A Literature Review of Pain Management and Opioid Use: Approach to Formalize Psychological and Behavioral Characteristics in a Virtual Human Patient Simulation

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Objective. To acquire clinical data on pain management and opioid use disorder in order to provide the relevant artificial intelligence content and foundation to help develop a virtual human patient simulation model.
Methods. A systematized search of the PubMed database was conducted using search terms related to opioid drugs and psychological and behavioral processes. A stepwise approach was used to refine and limit search terms and keywords based on the number of results returned. Resulting articles were extracted and used to derive "if-then rules" that reflect each psychological or behavioral change influenced by opioid use.
Results. A search from January 2017 to February 2018 identified 62 full-text articles that were included in the literature review. 273 "if-then rules" were derived, with 247 focusing on psychological processes and 26 focusing on behavioral processes. A number of studies involved methadone (33.9%), multiple opioids (24.2%), and buprenorphine (22.6%). Opioid dependence was reported in 41.9% of the studies.
Conclusion. This literature review supports the rising interest in opioid replacement therapy, most notably in methadone and buprenorphine, in light of the U.S. opioid epidemic in recent years. Additional research is needed to focus on the effects of opioids on behavioral processes.

INTRODUCTION

Today, there is an increased demand for the pharmacy profession and curricula to focus on the development of patient care skills, with emphasis on patient-centered care. The Accreditation Council for Pharmacy Education (ACPE) Guidance of Standards 2016 recommends pharmacy curricula to incorporate self-directed, active learning strategies to facilitate learning experiences and improve learning outcomes.[1] To address this recommendation in the pharmacy curricula, virtual human (VH) patient simulation has been used to teach chronic disease management,[2] assess learner core competencies prior to Advanced Pharmacy Practice Experiences (APPE),[3] and promote self-directed learning with various disease states, such as postoperative nausea and vomiting and anemia of chronic kidney disease.[4]

For the purpose of this study, VH simulation can be defined as a "computer-generated three-dimensional (3-D) model that simulates real-life clinical scenarios and patient encounters".[5] VH simulation has many functional layers. With artificial intelligence (AI) and natural language processes, simulation can provide a platform to develop interpersonal skills with virtual patients that can be translated into highly effective patient-provider interaction with real patients.[6] VH

simulation enables learners to take on the roles of healthcare providers to obtain a medical history, conduct a physical exam, and make diagnostic and therapeutic decisions.[7] By repeatedly exposing learners to an extensive list of clinical variation, some researchers argued that VH simulation can help reinforce core knowledge and foster clinical reasoning processes to help learners to consider alternative options, reflect on a case's objectives, and contrast with other cases.[8] With the recent advances in educational technologies and rapidly changing landscape of health education, simulation represents a unique opportunity to teach and train tomorrow's health professionals. Considering that nearly all schools and colleges of pharmacy in the U.S. reported using some type of educational technology in 2011, it can be proposed that the use of VH simulation is an especially important consideration for the field of pharmacy and pharmacy education.[9]

This current study is a component of a larger study focused on developing a VH simulation to teach and train in pain management. To our knowledge, there is limited use of VH simulation in pharmacy education that targets pain management, with emphasis on opioid use disorder. Opioids are a class of natural and synthetic chemicals that are frequently prescribed to help alleviate moderate-to-severe pain associated with medical disease or condition, injury, or medical treatment. Although the benefits of opioids outweigh the risks with intended use, the misuse and abuse of these medications often predispose patients to more serious risks, such as physical dependence and overdose.[10] In 2013, the overall healthcare cost of prescription opioid overdose, abuse, and dependence was estimated to exceed $78.5 billion per year.[10] In 2014, approximately 2 million Americans reported dependence or abuse of prescription opioids.[11] Today, the opioid epidemic remains one of the most prevailing healthcare issues facing the U.S. According to the CDC, 115 Americans die from opioid overdose every day.[11] Although patients with a history of mental illness and drug abuse are more vulnerable to develop opioid abuse, the risk of opioid overdose is not limited to patient factors. Since the 1990s, there has been a rapid increase in opioid prescriptions due to the lack of adequate pain management in certain patient populations, including females, elderly, and patients with cancer pain.[12] Pain management changes in the 1990s gave rise to ongoing high-risk prescribing practices in the 2000s, such as high-dose prescribing and overlapping prescriptions from multiple providers. In 2013, healthcare providers prescribed approximately a quarter of a billion opioid medications – enough medications for every adult to have his or her own bottle of pills.[11] In March 2016, as an acknowledgement to the provider's role in the opioid overdose epidemic, the CDC released its Guideline for Prescribing Opioids for Chronic Pain in order to address the concern of over-prescription. However, due to the subjective nature of pain, the prevention, assessment, and treatment of pain remains a major challenge for healthcare providers.[11]

