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The Effects of Cannabis: Implications for the Surgical Patient

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Background: Cannabis use is increasingly prevalent. Cannabinoid receptors regulate pro-inflammatory cytokines, and compounds in marijuana exert diverse physiologic effects. As more patients use cannabis, clinicians should recognize implications of perioperative cannabis use. Although the role of cannabis use in perioperative pain control has been explored, little is known about its effect on perioperative wound healing or on hematologic, pulmonary, and cardiovascular physiology.

Methods: We searched PubMed for English-language articles related to cannabis (ie, marijuana, cannabidiol oil, and tetrahydrocannabinol) and wound healing, cardiovascular, pulmonary, or hematologic outcomes, and surgery. Titles and abstracts were reviewed, and relevant articles were analyzed. Human, animal, and pathology studies were included. Editorials, case reports, and review articles were excluded.

Results: In total, 2549 wound healing articles were identified; 5 human studies and 8 animal/pathology studies were included. Results were conflicting. An estimated 2900 articles related to cardiovascular effects were identified, of which 2 human studies were included, which showed tetrahydrocannabinol and marijuana caused tachycardia. A total of 142 studies regarding pulmonary effects were identified. Three human studies were included, which found no difference in respiratory complications. In total, 114 studies regarding hematologic effects were identified. The 3 included human studies found conflicting venous thromboembolism risks. The overall study quality was poor. Information about dose/duration, administration route, and follow-up was reported with variable completeness.

Conclusions: Surgeons should consider effects of cannabis in the perioperative setting. Little is known about its perioperative effects on wound healing, or on cardiovascular, pulmonary, and hematologic physiology. Further research should elucidate the effects of administration route, dose, and timing of cannabis use among surgical patients. *(Plast Reconstr Surg Glob Open 2021;9:e3448; doi: 10.1097/GOX.0000000000003448; Published online 15 March 2021.)*

INTRODUCTION

Cannabis use has become increasingly prevalent, with over 147 million users worldwide and 19.8 million current marijuana users in the United States alone.[1,2] Cannabinoid receptors are involved in regulating pro-inflammatory cytokines, and over 500 chemical compounds contained in marijuana exert diverse physiologic effects.[3–5] Cannabidiol, the active cannabinoid found in cannabis, has been reported to have anti-inflammatory, analgesic, antiemetic, and muscle relaxant effects. Some studies tout potential benefits of cannabidiol, whereas others caution about potential respiratory and cardiovascular complications.[5–8] As more patients use cannabis in various formulations and quantities, clinicians should recognize the implications of cannabis use in the perioperative period. Although the role of cannabis use in perioperative pain control has been explored, little is known about its effect on wound healing or on the pulmonary, hematologic, or cardiovascular systems. We conducted a comprehensive review of the literature to elucidate the effects of cannabis in the perioperative period, with a focus on wound healing, and on pulmonary, hematologic, and cardiovascular effects.

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METHODS

We searched the PubMed database for English-language articles through April 2020 related to cannabis [ie, marijuana, cannabis, cannabidiol (CBD) oil, tetrahydrocannabinol (THC)] and wound healing, surgery, or pulmonary, hematologic, or cardiovascular effects. Titles and abstracts of identified articles were reviewed, and relevant articles analyzed. Human, animal, and pathology studies were included and were assigned a level of evidence based on the "ASPS Evidence Rating Scale"[9] and "Scale for Grading Recommendations."[10] Editorials, review articles, and case reports were excluded. Articles that did not discuss physiologic effects specifically in the surgical or perioperative setting were excluded from formal analysis. Included articles were categorized as related to wound healing, pulmonary pathophysiology, cardiovascular pathophysiology, or hematologic pathophysiology, and each category was analyzed separately.

RESULTS

Review of the PubMed database identified 2549 articles related to wound healing, of which 5 human studies and 8 animal or pathology studies met the inclusion criteria. There were 2900 English-language articles related to the cardiovascular effects of cannabis in the surgical patient, of which 2 studies from the same manuscript met the inclusion criteria. Among the 730 identified animal or pathology studies, 3 examined in vitro effects of cannabis on vasculature, though none involved surgical subjects specifically. Review of the literature regarding the pulmonary effects of cannabis in surgical patients identified 142 studies in humans (of which 3 met the inclusion criteria), and 48 animal and pathology studies (of which none were eligible for inclusion). In total, 114 English-language studies related to hematologic effects of cannabis in humans were identified, of which 3 were included. No animal or pathology studies met the inclusion criteria. Diagrams of the search methodology for each area are depicted in Figures 1–4 and a summary of included articles is listed in Tables 1–4. Among all included studies, information about dose, duration of use, route of administration, outcome metrics, and follow-up were reported with variable completeness, and outcomes were conflicting.

DISCUSSION

According to the World Health Organization, cannabis abuse has increased faster than opiate and cocaine abuse, with the most rapid growth in North America, Western Europe, and Australia.[2] The effects of cannabis in pain management have been studied extensively and are beyond the scope of this article. However, less is known about the effects of cannabis on perioperative wound healing and on pulmonary, cardiovascular, and hematologic function.

