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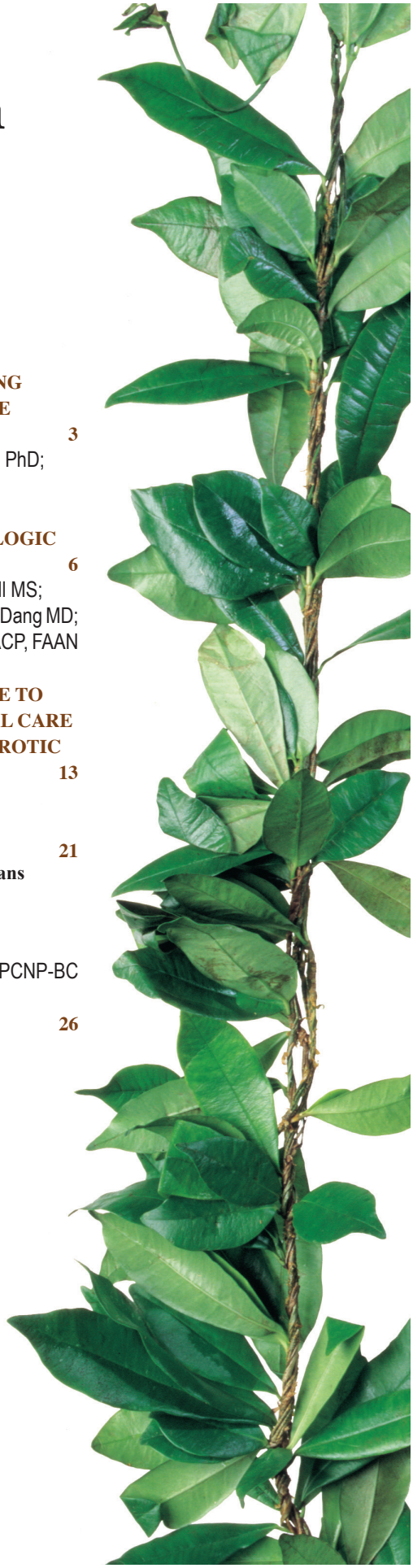

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Mothball Ingestion in the Setting of G6PD Deficiency Causing Severe Hemolytic Anemia, Methemoglobinemia, and Multiple Organ Failure in a Toddler

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Abstract

Mothballs containing naphthalene or paradichlorobenzene are known to cause hemolysis and methemoglobinemia. They can also affect the other organs, including the kidneys, liver, lungs, and skeletal muscles. The involvement of 1 or 2 organs at a time has been commonly reported. However, more than 2 organ dysfunction in mothball intoxication is rare and usually indicates severe illness. The intoxication can have more pronounced symptoms in children with glucose-6-phosphate dehydrogenase (G6PD) deficiency. We report this case of a previously healthy 13-month-old patient who presented with severe hemolysis, lactic acidosis, methemoglobinemia, acute renal failure, hepatic dysfunction, and rhabdomyolysis. He required aggressive fluid resuscitation, blood transfusions, and mechanical ventilation. The underlying etiology of his illness was initially unclear; however, upon repeated questioning, the father recalled the patient chewing on a mothball 3–4 days before admission. Hence, mothball intoxication was considered the most plausible clinical diagnosis in this patient. He was given N-acetylcysteine, instead of methylene blue, because of hepatic dysfunction and the fact that G6PD deficiency could not be ruled out in the presence of acute hemolysis. The patient made a full recovery after 2 weeks of intensive care unit management. G6PD testing after 3 months confirmed the deficiency. These mothballs are available in Hawai'i, but this is the first report of such a severe presentation to our knowledge. The presence of methemoglobinemia, severe hemolysis, and thorough history-taking helped us determine the diagnosis of mothball intoxication and enabled definitive treatment.

Keywords

hemolysis, anemia, methemoglobinemia, multiple organ failure, mothball, naphthalene

Abbreviations and Acronyms

ALT = alanine aminotransferase
AST = aspartate aminotransferase
BUN = blood urea nitrogen
DIC = disseminated intravascular coagulation
ED = emergency department
G6PD = glucose-6-phosphate dehydrogenase
HUS = hemolytic uremic syndrome
LDH = lactate dehydrogenase
NAC = N-acetylcysteine
NADPH = nicotinamide adenine dinucleotide phosphate
PRBC = packed red blood cell
PICU = pediatric intensive care unit
RBC = red blood cells
TTP = thrombotic thrombocytopenic purpura
WBC = white blood cells
UA = urinalysis

Introduction

Naphthalene is an aromatic hydrocarbon used in mothballs and some insecticides. Paradichlorobenzene has also been used in mothballs and is less toxic than naphthalene.[1,2] These toxins are known to cause hemolysis by oxidative stress. A little over 1000 cases of mothball intoxication were reported in the United States in 2018. A majority of these cases occurred in children younger than 5 years of age, and 95.8% of the cases were accidental.[1] Intoxication occurs upon ingestion, inhalation, or dermal exposure. The symptoms are proportionate to the degree of exposure. Clinical course after intoxication can be self-limiting in otherwise healthy individuals.[2-4] Mild symptoms include nausea, vomiting, diarrhea, fever, abdominal pain, and headache.

Intoxication can have more pronounced symptoms in children with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Severe hemolysis and the need for multiple transfusions have been reported in this population.[4] G6PD is an enzyme that protects against oxidative stress by providing a source of nicotinamide adenine dinucleotide phosphate (NADPH) through the pentose phosphate pathway. Red blood cells (RBC) rely on the pentose phosphate pathway to provide the protective effects of NADPH, especially in times of oxidative stress.[5] Severe complications like renal failure, hepatic dysfunction, cerebral edema, rhabdomyolysis, respiratory depression, and methemoglobinemia have been reported in mothball intoxication.[2-4,6-10] The degree of organ involvement varies according to the severity of illness. While the involvement of 1 or 2 organ systems is commonly reported, more than 2 organ system dysfunction is less frequent and indicates severe illness.[2-4,6-7] Hemolysis and methemoglobinemia can be prolonged without intervention and can lead to severe complications, such as renal failure requiring dialysis or even death.[6-12] Therefore, prompt recognition and a high index of suspicion are critical in these cases to administer appropriate interventions, including ascorbic acid or N-acetylcysteine (NAC). Methylene blue is commonly used to treat methemoglobinemia but is contraindicated in patients with G6PD deficiency because of the risk of worsening hemolysis.[2,3]

We report this case of a 13-month-old patient who presented with severe hemolytic anemia, methemoglobinemia, lactic acidosis, and multiple organ failure after exposure to mothballs.

Case Report

A previously healthy 13-month-old male developed a cough, runny nose, and fever. Four days later, this progressed to lethargy, pallor, jaundice, vomiting, and diarrhea. He presented to the emergency department (ED) with tachypnea and decreased urine output. His vital signs in the ED included a temperature of 100.8° Fahrenheit, heart rate 170/min, respiratory rate 70/min with severe distress, and hypoxemia to 80% on room air, which improved to 85% on supplemental oxygen via a non-rebreather face mask. His initial workup showed hemoglobin of 2.7 g/dL, absolute and corrected reticulocyte counts were 0.047 x 10^{12} and 1.2%, respectively, with a peripheral blood smear showing evidence of hemolysis, white blood cells (WBC) 46.8 x 10^9/L, platelets 351 x 10^9/L, indirect bilirubin 4.4 mg/dL, blood urea nitrogen (BUN) 36 mg/dL, creatinine 1.07 mg/dL, anion gap 22 mEq/L, aspartate aminotransferase (AST) 120 U/L, and urinalysis (UA) with large blood by dipstick but only 5–10 RBC per high power field and elevated urobilinogen. His blood gas showed metabolic acidosis with pH 6.75, PCO_2 of 26.5 mm Hg, bicarbonate 3.6 mmol/L, lactate 15.47 mmol/L, methemoglobin 6.4% (normal range, 0.4% to 1.1%). The remainder of his initial workup was unremarkable.

He required intubation, mechanical ventilation, intravenous fluid resuscitation, and 3 units of packed red blood cell (PRBC) transfusion in the ED. After initial stabilization, he was admitted to the pediatric intensive care unit (PICU) for further management.

Critical care was continued, and a thorough history was obtained in the PICU. The history included diet and other occurrences spanning the days before hospitalization to identify potential triggers for his presentation. Upon repeated and thorough questioning, the father recalled the patient chewing on a mothball 3-4 days before admission. An uncertain portion of the mothball appeared to have been ingested. Medical attention was not pursued at that time because of an apparent lack of symptoms.

The patient developed multiple organ system dysfunction including hemolytic anemia with peak values of haptoglobin 17 mg/dL, lactate dehydrogenase (LDH) 5439 U/L, methemoglobinemia 6.4%, creatine kinase (CK) 3412 U/L (indicating myolysis), creatinine 3.7 mg/dL, BUN 93 mg/dL, alanine aminotransferase (ALT) 1431 U/L, and respiratory failure. The patient required multiple blood products, including PRBC, fresh frozen plasma, and platelet transfusions. He exhibited signs of fluid overload from ongoing fluid resuscitation and blood transfusions in the setting of acute renal failure. Renal replacement therapy was considered but was avoided with medical management. A respiratory viral panel was positive for rhinovirus/enterovirus, which was suspected of contributing to his respiratory failure. Blood, urine, respiratory, and stool cultures were all negative. Abdominal and renal ultrasounds found hepatomegaly and increased renal parenchymal echogenicity, respectively. NAC was administered per recommendations by the Hawai‘i Poison Center.

His organ dysfunction gradually improved and normalized during approximately 24 days of hospitalization, although he continued to have mild hemolysis with elevated LDH. Following extubation, he was deconditioned with muscle weakness, hypotonia, and dysphagia, which returned nearly to baseline by the time of discharge following 10 days of extensive rehabilitation. Magnetic resonance imaging of the brain showed no evidence of hypoxic injury. He required hydralazine and clonidine for hypertension, most likely due to renal injury, which was weaned over 3 months following discharge. Renal function and blood pressure were normal at his last nephrology follow-up, 18 months after the hospital discharge.

Although initial testing was negative for G6PD deficiency, a follow-up outpatient testing revealed a deficiency with levels at 3 u/gHgb@37 dg (normal value, 7.0 to 20.5).

Discussion

This case report describes rare and severe manifestations of multiple organ system failure after mothball ingestion.