Pharmacists can serve on the forefront of helping to manage the opioid epidemic. As members of one of the most accessible health professionals, pharmacists can play an active role in identifying misuse and addressing abuse in the community. Thus, it is important for pharmacy learners to be exposed to the education and training on pain management and opioid use disorder early on in the pharmacy curriculum. VH simulation exists as one innovative technological solution that can provide learning opportunities for these learners. The simulated patient can capture and display pain expressions and behavioral characteristics for learner recognition. The simulated environment allows pharmacy learners to interact with a virtual patient with human characteristics and behaviors that mimic a real patient. In these scenarios, learners must learn how to gather pertinent information and cultivate the clinical reasoning skills necessary to identify and address concerns and risks of opioid use, including overdose, abuse, and dependence. With adequate education and training, learners can then transfer knowledge and apply clinical reasoning skills learned with the virtual patients to real-life encounters with patients.

To ensure that the AI underlying the current VH simulation is robust and comprehensive, the objective of this study was to conduct a literature review and perform data acquisition to provide the relevant AI background content and framework on pain management and opioid use disorder.

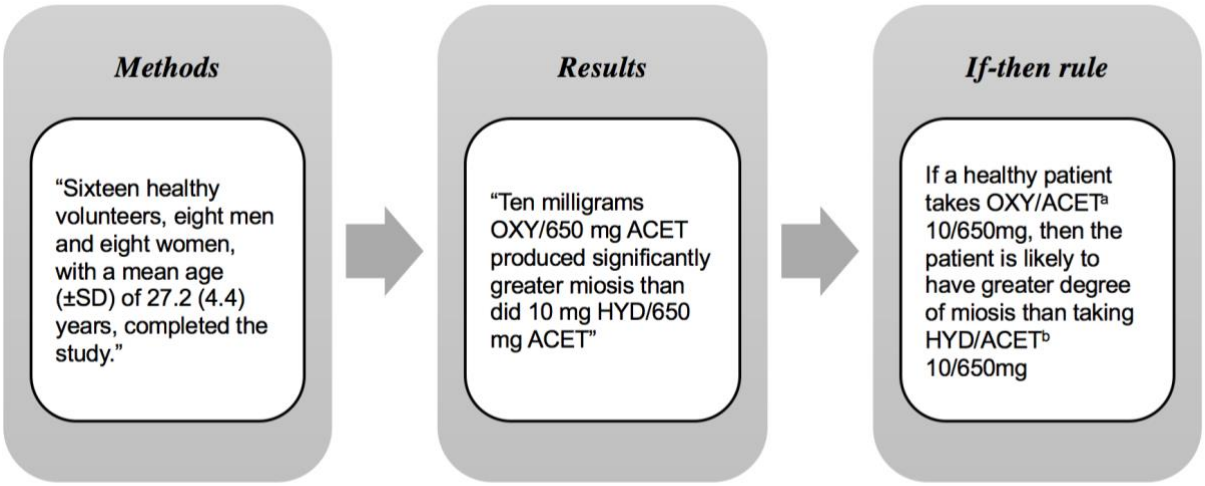
METHODS

A systematized search of literature on the PubMed database was conducted from January 2017 to February 2018 to determine the psychological and behavioral impacts of opioid use on patients with pain. Since this was a literature review of published data, no approval was required from the University's Institutional Review Board. Initially, a list of search terms created by PubMed's Medical Subject Headings (MeSH) database included 47 opioid drugs and three specific keywords: *opioids, opiate*, and *opiates*. To generate a more tractable set of studies while maintaining breadth, the list was narrowed down to 11 common opioid drugs in the United States: *buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, oxymorphone,* and *tramadol.* To support the VH simulation, and in particular, the AI necessary to guide the VH patient's behaviors, the primary endpoint was to identify five psychological and five behavioral processes to be used as search terms. After considering common topics presented in the behavioral sciences literature, the following 10 search terms were combined with the list of opioid drugs and keywords: *interpersonal, memory, attention, arousal, decision-making, facial expression, posture, gesture, body language,* and *eye contact.