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The editors of *MSRJ* would like to extend our warm wishes in the winter season and hope that it has been filled with joy, family, and good fortune. We are very excited to introduce the first issue of 2014, as well as the second issue of the 2013–2014 academic year. As medical students around the world return to their books and clinic duties, we present educational and stimulating new articles. The published works in this issue highlight the efforts of students from Creighton University School of Medicine, Wayne State University School of Medicine, and Michigan State University College of Human Medicine.

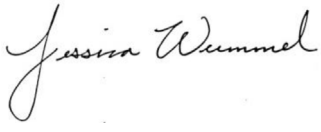
Since the release of our latest issue, this journal has experienced a steady influx of submissions from all over the world. We feel overjoyed that medical students are keeping us busy by sending in their hard work, and we are constantly impressed by the high caliber of articles that we receive. At the time our last issue went to print, our submission contest came to a close. This contest gave medical students, who submitted articles to us, a chance to win cash prizes. Prizes will be awarded to the best article in the following four categories: original manuscript/brief report, case reports, reviews, and reflections; *MSRJ* staff members are currently working hard to grade each submission and determine a winner for each category. This contest was a tremendous success: not only did the journal have a substantial increase in submissions but the quality of articles was also top notch. We encourage readers to stay tuned for the announcement of the contest winners and to keep their eyes open for a potential second version of the submission contest.

Our editorial staff members continue to amaze us. We are constantly learning from each other's innovative ideas in an effort to make our journal the best it can be for our readers and authors. Seeing our bright staff work together never fails to excite us about our journal's future and what we will have in store for future readers.

As *MSRJ* forges ahead, we are on the verge of some very exciting events. We are currently beginning our spring elective program for first- and second-year students at MSU–CHM. This elective has a dual purpose: to give interested students an education about how to critically appraise the literature (a skill imperative to our evidence-based medical society) and to recruit new members for our editorial staff. We are excited to see what these new students have to offer and to kick off another great year for *MSRJ*. The journal will be instituting digital object identifiers for past and future articles to prove the longevity of the journal and respond to author requests. The editors plan to visit scientific conferences throughout the year to spread the word of our publication/educational opportunities. In addition, the editorial board is in the planning stages of accepting abstracts and audio/visual submissions. We will continue to update readers of our progress through posts on Facebook and Twitter, as well as bring news about interesting events in the medical and research communities.

Again, we thank the Michigan State University College of Human Medicine for their continued support. We also acknowledge the hard work of our talented staff in making this issue possible; without them, the journal would not have all of the life and excitement that they bring. We hope that our readers will continue to follow the progress of the *MSRJ* both on Facebook and Twitter, and on our website at http://www.MSRJ.org. Please continue to send your wonderful manuscripts as we love learning and teaching, striving to help improve the academic skills of medical students from around the globe.

Sincerely,



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Spirit Queen

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Preface: In my childhood, I lived with a family member suffering from paranoid schizophrenia. The painting is my interpretation of the inner turmoil that this family member faces regularly. It is my hope that the viewers of this painting can gain some insight into the difficulties involved in living with a chronic mental illness that cannot be fully understood. The painting depicts a person with paranoid schizophrenia attempting to balance her perceived reality between cultural beliefs, logical reasoning, and schizophrenic delusion. The image shows a young child looking down on her brain encased in a coiled golden ribbon to illustrate the dichotomy of the body and mind. The four corners of the painting are weathered and deteriorating to demonstrate the progressive nature of the disease/illness.

The physical self: The brain, along with the snake-like ribbon and the roots emanating from the spinal

cord, represents scientific medicine and the child's corporeal body. The spinal roots spread and tangle chaotically to convey the individual's inability to control the health of her own body. The child cannot fully understand the physical self that she is analyzing and, thus, keeps her hands distant from it.

The psychological self: The individual is depicted as a child to emphasize her innocence and naiveté regarding her condition. To her, she believes that she is a wealthy and powerful queen (as demonstrated by her many accessories and jewelry) that has been possessed by demons that are hindering her life in a multitude of ways that only she can understand. I illustrate the demons here as golden orbs floating above her in the heavy purple mist bearing down on her mind.

The social self: The child bears an immense robe that simultaneously protects her and acts as a heavy burden. The robe, adorned with homeopathic herbs and bandages, represents cultural healing. In the individual's culture, the illness is curable through alternative medications and spiritual cleansing. While the individual has been trying her best to ward away her demons, she is burdened by their inevitable presence within her mind/spirit. The scarf that wraps around her is covered in eyes, representing society and the paranoia that she is constantly being observed and judged. The scarf is purposely reflected out of the border as a reminder to the viewer that we, society, are indeed observing and judging these individuals unintentionally or intentionally.

The message: Four extra hands are depicted around the image. These hands are instructions. Starting with the hand holding the flame, in the bottom right; I remind myself and the viewer that interacting with a person with paranoid schizophrenia can be extremely frustrating and discouraging. However, one must learn to temper frustrations in order to make the best decisions. The next hand holding the flower in the bottom left represents the fragility of interaction. One must realize that being over protective or judgmental can destroy the mutual relationship. Yet, being too passive will not lead to any changes in behavior. Thus, one must balance interactions carefully, as if holding a flower that can be easily crushed. Next, a hand holds its palm outward on the top right. This hand is an indicator to ''stop and think'' about how we are influenced by social stereotypes and biases before passing judgment on individuals with mental illness. The last hand, pointing upward on the top left, is a reminder that dealing with mental illness takes lots and lots of time. Thus, we should take our steps one at a time, day by day, week by week, with patience and integrity.

Declaration of Helsinki: What Does the Future Hold?

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Keywords: *research ethics; medicine; human research subject protection; informed consent; Helsinki declaration; bioethics.*

As medical students, we are mainly exposed to the rules and regulations that are set out in front of us; always wear your name tag, never be late, no whispering during tests, do not talk unless spoken to during your surgery rotation (just kidding on the last one). However, that is just the beginning of the ubiquitous rules that are present in medicine, with medical research being no exception.

Within the world of medical research, the Declaration of Helsinki (DoH) has long been considered the cornerstone document explaining the 'rules' of ethical human research. Developed in 1964 by the World Medical Association to protect the rights of research subjects, it originally contained a set of 11 articles explaining the basic ethical duties of physicians in regards to research. The original version took aspects of the Nuremburg Code and Declaration of Geneva to incorporate human experimentation with the physician's ethical role in the process and delineated a patient's rights regarding informed consent, privacy, and safety.[1,2] Since then, it has undergone seven revisions and has grown from 11 to now 37 articles, with categories ranging from General Principles to Risks to Informed Consent (http://www.wma.net/en/30publications/10policies/b3/index.html).[3] Though considered comprehensive and accurate in some aspects, it has not been without controversy over the years. Therefore, this year, which commemorates the 50th anniversary of the document, we must ask, how has the relevance of DoH changed, and will it change further in the future?

IMPORTANT CHANGES

The DoH has always been important as a regulatory tool for researchers. Though a researcher cannot be implicated under law for violating its terms, many countries have adopted legislation that has been guided by the declaration.[4] Over the years, many revisions and additions have been made, including the 1975 suggestion of research oversight by an 'independent committee' (Article 13), which would become the basis of institutional review boards (IRB) in the United States. Subsequent revisions sought consent for minors (Articles 24, 25) in 1989 and a set of standards for the use of placebos as treatment (Article 29) in 2000. The most recent revision in 2013 contains additional clauses including the importance of disseminating research results regardless of whether they are positive, negative or inconclusive (Articles 23, 35, 36), compensation and treatment for research subjects (Article 15), protection of vulnerable groups (Article 19), and database registration for all ongoing studies (Article 35).[5] In many regards, this document has been at the forefront in the evolution of ethical standards and has helped guide research in a manner that is beneficial for both the research participant and the field.

