's cells via blood smear[1]. The medical case of the Grenadian with "pear-shaped and elongated" cells and bone pain was published and similar reports were shared from physicians practicing in other states until the strange disease was named "sickle cell anemia" by Vernon Mason in 1922.

Two decades passed until Linus Pauling and Harvey Itano first described sickle cell anemia (SCA) as a "molecular disease." They hypothesized that the distorted shape of sickle cells arose from defects in the hemoglobin structure. Electrophoresis, then a new innovation, proved that the hemoglobin protein from sickle cell patients differed in both size and charge from healthy patients. This finding, Pauling believed, transformed medicine into a "real science." Disordered protein could cause human disease.

Since the early 20th century, many scientists including J.B.S. Haldane and A.C. Alison made observations that regions with high incidence of malaria also had peoples with blood disorders like the thalassemias and SCA. Over time, it has been postulated that heterozygous carriers of a mutated SCA gene better survive and resist fatal cases of malaria[2,3]. Today, it is well known that a missense mutation in the beta-globin gene locus found on the 11th chromosome promotes the aberrant generation of the amino acid valine instead of glutamic acid[4]. This amino acid change gives rise to the production of sickle hemoglobin—the key underpinning of sickle cell anemia. Particularly in low oxygen environments, this altered biochemistry causes the hemoglobin molecules to intracellularly polymerize, distorting the cell's shape. Stiff, and elongated, these red blood cells (RBCs)

occlude and damage the body's vasculature. The natural history of SCA often includes the failure of multiple organ systems –especially respiratory failure secondary to acute chest syndrome (ACS), cerebrovascular incidents and sepsis. Millions live with SCA most commonly in malaria-endemic regions in west and central Africa, eastern Saudi Arabia and central India with sickle cell trait reaching a prevalence of 40% in some areas[5,6]. 1,000 babies are born each day in Africa with SCA and half will die before five years of age mostly from infectious causes[7].

In the United States during the 1970s, the average person with SCA lived until about 14 years of age[8]. Today, comprehensive care and improved management have pushed the life expectancy to 50-60 years of age in the United States and Great Britain with over 90% of children living into adulthood[9]. Over the course of the average lifespan of a patient with SCA living to 45 years, $1 million will be incurred in hospital fees as admissions and complications are frequent[10].

With such a personal, financial and global burden of disease, a safe, universal cure for SCA is paramount. To date, stem cell therapy is the only source of a cure for SCA in select patients. While hematopoietic stem cell transplantation (HSCT) is the only means to cure SCA, it is far from universal. This review will focus on the historical, current and future uses of stem cells for the cure of SCA.

The Birth of Hematopoietic Stem Cell Transplantation

The world was unofficially introduced to hematopoietic or "blood-forming" stem cell transplantation following World War II. Ten years after the end of US involvement in WWII, the civilian populations of Nagasaki and Hiroshima, Japan were exposed to large amounts of radiation and were dying of hematopoietic failure and leukemia. Richmond Main and Joan Prehn discovered that radiation syndrome similarly found in mouse models could be prevented by using lead to protect the spleen or injecting it with cells from the bone marrow or spleen. Thus, they discovered that allogenic transplantation of bone marrow into radiated mice could have extremely successful results if there was no graft rejection[11].

The first ever HSCT procedure in humans with leukemia was reported in 1957 by E. Donnall Thomas and although two out of six patients experienced engraftment of the HSCs, none survived after 100 days[12]. While all six patients in the study died, knowledge about human leukocyte antigens (HLA) and their role in adaptive immunity was still in its infancy. Nonetheless, many from the scientific community embraced the idea of stem cell therapy to cure the disease of the bone marrow. HLA proteins are found on every cell and uniquely mark them as belonging to the host. When foreign cells are delivered to a patient during transplant, they may not be histocompatible with the host's immune system, increasing the risk of graft rejection.

By the early 1980s, clinical bone marrow transplantation became a much more standard procedure in both autologous (when graft comes from patient) and allogeneic cases. In 1984, a child with acute myelogenous leukemia was cured of both their cancer and SCA using transplant thereby becoming the first patient cured of sickle cell anemia. By the mid-90s, larger studies with more patients were reported. Often the patients chosen were less than 16 years of age with disease complicated by stroke, recurrent ACS and other forms of organ damage. Within two years of the landmark study, 90% were still living after receiving immunosuppressive agents[13]. 18% of patients rejected the graft and others experienced neurologic complications like seizure and hemorrhage. Although the risk of repeat cerebrovascular incident in patients following transplant is reduced, complications like these have resulted in some apprehension to HSCT

Transplant in Sickle Cell Anemia

While HSCT is curative, it is an under-utilized procedure. The barriers to universal use are the issues of safety of transplant preconditioning procedures as well as the availability of (HLA)-matched donors to reduce the risk of graft versus host disease (GVHD). Classically, a patient's bone marrow is depleted of cells with radiation and their immune system is suppressed with chemotherapy prior to the addition of new HSCs. Despite SCA cure rates well

over 80%, transplant related mortality and cost has been a key deterrent for parents, patients, and pharmaceutical companies[14]. Myeloablative therapies result in increased treatment related mortality (TRM) in comparison to non-ablative therapies (5.1% v 1.7%) but with decreased rates of graft rejection (15% v 23%) in a series of studies from 1998-2014[15].

Today, physicians endeavor to strike a balance between providing safe, and effective transplant for patients (i.e., low rates of TRM and high levels of engraftment). Moreover, the safety of the procedure is limited by the quality, compatibility and availability of the hematopoietic stem cells for the patient. Less than 20% of sickle cell patients have HLA-matched sibling donor[16]. Without any gene-editing, some physicians have sought ways to increase transplantation success from half HLA-matched donors.