*[13] Any search term that yielded too many results was subdivided into more specialized terms. To be included in the review, studies must have been full-text articles published in English and have described, regardless of methodology, the psychological or behavioral impacts of opioid use on human patients with pain. Initially, search results were limited to studies that were published in the past five years. For search terms with too few results, the inclusion criterion was extended first to studies published in the past 10 years, then to studies published from any year.

One reviewer (HL) scanned the titles of all studies. Studies were excluded if their titles focused on the opioid pharmacology, pharmacokinetics, or pharmacodynamics. Studies were also excluded if their titles focused on opioid use disorder epidemiology. If the first reviewer felt that the title was potentially eligible for inclusion, as needed in consultation with the second author (RH), then the abstract was screened. Following this, the reviewer read the full-text article to determine if the study met the inclusion criteria. Studies were excluded if they included non-adult patients, current heroin users, or prescribers' perspective on opioid use disorder, as these details were not expected to be useful for generating AI for the current VH simulation. Studies were also excluded if they included opioid use for unrelated indications (ephdrone-induced Parkinsonism), or use of unrelated drugs (oxytocin, ketamine, etoricoxib, topical morphine) for pain management. Additional studies were screened for inclusion by searching the reference lists of relevant literature identified in these searches.

The following data were collected from all included studies: first author, year, study location, study design, sample size, mean age of participants, sex of participants, opioids studied, type of pain studied (chronic versus acute), and the presence of opioid dependence (yes versus no). Furthermore, data from all included studies were extracted to yield relevant methods, summarized results, and overall implications regarding the psychological and behavioral impacts of opioid use. The secondary endpoint was to generate "if-then rules" by analyzing data extracted from the literature. An "if-then rule" is a form of specification for AI in which a set of actions (then statements) can be performed when one or more conditions (if statements) are satisfied.[14] Figure

1 illustrates an example of an “if-then rule.” The “if-then rules” that derived from the current study could be translated into codes and incorporated into the AI language of the VH simulation by a separate team of computer programmers.