CONTROVERSY

However, this document is not without discrepancies. The DoH states that it is a set of rules for physicians, but nowadays medical research is conducted by a team, including investigators, coordinators, assistants, and others who are not necessarily physicians.[1] This inaccurate focus may deter the appropriate population from using this document to its fullest. Also, the DoH states that the 'rights and interests' of subjects are most important (Article 8), but 'research ... may only be conducted if the importance of the objective outweighs the risks and burdens' (Article 16). This discrepancy makes it unclear as to when a subject's interests can be compromised in favor of an objective, which unfortunately blurs the lines between ethical and unethical treatment of patients. Most recently, the addition of special protection for vulnerable populations is ad-

dressed (Articles 19, 20), but there is no explanation as to what the 'special protection' entails.[1] It is fair to want to protect vulnerable populations, but a vague statement does not help a researcher implement this goal in a real-world setting. It seems that as time goes on, more articles are being added with good intentions, but without thorough explanations. The committee has historically brought up important points for protecting research participants and making sure they are not put at risk, but sometimes it is impossible to remove all risk to research subjects. It also appears that as articles are constantly being revised and added, it is inevitable that they begin to contradict each other, making it more difficult to know which principles are the most important to focus on. It may be beneficial to pare down the document so that it includes the essentials most prominently, with minimized contradictions.

CHANGING TIMES

As we move further into the 21st century, the field of medical research continues to change, which brings about new problems and novel ethical dilemmas. Due to the numerous revisions that it has undergone, the DoH has received mixed feedback, with some saying that multiple revisions undermines its authority while others say that multiple revisions deem it an active document that is evolving. Others say that the DoH should focus more on basic principles rather than clinical practice guidelines which can cause controversy.[1] Another hurdle that the DoH has faced is the development of other documents outlining the ethical treatment principles, which in some cases have replaced the DoH.[2] The International Conference on Harmonisation of Technology Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the Council for International Organizations of Medical Sciences (CIOMS) are two examples that have gained popularity in recent years. The ICH is a group of regulators and pharmaceutical experts that discuss the scientific and technical aspects of drug registration. This group publishes the Good Clinical Practice (GCP) guidelines, which includes standards on how clinical trials should be conducted by defining the roles and responsibilities of sponsors, investigators, and monitors and is used by various government institutions worldwide.[2] CIOMS is an organization established by the WHO and United Nations Educational, Scientific and Cultural Organization (UNESCO) that also publishes guidelines for ethical research. Their document focuses more on the implementation of clinical studies in resource-poor countries and is more often used by groups conducting research outside of their home country.

In April 2008, the United States Food and Drug Agency (FDA) stopped using the DoH as their standard for ethical practice and began using the GCP instead due to controversy over the use of placebos.[5] The DoH had added the phrase 'this does not exclude the use of inert placebo in studies of where no proven diagnostic or therapeutic method exists', which seemed to rule out the use of placebo in any study where a proven therapy already exists, making it more difficult to assess the safety and efficacy of new drugs.[3] Therefore, as the field keeps changing and more resources become available, it is no surprise that the DoH has lost some of its hold as the sole regulator of ethical behavior for human research subjects.

CONCLUSIONS

The DoH has provided a set of ethical guidelines for medical researchers to follow and has been essential for regulation within this field. However, as time has passed, with the addition of controversial articles and the development of other human subjects' research guidelines, attention to and use of the DoH has been compromised. The document is comprehensive and puts the subjects' well-being at the forefront of the research study, which is essential for protecting the patient, but it is not without faults. Some articles are unclear while others are contradictory to each other. With the 50th anniversary of this historical document, we visited its evolution and saw that it is still relevant to today's changing world of medical ethics and it has its place in the complicated world of medical ethics despite its flaws.

As we set out on the road toward residency and beyond, there will be plenty more rules to learn and follow. To accommodate an easier transition for new researchers, it would be beneficial to simplify the guidelines of medical research ethics. It would be most relevant for students and new researchers to have a central document to learn from and understand in order to know the ethical standards that are needed to conduct research. It is great that there are esteemed members of the medical field that are continuously revising this document, but the excessive revision and addition of unclear and contradictory articles does not help its evolution. To continue to be a revered document in the international health community, it is important that the nebulous articles are revised, the contradictions are taken out and the most important

clauses are fleshed out so that they are clear and concise. Presently, it does not seem that there is a large emphasis on teaching about the DoH in medical schools. A clearer document would assist with appropriate education as it could be incorporated into medical ethics classes with greater ease when those who teach the class can understand the intricacies of the document. If students are exposed earlier, such as in their first or second year, they can incorporate these factors into their continued perception of research and effectively use this information when they conduct their own studies as residents and attending physicians. With the appropriate changes, the DoH may continue to be at the forefront of medical ethics research and be essential for everyone hoping to conduct research in the future.

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Morphine-induced Myoclonus in a Patient with End-stage Renal Disease

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Introduction and Patient Profile: *Pain is a common complaint, and pain control is frequently challenging. End-stage renal disease (ESRD) patients constitute a special population in whom commonly prescribed medications, including pain medications, must be adjusted or discontinued for safety. We describe a patient with ESRD in whom myoclonus developed after he received 60 days of morphine.*

Interventions and Outcomes: *Morphine was discontinued, and symptoms resolved.*

Discussion: *Morphine is hepatically metabolized to morphine-3-glucuronide (M3G), which is renally cleared. In patients with ESRD, M3G and other metabolites are neither renally cleared nor easily removed by dialysis, increasing the risk of neuroexcitatory symptoms such as myoclonus. The use and dosing of renally cleared medications in ESRD patients should be carefully reviewed by prescribers and pharmacists.*

Keywords: *end-stage renal disease; dialysis; myoclonus; morphine; opioid rotation.*

INTRODUCTION AND PATIENT PROFILE

The patient presented is a 59-year-old African-American man with end-stage renal disease (ESRD). ESRD is a subset of chronic kidney disease (CKD) stage 5, in which patients undergo dialysis or receive a kidney transplant. Patients with CKD stage 5 have a glomerular filtration rate (GFR) < 15 mL/min, and such patients frequently do not have sufficient nephron mass to properly filter toxins from the blood and to maintain fluid and electrolyte balance.

The patient presented with an infected stage 4 decubitus ulcer. He reported discharge from the ulcer as well as increasing pain, for which he had been prescribed morphine sulfate 30 mg orally twice daily starting 60 days prior to admission. The ulcer, located in the sacrococcygeal region, was the site of *Pseudomonas* and *Klebsiella* osteomyelitis, for which the patient had recently completed 6 weeks of treatment with doripenem. He was afebrile and without leukocytosis, and computed tomography of the spine revealed acute-on-chronic osteomyelitis. The patient was empirically retreated with meropenem and local wound care therapy. The patient continued to receive dialysis three times weekly, with only one missed session due to pain from the infected ulcer. He was continued on scheduled morphine and acetaminophen–codeine for breakthrough pain.

The patient noted a jerking movement in the upper extremities that had progressively worsened over the previous 2 weeks. At first, this symptom was an inconvenience, but it soon progressed to an interference with his activities of daily living. He was unable to feed himself because he could not hold utensils or cups. Neurology diagnosed him with myoclonus, which was attributed to uremia. Uremia seemed an unlikely cause, however, since myoclonus did not correlate with levels of blood urea nitrogen (BUN), which were low and at baseline because of adequate dialysis. Moreover, he did not have other symptoms of uremia such as nausea, vomiting, hiccups, peripheral neuropathy, pericarditis, asterixis, or altered mental status.

The differential diagnosis for myoclonus also included seizures, osteomyelitis, and side effects of other medications. The patient had no history of seizures, and neurology ruled out this possibility. Osteomyelitis was also believed to be unlikely because the patient had been undergoing treatment with antibiotics and his infection improved during the course of hospitalization. Finally, there had been no changes to the

patient's medication regimen besides the morphine previously mentioned.

INTERVENTIONS AND OUTCOMES

After ruling out other causes of myoclonus, the patient was evaluated for the possibility of opioid-induced myoclonus. Pain management specialists agreed to switch his regimen from morphine sulfate to hydromorphone hydrochloride 4 mg orally every 4 hours and a fentanyl 25 μg transdermal patch every 72 hours. After discontinuing his morphine, his myoclonus resolved within 2 days.