Making the State of the Art Safer

From the early days of bone marrow transplantation, increasing age in the patient was a poor prognostic indicator for both success and safety of the procedure. As a result, adults with SCA were much less likely to be cured. In recent years, donor stem cells from unrelated, half HLA-matched donors have been used to cure adults with SCA via improved clinical protocols. In a recent study from the University of Illinois at Chicago, eight adult patients underwent the procedure seven achieved 95% or higher engraftment and one developed GVHD and died of unknown causes[17]. The curing of adults with SCA demonstrates the mileage the medical community has traveled to improve transplant protocols for patients. What may be even more tantalizing is the idea that patients with SCA would have a genetically identical stem cell donor—themselves. The advent of gene-editing and gene therapy has autologous transplant possible for a growing number of patients.

Dealing with Beta-Globin

The approaches below detail the modification of sickle beta-globin expression such that the patient achieves clinical silence of the disease. With the dawn of CRISPR-Cas9 mediated genome editing in 2012, gene-editing has become more promising than it has ever been. SCA as a monogenetic disorder serves as an excellent disease to attempt gene-correction, and scientists have developed multiple approaches to correcting the genetic defect. Cas9 is a protein that functions as a "molecular scissors" by harnessing an attached guide RNA sequence to bind to a complementary DNA sequence that will be modified[18]. Thus, this complex can "recognize" the mutated DNA sequence and disable it. A corrected form of that DNA can also replace the mutated form. Therefore, the single nucleotide substitution can be corrected in HSCs harvested from the patient via granulocyte colony stimulating factor (GCSF) mobilization or bone marrow aspiration. The challenging component is an assessment on how many stem cells need to be corrected to produce a desired healthy phenotype in a

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patient[19]. In the end, the goal is not 100% correction of the genotype, but the generation of a healthy phenotype. People with sickle cell trait carry a copy of mutated beta-globin but by and large live relatively healthy lives. While some scientists aim to edit at the nucleotide level, others wish to modify beta globin expression by lentiviral gene transfer.

Lentiviral gene transfer, a form of gene therapy, allows scientists to add variants of the beta-globin or gamma globin gene to the HSCs of sickle cell patients. This method uses a patient's own HSCs for therapy as well, but instead of using CRISPR to edit, they can add genes using a lentivirus. Gene therapy is becoming a booming industry with different companies engineering their own lentiviral constructs. Bluebird Bio, one of many companies in the increasingly widening gene therapy sector, produced LentiGlobin BB305. This vector in a preliminary study had been delivered to nine patients and four experienced amelioration of their symptoms of SCA[20]. In the coming years, more patients will benefit from this new therapy with an expanded trial set to begin in 2022. Other groups have added vectors containing a variant of the gamma globin gene responsible for fetal hemoglobin production with similar results[21]. In addition to unmutated gene addition, other studies have taken a differing approach to a cure with the reactivation of fetal hemoglobin.

Reactivating Fetal Hemoglobin

The SCA mutation of adult hemoglobin, found in the beta-globin gene, is not robustly expressed in the fetus and in the first year of life. Fetal hemoglobin is composed of two alpha and two gamma chains and is resistant to sickling. For decades, scientists have endeavored to harness the anti-sickling capacity of fetal hemoglobin as a therapy for those suffering from the SCA and other beta-hemoglobinopathies[22]. In 2008, Vijay Sankaran and Stuart Orkin at Harvard Medical School discovered the "molecular switch" that turns on adult globins: BCL11A, a transcription factor which suppresses fetal hemoglobin expression[23]. This transcription factor now serves as a therapeutic target. A new clinical trial at Boston Children's Hospital led by David Williams currently aims to deliver lentiviral construct containing a vector inactivates the BCL11A in erythroid precursors only. BCL11A activity is important in B cell production, which therefore necessitates a targeted inactivation of BCL11A as opposed to a non-specific knockdown. Preliminary data has shown fetal reactivation of at least 80%--well beyond what is needed for a disease-free presentation[24].

Towards a Universal Cure

In March 2018, the National Institutes of Health held a special meeting entitled "Accelerating Cures in Hemoglobinopathies." There, Matthew Porteus of Stanford University posed a challenge to national leaders in SCA "to cure every three year old in the world." He imagined an age where children with SCA were cured before developing end organ damage. The use of HSCT as a universal cure has not been accomplished in the United States and is even further from implementation in the developing world where the incidence of the disease is the highest. But, as researchers aim to implement key advances in stem cell therapy patients and physicians need to know that these new options now exist. A recent New York Times article shares the stories of patients who are experiencing sickle cell anemia-free living following HSCT with gene-modified autologous HSCs[25]. These patients are filled with excitement and hope.

In 2019, there are now more successful transplants for every failure and physicians and scientists have developed novel and effective ways to use HSCs to cure SCA. As pre- and post-transplantation regimens improve, the toxicities linked to chemo-radiation will make HSCT more attractive for patients and families.

Scientific advancement can only take place if physicians and patients work together. The responsibility for improved outcomes is in the hands of providers optimizing the procedures as well as patients willing to participate in the much-needed clinical trials. With increased publicity surrounding these new breakthroughs in gene therapy there is hope that when physicians deliver the news of a SCA diagnosis that can also "use the C word" according to NIH Director Francis Collins. What does he mean?

"Cure."