The differential diagnosis in our patient included hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), sepsis with disseminated intravascular coagulation (DIC), and mothball intoxication. Lack of thrombocytopenia excluded HUS, TTP, and DIC. Negative blood, urine, and respiratory cultures made sepsis less likely. Our patient's initial cough and runny nose can be attributed to rhinovirus infection. However, severe hemolysis, methemoglobinemia, and extreme multiple organ failure have not been described in this context. Conversely, respiratory tract involvement with congestion, fever, and acute respiratory distress syndrome have been reported from mothball intoxication.[11] Congenital methemoglobinemia usually presents within the first few hours to days of life.[15,16] A new-onset methemoglobinemia at 13 months in our patient resolved with treatment, making an acquired etiology more likely. Certain medications, dietary, environmental substances can cause acquired methemoglobinemia.[5] These etiologies were ruled out by detailed history-taking. Therefore, mothball intoxication was the most plausible clinical diagnosis in our patient. In our literature review, a history of mothball exposure followed by hemolysis, methemoglobinemia, with or without organ failure, was considered diagnostic of mothball intoxication.[2,3,6,9,11-14] In some case reports, there was a definite history of mothball exposure followed by the development of hemolysis or methemoglobinemia, with or without organ failure.[6,8,10,11,13,14] In other cases, the patients had a similar presentation, and the mothball exposure was identified in retrospect due to a high index of suspicion.[3,9,12] The latter was similar to our case. Naphthalene levels were not obtained in those other reported cases.[2,3,6,9,11-14]

Naphthalene and paradichlorobenzene can cause hemolysis by oxidative stress. Methemoglobinemia occurs because of the inability of heme to be reduced from the ferric (3+) state back to the ferrous (2+) state, and therefore, the oxygen-carrying capacity

is severely compromised.[2] A methemoglobin level of more than 1.5% can be associated with cyanosis.[15] Rhabdomyolysis is likely due to very high amounts of oxidative stress leading directly to muscle breakdown.[12]Skeletal muscles can be the source of AST and ALT,[17] though direct hepatic dysfunction and death have been reported from naphthalene toxicity.[18] Our patient's AST and ALT elevation could be related to rhabdomyolysis or from direct hepatic injury from the mothball intoxication. Renal failure is usually associated with direct damage by the free filtering of hemoglobin following hemolysis and myoglobin following rhabdomyolysis.[2,3,6,9,14] Respiratory failure may occur due to methemoglobinemia-induced endothelial dysfunction.[19]

The diagnosis of G6PD deficiency is based on enzymatic activity. The activity can be falsely elevated in the presence of hemolysis, reticulocytosis, or after blood transfusion.[2,3,5] We repeated the assay after 3 months, which confirmed the diagnosis of G6PD deficiency. The rationale of repeating the test after 3 months was based on the expectation of hemolysis resolution and the anticipation of transfused RBC replacement by native RBC.

Decontamination with activated charcoal has been recommended within the first 4 hours of ingestion, and further decontamination with whole-bowel irrigation with polyethylene glycol can be considered.[2] This treatment was not indicated in our patient because he presented after 3-4 days of exposure. The toxic dose of mothballs is unknown in the pediatric population, but any amount of ingestion should warrant thorough workup and close monitoring. More than 1 mothball (0.5 g) can be potentially toxic in an adult patient. [2] Naphthalene toxicity is treated with supportive care, hydration, and blood transfusion.[2,3,11,13] Ascorbic acid or NAC may be used in these situations to reduce oxidative stress.[2,3,11] NAC is also a source of glutathione and supports hepatic recovery.[2,3,11,15,16] Our patient had both methemoglobinemia and hepatic dysfunction. Therefore, NAC was the treatment of choice in our case. Since G6PD deficiency could not be ruled out in our patient during the acute hemolytic phase, he did not receive methylene blue. Renal replacement therapy and hemodialysis have been described in other cases; however, we avoided this with medical management.[9,11,14] Rhabdomyolysis has been rarely reported, and our patient had a more severe presentation than the existing literature.[12] To our knowledge, our patient represents 1 of the more severe cases of mothball intoxication described, made even more noteworthy by his complete recovery.

Conclusion

Our case report revealed the following recommendations: (1) Intoxication from mothball containing naphthalene or paradichlorobenzene should be considered in cases presenting with severe hemolysis and methemoglobinemia with or without organ dysfunction.[2-4,6-11] This clinical diagnosis can be supported by quantitative serum or urine analysis for naphthalene levels but not required;[2,3,6,9,11-14] (2) Hemolysis and methemoglobinemia can be prolonged without intervention[10], leading to severe complications such as renal failure requiring dialysis or even death.[2,6,8,9,11,14] Therefore, prompt recognition and treatment are pivotal. Diagnosis of such intoxication is also essential for the family's education to prevent such recurrences and seek early medical attention; (3) Supportive care with fluid resuscitation and blood transfusion is the mainstay of the treatment of mothball-induced hemolysis. Methylene blue is commonly used for the treatment of methemoglobinemia but is contraindicated in patients with G6PD deficiency. Ascorbic acid or NAC can be considered in such cases[2,3,11]; (4) Diagnosis of G6PD in the acute phase may not be possible; therefore, it should be repeated approximately 3 months after the acute phase is over.

Conflict of Interest

None of the authors identify any conflict of interest.

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Early Impact of the COVID-19 Pandemic on Outpatient Neurologic Care in Hawai'i

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Abstract

In March 2020, Hawai'i instituted public health measures to prevent the spread of Coronavirus disease 2019 (COVID-19), including stay-at-home orders, closure of non-essential businesses and parks, use of facial coverings, social distancing, and a mandatory 14-day quarantine for travelers. In response to these measures, Hawai'i Pacific Neuroscience (HPN) modified practice processes to ensure continuity of neurological treatment. A survey of patients was performed to assess the impact of the COVID-19 pandemic and pandemic-related practice processes for quality improvement. Overall, 367 patients seen at HPN between April 22, 2020, and May 18, 2020, were surveyed via telephone. Almost half (49.6%) participated in a telemedicine appointment, with the majority finding it easy to use (87.4%) and as valuable as face-to-face appointments (68.7%). Many (44.5%) patients said they would have missed a health care appointment without the availability of telemedicine, and 47.3% indicated they might prefer to use telemedicine over in-person appointments in the future. Many reported new or worsening mental health problems, including depression (27.6%), anxiety (38.3%), or sleep disturbances (37.4%). A significant number reported worsening of their condition, with 33.1% of patients who experience migraines reporting increased symptom severity or frequency, 45.8% patients with Alzheimer's disease reporting worsened symptoms, 38.5% of patients with Parkinson's disease who had a recent fall, and 50.0% of patients with multiple sclerosis experiencing new or worsened symptoms. Insights from this survey applied to the practice's pandemic-related processes include emphasizing lifestyle modification, screening for changes in mental health, optimizing treatment plans, and continuing the option of telemedicine.

Keywords

COVID-19, pandemic, outpatient care, telemedicine, survey

Acronyms and Abbreviations

COVID-19 = Coronavirus disease 2019
ER = emergency room
HPN = Hawai'i Pacific Neuroscience
NHOPI = Native Hawaiian and Other Pacific Islander
QI = quality improvement
TIA = transient ischemic attack
US = United States

Introduction

While the United States (US) is experiencing difficult times due to the Coronavirus disease 2019 (COVID-19) pandemic, the disease burden has been unequally shared among each state. In April 2020, Hawai'i's COVID-19 infection rate per capita was the third-lowest in the United States with 36 cases per 100 000 population, far below the national rate of 177 cases per 100 000.[1] Nevertheless, the highly contagious nature of the virus, the high proportion of asymptomatic carriers, relatively high mortality in the subset of patients afflicted with severe acute respiratory syndrome, along with constant media coverage and financial burden caused by quarantine, have contributed to heightened levels of anxiety among the public.[2–4] Early government action in Hawai'I has been credited with "flattening the curve." These measures, beginning in March 2020, included stay-at-home orders, closure of non-essential businesses and parks, use of facial coverings, social distancing, and a mandatory 14-day quarantine for travelers.[5] Though these measures promote public health and safety, it's important to identify unforeseen consequences on people and implement ways to mitigate these impacts.

Patients with neurological disease are vulnerable to mental and physical deterioration with limited access to health care or healthy lifestyle options. The prevalence of depression, one of the most common comorbid psychiatric disorders in patients with epilepsy, multiple sclerosis, and Parkinson's disease, is between 20% and 50%.[6,7] An increase in depression incidence is clinically significant, as numerous studies have linked depression to increased all-cause mortality.[8] Exercise is also important for neurological patients. Many patients have symptoms of neuromuscular weakness, leading to an inability to perform activities of daily living and a decline in quality of life.[9] For patients with Parkinson's disease, studies have shown that those who regularly exercise had slower declines in mobility and health-related quality of life than non-exercisers.[10] Additionally, exercise has been shown to improve depressive symptoms in patients with neurological disorders, such as multiple sclerosis, Parkinson's disease, and epilepsy.[11–13] Ultimately, ensuring patients at increased risk of decompensation are connected to health care services that protect their well-being is imperative.

With the advent of stay-at-home orders and new protective measures, health care facilities across the state hastened to adjust their previously routine procedures and protocols. The authors are associated with Hawai'I Pacific Neuroscience (HPN), a large neuroscience care and clinical research center that provides care

to over 20 000 patients annually with a multidisciplinary team of neurology, neurosurgery, physical medicine, rehabilitation, geriatrics, and sleep medicine health care professionals. Practice procedures were modified to follow recommendations from the Centers for Disease Control and Prevention and the American Academy of Neurology. In addition, HPN greatly expanded its telemedicine capacity to allow continuity of care for patients while minimizing coronavirus spread.

Due to these practice changes and concern for potential patient deterioration, a survey of patients was performed during the early stages of the COVID-19 pandemic. The purpose of this survey was to assess patients' needs and changes to accessing health care, general and mental well-being, and neurologic conditions to implement practice processes for quality improvement (QI). At the time of this study, no prior report investigated the observed health impact on patients with neurological conditions during the COVID-19 pandemic in a low disease prevalence area, such as Hawai'i.

Methods

A voluntary telephone survey was conducted on new and follow-up patients seen at HPN between April 22, 2020, and May 18, 2020, to investigate their health and well-being during the COVID-19 pandemic. Patients were seen in HPN locations across the state of Hawai'i: Honolulu, Kailua, and Waikele on O'ahu island and Kona on Hawai'i island. Interviewers were trained in survey administration to ensure consistency of data collection. Surveys lasted about 15 minutes, and the surveyor documented patient responses to the survey in a de-identified online form in Google Docs (Google, Mountain View, CA). All patients gave verbal consent and acknowledged the right to decline the survey at any point. Patients were not offered incentives for survey completion. The study was conducted as a clinic-oriented, QI survey and was therefore deemed exempt from the Institutional Review Board. The inclusion criteria were the patients seen at HPN either in-person or via video teleconferencing during the above time frame. Patients who declined or failed to complete the survey were excluded from the study. When appropriate, the principal caregiver for the patient was interviewed.