Cannabis is a generic term that refers to the various formulations of the *Cannabis sativa* plant. Marijuana refers to the dried leaves, flowers, stems, or seeds of the *Cannabis sativa* plant and can be smoked, vaporized, or ingested. Marijuana contains hundreds of compounds, including varying quantities of the mind-altering chemical delta-9-tetrahydrocannabinol (THC).[1] Cannabidiol is another active ingredient in cannabis.[11]

In addition to the chemical formulation, the route of cannabis administration impacts its bioavailability and resultant physiologic and potential clinical effects in the perioperative period.[12] The high lipophilicity of CBD may substantially alter the drug's effects, with absorption varying from 20% to 30% and from 10% to 60% for the oral and inhalational route, respectively. Similarly, this may also cause increased absorption in the sebaceous glands when administered topically. For edible formulations, for instance, recent eating may impact absorption, while depth of inhalation, duration of inhalation, and vaporizer temperature may affect inhaled cannabinoid absorption.[34] THC is lipophilic and has an affinity for the brain and fatty tissues, which results in slow metabolization over time and a long half-life.[12] This may be important when considering potential residual effects in the surgical patient. THC is primarily metabolized by the cytochrome P450 enzyme system, CYP2C9 and CYP2C19 via hydroxylation and oxidation in the liver. THC is metabolized to 11-carboxy-THC and then glucuronide. Inhaled THC does not undergo first-pass metabolism by the liver and is instead rapidly absorbed via the bloodstream. Ingested forms may be absorbed through the gastrointestinal tract over an hour or more.[13]

Cannabinoids are compounds that are structurally similar to THC and include plant cannabinoids, also known as phytocannabinoids, endocannabinoids, and the synthetic analogues of both groups.[2,14] Cannabinoid receptors and their ligands together make up the endocannabinoid system.[15] There are 2 known cannabinoid receptors in humans, CB1 and CB2. These G-coupled receptors are widely distributed throughout the body.[16] CB1 receptors are predominantly responsible for the analgesic effects of cannabis, whereas CB2 receptors exhibit anti-inflammatory effects and modify cytokine release from immune cells, including interleukin-2 and interleukin-c, interleukin 1a and 1b, and tumor necrosis factor alpha (TNF-α).[17,18] CB1 receptors are also coupled to various ion channels such as N-type and P/Q-type calcium channels and A-type and potassium channels.[15]

Synthetic cannabinoid receptor agonists can also have anti-histamine effects. Through manipulation of these inflammatory and cytokine pathways, cannabis has been hypothesized to decrease toll-like receptor activation,[19] decrease proliferation of cultured human epidermal keratinocytes, increase apoptotic reactions,[20] and to have potential utility for treatment of inflammatory conditions such as acne vulgaris, encephalomyelitis, and multiple sclerosis.[21]

Beyond potential implications for wound healing, cannabis also affects the respiratory and cardiovascular systems. Pulmonary effects include increased airway edema and obstruction and reduced pulmonary function among cannabis users.[7,19] In particular, chronic inhalational use is associated with injury of the tracheal and bronchial endothelium, and generalized lung inflammation and impaired