DISCUSSION

Morphine, although effective for pain control, can be dangerous at high concentrations. The presentation of morphine toxicity may vary from myoclonus to respiratory depression and coma. The most severe consequences of morphine intoxication are apnea or aspiration of gastric contents. Therefore, in patients who have difficulty excreting morphine, such as those with CKD stages 4–5, morphine is not recommended.[1] Unmetabolized morphine is eliminated without difficulty in patients with CKD; however, only a fraction of an administered morphine dose remains unmetabolized. Most of the parent compound is metabolized by the liver to products that are not effectively renally cleared in patients with CKD. These metabolites thus accumulate, and the ratio of metabolites to morphine may be increased by 5.5–13.5% in patients with CKD.[2] Although both morphine and its metabolites are partially cleared by hemodialysis, rebound of serum levels can occur between dialysis sessions due to mobilization from tissue stores.[3]

Morphine undergoes glucuronidation by uridine 5′-diphospho-glucuronosyltransferase (UGT2B7) in the liver. The products are morphine-6-glucuronide (MG6) and morphine-3-glucuronide (M3G). M6G is more potent than morphine itself and is responsible for most analgesic effects. M3G has little affinity for the opioid receptor, and therefore does not play a role in pain relief.[4]

Once a threshold concentration of M3G is reached, neuroexcitatory effects including myoclonus and seizure may occur.[5] The exact mechanism of neurotoxicity is unknown, but activation of *N*-methyl-D-aspartate receptors, leading to a rise in intracellular calcium and subsequent neurotransmitter release has been postulated. Interestingly, only morphine metabolites, not morphine itself, cause these side effects.[5] Those that develop these symptoms have been changed from systemic to intraventricular morphine with resolution of symptoms, likely because direct injection of morphine into the cerebrospinal fluid bypasses hepatic metabolism and generation of M3G.[5]

One approach to the treatment of neuroexcitatory side effects is opioid rotation, in which one opioid is switched to another in order to diminish toxicity of specific metabolites or to improve effectiveness. With this strategy, substitution of a chemically distinct opioid at an equivalent dose results in similar analgesia while avoiding side effects.[6] In one study, patients with CKD who did not tolerate morphine were switched to oxycodone, whereupon concentrations of morphine metabolites were five to six-fold lower. Higher doses of oxycodone than morphine were thus tolerated with improved pain control.[7]

In this case, the regimen was changed from morphine to hydromorphone and fentanyl. Hydromorphone is hepatically metabolized to hydromorphone-3-glucuronide (H3G), which is structurally similar to M3G and mimics its neuroexcitatory effects.[8] Hydromorphone, as morphine, should be used cautiously in patients with CKD, with a recommended starting dose of 0.5–1.3 mg every 6 hours.[9,10] The patient was prescribed 4 mg every 4 hours as needed, but we were unable to follow up with him after discharge to determine whether he required the maximal dosage of hydromorphone prescribed, and if so, whether myoclonus recurred. One study showed that patients with CKD who were changed from morphine to hydromorphone experienced greater pain relief with fewer side effects.[10]

The use of opioids to control pain is problematic in patients with decreased kidney function. CKD alters the pharmacokinetics of opioid metabolism, specifically, the rate of elimination, volume of distribution, carriage by serum proteins, and acid–base status. Furthermore, many commonly used opioids have not been well studied in patients with CKD or ESRD, and more research, including epidemiology and extent of the problem, is needed to develop guidelines for pain control in this population.

LEARNING POINTS

1. Patients with CKD stage 5 have a GFR < 15 mL/min and an inability to properly filter the blood and maintain fluid and electrolyte balance. ESRD is a subset of CKD stage 5, in which patients require dialysis or kidney transplantation.

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2. Morphine and its metabolites are renally excreted, so morphine should be used cautiously or avoided in patients with CKD or ESRD.
3. Morphine metabolism produces two products, M3G and M6G. M6G is responsible for the analgesic effects of morphine, while M3G produces the neurotoxic side effects.
4. Morphine toxicity symptoms include pinpoint pupils, nausea, vomiting, constipation, myoclonus, coma, and respiratory depression.
5. One way to treat morphine toxicity is with opioid rotation, in which morphine is switched to another opioid with a different chemical structure.
6. More research is needed to develop guidelines regarding opioid use in CKD and ESRD patients.

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Substance Use Among Physicians and Medical Students

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Background: *Physicians and medical students whose substance use causes impairment pose a risk to both themselves and their patients. Drug abuse is a documented problem in physicians; however, few studies have investigated the rates of drug abuse in medical students. While treatment plans may be tailored for both students and attending physicians, there is often a reluctance to refer one's self or a colleague due to a variety of reasons related to fear of repercussions, belief the problem has already been addressed, failure to recognize, or ignorance. This review provides a brief background on common signs and symptoms of potential abuse and resources available to doctors in training at various stages of their career, along with providing a clear picture of the literature as it pertains to physician and medical student substance abuse.*

Methods: *Extensive search of the literature utilized physical and electronic resources available at the National Institutes of Health Library and the National Library of Medicine with search results limited to the topics of physician or medical student substance use, substance abuse, impairment, and treatment.*

Results: *Sparse recent data regarding physician and medical student substance abuse are available. Studies completed two decades ago demonstrate that drug abuse was a significant problem for doctors and medical students at that time.*

Conclusion: *Due to outdated, and/or incomplete data on substance abuse in physicians and especially medical students, it is difficult to report the current extent of substance abuse in these groups. Nonetheless, it is important to recognize substance abuse in these populations and promote referral to substance abuse programs. Early rehabilitation and treatment improves both career and patient outcomes. This study highly suggests the need for up-to-date information regarding substance abuse in the medical community so that appropriate resources can be developed and effectively utilized.*

Keywords: *substance-related disorders; alcohol abuse; physician health programs; drug use; drug abuse.*

INTRODUCTION

Substance abuse[†] is an ongoing public health concern. Worldwide, an estimated 167–315 million people between the ages of 15–64 use illicit substances.[3] Although the prevalence of some drug use has been largely decreasing over the past decade, the overall use of illicit substances in the United States has been slightly increasing.[4] For instance, in the past decade prescription opioid abuse has reached epidemic proportions.[5] Use of illicit and controlled substances, in addition to excessive use of alcohol, is strongly influenced by many factors, including: age, gender, family history, and the presence of co-occurring psychiatric disorders. While drugs are abused by persons of all ages, young persons aged 16–35 use the largest proportion of drugs of any age group.[4] Many additional factors, including: race, geographic location, arrest history, and age at first use of drugs predispose individuals to drug abuse.[4]

[†]Several terms for the purpose of this review: 'Drugs' includes prescription pharmaceuticals, non-prescription pharmaceuticals, alcohol, and other substances of abuse. The term 'drug abuse' is defined as a pattern of drug use that causes recurrent problems for the individual. 'Drug dependence' and 'drug addiction' are used synonymously to mean the use of drugs such that it not only causes problems, but also renders the user unable to control his use. Although the diagnostic and statistical manual 5 (DSM-5) finds insufficient validity to support drug abuse or drug dependence as diagnostic entities and combines them into a single 'substance use disorder' diagnosis, the studies cited in this review occurred prior to DSM-5.[1] Therefore, use of the terms 'abuse' and 'dependence' or 'addiction', with knowledge that nosology in this area is evolving, is preserved. 'Impairment', as recommended by the Federation of State Medical Boards, is defined as substance use that causes the inability to practice medicine with usual skill and safety.[2]

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While certain risk factors for clinicians and medical students are similar to that of the general population, clinicians and medical students each have distinct stressors and predispositions for drug abuse. The data on drug use in these populations pale in comparison to the vast data collected on the general population. One of the first major publications reporting on physician drug use and resultant impairment was 'The Sick Physician' published in 1973.[6] This seminal paper called for the need to treat impaired physicians and led to the development of physician health programs (PHPs). These state programs were put in place in order to treat and rehabilitate impaired physicians. While studies regarding physician substance use followed this initial paper, several of the commonly cited comprehensive articles used to draw conclusions regarding the prevalence of substance use among physicians are more than two decades old. Moreover, data regarding the prevalence of medical student substance abuse are even more sparse. The original purpose of this article was to examine and report on the current prevalence of physician and medical student substance abuse. However, available data are outdated and often incomplete. Therefore, the goal of this article was modified to instead offer a thorough review of the currently available literature reporting on substance abuse in physicians and medical students, available treatment of substance abuse for both groups, and means to recognize an impaired colleague.