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Case Report
Surgery

Large benign granular cell tumor with skin involvement: a case report

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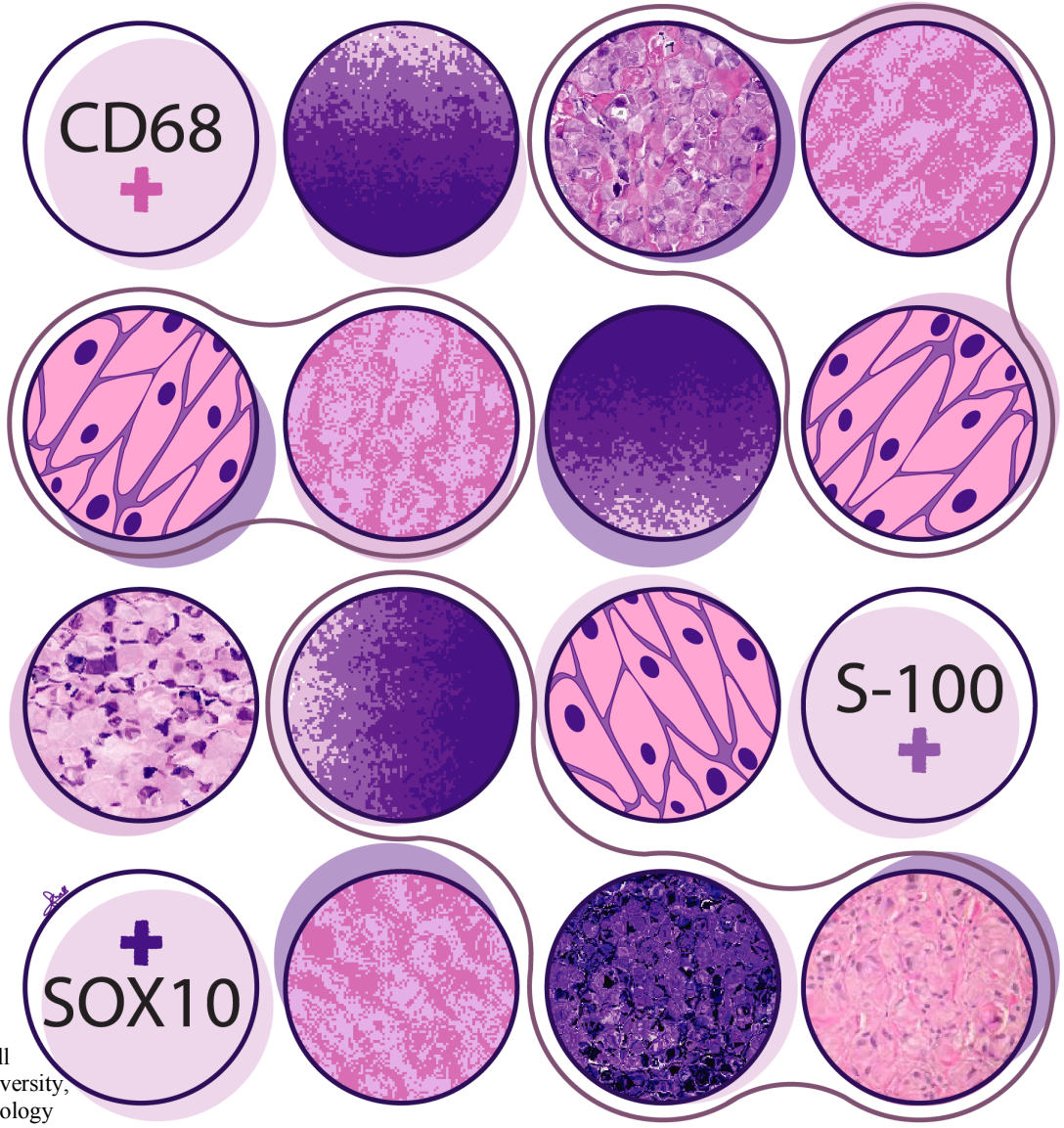
Granular cell tumors (GCT) are a rare soft tissue neoplasm of Schwann cell origin. This form of tumor is generally benign (0.5-2% malignant) and in these cases, involvement of the skin and deeper structures are not common, presenting usually as a solitary, slow-growing, painless mass (McGuire et al. 2014). This case report presents a 43-year-old woman with multiple benign slow growing masses on the back for 15 years, later biopsied to reveal benign granular cell tumor. Wide local excision of 2 masses and placement of wound VAC was performed by plastic surgery team with primary specimen measuring 11.5 x 12.5 x 2.5cm with skin and deep structure involvement, and a smaller mass measuring 6 x 3.1 & 5 x 2.1cm. Split-thickness skin graft was performed a week after confirmation from pathology on its benign nature. This case highlights an abnormal presentation of benign GCT due to size, skin and deep structure involvement, multiple lesions and appropriate management.

Introduction

Granular cell tumors, also less commonly known as Abrikossoff tumors, are a rare soft tissue neoplasm consisting of only 0.5% of all soft cell tumors (Battistella et al. 2014). GCT is believed to be of neural origin and is characterized by large polyhedral cells containing eosinophilic cytoplasm and immunohistologically positive for S-100 and CD68 (Gündüz, 2016). These forms of tumor are generally benign (0.5-2% malignant) and are rarely multifocal, affecting age ranges of 30-50 years (Goel, 2013). In benign cases, involvement of the skin and deeper structures are not common. GCT tends to affect African-Americans more than whites, and are more likely to affect females 2x more than males (Fragulidis, 2011). These generally solitary, slow growing neoplasms are mainly found on the tongue, oral cavity, skin, and rarely in internal organs. Its malignant form tends to have deeper tissue invasion, large size recorded up to 15 cm, and rapid growth, with poor prognosis (McGuire, 2014).

