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COVER THEME The Opoioid Crisis

Opioid misuse and abuse continues to be a serious problem in communities throughout the United States, and combatting the problem requires collective, collaborative solutions. In this issue of *WMJ*, several articles look at different aspects of the crisis and suggest innovative approaches to tackling the problem.

Cover design by Jane Lee

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HEALTH INNOVATIONS

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YOUR PRACTICE

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Travel During Pregnancy

To the Editor:

The study you published on travel during pregnancy is very interesting. In this study, Antony et al found that both local and international travel during pregnancy was not uncommon and that some patients reported visiting Zika virus outbreak areas, but there was no data on the abnormal ultrasonography and pregnancy outcomes.¹

We would like to share ideas and observations on this finding. In our setting, tropical Indochina, the ultrasonography is also widely used in obstetrics. The Zika virus is endemic and the risk of exposure to Zika virus infection can be expected regardless of travel to other destinations. Of interest, there is still no observation on the increased rate of ultrasonography use, and there is also no report on the increasing incidence of abnormal ultrasound finding.² Almost all cases of women infected with Zika virus are asymptomatic.³

-Beuy Joob, Viroj Wiwanitkit

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 Wiwanitkit S, Wiwanitkit V. Afebrile, asymptomatic and non-thrombocytopenic Zika virus infection: Don't miss it! *Asian Pac J Trop Med.* 2016 May;9(5):513.

Severe Maternal Morbidity During Pregnancy

To the Editor:

I would like to commend the authors of the recent article "Severe Maternal Morbidity During Pregnancy"¹ for publishing the first study of its type to document severe maternal morbidity in Wisconsin. I would also like to humbly thank the authors for recognizing my contributions to their manuscript. Having helped restart the maternal mortality review process in Wisconsin in the late 1990s and then having chaired the review process in Wisconsin for the past 18 years I also have tried on multiple occasions to promote critical review of maternal morbidity cases in Wisconsin hospitals without significant success.

I participated in the initial attempt by the American Congress of Obstetricians and Gynecologists (ACOG)² to promote the idea of maternal morbidity reviews on a nationwide basis. ACOG, through the Alliance for Innovation on Maternal Health, has taken this work a step further, and now has a program accessible on the ACOG website (Council on Patient Safety in Women's Health Care)³ to perform these types of reviews. Also, the Joint Commission of Accreditation of Healthcare Organizations (JCAHO) published in January 2015 a mandate to consider these cases as sentinel events, and to perform a root cause analysis of all of these cases in all JCAHO-accredited hospitals. This mandate was subsequently rescinded after release of a joint statement by ACOG and the Society of Maternal and Fetal Medicine⁴ that clarified a potential screening and review process for maternal morbidities. As stated in the WMJ article, maternal morbidities far outnumber maternal mortalities, and critical review of these cases would provide a significantly greater source of information to effectively study maternal disease and accurately track the quality of maternal care.

Unfortunately, many hospitals in Wisconsin, and indeed nationwide, have not taken this message to heart. There still is a great paucity of concrete data in Wisconsin concerning critical review of these cases. It is well documented that careful and complete reviews of these events can improve the quality of maternal health care where they are being done.⁴

I implore organizations like the Wisconsin Medical Society and the Wisconsin Hospital Association to address this issue. These types of reviews could be done on a local level as suggested by ACOG.2,3 The data could then be analyzed on a statewide basis in a similar fashion to the Wisconsin Maternal Mortality Review. Wisconsin now has a Perinatal Quality Collaborative recently established and currently managed by the Wisconsin Association of Perinatal Care (WAPC). With the support of the above-mentioned groups as well as the Wisconsin Section-ACOG and the WAPC, this dream could become reality. However, appropriate specific changes in the Wisconsin state statutes would probably be required to protect the confidentiality of these reviews (as is the case with the current maternal mortality reviews in Wisconsin), to allow for accurate and complete collection of hospital

records, and to establish and maintain of a privileged status of this information from medical-legal review. With these changes I believe that a comprehensive review of these cases would be possible, and meaningful strides in improving maternal healthcare in Wisconsin could be made.

-Michael A. Schellpfeffer, MD, MS

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Opioid as a Wicked Problem

John J. Frey III, MD, WMJ Medical Editor

wicked problem is one that seems so intractable and resistant to solutions that people either give up trying or experience so much discord and conflict that they retreat from working on it together. The term was first used in the business literature to characterize a sense of "stuckness" that trapped businesses and industry in practices that threatened their existence.¹ The term has been applied in environmental and health policy to reflect on long-term issues - climate change, smoking behavior, gun deaths, and environmental degradation - that seem immune to proposed solutions. Certainly, the issue of narcotic overuse, opioid-related overdoses, deaths, and the destruction that the overuse is causing to communities all over the country should be classified as a wicked problem.

Wicked problems require approaches that are collective, collaborative, nonjudgmental, and incremental with clear measures of progress and clear goals. They also require patience and hope. The flood of opinions, publicity, and blame about how, who, and why opioids are such a pervasive problem has the potential to take planning away from stepwise, collaborative approaches to one that pits positions against one another in constant adversarial arguments. One of the largest problems with the opioid crisis is that it is not a we/they problem but much more of an "us" problem, with terrible loss of life in all communities. One would think that the pervasiveness would make everyone want to join in solutions, and while we may be making some progress, it's not enough.

We need information and thoughtful

research to begin to tackle this wicked problem. This issue of the *WMJ* brings together a number of articles written about the opioid overdose problem from a number of perspectives. Kohlbeck and colleagues² interviewed a mation about alternatives and discontinuation of opioids. Both groups demonstrated some gaps in information and some underlying misconceptions about who would not be a high-risk patient. Their work, just like that

Wicked problems require approaches that are collective, collaborative, nonjudgmental, and incremental with clear measures of progress and clear goals. They also require patience and hope.

group of emergency department physicians, residents, and allied health personnel to learn what they know and understand about the Prescription Drug Monitoring Program before its use was mandatory, as it is now. The program was designed to avoid over prescribing of narcotics from multiple sources, and one important assessment about its use was to identify obstacles that might find it used less than it should. Kohlbeck et al found that health systems, hospitals, clinicians, and patients all posed challenges to the use of the system and provide valuable information to help implement the program successfully.²

Chouinard, Prasad, and Brown³ carried out a survey of medical students and practicing family physicians to find out knowledge, attitudes, and beliefs about patients and opioid use. As might be expected, students—most of whom were in their preclinical years—were more focused on problems of addiction, and the practicing physicians wanted more inforof Kohlbeck, should be used to design educational methods for the medical community.

Rooney and colleagues⁴ used data from their hospital in LaCrosse to better understand the epidemiology of intentional and unintentional overdoses in their region. Perhaps one of the more interesting aspects of their study was the differences they found in their patient population compared to national trends: the majority of their patients were insured, there were not the rural/urban disparities to the degree that there are nationally, but their trends of sex and age did match national trends. The most interesting aspect of their study was the use of geographic mapping using census tracts to identify "hot spots" or high-risk areas in their region that might be addressed with focused community interventions rather than global ones. Coupling their approach with clinical information about people at high risk to overdose could be replicated in all regions of the country as a way of guiding resources to where they are most needed.

Faryar, Kohlbeck, and Schreiber⁵ examine the trends in alcohol and drugs found in the blood of people who died in motor vehicle accidents in Milwaukee County. They used Medical Examiner's findings from deaths from 2010 to 2016 and found that two-thirds of those who died had at least one substance in their blood and more than one substance was found in 27%. Alcohol remains the primary problem in Wisconsin, even though its use decreased in the timeframe of the study, with deaths in the state still at a higher rate than national averages. We are a binge drinking state and seemingly disregard its effects on our communities, particularly in rural communities.⁶ But the authors report a significant increase in opioids and other drugs that is worrisome since, as the campaign to decrease drunk driving succeeds, it is being replaced by drugged driving.

Prevention really has to start early, particularly as more studies report on adverse childhood events and their effects long term on children and adults. The program described by Budzak-Garza and colleagues from the Gunderson Clinic identifies newborns of mothers who have struggled with addiction issues and concentrates a number of services, community-based resources, and medical care to improve the chances for those newborns and their families.⁷ GunderKids is a proactive program that has been met with relief rather than resistance from at-risk mothers and families. If society genuinely wants to address wicked problems like addiction rather than engage in endless handwringing about it, investments need to be made in supporting time, effort, and a workforce that will work on ideas like GunderKids. America has lost the idea of longterm investment, whether in its people or the environment but if it can begin in communities and states, perhaps there is hope for the future.

In Other News

A review of cases of heparin-induced thrombocytopenia matched with controls from a large North Dakota health system discovered a much higher than predicted link to autoimmune diseases, leaving open the importance of studying the nature of the relationship. More importantly perhaps, for clinicians, patients with autoimmune diagnoses should be alert for thrombocytopenia and perhaps monitor patients preventively.⁸

Finally, an important study from the University of Wisconsin-Eau Claire about the attitudes of directors of palliative care programs in Wisconsin found that the majority felt that giving patients oxygen at the end of their lives was not helpful.⁹ They said that the reasons that oxygen was used, despite evidence that it was not comforting and may be irritating, is for emotional support of family or staff. The lesson from this study is that all clinicians who care for patients at the end of life and the programs in which they work should counsel both patients and families about the lack of effect of oxygen so that all are prepared better for the dying process.

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Use of Oxygen at the End of Life: Attitudes, Beliefs, and Practices in Wisconsin

Lisa Quinn-Lee, PhD, MSSW; Jeanne Weggel, MSN, APNP; Susan D. Moch, PhD, RN

ABSTRACT

Introduction: Oxygen therapy for the management of breathlessness remains controversial and little information is available regarding the practice of using oxygen at end of life. Oxygen use in end-of-life care is increasingly being questioned, while the use of oxygen for routine "comfort care" at end of life continues.

Objective: The purpose of this study was to investigate the use of oxygen at the end of life and to understand its role in contemporary palliative care practice.

Methods: The project involved a survey to learn about medical facility practices regarding the use of oxygen at the end of life and attitudes and beliefs regarding these practices, specifically the opinion of whether or not oxygen prolongs the dying process at the end of life. Questionnaires were mailed to 42 directors, coordinators, or managers of palliative care services in hospitals throughout Wisconsin. Twenty-five surveys were returned for a response rate of 59.5%.

Results: Forty-three percent of respondents believed that oxygen use at the very end of life affects the timeline of natural death by prolonging the dying process. Ninety-six percent of the respondents' facilities had a standard "comfort care" protocol for end-of-life patients that offered oxygen, regardless of whether patients had breathlessness or not. Respondents cited reasons that staff might use oxygen for these patients: patient comfort, family request, emotional comfort of family, prolongation of life when that was a patient goal, emotional comfort of staff. Respondents also cited reasons that staff might not use oxygen for these patients: oxygen did not seem to bring comfort, oxygen was an irritant to patient, prolongation of natural death was not a patient/family goal, oxygen use did not add to the emotional comfort of patient/family/staff.

Conclusion: Current practice on oxygen use in palliative care was identified and the information helps to determine how decisions are made regarding oxygen use. The research adds to palliative care practice knowledge and supports continuing research and dialogue on practice issues.

INTRODUCTION

It is relevant to study the dying timeline for patients who are receiving comfort care and to look at what might potentially delay the natural timing of dying. Patients at end of life often wish for a death without any measures to prolong life beyond the natural time of death. The extension of dying time may be especially impactful for patients who are experiencing end of life in a hospital setting. Family members can become exhausted from a prolonged vigil at the bedside. Fragile patients on comfort care who do not die within an allotted timeframe (usually several days) might be transferred away from the hospital to complete their dying process in another facility. In these cases, there can be a physical, emotional, and financial toll for patients and families. Patient and family goals should dictate what measures are used or not used during this time, and survey research can stimulate dialogue and further exploration to understand the benefit and burdens of the measures offered.

Dyspnea—shortness of breath—is one of the most distressing and prevalent symptoms for patients at the end of life. It is also pro-

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foundly distressing for caregivers and health professionals who witness it.¹ Dyspnea is a "complex subjective experience" that is common in terminal illness, and it includes physical, psychological, social and spiritual components, and it is important to recognize how each of these contributes to the total suffering of dyspnea.² The management of terminal dyspnea involves both pharmacological and nonpharmacological treatment, with the main pharmacological palliative treatments being oxygen and opioids.²(p327)

Oxygen therapy for the management of breathlessness remains controversial, and little information is available regarding the practice of using oxygen at end of life. In a published literature review, that served as a basis for this introductory survey research of palliative care coordinators, the use of oxygen in end-of-life care was questioned by cited authors, and growing evidence suggests that oxygen use may not always be indicated³ and may be unbeneficial⁴ and unnecessary⁵ at the end of life. In addition, some professionals have postulated that oxygen use at the very end of life may prolong the dying process^{6,7} and have questioned whether oxygen is needed for routine care for patients or for easing family member anxiety.8 Further, more definitive research is necessary, but gaining information on this topic is important. The purpose of this survey research was to investigate the use of oxygen at the end of life and to understand its role in contemporary palliative care practice. The project involved learning about palliative care practices in hospital settings regarding the use of oxygen for patients at the very end of life as well as attitudes and beliefs regarding these practices.

Literature Review

The literature indicates a need for further research on the topic of oxygen use at end of life.^{3(p372)} In a prior published review, the authors found no studies that looked at the question of interest: "Does oxygen at very end of life prolong the dying process?" However, there were studies that addressed some surrounding issues. The research studies found in the literature review were grouped into 3 questions that were subsequently used to devise the survey tool for this research project: "Does oxygen help alleviate breathlessness?", "What other options are available to alleviate breathlessness?", and "How do patients and families feel about the use of oxygen?" Each question is summarized briefly below.

Does Oxygen Help Alleviate Breathlessness?

Oxygen should not be given solely based on "intuitive assumption of benefit."⁹ Yet, oxygen is commonly used to treat breathlessness in advanced disease, although there is no evidence that it is effective^{10,11} and its place in palliative care remains controversial.¹² It is often given on a "compassionate basis," since many palliative care patients are otherwise not eligible for oxygen therapy.^{5(p989)}

Breathlessness, subjective sensation of inability to catch one's breath or an uncomfortable awareness of breathing, is a common symptom at the end of life with reported prevalence of 21% to 70%.¹³ Although the majority of patients with dyspnea do not have demonstrated hypoxemia, those who do have low oxygen saturation may benefit from oxygen.^{13(p380)} However, oxygen effectiveness for alleviation of breathlessness in nonhypoxemic patients is minimal.^{5(p991),14} Undesirable consequences of oxygen use include high cost, discomfort, airway damage, and prolongation of the dying process in patients who are ready to accept the natural timing of death.^{7(p1030)} One study found that physicians have not reached consensus regarding prescription and benefits of home oxygen for palliative cancer patients, and this is likely due to a lack of evidence since it is challenging to apply an evidence-based approach in palliative care.¹⁵ Mixed results have been recorded on patients with breathlessness prescribed oxygen therapy versus room air.¹⁶ Several studies found little benefit from oxygen when the patient has nonhypoxemic dyspnea.^{12,14}

What Other Options Are Available to Relieve Breathlessness?

The literature review identified that less burdensome strategies should be considered after brief assessment of the effect of oxygen therapy on the individual patient.^{12(p790-791)} One systematic review and meta-analysis demonstrated a statistically significant effect of oral and parenteral opioids on the sensation of breathlessness.¹⁷ Another trial yielded similar results in that patients receiving morphine had a significant decrease in breathlessness without depression of respiratory rate, sedation, or obtundation.¹⁸ In another study, opioids worked significantly better than oxygen in reducing the intensity of dyspnea even in hypoxic patients.^{9(p375)} Since breathlessness is related to anxiety, benzodiazepines or anxiolytic drugs have been widely used to reduce the sensation of breathlessness even though evidence regarding their effectiveness is unclear.¹⁹

There needs to be more research into the role of nonpharmacological measures. Alternatives include increasing air circulation, breathing training, repositioning, and utilizing relaxation practices; these can provide simple and practical ways to reduce breathlessness without serious side effects. Attention to the patient's psychosocial status can decrease breathlessness. Dyspnea may be "a significant component of the quality-of-life experience," and addressing coping strategies that target anxiety and depression for patients at the end of life can enhance the overall quality of life."²⁰

How Do Patients and Families Feel About the Use of Oxygen?

