Retrospective Observational Database Study of Patients with Long COVID with Multi-Site Pain, Fatigue, and Insomnia: A Real-World Analysis of Symptomatology and Opioid Use

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INTRODUCTION

Post-Acute sequelae of SARS-CoV-2 infection (PASC), or Long COVID, includes a broad constellation of symptoms that persist after resolution of acute COVID-19 infection. Descriptions of pain reported in PASC patients include diffuse myalgias, arthralgias, musculoskeletal pain, headaches, chest pain, abdominal pain, and generalized "body ache". In many patients, multiple sources/sites of pain are reported (Lambert et al., 2021). The prevalence of persistent pain (i.e., at 8 to 12 weeks) reported in PASC patients has been shown to vary from 20% to 64% with an overall average of approximately 30% (Lambert et al., 2021; Jiang et al., 2021). The co-occurrence of multi-site pain, fatigue, and sleep disturbance is similar to central sensitization symptoms found in other post-viral pain syndromes, which may reflect a common underlying nociplastic mechanism (Clauw et al., 2020, Goudman et al., 2021). Fibromyalgia and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) are examples of such chronic overlapping pain syndromes. Much remains to be learned about the prevalence and overlaps of these symptoms, particularly multi-site pain, fatigue, and insomnia, which characterize these nociplastic pain syndromes. The present study retrospectively evaluated the prevalence, clinical features, demographics, and use of opioids analgesics in PASC patients with chronic complex multi-site pain, fatigue, and insomnia.

METHODS

We conducted a retrospective observational electronic health record (EHR) database study based on data from a federated network of linked electronic health records from 48 healthcare organizations, totaling 75.2 million patients since 2010. The analysis sample included patients aged 18-65 years with confirmed COVID-19 diagnosis or positive PCR test in any setting of care (January, 2020 to November, 2021), a PASC diagnosis based on the identification algorithm developed by Taquet, at least one healthcare encounter ≥ 180 days following the first COVID-19 diagnosis code or positive PCR test (index date), at least one PASC symptom as defined by Topalogu (Topaloglu et al., 2018), and multi-site pain present over days 91-180 post-index (Taquet et al., 2021). Diagnostic codes (Figure 1, Table 2) were used to capture centrally-mediated, nociplastic pain components. An algorithm for patient selection included diagnoses associated with diffuse pain or more than two anatomically distinct sources of pain (i.e., multi-site pain). Patients with multi-site pain were further divided into four non-overlapping groups: (1) pain only, (2) pain with fatigue, (3) pain with insomnia, and (4) pain with fatigue and insomnia.

Figure 1: Diagnostic Codes

Confirmed COVID-19: Any COVID-19 related diagnosis code (ICD-10-CM) or positive PCR test (LOINC) occurring on or after January 20, 2020.

- J12.82 Pneumonia due to COVID-19 — > 18-65 years
- OR
- B34.2 Coronavirus infection, unspecified — > 18-65 years
- OR
- B97.29 Other coronavirus as the cause of diseases classified elsewhere — > 18-65 years
- OR
- J12.81 Pneumonia due to SARS-associated coronavirus — > 18-65 years
- OR
- U07.1 COVID-19 — > 18-65 years
- OR
- U09.9 Post COVID-19 condition, unspecified — > 18-65 years
- OR
- 9088 SARS coronavirus 2 and related RNA [Presence] — > 18-65 years AND Positive, ever

Excluding those with diagnosis of other specified viral infection on or after January 20, 2020
- 079.89 Other specified viral infection

Fatigue
- R53 Malaise and fatigue
- OR
- G93.3 Postviral fatigue syndrome

Insomnia
- G47.0 Insomnia
- OR
- F51.0 Insomnia not due to a substance or known physiological condition

Table 1: Demographics

Measure	COVID-19	All PASC	PASC No Multi-site Pain	PASC Multi-site Pain
n	260,082	52,322	30,628	21,694
Age	43.7±13.7	43.8±13.2	43.6±13.5	47.3±12.4
Female	62.2%	69.4%	69.2%	69.7%
Race				
Caucasian	62.3%	66.6%	68.9%	62.9%
Black	22.0%	20.3%	18.5%	24.8%
Other	2.7%	2.1%	2.1%	2.1%
Unknown	13.0%	10.0%	10.5%	10.2%