Granular cell tumor was initially believed to be of myoblastic origin for a long time due to similarities in appearance to skeletal cell tumors, however recent literature seems to point it of neural crest cell origin as demonstrated by S-100, CD68, SOX10 and peripheral nerve myelin protein positivity. These lesions tend to appear as large polygonal cells, small nuclei, and granular cytoplasm (Gayen et al., 2015). Upon histology, these cells are commonly separated by bands of collagen and fibrinous material. Cytoplasm granularity is due to large lysosomes which are filled with various cellular debris such as myelin

proteins, mitochondria and rough endoplasmic reticulum fragments (Fragulidis, 2011).



Artist:
Jonnell Small
Harvard University,
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Typical granular cell tumor presentations are during the ages of 30-40, with higher incidence in African-American females. A large majority of these lesions are benign, solitary, slow-growing, asymptomatic, firm nodule from 0.5 to 3.0 cm diameters. Prognosis of GCT tends to be very good after surgery with very few (2%) of GCT resulting in malignancy (Singh et al. 2015). Malignant GCT present as recurrent, fast growing, large lesions, lymph node involvement that have poor prognosis due to metastasis. Malignant GCT are characterized with necrosis, increased mitotic activity and increased nuclear to cytoplasm ratio with pleomorphism. Invasion to deep structures, vascular invasion, or involvement of skin are much more common in malignant GCT, however can happen in some cases of benign GCT (Battistella et al. 2013). In a large majority of benign GCT, excision is curative. In aggressive malignant forms, radiotherapy has seen some success in other forms of GCT, but prognosis remains poor and wide local excision remains gold standard in treatment (Gündüz, 2016).

In present literature, there are multiple cases presenting these lesions in different locations and various sizes. However, in this case, we present an unusual presentation of multiple benign, large GCT masses in a 43-year-old woman located on the back,

with a large primary mass (11.5 x 12.5 x 2.5cm) with skin and deep structure involvement, and a smaller more typical GCT lesion on the back; uncommon in present literature for benign presentation.

Case Report

The patient is a 43-year-old African-American female with complaints of a 15-year history of an enlarging mass on her right back. She denied any fever, chills, change of color or discharge, but described that within a year, the mass had progressively increased in size accompanied with pain and pruritus. The patient described pain when leaning on the lesion. Previous CAT scan had shown a 4x6cm mass but upon clinical examination 2 years later, revealed an 8x8 cm subcutaneous mass on the right mid-paramedial back as well as a secondary soft tissue non-characterized mass at her lower right paramedial back. FNA biopsy was performed, and histopathology revealed subcutaneous proliferation of cells between strands of dense fibrous tissue. Cells were medium in size and eosinophilic and granular cytoplasm. Nuclei were relatively small and uniform. Immunohistochemical staining revealed CD68 and S100, but negative MART1 expression; confirming diagnosis of GCT. Due to lesion's extensive attachment to the skin, patient was referred to the plastic surgeon for reconstruction. MRI revealed primary mass involvement of the paraspinous musculature. Secondary mass on the lower right side of the back showed non-adherence to the skin, but extensive attachment to the underlying fascia and musculature. Excision of the primary mass was deep into the back fascia and some of the latissimus and paraspinous musculature due to lesion fixation. A separate incision was made at the lower back for the secondary lesion, in which the mass with some paraspinous musculature was excised. Final surgical pathology was 11.5 x 12.5 x 2.8cm (Figure 1) for the primary mass on the upper back and 6 x 3.1 & 5 x 2.1 cm (Figure 2) for the smaller secondary mass at the lower back. Both lesions were sent to the pathology lab with additional deep tissue to confirm diagnosis. The secondary lesion was closed in layers of Monocryl sutures (8.3cm), while the primary lesion was installed a wound VAC pending pathology results due to size of lesion and reconstruction modality determination. Pathology results were negative for malignancy and invasion of surrounding tissue, and STSG reconstruction was done with Prevena wound VAC placement with no complications. Patient was sent home same day with no complications.

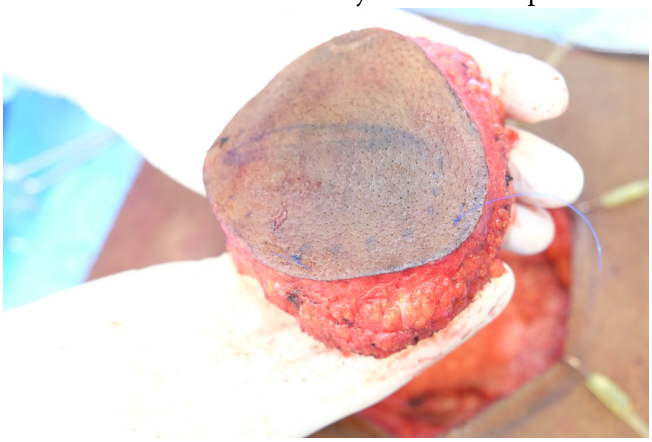

Figure 1: Primary Mass (11.5x12.5x2.8cm)

Figure 2: Secondary Mass (6x3.5cm & 5x2.1cm)

Discussion

The patient of this case review was a 43-year-old African-American female with a 15-year history of an enlarging mass on her right middle back. She denied any fever, chills, change of color or discharge. Initially, the patient suspected the mass was a lipoma with its initially mobility and no other accompanying symptoms. However, within the past year, the mass rapidly expanded with pain and pruritus described "under the skin". The mass was noted to be especially tender on palpation and rubbing of the overlying skin. Our patient was in distress with complaints that the mass had impacted her life and made putting on clothing difficult. Upon ultrasound imaging revealed 8x8cm solid mass with signs of infiltration

into the latissimus and paraspinous musculature. Further exploration in the OR revealed smaller secondary masses; unusual for benign GCT. Despite the abnormal presentation of GCT, the decision was made for wide excision of the mass with hopes that the tumor had not extensively infiltrated the muscle and that the tumor remained proximal to the skin. Based on current literature, wide base excision would have been the gold standard therapy, however there was initial worry of the extent of muscle invasion underneath which would have altered the decision with fears of damaging the muscles. Fortunately, the mass had not reached into the deep back muscles and minimal musculature removal was required. If lesion had infiltrated past the deep fascia with extensive muscle involvement, consideration for radiotherapy/chemotherapy would be considered to reduce tumor size.