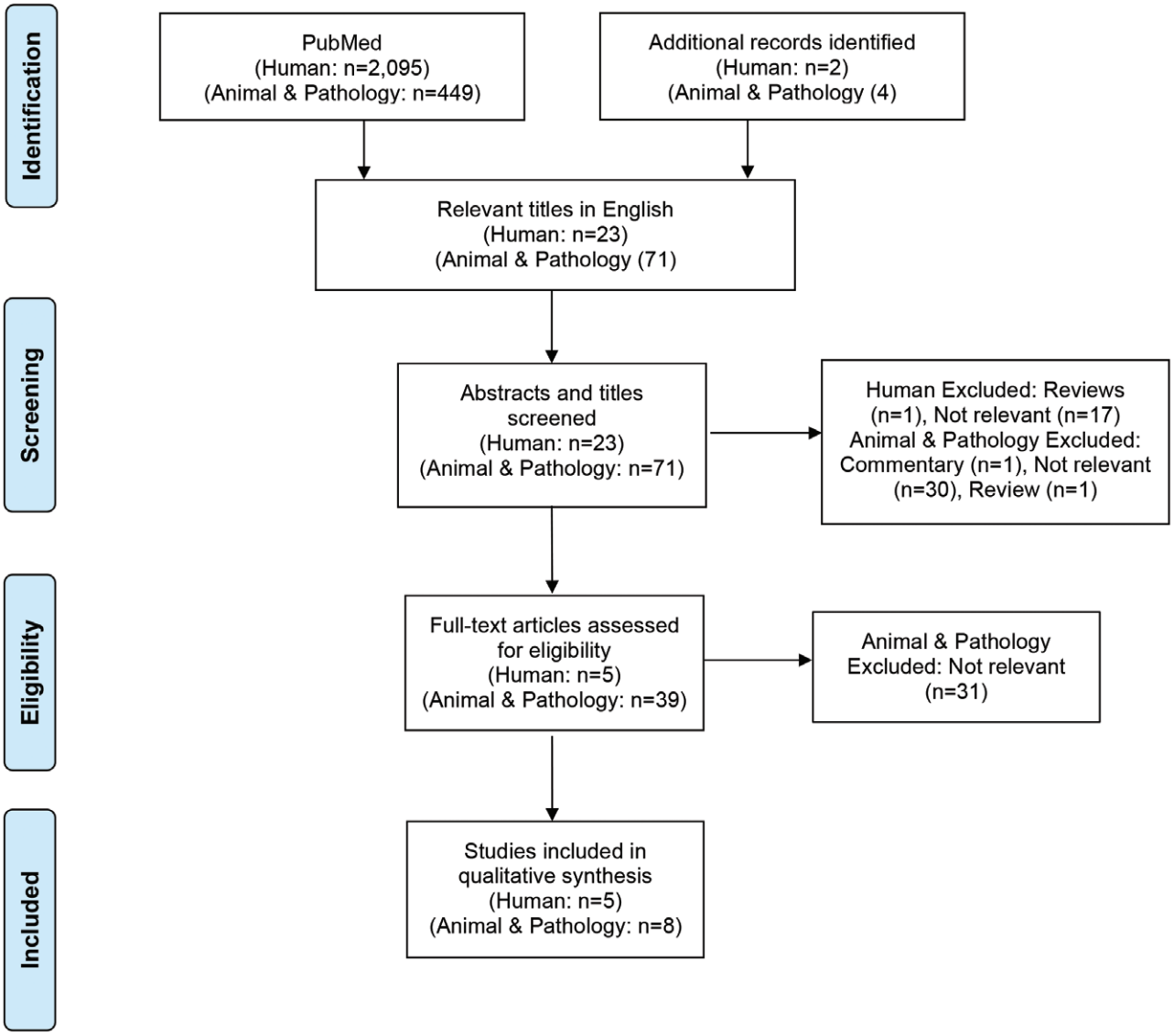

Fig. 1. Flow diagram of search methodology for wound healing effects of cannabis.

respiratory defense against infection.[2] Cardiovascular complications include myocardial ischemia, arrhythmia, asystole, and sudden death. Specifically, the risk of myocardial infarction is elevated 5-fold in the hour after cannabis use.[22] Additionally, vasomotor reflexes may be impaired by cannabis, which can increase a patient's risk for postural dizziness, orthostatic hypotension, and syncope. Notably, these events sometimes occurred in patients without pre-existing cardiovascular disease.[8] Furthermore, cannabis users may suffer from withdrawal, anxiety, restlessness, irritability, depression, agitation, insomnia, changes in appetite, and weight loss in the perioperative period.[5]

These myriad physiologic effects may be exacerbated in the perioperative period. In clinical practice, many screening protocols fail to quantify cannabis use.[35] Several in vitro studies suggest a dose-dependent effect of THC and other cannabinoids on cellular apoptosis and local inflammatory processes, such as COX-2 activation, cytokine expression, and caspase-3 production.[16,23] Given the widespread use of cannabis in the general population, it is critical that clinicians understand the potential implications of cannabis in the surgical patient.

Cannabis and Wound Healing

There were 4 human studies and 8 animal or pathology studies related to wound healing that met inclusion criteria. The overall quality of these studies was poor and results were conflicting. Among animal and pathology studies, there were 4 studies of injected CBD or THC, 2 of CBD-impregnated implants, 1 of inhaled THC, and 1 of cultured THC application.[24–31] In addition to the route of administration and formulation, the dose and frequency of drug delivery varied among studies. Tissue types included oral/periodontal (2 studies), subcutaneous tissue or skin grafts (3 studies), or bone (3 studies). Overall, 4 studies showed improved wound or bone healing or skin graft take, whereas an equal number demonstrated impairment. Notably, in a study of 30 rats with titanium