Dyspnea is a very frightening experience for the patient at the end of life. The authors' review of literature found that current studies on patient and family perception of oxygen use pertained to patients who were not at end of life. These patients who were earlier in their disease process identified more advantages than disadvantages to using oxygen, including improvement of shortness of breath, nausea, appetite, and skin color.²¹

Furthermore, when clinicians were asked about why they prescribed palliative oxygen, a common reason was patient or family request.²² Even if oxygen was not clinically indicated, it is sometimes easier to initiate oxygen to "treat the caregiver's anxiety."^{22(p270)} Breathlessness creates significant suffering both for patients and for caregivers, and this often creates a feeling of

helplessness in the conscious patient as well as for families and friends and also the clinicians trying to provide relief.^{23 (p932)} In the last hours and days of life, caregiver stress may predominate over patient distress in assessing levels of breathlessness, especially if patients are unable to participate in the ranking of their symptoms due to reduced levels of consciousness.²⁴ Palliative oxygen is also sometimes prescribed simply to "do something."^{4(p522)}

One qualitative study looked at nurses' and patients' perspectives on oxygen therapy.²⁵ Device comfort was the most common factor raised by patients. Patients also commented that at times their ability to talk, eat, and drink was restricted while receiving oxygen therapy. However, despite their concerns, all patients interviewed considered low flow oxygen to be effective.

METHODS

Although patients at end of life can be found in many settings (hospital, skilled nursing facility, home/hospice, communitybased residential facility, assisted living facility), a decision was made to narrow the focus of this study to practices and beliefs surrounding use of oxygen for hospitalized patients. Keeping in mind the area of interest, the target audience became health care professionals who cared for end-of-life patients in a hospital setting. Inpatient palliative care professionals were presumed to have knowledge of the end-of-life practices and beliefs in their own hospitals. Forty-two inpatient palliative care services were identified throughout Wisconsin. The director/coordinator/ manager of these programs was thought to be the best access to the needed information, and a survey study that included a 13-question questionnaire was sent to each.

Purposive sampling was utilized for this study. Using purposive sampling for this exploratory study allowed the researchers to focus on particular characteristics of the population of interest, best enabling the authors to answer the research questions. The institutional review board at the university at which the lead author works formally reviewed and approved this study. A cover letter explaining the study and informed consent was provided to potential participants, which stated that informed consent is implied upon completion of the survey. Participants were encouraged to ask any questions before they participated.

Survey

The survey questions were based on the literature research questions and were expanded upon through author discussion and consultation with end-of-life clinicians. The major survey research questions were: "Does oxygen help alleviate breathlessness?"; "What other options are available to alleviate breathlessness?"; "What other options are available to alleviate breathlessness?"; and "How do patients and families feel about the use of oxygen?" The question that emerged through the literature review and through discussions with clinicions is "Does oxygen at the very end prolong the dying process?" Therefore, questions about the perceptions of the use of oxygen were included in the survey. We asked the respondents to answer based on patients who are "within days of their expected death and who will most likely be staying at your facility until time of death."

Research Question-Survey Question Example

Regarding the question of whether oxygen helps alleviate breathlessness, the survey asked, "What are the reasons your facility might use oxygen for "comfort care" patients who are within days of their expected death and who will most likely be staying at your facility until time of death?"

Related to the question of what other options are available to alleviate breathlessness, 1 survey question asked, "Other than oxygen, what practices or care are commonly used at your facility at the end of life to achieve respiratory comfort?"

Related to the question of how patients and families feel about the use of oxygen, the survey asked, "What thoughts/concerns have family members shared about oxygen use?" and "Have you ever put oxygen on a patient to please a family?"

Related to the question of whether oxygen at the very end prolongs the dying process, 1 survey question asked, "In your experience or opinion, do you personally believe oxygen affects the timeline of the dying process?"

Process

Questionnaires were mailed to 42 directors, coordinators, or managers of palliative care services in hospitals throughout Wisconsin. Twenty-five surveys were returned for a response rate of 59.5%. The survey asked a series of questions referring to oxygen use at the end of life, the standard practices of the hospital, and also ascertained demographic information. Participants completed a 13-question survey with both closed- and open-ended questions. Participants were sent a cover letter and hard copy of the survey through the mail. Then, 1 to 2 weeks later, they were sent an email cover letter and survey link in order to increase participation. Participants were given the instructions twice to only complete 1 survey - either the email or the hard copy survey. Subjects who completed the online survey did so utilizing the Qualtrics online survey program. Subjects who completed the survey on paper mailed back their surveys; their surveys were then entered into Qualtrics. All survey responses were anonymous.

Demographics

Of the 25 directors/coordinators/managers of hospital-based palliative care services who responded to the survey, all were health care professionals: physicians with specialty fellowships in palliative care (2), registered nurses with advanced degrees (15), and registered nurses (8). All had worked in palliative care for at least 2 years, with several working 10 to 20 years in the field. The average age of respondents was mid-forties, with the youngest at 30 and the oldest at 64.

Significant diversity was found in regard to the environments in which they provided palliative care services. Fifty-five percent of the respondents practiced in an urban area (defined as a population of 50,000 or more), 25% practiced in a rural area (population of less than 2,500), and 15% were suburban (population of 2,500 to 49,999). Thirty-five percent of participants practiced in a community-based hospital and 10% were in an academic or teaching hospital. The total number of overall hospital beds ranged from 18 to 700. Many facilities had no designated beds dedicated to palliative care, noting that palliative care patients can go into any hospital bed. Those that had dedicated palliative care beds had anywhere from 4 to 15 beds. The number of palliative care patients served per year ranged from 10 to 1,600. Fifty-two percent of the palliative care services have a palliative care physician involved in the day-to-day management of patient care. Most programs only had 1 to 2 total full-time equivalent employees.

Data Analysis

Data analysis included a mixed methods approach. Quantitative data were entered into the statistical software program SPSS for analysis. Descriptive statistics were performed on demographic data. Responses to the open-ended survey data were coded and categorized into thematic categories. Qualitative responses were analyzed through content analysis. Responses Constant comparison was utilized until identified patterns and themes emerged. NVivo statistical software program supported the qualitative coding process.

RESULTS

Does Oxygen Help Alleviate Breathlessness and Does Oxygen at the Very End Prolong the Dying Process?

Data analysis was conducted to determine respondents' perspectives on the use of oxygen at the end of life within the context of their hospital's standard of practice. Forty-three percent of respondents believe oxygen use affects the timeline of the dying process; 100% of those respondents also believe that oxygen use prolongs the dying process. Ninety-six percent of the respondents' facilities have a standard "comfort care" protocol or order set for patients who are within a few days of their expected death and who will most likely be staying at their facility until time of death. The majority of respondents have oxygen as part of the standard order set for patients at the end of life, regardless of whether patients have symptoms of breathlessness or not. One participant commented "nobody thinks to take it [oxygen] off when the goals change."

Respondents cited the following reasons their facility used oxygen for "comfort care" of patients who are within days of their expected death: increased physical comfort of patient (71%), family requests oxygen (63%), increased emotional comfort of family (63%), patient's goal is to prolong life (29%), makes the staff feel as though they can at least offer something (25%), increased emotional comfort of staff (25%), other (including emotional support of patient) (21%). In terms of why a facility might not use oxygen for "comfort care" patients who are within a few days of their expected death, the following reasons were cited: does not seem to add to patient's physical comfort (83%), oxygen is an irritant (78%), seems to prolong the dying process, which is not the patient and/or family goal (61%), does not seem to add to the emotional comfort of the patient (61%), does not seem to add to the emotional comfort of the family (35%), does not seem to add to the emotional comfort of staff (26%), and other (1.4%).

In terms of why oxygen is utilized for patients at the end of life, respondents cited a variety of examples of how they have found this procedure helpful. A respondent stated, "We also use it for emotional comfort of the patient. If oxygen was used prior to comfort care, we typically do not immediately remove it unless we have the conversation with the patient/family." Another respondent stated, "We keep oxygen on when the patient goal is to prolong life (eg, waiting for family to arrive to say goodbye)."

What Other Options Are Available to Alleviate Breathlessness?

Results indicated that many facilities use alternatives to providing oxygen at end of life, including medications (95%), repositioning (90%), increasing air circulation (86%), spiritual practices (81%), breathing exercises (38%), music therapy (17%), aromatherapy (14%), massage therapy (10%), relaxation exercises (10%), and cognitive-behavioral therapy (10%). None of the facilities utilized acupressure/acupuncture. The medications utilized were opioids (85%—with morphine being the most common), benzodiazepines (75%—with lorazepam being the most common), and anticholinergics (30%).

How Do Patients and Families Feel About the Use of Oxygen?

Eighty-two percent of respondents have put oxygen on a patient to please a patient's family member; many of these respondents indicated that this was for the emotional support of the family members and to feel like they were "doing something" as opposed to actually decreasing patients' symptoms of breathlessness. Several respondents explained they provide the family with further explanation regarding the role of oxygen as well as potential benefits and complications.

Many respondents cited the views of the patient and their family as significant factors in determining whether or not oxygen was utilized at the end of life, which is supported by the literature. A respondent shared, "They want to feel like they and we are doing something for their loved one. They think the patient will suffer or suffocate without it." Numerous respondents also cited family members' desire for a peaceful death for their loved one and their concern that their loved one would be "gasping for air" during the final moments of life. Several also expressed having ongoing conversations with the patient's family in determining the appropriateness of the use of oxygen. A respondent shared, "We tend to treat families as extensions of patients and often will place oxygen for their comfort—at least initially. If providing oxygen becomes a discomfort to a patient or serves to prolong the dying process, then we continue to address this with the family." Another respondent stated, "I will typically provide information on the benefits/ burdens of supplemental oxygen and allow families control of this, especially if it seems they need this."

DISCUSSION

Many hospitals use oxygen at the end of life and their reasons vary. Through this study, the attitudes and practices of inpatient palliative care directors/coordinators/managers in Wisconsin were examined to gain a contemporary image of the use of oxygen in hospital-based palliative care practice. It was determined there is a divergence of opinion among the respondents in regard to whether oxygen impacts the timeline of the dying process. Fifty-seven percent reported they do not believe it impacts the process, while 43% of respondents not only believe the use of oxygen does impact the dying process, they also believe it prolongs the process. Further, nearly all of the respondents who indicated oxygen use prolonged the timeline of the dying process reported oxygen use was especially impactful in prolonging the dying process when a patient was experiencing hypoxia. One respondent stated, "If a patient is hypoxic or having a respiratory death, it often does (prolong the dying process). But if it is a nonrespiratory death-there is none or minimum influence." These findings warrant further examination into the impact of the use of oxygen on the timeline of the dying process in respiratory versus nonrespiratory deaths.

It is also intriguing to consider that 100% of the facilities that have a standardized "comfort care" protocol for patients have oxygen available for patient use in the order set. A respondent stated, "Nobody thinks to take it (oxygen) off when the goals change." This raises the question of whether oxygen use is a routine element of comfort care rather than an option that necessitates individual assessment before it is used.

Our results also strongly emphasized the influence of the family in determining whether oxygen was used at the end of life. Numerous respondents indicated the importance of having this as an ongoing topic of discussion with the patient's family. This suggests that attaining a delicate balance between assessing the particular patient's situation, providing education to the patient's family, and supporting the wishes and well-being of all involved may be important.

Ultimately, our results suggested that these palliative care

respondents have a divergence of views in regard to the use of oxygen at the end of life. Some perceived that oxygen use may affect the timing of a natural death and posed that this frequently used approach be more of an individualized practice at the end of life - based on patient/family goals and involving education and support. More definitive research is necessary and there are many avenues of further research, but research suggestions include additional distribution of regional and national surveys detailing the attitudes and beliefs of health care professionals, patients, and family members related to oxygen use at end of life. Providers who care for end-of-life patients in nonhospital settings (skilled nursing facilities, home, hospice facility, etc.) should be surveyed. Other research suggestions include examining the physiological nature of the use of oxygen at the end of life and exploring education for families on the use of oxygen (how best to educate, family reactions to education and whether oxygen use is modified through education and discussion). Hopefully, this introductory research will encourage a continuing dialogue on end-of-life care and continuing research that supports optimum care for patients and families.

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Is There an Association Between Heparin-Induced Thrombocytopenia (HIT) and Autoimmune Disease?

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ABSTRACT

Background: Heparin-induced thrombocytopenia (HIT) is a drug-induced, immunoglobulin G medicated autoimmune disorder associated with several negative clinical outcomes including increased morbidity, mortality, and increased medical costs. Previous studies have shown associations between comorbid autoimmune diseases, but there is little known about associations between HIT and autoimmunity.

Purpose: To provide clinical data to suggest an association between HIT and autoimmunity.

Methods: Retrospective chart review of 59 cases with a diagnosis of HIT and 251 matched controls without a HIT diagnosis, comparing the prevalence of autoimmunity in each group.

Setting: A single, large upper Midwest health care system.

Results: Patients with a diagnosis of HIT were significantly more likely to have a comorbid autoimmune disease than those without a HIT diagnosis (55.9% vs 10.8%, P<0.001). In disease-specific analyses, patients with a diagnosis of HIT were significantly more likely to have a diagnosis of antiphospholipid syndrome (15.3% vs 0.0%, P<0.001), systemic lupus erythematous (8.5% vs 0.4%, P=0.001), rheumatoid arthritis (5.1% vs 0.0%, P=0.007), Hashimoto's thyroiditis (13.6% vs 3.6%, P=0.006), or nonischemic cardiomyopathy (5.1% vs 0.0%, P=0.007). Patients diagnosed with HIT were significantly older than controls (P<0.001).

Conclusion: This novel study gives evidence to suggest an association between HIT and autoimmune disease and suggests a need for more research into the relationship between HIT and autoimmunity. These results could alter the anticoagulation management of venous thromboembolism and acute coronary syndrome in patients with a previously identified autoimmune disease.

INTRODUCTION

Associations between specific autoimmune diseases have been widely documented and often complicate the management of these disease entities.¹⁻⁴ It is also widely believed that autoimmune diseases are grossly underdiagnosed or unrecognized, which fur-

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Corresponding Author: Brent Klinkhammer MD, PharmD, University of Nebraska Medical Center, 982055 Nebraska Medical Center, Omaha, NE 68198-2055; phone 218.261.0967; email brent.klinkhammer@unmc.edu. ther conceals important associations and shared risk factors between these clinical syndromes. Given the current lack of understanding of autoimmunity, the likely shared commonalities in pathogenesis and etiology, and clinical ramifications of autoimmunity on patient outcomes, it is important to elucidate the relationships between autoimmune conditions to improve patient care.⁵

Heparin-induced thrombocytopenia (HIT) is believed to be a drug-induced, immunoglobulin G (IgG) medicated autoimmune disorder, in which autoantibodies are formed against and bind to conformationally altered epitopes on platelet factor 4 (PF4) when complexed with heparin-based therapeutic agents. This clinical syndrome has the potential to lead to several serious complications, most commonly thromboembolic events including deep-vein thrombosis, pulmonary embolism, myocardial infarction, stroke, peripheral arterial

thrombosis, and critical limb ischemia.⁶ Less commonly, HIT has been associated with bleeding complications, including adrenal hemorrhage and gastrointestinal bleeding.^{7,8} HIT also manifests in acute systemic (anaphylaxis and anaphylactoid) reactions, which have the potential to be fatal, and local skin necrosis.^{9,10} The mortality associated with HIT is approximately 5% to 10%, usually secondary to thrombotic complications.⁶

The commonly held belief that HIT is an idiosyncratic drug reaction is inadequate. It has been well-documented in the past that anti-PF4 autoantibodies can exist in patients who have never been exposed to a heparin-based therapeutic agent.^{11,12} Even more enlightening is the fact that a HIT-like syndrome, meeting both the clinical and serologic features of the disease, has been described in heparin-naïve patients as well.^{13,14} This

seemingly suggests that a complex autoimmune pathogenesis may indeed underlie the etiology of this disease entity.