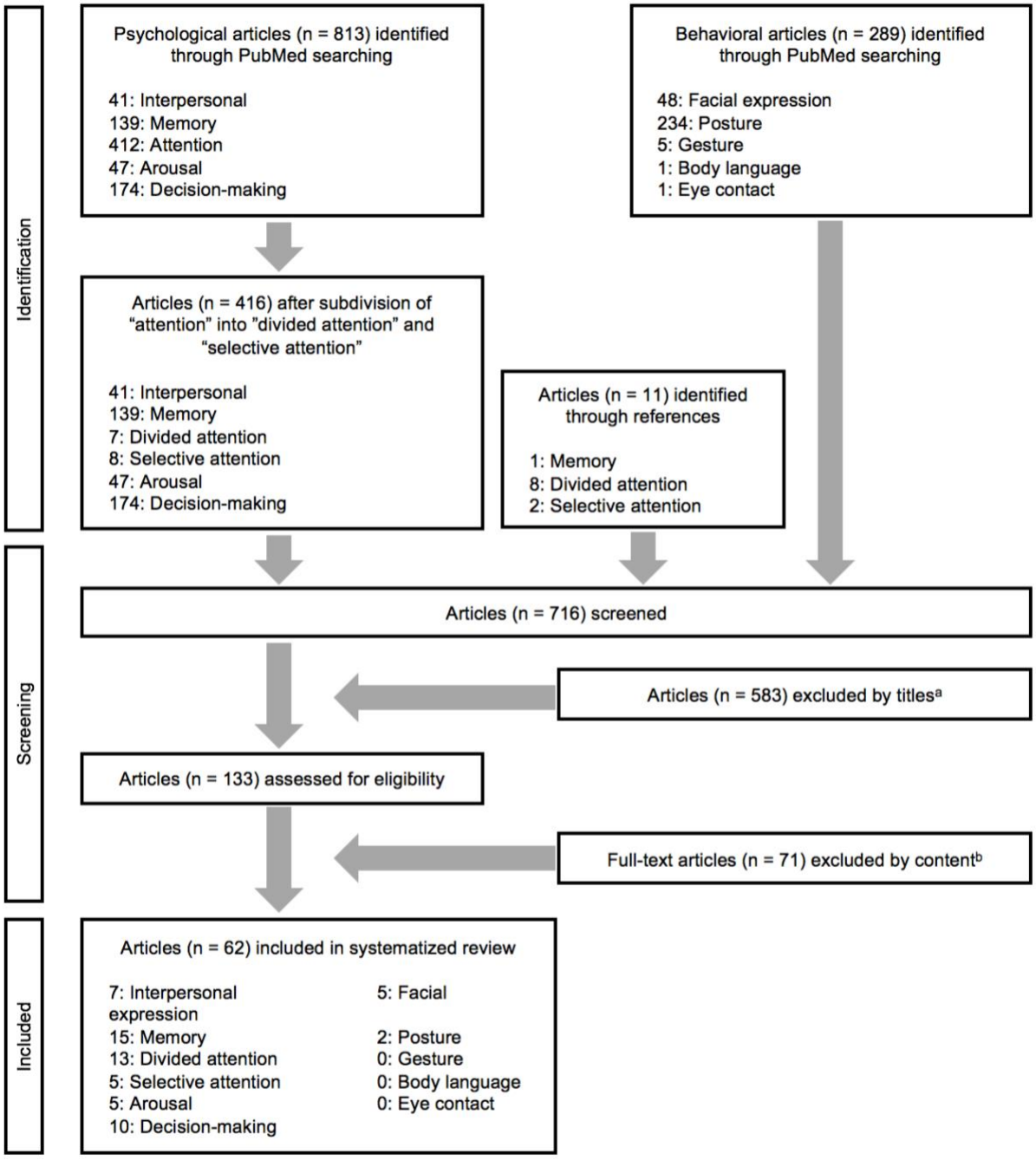


[a] OXY/ACET = oxycodone/acetaminophen, [b] HYD/ACET= hydrocodone/acetaminophen

Figure 1. An example of “if-then rule” derived from a study by Zacny & Gutierrez.[15]

RESULTS

The selection of studies for the systematized literature review is shown in Figure 2. Initial literature searches identified 1102 studies; further investigation identified a need to subdivide the search term *attention* (n = 412) into more specific keywords: *divided attention* (n = 7) and *selective attention* (n = 8). Upon including 11 articles searched through reference lists of included studies, 716 studies were identified to be screened. After title scans, 133 studies remained. The abstracts were assessed for potential eligibility. A total of 62 full-text articles were included in the systematized review, including 55 studies related to psychological processes and seven studies related to behavioral processes.



[a] Excluded duplications and titles focused on opioid pharmacology, pharmacokinetics, or pharmacodynamics, or opioid use disorder epidemiology
[b] Excluded articles that focused on opioid pharmacology, pharmacokinetics, or pharmacodynamics or solely on prescribers' perspective on opioid use disorder. Also excluded articles that included non-adult patients, current heroin users, opioid use for unrelated indications, or use of unrelated drugs for pain management