HPN utilized the eClinicalWorks Electronic Health Record service (healow, Westborough, MA) for video teleconferencing appointments; this platform is compliant with all federal Health Insurance Portability and Accountability Act regulations. Patients were contacted by a designated telehealth team before their appointments to ensure connectivity and troubleshoot technological issues. Zoom (Zoom Video Communications, San Jose, CA) was available as a backup option if there were connectivity issues.

The survey questions addressed 4 areas related to the patients' outpatient experience: general issues regarding their care, experience with telemedicine, general health and well-being, and disease-specific questions, and demographics. Patients with self-reported diagnoses of migraine, epilepsy, multiple sclerosis, Alzheimer's disease, Parkinson's disease, and cerebrovascular disease were asked tailored questions. Questions were easy to understand, requiring simple answers, such as affirmation ("yes" vs "no") or a change in condition ("increased," "decreased," "no change").

Descriptive statistics were conducted. Chi-square tests were run in IBM Statistical Product and Service Solutions (Version 23, IBM Corporation, Armonk, NY) to determine the relationship between participants' demographic characteristics and responses to survey questions regarding their perception of telemedicine and their general health and well-being.

Results

Out of the 928 patients seen across the HPN outpatient facilities from April 22, 2020, to May 18, 2020, telephone contact was established with 429 (46.2%) patients. Of those, 367 (85.5%) agreed to participate. Participant demographics are presented in Table 1. Participants had a median age of 56 years and a mean age of 54.1 years. Women accounted for 212 (57.8%) of the respondents. The most common racial and ethnic groups represented were White (n = 115, 39.7%), Native Hawaiian and Other Pacific Islander (NHOPI; n = 89, 30.7), and Asian (n = 58, 20.0%). Patients were asked if they had been diagnosed with conditions of special interest to the researchers, including 118 (32.2%) with migraine, 24 (6.5%) with Alzheimer's disease, 48 (13.1%) with epilepsy or other seizure disorder, 35 (9.5%) with a history of stroke or transient ischemic attack (TIA), 13 (3.5%) with Parkinson's disease, and 4 (1.1%) with multiple sclerosis.

Access to health care appears generally unaffected, as most patients denied difficulty obtaining medications (91.0%) or difficulty attending scheduled doctor visits (75.5%) (Table 2). However, 16.4% of patients reported they avoided accessing health care for new health problems from March to May 2020.

Between March and May 2020, HPN encouraged patients to utilize telemedicine but offered in-person appointments if preferred. Half (49.6%) of respondents reported participating in a telemedicine appointment during this period (Table 2). Most patients who used telemedicine found that it was easy to use (87.4%) and was as valuable as a face-to-face appointment (68.7%). A little less than half of patients (44.5%) said they would have missed a health care appointment without the availability of telemedicine. Patients were asked if they would prefer to use telemedicine over in-person appointments in the future once the COVID-19 pandemic resolved. Close to half (47.3%) of respondents reported they would prefer telemedicine in the future, and an additional 20.3% said they might prefer telemedicine for some appointments.

Patients were also surveyed on how their mental health changed after March 2020. More than a quarter of surveyed patients reported new or worsening mental health problems, including depression (27.6%), anxiety (38.3%), or sleep disturbances (37.4%) (Table 2). Patients younger than 65 years were more likely to experience new or worsening sleep disturbances (44.1% vs 20.8%, $P < .001$) than their older peers (Table 3). Differences in depression (30.3% vs 20.8%, $P = .064$) and anxiety (40.2% vs 33.0%, $P = .197$) were also seen between the age groups but were not statistically significant.

Participants with 1 or more diagnoses of interest (ie, migraine, epilepsy, Alzheimer's disease, Parkinson's disease, multiple sclerosis, and cerebrovascular disease) accounted for 66.0% (n = 242) of the pool of participants (Table 4). Overall, 33.1% of patients who experience migraines reported increased symptom severity or frequency, 45.8% of patients with Alzheimer's disease reported worsened symptoms, 38.5% of patients with Parkinson's disease reported an increase in recent falls, and 50.0% of patients with multiple sclerosis reported new or worsened symptoms.

Table 1. Demographics of Study Participants (N = 367)

Age (years)	
<29 (%)	41 (11.2)
30-49 (%)	107 (29.2)
50-64 (%)	113 (30.8)
≥65 (%)	106 (28.9)
Median	56
Mean	54.1
Sex	
Men (%)	155 (42.2)
Women (%)	212 (57.8)
Race/ethnicity	
White (%)	115 (39.7)
NHOPI (%)	89 (30.7)
Asian (%)	58 (20.0)
Hispanic (%)	9 (3.1)
African American (%)	4 (1.4)
American Indian/Alaskan Native (%)	2 (0.7)
Other/Mixed (%)	13 (4.5)
Missing (%)	77 (21.0)
Selected Diagnoses	
Migraine	118 (32.2)
Alzheimer's Disease	24 (6.5)
Epilepsy	48 (13.1)
Parkinson's Disease	13 (3.5)
Multiple Sclerosis	4 (1.1)
Stroke/TIA history	35 (9.5)

Abbreviation: TIA, transient ischemic attack.

Discussion

Even though Hawai'I, at the time of this writing, is one of the states with the least per capita COVID-19 infections, neurological patients and their health care have not been spared from the impact of the COVID-19 pandemic. The COVID-19 pandemic continues to shift the structure of health care rapidly. Amid this crisis, there is an opportunity to improve upon the approach to the care of neurological patients. In this spirit, health care providers have turned to each other to determine the best procedures to mitigate the effect of the pandemic on their practices.[14–17]

The strict measures imposed to safeguard public health in Hawai'I have had significant economic repercussions, as the state is heavily dependent on tourism. Data from the Department of Labor and Industrial Relations shows that Hawai'i's unemployment rate in April 2020 jumped to 23.5%, in contrast to a pre-COVID-19 unemployment rate of 2.5%. Hawai'i's economic growth rate is expected to drop by 12.1% in 2020.[18] Data from this survey reflects employment loss seen in the greater population, with 22.4% of those employed before the start of the pandemic reporting loss of employment.

With health insurance potentially tied to employment, there is a concern that patients would have difficulty accessing health care. Of those surveyed, most responses to questions regarding medical care access (eg, challenges obtaining medications, missing appointments, and lack of health insurance) did not suggest a negative impact. However, HPN noted a significant reduction of about 40% of the monthly outpatient caseload during the 4 weeks the survey was conducted, limiting the generalizability of these results. The mandatory stay-at-home orders, financial concerns, and pandemic-related fears could have contributed to decreased visits.

Telemedicine may assist in maintaining access to health care.[19] A clinically relevant number of patients (16.4%) reported they avoided accessing health care for new health problems since the start of the pandemic. A national survey estimated that 40.9% of US adults avoided medical care during the pandemic because of concerns about COVID-19. Other than the fear of exposure to COVID-19, barriers to care include reduced availability of public transportation, increased financial burden, loss of health insurance, and adherence to public health recommendations.[20] Telemedicine has the opportunity to increase access to health care by reducing the risk of exposure, decreasing transportation needs, and limiting time taken off from work. Of patients who had a telemedicine appointment, 44.5% responded they would have missed that appointment without the availability of telemedicine. The ability to attend a medical appointment from one's own home is even more vital in Hawai'I, where patients from neighboring islands (Maui, Kaua'I, Moloka'I, and Hawai'I islands) routinely fly into Honolulu (O'ahu) for specialized medical care. The state-mandated 14-day quarantine for travelers, including inter-island travel, could make it

Table 2. Self-reported Changes in Access to Health Care, Telemedicine Usage, and Mental and General Well-Being During the COVID-19 Pandemic

Access to health care	**N**	**Yes n (%)**	**No n (%)**			
Difficulty obtaining medications	367	33 (9.0)	334 (91.0)			
Missed medical appointment	367	90 (24.5)	277 (75.5)			
Unable to obtain diagnostic testing	367	39 (10.6)	328 (89.4)			
Avoided medical care despite new health concern	367	60 (16.4)	307 (83.7)			
Difficulty with health insurance premiums or coverage	367	26 (7.1)	341 (92.9)			
Lost health insurance	367	4 (1.1)	363 (98.9)			
Telemedicine	**N**	**Yes n (%)**	**No n (%)**	**Maybe n (%)**		
Participated in a telemedicine visit	367	182 (49.6)	185 (50.4)	0 (0.0)		
Telemedicine was easy to use	182	159 (87.4)	23 (12.6)	0 (0.0)		
Telemedicine is as valuable as in-person appointments	182	125 (68.7)	57 (31.3)	0 (0.0)		
Would have missed an appointment without the option of telemedicine	182	81 (44.5)	101 (55.5)	0 (0.0)		
Would prefer telemedicine over in-person appointments in the future	182	86 (47.3)	59 (32.4)	37 (20.3)		
Mental and general well-being	**N**	**Yes n (%)**	**No n (%)**			**No Response n (%)**
New or worsening depression	367	101 (27.6)	265 (72.4)			1 (0.0)
New or worsening anxiety	367	140 (38.3)	226 (61.8)			1 (0.0)
New or worsening sleep problems	367	137 (37.4)	229 (62.6)			1 (0.0)
		Increased n (%)	**Decreased n (%)**	**No change n (%)**		
Frequency of exercise	367	29 (7.9)	132 (36.0)	132 (36.0)		74 (20.1)
Weight change	367	89 (24.3)	45 (5.2)	232 (63.4)		
		Increased n (%)	**Decreased n (%)**	**No change n (%)**	**None n (%)**	
Alcohol consumption	367	22 (6.0)	19 (5.2)	171 (46.7)	154 (42.1)	
		Remained employed n (%)	**Lost employment n (%)**	**Retired before March 2020 n (%)**	**Unemployed before March 2020 n (%)**	
Employment	367	191 (52.0)	55 (15.0)	88 (24.0)	33 (9.0)	

prohibitively difficult for those patients to obtain the care they need in person.[5] Some advantages of telemedicine over in-person visits may include reductions in travel (time and cost savings), care-partner burden, and indirect costs (time off work).[21–23]

Telemedicine offers quality care to neurologic patients without a significant decrease in patient satisfaction. While telemedicine may have limitations for detailed neurological examinations, studies of its use in neurologic conditions demonstrated the ability to achieve appointment goals from both a patient and clinician perspective.[24,25] Studies of telemedicine in neurology practices before the COVID-19 pandemic likewise showed high marks of patient satisfaction.[22,23] In this study, most telemedicine users responded positively in terms of their ease of use (87.4%) and value (68.7%). Almost half of the telemedicine users reported they would prefer telemedicine over in-person appointments in the future (47.3%), with an additional 20.3% stating that they would prefer telemedicine in some instances. The increased exposure of patients to telemedicine during the pandemic will likely have long-lasting changes to how health care is delivered.