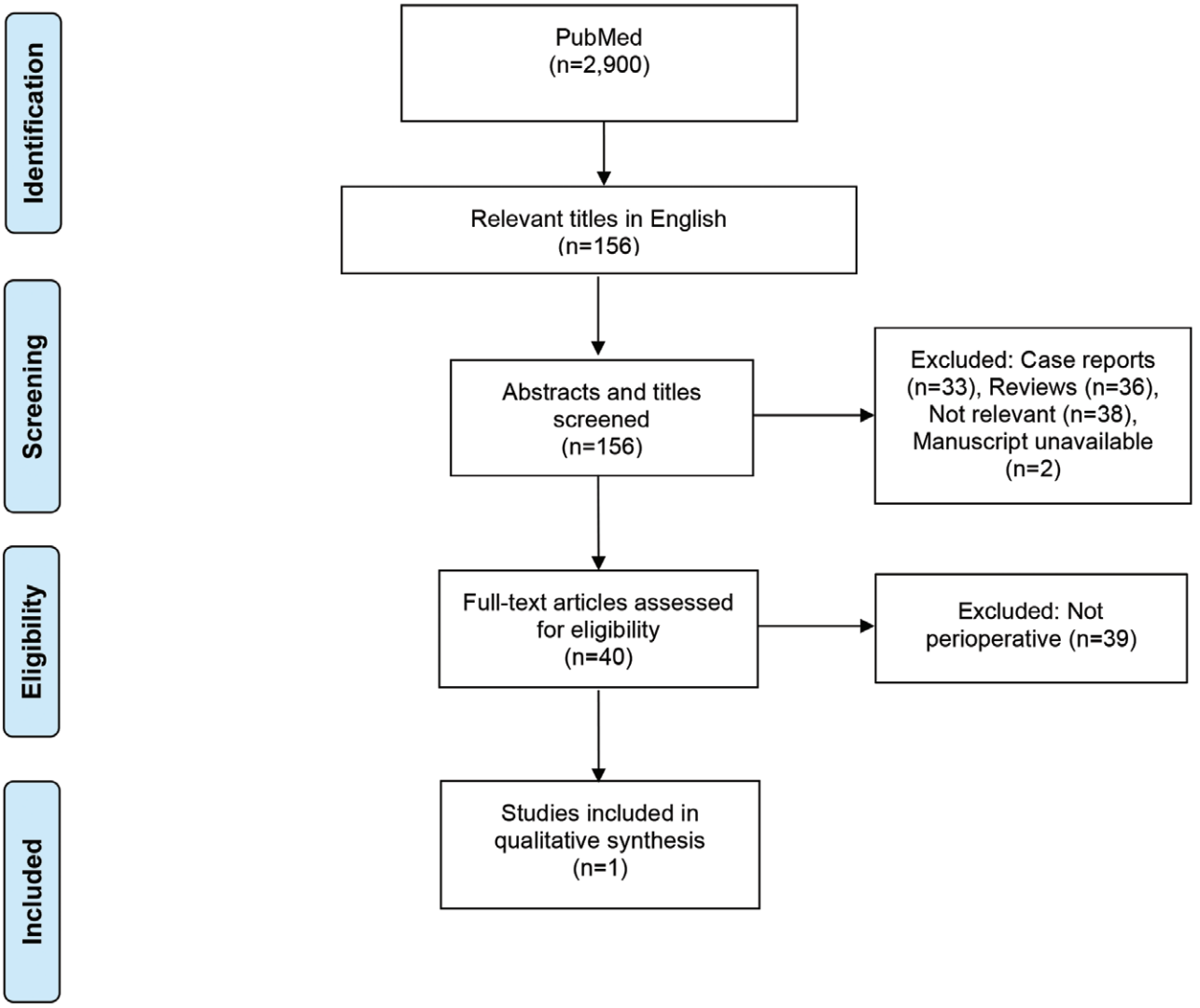

Fig. 2. Flow diagram of search methodology for cardiovascular effects of cannabis.

bone implants treated with inhaled THC for 8 minutes daily for 60 days, 7 died due to respiratory failure.[26]

Among human studies, 2 suggested improvement in wound healing parameters with topical CBD, though the dose and duration varied between the 2 studies and among patients within studies. In one case series of 20 patients with dermatologic wounds treated with topical CBD twice daily for 90 days, there was objective improvement in skin hydration and elasticity, photographic improvement in wound appearance, and subjective symptom relief.[18] Observations in another small case series of 3 patients suggested subjective improvement in open epidermolysis bullosa wounds treated with varying frequency and duration of topical CBD ointment.[6] Although these studies suggest improved wound healing with topical CBD, they are limited by small sample size and variable methodology. A third study of marijuana use among 434 patients undergoing bariatric surgery showed no difference in postoperative infections between users versus non-users, though the authors did not comment specifically on wound healing.[6] Marijuana use was defined as smoking marijuana at least once monthly, which may not be a sufficient dose to produce a beneficial or harmful effect on wound healing. Additionally, this study is limited by its retrospective methodology and reliance on patient reported use, which may be subject to bias. In contrast, another large database review of 2,718,023 patients undergoing total knee arthroplasty identified an increased revision rate between marijuana users versus non-users (12.8% versus 9.1%, $P < 0.001$). Marijuana use was defined according to the International Classification of Diseases, Ninth Revision code (ICD-9) documentation in the medical record; however, the frequency of use was not available. This study is also limited by retrospective design.[32] Neither of these reviews included comments on whether patients were using other forms of cannabis in addition to inhaled marijuana.

In summary, few studies have examined the effects of cannabis use on wound healing, and results are conflicting, with some suggesting cannabis may improve objective

