

Comorbidities in a Lymphedema Population Receiving Suboxone or Methadone Treatment

Sondra Willis OTR/L, CLT-LANA

Katelynn Callahan OTR/L, CLT

Berkshire Medical Center

Author Note

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Abstract

Interest in this study developed when therapists at Massachusetts' Berkshire Medical Lymphedema Clinic observed a pattern of pain, fibrosis, and rapid onset of edema in the patient population prescribed suboxone or methadone. Additionally, response to Combined Decongestive Therapy (CDT) was slower- often with incomplete resolution. Research has demonstrated that preventative intervention can limit the progression of lymphedema (Dietrich et al., 2022). If providers were aware of risk factors for developing lymphedema, then they could become partners in prevention of secondary lymphedema in this patient population.

A retrospective chart review was performed of 24 patients. Some patients were in substance use recovery, and some were prescribed suboxone as an alternative to opioid pain management. These patients, 9 males and 15 females, had participated in an initial evaluation with a certified lymphedema therapist. They were prescribed either Suboxone 16/24 or Methadone 8/24 therapy. These patients ranged in age from 24- 72 with a mean age of 48. 96% had lower extremity lymphedema.

The 285 individual comorbid diagnoses were categorized into systems. 18% of the diagnoses were not easily narrowed to one system. These were labeled as multi-system. The three most frequent categorizable systems were: digestive which occurred at a rate of 10.4%, integumentary at 8.98%, and respiratory at a rate of 8.60%.

Known comorbidities for lymphedema in the general population occur frequently within the population of persons taking Suboxone or Methadone. The most common diagnoses included cellulitis (56%), hypertension (48%), anxiety (48%), obesity (44%), depression (40%) and neuropathy and/or orthopedic injury (40%).

Two diagnoses occurring more frequently than the general population are nicotine dependence (60%) and abdominal pain (40%). This warrants further investigation, as these diagnoses are associated

with inflammation which can cause disruption to lymphatic function. (Lee, Taneja & Vassallo, 2012) (Ly, Kataru & Babak, 2017)

Recovering from opioid addiction is challenging. Prescription use of Methadone or Suboxone has become a foundation for substance use recovery. Unfortunately, edema or swelling is a possible side effect of Suboxone and Methadone (Merative, Micromedex, 2023; O'Connor, Woody, Yeh, Manny, et al. 1991). When this swelling becomes chronic, it is a sign of lymphatic dysfunction, or lymphedema. Suggested causes of Suboxone and Methadone edema include inflammatory cell response, as well as mechanisms which increase venous permeability (O'Connor et al. 1991, Radparvar, 2022). This is an introductory study which attempted to see if pre-existing medical conditions could be used to identify patients at higher risk for developing lymphedema when prescribed Suboxone or Methadone. With this knowledge, providers could refer at-risk patients for prospective surveillance lymphedema care.

Interest in this study developed when therapists at Massachusetts' Berkshire Medical Lymphedema Clinic observed a pattern of pain, fibrosis, and rapid onset in patients referred for lymphedema care who were prescribed Suboxone or Methadone. Additionally, response to Combined Decongestive Therapy (CDT) for these patients was slower - often with incomplete resolution. Although there is limited research on lymphedema in this population, there is extensive research on lymphedema of other etiologies which shows that early or preventative intervention can limit disease progression (Dietrich, Gaitatzis, Koelmeyer, Boyages, et al. 2022).

The goal of this study was to identify medical conditions that may predispose this patient population to develop lymphedema. It is very important to understand that the following diagnoses are not being suggested as proof of lymphedema causation. This is just a starting point for consideration as lymphedema is a complex condition that continues to be better understood every day.

Method

Method and Participants

A retrospective chart review was performed on 24 patients. Nineteen patients were documented as substance use recovery patients, four were prescribed suboxone as an alternative to

opioid pain management, and one person had an uncertain history of illicit drug use. They were prescribed either Suboxone 16/24, or Methadone 8/24. These patients, 9 males and 15 females, had participated in an initial evaluation with a certified lymphedema therapist. Patients ranged in age from 24 - 72 with a mean age of 48. Ninety six percent had lower extremity lymphedema- the remaining had upper extremity lymphedema.