In this case-control study, we attempted to describe an association between HIT and autoimmunity, including specific disease-disease interactions between HIT and particular autoimmune diseases. To our knowledge, no prior associations have been made between HIT and autoimmunity in general, and previous published literature into this topic matter has been tenuous.¹⁵

METHODS

A hospital-based, case-control study was conducted using data from a large, upper Midwestern integrated health system. We performed a retrospective chart review of adults (n=59) 18 years of age and older diagnosed with heparin-induced thrombocytopenia (HIT), between May 1, 2009 and December 31, 2015 at Sanford Health System. The ICD-9 code used to identify HIT cases was 289.84. The primary analysis was a comparison of the prevalence of any autoimmune disease in the group of patients with HIT to the prevalence of any autoimmune disease in a matched control group without HIT (n=251). In order to be included as a case in this study, patients must have met the clinical and laboratory definition of HIT, in that they needed to have either a positive titer of anti-PF4

antibodies or serotonin release assay along with either thrombocytopenia or thrombosis that was not otherwise explained. Control patients were chosen from a random sample of patients who were identified using the ICD-9 code V70.0, which codes for a general medical exam. Secondary analyses were made to examine the association between the prevalence of any one specific autoimmune disease and HIT. For the purposes of this study, "autoimmune disease" was defined as any disease that appears on the American Autoimmune Related Disease Association's (AARDA) "List of Diseases: Autoimmune and Autoimmune-Related Diseases" at the time of data collection.¹⁶ Excluded were patients <18 years of age. Recorded data included the following: age, sex, race, and diagnoses. Informed consent was not required for inclusion in our retrospective study due to the nature of the study, the absence of any direct interventions, and because there was no physical interaction between the principal investigators and the patients whose charts were reviewed at any time. This study protocol [IRB-201601-233 (UND), STUDY00000624 (Sanford Health) received

 Table 1. Baseline Characteristics of the Study Patients

Explanatory Variable	Patients with HIT	Control Patients	P-value
	N=59	N=251	
Sex			0.251
Male	32.2% (n=19)	24.7% (n=62)	
Female	67.8% (n=40)	75.3% (n=189)	
Age			
Mean	57.47 (95 % CI: 52.1 to 62.84)	31.75 (95% CI: 31.02 to 32.48)	<0.001
Race			.319
White	98.3% (n=58)	94.4% (n=237)	
Minority	1.7% (n=1)	5.6% (n=14)	
American Indian	1.7% (n=1)	0.8% (n=2)	
Black	0.0% (n=0)	1.6% (n=4)	
Asian	0.0% (n=0)	2.0% (n=5)	
Other	0.0% (n=0)	1.2% (n=3)	

Explanatory Variable	Patients with HIT N=59	Control Patients N=251	<i>P</i> -value
Autoimmune Disease	55.9% (n=33)	10.8% (n=27)	<0.001
Antiphospholipid Syndrome	5.3% (n=9)	0.0% (n=0)	<0.001
Systemic Lupus Erythematous	8.5% (n=5)	0.4% (n=1)	0.001
Rheumatoid Arthritis	5.1% (n=3)	0.0% (n=0)	0.007
Hashimoto's Thyroiditis	13.6% (n=8)	3.6% (n=9)	0.006
Nonischemic Cardiomyopathy	5.1% (n=3)	0.0% (n=0)	0.007
Endometriosis	0.0% (n=0)	1.6% (n=4)	0.738

dual IRB approval from the University of North Dakota IRB and from the Sanford Health IRB on January 25, 2016 and March 24, 2016, respectively.

SPSS 23.0 for Windows was used to analyze demographic and clinical characteristics of patients. Frequencies and relative percentages were computed for each categorical variable. Fisher's exact test was performed to determine statistical significance of categorical data and *t*-test/ANOVA was used to determine the statistical significance of continuous variables. All *P*-values were 2-sided, and *P*-values < 0.05 were considered significant.

RESULTS

A total of 60 HIT cases were matched with 251 controls without a HIT diagnosis. One case was excluded due to the patient being less than 18 years of age at time of data acquisition. Baseline characteristics of patients in both groups are reported in Table 1. The only statistically significant difference between the two groups was age, in that patients in the HIT group were significantly older than those in the control (mean age 57.47 vs 31.75 P < 0.001).

The results of this study are reported in Table 2. Patients with a diagnosis of HIT were significantly more likely to have a comorbid autoimmune disease than those without a HIT diagnosis (55.9% vs 10.8%, P<0.001). Subgroup analyses were conducted on the most frequently occurring autoimmune diseases. Patients with a diagnosis of HIT were significantly more likely to have a diagnosis of antiphospholipid syndrome (15.3% vs 0.0%, P < 0.001), systemic lupus erythematous (8.5% vs 0.4%, P = 0.001), rheumatoid arthritis (5.1% vs 0.0%, P=0.007), Hashimoto's thyroiditis (13.6% vs 3.6%, P=0.006), or nonischemic cardiomyopathy (5.1% vs 0.0%, P=0.007). There was no statistical significance between the case and control groups in terms of a diagnosis of endometriosis (P=0.738). A second set of analyses was done to correct for difference in age between HIT case and control groups by eliminating extremes of age in both groups. This second adjusted analysis yielded similar results to the primary analysis reported here.

DISCUSSION

In what we believe is the first of its kind, our study provides evidence to suggest an association between heparin-induced thrombocytopenia and autoimmune disease as defined by the AARDA. It also establishes a relationship between two of the "organ-specific" autoimmune diseases, Hashimoto's thyroiditis and nonischemic cardiomyopathy, and HIT. These findings imply that the underlying disease mechanisms that allow for the development of HIT have some commonality with other autoimmune diseases. Although a cause-and-effect relationship cannot be inferred from a single study, this data provides evidence that comorbid autoimmune disease may indeed be a risk factor for the development of HIT. Additionally, our findings confirm and extend those of other studies that suggested a relationship between HIT and antiphospholipid syndrome.^{15,17} Our results are also consistent with a previous report of an increased incidence of HIT in women, although there was no statistically significant difference in sex between the HIT and control groups in our study.18

HIT shares several mechanisms with specific autoimmune diseases, which suggests that the development of an autoimmune disease and HIT may have some commonality. First, HIT requires the formation of a specific heparin-PF4 complex "neoantigen," which is similar to the citrullinated proteins that are central to the pathogenesis of rheumatoid arthritis.^{19,20} Next, there exists a period of time when IgG antibodies are formed against this complex, similar to a post-vaccination Arthus reaction (type III hypersensitivity reaction).²¹ The binding of anti-PF4 antibodies triggers monocyte-mediated response leading to formation release of antigenic PF4, which is similar to the damage mediated release of myelin basic protein in multiple sclerosis.^{21,22} Additional features shared between autoimmunity and HIT are the existence of seropositive asymptomatic patients, relapsing-remitting disease course, endothelial cell activation and dysfunction, induced procoagulant effect, inhibition activated protein C, and expression of inflammatory cytokines.^{21,23,24,25} HIT also has several shared risk factors with autoimmune disease, such as an increased incidence in women and increasing age.^{18,26}

The evidence for this association is supported by the fact that the prevalence of autoimmunity in the HIT group was more than 5 times the rate found in the control group. This association is further supported by the fact that the 10.8% prevalence rate of autoimmunity in the control group in our study is consistent with the estimated nationwide prevalence of autoimmunity suggested by the National Institutes of Health (~7%) and the AARDA (~15%).²⁷ A similar finding also was observed in our study in the Hashimoto's thyroiditis subgroup.²⁸

Our case-control study does have some limitations. In using the V70.0 ICD-9 code in an effort to select appropriately matched controls without other disease or procedure confounders, we developed a statistically significant difference in age between HIT cases and controls. There is a limited amount of data provided by one study to suggest that age is a risk factor for HIT, although little collaborating evidence exists.²⁹ Nevertheless, age may be an important confounding factor in our study. No other statistically significant difference between cases and controls were found in terms of sex or race. Some potential for selection bias also exists, in that patients with documented autoimmunity may be more likely to have hematological derangements and subsequently be tested for HIT more frequently than patients without an underlying autoimmune disease.

Another limitation of our study is that it does not establish a timeline between the diagnosis of an autoimmune disease and the diagnosis of HIT. However, the validity of designing a study that would accomplish this feat would be in question given that autoimmune diseases are often underdiagnosed and unreported, likely due the lack of provider knowledge of autoimmune disease and the episodic and unspecific presentation of many autoimmune diseases. It also would be difficult to determine at which point an autoimmune disease might confer a risk of HIT given that autoimmune diseases are diagnosed based on both subjective and objective clinical criteria, and that the immunological evidence of an underlying autoimmune disease often predates a diagnosis by a considerable time period. For example, it has also been reported that up to 88% of patients with diagnosed systemic lupus erythematosus (SLE) have a SLE autoantibody present before the diagnosis, sometimes more than 9 years before their eventual diagnosis.³⁰

Finally, our study is limited in that only 59 HIT cases were identified using the ICD-9 diagnosis code of 289.84. We would have liked to have an equal amount of cases and controls in our study, however HIT is an uncommonly diagnosed clinical entity. Previous studies have determined the incidence of HIT in trauma patients who receive low-molecular-weight heparin as thromboprophylaxis to be 0.36% and 0.51% in admitted adult medical patients receiving unfractionated heparin to prevent venous thromboembolism. $^{31,32}\,$

If the results of our study could be replicated and confirmed, it could have a paradigm-shifting effect on the treatment of venous thromboembolism and its prevention strategies, and the management of acute coronary syndrome in patients with a previously identified autoimmune disease. Based on our data, this may be particularly true in patients with comorbid SLE, antiphospholipid syndrome, rheumatoid arthritis, Hashimoto's thyroiditis, and nonischemic cardiomyopathy. The associated mortality, morbidity, and increased medical costs of HIT potentially could be avoided through the use of agents that have not been associated with HIT.6 Additionally, many of these agents already have been shown to be a reasonable alternative or even superior to heparin-based therapeutic agents.^{6,9,10,32} Thus far, provider unfamiliarity and increased drug costs have prevented some of the non-HIT associated agents from widespread use, however, given that previously published studies have found that a HIT diagnosis increases the cost of a medical admission by more than \$30,000, it could make sense to employ these agents more widespread when indicated.³²

Fondaparinux is a synthetic, parenterally available, factor Xa inhibitor with favorable pharmacokinetic behavior versus low-molecular-weight heparin or unfractionated heparin. Previous studies have shown fondaparinux to be superior to enoxaparin for the treatment of acute coronary syndromes in terms of reducing major bleeding and 30-day mortality.^{33,34} Fondaparinux (2.5 mg once daily) also has been shown to be more effective than standard 40-mg once-daily enoxaparin for preventing venous thromboembolism and proximal deep-vein thrombosis following total hip replacement/hip fracture surgery.³⁵ Caveats to using fondaparinux in HIT patients are that fondaparinux is contraindicated in patients with a creatinine clearance of less than 30 mL/min or a body weight less than 50kg.³³ It also currently lacks approval by the Food and Drug Administration (FDA) for HIT, however previous studies have shown it to be a viable option.^{36,37,38}

Currently, the only FDA-approved treatments for HIT are the direct thrombin inhibitors argatroban and bivalirudin (in patients undergoing percutaneous coronary intervention). Lepirudin, another direct thrombin inhibitor, did have an indication for HIT, however it has been discontinued by its manufacturer for nonclinical reasons.³³ Of the FDA-approved options, argatroban has proven to be the therapy of choice, however it is a difficult agent to use clinically.³⁹ Argatroban is given as a continuous intravenous infusion and has the potential to elevate international normalized ratio (INR), making a therapeutic transition to warfarin or other vitamin K antagonists challenging.³³ Additionally, argatroban is considerably cost prohibitive in that a 10-day infusion costs approximately \$7,440 more than fondaparinux.⁴⁰

More recently, the FDA has approved several direct oral anticoagulants that also could be used instead of heparin-based therapeutics for common indications. The orally available factor Xa inhibitors rivaroxaban and apixaban are both FDA-approved for the prophylaxis and treatment of venous thromboembolism and for the stroke prevention in patients with nonvalvular atrial fibrillation; however, they are not FDA-approved for the treatment of HIT at this time.³³ Large randomized trials have shown these agents to be noninferior to treatment with enoxaparin and warfarin for venous thromboembolism with reduced rates of major bleeding.^{41,42} The most recent CHEST guidelines have adopted the factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and the oral direct thrombin inhibitor (dabigatran) as their preferred treatment of acute venous thromboembolism.⁴³

Given the results our study, the clinical impact of HIT, and the availability and effectiveness of other non-heparin-based therapeutics, we believe that the association between HIT and autoimmunity and specific autoimmune disease, such as SLE, antiphospholipid syndrome, and Hashimoto's thyroiditis, is nontrivial and deserves more study. A longitudinal study to look at long-term outcomes of avoiding the use of heparin-based therapeutics in patients with a history of autoimmune disease and/or other documented risk factors for HIT could shed more light on the management of anticoagulation in this patient population. Furthermore, we believe our study should encourage more research into drugdisease interactions between autoimmune disease and other drugs with what is currently believed to be idiosyncratic adverse events. Further research may help to elucidate the underlying mechanisms that predispose certain patients to adverse drug events given the patient's comorbidities.

CONCLUSIONS

In this novel case-control study, a statistically significant association between the prevalence of heparin-induced thrombocytopenia (HIT) and the prevalence of autoimmune and autoimmunerelated disease was found. A statistically significant association also was found between the prevalence of HIT and several specific autoimmune diseases including antiphospholipid syndrome, systemic lupus erythematous, rheumatoid arthritis, Hashimoto's thyroiditis, and nonischemic cardiomyopathy. To our knowledge, our study is also the first to imply a relationship between HIT and two "organ-specific" autoimmune diseases: Hashimoto's thyroiditis and nonischemic cardiomyopathy. Age was an important confounding variable as well. These findings emphasize the need for further research into this relationship and for more study into other drug-disease interactions. The results of this study could suggest a need for change in the management of anticoagulation in patients with a history of autoimmune disease and improved patient outcomes by means of potentially reducing the incidence of HIT in this patient population.

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Mapping Drug Overdose Demographic and Socioeconomic Characteristics in the Community

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ABSTRACT

Introduction: Drug use and drug overdose have increased at an alarming rate.

Objective: To identify demographic and neighborhood social and economic factors associated with higher risk of overdose. These findings can be used to inform development of community programs and appropriately devote resources to prevent and treat drug abuse.

Methods: The electronic health records of all patients seen in the emergency department or admitted to the hospital for a drug overdose in 2016 at Gundersen Health System in La Crosse, Wisconsin, were reviewed retrospectively. Patient data collected included age, sex, race/eth-nicity, insurance type, overdose intention (intentional, unintentional), drug involved, and total charge for the episode of care. Patient residence was geocode mapped to census tract to analyze the relationship of drug overdose to neighborhood characteristics. Overdose rates were calculated by census tract and compared by several sociodemographic characteristics.

Results: Four hundred nineteen patients were included in this study. Forty percent of overdoses were unintentional. Patients who were older, male, nonwhite, and who had no insurance were more likely to have unintentional overdoses. Opiates and heroin were most commonly present in unintentional overdoses, whereas benzodiazepines and sedatives were more common in intentional overdoses. Patients living in census tracts with a higher percentage of residents with some college also had a higher rate of unintentional overdose. Rates of overdose at the census tract level varied and were higher in tracts with lower median income, low income inequality ratio, high percentage of college attendance, and higher percentage of nonwhite residents. The average charge per overdose was \$14,771 (median = \$9,497) and totaled \$6,188,923 for the year.

Conclusions: This study provides demographic, geographic, and socioeconomic detail about drug overdose in the community that can be used to focus future treatment and prevention interventions.

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BACKGROUND

According to the Centers for Disease Control and Prevention, opioid and drugrelated overdoses have reached epidemic proportions in the United States, with overdose deaths nearly tripling between 1999 and 2014.1 From 2000 to 2014, the rate of death from overdose rose 137%, including a 200% increase in the rate of overdose deaths involving opioids.² In 2015, more than 52,000 Americans lost their lives from overdose,3 including 878 Wisconsin residents.⁴ In order to combat this alarming trend and save more lives, communities must increase access to antidotes, ensure rapid deployment of emergency medical services, provide preventive policing, and expand programs that educate community and family members. Each community must take an in-depth view of its population to better approach treating and preventing drug overdoses. Using the data from this study, we hope to provide a focused approach toward solving the epidemic across our counties, state, and country.