The COVID-19 pandemic has had a serious impact on the mental health of the public. Pandemic-related anxiety includes fear of contagion through exposure to carriers and contaminated surfaces, fear of foreigners, fear of economic consequences,

Table 3. Relationship Between Participant Demographic Characteristics and Self-Reported Changes in Mental Health During the COVID-19 Pandemic				
	N	**New/Worsening Depression n (%)**	**New/Worsening Anxiety n (%)**	**New/Worsening Sleep Problems n (%)**
Total	367	101 (27.6)	140 (38.2)	137 (37.4)
Age (years)				
Younger than 65	261	79 (30.3)	105 (40.2)	115 (44.1)
65 and older	106	22 (20.8)	35 (33.0)	22 (20.8)
		χ^2 = 3.420, *P* = .064	χ^2 = 1.661, *P* = .197	χ^2 = 17.503, *P* < .001
Sex				
Men	155	39 (25.2)	55 (35.5)	51 (32.9)
Women	212	62 (29.2)	85 (40.1)	86 (40.6)
		χ^2 = .749, *P* = .387	χ^2 = .807, *P* = .369	χ^2 = 2.247, *P* = .134
Race/ethnicity				
NHOPI	88	28 (31.8)	88 (34.1)	40 (45.5)
Non-NHOPI	202	56 (27.7)	80 (39.6)	71 (35.1)
		χ^2 = .500, *P* = .480	χ^2 = .791, *P* = .374	χ^2 = 2.756, *P* = .097

Abbreviation: NHOPI, Native Hawaiian and Other Pacific Islander.

Table 4. Self-Reported Changes in Specific Neurologic Conditions During the COVID-19 Pandemic[a]				
Migraine	**N**	**Increased n (%)**	**Decreased n (%)**	**No Change n (%)**
Symptom severity or frequency	118	39 (33.1)	4 (3.4)	75 (63.6)
		Yes n (%)	**No n (%)**	
Used more abortive therapy	118	19 (16.1)	99 (83.9)	
Stroke or TIA history	**N**	**Yes n (%)**	**No n (%)**	
Change in diet	35	8 (22.9)	27 (77.1)	
Recent symptoms	35	12 (34.3)	23 (65.7)	
Received treatment for symptoms	12	9 (75.0)	3 (25.0)	
Alzheimer's disease	**N**	**Yes n (%)**	**No n (%)**	
Worsened symptoms	24	11 (45.8)	13 (54.2)	
Epilepsy or other seizure disorder	**N**	**Yes n (%)**	**No n (%)**	
Recent seizure	48	17 (35.4)	31 (64.6)	
Parkinson's disease	**N**	**Yes n (%)**	**No n (%)**	
Worsened symptoms	13	3 (23.1)	10 (77.0)	
Recent fall	13	5 (38.5)	8 (61.5)	
Multiple sclerosis	**N**	**Yes n (%)**	**No n (%)**	
New or worsened symptoms	4	2 (50.0)	2 (50.0)	

Abbreviation: TIA, transient ischemic attack.
[a]Total N = 367.

panic buying, binge-watching media outlets, negative intrusive thoughts, and nightmares.[3,26,27] A clinically relevant number of patients answered questions affirmatively with regards to new or worsening depression (27.6%), anxiety (38.3%), sleep difficulties (37.4%), along with negative health consequences, such as a decrease in exercise (36.0%) and changes in body weight (29.5%) during the period of March to May 2020. Similarly, a 20–40% prevalence of anxiety and depression symptoms related to the COVID-19 pandemic has been reported in surveys from China, Italy, and Spain.[4,28,29] Associated risk factors reported include imposed isolation, younger age, female gender, excessive pandemic-related media exposure, and medical problems. This survey corroborated the effect of age; patients younger than 65 years reported disturbed sleep more frequently than their elders. They also reported new or worsening depression and anxiety more frequently, but this finding was not statistically significant.

Neurologic conditions characterized by acute episodic attacks represented over two-fifths of the survey responders. Patients who experience migraines accounted for 118 of the participants, of which 33% indicated a worsening of their headache frequency or severity. For patients with seizures or epilepsy, 35% reported 1 or more seizures in the weeks before their appointments. This percentage is similar to the proportion of patients with epilepsy reported in the literature who cannot achieve seizure freedom despite receiving anti-seizure medication.[30] Data on baseline seizure frequency for these patients is not available, so it cannot be determined if this finding represents increased seizure frequency. Significant stress levels are known triggers for both migraine and epilepsy; depressive symptoms are also associated with poor adherence to medical regimens; unrelenting migraine headaches or prolonged seizures are well-known reasons for emergency room (ER) visits.[31–34] Minimizing ER visits serves a dual purpose of decreasing the risk of contagion for the patient and decreasing the patient load on an already overburdened system.

Neurodegenerative conditions represented fewer survey respondents, with Alzheimer's disease accounting for 24 patients and Parkinson's disease for 13 patients. Although the numbers are small, more than one-third of patients with Alzheimer's disease or Parkinson's disease reported worsening symptoms. Of the patients with Parkinson's disease, 38.5% surveyed experienced a recent fall, the leading cause of fatal and nonfatal injuries in people older than 65 years.[35] Recent studies have shown worsening neuropsychiatric symptoms (eg, agitation, apathy, and aberrant motor activity) in patients with dementia during COVID-19 pandemic mandatory home confinement.[36] A survey of 38 patients with Parkinson's disease showed a statistically significant decline of physical activity compared to pre-lockdown levels; patients also experienced worse stress, depression, and anxiety.[37]

Limitations

This study cannot establish a direct causal relationship between the COVID-19 pandemic and changes investigated in this survey. However, survey questions were framed to ask patients to compare their current experiences to their experiences before March 2020, when the government interventions to prevent the spread of COVID-19 began. This data thus represents the patient's perception of the impact of the COVID-19 pandemic. This study only included patients who completed either a traditional or virtual visit at HPN during the survey period. People more significantly impacted by a loss of employment, loss of health insurance or changes to physical and mental health may not be well represented as they may not be able to attend appointments. Thus, this survey may underestimate changes during this period, and the generalizability of the results is limited. Nevertheless, the health and well-being of patients during this time may still be explored, and future studies will yield longitudinal results to provide more insight.

Conclusions

This survey provides important insights into patients' perception of changes to their health and lifestyle during the early months of the COVID-19 pandemic, aiding providers in implementing practice processes for quality improvement. This study suggests that patients with neurological conditions are susceptible to the psychological effects of a pandemic and strict public health strategies. Thus, it is important to actively screen patients for depression, anxiety, sleep disturbance, and adherence to treatment plans. Many surveyed patients reported worsening symptoms of their neurologic condition. Treatment plans need to include strategies to minimize symptom exacerbations and injuries, resulting in unnecessary hospital ER visits (eg, optimizing drug therapies, use of at-home rescue medications, and regular exercise and sleep routines). Increased utilization of telemedicine may improve access to health care and be already widely accepted by survey participants. The option for patients to have telemedicine follow-ups should be maintained after the pandemic.

Conflict of Interest

None of the authors identify a conflict of interest.

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2020 Writing Contest Post-graduate Winner

Impact of Pharmacists in Therapeutic Optimization Relative to the 2020 American Diabetes Association Standards of Medical Care in Diabetes Guidelines in Patients with Clinical Atherosclerotic Cardiovascular Disease

Donald Waddell PharmD, MS; Jarred Prudencio PharmD

Donald Waddell PharmD, MS

Donald Waddell was born and raised in West Virginia and moved to O'ahu in 2010. He received his B.S. in Mathematics and M.S. in Cell and Molecular Biology from the University of Hawai'i at Mānoa. He earned his Pharm.D. from The Daniel K. Inouye College of Pharmacy at the University of Hawai'i at Hilo in May of 2021 with a Certificate in Healthcare Research.

His winning manuscript, "Impact of pharmacists in therapeutic optimization relative to the 2020 American Diabetes Association Standards of Medical Care in Diabetes Guidelines in patients with clinical atherosclerotic cardiovascular disease," examines the role of the ambulatory pharmacist in optimizing patient therapy. Under the mentorship of Dr. Jarred Prudencio, Associate Professor of Pharmacy Practice at The Daniel K. Inouye College of Pharmacy, this research evaluated the therapeutic regimens of patients with both type II diabetes and atherosclerotic cardiovascular disease at a rural clinic in East Hawai'i. The data analysis showed statistically significant differences in therapeutic optimization between patients who had a pharmacist involved in their care versus those patients without a pharmacist involved in their care. This research not only reinforced the value of the ambulatory pharmacist as a member of the healthcare team but also allowed for an examination of potential factors associated with the differential prescribing practices of practitioners.

Abstract

In 2020, the American Diabetes Association (ADA) Standards of Medical Care in Diabetes Guidelines newly recommended adding a sodium-glucose cotransporter-2 (SGLT-2) inhibitor or a glucagon-like peptide 1 (GLP-1) receptor agonist in patients with both type 2 diabetes and atherosclerotic cardiovascular disease, regardless of hemoglobin A1c (HbA1c) levels. In this study, the primary objective was to assess the pharmacist's role in the therapeutic optimization of patients with both type 2 diabetes and atherosclerotic cardiovascular disease relative to the new recommendations. The secondary objectives were to assess other factors affecting therapeutic optimization and clinician familiarity with the recommendations. This study, conducted at the East Hawai'i Health Clinic, included 60 patients with type 2 diabetes and atherosclerotic cardiovascular disease. Anonymous surveys were sent to clinicians at the clinic to assess recommendation familiarity. Patients seen by a pharmacist were significantly more likely to be therapeutically optimized per the 2020 ADA guidelines than those not seen by a pharmacist. HbA1c and age also influenced SGLT-2/GLP-1 therapy use. All clinicians were more likely to prescribe SGLT-2/GLP-1 therapy for patients with uncontrolled HbA1c but were less likely to prescribe additional therapy for patients with controlled HbA1c, even in patients with previous atherosclerotic events.