Due to the large size of the mass, consideration was taken into account into reconstructive options for the patient. A wound Vac was placed temporarily, and a future reconstructive surgery was scheduled for potential STSG for the patient. An additional smaller mass was also removed on the lower right back with minimal infiltration into the paraspinous muscle. Due to its small size, wound Vac was not needed and was promptly closed with stitches. The wide excision removal was an overlying success with the patient having minimal complications post-operation. With the application of wound Vac, patient did not experience excessive drainage from the site, and wound remained clean without purulence or necrosis. Patient immediately experienced relief from symptoms due to mass, and other than pain from surgery experienced no complications. Use of the wound Vac had not been previously documented in previous literature for wide local excision of GCT, yet was met with positive results in this specific case, and may serve for further investigation regarding recovery from wide excision of deep GCT.

Regardless of tumor malignant status, wide local excision of lesion is recommended to prevent recurrence and potential future malignant transformation. Despite this case of abnormal presentation of GCT with deep fascia and musculature involvement, wide local excision still had immediate results and improvement of patient symptoms with minimal complications. Follow up with the patient a month from the procedure showed minimal complications with failure of tumor reoccurrence. In comparison with current literature, excision of the mass appears to remain the gold standard in management of GCT. Although radiotherapy/chemotherapy was considered in this patient due to abnormal presentation, multiple nodules, and relatively deep fascia involvement, lack of malignancy and lymph node involvement pushed the decision for excision opposed to radiation. Some literature has seen some success with local steroidal treatment and silicone blocks to prevent reoccurrence and excess scar hypertrophy (Yilmaz et al. 2007). Such management was not necessary in this case due to lack of reoccurrence and no additional symptoms.

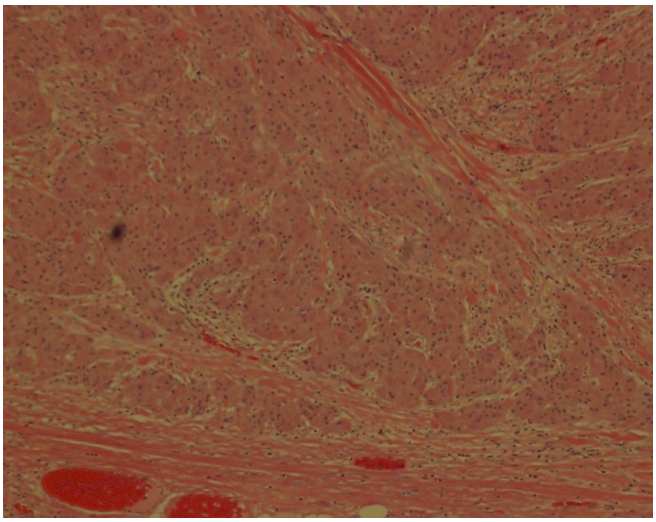

Figure 3 H&M stain demonstrating characteristic bands of collagen and fibrinous material

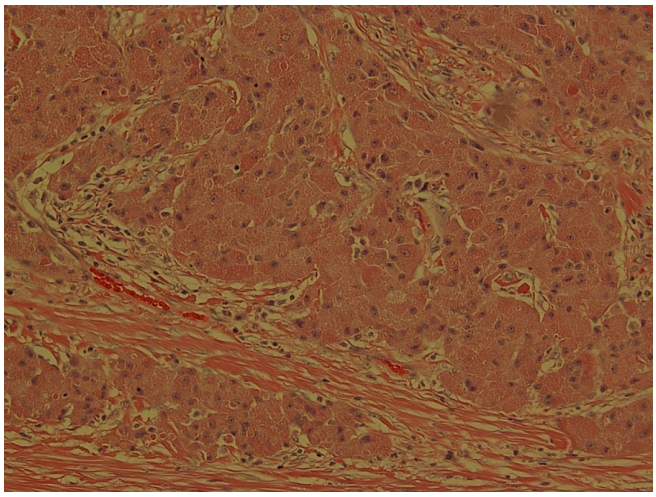

Figure 4 H&M stain demonstrating characteristic large polygonal cells with eosinophilic cytoplasm

Conclusion

Granular cell tumor (GCT) is a rare, usually benign neoplasm. Malignancy are rare, occurring in only 0.5-2% of patients. Typical neoplastic locations are at the tongue, oral cavity, and skin with rarer types occurring at the extremities and internal organs. Generally, benign GCT has a distinct histological appearance and tends to lack skin involvement. Current literature describes benign GCT to be solitary, smaller lesions than malignant GCT. This case presents a rare occurrence with patient with multiple, painful benign GCTs with skin involvement and large size; not seen in current literature presentation. Management with wide local excision was performed, and remains consistent with current literature as the gold standard in GCT management despite uncommon tumor presentation and appearance as shown with positive patient response to management and lack of reoccurrence.

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Are medical students biased toward chronic pain patients?