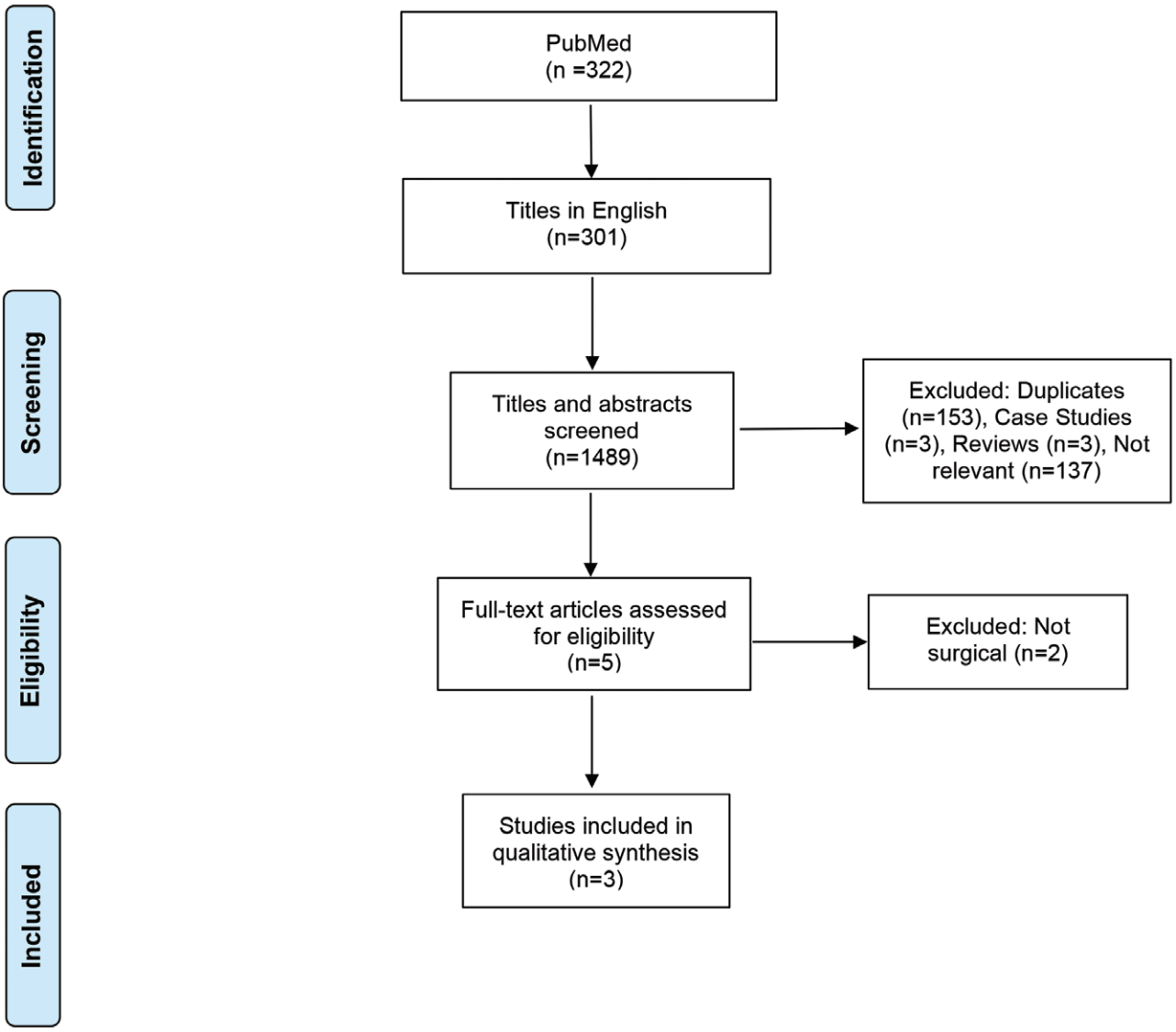

Fig. 3. Flow diagram of search methodology for pulmonary effects of cannabis.

and subjective metrics of wound healing, whereas others demonstrate impaired healing. Data are limited by wide heterogeneity in wound type; follow-up; and drug dose, route, and frequency of administration.

Cardiovascular Effects

Although there is an abundance of literature on the cardiovascular effects of cannabis, less has been published on these effects in surgical patients. It is particularly important that surgeons be aware of a patient's cannabis use preoperatively, as it is associated with premature cardiovascular aging, arterial stiffness, and alterations in microvascular integrity.[33,34]

Literature review identified no animal or pathology studies examining the effects of cannabis on the cardiovascular system in the perioperative period. Two human studies examined the cardiovascular effects of cannabis use in patients undergoing oral surgery.[35] In one study, 10 otherwise healthy men with a history of marijuana use underwent dental extraction during four separate visits. Subjects were premedicated with either intravenous high-dose THC (0.044mg/kg), low-dose THC 0.022mg/kg, diazepam or placebo administered in random order over 4 consecutive weeks. Outcomes were compared with 5 nonsurgical controls who received the higher THC dose. Heart rate and blood pressure was recorded every 2 minutes. Peak heart rate in patients who received high-dose THC was 34% higher ($P< 0.05$) than in controls. The authors attribute this to a possible synergistic effect of THC and surgical stress.

In the second study, 10 participants underwent molar extraction under general anesthesia. Five patients smoked marijuana within 72 hours of surgery, though the precise frequency, duration, and quantity of use were not recorded. Blood pressure, heart rate, respiratory rate, arterial blood gases, and electrocardiogram were recorded preoperatively, post-induction, at peak anesthetic, and post-anesthetic. The marijuana group had a mean peak heart rate of 64.8% above baseline, which did not return to baseline