Figure 2. Systematized literature review flow diagram

The characteristics of the studies included in the systematized review are shown in Table 1. Most studies were published between 2000 and 2018 (n = 60). The oldest study was published in 1983. A total of 34 studies were conducted in North America (54.8%), including 28 studies in the United States (45.2%). A number of studies were also conducted on the following continents: 14 studies in Europe, 7 studies in Australia, 3 studies in Africa, 3 studies in Asia, and 1 study in multiple countries. With regards to study design, the majority of the studies were either controlled trial studies (37.1%) or comparative studies (35.5%). There was a total of nine qualitative interviews, and 88.9% of the interviews were conducted to assess decision-making processes with opioid use (Table 1). The remaining studies were conducted as meta-analyses (n = 4), case control studies (n = 2), and retrospective analyses (n = 2). Excluding the meta-analyses (n = 4), most studies had small sample sizes of less than 50 patients (58.6%). Thirteen studies had patient sample sizes of 50 to 100 and 11 studies had patient sample sizes of more than 100. Most studies included patients in the following range of ages: 33 studies included patients with mean ages between 20 and 39 years and 21 studies included patients with mean ages between 40 and 59 years old. One study included patients with a mean age of 65.2 years old[23], 2 studies included patients with mean ages between 29 and 84 years old, and 5 studies did not report the mean age. Nine studies had the same percentage of male and female patients included in the studies. A number of studies had more male patients (n = 24), more female patients (n = 23), or did not report sex percentages (n = 6).

Table 1. Characteristics of studies included in literature review

First author (Year)	Study location	Study design	Sample size (no. of patients)
Interpersonal			
Xia (2013)[16]	China	Qualitative interviews	27
Inagaki (2015)[17]	USA	Controlled trial	31
Sun (2015)[18]	China	Meta-analysis	38 studies
Bershad (2016)[19]	USA	Controlled trial	36
Burgdorf (2016)[20]	Germany	Controlled trial	48
Inagaki (2016)[21]	USA	Controlled trial	31
Bershad (2018)[22]	USA	Controlled trial	38
Memory			
Kamboj (2005)[23]	UK	Comparative	14
Darke (2012)[24]	Australia	Case Control	225
Anderson (2013)[25]	USA	Controlled trial	34
Gandolphe (2013)[26]	France	Comparative	110
McDonald (2013)[27]	Australia	Case Control	225
Kamboj (2014)[28]	UK	Controlled trial	20
Schiltenwolf (2014)[29]	Germany	Comparative	95
Spierings (2014)[30]	USA	Controlled trial	30
Terrett (2014)[31]	Australia	Comparative	56
Kurita (2015)[32]	Denmark	Controlled trial	22
Mercuri (2015)[33]	Australia	Comparative	96
Rass (2015)[34]	USA	Controlled trial	56
Syal (2015)[35]	South Africa	Controlled trial	38
Bell (2016)[36]	USA	Comparative	48
Bassiony (2017)[37]	Egypt	Comparative	100
Attention, Divided			
Hill (2000)[38]	USA	Controlled trial	17
Zacny (2003)[39]	USA	Controlled trial	18

Zacny (2005)[40]	USA	Controlled trial	18
Walsh (2008)[41]	USA	Controlled trial	9
Zacny & Gutierrez (2008)[42]	USA	Controlled trial	16
Zacny & Lichtor (2008)[43]	USA	Controlled trial	20
Sproule (2009)[44]	USA	Retrospective analysis	428
Zacny (2009)[45]	USA	Controlled trial	20
Mintzer (2010)[46]	USA	Controlled trial	9
Schoedel (2010)[47]	Canada	Controlled trial	35
Henry (2012)[48]	USA	Comparative	77
Mailis-Gagnon (2012)[49]	Canada	Meta-analysis	35 studies
Rass (2014)[50]	USA	Comparative	51
Attention, Selective			
Pirastu (2006)[51]	Italy	Comparative	69
Rapeli (2007)[52]	Finland	Comparative	50
Soyka (2008)[53]	Germany	Controlled trial	70
Nejati (2011)[54]	Iran	Comparative	60
Bracken (2012)[55]	USA	Comparative	35
Arousal			
David (2013)[56]	Multiple countries	Meta-analysis	8 studies
Garland (2013)[57]	USA	Comparative	65
Ajo (2016)[58]	Spain	Comparative	263
Smith (2016)[59]	USA	Retrospective analysis	34,566
Wardle (2016)[60]	USA	Comparative	34
Decision-Making			
Vallerand (2009)[61]	USA	Qualitative interviews	22
Vallerand (2010)[62]	USA	Qualitative interviews	22
Esquibel (2014)[63]	USA	Qualitative interviews	21
Brooks (2015)[64]	Nova Scotia	Qualitative interviews	9
McCrorie (2015)[65]	UK	Qualitative interviews	23
Smith (2015)[66]	USA	Qualitative interviews	23
Biernacki (2016)[67]	Australia	Meta-analysis	22 studies
Paterson (2016)[68]	Australia	Qualitative interviews	20
Yarborough (2016)[69]	USA	Qualitative interviews	283
Garami (2017)[70]	Australia	Comparative	183
Facial Expression			
Hadjistavropoulos (1994)[71]	Canada	Comparative	90
Kornreich (2003)[72]	Belgium	Comparative	150
Martin (2006)[73]	UK	Comparative	61
Carroll (2011)[74]	UK	Comparative	20
Ipser (2013)[75]	South Africa	Controlled trial	20
Posture			
Rubin (1983)[76]	USA	Controlled trial	16
Fan (2012)[77]	Canada	Comparative	223