Gundersen Health System is headquartered in La Crosse, Wisconsin, and serves La Crosse County, which has a population of approximately 120,000,⁵ as well as surrounding counties in Western Wisconsin, Northeastern Iowa, and Southeastern Minnesota.⁶ Gundersen Lutheran Medical Center is a 325-bed hospital with approximately 14,000 hospital admissions and over 56,600 emergency department (ED) visits in 2016. Over the past 5 years, deidentified summary data regarding overdoserelated hospital admissions and ED visits at Gundersen Health System have been shared with the local community's Heroin and Other Drug Task Force to track opiate and drug use. The health system has experienced a 148% increase in drug-related hospitalizations since 2013.

We set out to better understand the differences between intentional and unintentional overdoses treated by our health system. In order to improve the community's approach to the growing drug abuse problem, we examined how patient-level characteristics (eg, age, sex, race, insurance availability) and population-level characteristics (socioeconomic, educational, and neighborhood) are related to these overdoses so that resources can be allocated properly. When these trends are better understood and addressed at the local community level, the enormous monetary and human toll exacted by drug abuse can be reduced.

METHODS

Following approval of the study by the Gundersen Clinic, Ltd Human Subjects Committee/Institutional Review Board, we conducted a retrospective review of the electronic health records (EHRs) of all 472 patients seen in the ED or admitted to the hospital at Gundersen Lutheran Medical Center in La Crosse, Wisconsin for overdose in 2016. Patients were identified by querying our EHR system using the International Classification of Diseases, Tenth Revision (ICD-10) codes T40, T42-T48, and T50. Patients with "adverse effects of" or "underdosing" as a poisoning type description were excluded. Some validation of results was done by reviewing patients' EHRs to support the exclusion of these poisoning types. Patients under the age of 10 years and older adults with diagnoses for adverse effects of hematological agents or medications for the cardiovascular and gastrointestinal systems also were excluded. These events were deemed incidental and outside the scope of this study. After excluding these incidental overdoses, 419 discrete patients met inclusion criteria. Patients who died before arriving at the hospital were not included in the study because no information was available for them in the EHR system.

We conducted analyses to understand differences in overdose intention (unintentional, intentional) by examining patient-level and population-level data. Data collected at the patient level included age, sex, race/ethnicity, insurance type, drug involved, and total charge for each episode of care. The EHRs of patients whose intentions were initially undetermined were reviewed and intention was coded as *intentional* if there was evidence the patient had intended to harm himself/herself.

Population-level data were based on where the patients resided. In 2016, we began mapping patients' residential locations to census tract using a geographic information system coder. To maintain patient confidentiality, we could neither map patients' exact location of the residence, nor could we assign patients to a more granular level such as census block group or census block. Census tract level data were obtained for each patient from the American Community Survey (https:// www.census.gov/programs-surveys/acs/) and included information from 2015 on income (poverty, children in poverty, median household income, income inequality ratio at the 80th and 20th percentiles), education (high school graduation, some college), unemployment rate, and neighborhood/social characteristics (nonwhite population, rental property, and disability). Based on the overall distribution of the sociodemographic characteristics in the 142 census tracts in the health system's service area, census tracts were categorized as being in the top 25% or bottom 75% of risk for each of these characteristics. We chose to split each census tract variable in this way in part because they were not normally distributed, but also because it allowed us to better compare and contrast high- and low-risk census tracts on a certain characteristic in a fairly homogeneous geographical area.

A second analysis was conducted at the census tract level. Overdose rates (overall, unintentional, and intentional) for each census tract were calculated by dividing the number of overdoses in the census tract by the population of that census tract in 2015 and expressing it as a rate per 100,000. These rates were then compared by the sociodemographic characteristics of the census tracts.

Statistical Analysis

For the analysis predicting overdose intention, descriptive statistics comparing patient and population characteristics were analyzed using χ^2 tests or analysis of variance (ANOVA) or nonparametric ANOVA tests for age. A multivariate model was built with logistic regression using backward elimination.⁷ To determine whether population predictors would contribute to the overall model, rather than including only those variables significant from the univariate analysis, we forced all the population predictors in the model to start and allowed them to be removed when the *P* value was <.10. Odds ratios and 95% confidence limits for the final model were calculated.

Census tract overdose (overall, unintentional, and intentional) rates were compared with census tract characteristics based on this 25%/75% distribution split using ANOVA. A multiple regression was conducted with backward elimination of the significant variables from the univariate analysis.⁸ Characteristics not significant at the P < .10 level were removed until no additional variables met this criterion. Regression coefficients of the significant variables and their standard error are provided, as well as an R^2 , which indicates the amount of variability in the overdose rates explained by the variables in the model. P values of <.05 were considered statistically significant for all comparisons and statistical tests. All analyses were conducted in SAS 9.4 (SAS Institute Inc, Cary, North Carolina).

Predictors	Overall	Unintentional	Intentional		
	N=419 (%)	n=169 (%)	n=250	<i>P</i> value	
Patient predictors					
Age group, years					
≤24	122 (29.1)	23.8	76.2	.0001	
25-49	219 (52.3)	43.4	56.6		
≥50	78 (18.6)	57.7	42.3		
Mean (SD), median	35.1 (15.3)	39.83 (16.5)	31.92 (13.6)	.0001	
	32.6	35.9	29.2		
Sex					
Female	257 (61.3)	30.0	70.0		
Male	162 (38.7)	56.8	43.2	.0001	
Race/ethnicity					
White	388 (92.6)	39.4	60.6	.1834	
Nonwhite	31 (7.4)	51.6	48.4		
Insurance					
Private	239 (57.0)	40.2	59.8	.0362	
Government	155 (37.0)	36.8	63.2		
None	25 (6.0)	64.0	36.0		
Drug type					
Benzodiazepine-based	84 (20.1)	28.6	71.4	.0140	
Opiates and related narcotics	54 (12.9)	75.9	24.1	.0001	
Heroin	47 (11.2)	85.1	14.9	.0001	
Sedatives and hypnotics	166 (39.6)	21.1	78.9	.0001	
Amphetamines and stimulants	31 (7.4)	45.2	54.8	.5691	
Population predictors, census tra	ict averages				
Poverty rate	15.0	14.5	15.3	.4615	
Child in poverty rate	18.1	18.4	18.0	.7396	
Median income	\$46,333	\$46,353	\$46,320	.9807	
Income inequality rate	3.78	3.74	3.81	.1613	
No high school degree	8.7	8.8	8.7	.6533	
Some college	61.5	61.0	61.8	.4757	
Unemployment rate	4.6	4.6	4.7	.6211	
Nonwhite	10.1	10.1	10.1	.9426	
Renters	34.0	34.0	34.0	.9726	
Disabled	11.7	11.7	11.7	.8931	

 Table 2. Multivariate Model of Unintentional Overdose Using Patient and Population Predictors

Predictors	Unintentional : Intentional	
Patient predictors		
Age	1.04 (1.02, 1.06)	
Sex		
Male	1.87 (1.14, 3.08)	
Female	Ref	
Race/ethnicity		
White	Ref	
Nonwhite	2.69 (1.08, 6.67)	
Insurance		
Private	Ref	
Government	0.66 (0.39, 1.10)	
None	2.53 (0.90, 7.08)	
Drug type		
Benzodiazepine-based	0.49 (0.25, 0.98)	
Opiates and related narcotics	3.15 (1.36, 7.32)	
Heroin	10.34 (3.93, 27.21)	
Sedatives and hypnotics	0.39 (0.21, 0.73)	
Population predictors		
% some college	1.89 (1.01, 3.56)	

RESULTS

Patient- and population-level predictors overall and by overdose intention are shown in Table 1. Patients seen for unintentional overdoses were older and more likely to be men. Nonwhite patients and those with no health insurance also were more likely to have an unintentional overdose. The most common drugs for unintentional overdoses were opiates and heroin, whereas the most common drugs for intentional overdoses were benzodiazepines or sedatives and hypnotics. None of the patients' population-level predictors varied significantly by overdose intention.

Only 3 patients treated for an overdose died during their stay. The mean and median charges per overdose were \$14,771 and \$9,497, respectively, and the total charge for this single episode of care for all 419 patients who overdosed in 2016 was \$6,188,923. Total charge varied by overdose intent: unintentional overdose charges averaged \$9,795 (median \$3,213), whereas intentional overdoses charges averaged \$17,992 (median \$12,756), probably a reflection of the higher rate of hospitalization among intentional overdose patients. The median charge was highest among the overdoses for amphetamines (\$14,619), followed by benzodiazepines (\$11,165), and sedatives and hypnotics (\$11,007). Median

charge was lowest for overdoses in which heroin was involved (\$2,442). Total charge to treat all patients in 2016 was highest for sedatives and hypnotics (\$2.7 million) and benzodiazepines (\$1.4 million). Opiate overdoses in 2016 incurred \$720,000 in charges, and heroin incurred \$500,000.

The multivariate model to predict unintentional overdose is shown in Table 2. With every 1 year increase in age, the risk of unintentional overdose increased by 4%. Men were 1.87 times more likely than women to have an unintentional overdose. Nonwhite patients were 2.7 times more likely than white patients to have an unintentional overdose, and those without health insurance were 2.5 times more likely than those with health insurance. Patients admitted with opiate or heroin were much more likely to have unintentional overdoses. Those patients who lived in census tracts with higher college attendance also had higher unintentional overdoses.

Overdose rates by census tract are shown in Figure 1. Unintentional overdose poisoning rates are shown in Figure 2, and intentional overdose poisoning rates are shown in Figure 3.





Census tracts within La Crosse County, the most populous, had a higher overall rate and a higher intentional rate of overdose poisonings than those in other counties in the health system service area. Unintentional overdose rates, most of which did not result in Figure 3. 2016 Intentional Overdose Poisoning Rate by Census Tract for Patients Treated at Gundersen Health System



an admission, although high in La Crosse County tracts, also were distributed throughout the rest of the service area. This is probably an underestimate of unintentional overdoses, since many of the unintentional overdoses occurring in the service area were probably treated at regional emergency departments.

Census tract overdose rates were compared by neighborhood social factors (Table 3). The best predictors of high overdose rates overall were low median income, low income inequality ratio, high percentage of some college, and high percentage of nonwhite population. The best predictors of unintentional overdose rates were low income inequality ratio and high rate of rental property. The best predictors of intentional overdose rates were low median income, low income inequality ratio, high percentage of some college, and high percentage of nonwhite population. Overall, these models predicted between 18% and 27% of the variability in overdose rates at the census tract level.

DISCUSSION

An examination of ED visits and hospitalizations at Gundersen Health System for drug overdoses gives important information in the approach to combating drug abuse in the community. In Wisconsin, the age-adjusted rate of drug overdose deaths has risen significantly from 2010 to 2015.¹ To reverse this trend, better understanding of the issue within the local community is critical.

Our study showed that a majority of patients had private insurance versus Medicaid/Medicare or no insurance. This is contrary to findings in research of the United States as a whole,⁹⁻¹² so it

Predictors	Overall	Unintentional	Intentional
	Parameter (SEM)	Parameter (SEM)	Parameter (SEM)
Intercept	101.02 (14.82)	38.99 (7.04)	56.71 (8.82)
Poverty risk	-	-	-
Children in poverty risk	-	-	-
Median income risk	61.92 (23.23)	-	41.01 (13.82)
Income inequality risk	-74.80 (23.37)	-38.2 (12.14)	-30.77 (13.90)
No high school diploma risk	-	-	-
No college risk	-72.10 (23.36)	-	-50.46 (13.89)
Unemployment risk	-	-	-
Nonwhite risk	52.83 (21.77)	-	30.42 (12.95)
Rental property risk	-	36.55 (11.21)	-
Disability risk	-	-	-
Final model R ²	0.2660	0.2730	0.1834

may be an important aspect to recognize in the region. Patients living outside La Crosse County were slightly more likely to be insured than those living in La Crosse County, which is consistent with the fact that many of these patients are transferred from other facilities for the primary purpose of admission to the hospital. This process contributed to the higher rate of admission from outside counties (68%) compared with La Crosse County (32%). Sixtyeight percent of unintentional overdoses were treated in the ED without admission to the hospital, which likely reflects the ability to reverse heroin overdose with naloxone and discharge patients without hospital treatment or admission. Opiates and related narcotics accounted for 24% of unintentional overdoses and were found to be consistent across counties. In previous studies, more rural and more impoverished counties tended to have higher prescription drug overdose death rates.¹³ Although Gundersen's service area is largely rural, this study's sample size was not sufficiently large to illustrate this trend.

It should be noted that women accounted for 61% of our study population, which is consistent with previous studies,^{10,14} but they disproportionately represented 72% of intentional overdoses. Conversely, men represented 39% of the study population yet accounted for 55% of unintentional overdoses. Consistent with all opiate overdoses, 70% of heroin overdoses in 2016 were in men. This is consistent with previous studies in which rates of heroin initiation were highest among men.^{14,15}

The overdose epidemic should be viewed through the lens of community impact. Not only are lives being affected by this problem in our counties, but the resource allocation is significant. The charge for unintentional overdoses averaged \$9,795, while intentional overdoses averaged \$17,992. The discrepancy is mainly due to the larger number of intentional overdoses admitted to the hospital and the follow-up care involving Behavioral Health. The 419 patients in this study accrued \$6,188,923 in hospital charges in 2016, and this does not include the cost of prehospital care, the allocation of law enforcement resources, and other costly social service assistance. Overall, charges for drug-related hospitalizations in Wisconsin totaled \$327 million in 2012, an increase of 49% from 2006,¹⁶ and a number that continues to rise. It is prudent to look toward prevention of overdose to minimize the large expenditures that arise from the acute abuse episodes.

Use of a census tract study is a novel way to examine drug abuse issues in the community and is essential in uncovering the most susceptible hot spots. In our study, higher rates of overdose were found in neighborhoods with low median income, low income inequality, higher

percentage of nonwhite residents, higher rates of some college, and a high percentage of rental properties—characteristics common in many La Crosse County census tracts.

Many public health problems correlate lower income, less education, and being nonwhite to higher intensity of the problem. In 1997, Kawachi et al found a higher rate of mortality in populations with a higher income inequality rate, suggesting that income inequality leads to increased mortality via disinvestment in social capital.¹⁴ However, in our study, overdose rates in census tracts with higher rates of the positive social indicators of high rates of some college education and lower income inequality ratios were found to have higher rates of overdose. This was likely due to the higher level of education overall and low variability in these census tracts, and the high rate of intentional overdoses in these census tracts with other behavioral issues, such as depression. This would be an important consideration when developing and targeting interventions, and would be important to examine in future research.

One limitation to this study was that the geo-mapping was done using the patient's documented county of residence, although that county and the location of the overdose may be different. For example, a student at a local university may experience an overdose on campus but have a permanent address outside the service area, which limits accuracy of the data. Future research could mitigate this limitation by incorporating ambulance service data to explore where the risky behavior was occurring.

This study included patients who were treated at only 1 of the 2 health care facilities in the community, thus underrepresenting the overdose poisoning rates per census tract. We do not believe that the demographic and socioeconomic relationships we found would differ if patients from both facilities had been included. The overall service area and referral systems of the second health system are similar to Gundersen's. Patients who do not or cannot state a health care facility preference are randomly transported to one or the other. Preliminary statistics reported to the Heroin and Other Drug Task Force in La Crosse County from the sec-

ond health system indicate that the number and distribution of overdoses are similar to those reported here. Unfortunately, including the other health system's data in this study was not possible. The degree to which unintentional overdoses are managed at other nonaffiliated critical care hospitals in the region and not transported to either La Crosse hospital is unknown; thus, the rate of unintentional overdoses in the service area may be further underestimated.

Deaths reported by the La Crosse County Medical Examiner for 2016 were reported to the Heroin and Other Drug Task Force and were mapped to census tracts in La Crosse County.¹⁷ This information was based on where the death occurred rather than where the person lived; nevertheless, the 25 deaths that occurred in La Crosse County occurred in those census tracts with the highest overdose rates, further corroborating the findings reported here. Unfortunately, this information is not available to us for other counties in our service area.

Another consideration is that heroin overdoses tend to be coded as *unintentional* unless the patient specifically described intent of self-harm. Some may argue that any ingestion of heroin could be regarded as *passively intentional* overdose. Also, the overdoses of many of the patients who have mental illnesses were coded as *unintentional*, although the intent of these overdoses is difficult to determine based upon their mental state. Although the assessment of the impact mental health has on the abuse of drugs was outside the scope of this project, it would be a crucial item to examine in future studies, as both have become more prevalent.