METHODS

Literature review

Research related to substance use among physicians and medical students was searched using resources available at the National Institutes of Health, including the National Institutes of Health Library and the National Library of Medicine. We used a three step screening process to retrieve relevant papers. (1) Using PubMed as the primary search engine, key words entered included combinations of the terms: 'physician', 'medical student', 'abuse', 'drugs', 'drug use', 'impairment', 'treatment', and 'PHPs'. (2) The abstracts of all retrieved studies were reviewed to determine relevance to our paper. Relevance was determined by the presence of primary data collected from physicians and/or medical students or references to primary data. (3) All studies deemed relevant were fully reviewed. Further, the references cited in the selected publications were subsequently reviewed for additional relevant articles that were absent from the PubMed search. These papers were retrieved, if possible, and subjected to steps 2 and 3 of the same 3-step screening process as those papers initially retrieved from PubMed.

PHP information

Information regarding individual PHPs was retrieved through one of two methods. First, some articles retrieved in the literature review contained information pertaining to PHPs, including PHP practices, success rates, and programs. Second, information on PHPs was retrieved from the Federation of State Physician Health Programs website (FSPHP) or directly from the individual state PHP website. The FSPHP website had information about PHPs in general without focusing on any single state's PHP practices. The individual state PHP websites contained information and practices particular to its PHP. This review focuses upon the general practices of PHP, and not directly on any specific state's practices.

Medical school handbook retrieval

Thirty medical schools were selected randomly from a list of all current medical schools in the United States. Handbooks for these medical schools were retrieved from publicly accessible material posted on medical school websites using the Google search engine. Search terms used to retrieve handbooks included 'medical school handbook', 'substance abuse policy in medical school', or 'medical student impairment'. The results were limited to schools whose handbooks were available online and were therefore not completely random. Handbooks were found by this retrieval method for 21 of 30 medical schools searched. The most recent edition of each medical school handbook was searched for an individual medical school's substance abuse policy. When possible, older editions of the medical school handbooks were compared to newer editions of the handbooks to track changes over time of medical student substance abuse policies.

RESULTS

Literature on drug abuse by physicians

Physicians and medical students are by no means exempt from illicit and inappropriate drug use or abuse. Physicians abuse drugs, both controlled substances and illicit drugs, at similar rates to the general population. However, physicians abuse prescription drugs at higher rates.[7] A more recent study showed relatively high rates of alcohol abuse and dependence in a sample of surgeons, with the highest rates in women.[8] The stress involved in medical training and providing medical care to patients results in extreme educational and professional demands – two major

factors that students and doctors, respectively, must manage on a daily basis. Relatively high rates of burnout in medical students and physicians may reflect the impact of these stressors.[9,10] Medicine presents a unique situation in that personnel are placed within easy access of substances with addictive potential, though newer techniques of tracking the use of potentially addictive substances in medical settings has improved.[11] Medical education should address the issue of how drug abuse impacts physician health and how to help oneself and colleagues. Reluctance to report an impaired colleague tends to delay treatment and may endanger patients, presenting a potentially serious problem.[12]

Misuse of medications may begin as self-treatment with prescription drugs. Drug use may also involve diversion of controlled medications from patients or use of illicit drugs and alcohol.[13] Within practicing physicians, select specialties have significantly higher rates of abuse than others.[14] For example, anesthesiologists most commonly abuse opioids due to their relative ease of access in the operating room, whereas most other physicians abuse substances that they may find easier to obtain.[15,16] Other examples of cited abuse patterns in physicians include psychiatrists and emergency physicians abusing benzodiazepines and marijuana, respectively.[17]

Treatment of impairment due to drug abuse beyond medical school

Most states have an established program, PHP, managed by the state to treat impaired physicians and other medical personnel.[18] State PHPs were designed to provide confidential support to the impaired physician in addition to protecting the public. These programs provide case management for physicians struggling with substance use disorders. Compared to alternative treatment options for substance use disorders with less intensive treatment and less rigorous monitoring of participants, PHPs have shown significantly higher success rates.[19]

In order to encourage early stage treatment, state laws may allow the identity of physicians who report themselves to remain confidential without necessarily disclosing his/her identity to the National Practitioner Data Bank or even to the state medical board.[20] The success rate of PHPs is in part due to the complete care and oversight that is provided as well as a customized treatment plan.[19] The contract that a physician makes with a PHP upon entering includes intense treatment from a choice of providers in addition to mutual help groups such as alcoholics or narcotics anonymous. In general, they must also submit to workplace visits and random drug testing for a period of time during and after treatment. In many cases, participation in a PHP can last up to 5 years.[19,20] Due to their successful outcomes, some PHPs have expanded their programs to include residents, nurses, physician assistants, dentists, pharmacists, and veterinarians.[21–23]

Literature on drug abuse by medical students

While physician data are more readily available, there have been few publications reporting on the prevalence of drug abuse and impairment of medical school students.[24–34] The study that offers the strongest possibility of drawing conclusions regarding prevalence of drug abuse among medical students in the US was completed in 1991 and surveyed $\sim$2000 students at 23 medical schools representing $\sim$20% of US medical schools. Of the remaining studies, two represent between 10% and 20%, and the rest $<$5% of US medical schools. Examining these data accurately can be challenging due in part to differences in data collection methodology, substances studied, changes in cultural attitudes during the duration of the study, and traditionally small samples of medical students or medical schools. Even with these differences, some observations may be made from the available literature regarding medical student drug abuse.

Available research indicates that, traditionally, the actual rate of drug use in medical school has been similar, if not lower, than that of an equivalent non-medical school population for many drugs.[24] However, medical students have still been reported to use alcohol, marijuana, psychedelics, tranquilizers, and opioids. A recent survey at one medical school showed that 10% of medical students had a history of unprescribed use of prescription stimulants.[35] A medical student's drug use behavior typically begins prior to initiating their medical education during high school and college.[24] Abuse of tranquilizers (e.g., benzodiazepines) is an exception in that its use more frequently begins during medical school.[24,31] The rate of drug abuse seen in medical school may involve the stress of medical school, family history, and emotional distress.[31,36] A substance use disorder most likely originates from a combination of these factors.[37] One of the best available studies finds that binge drinking episodes are correlated with experiences of belittlement and harassment in school.[34] Medical student drug abuse data, while reflecting general trends, may be inaccurate due to the bias of

self-reporting – a problem seen with data collected in other fields.

The most comprehensive studies regarding drug use typically cited for medical students are predominantly from the 1980s and 1990s (Table 1). While the data in Table 1 have been offered as a representation of the available data on substance use by medical students, the use of each substance reported on may or may not reflect the current use of these substances by medical students. This unfortunately limits the conclusions that may be drawn from these studies. Therefore, without more recent data on medical student drug use, and with changing drug use trends seen in the general population, newer studies are needed to better characterize the behavior of this population. Furthermore, comparison of the data in the cited studies is less meaningful because of inconsistency in methods used to collect data from dissimilar populations.