Results

A total of 285 individual comorbid diagnoses were identified with a rate of occurrence of 779. Those occurring at a rate of 40% or higher are in Table 1. The most frequent diagnoses were, as expected, lymphedema/edema at 88% or 22/24 patients, opioid use disorder 64% or 16/24 patients and substance use disorder 44% or 11/24 patients. Following these diagnoses were: tobacco/nicotine dependence 60% or 15/24 patients, cellulitis 56% or 14/24 patients, anxiety and hypertension both at 48% or 12/24 patients, obesity and vitamin D deficiency both at 44% or 11/24 patients, and abdominal pain, depression, headache/migraines, neuropathy, and orthopedic injury all at 40% or 10/24 patients.

In order to better analyze the 285 diverse diagnoses, the individual diagnoses were categorized into 14 systems or categories. Approximately 18% of the comorbid diagnoses were not easily narrowed to one system. These were labeled as multi-system. The multi-system category consisted of 51 comorbid diagnoses with a total of 194/779 or 25% of total occurrences. Details of the 16 multi-system diagnoses that affected more than 20% of the patients in this study are in Table 2. As shown in column one, this is the only category in which the number of occurrences is equal to the number of patients with that comorbid diagnosis. Tobacco use disorder occurred most frequently as 60% of the multi-system diagnoses, but this was only 7.7% of all of the multi-system diagnoses. Obesity and Vitamin D deficiency were also labeled as a multi-system disorders and they each affected 44% the patients with 5.7% of the occurrences. Forty percent of patients were diagnosed with headaches or migraines which made up 5.2% of the multi-system occurrences. Hypokalemia, or below normal blood potassium level, occurred in

36% of this population which is 4.6% of multi-system occurrences. Anemia, chronic fatigue syndrome, ear pain, and insomnia each affected 24% of the patients with an occurrence of 3.1%. The last group of comorbid diagnoses which each affected 20% of this population included: alcohol abuse, COVID 19, fall risk, liver steatosis, post-concussion syndrome, and sepsis at a rate of 2.6% of the 194 multi-system occurrences.

Diagnoses which were able to be assigned to a category can be found in Table 3. Following the multi-system category with 24.9% of the diagnoses was digestive with 10.4% of the diagnoses. The digestive category was comprised of 35 comorbid diagnoses which occurred 87 times in this patient population. The integumentary category followed with 34 comorbid diagnoses which occurred 70 times comprising 9% of the diagnoses. There were 21 diagnoses assigned to the respiratory category with an occurrence of 67 times or 8.6% of the diagnoses. The mental health category had 12 diagnoses which occurred 56 times which is 7.2% of the diagnoses. The skeletal category had 26 diagnoses which occurred 54 times making up 6.9% of the diagnoses. The lymphatic category also included immune diagnoses as these systems are closely related. It is interesting to note that not all patients were diagnosed with lymphedema despite the fact that they all had been referred for lymphedema evaluation and treatment. The lymphatic/immune category had 16 diagnoses which occurred 52 times or 6.7% of the diagnoses. The nervous system was another category with 52 occurrences or 6.7% of the diagnoses, however, this category had 23 different diagnoses. The cardiovascular category was comprised of 17 different comorbidities with 43 occurrences or 5.5% of the total. All remaining categories of: reproductive, urinary, vascular, endocrine, and muscular had less than 5% of the occurrences.

Table 1

Comorbid Diagnoses

Diagnosis	Number (out of 24 patients)	Percent (number/24 patients)
Edema/ Lymphedema	22	88%
Opioid use disorder/substance use disorder	16/ 11	64%/ 44%
Tobacco/nicotine dependence	15	60%
Cellulitis	14	56%
Anxiety (w/ and w/o attacks)	12	48%
Hypertension	12	48%
Obesity/Morbid Obesity	11	44%
Vitamin D deficiency	11	44%
Abdominal pain	10	40%
Depression/Major Depressive disorder	10	40%
Headache/ Migraines	10	40%
Neuropathy	10	40%
Orthopedic Injury	10	40%

Table 2

Multi-Symptom Diagnoses

Diagnosis	Number (out of 24 patients,194 multi-system diagnoses)	Percent of patients (number/24 patients)	Percent of multi- system diagnoses (number/194)
Tobacco use disorder	15	60	7.7%
Obesity	11	44	5.7%
Vitamin D deficiency	11	44	5.7%
Headache/ Migraine	10	40	5.2%
Hypokalemia	9	36	4.6%
Chronic pain syndrome	7	28	3.6%
Anemia	6	24	3.1%
Chronic Fatigue syndrome	6	24	3.1%
Ear pain/dysfunction	6	24	3.1%
Insomnia	6	24	3.1%
Alcohol abuse	5	20	2.6%
COVID 19	5	20	2.6%
Fall/Fall risk	5	20	2.6%
Liver steatosis	5	20	2.6%
Post concussion syndrome	5	20	2.6%
Sepsis	5	20	2.6%