The number of studies and “if-then rules” corresponding to each psychological or behavioral process are shown in Table 2 and 3, respectively. A total of 273 rules were derived from relevant literature, including 247 rules related to psychological processes and 26 rules related to behavioral processes.

Table 2. Summary of literature and rules related to psychological processes

Psychological processes	No. of studies	No. of rules
Interpersonal	7	17
Memory	15	56
Attention		
Attention, Divided	13	61
Attention, Selective	5	18
Arousal	5	27
Decision-Making	10	68
Total	**55**	**247**

Table 3. Summary of literature and rules related to behavioral processes

Behavioral processes	No. of studies	No. of rules
Facial Expression	5	22
Posture	2	4
Gesture	0	0
Body Language	0	0
Eye Contact	0	0
Total	**7**	**26**

A number of studies involved methadone (33.9%), multiple opioids (24.2%), and buprenorphine (22.6%). There was an equal number of studies focusing on patients with chronic pain (n = 17) and healthy volunteers with no pain (n = 17). Twenty-six studies involved opioid-abusing patients with no pain and two studies involved patients with acute pain. Opioid dependence was reported in 41.9% of the studies. A number of studies did not include patients with opioid dependence (n = 23) or did not report presence of opioid dependence (n = 13).

Table 4. Number of studies and rules, by opioids studied

Opioids studied	No. of studies	No. of rules
Buprenorphine	14	57
Buprenorphine/Naloxone	4	22
Hydrocodone	3	27
Hydromorphone	2	8
Methadone	21	89
Morphine	8	35
Naltrexone	5	10
Oxycodone	4	34
Oxymorphone	2	4
Tramadol	2	6
Multiple Opioids[a]	15	92
Other[b]	4	9

[a]Not included in the studies or rules for individual opioid listed
[b]Opioids with one resulting article (DAMME, remifentanil, naloxone, no opioids)

Table 5. Number of studies and rules, by type of pain

Type of pain	No. of studies	No. of rules
Acute pain	2	11
Chronic pain	17	92
Opioid abusers (no pain)	26	106
Healthy volunteers (no pain)	17	66
Not reported	1	1

Table 6. Number of studies and rules, by presence of opioid dependence

Opioid Dependence	No. of studies	No. of if-then rules
Yes	26	106
No	23	93
Not reported	13	74

DISCUSSION

This systematized literature review is the first study to provide the clinical knowledge of pain management and opioid use disorder necessary to help develop a VH simulation. We derived a total of 273 “if-then rules” to be programmed into the AI language underlying the VH simulation. Approximately 90.5% of those “rules” can be attributed to the effects of opioids on psychological processes. The small number of articles found in this literature review that focus on behavioral characteristics suggests that there are research needs in this area, particularly studies that evaluate the impact of opioid use on gesture, body language, and eye contact, since these behaviors may be informative to a pharmacist.