Treatment of impairment due to drug abuse during medical school

The problem of medical student drug use and abuse has been reported for years and only more recently have medical schools formally started addressing the issue with the inclusion of policies and procedures in student handbooks that may not have existed as little as 10 years ago.[45,46] While there is no standard policy for treating impaired medical students across institutions, there are certain similarities in processing of cases. Many schools publish their student handbooks containing impairment policies online, some of which are discussed in the current review.[46–65]

Sixteen of the 21 medical school policies researched, which we use as a sample of current medical school practices, required direct referrals of suspected impairment due to substance abuse to Student Health Services (or an equivalent service), an associate Dean, or a student-faculty committee.[46–48,51–55,57–60,62,64] To encourage students to seek early intervention, nearly one-third of medical schools in our cohort listed in their handbooks that they will forego disciplinary action of impaired students who self-refer for treatment.[47,50,56,57,59,60,62,64] This one-third of medical schools listed the following common ideas regarding treatment and reintegration of the impaired medical student following identification: (1) Evaluation – The impaired individuals would receive an evaluation to determine the extent of the problem. (2) Treatment – The medical student must undergo a recommended course of treatment if indicated. The treatment would be tailored to the individual medical student by an addiction specialist. (3) Confidentiality – In order to offer the greatest degree of confidentiality to the student, treatment professionals should use discretion in what information is provided to the medical school and to whom in the medical school it is provided. Appropriate treatment should provide the impaired student with the best chance of reintegration into their educational and clinical duties. Many medical schools show flexibility in accommodating the recommended treatment plan into the course of a student's studies. Due to the sensitive nature of the subject, medical schools treat cases of impairment with confidentiality, as legally permitted, to reduce the stigma associated with impairment and encourage individuals to receive help.[46–65]

Recognizing addictive behavior

Recognizing a peer who may be impaired due to drug abuse is the first step toward trying to provide an individual with treatment. Interestingly, a change in work performance is often not obvious until late in the timeline of drug abuse. Many physicians struggle with drug abuse or addiction for years before it is evident at work due to impairment.[37,66] Since many physicians and students struggling with chemical dependence are still able to function at a reasonably high level, along with the fear of repercussions resulting from seeking treatment, many believe they can manage their own recovery.[11]

Although impaired physicians and medical students have the capability to mask their abuse of drugs, the effect that it has on their ability to perform professionally may be manifested in a variety of ways (Table 2). Physical, social, and emotional changes in the individual may be noted. Some of the more common signs of drug addiction include changes in diet or appearance, anxiety, defensiveness or otherwise disruptive behavior, unusual drug orders, domestic distress, and depression.[37,67] One key change in behavior includes inaccessibility and withdrawal from social settings with colleagues or 'preferred solitude'.[11,66,67] It is not to say that everyone who has any change in personality or behavior is abusing drugs, rather that noticeable long term changes that appear to be interfering with everyday life and duties should be noted and examined more carefully.

The problem of recognition lies not only with the impaired physician, but also with his or her peers. The failure of a colleague to report the impaired physician can be a result of several factors. Commonly, colleagues of impaired physicians believe that the problem has

Table 1. Results of substance use and abuse among US medical students reported from 1973 to 2013

		Number of medical schools	Number of medical students	Alcohol usage	Tobacco usage	Stimulant/ amphetamine usage	Cocaine usage (%)	Marijuana usage
Lipp et al., 1971		4	1,063					47% lifetime
								28% current
								10.7% > 100 times
Solursh et al., 1971		1	85	2% never	39% never			27% never
				60% weekly	11% weekly			17% weekly
				11% daily	11% daily			1% daily
Mechanick et al., 1973	1970	1	463					54% lifetime
								21% > 50 times
	1972		449					70% lifetime
								30% > 50 times
Rochford et al., 1977		Not reported	144					26% never
								46.5% < 50 times
								27% > 50 times
Maddux et al., 1986	Ever used	Not reported	133	96%	44%	22%	20%	57%
	Last 30 days			82%	12%	3%	3%	13%
McAuliffe et al., 1986	Ever used	Multiple	504				39%	72%
	Regular use						4%	12%
Conard et al., 1988	Ever used	13	604	97.3%		27%	36.2%	73.7%
	Regular use			87.8%	9%	1.2%	5.6%	17.3%
Baldwin et al., 1991	Ever used	23	2,046	98.1%	55.3%	22.8%	32.5%	66.4%
	Regular use			87.5%	10%	0.3%	2.8%	10%

Table 1 (*Continued*)

		Number of medical schools	Number of medical students	Alcohol usage	Tobacco usage	Stimulant/ amphetamine usage	Cocaine usage (%)	Marijuana usage
Frank et al., 2008		16	1,428	21% not in past 30 days				
				37% excessive* in past 30 days				
Horowitz et al., 2008		1	340				5.9%	4.1%
Choi et al., 2013		1	319	84% in past 30 days		5%		1%
				31% excessively*				
Webb et al., 2013		Not reported	144			20% at least once		
						15% during medical school		
Lipp et al., 1971		4	1,063					47% lifetime use
								28% current use
								10.7% > 100 times
Solursh et al., 1971		1	85	2% never used	39% never used			27% never used
				60% weekly use	11% weekly use			17% weekly use
				11% daily use	11% daily use			1% daily use
Mechanick et al., 1973	1970	1	463					54% lifetime use
								21% > 50 times used
	1972		449					70% lifetime use
								30% > 50 times used
Rochford et al., 1977		Not reported	144					26% never used
								46.5% < 50 times used
								27% > 50 times used
Maddux et al., 1986	Ever used	Not reported	133	96%	44%	22%	20%	57%
	Last 30 days			82%	12%	3%	3%	13%
McAuliffe et al., 1986	Ever used	Multiple	504				39%	72%
	Regular use						4%	12%

Table 1 (*Continued*)

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	Regular use			87.8%	9%	1.2%	5.6%	17.3%
Baldwin et al., 1991	Ever used	23	2,046	98.1%	55.3%	22.8%	32.5%	66.4%
	Regular use			87.5%	10%	0.3%	2.8%	10%
Frank et al., 2008		16	1,428	21% not in past 30 days				
				37% excessive* in past 30 days				
Horowitz et al., 2008		1	340				5.9%	4.1%
Choi et al., 2013		1	319	84% in past 30 days		5%		1%
				31% excessively*				
Webb et al., 2013		Not reported	144			20% at least once		
						15% during medical school		

Blank sections correspond to substances that were not addressed by the listed paper.[24,26,31,32,34,38–44]

*Excessive defined as meeting at least one of the following: $\geq$5 drinks on one occasion (binge drinking), men averaging $\geq$2 drinks/day or women averaging $\geq$1 drinks/day.[34,43]

Table 2. Common symptoms of a physician with substance abuse problems

Socially removed	Sexual promiscuity
Decreased performance	Smell of alcohol
Spending more time at work	Heavy drinking at events
Change in diet/appearance	Problems with law enforcement
Inaccessibility/frequent absences	Excessive sweating
Defensiveness/irritability/conflicts with co-workers	Patient complaints
Unusual drug orders	Frequent illness/injury
Domestic distress	Isolates themselves in office
Mood swings (euphoria/depression/anxiety)	Ataxic gait/slurred speech/tremors

The actual symptoms associated with substance abuse are highly variable. The list of substance abuse symptoms is a non-exhaustive list intended only to describe common presentations of substance abuse in medical students/physicians.[11,15,37,66–69]

already been addressed.[12] Other factors include the belief that reporting might not lead to action and the fear that reporting will affect their own career.[12] Medical students, in particular, overwhelmingly fail to report peers with symptoms characteristic of addictive behaviors possibly due to downplaying of the scenario or a failure to recognize its serious nature.[33] The medical profession as a whole often employs the 'conspiracy of silence' in an attempt to preserve the image of the physician.[37,66] It is the responsibility of colleagues and peers to refer a possibly impaired individual to the appropriate professionals as the impaired physician or student is less likely to seek treatment on his or her own. Medical training should include discussion of this responsibility and health care organizations should provide consultation and support for physicians and students who come forward with concerns about the health of peers.

CONCLUSIONS

Drug abuse by physicians and medical students was determined to be a significant problem in studies completed 20 or more years ago. Unfortunately, these studies have not been repeated in large numbers. The the current extent of physician and medical student drug abuse and related impairment issues are not well known. Complicating the issue is the challenge of diagnosing and referring colleagues in a system where self-preservation is seen as key to a physician's success. An awareness of symptoms and a willingness to refer a fellow student could lead to earlier recognition of the impairment, significantly impacting and potentially improving the career path of the medical student and future colleague.