RESULTS

- 21,694 patients met the criteria for PASC and multi-site pain (41.5% of the sample) **(Figure 2).**
- Patients with PASC were similar in age to patients with acute COVID (43.7 years versus 43.8 years, respectively).
- PASC symptoms were present in a predominantly female population (69.2% female among PASC patients with no multi-site pain and 69.7% female among PASC patients with multi-site pain) **(Table 1)**.
- Somatic symptoms of PASC involving the respiratory and gastrointestinal systems occur in approximately equal frequencies 12.2-12.7% (respiratory) and 15.6-17.3% (abdominal) whether or not multisite pain is present. Patients with insomnia or fatigue generally had increased prevalence of respiratory (31.5-38.6%) and GI symptoms (23.4-36.5%).
- Anxiety and depression were present in almost 70% of the PASC study population. However, patients with multi-site pain reported lower symptoms of depression and anxiety (29.7%) **(Figure 3)**.
- Opioid use in PASC patients without multi-site pain was approximately 19% and in patients with multi-site pain was 34.0%. Increased opioid use was observed in patients with multi-site pain and fatigue (39%) or insomnia (50%) and both fatigue and insomnia (51%) **(Figure 4).**
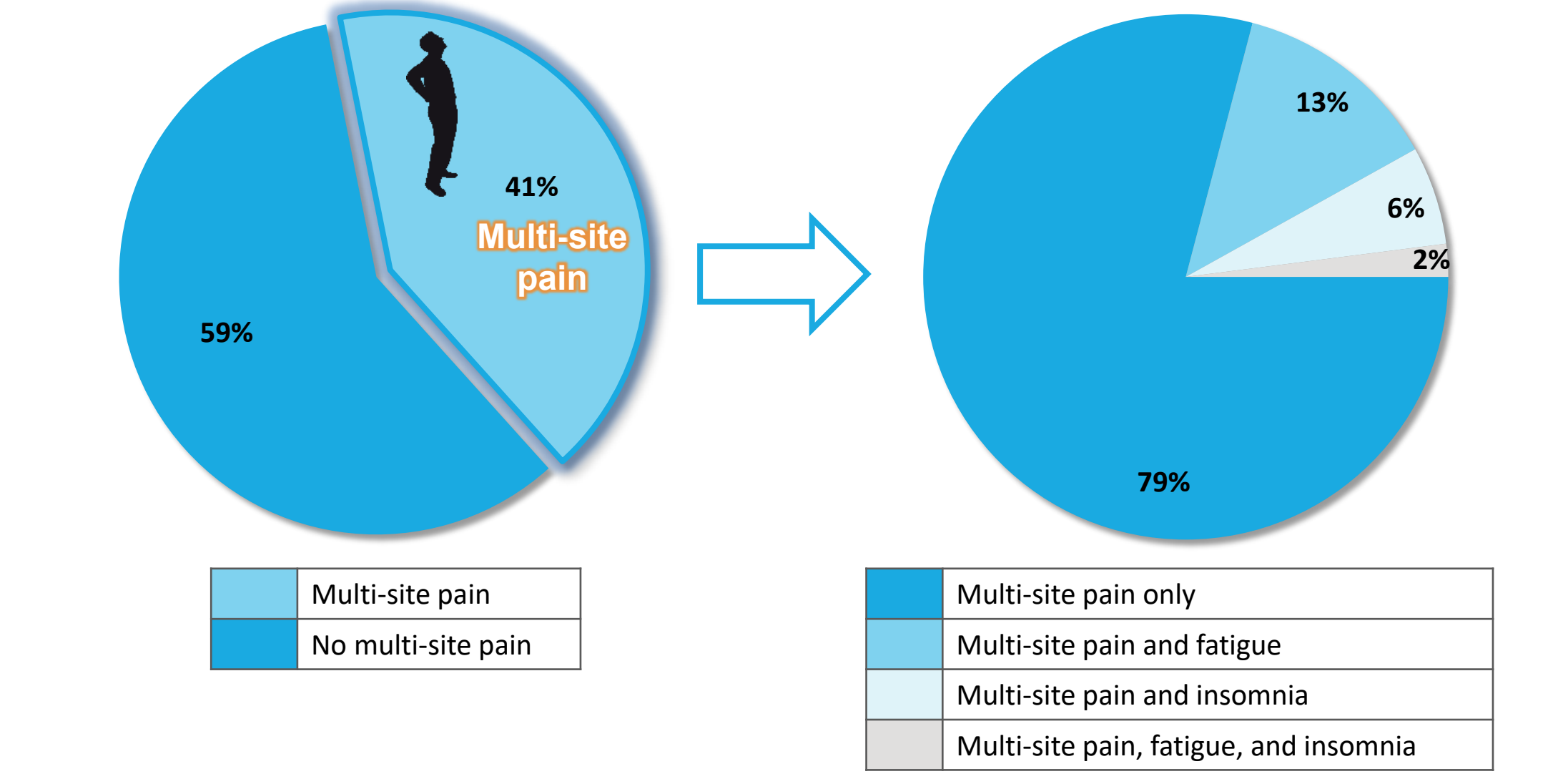
Figure 2: Multi-Site Pain in Approximately 40% of Patients