This literature search found a number of articles focused on methadone and buprenorphine (21 and 14 studies, respectively). Methadone and buprenorphine are part of medication-assisted treatments (MAT), which combines opioid treatment programs (OTPs) with behavioral therapy to treat opioid use disorder and addiction.[78] Methadone, an opioid agonist, and buprenorphine, a partial opioid agonist, are commonly used to help relieve withdrawal symptoms for opioid-dependent patients as part of the detoxification process. Since most articles (96.8%) found in our literature review were published within the last 18 years, the number of articles found for these drugs suggests that there has been a recent increase in interest and research in opioid replacement therapy within the last few years. This finding is not surprising, as our healthcare and federal government has shifted its focus to opioid detoxification within the recent years in light of the U.S. opioid epidemic. According to the Substance Abuse and Mental Health Service Administration (SAMHSA), both the number of patients receiving methadone and buprenorphine increased from 227,003 and 727, respectively, in 2003 and 2004, to 356,842 and 21,628 in 2015, respectively.[78] In fact, the percentage of OTPs with buprenorphine increased from 11% in 2003 to 58% in 2015, and approximately 21-25% of all patients who receive substance abuse treatment each year are patients who receive methadone as part of their MAT.[78] In the state policy arena, Burns et al reported that there has been an increase in Medicaid coverage of both methadone and buprenorphine from 21 states in 2004 to 32 states in 2013.[79] Despite increasing data on its efficacy and cost-effectiveness, further research on methadone and buprenorphine is necessary to prompt the remaining state Medicaid to grant coverage.

In this literature search, the 24.2% of articles that constitute “multiple opioids” fall into the study design categories of meta-analyses, retrospective analyses, and qualitative interviews, in which the studies assessed overall patient experience with any opioid rather than with individual opioid. This literature review suggests there is a gap in literature studying the effects of other opioids drugs, such as hydromorphone, oxymorphone, and tramadol, on psychological and behavioral characteristics.

Twenty-six articles studying opioid abusers (Table 5) are consistent with the number of articles studying methadone and buprenorphine (Table 4). A strength of this study is the equal number of articles studying effect of opioids on patients with chronic pain and healthy volunteers (Table 5). The results of this literature review also show proportional representation between opioid-dependent and non-opioid-dependent patients (Table 6). Initially, we intended to search for research articles on prescription drug abuse. One limitation of this current study is that we did not exclude heroin from our search terms. As a result, many of the articles we found focused on heroin abusers, rather than prescription drug abusers. Related research in the future should establish more well-defined exclusion criteria. Furthermore, additional research in the future should utilize multidisciplinary healthcare providers to help review and evaluate the clinical relevance of literature findings. Pain specialists can also contribute clinical knowledge to support the development of educational contents that may not have been studied or addressed in the primary literature. In addition, the integrative expert opinions and clinical experiences of the team can help fill in the literature gaps surrounding behavioral characteristics and provide a more comprehensive understanding of pain management and opioid use disorder.

CONCLUSION

The development of VH simulation can provide an innovative way to transform the teaching, learning, and practice of clinical healthcare. VH simulation can capture and display pain expressions and characteristics for learner recognition and present realistic cases to learners to encourage active learning. In addition, VH simulation can simulate clinical scenarios of opioid overdose, abuse, and dependence, which can help learners develop the clinical reasoning skills necessary to address concerns and risks of opioid use in a virtual setting. The rationale to develop a VH opioid patient simulation in the pharmacy curricula lies in the role that pharmacists can play due to the continued rise of opioid overdose deaths in the U.S.[11] As members of one of the most accessible health professionals, pharmacists are in a unique position to identify at-risk patients for opioid use disorder and prevent opioid overdose, misuse, and abuse in the community. Although the use of VH simulation has been explored in health education, the specific technological platform that will utilize the “if-then rules” derived from this study is intended to dramatically improve education and training in patient-centered care in the pharmacy curriculum. The impact of this study lies in the education and learning of future health providers, particularly pharmacists. The continuing impact of this study may extend beyond healthcare education to the development of healthcare policies that may shape the management of the U.S. opioid epidemic in the future.

In this systematized literature review, more than 270 “if-then rules” that reflect psychological and behavioral effects of opioids were derived to support the development of a VH patient simulation. A number of articles focusing on the effects of methadone and buprenorphine support the increasing research and interest in opioid replacement therapy within the recent years due to the U.S. opioid epidemic. Gaps in the literature and future research needs focusing on behavioral

effects of opioids were identified in this literature search. Similar studies in the future should determine more well-defined exclusion criteria with the focus on prescription drug abuse.

ADDENDA

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