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Background: Little research has been done into exploring medical students' perspectives of chronic pain patients despite increasing media attention on the opioid epidemic and their encounters during medical school.

Methods: To investigate, all medical students at Michigan State University College of Human Medicine were emailed an invitation to voluntarily participate in an online survey. Students were randomized between two identical patient vignettes, one was the control and the other was identical with the exception of a history of chronic back pain and opioid dependence. Students were then asked a series of questions regarding their perceptions, biases, and attitudes towards the patient in their vignette. Eleven questions were asked using a 0-10 scale.

Results: Results between the control and pain patient were quantified using an unpaired t-test. Students rated the chronic pain patient worse than the control in 8 of the 11 questions. There was no significant difference between the control and pain patient in the remaining 3 questions.

Discussion: Our survey showed that medical students had more negative perceptions of chronic pain patients in terms of their health, self-care, self-discipline, and compliance. Students believed a chronic pain patient would require higher levels of patience, be more annoying, and students felt less positive towards a chronic pain patient compared to a control. Although these results may not correlate with clinical differences in practice, medical schools should be aware of how medical students' perceptions of chronic pain patients could affect the quality of care provided as future physicians.

Introduction

Medical students, who are destined to encounter pain-related complaints in practice,[1] often have little personal or medical knowledge of pain prior to matriculation. Students may be more likely to develop their understanding of chronic pain from media consumption and by picking up cues from physicians they work with in medical school. Over the last decade, the media has focused on the opioid epidemic, which has shaped our national understanding of chronic pain and pain treatment. In addition a student's perception could also be contributed to working one-on-one with attending physicians whose own biases may shape a student's schema of a patient population. And, often times primary care providers are more biased towards chronic pain patients.[2] Bias being defined as an "inclination or prejudice for or against one person or group, especially in a way considered to be unfair."[2] Reasons cited by primary care providers for less positive feelings towards chronic pain patients include, difficult patient interactions,[3] comorbid psychological issues,[4] requiring more time,[4] worries about dependence and addiction,[4] and compliance.[4]

While primary care providers feel more negative towards chronic pain patients, medical students are not bound by the same patient-provider relationship as physicians, nor face any prescribing scrutiny.

Despite the lack of quantitative studies establishing medical students have a negative perception towards chronic pain patients, there have been preliminary evidence supporting this theory. In a qualitative review of forty-four first year medical student journals, researchers found 75% of references to pain patients were negative, noting concerns about truthfulness and opioid prescribing.[5] Other studies examined medical students' judgment of the level of pain in chronic pain patients using differing degrees of medical evidence, empathy, and accountability in vignettes and found that these variables can influence students' perception of chronic pain patients.[6,7] Finally, in an interview with eight medical students, researchers at the University of Toronto reported that students working with chronic pain patients found their experiences frustrating due to the incurable nature of chronic pain and believed those encounters held little educational value.[8]

Methods

In order to address the question 'Are medical students biased towards chronic pain patients?' an online survey was developed. The study qualified for exemption by the Michigan State University IRB. All medical students (year 1 through year 4) at Michigan State University College of Human Medicine were emailed an invitation to voluntarily participate in an online survey through Qualtrics.

Although a few studies have analyzed medical student judgement towards chronic pain patients, none had developed a questionnaire to investigate medical student bias towards chronic pain patients versus a control, so our questionnaire was modeled after a study assessing medical student bias towards patients with obesity.[9] The survey was divided into two identical vignettes, one was the control patient and the other included a history of chronic back pain and long-term opioid use (See Figure 1 and Figure 2 in appendix). Students were randomized into one of the two patient vignettes. After reading the patient vignette prompt, students were asked a series of questions regarding their thoughts on the vignette patient. Eleven questions were asked regarding students' perceptions of the patient in the vignette using a 0-10 scale. Questions were meant to assess differences in students' perceptions, biases, and attitudes towards chronic vs. non-chronic pain patients. Questions asked included the following:

1. Estimate the health of the patient
2. Rate the patient's level of pain
3. How well does the patient take care of himself?
4. How self-disciplined is the patient?
5. Rate the seriousness of the medical problem
6. How much of a waste of time is this patient encounter?
7. How much patience will be required during this encounter?
8. How annoying can this encounter become?
9. What is your personal desire to help this patient?
10. What is the likelihood that the patient will comply with medical advice?
11. What is your overall level of positivity towards the patient?

Results

Up to 128 students responded to the chronic pain patient survey and up to 129 different students responded to the control patient survey. Using GraphPad, an unpaired t-test for each question was run to assess statistical significance between the means.

The results were extremely significant when students rated the chronic pain patient poorer in terms of health ($p = 0.0001$, $t= 6.6930$, $df= 255$), worse self-care ($p= 0.0012$, $t= 3.2779$, $df= 253$), requiring a higher level of patience during the encounter ($p=0.0002$, $t= 3.7609$, $df= 252$), and lower positivity towards the chronic pain patient ($p=0.0004$, $t= 3.5788$, $df= 250$). There were additional statistically significant differences as students rated the chronic pain patient as having lower self-discipline ($p=0.0475$, $t= 1.9917$, $df= 252$), causing a higher level of annoyance ($p=0.0148$, $t= 2.4537$, $df= 253$), and poorer compliance ($p=$

0.0048, t= 2.8435, df= 250). Students also rated the chronic pain patient as having higher amount of acute pain compared to the control (p=0.0001, t= 4.7258, df= 252). There was no difference in medical students' desire to help (p=0.1992, t= 1.2873, df= 254), feeling the encounter is a waste of time (p=0.3368, t= 0.9623, df= 254), or assessing the seriousness of an acute presentation (p=0.297, t= 1.0451, df= 253) between the chronic pain and control patient.