Abbreviations and Acronyms

ADA = American Diabetes Association
ASCVD = atherosclerotic cardiovascular disease
CVOT = cardiovascular outcome trial
EHR = electronic health record
FDA = US Food and Drug Administration
GLP-1 = glucagon-like peptide 1
HbA1c = hemoglobin a1c
SGLT-2 = sodium glucose transporter-2
TZD = thiazolidinediones

Introduction

In the Centers for Disease Control and Prevention's 2020 National Diabetes Statistics Report, it is estimated that 10.2% of American adults were diagnosed with type 2 diabetes mellitus in 2018.[1] Atherosclerotic cardiovascular disease (ASCVD), which is collectively defined as coronary heart disease, myocardial infarction, stroke, and peripheral artery disease of atherosclerotic origin, is 1 of the leading causes of morbidity and mortality in patients with diabetes.[2] Other risk factors associated with ASCVD include dyslipidemia and hypertension, both of which are comorbidities commonly afflicting patients with diabetes.[3]

Before 2008, antihyperglycemic effects were the sole focus in the development and study of antidiabetic drugs. Improvements in hemoglobin A1c (HbA1c) values served as surrogate markers for improved microvascular outcomes, and cardiovascular risk assessment was based on investigator-reported adverse events. At this time, clinical trials were relatively short, ranging from 6 to 12 months.[4] These trials were also often performed in patients with newly onset diabetes; given the decreased duration of time with the disease, patient risk for adverse cardiac events was generally low.[4,5] In 2008, concerns with rosiglitazone, a medication belonging to the class of thiazolidinediones (TZDs), was found to be associated with a significant increase in the risk of

myocardial infarction and heart failure in patients and prompted the US Food and Drug Administration (FDA) to reevaluate the process through which it determines cardiovascular safety for antihyperglycemic medications.[5,6] In response, the FDA set forth a Guidance for Industry, specifying cardiovascular risk evaluation criteria in new antidiabetic therapies.[4] Drug developers would be required to demonstrate that the treatment does not result in an unacceptable increase in cardiovascular risk in patients. Specific recommendations outlined in the guidance include a recommendation for establishing an independent cardiovascular endpoints committee and the inclusion of patients deemed high-risk for cardiovascular events in phase 2 and 3 trials.[4] In 2018, the guidance was further modified, detailing specific durations that therapy must be studied in patients to assess safety and requiring more stringent patient criteria. At least 1500 patients should be exposed to the drug for at least 1 year, and at least 500 patients should be exposed to the new drug for at least 2 years to assess safety.[7]

The collection of trials for new medications developed following the FDA guidance are collectively referred to as cardiovascular outcomes trials (CVOTs). As a result of these trials, specific agents in 2 classes of medications, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and glucagon-like peptide 1 (GLP-1) agonists, demonstrated not only cardiovascular safety but also cardiovascular risk reduction. As the evidence supporting these findings increased, the value of SGLT-2 inhibitor and GLP-1 agonist therapy for more than just HbA1c lowering became more apparent. Currently, some medications are being examined in alternative therapeutic avenues outside of antidiabetic treatment, including to treat heart failure.[8]

GLP-1 receptor agonist medications are injectable (except for 1 oral formulation currently available) peptides that mimic the effects of incretin in the body. Incretins are released in response to the ingestion of food and regulate insulin secretion, glucagon inhibition, and gastric emptying, among other mechanisms.[9] Incretins generally have a short half-life in the body due to being broken down quickly by an enzyme called dipeptidyl peptidase-4, but the addition of exogenous incretin-mimetics allows for an increased duration of effect. The increase in insulin and decrease in glucagon serve to decrease blood sugar levels, while the delay in gastric emptying helps patients feel full longer and can lead to weight loss.[9]

SGLT-2 inhibitors are a class of oral medications that function in the kidney to prevent glucose reabsorption. These medications inhibit the sodium-glucose transport protein 2, which would generally reabsorb glucose and sodium, resulting in a net decrease of glucose in the body. SGLT-2 inhibitors have also been shown to promote weight loss and natriuresis, which may reduce blood pressure.[10]

The 2019 American Diabetes Association (ADA) Standards of Medical Care in Diabetes Guidelines recommend metformin as the first-line treatment for patients with type 2 diabetes, and a GLP-1 receptor agonist or SGLT-2 inhibitor as a second-line option if the patient's HbA1c is not sufficiently controlled on metformin and they have a history of clinical ASCVD. In 2020, the ADA updated this recommendation, given the new evidence from various CVOTs. Metformin remains first-line therapy, but in patients with indicators of high-risk or established ASCVD, regardless of HbA1c, a GLP-1 receptor agonist or SGLT-2 inhibitor is recommended to be added to their regimen for cardiovascular risk reduction.[11]

These recommendations are relatively new, and the concept of adding therapy when HbA1c is already controlled is also novel in type 2 diabetes. For these reasons, this research project sought to identify if patients at the East Hawai'i Health Clinic were appropriately prescribed SGLT-2 inhibitor or GLP-1 agonist therapy as recommended by the 2020 ADA guidelines, and specifically the pharmacist's role in therapeutic optimization.

Methods

This retrospective study was conducted at the East Hawai'i Health Clinic, a primary care clinic where clinical pharmacists from the University of Hawai'i work as part of the interdisciplinary team alongside medical residents, nurse practitioners, and faculty physicians to provide comprehensive medication management; clinical pharmacists work under a progressive, collaborative practice agreement. Patients are referred to the clinical pharmacists' care by their primary care provider for more complex and comprehensive medication management of chronic conditions. Institutional review board approval was procured under protocol ID 2020-00041.

Patient data were examined via the institution's electronic health record (EHR) and visit information between May 2017 and April 2020 was assessed. Patients were included in the study if they were diagnosed with type 2 diabetes and a confirmed clinical atherosclerotic event: coronary artery disease, peripheral artery disease, myocardial infarction, or stroke. There were no exclusion criteria.

The primary objective of this study was to evaluate the pharmacist's role in therapy optimization for patients with type 2 diabetes and ASCVD relative to the 2020 ADA guideline. This objective was assessed by comparing the prescribing rates of SGLT-2 inhibitors and GLP-1 agonists for patients managed by a clinical pharmacist versus those without a pharmacist involved in their care in this sample population.

The secondary outcomes included assessing other factors affecting the use of SGLT-2/GLP-1 therapy in the described patient populations and examining prescriber familiarity with the most recent ADA guidelines. Demographic information, including age, sex, weight, and laboratory values such as HbA1c, estimated glomerular filtration rate, and urine albumin-to-creatinine ratio,

were examined. Other factors assessed include the number of clinic visits and additional medication regimen components: other antihyperglycemic medications, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, HMG-CoA reductase inhibitors, beta-blockers, and aspirin. Continuous variables were analyzed using a *t*-test, and categorical variables were examined using Fisher's exact test.

A 10-question, anonymous survey was disseminated by email via SurveyMonkey to assess clinician likelihood of implementing the 2020 ADA guidelines into general practice. All 29 clinicians were sent the survey, including ambulatory care pharmacists, medical residents, and faculty physicians employed at the East Hawai'i Health Clinic. The questions were developed by the primary author and reviewed by the supervising pharmacist who is credentialed in diabetes management. Questions in the survey addressed respondent demographics, including professional position and time spent practicing as a medical professional, self-rated familiarity with current and previous ADA recommendations, familiarity with the diabetes CVOTs, and general prescribing practices relative to critical scenarios. Respondents ranked their familiarity via a 5-point Likert scale and ranked drug prescribing preferences given scenarios on a 4-point Likert scale.

Results

A total of 60 patients were identified with type 2 diabetes and ASCVD and included in the analysis (Figure 1). Of these, 32 patients had been seen by a clinical pharmacist at the East Hawai'i Health Clinic as part of their healthcare team, while a clinical pharmacist had not seen the remaining 28. Of the 32 patients, 14 (44%) were appropriately prescribed SGLT-2/GLP-1 therapy, as recommended by the 2020 ADA Guidelines compared to 4 of the 28 (14%) patients prescribed SGLT-2/GLP-1 therapy who had not been seen by a pharmacist (P=.02).

In assessing secondary outcomes, significance was also detected when examining the difference in age of patients prescribed SGLT-2/GLP-1 therapy (Table 1). The mean age of patients prescribed the target medications was 57.67 years, while the age of those not prescribed SGLT-2/GLP-1 therapy averaged 66.79 years (P=.006). Significance was also detected when examining baseline HbA1c as a factor associated with differential SGLT-2/GLP-1 therapy use (Table 2). For the patients who would eventually be placed on SGLT-2/GLP-1 therapy, their pre-SGLT-2/GLP-1 HbA1c values averaged 9.62%, while the patients who were not on SGLT-2/GLP-1 therapy averaged 7.14% (P<.001). The most recent mean HbA1c of the patients seen by the pharmacist was 7.64%, while the mean HbA1c for patients who the pharmacist did not see was roughly 6.86% (P=.05). This difference of approximately 0.8%, although not statistically significant, is trending towards significance and is clinically relevant.

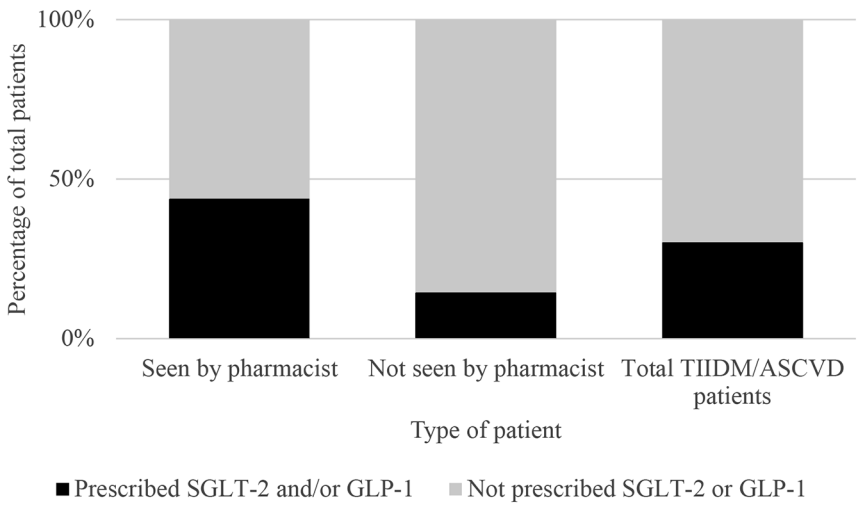

Figure 1. This figure illustrates the number of patients seen by a pharmacist who are on SGLT-2 inhibitor or GLP-1 therapy versus those who are not. It also compares the number of patients not seen by a pharmacist who are on the target therapies versus those who are not.