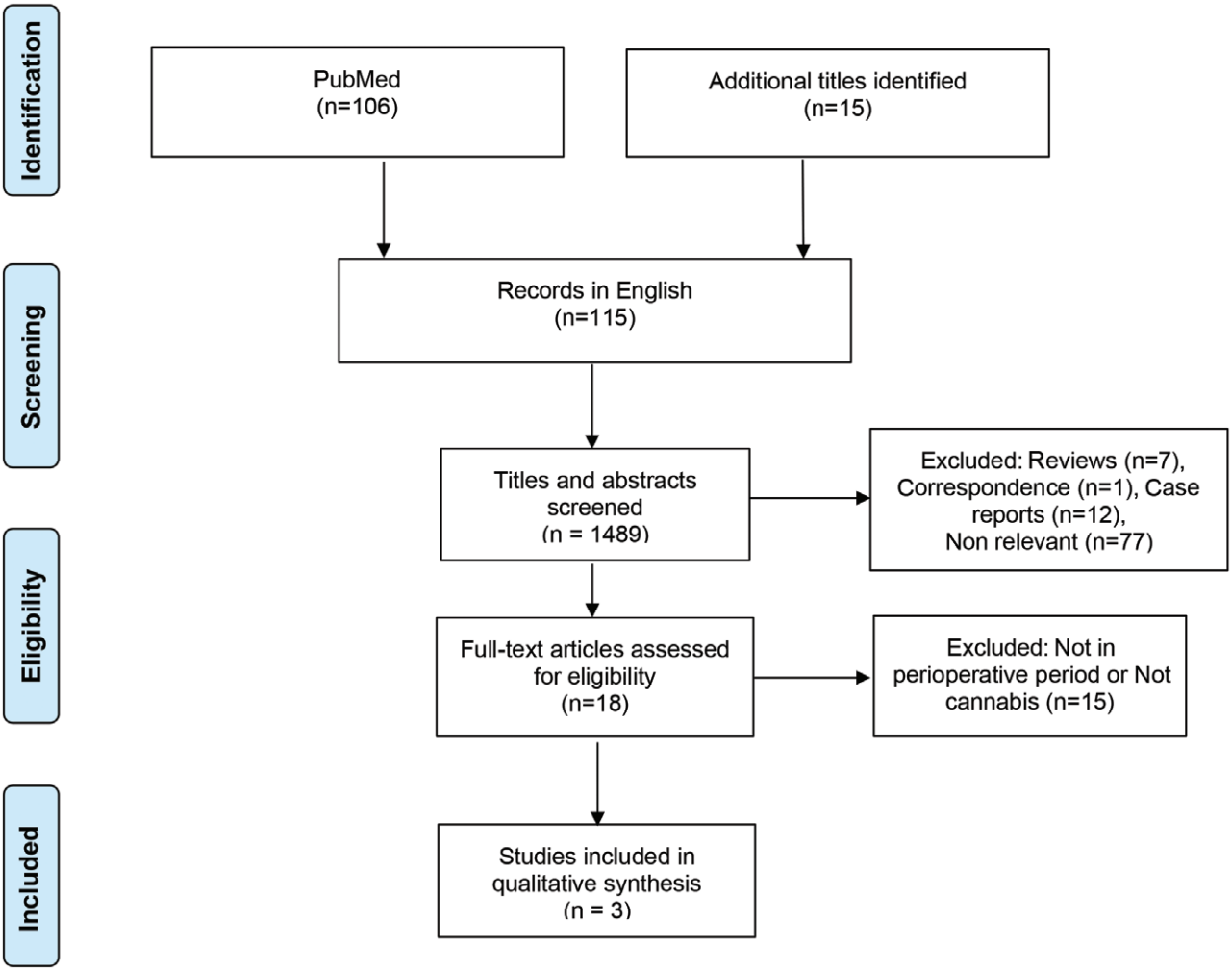

Fig. 4. Flow diagram of search methodology for hematologic effects of cannabis.

for 38 minutes, on average. In contrast, the non-marijuana group had a mean peak heart rate of 39% above baseline, which returned to normal within 19 minutes after anesthesia ($P < 0.05$). These differences were attributed to drug interactions between marijuana and anesthetics. The clinical implications of tachycardia were not explored in either study. It remains unclear whether these effects would be larger with more invasive procedures. Additionally, both studies are limited by small sample size.

Although not specific to the perioperative period, several studies have explored the cardiovascular effects of cannabis in its various forms. Data regarding the cardiovascular effects of cannabis are conflicting. One study reported an increased incidence of acute ischemic stroke in patients using marijuana,[31] whereas other studies found no significant association between long-term exposure and cardiovascular risk,[36,37] and effects may vary with acute versus chronic use.[38,39] As with the 2 human studies mentioned, tachycardia has been commonly observed with acute use, though this change appears to attenuate with chronic use.[38,39] In in vitro studies, THC and other cannabinoids caused vasorelaxation in pre-constricted rat aortas, but these effects diminished after prolonged exposure to synthetic cannabinoids ($P < 0.05$).[40]

A potential confounder in clinical practice and in several studies is the concurrent use of tobacco and cannabis, as 96% of ever tobacco smokers have also ever smoked marijuana.[41] However, there is a potential additive effect of marijuana use with concurrent tobacco use, in terms of risk of cardiovascular disease.[36] Although several studies adjusted for concurrent tobacco use and found no detrimental cardiovascular effects of marijuana,[26] the inability to control for this is a limitation of other studies.[37,41]

In summary, there are limited data on the cardiovascular effects of marijuana in surgical patients. However, the few available studies suggest that cannabis use in various forms during the perioperative period may cause tachycardia and increase the risk of arrhythmias and myocardial infarction.[36] Although studies have shown that sustained intraoperative tachycardia is associated with worse surgical outcomes, further investigations are needed to clarify the clinical implications of tachycardia related to marijuana use in the perioperative period.[42]

Table 1. Summary of Articles (Human and Animal and Pathology Studies) Examining Effects of Cannabis on Wound Healing