Substance use disorders are as treatable as other illnesses that require behavioral changes, especially with early intervention.[70,71] Seeking professional help for one's self or a colleague significantly improves outcomes and help is available through many avenues including medical schools and PHPs. Attempts to self-treat or manage the care of a colleague informally may be misguided and are ill-advised, particularly given the success of structured rehabilitation programs. Of note, fear of possibly destroying one's career is also a concern of medical students and physicians. In an attempt to remove this barrier to seeking help, many interventions focus on successfully rehabilitating medical students and physicians while preserving their ability to continue to practice medicine.

Finally, the magnitude of drug abuse in medical students has not been recently assessed and may be different from historical data due to changing drug habits and cultural shifts as paralleled in the general population. Furthermore, the environments in medical schools and hospitals have also changed, which could also impact drug use. An updated, comprehensive study of medical student drug abuse is needed to provide a better scope of trends in drug abuse among medical students and perhaps lead to improved education, awareness, prevention, and treatment.

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Vemurafenib: Background, Patterns of Resistance, and Strategies to Combat Resistance in Melanoma

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Introduction: *Finding an effective treatment for metastatic melanoma has posed a series of challenges. Vemurafenib, a B-RAF tyrosine kinase inhibitor, has been one of the most successful medications to date in the treatment of metastatic melanoma. B-RAF is a serine/threonine kinase that is a part of the RAS-RAF-MEK-ERK signal transduction pathway, which plays a pivotal role in cellular proliferation, differentiation, and survival. Mutations in the B-RAF protein lead to a deregulated activation of MAPK and ERK. The focus of this review article is resulting resistance to vemurafenib and its clinical implications on the treatment of metastatic melanoma. This paper aims to highlight mechanisms of vemurafenib resistance that have been observed so far and offer potential clinical approaches to overcome resistance.*

Methods: *PubMed, Google Scholar, and EMBASE were searched using the following free text terms: 'vemurafenib', 'vemurafenib resistance', 'vemurafenib tyrosine-kinase inhibitor', 'vemurafenib metastatic melanoma', 'vemurafenib alternatives', and 'vemurafenib cancer'. The Cochrane database was searched for randomized controlled trials and systematic reviews using the same search terms above. Two independent reviewers analyzed the search results and corresponding articles.*

Discussion: *Research over the last decade, most notably in the past 2 years, has revealed a multitude of mechanisms of resistance to vemurafenib. Resistance to therapy with vemurafenib in metastatic melanoma could be explained by the presence of cancer stem cells.*

Conclusion: *In order to effectively circumvent resistance, it would behoove clinicians to approach metastatic melanoma with a cocktail of inhibitors as opposed to monotherapy.*

Keywords: *vemurafenib; molecular targeted therapy; melanoma drug resistance; metastatic melanoma; tyrosine kinase inhibitor; melanoma treatment.*

INTRODUCTION

Finding an effective treatment for metastatic melanoma has posed a series of challenges.[1] Patients have historically had very few treatment options from which to choose. In 2011 alone, malignant melanoma, the fifth most common cancer in the US, caused over 9,000 deaths in the United States and 40,000 deaths worldwide.[1–3] While metastatic melanoma is the most common cause of skin cancer–associated deaths, it is only a small portion of all melanomas.[4] It takes approximately 3 years for the first metastases to appear clinically from the time a primary melanoma is diagnosed and more commonly occurs in older individuals in the head and neck regions.[3,5] However, 10–15% of patients already have metastases at the time of diagnosis.[1] The most common sites of metastases are the lymph nodes and the lungs (79%).[3] The highest incidence of melanoma occurs in countries with fair-skinned populations, such as those in Northern Europe, the US, Australia, and New Zealand, suggesting that ultraviolet light acts as a potent carcinogen in melanoma.[6]

Vemurafenib, a B-RAF tyrosine kinase inhibitor, has been one of the most successful medications to date in the treatment of metastatic melanoma.[4,7] Patients taking vemurafenib have an 84% survival rate at 6 months.[4] The period of progression-free survival in vemurafenib is approximately 5.3 months and median overall survival has been observed to be 16 months.[8] Roughly, 40–70% of melanomas are positive for a B-RAF mutation.[2,9,10] B-RAF is a serine/threonine kinase that is a part of the RAS-RAF-MEK-ERK signal transduction pathway, which plays a pivotal role in cellular growth, proliferation, differentiation, and survival.[6–8] Mutations in the B-RAF protein lead to a deregulated activation of MAPK and ERK. Other hypotheses surrounding the effect of B-RAF mutations include some of the remaining 'hallmarks of cancer' and 'emerging hallmarks', including resisting cell death, sustaining

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proliferative signaling, inducing angiogenesis, activating tissue invasion and metastasis, and evading immune destruction.[3,8,11,12]

Interestingly, B-RAF mutations are more commonly associated with melanomas occurring in regions of the body that are less frequently exposed to the sun, such as the trunk.[1] Mucosal and acral site melanomas rarely have B-RAF mutations.[8] Mutations in cyclinD1 are more commonly associated with melanomas occurring in areas with frequent sun exposure, such as the face and arms.[1] Mutations in the L597 and V600 (substitution of glutamic acid for valine at codon 600) locations of the *B-RAF gene* in exon 15 are most commonly associated with melanoma progression, warranting screening early in the disease process.[1,2] Since V600 mutations have been deemed as one of the most compelling reasons to use vemurafenib, some researchers have promoted the use of monoclonal antibodies to detect the particular mutation and ensure that all cases are observed.[13] V600E mutations have been more commonly associated with younger patients, whereas V600K mutations have been noted more often in older patients.[1] These mutations are present in the activating segment of the tyrosine kinase, offering a logical connection to cancer progression.[2]

Now, research shows that a combination therapy with B-RAF and MEK inhibitors shows greater promise than vemurafenib alone, likely conferred by increased mutation targeting.[1] The focus of this paper is resistance to vemurafenib and its clinical implications on the treatment of metastatic melanoma. An array of studies has shown that resulting resistance to vemurafenib is acquired by an intricate interaction between multiple cellular pathways.[10] Here we discuss some of those pathways (Fig. 1) and suggest potential clinical remedies to tackle the challenges of resistance.

METHODS

PubMed, Google Scholar, and EMBASE were searched using the following free text terms: 'vemurafenib', 'vemurafenib resistance', 'vemurafenib tyrosine-kinase inhibitor', 'vemurafenib metastatic melanoma', 'vemurafenib alternatives', and 'vemurafenib cancer'. The Cochrane database was searched for randomized controlled trials and systematic reviews using these same search terms. Two independent reviewers analyzed the search results and corresponding articles. Many randomized control trials, review articles, and opinion pieces were included. Unpublished abstracts, conference proceedings, and current ongoing studies were excluded.

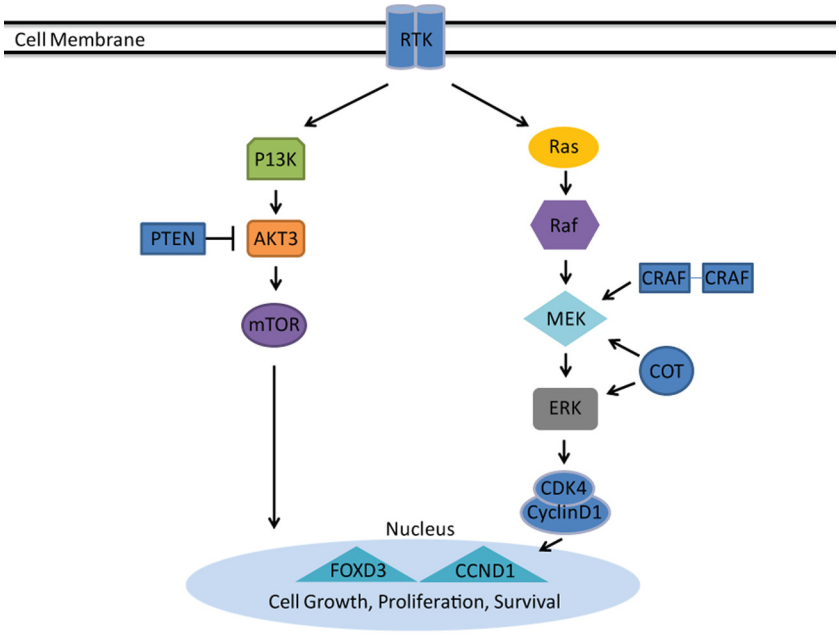

Figure 1. Simplified schematic of the MAPK and P13K pathways. When bound by their ligands, receptor tyrosine kinases activate RAS and P13K and their signaling cascades. The end result is survival, growth and proliferation of melanoma tumors. Mechanisms of BRAF-inhibitor resistance include, but are not limited to, PDFGR-beta upregulation, NRAS mutations, elevated CRAF, COT activation of ERK without the need for RAF signaling, loss of PTEN, CDK4 mutation and CCND1 amplification, CDK4 and cyclinD1 overexpression, AKT3 upregulation, and elevation of FOXD3. RTK: receptor tyrosine kinase (PDGFR-beta, IGF1-R, FGFR3).