Table 1. Mean Age of Patient Subgroups by Their Drug Therapies and Pharmacy Status		
	Mean age (years)	***P* value**
Total	64.04	
SGLT-2 patients	56.83	.73
GLP-1 patients	58.53	
SGLT-2 and/or GLP-1 patients	57.67	.006
Non-SGLT-2/GLP-1 patients	66.79	
Pharmacy patients	64.06	.99
Non-pharmacy patients	64.04	

Table 2. Most Recent Mean Hemoglobin A1c Values of Patient Subgroups by Their Drug Therapies and Pharmacy Status		
	Mean HbA1c (%)	***P value***
Total (most recent)	7.27	
SGLT-2 and/or GLP-1 patients (Pre-SGLT-2/GLP-1)	9.62	.001
Non-SGLT-2/GLP-1 patients (most recent)	7.14	
SGLT-2 and/or GLP-1 patients (most recent)	7.85	.07
Non-SGLT-2/GLP-1 patients (most recent)	7.14	
Pharmacy patients (most recent)	7.64	.054
Non-pharmacy patients (most recent)	6.86	

Finally, of the 60 patients with type 2 diabetes and ASCVD, a total of 42 were not on target therapy (Figure 2). There were various reasons for this, the most common being that the patients were currently controlled (defined here as HbA1c < 7%) on their regimen. Fifteen patients (36%) were considered controlled on their current regimen. Other reasons include contraindication to target therapy due to chronic kidney disease, contraindication due to current therapeutic interactions, combinations of the reasons above, or there may have been no apparent reason that the patient was not on the targeted therapy.

Of the emailed surveys, a total of 15 responses were received out of 29 target recipients. Among those that responded were 3 faculty physicians, 8 medical residents, and 4 clinical pharmacists (Table 3). All respondents rated themselves as "somewhat familiar" or greater with the 2019 ADA Guidelines, and the majority, 73%, were "somewhat familiar" with the 2020 ADA Guidelines. Overall, pharmacists were more likely to self-assess as "very familiar" or "extremely familiar" with the material regarding guidelines and trials than other respondents. In contrast, medical residents were more likely to self-assess as "somewhat familiar" or "not so familiar."

Given a patient case with a patient diagnosed with diabetes with an uncontrolled HbA1c of 8.5% and a past myocardial infarction who is already prescribed a maximum metformin dose, all respondents were either "likely" or "extremely likely" to introduce a second therapeutic agent, with SGLT-2 inhibitors or GLP-1 agonists most chosen (Figure 3). Pharmacists preferred SGLT-2/GLP-1 therapy relative to other practitioners, with all pharmacists surveyed "extremely likely" to add a GLP-1 agonist. When given a patient with a controlled HbA1c of 6.5%

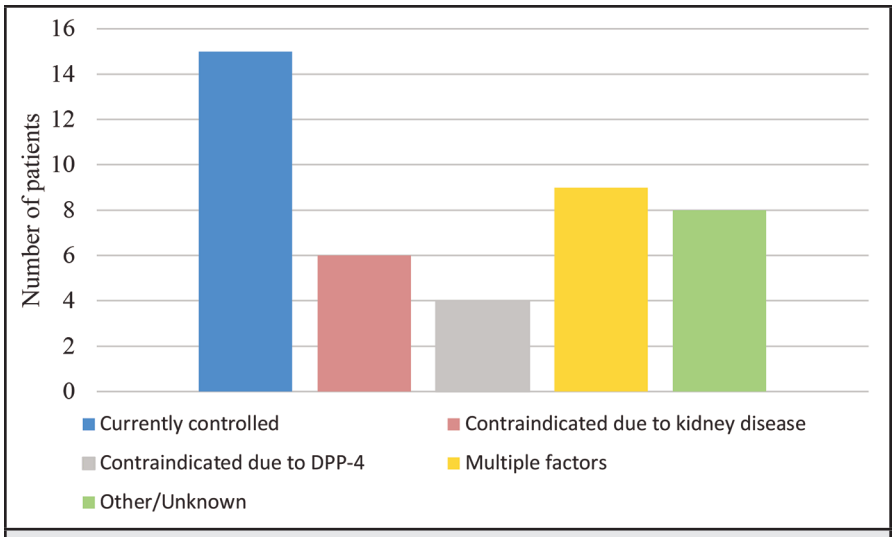

Figure 2. This figure illustrates the various factors influencing the lack of SGLT-2/GLP-1 use in the 42 patients with clinical atherosclerotic cardiovascular disease and type II diabetes that are not currently prescribed target therapy.

and a past myocardial infarction or a patient with HbA1c of 6.5% with no history of but at high risk for ASCVD, the likelihood of adding SGLT-2/GLP-1 therapy was much lower than in the uncontrolled patient for all practitioners (Figures 4 and 5). The likelihood of prescribing additional therapy was also similar between the controlled patient with a history of ASCVD and the controlled patient without a history of ASCVD for all practitioners.

Table 3. Responses to Survey Background Information

Survey Question	Response	Number of Respondents
Which best describes you as a medical professional?	Faculty physician	3
	Medial resident	8
	Pharmacist	4
How long have you practiced as a medical professional?	3 years or less	7
	Between 3 and 10 years	5
	10 years or more	3

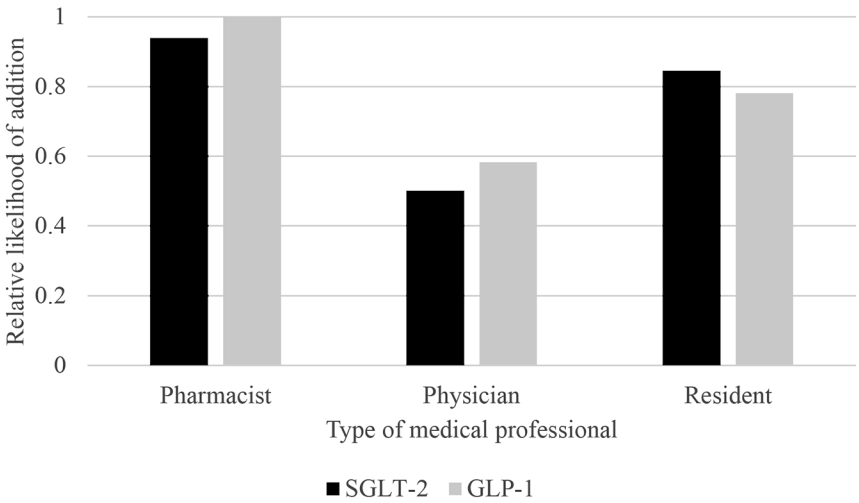

Figure 3. The figure illustrates the relative likelihood of prescribing an SGLT-2 inhibitor or GLP-1 agonist in a 60-year-old patient with a hemoglobin A1c of 8.5% currently maxed on metformin with a history of myocardial infarction but otherwise healthy.

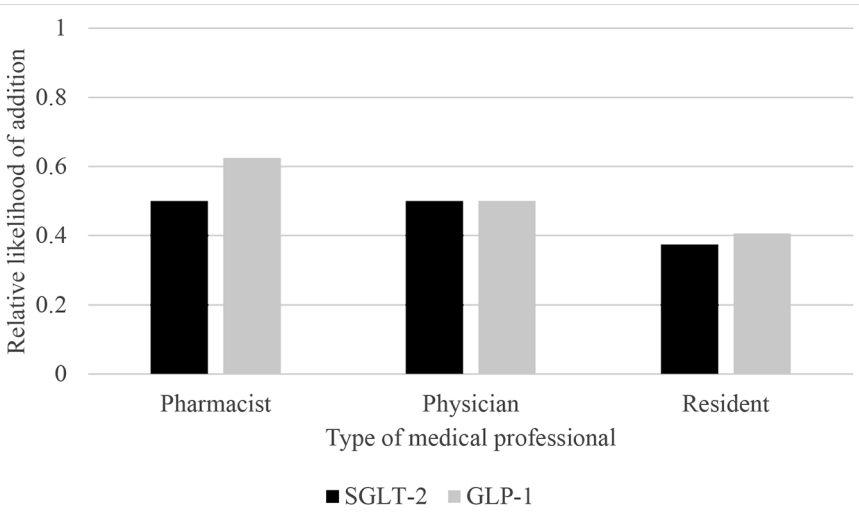

Figure 4. This figure illustrates the relative likelihood of prescribing an SGLT-2 inhibitor or GLP-1 agonist in a 60-year-old patient with a hemoglobin A1c of 6.5% currently maxed on metformin with a history of myocardial infarction but otherwise healthy.

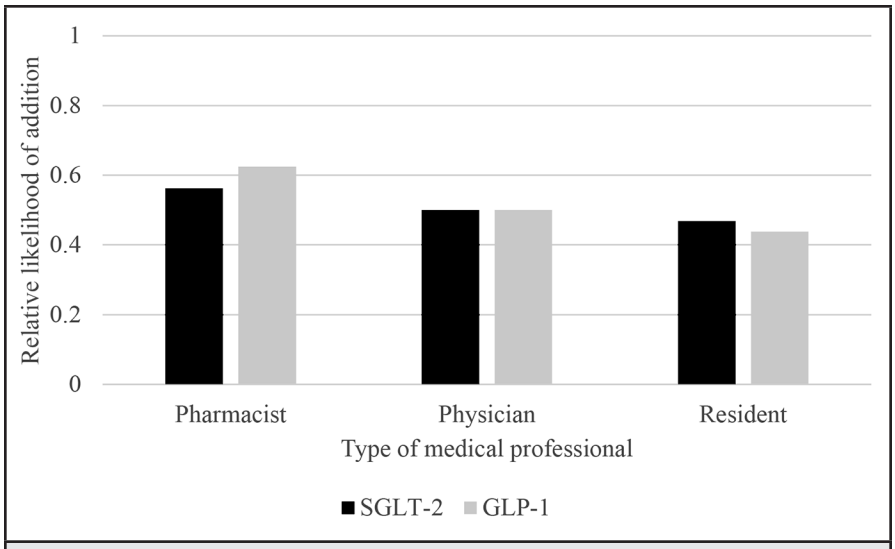

Figure 5. This figure illustrates the relative likelihood of prescribing an SGLT-2 inhibitor or GLP-1 agonist in a 60-year-old patient with a hemoglobin A1c of 6.5% currently maxed on metformin with no history of atherosclerotic cardiovascular disease (ASCVD) but at high risk for ASCVD.