Authors and Year	Methods	Surgery/ Wound Type	Total No. Subjects	Total No. Users	Drug	Administration Route	Dose	Outcomes	Level of Evidence*
Human Studies									
Palmieri, 2019	Retrospective review of anecdotal experience	Psoriasis, atopic dermatitis, and scars	20	20	CBD	Topical	BID × 90 d	Improved hydration, tissue elasticity, transepidermal water loss. Subjective photographic improvement.	Grade C (level IV)
Chelliah, 2018	Retrospective review of self-initiated treatment	Epidermolysis bullosa	3	3	CBD	Topical	BID-TID (variable duration)	Subjective improvement	Grade C (level IV)
Dakour-Aridi, 2019	Retrospective database review based on ICD-9 codes	Lower extremity bypass grafts	50,976	372	Cannabis	NR	NR	Increased graft complications. No difference in overall complications.	Grade C (level II)
Bauer, 2018	Prospective cohort, survey of cannabis use	Bariatric surgery	434	36	Marijuana	Inhaled	At least once in 30 d	No difference in complications	Grade C (level II)
Law, 2018	Retrospective database review based on ICD-9 codes	TKA	2,718,023	18,875	Marijuana	Inhaled	NR	Increased revision rate	Grade C (level II)
Animal & Pathology Studies									
Kamali A, 2019	Bone defects treated with CBD-loaded microspheres	Osteotomy defect	40	NA	CBD	CBD-impregnated implant versus autograft	1-mg CBD-PLGA	Promoted bone healing	Grade C (level V)
Klein M, 2018	Tongue ulcers treated with topical CBD	Punch biopsy-induced tongue wounds	40	20	CBD	Injection	5 mg/kg or 10 mg/kg × 3 or 7 d	Impaired wound healing	Grade C (level V)
Solinas M, 2012	Cell wound healing assay treated with topical CBD	Subcutaneous tissue	40	NA	CBD	CBD-impregnated Matrigel solution injected	Varying levels	Impaired wound healing and angiogenesis	Grade C (level V)
Kogan NM, 2015	Rat femur fractures treated with THC, CBD, THC + CBD, or control	Mid-diaphyseal femur fractures	5–13	NA	THC versus CBD versus CBD + THC versus control	Injection	5 mg/kg CBD and/or 5 mg/kg THC	CBD promoted bone healing; effect potentiated by THC. THC alone did not promote healing.	Grade C (level V)
Nogueira-Filho GR, 2008	Rats with titanium implants exposed to marijuana smoke	Titanium bone implant	30	15	THC	Inhaled	Experimental group inhaled marijuana smoke for 8 min × 60 d	Impaired bone healing. 7 experimental group rats died from respiratory failure.	Grade C (level V)
Liu C, 2019	Periodontal fibroblast cells cultured with THC, CB1 antagonist, or CB2 antagonist media	Human periodontal fibroblast cells	NA	NA	THC versus control	Added to cell culture media	1 μM THC in culture media	Promoted wound healing. Increased fibroblast migration and adhesion.	Grade C (level V)
Del Rio C, 2016	Bleomycin-induced fibrotic wounds treated with CB2 or PPAR agonist CBD quinol	Subcutaneous wounds with bleomycin-induced fibrosis	64	NA	Novel CB2 or PPAR agonist CBD quinol	Injection	Daily 10 mg/kg or 20 mg/kg CBD or PPAR agonist	Impaired wound healing. Decreased fibroblast migration.	Grade C (level V)
Sido JM, 2015	Mouse skin grafts treated with intraperitoneal THC ± CB1 antagonist or control	Allograft and autograft skin graft	45	N/A	THC ± CB1 antagonist versus control	Injection	20 mg/kg THC or 20 mg/kg CB1 antagonist every other day × 14 d	Increased graft survival	Grade C (level V)

*Level of evidence assigned based on the American Society of Plastic Surgeons Evidence Rating Scale and Scale for Grading Recommendations.

BID: twice daily; CB: cannabinoid receptor; CBD: cannibidiol; d: day; NA: Not applicable; NR: Not recorded; PLGA: poly(lactic-co-glycolic acid); PPAR: peroxisome proliferator-activated receptor; min: minutes; TID: 3 times daily; THC: Δ^9-tetrahydrocannibinol; TKA: total knee arthroplasty.

Table 2. Summary of Articles (Human Studies) Examining the Cardiovascular Effects of Cannabis in the Perioperative Period

Authors and Year	Methods	Surgery/ Wound Type	Total No. Surgical Patients	Total No. Users	Drug	Administration Route	Dose	Outcomes	Level of Evidence*
Gregg, 1976	Double-blinded cohort study	Oral	10	10	THC	Intravenous	0.022 mg/kg, 0.044 mg/kg	Increased dose-dependent tachycardia. No difference in blood pressure change	Grade B (level II)
Gregg, 1976	Retrospective cohort	Oral	10	5	Marijuana	Inhaled	Within 72 h of surgery	Increased tachycardia in the post-anesthetic period	Grade B (level II)

* Level of Evidence assigned based on the American Society of Plastic Surgeons Evidence Rating Scale and Scale for Grading Recommendations.
THC: Δ^9-Tetrahydrocannibinol.

Table 3. Summary of Articles (Human Studies) Examining Pulmonary Effects of Cannabis in Perioperative Period

Authors and Year	Methods	Surgery/ Wound Type	Total No. Subjects	Total No. Users	Drug	Administration Route	Dose	Outcomes	Level of Evidence*
Dakour-Aridi, 2019	Retrospective database review based on ICD-9 codes	Lower extremity bypass grafts	50,976	372	Cannabis	NR	NR	Increased graft complications. No difference in overall complications.	Grade C (level II)
Goel, 2020	Retrospective database review based on ICD-9 codes	Various elective surgeries	27,206	13,603	Cannabis	NR	NR	No difference in perioperative respiratory failure.	Grade C (level II)
Mohite, 2017	Retrospective cohort study	Lung transplant	302	19	Cannabis	NR	NR	No different in postoperative pulmonary function among lungs received from user versus non-user donors.	Grade C (level II)

*Level of Evidence assigned based on the American Society of Plastic Surgeons Evidence Rating Scale and Scale for Grading Recommendations.
ICD-9: International Classification of Diseases, Ninth Revision; NR: No t recorded.