- 59% No multi-site pain
- 41% Multi-site pain
- 13% Multi-site pain only
- 79% Multi-site pain and fatigue
- 6% Multi-site pain and insomnia
- 2% Multi-site pain, fatigue, and insomnia

Table 2: Pain-Related Diagnoses for Multi-site Pain

Pain Diagnosis (ICD-10-CM)	PASC Multi-site Pain Cohort			
	- Fatigue - Insomnia	+ Fatigue - Insomnia	- Fatigue + Insomnia	+ Fatigue + Insomnia
n	17,160	2,782	1,314	438
Migraine (G43)	14.9%	18.4%	21.4%	25.8%
Other headache syndromes (G44)	4.9%	6.1%	6.5%	7.1%
Pain, not elsewhere classified (G89)	50.5%	42.3%	59.6%	54.8%
Chronic pain not elsewhere classified (G89.2)	40.4%	33.1%	47.3%	44.7%
Chronic pain syndrome (G89.4)	6.6%	6.6%	10.4%	9.1%
Pain in joint (M25.5)	39.1%	37.6%	37.3%	41.3%
Lumbago with sciatica (M54.4)	6.1%	4.6%	7.1%	8.0%
Lower back pain (M54.5)	17.2%	15.6%	17.2%	20.8%
Other dorsalgia (M54.89)	0.9%	1.2%	1.5%	N/A
Myositis (M60)	2.3%	3.1%	2.8%	N/A
Other and unspecified soft tissue disorders, not elsewhere classified (M79)	42.0%	50.2%	39.5%	53.4%
Myalgia (M79.1)	12.3%	20.5%	9.9%	26.5%
Pain in hand, foot, fingers and toes (M79.7)	22.7%	22.6%	19.5%	19.4%
Fibromyalgia (M79.7)	9.6%	11.9%	13.7%	15.1%
Pain in throat and chest (R07)	18.5%	27.5%	19.6%	29.7%
Headache (R51)	14.3%	24.1%	15.3%	26.0%
Pain, unspecified (R52)	8.6%	12.3%	6.6%	13.0%