Discussion and Conclusion

Patients with both type 2 diabetes and ASCVD with a pharmacist involved in their care at the East Hawai‘i Health Clinic are significantly more likely to be placed on SGLT-2/GLP-1 therapy as recommended by the 2020 ADA Guidelines. The ADA annually updates its recommendations and given that diabetes management is primarily medication-based, the pharmacist can play a vital role in managing this disease state. Multiple factors may contribute to the disparity between therapeutic optimization between patients seen versus not seen by a pharmacist.

At the East Hawai‘i Health Clinic, patients are referred to a pharmacist's care by their primary care provider. These patients are generally more complex and require intense medication management for their chronic conditions. They may present with significant adherence barriers, varying degrees of treatment resistance, or other factors. It could be that clinically, these patients require SGLT-2 or GLP-1 therapy as part of their HbA1c lowering regimen regardless of ASCVD benefit. The propensity for more complex patients may also contribute to the difference in HbA1c seen in patients with a pharmacist involved in their care versus those without a pharmacist involved in their care.

Looking at age as a factor influencing SGLT-2/GLP-1 therapy, patients with the target therapies have a mean age of 58 years while patients without have a mean age of 67 years. There may be multiple factors influencing this result, the first of which may be the guidelines themselves. As patients age, they develop more comorbidities, and the benefit of aggressive diabetes treatment begins to lessen as the risk of hypoglycemia becomes more prevalent. The 2020 ADA Guidelines recommend a less stringent HbA1c goal of less than 8% in older patients. Alternatively, more aggressive treatment may be warranted in younger individuals to prevent complications associated with diabetes. These patients typically have HbA1c goals lower than 7%, as long as they may be achieved with minimal hypoglycemic risk. Additionally, SGLT-2 inhibitors carry common side effects such as urinary tract infections or dizziness, and GLP-1 agonists have gastrointestinal upset, appetite suppression, and weight loss as common side effects. Some clinicians may view these risks as outweighing the benefits in some patients, especially older adults.

The HbA1c values for the SGLT-2/GLP-1 patients before initiating their therapy were significantly higher than the current HbA1c value of patients not on SGLT-2/GLP-1 therapy. This finding suggests again that SGLT-2 inhibitors and GLP-1 agonists may be utilized primarily for their HbA1c lowering potential with an added benefit of ASCVD risk lowering.

Of the 60 patients at the clinic with type 2 diabetes and ASCVD, 42 were not on the target SGLT-2/GLP-1 therapy. Fifteen of these 42 were considered controlled on their current therapy and did not require additional therapeutics. Patients with a controlled HbA1c in previous guidelines had not been recommended additional medications, but the 2020 ADA Guidelines newly recommend SGLT-2 or GLP-1 therapy in patients, regardless of HbA1c, with type 2 diabetes and a history of ASCVD. Although these patients' HbA1c levels were considered controlled, there may have been other factors influencing the lack of SGLT-2/GLP-1 use.

Most of the prescribers at the clinic are unlikely to prescribe an additional medication to patients with both type 2 diabetes and ASCVD with a currently controlled HbA1c. Although some of these prescribers are familiar with the new recommendations and associated trials, the evidence may not be compelling enough to justify the addition in every situation. There may also be situations where patients are not amenable to additional therapy, especially injectable therapy such as a GLP-1 agonist; insurance issues may prevent the addition of SGLT-2/GLP-1 therapy as well.

Ten of the patients had a contraindication to one of the two therapeutic options. Patients with severe chronic kidney disease have a contraindication to SGLT-2 inhibitors. Patients currently being treated with a drug in a class of medications known as dipeptidyl peptidase-4 inhibitors should not be placed on GLP-1 agonists due to overlap in the mechanism of action. Eight of the patients not currently on SGLT-2 inhibitor or GLP-1 agonist therapy had no clear indication in their chart for the lack of medication. There may be patient-specific factors at play, such as a refusal to inject themselves or insurance issues. These eight patients are critical patients to follow up with for medication management.

This analysis does carry limitations. Since this was a retrospective EHR review and patients were not contacted or interviewed as part of this study, there may be pieces of the clinical picture that were not depicted in the analysis. Another limitation would be the relatively small number of survey responses in examining clinician familiarity and prescriptive preferences.

In conclusion, the clinical pharmacist plays an important role in optimizing patient care at the East Hawai‘i Health Clinic; there were significantly more patients on ADA-recommended therapies when a pharmacist was directly involved in patient care. However, there are other factors that may influence the use of SGLT-2/GLP-1 therapy in the target population. It is vital to understand that although the ADA 2020 guidelines are evidence-based recommendations, healthcare providers must adjust medication regimens according to patient-specific factors. The next steps in this research project include follow-up of the individual patients identified and discussion with the clinicians to identify if medication adjustments following the 2020 ADA guidelines would be appropriate.

Conflict of Interest

None of the authors identify any conflict of interest.

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Appendix

Survey

Question 1.
Which of the following best describes you as a medical professional?
A. Faculty Physician
B. Medical Resident
C. Pharmacist

Question 2.
How long have you practiced as a licensed medical professional?
A. 3 years or less
B. Between 3 and 10 years
C. 10 years or more

Question 3.
How would you rate your familiarity with the 2019 American Diabetes Association Standards of Medical Care in Diabetes, Pharmacologic Treatment Guidelines?
A. Extremely familiar
B. Very familiar
C. Somewhat familiar
D. Not so familiar
E. Not at all familiar

Question 4.
How would you rate your familiarity with the 2020 American Diabetes Association Standards of Medical Care in Diabetes, Pharmacologic Treatment Guidelines?

A. Extremely familiar
B. Very familiar
C. Somewhat familiar
D. Not so familiar
E. Not at all familiar

Question 5.
How would you rate your familiarity with the cardiovascular outcomes trials (CVOTs) relating to diabetes medications?

A. I have read the majority of the CVOTs
B. I have read a few of the CVOTs
C. I have listened to presentations or completed CE's on this topic
D. I have heard the general outcomes
E. I have not heard of these trials

Question 6.
How often do you prescribe the following drug classes as second-line therapy (after metformin) in patients diagnosed with uncontrolled type II diabetes mellitus:

SGLT-2 Inhibitors?
A. Greater than 75% of the time
B. Between 50% and 75% of the time
C. Between 25% and 50% of the time
D. Less than 25% of the time

DPP-4 Inhibitors?
A. Greater than 75% of the time
B. Between 50% and 75% of the time
C. Between 25% and 50% of the time
D. Less than 25% of the time

GLP-1 Agonists?
A. Greater than 75% of the time
B. Between 50% and 75% of the time
C. Between 25% and 50% of the time
D. Less than 25% of the time

TZDs?
A. Greater than 75% of the time
B. Between 50% and 75% of the time
C. Between 25% and 50% of the time
D. Less than 25% of the time

Sulfonylureas?
A. Greater than 75% of the time
B. Between 50% and 75% of the time
C. Between 25% and 50% of the time
D. Less than 25% of the time

Question 7.
Given a 60 year old patient currently taking metformin ER 1000mg BID with an A1c of 8.5% and a history of myocardial infarction but otherwise healthy, rate the likelihood with which you would prescribe the following:

SGLT-2 Inhibitors?
A. Extremely likely
B. Likely
C. Unlikely
D. Extremely unlikely

Sulfonylureas?
A. Extremely likely
B. Likely
C. Unlikely
D. Extremely unlikely

GLP-1 Agonists?
A. Extremely likely
B. Likely
C. Unlikely
D. Extremely unlikely

DPP-4 Inhibitors?
A. Extremely likely
B. Likely
C. Unlikely
D. Extremely unlikely

TZDs?
A. Extremely likely
B. Likely
C. Unlikely
D. Extremely unlikely

No additional medications?
A. Extremely likely
B. Likely
C. Unlikely
D. Extremely unlikely

Question 8.
Given a 60 year old patient currently taking metformin ER 1000mg BID with an A1c of 6.5% and a history of myocardial infarction but otherwise healthy, rate the likelihood with which you would prescribe the following:

SGLT-2 Inhibitors?
A. Extremely likely
B. Likely
C. Unlikely
D. Extremely unlikely

DPP-4 Inhibitors?
A. Extremely likely
B. Likely
C. Unlikely
D. Extremely unlikely

GLP-1 Agonists?
A. Extremely likely
B. Likely
C. Unlikely
D. Extremely unlikely

TZDs?
A. Extremely likely
B. Likely
C. Unlikely
D. Extremely unlikely

Sulfonylureas?
A. Extremely likely
B. Likely
C. Unlikely
D. Extremely unlikely

No additional medications?
A. Extremely likely
B. Likely
C. Unlikely
D. Extremely unlikely

Question 9.
Given a patient currently taking metformin ER 1000mg BID with an A1c of 6.5% at high risk for ASCVD (age 55 or older with coronary, carotid, or lower extremity artery stenosis) but otherwise healthy, rate the likelihood with which you would prescribe the following:

SGLT-2 Inhibitors?
A. Extremely likely
B. Likely
C. Unlikely
D. Extremely unlikely

GLP-1 Agonists?
A. Extremely likely
B. Likely
C. Unlikely
D. Extremely unlikely

Sulfonylureas?
A. Extremely likely
B. Likely
C. Unlikely
D. Extremely unlikely

TZDs?
A. Extremely likely
B. Likely
C. Unlikely
D. Extremely unlikely

DPP-4 Inhibitors?
A. Extremely likely
B. Likely
C. Unlikely
D. Extremely unlikely

No additional medications?
A. Extremely likely
B. Likely
C. Unlikely
D. Extremely unlikely

10. Thank you very much for taking the time to complete the survey. Please enter any general comments you have on the medications, survey questions, or cases.

Rapid Response: The Development of Just-in-Time Education for Nursing Clinicians and Students

Lorrie Wong PhD, RN, CHSE-A; Kristine Qureshi PhD, RN, CEN, PHNA-BC, FAAN; Gary Glauberman PhD, RN, PHNA-BC, NHDP-BC; Michele Bray DNP, RN, PHNA-BC; Katherine Finn Davis PhD, RN, APRN, CPNP, FAAN; Laura Reichhardt, MS, APRN, AGPCNP-BC

The Spotlight on Nursing is a recurring column from the Nancy Atmospera-Walch School of Nursing, University of Hawai'i at Mānoa (NAWSON). It is edited by Mary G. Boland DrPH, RN, FAAN, Former Dean of NAWSON; and Joanne R. Loos PhD, Science Writer for NAWSON.