Graphs of response data for each question are located in the appendix, Figures 3-13.

Discussion

Pain-related complaints are one of the leading causes for doctor visits in the United States.[1] In addition, there has been increasing media attention surrounding chronic pain and the opioid epidemic. Our survey showed that medical students had more negative perceptions of chronic pain patients in terms of their health, self-care, self-discipline, and compliance. Students felt a chronic pain patient would require higher levels of patience, be more annoying, and students felt less positive towards a chronic pain patient compared to a control.

There were some limitations to this study. As the experience, understanding, and perception of pain are multifactorial there is endless amounts of both qualitative and quantitative data that can be gathered on the topic. For the purposes of a narrow study, this survey exclusively examined students' perceptions of a chronic pain patient versus a patient without chronic pain. In addition, the survey did not assess student against provider attitudes regarding chronic pain patients, and therefore there is no data measuring the magnitude of difference between student and medical provider bias. Finally, the online questionnaire did not stratify for gender, age, or medical student year, so further understanding of how gender, age, and clinical experiences shape perceptions cannot be deduced from this data.

In addition, this study did not assess if there would be a difference in future patient care based on student bias. Nevertheless, a previous study has shown that primary care providers who are biased towards chronic pain patients are more likely to under-treat and mismanage these patients.[12] Although our results may not correlate with clinical differences in practice, medical schools should be aware of how medical students' perceptions of chronic pain patients could affect the quality of care provided as future physicians.

We advocate that medical schools, residencies, and physicians be mindful of stigmas towards chronic pain patients, and incorporate chronic pain concepts into an educational curriculum. Addressing this pervasive stigma in the medical community may be an important first step towards treating the millions of patients who suffer from chronic pain and effectively combating the opioid epidemic.

Artist: Jonnell Small
Harvard University, Chemical Biology

Appendix

Figure 1: Control vignette

By completing the survey you voluntarily agree to participate in this research project.

The survey participation is anonymous and voluntary and you can withdraw at any time. The survey is for research purposes only. The risks of completing the survey are minimal, but could include anxiety while reflecting on the questions.

If you have questions or concerns regarding this study, please contact the research study team at pourzang@msu.edu. If you have concerns about your role and rights as a research participant, you may contact MSU's Human Research Protection Program at (517) 355-2190 or email irb@msu.edu.

Patient Information

Name: Anthony Brown	DOB: 10/15/1963
Gender: Male	Age: 55

Vitals:

Height: 6 ft., 0 in.	Temp: 98.4
Weight: 180 lbs.	BP: 120/70
BMI: 24.4	Pulse: 74

Problem List:
1. Hypertension since 2013
2. Benign prostatic hyperplasia since 2013

Current Medications:
1. Hydrochlorothiazide (HCTZ) 25 mg., BID
2. Tamsulosin (Flomax) 0.4 mg., QD

Comments: Patient is coming in for new onset right knee pain.

Figure 2: Chronic pain vignette

By completing the survey you voluntarily agree to participate in this research project.

The survey participation is anonymous and voluntary and you can withdraw at any time. The survey is for research purposes only. The risks of completing the survey are minimal, but could include anxiety while reflecting on the questions.

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Patient Information

Name: Anthony Brown	DOB: 10/15/1963
Gender: Male	Age: 55

Vitals:

Height: 6 ft., 0 in.	Temp: 98.4
Weight: 180 lbs.	BP: 120/70
BMI: 24.4	Pulse: 74

Problem List:
1. Chronic low back pain since 2012
2. Hypertension since 2013
3. Benign prostatic hyperplasia since 2013

Current Medications:
1. Hydrocodone/ Acetaminophen (Norco) 7.5-325 mg., TID
2. Hydrochlorothiazide (HCTZ) 25 mg., BID
3. Tamsulosin (Flomax) 0.4 mg., QD

Comments: Patient is coming in for new onset right knee pain.