Table 4. Summary of Articles (Human Studies) Examining the Hematologic Effects of Cannabis in the Perioperative Period

Authors and Year	Methods	Surgery/ Wound Type	Total No. Surgical Patients	Total No. Users	Drug	Administration Route	Dose	Outcomes	Level of Evidence*
Dakour-Aridi, 2019	Retrospective database review based on ICD-9 codes	Lower extremity bypass grafts	50,976	372	Cannabis	NR	NR	No difference in postoperative bleeding or VTE	Grade B (level II)
Shockcor, 2020	Retrospective database review	Bariatric surgery	146	73	Cannabis	NR	NR	No difference in postoperative bleeding or VTE	Grade B (level II)
Vakharia, 2020	Retrospective database review based on ICD-9 codes	Total knee arthroplasty	18,388	3680	Cannabis	NR	NR	Increased risk of VTE	Grade C (level II)

* Level of Evidence assigned based on the American Society of Plastic Surgeons Evidence Rating Scale and Scale for Grading Recommendations.
ICD-9: International Classification of Diseases, Ninth Revision; NR: not recorded; VTE: venous thromboembolism.

Pulmonary Effects

Much has been written about the acute and chronic pulmonary effects of marijuana use in the general population, including reports of chronic bronchitis, impaired alveolar macrophage function, and higher rates of pulmonary infection.[43] Animal studies suggest that THC may cause respiratory depression via effects on the central nervous system.[44] However, little is known about these effects in surgical patients. Literature review identified only 3 human studies and no animal or pathology studies that addressed the perioperative implications of these effects in the perioperative period.

Among human studies meeting inclusion criteria, 3 retrospective cohort studies examined marijuana use.[45–47] In 1 study, the investigators examined the effect of any recreational drug use (based on ICD-9 codes) on perioperative outcomes among 50,976 patients who underwent lower extremity bypass grafting. When stratified by drug type, there was no difference in risk of pneumonia or respiratory failure among marijuana users compared with non-drug users ($P = 0.36$ and 0.59, respectively). This study is limited by reliance on ICD-9 coding in the electronic medical record and its inability to document the frequency of marijuana administration, which may impact outcomes. Additionally, the study focused on patients undergoing a single type of surgical procedure, but outcomes may differ in patients undergoing procedures of longer duration.[45]

A second retrospective cohort study of 27,206 patients compared perioperative complication rates between cannabis users versus non-users undergoing a variety of

elective surgeries, including cardiac, gynecologic, orthopedic, and general surgery. There was no significant difference in the incidence of respiratory failure in cannabis users compared with non-users (OR = 0.91, CI 0.74–1.13, $P = 0.396$). Although this study examined patients undergoing a wide range of surgical procedures, it is limited by reliance on medical record review.[46]

A third study examined the effect of cannabis smoking in lung donors on the perioperative outcomes of the lung transplant recipients. In total, 302 patients (19 cannabis users, 283 non-users) were monitored for an average of 6 years after lung transplant. There were no significant differences in postoperative pulmonary function testing, as measured by forced expiratory volume (FEV1) in patients who received lungs from cannabis users versus recipients of lungs from non-users. This study is limited by the small number of cannabis users and reliance on medical record documentation and family reports to determine whether donors were cannabis users.[47]

Overall, very few studies have examined the role of cannabis on pulmonary physiology. Animal and human studies in nonsurgical settings suggest that THC has detrimental effects on respiratory rate, tidal volume, CO_2 retention, and development of pneumonia or bronchitis.[48] Surprisingly, the few studies we identified examining the pulmonary effects of cannabis in surgical patients did not observe a difference in pulmonary outcomes. However, these are limited by retrospective methodology and small sample sizes. It remains unclear whether other formulations of cannabis, doses, or routes of administration would have different effects on pulmonary physiology. Additional research is needed in this area to clarify the pulmonary effects of cannabis on surgical patients.

Hematologic Effects

Reports of in vitro and in vivo effects of cannabinoids on platelet activity are inconsistent. Although some demonstrate that THC and CBD inhibit platelet aggregation in a dose-dependent manner,[49] others suggest the opposite.[50] No animal or pathology studies met the inclusion criteria. Only 3 human studies met the inclusion criteria, and these were retrospective cohort studies with contradictory outcomes. One study of bariatric patients found no difference in complications between cannabis users (n = 73) and non-users (n = 73).[51] Specifically, there was no difference in rates of bleeding or venous thromboembolism (VTE) ($P = 0.154$ and 0.316, respectively) in this study with a small sample size. In a study examining outcomes in cannabis versus non-users undergoing lower extremity bypass procedures (n = 50,976), there was an increased incidence of vascular graft complications among cannabis users ($P = 0.03$). However, there was no difference in rates of deep vein thrombosis or pulmonary embolism ($P = 1.00$ and $P = 0.44$, respectively).[45] In contrast, Vakharia *et al.* found an increased rate of VTE and pulmonary embolism among cannabis users following total knee arthroplasty ($P < 0.001$, OR 1.58 and $P < 0.01$, OR 1.58, respectively).[52] Notably, all studies lacked data regarding cannabis dosing, frequency, and administration route, as cannabis users were identified using ICD-9 coding. Given these conflicting outcomes and variable methodologies, additional research in this area is required.

CONCLUSIONS

As cannabis use has become increasingly prevalent, surgeons must be aware of its potential effects in the perioperative setting, particularly as these relate to wound healing and cardiovascular, pulmonary, and hematologic function. Several studies have explored the effects of cannabis on perioperative pain, but little is known about its effects on wound healing, or cardiovascular, pulmonary, or hematologic physiology. Much of the literature examining the effects of cannabis is limited by inconsistent formulation, route, and timing of administration. Further research is needed to elucidate the effects of route of administration (eg, topical, ingestible, inhalational), dose/duration, and timing of cannabis use among surgical patients, and other potential side effects of cannabis.

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