Introduction

When the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) a global pandemic on March 11, 2020, the world knew little about severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the agent that causes COVID-19 disease. Health professionals, workers, and students were called to action to help slow the spread of a disease about which there was minimal knowledge. Many of them had little to no experience working with a novel pathogen, using/reusing isolation-level personal protective equipment (PPE), or dealing with acute shortages of PPE. Further, the public health principles of emergency preparedness and disaster response, including crisis standards of care, were unfamiliar to students, faculty, and practicing nurses. This column describes the rapid response of a public nursing school and its partners to develop, deliver, and evaluate just-in-time education for nurses and nursing students. The lessons learned from this experience will be useful to those developing just-in-time education in the first stage of a future pandemic.

Program

As the major public educator for entry-level and advanced practice nurses for the state of Hawai'i, the University of Hawai'i Nancy Atmospera-Walch School of Nursing (NAWSON), formerly the School of Nursing and Dental Hygiene, mobilized immediately. Nursing faculty rapidly developed an online, on-demand training program targeted to nurses and nursing students in Hawai'i and other states. In partnership with the Hawai'i State Center for Nursing (henceforth: Center) and the University of Hawai'i at Mānoa Outreach College, the faculty provided the expertise to develop, deliver, and evaluate program content in a modular format. The program, "Nursing During Pandemics-COVID-19," was designed to serve as an easily accessible online training that did not require a large time commitment to complete. Content focused on the SARS CoV-2 pathogen, provided the basic principles of public health that guide pandemic response, outlined health care workplace safety practices, illustrated proper procedures for the use of PPE, crisis standards of care, and discussed responder stress. The Center ensured content integrity and supported the evaluation process. It also provided continuing nursing education (CNE) credits as an American Nurses Credentialing Center (ANCC) accredited provider of nursing continuing professional development. Outreach College provided the online platform to host the modules and managed registration.

The Planning Committee, which consisted of the partners described above, determined the target audience would be nurses and nursing students in Hawai'i, although the content could be applicable to nurses in other states. Two nursing faculty members with extensive clinical experience and expertise in global health, public health, emergency response, and disaster management developed the initial program. Content experts from nursing, medicine, and public health then reviewed each of the program's 4 modules (Table 1). Each module required between 30 and 60 minutes to complete, and the modules could be completed separately. Outreach College offered the online, asynchronous program at no cost to participants. The Center provided participants the option to receive CNE credit for successful completion of each module, which could be used toward continuing competency requirements for licensed nurses. The program launched on April 12, 2020 and was available online on-demand through April 11, 2021. Participants provided demographic information related to location upon registering and subsequently provided information about professional licensures or student status in the evaluation. Only participants who completed an evaluation and met minimum post-test scores received CNE certificates.

Table 1. Nursing During Pandemics-COVID-19 Curriculum Overview	
Objective	**Content**
Module 1 Basic overview of COVID-19 and public health response	
Upon completion of the module, the learner will be able to: ● Identify key concepts for epidemic or pandemic prevention, detection, response, and recovery ● Use COVID-19 as a case example for epidemics and pandemics ● Summarize how to work within the US Federal Emergency Management Agency (FEMA) Incident Command System (ICS)	● Pandemics: historical context and impact on social determinants of health and populations ● COVID-19: overview of SARS-CoV-2 epidemiology ● Sources of reliable information about the disease ● Details about the virus ● Basic principles of epidemiology related to pandemic detection and response ● Public health response ● Public health system emergency response
Module 2 COVID-19 infection prevention and worker safety	
Upon completion of the module, the learner will be able to: ● Identify strategies to assure their own safety and well-being while providing care in the health care or community settings	● General principles of infection prevention ● Health care worker safety strategies during pandemic response ● Proper use of PPE for COVID-19 ● PPE supply issues and strategies to conserve ● Crisis standards of care ● Health care worker self-care resources
Module 3 Concepts of epidemiology that inform nursing response during pandemics	
Upon completion of the module, the learner will be able to: ● Identify strategies for nursing care during pandemics and epidemics	● Key public health concepts related to prevention, detection and response for pandemics (community burden of disease terms, disease states, modes of transmission and chain of infection, reproductive number, and herd immunity ● Screening and testing ● Nurses' strategies as part of a response team: pre-, peri-, and post-deployment, responder mental health protection ● Specific nursing roles in pandemics: contact tracing and case investigation, point of dispensing (POD) operations, triage, hotlines, mass care, and home care
Module 4 Practice, legal, moral issues and nursing preparedness	
Upon completion of the module, the learner will be able to: ● explain how to make a decision that is guided by legal and ethical principles and responsibilities ● explain how to assure personal and family preparedness	● Crisis standards of care ● Communication during difficult times ● Ethical considerations ● Serving as a volunteer ● Personal and family preparedness ● Moving on: expected impact of COVID-19 on individuals, families, populations, nations and the world

The committee piloted the program content with nursing students and faculty, making adjustments accordingly. Committee members consulted with all Hawai'i schools of nursing and their clinical practice partners statewide, who determined that these modules were essential to safe nursing practice. Every nursing school in the state required all 4 modules be completed prior to clinical education. The Healthcare Association of Hawai'i (HAH), the statewide organization representing hospitals, hospice, long-term care, and other healthcare organizations, also required health care students to complete module 2, which focused on PPE and worker safety, before entry into any clinical settings in the state. Some health care facilities also required completion of these modules by their staff.

Evaluation and Results

Across the 4 modules, 6538 certificates were earned. Overall, 84% of participants were in Hawai'i, 13% were in other US states or territories, and an additional 3% were international or of unknown origin. Slightly more than half (55%) were nursing students. The vast majority of nursing students (96%) reported they were enrolled in Hawai'i nursing schools.

A 5-point Likert scale (from Strongly Disagree to Strongly Agree) was used for questions about meeting the module learning objectives. Overall the training program was rated very highly: at least 94% of participants agreed or strongly agreed that they met each objective. Table 2 provides a summary of the key learning objectives and the level of agreement indicating the objectives were met.

Participants answered open-ended questions to provide feedback about the program. Findings indicate the program was beneficial on multiple levels. Attendees noted that the program strengthened their knowledge about COVID-19. They also felt more prepared to keep themselves and their communities safe and healthy.

One participant wrote: "*Overall, [the training] was very helpful and informative regarding nursing responsibilities/roles,*

Table 2. Nursing During Pandemics-COVID-19 Module Objective Results	
Objective	**N%**
Module 1 Basic overview of COVID-19 and public health response (n = 1594)	
I am able to identify key concepts for epidemic or pandemic prevention, detection, response, and recovery.	Strongly Disagree 2% Disagree 0% Neutral 1% Agree 38% Strongly Agree 59%
I am able to use COVID-19 as a case example for epidemics and pandemics.	Strongly Disagree 2% Disagree 0% Neutral 2% Agree 36% Strongly Agree 61%
I am able to summarize how to work within the US Federal Emergency Management Agency (FEMA) Incident Command System (ICS).	Strongly Disagree 2% Disagree 0% Neutral 4% Agree 46% Strongly Agree 48%
Module 2 COVID-19 infection prevention and worker safety (n = 2032)	
I am able to identify strategies to assure my own safety and well-being while providing care in the health care or community settings.	Strongly Disagree 1% Disagree 0% Neutral 2% Agree 37% Strongly Agree 60%
Module 3 Concepts of epidemiology that inform nursing response during pandemics (n = 1427)	
I am able to identify strategies for nursing care during pandemics and epidemics.	Strongly Disagree 0% Disagree 0% Neutral 1% Agree 39% Strongly Agree 59%
Module 4 Practice, legal, moral issues and nursing preparedness (n = 1413)	
I am able to explain how to make a decision that is guided by legal and ethical principles and responsibilities.	Strongly Disagree 1% Disagree 0% Neutral 2% Agree 41% Strongly Agree 56%
I am able to explain how to assure personal and family preparedness.	Strongly Disagree 1% Disagree 0% Neutral 2% Agree 40% Strongly Agree 57%

preparedness and safety during the COVID-19 pandemic. These modules helped to further my knowledge as this information is beneficial and can assist me in my nursing career."

Another participant stated: "*This module was engaging because it was giving real world examples of what a person might actually say. The information presented seemed very relevant to what's going [on] right now and made me feel prepared for a possible similar situation.*"

Discussion and Implications

Expedient implementation of this program supported professional development of Hawai'i's nursing workforce (including students) as they responded to the COVID-19 pandemic. The program standardized basic information, established shared goals for education and emergency response, and validated shared decision-making for the statewide nursing academic-practice community in a time of great uncertainty.

By quickly responding to knowledge and skill gaps, the program helped to establish a statewide baseline for nursing students, faculty, and nurses engaged in COVID-19 response in clinical settings. It clarified standards of practice for nursing personnel safety and public health response. The program also provided a starting point for nursing education and practice partners to develop shared clinical re-entry requirements after nursing students' clinical experiences were suspended during the initial months of the pandemic.

Conclusion

Swift development of nursing education materials supported learner needs and facilitated a collaborative and responsive environment among partners in a geographically isolated state. Outcome measures designed to assess the broad dissemination and educational value of the modules validated statewide engagement within the clinical education setting and provided valuable data related to students' self-assessed achievement of module objectives.

National and local attention to these modules, including by the HAH and recognition as an exemplar by the American Association of Colleges of Nursing (AACN), attracted additional users and expanded the program's reach and impact. The program was retired after 1 year due to the emergence of new evidence and increasing availability of comparable training.

The program's success demonstrated that the rapid development of online learning materials is a successful strategy for providing just-in-time training for nurses, nursing students, and other health care students and practicing professionals in the emergent phase of a global pandemic. Further, the online dissemination of free materials provides immediate access not only to the Hawai'i target audience but also to enrollees from around the globe seeking information during the initial phase of a global pandemic. The lessons learned from this effort can be used to guide just-in-time training during the emergence of future pandemics.

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Style Guide for the Use of Native Hawaiian Words and Diacritical Markings

The HJH&SW encourages authors to use the appropriate diacritical markings (the ‘okina and the kahakō) for all Hawaiian words. We recommend verifying words with the Hawaiian Language Dictionary (http://www.wehewehe.org/) or with the University of Hawai‘i Hawaiian Language Online (http://www.hawaii.edu/site/info/diacritics.php).

Authors should also note that Hawaiian refers to people of Native Hawaiian descent. People who live in Hawai‘i are referred to as Hawai‘i residents.

Hawaiian words that are not proper nouns (such as *keiki* and *kūpuna*) should be written in italics throughout the manuscript, and a definition should be provided in parentheses the first time the word is used in the manuscript.

Examples of Hawaiian words that may appear in the HJH&SW:

‘āina	***Mānoa***
ali‘i	***Māori***
Hawai‘i	***Moloka‘i***
kūpuna	***O‘ahu***
Kaua‘i	***‘ohana***
Lāna‘i	***Wai‘anae***

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