Figure 3: Graph for survey question 1

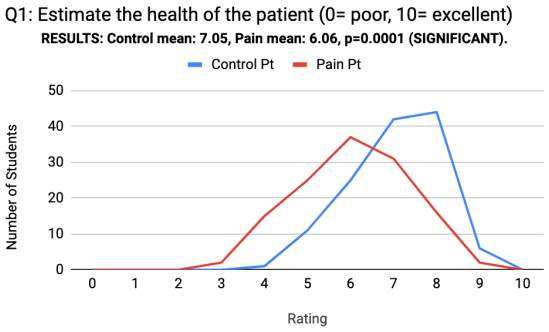


Figure 4: Graph for survey question 2

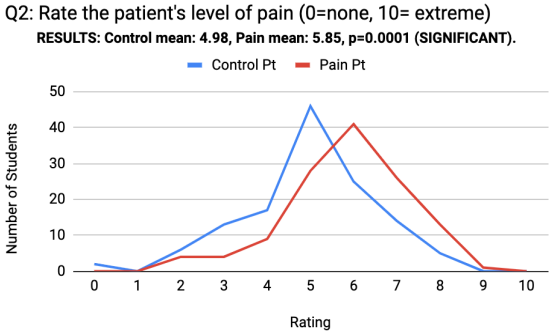


Figure 5: Graph for survey question 3

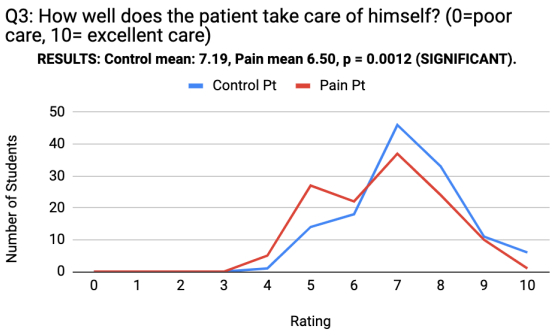


Figure 6: Graph for survey question 4

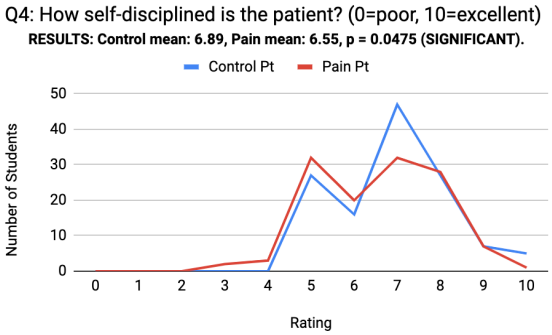


Figure 7: Graph for survey question 5

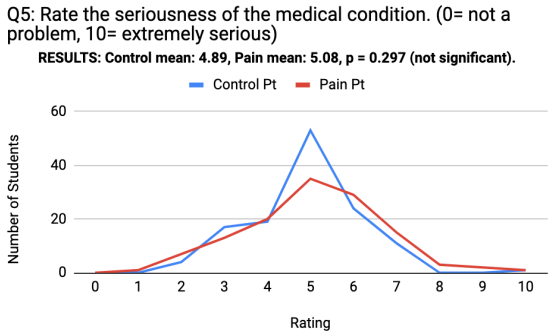


Figure 8: Graph for survey question 6

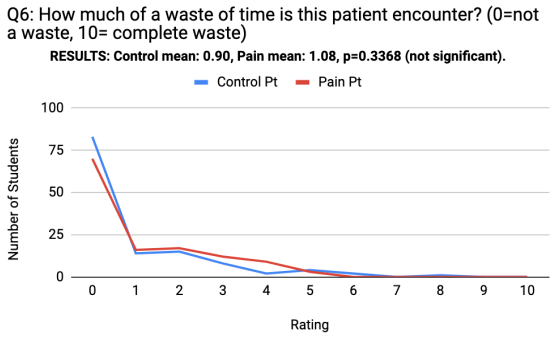


Figure 9: Graph for survey question 7

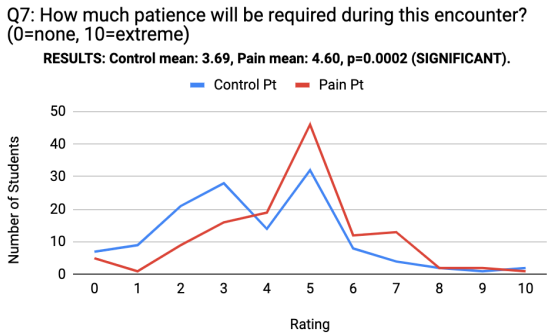


Figure 10: Graph for survey question 8

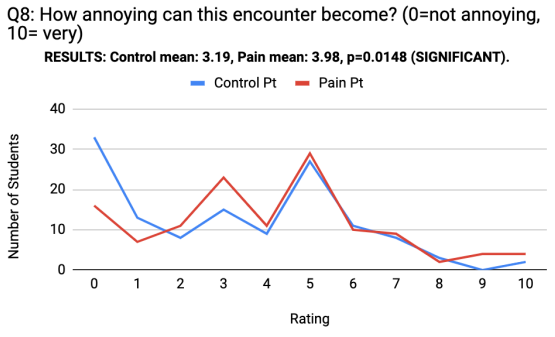


Figure 11: Graph for survey question 9

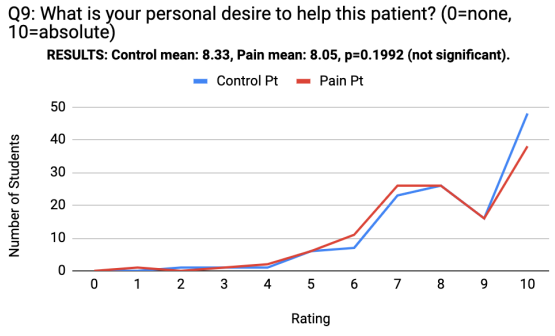


Figure 12: Graph for survey question 10

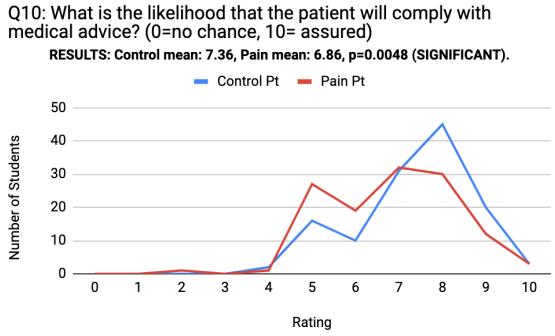
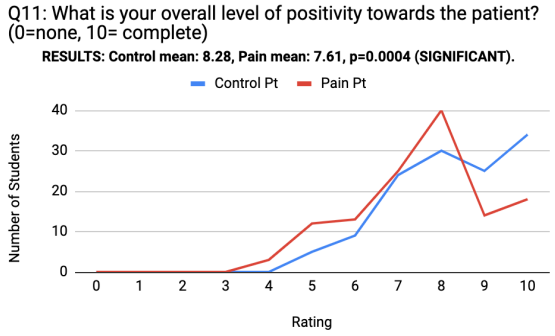


Figure 13: Graph for survey question 11



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