Table 3

Diagnoses by category

Category/System	Number of diagnoses (out of 285)	Occurrences (out of 779)	Rate of occurrence (system occurrence/779)
Multi-system	51	194	24.9%
Digestive	35	87	10.4%
Integumentary	34	70	9.0%
Respiratory	21	67	8.6%
Mental Health	12	56	7.2%
Skeletal	26	54	6.9%
Lymphatic/Immune	16	52	6.7%
Nervous	23	52	6.7%
Cardiovascular	17	43	5.5%
Reproductive	14	30	3.9%
Urinary	14	30	3.9%
Vascular	13	25	3.2%
Endocrine	5	10	1.8%
Muscular	2	3	0.4%

Discussion

This study found that many known comorbidities for lymphedema in the general population also occur frequently within the population of persons taking Suboxone or Methadone. It's important to note that this is a clinical observation as published lymphedema research in patients without cancer is scarce. In the following section, a discussion of the most frequent comorbidities is developed to suggest a possible rationale for their occurrence in this study population.

Cellulitis, Sepsis/Integumentary diagnoses

Cellulitis and wounds are often the impetus for a referral to a lymphedema therapist. In these cases, insults to the integumentary system often occur as a result of long-term lymphatic dysfunction. Additionally, scarring can create a setting in which lymphatic dysfunction progresses. Intravenous (IV) drug use increases the risk of cellulitis and wounds due to unsanitary needle use, infiltration and track

line scarring. Cellulitis or integumentary disorders such as wounds, eczema or psoriasis are possible risk factors for lymphedema in this population.

Abdominal pain, Obesity, Vitamin D deficiency/Digestive diagnoses

The lymphatic system plays a key role in digestion as it has the responsibility for picking up fatty acids and vitamins, such as vitamin D which are dissolved in fat making them too large to enter the venous capillaries (NIH National Cancer Institute, 2023). The lymphatic system returns these nutrients to the cardiovascular system to be used as needed throughout the body. The digestive and lymphatic systems develop closely during embryonic development which gives them a similar form and function relationship. (Pansky, 1982)

Inflammation is a hallmark of lymphedema (Ly, Kataru, & Mehrara, 2017). Persons who are diagnosed with obesity are at a higher risk for lymphedema as obesity has been accepted as “a persistent state of low-grade inflammation” (Emerenziani et al. 2019 Pancreatitis section, para 1). Patients with digestive diagnoses such as obesity, reflux, and frequent constipation may also be at risk for developing lymphedema.

Tobacco use disorder/Respiratory diagnoses

According to the CDC tobacco use in the general population is 11.5% (Center for Disease Control, 2023), however, the NIH reports that tobacco use rates are 65-85% among persons in substance use recovery. (NIDA, 2023) Cigarette smoke has been identified as a cause of inflammation and immune suppression (Lee, Taneja, & Vassalo, 2012). The lymphatic system has a key role in immune response and it becomes impaired when exposed to long-term inflammation. It follows that tobacco use, and diagnoses such as Asthma, Dyspnea, shortness of breath, obstructive sleep apnea, and/or a history of bronchitis or pneumonia could also indicate risk for the development of lymphedema.

Anxiety, Depression/Mental health diagnoses

Mental health diagnoses such as anxiety and depression are higher for the population in this study than the average in Massachusetts according to a recent study (KFF's Health Facts 2020-2023). Research does show that the lymphedema population experiences a higher rate of negative self-identity and emotional disturbance (Fu, Ridner, Hu, Stewart et. al.2013). Mental health as an isolated diagnosis does not easily lend itself to causation, however, it does play a strong role in stress and self-care which includes seeking professional help for edema.