It is possible that our study suffered from low power. Including additional years of data was complicated by the conversion from ICD-9 to ICD-10. Furthermore, we did not begin to geocode map our patients to census tract until 2016. Analysis at the census tract level may not be sufficiently granular, especially in mostly rural counties, to examine the true variability of socioeconomic characteristics or the impact on overdose rates; however, we believe that it is an improvement over examination at the county- or ZIP code-level because census tracts in La Crosse County reflect neighborhoods, where it is more possible to intervene with local solutions.

This study provided an expanded exploration inside our community drug problem. It is the hope that this information may be used to identify and further assess hot spots of drug abuse in order to address the growing overdose problem. According to a Centers for Disease Control and Prevention report, "a multifaceted, collaborative public health and law enforcement approach is urgently needed."¹ With improved comprehension of the concerns within the community, resources can be better utilized to combat the increasing drug epidemic—not only within La Crosse, Wisconsin, and its surrounding counties, but perhaps in similar communities.

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Shift in Drug vs Alcohol Prevalence in Milwaukee County Motor Vehicle Decedents, 2010–2016

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ABSTRACT

Objective: The purpose of this study is to examine the prevalence of alcohol and nonalcohol drugs in motor vehicle crash (MVC) decedents in Milwaukee County, Wisconsin.

Methods: A retrospective review of MVC decedents in Milwaukee County from 2010 to 2016 was performed. Substances were divided into 5 categories based on chemical composition and clinical effects: alcohol, cocaine and its metabolite benzoylecgonine, opioids, cannabinoids, amphetamines and methamphetamines. Decedents were determined to be positive if any of these substances were detected on blood toxicology analysis.

Results: Sixty-five percent (n=113) of MVC decedents tested positive for 1 substance, while polysubstance use (≥ 2 substances) was seen in 27% (n=47). Alcohol was the most prevalent substance (n=77, 44%), while cannabinoids were the second most prevalent (n=50, 29%), and opioids were third most prevalent (n=24, 14%). There was a statistically significant increase in the number of MVC decedents who tested positive for opioids from 2010 to 2016 (slope=3.9, P < 0.01). The number of decedents who tested positive for alcohol only from 2010 to 2016 decreased significantly (slope = -3.9, P < 0.05), and 2016 was the first year in which the number of drug-positive decedents exceeded the number of alcohol-positive decedents.

Conclusion: The prevalence of drugs exceeded that of alcohol in decedents for the first time in 2016 in Milwaukee County. While continued efforts to reduce alcohol-positive driving are encouraged, increased attention to drugged driving is needed to prevent further drug-positive fatalities.

INTRODUCTION

Drugged driving, defined as driving under the influence of illicit drugs or misuse of prescription drugs,¹ is a federal research priority. Multiple organizations such as the Office of National Drug

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Corresponding Author: Kiran Faryar, MD, MPH, Department of Emergency Medicine, University of Cincinnati, College of Medicine, 231 Albert Sabin Way, Cincinnati, Ohio 45267-0769; phone 513.884.6269; fax 513.558.4599; email faryarka@ucmail.uc.edu. Control Policy, the US Drug Enforcement Administration, and the National Highway Traffic and Safety Administration (NHTSA), have declared drugged driving a public health concern that warrants further research and community interventions.²⁻⁴ Conversations regarding the current opioid epidemic led to questions about drugged driving prevalence.⁵ With rates of opioid and heroin use on the rise, so too is the number of drivers testing positive for these substances.⁵ While the effects of driving under the influence of alcohol (termed "drunk driving") have been well studied, the effects of drug-positive driving are less clear.⁶⁻⁸

Few studies have examined drug prevalence in fatally injured drivers. One Canadian study of national road safety data found drug prevalence among decedents increased slightly (16.9% increase) from 2000 to 2012.⁸ National variations in both rates of drug prevalence in drivers and types of substance present make this

data less representative of US drug trends.^{7,8} Several US studies examined NHTSA Fatality Analysis Reporting System (FARS) data to delineate the type and prevalence of substance present.^{5,7,9} Romano and Pollini found alcohol prevalence (45.1%) exceeded drug prevalence (25.9%) among fatally injured drivers in the FARS database between 1998 and 2010. Among these fatally injured drug-positive drivers, stimulants and cannabinoids were most prevalent.⁷ Most recently, Chihuri and Li examined the prevalence of prescription opioids alone in fatally injured drivers in 6 states using the FARS database (1995-2015).⁵ The authors found increased prevalence of prescription opioids in drivers tested within 1 hour of death—a 620% increase.⁵ This study delineated prescription opioids from other nonalcohol drugs in primary analysis.⁵ No studies examining the prevalence of drugpositive driving (both opioids and other nonalcohol drugs) in fatally injured drivers have been conducted in the United States within the last 5 years. Given the rapidly evolving nature of drug trends, it is unclear if the same substances remain prevalent today.

Milwaukee County is an ideal setting to examine substance prevalence in drivers, as it is the most populous county in Wisconsin and it has a mixture of urban, suburban, and rural areas.^{10,11} The goal of this study was to determine which substances (alcohol, cocaine, opioids, amphetamines, or cannabis) were most prevalent in fatally injured drivers. The authors hypothesize opioid prevalence in motor vehicle decedents is increasing at a faster rate than other substances given its increased incidence nationwide.

METHODS

Study Design and Population

A retrospective review of motor vehicle crash (MVC) decedents in Milwaukee County, Wisconsin from 2010 to 2016 was performed. A list of MVC autopsies was obtained from the Milwaukee County Medical Examiner's Office. Inclusion criteria were adolescents and adults \geq 15 years old who expired due to acute crash-related injuries. Subjects were excluded if whole blood specimens were not available for complete toxicology analysis (N = 38) and if subjects were passengers, pedestrians, or cyclists (N = 164) (Figure 1).

Per county protocol, blood samples from each decedent are qualitatively screened (positive/negative) by enzyme-linked immunoassay for the following substances: benzodiazepines, cocaine and its metabolite benzoylecgonine, tetrahydrocannabinol (THC), amphetamines, methamphetamines, opiates, oxycodone, fentanyl, buprenorphine, and methadone. If a positive qualitative blood screen is obtained, the blood sample is confirmed by gas chromatography/mass spectrometry with the exception of THC. Decedents were determined to be negative if no substance was present or if the substance detected was administered after the crash (such as by emergency medical services or in the hospital) per the medical examiner report. Only blood samples were used for toxicology results due to the temporal unreliability of urine samples. Institutional Review Board approval was obtained through the Medical College of Wisconsin. Consent was obtained from the Milwaukee County Medical Examiner's Office.

Demographic, Crash, and Substance Variables

Demographic variables including age, race, and sex were collected for each subject. Crash related variables included rollover (yes/no), ejected (yes/no), seatbelt use (yes/no), helmet use (yes/ no), airbag deployment (yes/no), speed (in miles per hour), and evidence of pre-impact braking on scene (yes/no). Quantitative blood toxicology results were only available for the following substances: alcohol, cocaine, benzoylecgonine, oxycodone, methadone, morphine, fentanyl, oxymorphone, codeine, hydrocodone,



and 6-monoacetylmorphine. If these levels were > 0.00, they were considered positive. The remaining substances (buprenorphine, THC, amphetamines, methamphetamines, and opiates) were marked as either present or absent per blood immunoassay screen. Benzodiazepines were excluded from analysis because the majority were administered after the crash by emergency medical services or hospital providers.

Statistical Analysis

Descriptive analysis of autopsied decedent demographic characteristics, crash characteristics, and substance prevalence was performed. The substances were divided into 5 major categories based on their chemical composition and clinical effects: alcohol; cocaine and its metabolite benzoylecgonine; cannabinoids; opioids (including opiates, oxycodone, methadone, buprenorphine, norbuprenorphine, fentanyl, oxymorphone, codeine, morphine, hydrocodone, and 6-monoacetylmorphine); amphetamines and methamphetamines. Chi-square analysis was performed between each substance category and demographic and crash characteristic. Linear regression analysis was performed to determine trends in substance prevalence during the study period. IBM SPSS Statistics Version 21 was used for statistical analysis.

RESULTS

Demographic and Crash Characteristics

From 2010 to 2016, 174 decedents met the study criteria, 83% were male, and 17% were female. In comparison, according to US Census data from 2015, 51.7% of Milwaukee County residents identified as female and 48.3% as male.¹² The average age of study

			r
Characteristic		n	%
Sex	Male	144	83
	Female	30	17
Race	White	82	47
	Black	69	40
	Hispanic	20	11
	Asian	3	2
Mechanism of Injury	Single car	60	34
	2 car	50	29
	Multicar	7	4
	Single motorcycle	20	12
	Motorcycle vs auto	35	20
	Bicycle vs auto	2	1
Seatbelt	No	101	58
	Yes	38	22
	Unknown	35	20
Any substance detected	Negative	61	35
	Positive	113	65
Alcohol	Negative	97	56
	Positive	77	44
Cocaine	Negative	160	92
	Positive	14	8
Opioids	Negative	150	86
	Positive	24	14
Cannabinoids	Negative	124	71
	Positive	50	29
Amphetamines and			
methamphetamines	Negative	171	98
	Positive	3	2



decedents was 40 years old; 47% were white, 40% were black, 11% were Hispanic, and 2% were Asian (Table 1). In comparison, 27.1% of Milwaukee County residents were black, according to 2015 US Census data.¹²

Two-thirds of the car crashes involved 1 or more automobiles (67%), while almost one-third of the fatalities involved motorcycles (32%). The majority of decedents did not wear their seatbelt (58%). Seatbelts were worn in 22% of crashes; seatbelt use was unknown in 20% of crashes per investigation reports (Table 1).

Substance Use

Sixty-five percent (n = 113) of decedents tested positive for at least 1 substance, and polysubstance use (≥ 2 substances) was seen in 27.0% (n = 47) of crash decedents. Alcohol (> 0.00 grams per deciliter) was the most prevalent substance detected (n = 77, 44%), while cannabinoids were the second most prevalent substance (n = 50, 29%), and opioids the third most prevalent (n = 24, 14%). From 2010 to 2015, the percent of decedents who tested positive for alcohol alone exceeded the percent of decedents who tested positive for all nonalcohol drugs (cocaine, opioids, amphetamines, methamphetamines, and cannabinoids). In 2016, more decedents tested positive for drugs (19.2%) as compared to alcohol (3.8%). Specifically, isolated cannabis (11.5%) and opioids (7.7%) were more prevalent in decedents than alcohol alone. 2016 was the first year in which the number of decedents who tested positive for drugs exceeded those who tested positive for alcohol.

Statistical analysis

White drivers were 2.1 times (95% CI, 1.1-4.1) less likely to test positive for any substance as opposed to nonwhite drivers (P=0.021). There was no association between substance-positive drivers and sex, type of vehicle driven (car vs motorcycle), or single vs multi-vehicle collisions. For decedents who tested positive for alcohol, the risk of being in a single vehicle crash was 1.84 times (95% CI, 1.3-2.6) that of decedents involved in a multivehicle crash (P<0.01). There was no relationship between alcohol-positive decedents and sex, race, type of vehicle driven (car vs motorcycle), or presence of seatbelt. The presence of opioids and cocaine was not associated with sex, race, type of vehicle driven (car vs motorcycle), single vs multivehicle collision, or presence of seatbelt. There was an association between decedents who tested positive for cannabis and race; white decedents were 4.1 times (95% CI, 1.9-8.6) less likely to test positive for cannabis as opposed to nonwhite decedents (*P*<0.01).

There was a statistically significant increase in the number of MVC decedents who tested positive for opioids from 2010 to 2016 (slope = 3.9, P < 0.01) (Figure 2). The downward trend in the number of MVC decedents who tested positive for alcohol only from 2010 to 2016 was also statistically significant (slope = -3.9, P=0.011) (Figure 3). Linear regression analyses were not statistically significant for the remaining substance categories.

LIMITATIONS

This study cannot declare a causal relationship between substance use and motor vehicle crashes. The findings are associative. The effect of illegal drugs and prescription medications on each individual driver is dependent on multiple factors such as rate of absorption, distribution, mechanism of action, elimination, and tolerance. These factors are difficult to predict and quantify. The presence of substances in blood samples is more temporally and pharmacologically accurate than urine samples, therefore toxicology results were based on blood samples exclusively in this study. For drivers with polysubstance use, it is unclear what role each drug played in the motor vehicle crash. By examining only fatal crashes, the true prevalence of drug use in MVC drivers in this county is unknown. The medical examiner system in Wisconsin is decentralized; therefore only 1 county was examined. It is unclear if these results are applicable to all counties in the state or nationwide.

DISCUSSION

This study sought to determine the prevalence of drug-positive drivers in Milwaukee County MVC decedents from 2010 to 2016. The findings disclosed an increasing trend in the presence of opioids among motor vehicle decedents over time. Two unexpected trends were observed during analysis; the number of fatally injured drivers who tested positive for alcohol alone decreased significantly, and the number of drug-positive decedents exceeded alcohol-positive decedents for the first time in 2016. National organizations such as the Office of National Drug Control Policy ³ and the National Institutes of Health have defined drugged driving as driving after drug use; therefore, our findings indicate that in 2016 drugged driving exceeded drunk driving for the first time during the study period.

The rise in opioid-positive drivers highlights an urgent need to address drugged driving with current opioid users. Opioids are known to cause drowsiness and hinder reaction time, attention, and concentration while driving.^{1,5} In a study of heroin users, perceived risk of driving after use was low.¹³ Interviewed heroin users stated they attempted to reduce driving risk by limiting drug use to tolerable levels prior to driving and waiting until they no longer felt "high" before driving.¹³ McIntosh et al concluded that drugged driving educational campaigns would be ineffective because users believe they can mitigate these effects.¹³ They hypothesized drugged driving interventions would be most useful while users are in treatment facilities.¹³

Interventions immediately after a motor vehicle crash, such as in the emergency department, could prove advantageous since users would be faced with the negative consequences of their drug use in real-time. Such real-time interventions were performed in a population of alcohol abusers.¹⁴ Trauma surgeons in a Level 1 trauma center performed brief interventions in a population of patients who screened positive for alcohol abuse. Patients in the intervention group were found to have decreased rates of alcohol intake and trauma recidivism at 12-month follow-up.¹⁴

The dramatic decrease in the number of drivers who tested positive for alcohol alone is especially interesting given Wisconsin has a higher rate of binge-drinking and alcohol consumption than other US states.^{15,16} The rate of alcohol-positive crash fatalities in





Wisconsin (6.7 fatalities per 100,000) exceeds the national average (5.7 per 100,000).¹⁵ In comparison, national rates of alcoholpositive driving in nonfatal and fatal crashes are decreasing.^{16,17} Our alcohol-positive driving trends in Milwaukee County parallel national trends. According to 2013-2014 NHTSA survey data, the percent of US drivers of nonfatal crashes who tested positive for alcohol has decreased over time from 12.4% in 2007 to 8.3% in 2014—a 33% reduction.^{16,18} Among national MVC fatalities in 2014, the percent of alcohol-positive (>0.08 grams per deciliter) drivers decreased slightly compared to 2012, from 20% to 19.8%, a 1% reduction.¹⁹ This trend is likely multifactorial and can be attributed to extensive drunk driving media campaigns, schoolbased education programs, and ride share programs.^{8,15,16,18}

Surprisingly, in 2016 the presence of nonalcohol drugs exceeded alcohol in decedents. This is consistent with a report by the Governors Highway Safety Association (GHSA) in April 2017 that found more fatally injured drivers tested positive for drugs than alcohol.²⁰ The GHSA report used 2015 FARS data, the most recent data available.²⁰ A few years prior, using the same database, Romano and Pollini reported that alcohol-positive crashes still exceeded drug-positive crashes among fatally injured drivers.⁷ This indicates the predominance of drug-positive driving over alcoholpositive driving is a relatively new trend.