The reference lists of included articles were analyzed to determine additional relevant articles. For those studies not accessible in full print, abstracts were obtained and analyzed. Only articles published in English were included. The reviewers were also limited to analyzing abstracts and articles available to them through their institution's journal subscription database. Discrepancies between reviewers were resolved by a collaborative review of the article in question and reaching a consensus.

DISCUSSION

Despite the gains in survival made by vemurafenib in most B-RAF mutation–associated melanomas, researchers have observed that characteristics of resistance manifest as rapidly as the initial onset of the drug.[6,14–17] Resistance develops on average within 7 months of initial use.[18] Researchers have shown that resistance is generally not because of further adaptive mutations in B-RAF but rather mutations in genes coding for other important proteins.[6] This finding was confirmed with next-generation sequencing of 16 patients with clinical resistance to vemurafenib.[6] No secondary mutations were noted in the *B-RAF* gene. MAPK reactivation, noted in multiple studies of resistance, suggests other pathways (Fig. 1) play an integral role in the process of resulting resistance to vemurafenib.[19]

As mentioned before, resistance to vemurafenib generally occurs after an initial favorable response to the drug.[20] Research suggests that one form of resistance occurs as a result of upregulation of PDGFR-beta, a receptor tyrosine kinase (RTK), or NRAS mutations, a gene/protein associated with cell growth.[20,21] Specifically, the induction of a PDGFR-beta was shown to be a dominant feature of clinical resistance to vemurafenib.[20] Interestingly, those tumor cells found to have upregulated levels of PDGFR-beta exhibited low levels of RAS activity and demonstrated an insignificant increase in activity of MAPK with vemurafenib treatment. Tumor cells with high levels of NRAS, as a result of mutations, showed a significant increase in the activation of MAPK via hyperactivation of MEK-ERK1/2 pathway with vemurafenib treatment.[20,22] Such research helps support the hypothesis that, in order to treat vemurafenib-resistant melanomas, additional medications treating some of the other pathways discussed may be necessary to impede cancer growth. Studies attempting to determine the most effective treatment plan for melanoma proliferation, as a result of upregulation of PDGFR-beta, suggest the use of inhibitors of MEK1/2, PI3K, and mTOR1/2, which leads to the apoptosis of malignant cells.[23] Just as B-RAF inhibitors lead to resistance, other studies show that MEK inhibitors, used alone, lead to MEK inhibitor resistance via B-RAF mutations and amplification.[24,25] This concept has been shown in both melanoma and colorectal cancer–associated B-RAF mutations.[24,25]

A suggested therapeutic strategy to avoid this form of resistance is to use B-RAF and MEK inhibitor simultaneously.[24] Trametinib, a MEK1/2 inhibitor, has recently received FDA approval for the treatment of BRAF-mutant metastatic melanoma.[26] A phase I/II trial combination of dabrafenib, a BRAF-inhibitor, and trametinib is already underway.[26] The therapeutic advantage of using a combination treatment plan is the prevention of cancer cells from acquiring other MEK or B-RAF mutations capable of circumventing directed monotherapy.[27,28] Concurrent treatment with a MEK-inhibitor and a BRAF-inhibitor also appears to result in less toxicity.[26] There are two phase 1 combinations of BRAF plus MEK inhibitors showing such reductions in severity of toxicity along with improvements in efficacy. However, it should be noted that a particular mutation, the MEK1 (C121S) mutation, which increases kinase activity, is resistant to both RAF and MEK inhibition in vitro.[29]

Monoclonal antibodies play a huge role in the treatment of a wide array of cancers and autoimmune diseases. CSPG4-specific monoclonal antibody, used with vemurafenib, has the ability to block multiple signaling pathways important to cell growth.[30] The addition of this particular monoclonal antibody has the added benefit of extending the amount of time vemurafenib has to exert its effects before resistance forms.[30]

Vemurafenib and ipilimumab, a monoclonal antibody directed against CTLA-4, were both approved by the FDA in 2011.[26] By binding CTLA4, ipilimumab enhances T-cell activation.[26] Evidence suggests that oncogenic B-RAF can be immunosuppressive, making the combination of a B-RAF-inhibitor with an immunotherapy a compelling proposition in the treatment of metastatic melanoma. In addition, treatment with MAPK inhibitors is associated with enhanced expression of melanocytic antigens, antigen recognition by T cells, and an influx of cytotoxic lymphocytes, creating more incentive to combine targeted and immune therapies. However, the phase 1 trial of vemurafenib plus ipilimumab had to be terminated due to toxicity concerns, particularly hepatic toxicity. Based on the earlier discussion of reduced toxicity using MEK and BRAF inhibitors, perhaps a triple combination with vemurafenib, ipilimumab, and trametinib would be a safer and more effective treatment.

Researchers have been able to successfully test hypotheses on the development of resistance in targeted cancer therapies using pre-clinical models with animals.[31] Such pre-clinical models have effectively predicted erlotinib resistance in EGFR-associated lung cancer, imatinib resistance in BCR-ABL leukemia, resistance to smoothened inhibitors in Patched1-deficient medulloblastoma, as well as ALK inhibitors in ALK-translocated lung cancers.[31] Some studies have shown tumor cells treated with vemurafenib to have high levels of ERK, even with low levels of MEK. Researchers have hypothesized that the high levels of ERK were a result of the activation of the PI3K/AKT pathway, thus increasing ERK levels via an alternative method. Subsequent inhibition of PI3K/AKT or ERK1/2 showed reduced cancer cell viability.[32] Those melanomas that appear to be refractory to both B-RAF and MEK inhibitors might benefit from a PI3K/AKT inhibitor or an ERK1/2 inhibitor.

Simultaneous mTOR activation has been noted in some studies with melanomas resistant to both MEK and B-RAF inhibitors. Consequently, the inclusion of an mTOR inhibitor along with a PI3K inhibitor to a treatment cocktail would be prudent. A dual PI3K-mTOR inhibitor has been shown to be superior to inhibition achieved by either mTOR inhibition or P13K inhibition alone, perhaps by overcoming mTOR feedback loops.[33,34]

MAP3K8, the gene which encodes COT/Tpl2, is a MAPK pathway agonist that drives resistance to RAF inhibition in B-RAF (V600E) cell lines, thus conferring another viable way to evade long-term effective treatment using B-RAF inhibitors such as vemurafenib.[9] COT activates ERK without the need for RAF signaling. COT expression is associated with naturally inherent resistance in B-RAF (V600E) cell lines and acquired resistance in melanomas treated with both B-RAF and MEK inhibitors.[9,21] Perhaps, an addition of a COT inhibitor to a B-RAF and MEK inhibitor could prevent melanoma proliferation in cell lines identified as having a COT mutation.