"-" indicates absence of symptom; "+" indicates presence of symptom

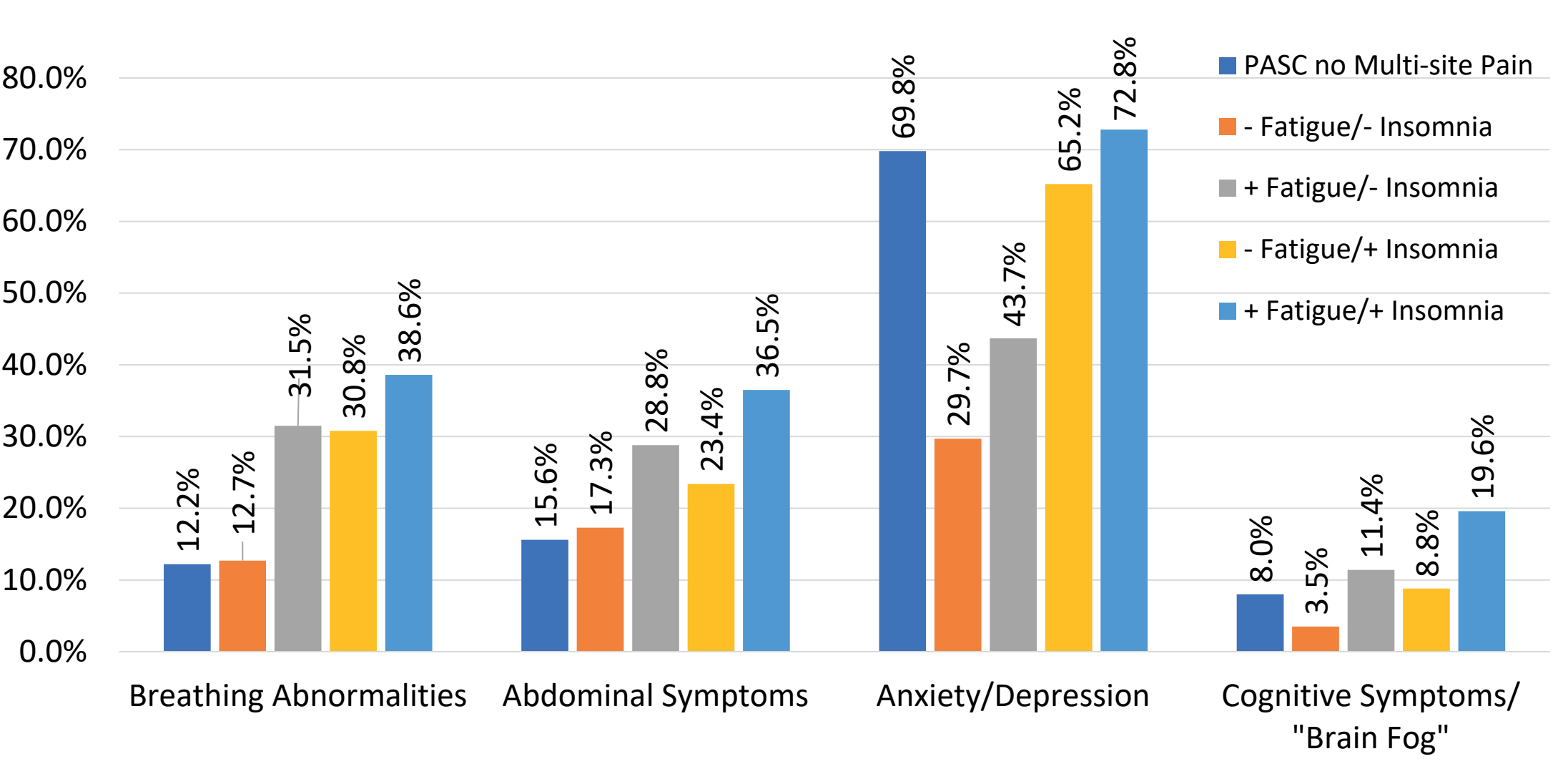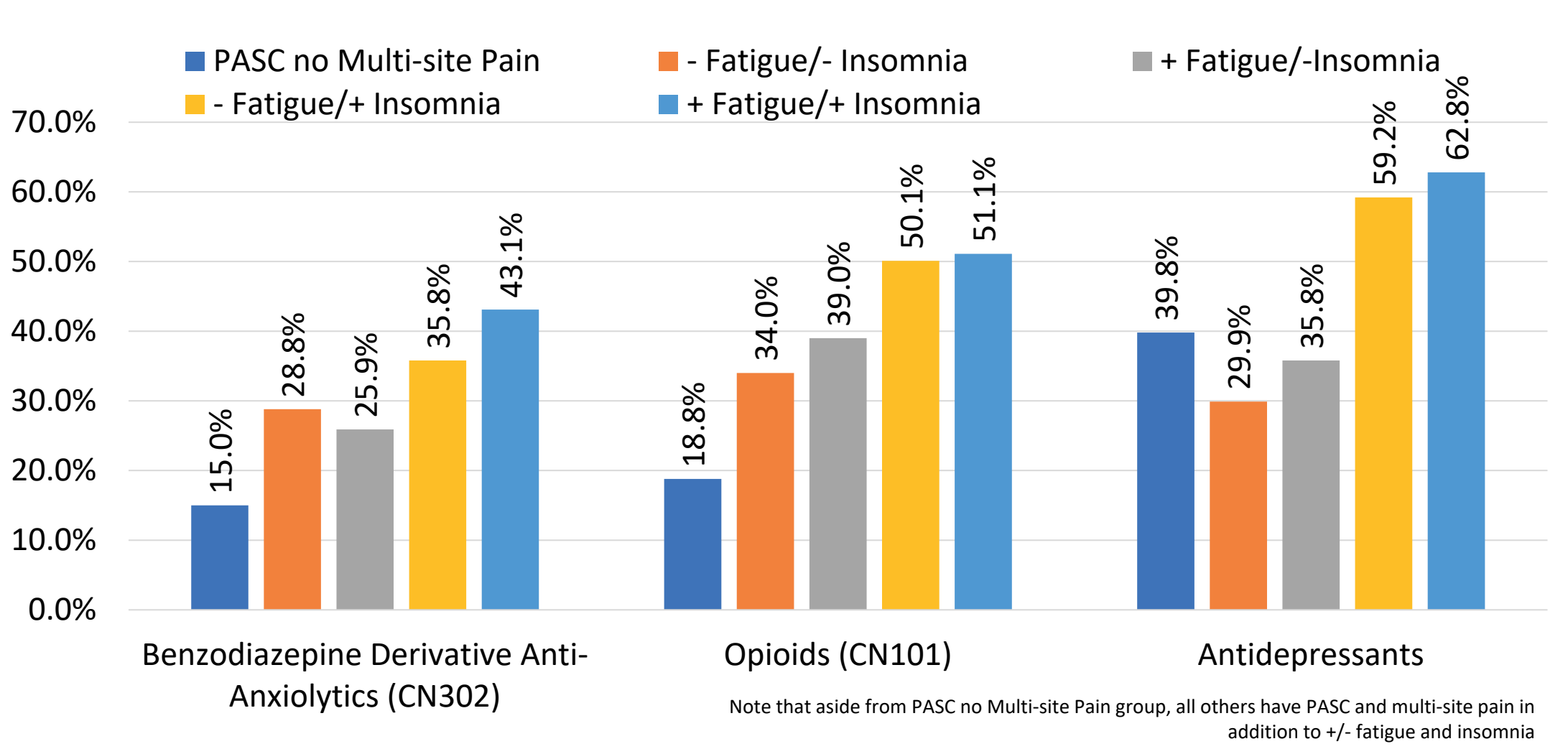### Figure 3: Prevalence of Core Symptoms in Patients with PASC