The etiology of this new trend can be attributed to several factors. The proportion of drivers who test positive for drugs is increasing nationally while alcohol-positive drivers are decreasing.^{8,21} According to a 2013-2014 NHTSA survey, drug-positive drivers of nonfatal crashes increased from 16.3% in 2007 to 20% in 2013-2014. With more surveyed drivers admitting to drug use, drug-positive crash risk also increases. Medical and recreational legalization of marijuana also contributed to the increased preva-

lence of drug-positive drivers. Several states such as Colorado, California, and Washington witnessed a rise in fatally injured marijuana-positive drivers after legalization.²²⁻²⁴ Similar to heroin users, marijuana users admit to use prior to driving and indicate a lack of self-awareness as to the harmful effects of marijuana on driving performance, such as slower reaction time and decreased ability to perform complex tasks.^{9,25} Given the trajectory of increased drug use and a lack of awareness as to its effects on driving performance, it is logical that drug-positive driving surpassed alcohol-positive driving.

CONCLUSIONS

Between 2010 and 2016, the number of fatally injured opioid-positive drivers disclosed a statistically significant increasing trend in Milwaukee County. In contrast, the number of fatally injured drivers who tested positive for alcohol alone decreased significantly. 2016 was the first year wherein drug-positive driving exceeded alcohol-positive driving. This data, coupled with driving perceptions of current and former drug users, can guide more effective educational campaigns and real-time interventions.

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GunderKids: Design of a Clinical Care Management Program for Parents With Substance Abuse and Their Newborn Children with a Focus on Preventing Child Abuse

Ann E. Budzak-Garza, MD; Allison L. Allmon Dixson, PhD; Renee A. Holzer, RN; Kaitlin E. Lillard-Pierce, RN; Carolynn J. Devine, CSW

ABSTRACT

Background: In response to an increased need to care for babies born to mothers with substance abuse issues, we developed GunderKids, a care management program that provides integrated medical care beyond standard-of-care, well-child appointments for these socially complex families.

Methods: The program incorporates frequent visits to the pediatrician and the care team, which includes pediatric nurses, a pediatric social worker, and a child psychologist. Enrollment is voluntary. Each visit addresses parenting challenges, home environment, basic needs, safety issues, and maintenance of sobriety, as well as child development and health issues.

Results/Discussion: We found that mothers and fathers (or parents) welcome intense support following delivery, appreciate the relationship that is built with the care team, and prefer frequent visits at the medical center over in-home visits, which they perceive as potentially intrusive. We describe here the planning and implementation of the program, as well as insights gained in our first year.

BACKGROUND

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Illicit drug use by the mother during and after pregnancy may have severe consequences for the newborn child. Children born to these mothers may sustain not only immediate effects from their mothers' substance abuse, such as low birth weight, neonatal abstinence syndrome (NAS), and complications attending preterm birth, but also long-term effects, such as difficulties with learning and behavior.¹ During childhood, they are more likely than their unaffected counterparts to experience or witness emotional, physical, or sexual abuse²—3 times more likely

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to be abused and 4 times as likely to be neglected.3 Furthermore, these experiences are strong predictors of decreased well-being and social functioning, increased health risks, and compromised learning.4,5 Indeed, these children often develop destructive emotional and social behaviors and, as adults, perpetuate the cycle of abuse they witnessed as children.6 Finally, according to the US Department of Health and Human Services, parental substance abuse was a factor in 32.2% of cases in which children were placed in foster care in 2015, an increase of 3.7% over 2012.

Parents with substance abuse issues

are 4 times less likely than parents without substance abuse issues to seek well-child care for their baby.⁷ The mothers' fear of being judged keeps them from seeking regular health care or from accepting community resources.⁷ They routinely decline community support services, such as Healthy Families, because they fear their child will be taken away. Thus, programs that build trusting, supportive relationships could encourage these parents to avail themselves of services that support healthy parenting.

To our knowledge, our program is the only clinic-based program focused on preventing child abuse in this population. Treatment and rehabilitation facilities and drug court programs assist these individuals in attaining and maintaining sobriety, but their focus is on abstaining from drug use, not on healthy parenting. There are effective programs with a relationship-based, nonjudgmental approach similar to that of GunderKids, but they are home-based—for example, CEDEN (Center for Development, Education, and Nutrition) and the Prenatal and Early Childhood Nurse Home Visitation Program—and are open to children of all high-risk mothers, not only those whose mothers have substance use disorder.⁸



Box 1. Metrics Collected by the GunderKids Program

- · Baby growth velocity
- Immunization compliance
- · Number of GunderKids appointments kept by the family
- Number of emergency department/urgent care visits
- Number of hospital admissions
- · Completion of behavioral health visits
- Parenting Stress Index (PSI) score analysis
- Child Abuse Potential Inventory (CAPI) score analysis
- Number of specialty appointments missed
- Percentage of patients improving on caregiver satisfaction and caregiver well-being
- Number of patients with a diagnosis of maltreatment
- Number of parents maintaining custody

Plan Development and Implementation

We developed GunderKids to provide anticipatory guidance, support services, and parenting education for at-risk families to prevent child abuse. A pediatrician and a social worker dedicated to working with this at-risk population envisioned the GunderKids program to prevent parents at high risk from abusing or neglecting their baby. Several steps were taken within Gundersen Health System departments to develop communication and the infrastructure necessary to conduct a pilot of the GunderKids program in this high-risk population. The pediatric department's clinical manager was approached, and her support was obtained for the pilot program. Approval for nursing support also was granted. Specifics of the program were then developed-visit structure, education to be provided at each visit, screening tools, and metrics. A project manager was assigned to assist with operational and program development. Webinars and a literature review provided necessary education about issues that were likely to be encountered in the pilot population.

A high-risk obstetrics team at Gundersen Health System had provided prenatal care for this population for several years. The model of care they used had been well-received, with patients often expressing a desire for it to continue postpartum. This care model involved an obstetrician, 2 nurse care coordinators, and a social worker who met with the expectant mother throughout the pregnancy. Patients were encouraged to receive therapy through Gundersen's addiction medicine department, which worked closely with this obstetrics team. The obstetrics team met with the GunderKids program developers to share their insight and experience. They were enthusiastic about the prospect of this new program and eager to partner with pediatrics to support it.

The GunderKids program was patterned after that of the successful high-risk obstetrics team program, emphasizing relationship building as the model for interaction with the parents. We developed a system of patient referral from the obstetrics team to our GunderKids nurses, who would meet with the expectant parents

during a prenatal appointment to introduce the program and invite future participation. The GunderKids program planners also met with the pediatric hospitalist team. The program was discussed with an emphasis on working together to ensure a smooth transition of care once babies were ready to leave the hospital. At Gundersen Health System, most babies with NAS begin their stay after birth on the postpartum unit with their mothers. Babies who require a prolonged hospital stay for treatment of NAS are moved to the inpatient pediatric unit, which is on the same floor as the postpartum unit. The pediatric hospitalists manage the care of the newborn until discharge. Very few babies with NAS go to the neonatal intensive care unit unless they have other health issues, such as prematurity, infection, or a congenital problem requiring immediate intervention. The GunderKids team attended nursing staff meetings for the newborn nursery, the neonatal intensive care unit, and the inpatient pediatrics unit to provide information on the new GunderKids program and to improve coordination of care.

Infrastructure Development

Necessary enhancements to the electronic health record (EHR) were identified. Templates for visit type were developed, and some of the screening tools to be used in the program were incorporated into the EHR (Box 1). There was a need to be notified electronically when mothers delivered and when babies enrolled in GunderKids were seen in other health system departments. The Gundersen quality improvement department assisted in the development of metrics to measure program outcomes; metrics data needed to be part of the EHR, as well. Information systems met with the team several times and incorporated all of these features into the EHR.

The Pilot: Structure and Insights

The GunderKids pilot program launched on December 1, 2015. More babies were quickly enrolled than had been anticipated. Parents were engaged and keeping appointments far better than was expected. Many were wary at the first few visits and expressed worry that GunderKids was aligned with Child Protective Services with the goal of taking their baby away. By the third to fourth visit, a trusting relationship had developed with most families, and parents began expressing the value they felt for the benefits of the program.

Given how rapidly the program was growing, the pediatric clinical manager requested an efficiency/time evaluation for the GunderKids pediatrician and nurses to determine GunderKids' capacity in the current practice structure. A meeting was held with administration to review efficiency results and to request formal support of the program, which was granted.

The obstetrics and GunderKids teams, as well as representatives from the inpatient pediatric, nursery, and pediatric hospitalists group, began meeting monthly, staffing each patient and addressing program development issues. Staff meetings were periodically dedicated to ongoing learning. For example, a pediatrics occupational therapist taught the group about the soothing techniques she teaches to parents of babies with NAS while they are still in the hospital. At another, a La Crosse County therapist taught the team about attachment disorder.

The Newborn Behavioral Observations (NBO) system, a program of the Brazelton Institute based at Boston Children's Hospital, provides ways to enhance attachment for newborns and their caregivers. Nurses trained in NBO help parents understand what their baby is trying to communicate and help with bonding. Babies born to mothers with addictions are at high risk for attachment disorder, so NBO would be a beneficial part of the GunderKids program. Gundersen Medical Foundation agreed to fund NBO training for the GunderKids nurses in Boston.

Once the pilot was underway, the GunderKids team met with the nursing research department to discuss possible research studies. The GunderKids research team was formed, and meetings were held biweekly to develop research protocols and identify possible funding sources.

Staff

GunderKids was initially led by a pediatrician and supported by 2 pediatric nurses, a social worker, and a child psychologist, who have since been joined by another pediatrician, another nurse, and a nurse practitioner. This level of staffing and



of GunderKids and important in developing and maintaining a trusting relationship with parents who are uncomfortable with other aspects of the social support system. GunderKids staff members all have training and interest in child health, well-being, and prevention of child maltreatment.

Medical appointments for the baby with the pediatrician and nursing staff are reimbursed through insurance. Funding for the family's time spent with the social worker and child psychologist, as well as nursing care coordination time, is provided by Gundersen Health System's pediatrics department.





GunderKids enrollment is voluntary. Women are approached by a GunderKids nurse during a prenatal visit around the 23rd through 25th week of pregnancy. They describe the type of support, education, and assistance available both through the clinic and in the community. Women who decline enrollment at the prenatal visit are approached again, either closer to their due dates or in the hospital after they have delivered (Figure 1). Figure 2 shows the number of mothers approached to participate in GunderKids and their current participation status.

A variety of concerns motivate parents to participate in a medi-

Once-a-Week Visits	Telephone: Follow-up Call	Telephone: Follow-up Call
Visit 1: Clinic Visit	Visit 8: Clinic Visit	Visit 13: Clinic Visit
Visit 2: Clinic Visit • Newborn Behavioral Observations (NBO) Visit 3: Clinic Visit • Demographic Intake Visit 4: Clinic Visit • Caregiver Wellbeing Questionnaire Visit 5: Clinic Visit • Parenting Stress Index (PSI)	 Caregiver Satisfaction and Confidence Questionnaire Adverse Childhood Experiences (ACEs) Screening/Behavioral Health Integration Telephone: Follow-up Call Visit 9: Clinic Visit Telephone: Follow-up Call Visit 10: Clinic Visit 	Every-6-week Visits and Every-Other-Month Telephone Calls Telephone: Follow-up Call Visit 14: Clinic Visit Telephone: Follow-up Call Visit 15: Clinic Visit • Caregiver Wellbeing Questionnaire Telephone: Follow up Call
rery-2-week Visits and rery-Other-Week Telephone Calls	Telephone: Follow-up Call Visit 11: Clinic Visit	Visit 16: Clinic Visit • Parenting Stress Index (PSI)
Telephone: Follow-up Call	Every-4-week Visits and	Telephone: Follow-up Call
Visit 6: Clinic Visit • Child Abuse Potential Inventory (CAPI) Telephone: Follow-up Call Visit 7: Clinic Visit	Every-Other-2-week Telephone Calls Telephone: Follow-up Call Visit 12: Clinic Visit	 Visit 17: Clinic Visit Caregiver Satisfaction and Confidence Questionnaire Child Abuse Potential Inventory (CAPI)

cally guided program. Initial motivations are fear of NAS withdrawal, fear of parenting without guidance, a desire to retain or regain custody of the child, or to demonstrate to authorities good parenting activities and a commitment to changing behaviors.

Care Plan

GunderKids is different from routine medical care. It provides more scheduled appointments during the first year of the baby's life. Visits occur within a medical clinic environment rather than in the mother's home, where she might feel vulnerable to officials entering her house. Parents can ask GunderKids for advice on parenting in a nonthreatening environment that allows for teachable moments. Clinic visits provide these families with trusted faces who are there for them consistently at each clinic visit and at any time between.

At each clinic appointment, the GunderKids nurse and social worker (1) review current stresses in the family; (2) improve the parent's knowledge of child development and child behavior; (3) discuss and give parents tools to deal with high-risk issues in child development; and (4) provide support and advise them of resources: food pantries, parent support groups, help with addictions, and housing options. Most of these parents have a history of trauma, which has adverse effects on mental and physical health. What's more, addiction is a chronic disease. Staff works with the family to break bad habits, such as the use of foul language, and to identify activities counterproductive to good parenting. Improving the health of the entire family is key to a healthy baby.

The desired appointment schedule and activities to be completed at each visit are provided in Box 2. Because these families often cannot keep scheduled appointments, the timing of activity completion varies. The GunderKids nurses follow up with the families by telephone and reschedule missed appointments. The team also works hard to accommodate those who present late to appointments or who appear at unscheduled times.

Our Experience

GunderKids is all about building relationships. After approximately 3 appointments, mothers become more positive and trusting of GunderKids. Their attitudes evolve from viewing the program as a necessary burden to maintain custody, to enjoying the relationship and trust that has developed with GunderKids staff wanting to demonstrate how well they are doing and to learn more about parenting. Key to this trusting relationship is treating mothers with respect and caring and the continuity of care provided by the GunderKids team.

Future

Word about the GunderKids program traveled quickly. The Heroin Taskforce, School District of La Crosse, La Crosse County Child Protective Services, and La Crosse County Child Abuse Multidisciplinary team all requested presentations about GunderKids. If community response is any indication, need for programs like GunderKids is enormous, which challenges our capacity to accommodate all families who would benefit from enrollment. Therefore, we are prepared to present our results at medical conferences and to share our resources and experiences to assist other health care systems that desire to develop similar programs. Because the medical visits are reimbursed by insurance, the GunderKids model of care should be sustainable at most major medical centers. However, to fully implement the care plan, medical centers or other health care resources, such as Medicaid, will need to provide funding for the social worker, the behavioral medicine provider, and nursing care coordination time.

The success of the program as the initial pilot year progressed

indicated that planning would be required for continuation beyond the first year of life. The close relationships built with the GunderKids families and the team made it clear that the program should continue at some level for the rest of childhood.

Long-Term Benefits

Planned research projects will provide evidence regarding the short- and long-term value of GunderKids, which might encourage other health systems to establish similar programs. These research projects will compare the GunderKids program outcomes to those of other programs, such as stationing addiction counselors in child welfare offices, providing mothers priority access to substance abuse treatment slots, and home visitation programs.

The annual health care cost of child maltreatment and exposure to violence has been estimated at \$333 billion to \$750 billion, with the public and social cost deemed "incalculable."⁹ Wisconsin is experiencing the same opioid epidemic as the rest of the country, as well as challenges with methamphetamine and other substances of abuse. The children of Wisconsin born into families with substance use disorder are at risk of maltreatment and neglect. Abuse prevention will lead to a healthier Wisconsin and save billions in health care dollars over time.

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Survey Assessing Medical Student and Physician Knowledge and Attitudes Regarding the Opioid Crisis

Skyler Chouinard, BS; Aman Prasad, PhD; Randall Brown, MD, PhD

ABSTRACT

Background: There is a national opioid misuse and overdose crisis. Consensus guidelines seek to inform practice and reduce risk; however, effect on clinician attitudes and knowledge remains unclear.

Methods: We surveyed 228 medical students and physicians in Wisconsin to assess their knowledge regarding at-risk patients, alternatives to opioids, and best treatment practices for opioid addiction. We also assessed attitudes about prescribing naloxone, relapse likelihood, and responsibility for the crisis.

Results: Knowledge and attitudes were similar, including that overprescribing by health care professionals is a driving factor. Attitudes on relapse likelihood were different, but both groups believed sustained recovery from addiction was possible.

Discussion: Enhancement of opioid-related education is both necessary to address knowledge gaps and desired by students and physicians.