Additional research has shown that some melanoma cell lines resistant to B-RAF inhibitors demonstrate elevated CRAF protein levels, which may play a significant role in resistance.[35] Researchers noted that a drug, known as geldanamycin, helps to degrade CRAF proteins, revealing its potential as an effective drug to overcome resistance in cases of refractory melanoma with elevated CRAF protein levels and resistance to vemurafenib.[35]

PTEN loss has been associated with resistance to B-RAF inhibitors in metastatic melanoma.[36,37] Up to 10% of melanomas resistant to a B-RAF inhibitor were shown to have a loss of PTEN expression.[36] PTEN does not play a role in cell growth, but rather plays a role in signaling for normal apoptosis of cells. Therefore, loss of PTEN expression predisposes cells to ineffective apoptotic signals.[37] PlX4720, a B-RAF inhibitor, was shown to stimulate AKT signaling in PTEN negative melanoma, but did not have the same effect in PTEN positive melanoma. Further investigation showed that the use of the B-RAF inhibitor increased BIM expression (a protein signal crucial for apoptosis) in PTEN positive melanoma, thus allowing for normal apoptotic signals to ensue, while PTEN negative melanomas did not have nearly as strong response. Furthermore, inhibition of BIM in PTEN positive melanoma revealed poor apoptosis in cell lines.[36] Studies have shown that apoptosis is dependent on the BH3-only proteins, Bim-EL and BMF, and inhibited by MCl-1.[38,39] Treatment with XL888, an HSP90 inhibitor, increased BIM expression, decreased Mcl-1 expression, and successfully led to apoptosis in B-RAF inhibitor-resistant melanomas.[40]

Furthermore, AKT3 upregulation and activation has been associated with the survival of melanoma cells, especially in mutant B-RAF melanoma cells. Melanoma cell lines that were known to express higher levels of AKT3 were resistant to B-RAF inhibitor treatments.[38] Only after targeting AKT3 did B-RAF inhibitors, such as vemurafenib, effectively and successfully target the melanoma cell lines.[38] This reveals yet another mechanism by which B-RAF-mutant melanomas confer resistance to B-RAF inhibitors.

Recent studies have shown that there are considerable variations in response to treatment with B-RAF inhibitors. A study addressing the role of CDK4 and cyclin D1 in B-RAF inhibitor resistance in V600E cell lines showed that CDK4 mutations alone did not alter sensitivity.[41] However, cell lines with both a CDK4 mutation and *CCND1* amplification conferred B-RAF inhibitor resistance.[41] Researchers noted that as many as 17% of melanomas showed *CCND1* amplifications. Furthermore, cyclin D1 overexpression increased resistance, most notably when cyclin D1 and CDK4 were simultaneously overexpressed, revealing more therapeutic targets in the treatment of metastatic melanoma.[41] Recently, a number of selective CDK4/6 inhibitors have shown both tolerance and clinical benefit in clinical trials, opening the possibility of combinational therapies.[42]

Some B-RAF inhibitor resistant melanomas show increased IGF-1R/PI3K signaling. In such situations, treatment with IGF-1R/PI3K and MEK inhibitors leads to the desired cell death of resistant melanoma.[43]

It is suggested that increased levels of IGF-1R in post-relapse cancer cells are reflective of a survival mechanism dependent on the IGF-1R/PI3K pathway.[43]

Upstream activation may be a crucial component of vemurafenib resistant melanoma. One study's findings suggest that resistance to B-RAF (V600E) could occur due to elevated RAS-GTP levels and increased levels of AKT phosphorylation. Researchers insist that reactivation of the RAS/RAF pathway by upstream signaling activation plays a critical role in resistance to vemurafenib.[44] *FOXD3* is upregulated after inhibition of B-RAF-MEK signaling in mutant B-RAF melanoma. Research suggests that *FOXD3* elevation confers resistance. This was observed when siRNA knockdown of *FOXD3* led to greater apoptosis of the melanoma cell lines.[45] Elevation of *FOXD3* appears to be an adaptive mechanism for some forms of melanoma being treated with standard B-RAF and MEK inhibitors.[45]

Studies assessing the microenvironment of malignant cells reveal that secretion of hepatocyte growth factor (HGF) results in the eventual activation of MAPK and PI3K-AKT pathways, leading to B-RAF inhibitor resistance and uncontrolled proliferation.[46] One study quantified HGF levels secreted by surrounding stroma and stated that it strongly correlated with RAF inhibitor resistance.[46] Therapeutic management in this scenario could potentially be a RAF inhibitor coupled with an inhibitory compound for HGF. Further understanding of a malignant cell's environment could reveal other factors that predispose cancers to unabated proliferation.[46]

Research has shown that MEK/ERK reactivation via Ras signaling serves as a resistance mechanism in some melanomas.[18] Microarray confirmation demonstrates elevated Ras and RTK in resistant melanomas. Importantly, increased activation of FGFR3 correlated to Ras and MAPK activation, thus leading to vemurafenib resistance.[18] Researchers noted that inhibition of FGFR3 re-established sensitivity in resistant melanoma cell lines, further supporting their hypothesis.[18]

Vemurafenib is a targeted cancer therapy. Speaking generally about cancer drugs, such specificity of action has the benefit of having relatively fewer off-target effects and less nonspecific toxicity.[12] Scientific literature suggests that most targeted cancer therapies exhibit acquired resistance, especially with continuous dosing.[47] This phenomenon could be explained by growing evidence that each 'hallmark of cancer' (sustaining proliferative signaling, evading growth suppression, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis) is regulated by partially redundant signaling pathways.[48] Thus, inhibiting only one key pathway in a tumor might allow some cells to survive and function until they or their progeny eventually adapt to utilize a different signaling pathway due to selective pressure of the imposed therapy. This adaptation property of cancers suggests that successful targeted therapy can only be achieved after elucidating alternative pathways leading to proliferation of cancer cells despite treatment, so that medications can be developed to target the involved proteins.[48] Even after targeting alternative signaling pathways, it is possible that cancer cells may also reduce their dependence on a particular hallmark capability and become more dependent on another. This has been seen in antiangiogenic therapies where clinical responses have been transitory. In some preclinical models, potent angiogenesis inhibitors show initial success, but the tumors then shift from a dependence on angiogenesis to invasiveness and metastasis. Such a transition leads the cancer cells from hypoxic conditions to well oxygenated, preexisting tissue vasculature. This preclinical model has been validated in human glioblastomas treated with antiangiogenic therapies. This kind of adaptation ability of tumors needs to be considered when developing cancer therapies, including therapy for metastatic melanoma.

Resistance to therapy with vemurafenib in metastatic melanoma could be explained by the presence of cancer stem cells. Evidence suggests that a variety of tumors contain a subpopulation of cells called cancer stem cells. Cancer stem cells are defined as cells that are efficient in initiating tumors upon xenotransplantation.[12] Cancer stem cells have the ability to self-renew along with the capacity to generate progeny at various levels of differentiation.[49] It seems that cells with properties of cancer stem cells are more resistant to common chemotherapeutic agents.[12] In addition to chemotherapy resistance, presence of cancer stem cells might explain disease recurrence, sometimes years to decades following apparently successful debulking of solid human tumors by radiation or chemotherapy.[12] The presence of a stem cell subpopulation in melanomas has been demonstrated.[50] Identifying and targeting this population of cells, in addition to treatment with vemurafenib, might lead to more effective treatments for metastatic melanoma.

A major limitation in this review includes the inability to access all full articles since articles were excluded if they were not written in English or unavailable to the reviewers through their institution's journal subscription database. The number of articles unavailable

through the institution journal subscription database was not recorded.

CONCLUSION

Vemurafenib shows an 84% survival rate at 6 months.[4] The period of progression free survival in vemurafenib is approximately 5.3 months and median overall survival for vemurafenib has been observed to be 16 months.[8] Resistance to vemurafenib develops on average within 7 months of initial use.[18]

A myriad of different pathways for resistance have been highlighted in this review of B-RAF inhibition of malignant melanoma, many of which have specific molecular inhibitors that can be utilized with human drug therapy. Combination therapy of B-RAF inhibitors and other targeted drugs may either prevent or modify the ability for the cancer to exhibit resistance, and potentially prolong life and decrease complications. We suggest that physicians consider utilizing this breadth of information to tailor therapies for patients with malignant melanoma, and if human trials are not currently underway, that clinicians and scientists work together to develop new treatment regimens. Clearly there are many different pathways for resistance highlighted in this review; one pathway may not be a suitable treatment for every patient, but a physician must determine the advantages and disadvantages of specific therapies with their patient as multiple drugs often carry higher risks and complications than single drug therapy.

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