Legend: PASC no Multi-site Pain; - Fatigue/- Insomnia; + Fatigue/- Insomnia; - Fatigue/+ Insomnia; + Fatigue/+ Insomnia

	PASC no Multi-site Pain	- Fatigue/- Insomnia	+ Fatigue/- Insomnia	- Fatigue/+ Insomnia	+ Fatigue/+ Insomnia
Breathing Abnormalities	12.2%	12.7%	31.5%	30.8%	38.6%
Abdominal Symptoms	15.6%	17.3%	28.8%	23.4%	36.5%
Anxiety/Depression	69.8%	29.7%	43.7%	65.2%	72.8%
Cognitive Symptoms/"Brain Fog"	8.0%	3.5%	11.4%	8.8%	19.6%

Figure 4: Opioid and Non-Opioid Analgesic Use among Patients with PASC

Legend: PASC no Multi-site Pain; - Fatigue/- Insomnia; - Fatigue/+ Insomnia; + Fatigue/-Insomnia; + Fatigue/+ Insomnia

	PASC no Multi-site Pain	- Fatigue/- Insomnia	+ Fatigue/-Insomnia	- Fatigue/+ Insomnia	+ Fatigue/+ Insomnia
Benzodiazepine Derivative Anti-Anxiolytics (CN302)	15.0%	28.8%	25.9%	35.8%	43.1%
Opioids (CN101)	18.8%	34.0%	39.0%	50.1%	51.1%
Antidepressants	39.8%	29.9%	35.8%	59.2%	62.8%

Note that aside from PASC no Multi-site Pain group, all others have PASC and multi-site pain in addition to +/- fatigue and insomnia

DISCUSSION & CONCLUSIONS

- PASC has been reported in approximately 30% of patients who recover from the acute infection.
- Complex multi-site pain symptoms are prevalent among patients with PASC (41.5%) and are often cited as most affecting quality of life and the ability to return to full-time work.
- Other symptoms commonly reported in patients with PASC are fatigue, sleep disturbances, and cognitive/memory issues. This cluster of symptoms is reminiscent of central sensitization syndromes, including fibromyalgia and ME/CFS (U.S. HHS National Research Action Plan on Long COVID August 9, 2022).
- PASC patients with multi-site pain had relatively low anxiety, which may relate to central processing of distress signals being differentially interpreted.
- The co-occurrence of fatigue and/or insomnia with multi-site pain symptoms was associated with greater medication burden including benzodiazepines, anti-inflammatory drugs, and analgesics.
- Opioid use noted was 34% in patients with multi-site pain only, further increased to 39% in patients with multi-site pain and fatigue, and exceeded 50% in patients with multi-site pain, fatigue, and insomnia. The high rate of opioid use in this large, growing and vulnerable population is a potentially significant emerging public health concern.
- Currently, there is no therapy approved by the FDA for the treatment of multi-site pain associated with PASC. The central sensitization (or nociplastic) characteristics of multi-site pain in PASC suggest classes of drugs such as opioids should be used with caution or avoided in this subset of patients.

References

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