INTRODUCTION

There is a crisis of opioid misuse, addiction, and overdose in the United States and in Wisconsin.¹ Prescription opioids caused 45% of overdose deaths in Wisconsin in 2013; heroin contributed an additional 27%.² Among addiction treatment admissions in Wisconsin, opioids now rank second (17.4%) after alcohol (62.6%) as the primary substances of misuse among treatment seekers.³

Prescribers are a major source of illicitly used opioids. Users most commonly obtain them from a prescriber, family member, or friend. Additionally, many heroin-addicted individuals began

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their opioid use with an opioid prescription.⁴ The education of prescribers and trainees regarding opioid-related issues and risk management is crucial to alleviating the current crisis.

Previous studies indicate that clinician education on substance use disorders needs enhancement.⁵ Specifically, medical students and physicians at all levels receive inadequate education about the assessment and management of substance use disorders. This may result in a lack of confidence and ability to identify and address substance use disorders.⁵

Multiple recent practice guidelines and state legislative efforts have sought to reduce opioid-related harms as related to opioid prescribing.⁶ The development of consensus guidelines is intended to reduce vari-

ability in prescribing habits, which may be worsened by pharmaceutical marketing practices, differences in training, and variable state policies for handling opioid abuse. The extent to which attitudes and practices have been modified in this evolving policy environment remains unclear, and recent studies have indicated persistent, wide variation in attitudes, knowledge, and behavior.⁷

This study aimed to characterize knowledge and attitudes pertinent to opioid prescribing and related risks along the spectrum of physician training and practice in Wisconsin. A brief survey was administered to medical students and practicing physicians affiliated with the University of Wisconsin (UW) School of Medicine and Public Health to compare knowledge and attitudes at various stages in training to inform educational interventions.

METHODS

Study Recruitment

We recruited UW School of Medicine and Public Health medical students and physicians from 2 institutional email listservs. One listserv included all medical students (n=770) and the other included all physicians associated with the Department of Family Medicine (n=167). We focused on the Department of Family Medicine list because these physicians are on the front lines of managing chronic pain and thus serve as a good representation of primary care knowledge and attitudes. Participation was voluntary and no remuneration was offered. Due to the voluntary, limited nature of the survey and its anonymity, the study was deemed exempt from formal review by the University of Wisconsin's Health Sciences Institutional Review Board. Prior approval from the school administration was obtained to utilize the listservs.

Survey

We created a 1-time, anonymous, web-based 10-question survey to assess facets of medical student and physician knowledge and attitudes regarding opioid addiction and related issues. (See Appendix available at https://www.wisconsinmedicalsociety.org/_WMS/publications/wmj/pdf/117/1/Appendix%201_ Supplementary%20Material%20Chouinard%20et%20 al%20-%20Survey.pdf.) Questions were written with input from medical students, an addiction education organization (Wisconsin Voices for Recovery), and 2 primary care clinicians including an addiction medicine specialist. We utilized the Qualtrics software to allow ease of distribution and data analysis. An email containing a brief explanation and survey link was distributed to the listservs. Participants had 10 days to complete the survey, and a reminder was provided on day 8. The "Prevent Ballot Box Stuffing" setting within Qualtrics was selected to ensure only 1 submission per link. In addition to identifying their training level and department (the only demographic questions asked), participants were asked questions assessing their attitudes and knowledge related to opioid prescribing, opioid addiction, and the current opioid crisis. Questions assessing knowledge included identifying the type of patient at highest risk for opioidrelated overdose, availability of naloxone, best treatment practices for opioid use disorder, and effective alternatives to opioid analgesics. Attitudes on prescribing naloxone, relapse likelihood, responsibility for the current opioid crisis, and chronic pain management practices also were queried. Finally, participants were asked an open-ended question on which related topics they would like to learn more about.

Data Analysis

We used Microsoft Excel 2016 to perform data analysis. Responses were compared between students and physicians using the chi-square test, with statistical significance defined as a *P*-value less than 0.05.

RESULTS

Of the 770 medical students who received the link, 170 surveys were completed (22% response rate, Figure 1). Fifty-eight percent (n = 98) of medical student respondents were in the preclinical years (M1 and M2), and 42% (n = 72) were in the clinical years (M3 and M4). Of the 167 physicians who received the link, 58 surveys were

Figure 1. Data Showing Survey Response Rate and Level of Training Among All Respondents

Medical Students	Physicians
770	167
170	58
22%	35%
	Medical Students 770 170 22%



completed (35% response rate). All were currently practicing, and 53 were in family medicine, 2 were in internal medicine, 1 was in psychiatry, and 2 were in urgent care. Twenty-six percent (n = 15) of physician respondents were in practice less than 10 years, and 74% (n = 43) were in practice for more than 10 years.

We found many similarities in the responses between groups, but also several key differences (Figure 2), which we address in turn.

Similarities—Knowledge

Regarding the "knowledge" questions, only 25% of students and 14% of physicians correctly identified the highest risk patient for opioid-related overdose, with both choosing a young white man rather than a middle-aged white woman. Most physicians correctly identified the legal availability of naloxone in Wisconsin and the best treatment practice for opioid use disorder. In contrast, less than half of students selected these choices, although this difference was not statistically significant. To manage a patient with recalcitrant chronic back pain, the top 2 choices for both groups were to obtain magnetic resonance imaging and to utilize a higher NSAID dose with addition of a muscle relaxant.

Similarities—Attitudes

Regarding the "attitude" questions, both physicians and students supported harm reduction strategies through increased access to naloxone. (See survey question 4 in Appendix available at https://www.wisconsinmedicalsociety.org/_WMS/publications/wmj/pdf/117/1/Appendix%201_Supplementary%20 Material%20Chouinard%20et%20al%20-%20Survey.pdf and lower risk alternatives to chronic pain management, such as physical therapy. Both groups also believed sustained recovery is

Survey Item ¹	Responses		<i>P</i> -value ²
	Medical Student	Physician	
Knowledge			
Correctly identified patient at highest risk of opioid overdose (Q3)	25% correct	14% correct	0.08
Correctly identified availability of naloxone in Wisconsin (Q4)	46% correct	57% correct	0.14
Correctly identified best treatment practice for opioid use disorder (Q5)	46% correct	57% correct	0.14
Next best step in management of chronic back pain not improved with NSAIDs and physical therapy (Q7)	 Top 3 responses: 1. Increase NSAID dose, add muscle relaxants, follow-up 2. MRI 3. Check PDMP and give oxycodone 	Top 3 responses: 1. MRI 2. Increase NSAID dose, add muscle relaxants, follow-up 3. Free responses: alternative medicine, steroid injections, x-ray	
Attitude			
Responsibility for current opioid epidemic (Q6)	Top 3 responses: 1. Health care professionals overprescribing 2. Pharmaceutical industry marketing practices 3. Addicted people themselves		
Believe relapse likelihood is high regardless of treatment approach (Q5) ³	40% Yes	14% Yes	0.0003
Believe sustained recovery is possible in patients with a history of opioid use disorder with proper support (Q8)	69% Yes	78% Yes	0.19
Identify low-risk alternatives to opioids for chronic pain (Q9)	Top 3 responses: 1. Physical therapy 2. Mindful meditation 3. NSAIDs	Top 3 responses: 1. Tricyclic antidepressants and SSRIs 2. Physical therapy 3. Gabapentin	
	1. Nonopioid treatment options and their efficacies 2. Indications for using opioids		
"Desired Future	3 Preventing addiction	4 Strategies to get patients off chronic narcotics	

¹See Appendix for free survey. Available online at https://www.wisconsinmedicalsociety.org/_WMS/publications/wmj/pdf/117/1/Appendix%201_Supplementary%20 Material%20Chouinard%20et%20al%20-%20Survey.pdf.

²P-values obtained by chi-square analysis.

³Only 1 statistically significant difference was found (question 5, relapse likelihood).

⁴Similarities and differences existed in student- vs physician-requested future learning topics.

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug; MRI, magnetic resonance imaging; SSRI, selective serotonin reuptake inhibitor.

possible with proper support. Both groups ranked health care professionals as most responsible for the current opioid crisis, followed by pharmaceutical companies, and then the addicted people themselves. Both groups desired to learn more about nonopioid treatment options and their efficacies, as well as when opioids are indicated.

Differences

A few key differences existed between groups (Figure 2). Students were more likely than physicians to believe that relapse is likely regardless of treatment approach (P = 0.0003). In addition, medical students requested more information on strategies to prevent addiction, while physicians requested more information about how to wean patients off chronic opioids.

DISCUSSION

This study assessed student and physician attitudes and knowledge about opioid misuse and addiction in a large Midwest academic hospital. This setting is particularly relevant because Wisconsin and the Midwest are among the regions hardest hit by the escalating opioid crisis.¹

Primary findings included that both groups acknowledged the key role of physician prescribing as the major source of opioids fueling the crisis. Students were more likely to believe that addicted patients have an elevated risk of relapse, regardless of treatment approach. This may suggest an early pessimism in trainees toward evidence-based therapies for use disorders. Given that relapse rates are as high as 91%,⁸ future opioid-related education should emphasize that relapse is a normal part of recovery. Similar knowledge deficits existed in physicians and students. Strikingly, both physicians and students failed to identify the highest-risk patient. Both groups expressed a desire for additional education on opioid addiction and alternatives for managing chronic pain.

Overall, our data demonstrate the need for meaningful changes to medical school curricula and for physician continuing educational opportunities. Medical education remains focused on the scientific aspect of disease and less on the human toll of chronic illnesses like opioid addiction. Efforts to change ingrained opioid prescribing habits may be enhanced by increasing learner exposure to this human toll.

Several studies have investigated attitudes and knowledge about opioid issues in students and clinicians, but only one included medical students.^{9,10} In this way, the current work expands on these previous studies by assessing both knowledge and attitudes, as well as suggesting possible areas to improve teaching.

There were several limitations that may affect the generalizability of our results. First, response rates were modest for both students and physicians. In addition, we chose to pool data from students in the M1-M2 "preclinical" and M3-M4 "clinical" years, which may blur differences by training stage. Second, although survey items were reviewed for content by multiple experts in opioid addiction, they were not rigorously validated. Third, in an effort to limit survey length and enhance response rates, we did not collect demographic information such as sex. This limits the ability to understand potential confounding or moderating factors. Finally, physician responses came primarily from family physicians. Different specialties may have different attitudes and knowledge about opioids. Future studies should investigate attitudes and knowledge in a larger pool of participants and should include other specialties, such as dentists, pharmacists, and nurses.

In conclusion, this work represents a step toward understanding educational needs of current and future clinicians. Such findings may guide curriculum and policy changes that could have a meaningful impact on the opioid abuse crisis, for which physicians play a central role as part of the current problem and must also be part of the solution.

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A Multistep Approach to Address Clinician Knowledge, Attitudes, and Behavior Around Opioid Prescribing

Sara Kohlbeck, MPH; Brenna Akert, BS; Caroline Pace, MD; Amy Zosel, MD, MSCS

ABSTRACT

Introduction: The Wisconsin Prescription Drug Monitoring Program (PDMP) was implemented in 2013 to reduce the misuse, abuse, and diversion of controlled substance prescriptions.

Objective: To evaluate provider knowledge, attitudes, and behaviors regarding the Wisconsin PDMP before and after study interventions.

Methods: An initial survey of clinicians, a focus group, pre- and posttests for an educational session, and a 3-month follow-up survey were utilized.

Results: Initial survey participants described PDMP use. Focus group themes included system, hospital, clinician, and patient factors. Educational session pre- and posttests showed an increase in provider knowledge. Follow-up surveys demonstrated practice change among providers.

Conclusion: This study can be useful for health care organizations, state PDMPs, and prevention organizations in tailoring messaging to clinicians around safe prescribing and PDMP use.

to 727 in 2015. Excess unintentional drug poisoning cases from 1999 levels account for more than 500 deaths per year in Wisconsin. Starting in 2011, unintentional poisoning injury deaths exceeded those of deaths due to motor vehicle crashes and became the second leading cause of unintentional injury death, behind falls, in Wisconsin.¹

Recently, the Heroin, Opioid Prevention and Education (HOPE) Agenda legislation was introduced in Wisconsin. This legislation aims to combat the state's heroin and opioid epidemic through bipartisan legislative support, which currently includes several bills that have been introduced and passed. One of the most salient policies introduced is a requirement that, as of April 1, 2017, clinicians must check the Wisconsin Prescription Drug Monitoring Program (PDMP) before prescribing con-

INTRODUCTION

Wisconsin is in the midst of an unintentional drug poisoning epidemic resulting in opioid-related injury and death. Over the last decade, the number of unintentional drug poisoning deaths in Wisconsin has increased by over 65% from 439 deaths in 2006 trolled substances, except in certain instances.²

Ours is a novel study that utilizes mixed methods to gather information on clinician use of the Wisconsin PDMP and chronic pain treatment and management through the use of an opioid prescribing pathway and scripting language. We administered our initial survey, focus group, and educational module prior to the April 1 HOPE Agenda legislation mandate.

METHODS

Initial Survey

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Southeastern Wisconsin emergency medicine (EM) providers were invited to participate in this anonymous online survey. The survey questions were formulated to gauge clinician readiness to use, understanding of, and attitudes regarding the Wisconsin PDMP.³ Information obtained from survey responses was used in order to evaluate current PDMP use in clinical practice and to tailor an educational module to better address the concerns and issues most relevant to this population of providers. Descriptive statistics were performed for all variables.

Focus Group

Emergency medicine physicians, advance practice providers, medical residents, and students were invited to participate in a focus group to gather in-depth, qualitative information on clinician attitudes about chronic pain management in their work setting and the use of the Wisconsin PDMP as a provider. Information from the focus group was used to inform our educational module's content. The focus group was conducted in October 2016 and was audio recorded and transcribed to allow for thematic analysis, using a grounded theory approach.

Training and Education Module for Local Providers

The educational module, which is approximately 1 hour long, was created by the study team for EM providers and was later tailored so that it could be administered to clinicians in other specialty groups, including Hematology/Oncology and Physical Medicine and Rehabilitation. The presentation included information on the scope of the opioid abuse and misuse epidemic, recently passed legislation and policies that will directly affect opioid prescribing, and registration, access, utilization/best practices, and applications of the Wisconsin PDMP. Assessment (pretest) and evaluation (posttest) surveys were administered to participants during each session. Descriptive statistics were performed for all variables.

Follow-up Survey

To evaluate longer-term effects of the educational module, training session participants were invited to participate in a 3-month follow-up survey. The intent of the survey was to gather information about self-reported changes in prescribing practices (including the use of non-opioid alternatives), changes in understanding of

Theme	Subthemes and Evidence
System	There is a lack of guidance around the HOPE legislation PDMP mandate.
	Prescribers feel a push to decrease the prescribing of pain medications but a lack of alternatives for certain prescriptions. ("we write prescriptions for Lidoderm patches, and theattending gets a phone call saying the patient can't afford it, or it's not on the formulary, and there isn't an alternative")
	Systems are not aligned in a manner that consistently allows providers to see what medications are prescribed by providers in different settings.
	Formalized community resources, such as pain contracts and pain management plans, may improve provider effectiveness in working with chronic pain patients.
PDMP in the Hospital	Time is a barrier to PDMP usage, especially in a busy emergency department setting. ("if there was an automatic login through EPICthat would save 5 or 10 minutes.")
	The need to remember the many login steps to access the PDMP is burdensome. The use of a chronic pain prescribing pathway, which includes information on how to integrate the PDMP into practice, is helpful, as is information on processes for managing challenging patient situations.
Providers	Using the PDMP is a routine. ("I personally try to PDMP everyone before I write a script of narcotics unless it is an obviously acute situation" "I use it on average once a shift")
	Providers rely on their own perceptions about a patient as a cue to access the PDMP. ("we take a lot of our own biases into these situations")
	Communication with providers' peers is helpful in treating pain patients, especially when a firm pain management plan is in place.
	Working with other providers can make the prescribing process more difficult. ("you see that other people are not necessarily making the best decision for that patient, and then you have to deal with it."
	User error (eg, using the wrong password and being locked out of the PDMP) is a barrier to PDMP use.
Patients	Patients have their own expectations regarding prescribing. ("it becomes very hard to manage their expectations in trying to get their pain to zero, and they may appear comfortable, they're saying their pain is a 10 out of 10.")
	Patient cues cause providers to check the PDMP before prescribing, in addition to patients reporting a lost or stolen prescription or failing to follow up with specialists.
	When patients are altered or are not aware of what is going on, providers use the PDMP to not only look at what medications have been prescribed, but also to determine and communicate with the providers who have worked with that patient.