Orthopedic injury/Neuropathy/Muscle & Skeletal diagnoses

Lymphedema can develop following orthopedic surgery or injury because the body's capacity to compensate for post insult swelling is overwhelmed. Every person has a different capacity for transporting lymph fluid. A person with a low lymphatic transport capacity will often be unaware of their predisposition until they are recovering from an injury which impairs muscle use. Muscle use promotes lower extremity venous fluid movement (Cleveland Clinic, 2022). A simple way of looking at this is that optimal venous motility relies on muscular mobility. Persons diagnosed with neuropathy and/or fall risk also have this higher risk of lymphedema due to altered/impaired muscle use. This is another example of the interrelationship between the venous motility and muscular mobility.

Hypokalemia/Hypertension/ Vascular diagnoses

It follows that, persons with vascular diagnoses such as deep vein thrombosis, and or chronic venous insufficiency (CVI) will also have a higher risk of lymphedema. The lymphatic system makes up for deficits in vascular function, however the lymphatic transport capacity of each person varies in its capacity. As explained previously venous malfunction can result in increased fluid in the interstitium which increases the lymphatic load.

Hypertension also increases the lymphatic load in a different way because it causes damage to the glycocalyx. Glycocalyx regulates the health of and the permeability of the lining of the vascular lumen. When it gets damaged by factors like hypertension and inflammation, interstitial permeability increases (Jin, Fang, Gao, Chen, et al.2021), this can lead to lymphedema.

The lymphatic system uses smooth muscle pumping action in the collecting vessels of the lymphangions for the transportation of lymphatic fluid. Hypokalemia impairs smooth muscle regulation. A 2017 study found preliminary evidence that persons with a variation in potassium channel genes were more likely to develop lymphedema following breast cancer treatment (Smoot, Kober, Paul, Levine et al.). Potassium's influence on lymphatic function is just starting to be understood, but should be a consideration when assessing lymphedema risk.

Some of the conditions that have not been addressed individually include: Chronic pain syndrome/Hepatitis C/Chronic Fatigue/Anemia/Post-concussive syndrome/Insomnia/ Ear pain/Alcohol abuse/ Liver steatosis/ Headaches. These are among many other diagnoses with a basis of inflammation, venous disorder, or impaired musculoskeletal use.

What this study means to practitioners

Health practitioners should use knowledge of their patient's past medical history, as well as severity and frequency of these comorbid diagnoses to decide if a patient is at risk of developing lymphedema. It is also important to know if the patient has track lines and where they are located. Track lines are areas of scarring that develop from frequent injection site use. This scarring could impair drainage in the inferior portion of the corresponding extremity. Appropriate referral for baseline measurements, education, and supportive monitoring could reduce the rate of lymphedema and its complications for this population. Perhaps use of bioimpedance spectroscopy, which has been used successfully to monitor for subclinical lymphedema in the breast cancer population, may also serve this

population. The overriding goal is to reduce the number of obstacles for persons in substance use recovery as well as persons dealing with chronic pain.

Areas for improvement

To improve upon this research, it would be important to identify which diagnoses pre-dated the use of Suboxone or Methadone. This chart review did not determine the dates for when each diagnosis was made. A greater number of study participants is always helpful. A more uniform set of diagnoses would also be helpful. For example, one practitioner may diagnose opioid use disorder where a different practitioner would diagnose substance use disorder. Furthermore, severity and frequency of diagnoses were not addressed in this study. Finally, the existence of and onset of edema would need to be accurately identified with pre and post medication use measurements.

In preparing for this research, it was found that most studies, outside of case studies, focused on upper extremity and puffy hand syndrome. Previous research focused on pregnancy, injection practices, and cellulitis or DVT history which is common in the intravenous (IV) drug use population (Dean, 2020, Gaghan, Bodie, & Mervak 2021). That makes the current study's information on lower extremity patients beneficial.

Directions for future research

Future research on patients with lymphedema taking Suboxone or Methadone could also consider that this group's tobacco use is significantly greater than the general population. Since tobacco use is associated with changes to the peripheral blood flow, this may be a key factor in the development of lymphedema, as well as the presentation of a more painful and more difficult to treat condition. The medications should also be studied independently. This study grouped Methadone, Suboxone (Buprenorphine/Naloxone), and Buprenorphine together. A case study suggested that the presence of Naloxone may be the trigger for edema/swelling (Radparvar, 2022). Another case study showed a direct

relationship to Methadone dosage and lower extremity edema (O'Connor, et. al 1991), These are different drugs with different effects on opioid receptor sites, so this should be investigated more critically.

It is hoped that this introductory study adds to and inspires research to further the understanding of and preventative treatment of lymphedema for persons who are prescribed Methadone or Suboxone.

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