 Table 2. Comparison of Assessment, Evaluation, and Follow-up Surveys with Pretest, Posttest, and
 Follow-up Scores

Indicator	Pretest Mean	Posttest Mean	Follow-up Survey Mean
I have a good understanding of opioid abuse and misuse	3.96	4.50*	4.25*
I know how to access the Prescription Drug Monitoring Program (PDMP).	3.26	4.53*	4.75
I am comfortable using the PDMP.	2.95	4.08*	4.67*
I understand the new PDMP mandate that will be enforced beginning on April 1, 2017.	3.17	4.61*	4.75
Physician utilization of the PDMP is important for patient care.	4.31	4.51*	4.83*
Physician utilization of the PDMP is important for public health.	4.36	4.55*	4.75
PDMPs are a necessary tool in effective patient care.	4.17	4.47*	4.58



the PDMP and in understanding of the opioid prescribing pathway, and to gauge behavior change related to use of the PDMP that may have resulted from the educational session. Descriptive statistics were performed for all variables, as well as 1-sample *t*-tests for changes in mean scores.

RESULTS

Initial Provider Survey

The Figure provides demographic and other information regarding survey participants. Ninety-six percent of respondents reported that they had heard of the PDMP; 78% were registered to use it. Among those not yet registered, a majority indicated that they did not know how to register (63%).

Fifty-five percent of those respondents who said they had registered for the PDMP indicated that it was either very easy, easy, or somewhat easy to use. A majority indicated that they use the PDMP at least 2 to 4 times per week, with almost 15% of respondents indicating that they use it more than 10 times per week.

The most indicated reasons for using the PDMP were identifying prescription drug abuse (100%) and confirming a patient's story (94%). The majority (98%) of survey respondents found the PDMP extremely to moderately useful for patient management.

Focus Group

The Figure presents a breakdown of focus group participants. The themes generated from the focus group are situated in a Social-Ecological framework, which allows for an understanding of the interplay among various environmental, systemic, and individuallevel factors. Detail regarding themes and corresponding subthemes is included in Table 1. The system-level, hospital-level, and provider-level themes all contribute to patient care, while patients themselves influence provider use of the PDMP.

Training and Education Module for Local Providers

The Figure provides information regarding module participants, including specialty area. Pretest score means were compared with posttest score means for significant changes (P < 0.05) using 1-sample *t* tests. Analyses were conducted using STATA software, Version 13.1. Results are shown in Table 2.

Follow-Up Survey

Information regarding follow-up survey participants and the response rates are included in the Figure. Means were calculated for each variable and were compared with means from the educational session presentation post-test means for significant changes (P < 0.05) using 1-sample *t* tests. Analyses were conducted using STATA software, Version 13.1. Results are shown in Table 2.

Of the 12 survey respondents, 6 (50%) indicated that their knowledge in safe prescribing practices and the use of nonopioid alternatives for pain increased as a result of the educational session, and 50% agreed that their skills in safe prescribing practices and the use of nonopioid alternatives for pain increased as a result of the educational session. Seventy-five percent of respondents reported that they either "completely agree" or "agree" with the statement, "As part of my clinical practice, I check the PDMP more consistently than I did prior [to the educational session]." Thirty-three percent of respondents agreed that they feel more comfortable when treating pain as a result of the educational session.

DISCUSSION

The opioid epidemic is a vexing public health issue. Clinicians are an important cohort to include in prevention strategies, as they have the unique responsibility of managing chronic and acute pain among their patients in a way that is both responsible in terms of prescribing, yet effective in terms of pain management. This study used mixed research methods to understand a number of provider-level factors relating to chronic pain prescribing practices, attitudes about, and knowledge regarding a state-level intervention to reduce the availability of opioids in the general population (the PDMP), and to create and evaluate an educational intervention that aimed to educate clinicians about these concepts.

One limitation of this study is that the surveys rely on selfreporting, so there may be issues relating to response or recall bias. One way this limitation could be addressed would be to access and analyze actual prescribing behavior and PDMP use from the PDMP itself. Also, our study may be susceptible to selection bias, as those clinicians who are keenly interested in the opioid epidemic or the Wisconsin PDMP may have been more likely to respond to our surveys or to attend our focus group or educational sessions, thereby ensuring that our sample is not truly representative of the population we intend to study. As this was a mainly descriptive study, we did not attempt to address this bias in our recruitment or analysis.

CONCLUSIONS

This study can be useful for health care organizations, state PDMPs, and prevention organizations in tailoring messaging to clinicians around safe prescribing and PDMP use, and in addressing barriers to safe prescribing and PDMP use in practice. It is an important first step in the understanding of a number of concepts around prescribing practice and PDMP use and provides a basis for further evaluation and research in this area.

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Acute Ischemic Stroke in a Young Woman With No Known Risk Factors

Noureldin Abdelhamid, MD; Salman Farooq, MD; Amrou Sarraj, MD

ABSTRACT

Introduction: We aim to highlight a potentially morbid consequence of foam-sclerotherapy for the treatment of varicose veins.

Case Report: We report a case of a 41-year-old woman with no significant medical history who presented to the emergency department with sudden onset of focal neurologic deficits. She had undergone varicose vein treatment with foam sclerotherapy 2 days prior. Magnetic resonance imaging of the brain showed acute cerebellar infarct. Computed tomography angiography was unremarkable. Transesophageal echocardiography showed the presence of a very small patent foramen ovale.

Discussion: Transient neurologic symptoms reported in patients undergoing venous foam sclerotherapy might have been transient ischemic attacks or acute ischemic strokes. The risk of these neurologic complications should be explained to all patients undergoing foam sclerotherapy so they can make an informed decision of screening echocardiography prior to the procedure.

Conclusion: Onset of neurologic symptoms can be immediate or delayed in patients undergoing venous foam sclerotherapy. Early recognition of neurologic deficits resulting from paradoxical gas embolism and its treatment with hyperbaric oxygen can prevent permanent disability.

including hyperpigmentation and pain.¹ Neurologic complications, including transient visual disturbances and headaches, have been reported in a few cases.¹⁻³ In addition, a few cases of acute ischemic stroke following foam sclerotherapy are reported in the literature, which raised a few morbidity/mortality concerns about the procedure but not sufficient enough to introduce the practice of routine screening echocardiogram in patients undergoing this procedure.²⁻⁵

CASE REPORT

A 41-year-old right-handed woman with no significant past medical history presented to the emergency department (ED) with sudden onset of slurred speech with right arm weakness and incoordination. She had undergone varicose vein treatment

BACKGROUND

Foam sclerotherapy has gained wide recognition for the treatment of varicose veins mainly because of its immediate efficacy and low complication rates. A few major trials demonstrated minor side effects from the procedure in only a few patients, and the most commonly reported side effects occurred at the site of injection

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with foam sclerotherapy 2 days prior. She was working at home when she developed a pain in her right lower extremity that felt like a charley horse at the site of the vein treatment. She stood up to stretch her leg, when she suddenly developed aphasia with intact thought process and cognition but inability to form words followed by slurred speech. She then became very dizzy and nauseous and noticed weakness and incoordination greatest in her right upper extremity and had difficulty dialing 911. She was transported to the ED, and the symptoms had resolved by the time she arrived about 45 minutes later.

During the episode, she reported some blurry vision and her husband also reported very mild right-sided facial droop that had since resolved. She denied any headaches, neck pain, vomiting, numbness, tingling or residual weakness. Head computed tomography (CT) was negative for acute ischemia or hemorrhage, and initial labs and vital signs were within normal limits. General

A. Diffusion-weighted image. B. Apparent Diffusion Coefficient image showing small focus of acute infarction in superior right cerebellum.

physical and neurological exam was normal. National Institutes of Health Stroke Scale was 0. Magnetic resonance imaging (MRI) of the brain showed a small focus of acute infarct in superior right cerebellum (Figure). The patient was not a candidate for reperfusion therapy. She was started on aspirin 325 mg and admitted for transient ischemic attack/stroke work-up. Duplex ultrasound of lower extremities was negative for deep vein thrombosis (DVT). CT angiography was negative for extracranial or intracranial atherosclerosis. Transthoracic echocardiography was unremarkable (no valvular abnormalities; normal chamber size, EF: 60-65%, no intra-cardiac shunt). Transesophageal echocardiography showed the presence of a very small patent foramen ovale. Magnetic resonance venography for pelvis was negative for DVT or residual foam/gas bubbles.

DISCUSSION

Foam sclerotherapy of varicose veins has gained popularity over other methods of sclerotherapy mainly because of its high success rate, low rate of complications, and almost negligible morbidity and mortality issues. In this procedure, a mixture of gas and liquid sclerosing solution is injected in the veins that produce endothelial damage and thrombus formation, resulting in vein occlusion.^{1,5} Complications commonly reported from this procedure include local pigmentation, skin necrosis, and malaise. Neurologic complications also have been uncommonly reported including headache, transient confusional status, and transient visual disturbance.¹⁻³ Acute ischemic stroke following foam sclerotherapy is reported in a few case reports, and the most common risk factor seen in these patients was the presence of an intracardiac or intrapulmonary shunt resulting in paradoxical embolism.²⁻⁵ Paradoxical gas emboli introduced by foam sclerotherapy block blood supply to small arteries supplying the brain with an immediate or delayed onset of stroke, as seen in our patient, after foam sclerotherapy. The proposed mechanisms of cerebral ischemia caused by gas embolism include local obstruction to blood flow, vasospasm, endothelial damage caused by the induction of platelets or direct activation of thrombin.^{3,5}

Unfortunately, no screening criteria have been established for the presence of intracardiac or extracardiac shunts when selecting patients for this procedure. The few reported cases of acute ischemic stroke following this procedure were all immediate in onset, but the onset of symptoms can be delayed as the entrapped air bubbles find a way into systemic circulation by increased activity or stretching of calf muscles, as seen in our case. And we believe that the previously reported cases of transient visual disturbance or confusion states following this procedure were possibly transient ischemic attacks resulting from paradoxical embolism of small gas bubbles.¹

If physicians are able to recognize the etiology by a good procedural history, permanent neurologic deficits from air embolism induced ischemia can be prevented by administration of hyperbaric oxygen, as reported by Adatia et al³ and Leslie-Mazwi et al.⁵ Hyperoxia induced by hyperbaric oxygen decreases the size of air bubbles by causing oxygen to diffuse into bubble and nitrogen to diffuse out of the bubble and also reduces adherence of platelets to damaged endothelium.^{3,5}

CONCLUSION

The risk of neurologic complications (including transient ischemic attack and acute ischemic stroke) should be explained to all patients undergoing venous foam sclerotherapy so they can make an informed decision of screening echocardiography prior to the procedure.

Onset of neurologic symptoms can be immediate or delayed in patients undergoing venous foam sclerotherapy. Early recognition of neurologic deficits resulting from paradoxical gas embolism and its treatment with hyperbaric oxygen can prevent permanent disability. All such patients should have a work-up to rule out the presence of gas bubbles in circulation that could pose a continued risk for further ischemic events.

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CAR T-cell Immunotherapy Bringing Hope Where None Existed

Joseph E. Kerschner, MD

Joseph E. Kerschner, MD

linicians who treat cancer patients have long battled the dual need to eradicate malignancy while doing the least amount of harm to the patient through side-effects of their treatment. Each of the traditional forms of cancer therapy - surgery, chemotherapy, and radiation therapy - often have left clinicians wanting new modalities that produce excellent cures with fewer difficulties. Recently, along with an increasing number of "targeted" pharmaceuticals, advances in immunotherapy have created an increasing promise to also deliver new treatment possibilities. Immunotherapy enlists and strengthens the power of a patient's immune system to attack malignancies.

Adoptive cell transfer (ACT), in which the patient's own immune cells are collected, modified, and then used to treat the patient's cancers, has several variations, but the one that has advanced the furthest in clinical development is chimeric antigen receptor (CAR) T-cell therapy.¹

Although the majority of CAR T-cell therapy innovations are being conducted at academic medical centers through clinical trials with relatively small enrollments for the treatment of hematologic malignancies, the Food and Drug Administration recently approved two broader

Joseph E. Kerschner, MD, is Dean, School of Medicine, and Provost and Executive Vice President, Medical College of Wisconsin, Milwaukee, Wis. CAR T-cell therapies – one for the treatment of children with acute lymphoblastic leukemia and the other for adults with advanced lymphomas. "Immuno-oncology using T-cell treatments shows incredible promise for patients with cancer," according to Parameswaran Hari, MD, MS, professor of medicine at the Medical College of the T cell then initiates its usual immunologic response to eradicate the tumor cells. There are currently more than 240 CAR T-cell clinical trials in progress internationally.²

One such historic clinical trial was announced on February 1, 2018, by physicians and researchers from MCW, Froedtert

"We are harnessing this knowledge from years of research and creating improved outcomes for patients. There is amazing potential here for the future of cancer treatment, and a healthier world is closer than ever..."

-Nirav Shah, MD

Wisconsin (MCW) and chief of hematology and oncology, who specializes in treating individuals with myeloma, leukemia, and lymphoma at the Froedtert & MCW Clinical Cancer Center.

The most common procedure for CAR T-cell therapy starts with the extraction of T cells from the patient, in a process called leukapheresis. The T cells are genetically modified to express a CAR, multiplied in the laboratory, and then infused back into the patient, where they further multiply to a number that will allow a potent immunologic response. The CAR on the modified T cells is a receptor that normally would not be present on the T cell and has the express purpose of recognizing a protein (antigen) on the surface of the malignant cells. Once this receptor recognizes the antigen, Hospital, Children's Hospital of Wisconsin, and BloodCenter of Wisconsin. In this announcement, the clinical and research team reported a successful, innovative CAR T-cell treatment developed by MCW researchers to combat lymphoma in a Wisconsin man who had failed all other forms of "traditional" therapy.

This patient was diagnosed with mantle cell lymphoma, a cancer of the immune system. Despite chemotherapy, stem cell transplants, and other directed pharmaceutical intervention in clinical trials, his lymphoma kept returning. He received the CAR T-cell dose in late October 2017, and just 6 weeks later, his lymphoma was in full remission.

"The patient's results from the CAR T-cell immunotherapy have been phenomenal,"

said Nirav Shah, MD, principal investigator of the trial and assistant professor of medicine (hematology and oncology) at MCW who specializes in lymphoma and stem cell transplant at Froedtert & MCW Clinical Cancer Center. Doctor Shah is a member of the Blood and Marrow Transplant (BMT) and Cellular Therapy team. "We are harnessing this knowledge from years of research and creating improved outcomes for patients. There is amazing potential here for the future of cancer treatment, and a healthier world is closer than ever," he added.

This success was a first-in-human clinical trial for a novel dual-targeted CAR T cell against CD19 and CD20 antigens. The team utilized innovative new technology³ that allowed a very rapid, onsite development of the CD19 and CD20 T-cell CARs, such that following leukapheresis the modified T cells were reinfused within 14 days. Precious time was saved for the patient by being able to perform the entire process at the Froedtert & MCW laboratories on the academic medical center campus. And the treatment also was able to be performed at substantively reduced cost.

The CAR T-cell therapy clinical trial is a wonderful example of how our researchers rapidly translate basic research into clinical applications – a unique ability provided at academic medical center and a substantial benefit to all members of the community and beyond. The successful launch of this clinical trial is the result of decades of collaborative cancer and cellular immunotherapy research at our BMT program. Pioneers in the field of immunotherapy, these researchers helped discover and develop how the body's own immune system has the power to fight cancer cells, leading to innovative ideas of alternatives to chemotherapy, radiation, and transplants.

This unique immunotherapy clinical trial – simultaneously targeting CD19 and CD20 – is continuing as the research team tracks the progress of the second participant, who received a dose of CAR T cells in December 2017. A third patient began treatment in February 2018, with 1 new participant being dosed every 6 weeks. Additionally, this trial also has been extended to pediatric patients, with a first patient expected to begin treatment at Children's Hospital of Wisconsin later this year.

This clinical trial is a great leap forward in personalized medicine and the future of cancer treatment – not just in our region but around the globe. It is our expectation that a significant number of patients will soon be benefiting from this discovery – a discovery that happened because of the linkage of research and clinical care at an academic medical center.

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Learn more at: DoseOfRealityWI.gov A message from Wisconsin Department of Justice, Brad Schimel, Attorney General, and the Wisconsin Department of Health Services



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