

The Burden of Pain Symptoms in Individuals with Uterine Fibroids—Results from a Prospective Observational Study in the USA

Elke Hunsche¹, Nell J Marshall², Jermyn Z See², Viatcheslav G Rakov¹, Barbara Levy³

¹Sumitomo Pharma Switzerland GmbH, Basel, Switzerland; ²Evidation Health Inc, San Mateo, CA, USA; ³Department of Obstetrics and Gynecology, University of California, San Diego, San Diego, CA, USA; Department of Obstetrics and Gynecology, The George Washington University, Washington, DC, USA

Correspondence: Elke Hunsche, Global Market Access and Health Economics / Outcomes Research, Sumitomo Pharma Switzerland GmbH, Aeschengraben 27, Basel, 4051, Switzerland, Tel +41 43 210 8129, Email elke.hunsche@ch.sumitomo-pharma.com

Purpose: To characterize the burden of uterine fibroids (UF) in individuals experiencing heavy menstrual bleeding (HMB) and moderate-to-severe UF-associated pain in terms of symptoms experienced, impact on work and activities, and pain medication use both on menstrual and non-menstrual days.

Patients and Methods: This prospective, real-world, observational study enrolled 350 participants in the USA with a self-reported UF diagnosis, HMB, and moderate-to-severe pain due to UF. Data collection took place from February 9 to July 19, 2021. Over 4 months, participants used an online platform to self-report daily menstrual status, bleeding intensity, UF-associated pain severity, and pain medication use, and to complete weekly work and productivity questionnaires. Results were analyzed descriptively and are reported for the overall population, by pain medication subgroups—defined based on the most potent medication taken—and menstrual versus non-menstrual days/weeks.

Results: The analysis population consisted of 307 participants with ≤ 5 consecutive missing days of daily survey responses or $\geq 75\%$ completion rate of the daily surveys. Mean age of participants (standard deviation; SD) was 37.2 (6.3) years. At baseline, 54.1% of participants reported not currently taking medication for treatment of HMB. Over the study period, mean UF-associated pain scores (SD; scale range 0–10) were higher on menstrual days (3.5 [2.7]) than non-menstrual days (1.0 [1.8]), and this was consistent across medication use subgroups. Pain medications were used more frequently on menstrual days than non-menstrual days (22.9% versus 3.7% days of pain medication use, respectively). Participants reported 31.5% work impairment on menstrual weeks versus a 12.7% work impairment on non-menstrual weeks.

Conclusion: In this study, UF-associated pain symptoms coincided with a reduction in individuals' ability to take part in both work and non-work activities and an increase in pain medication use, particularly during menstrual weeks. These results highlight the need for improved diagnosis and pain management strategies in UF.

Keywords: UF symptoms, heavy menstrual bleeding, pain medication, work productivity

Introduction

Uterine fibroids (UF) are the most common solid non-malignant neoplasms in females, and are estimated to occur in up to 70% of females prior to menopause.^{1–5} Although many individuals with UF remain asymptomatic, 20–50% experience symptoms⁶ including heavy menstrual bleeding (HMB, which may lead to anemia), menstrual and non-menstrual pelvic pain, pelvic pressure, and urinary as well as obstructive symptoms; impaired fertility may also be associated with UF.^{3,6–9} HMB, dysmenorrhea and non-menstrual pelvic pain are burdensome and distressing symptoms of UF that can adversely impact daily activities of affected females.^{10–12}

Quality of life (QoL) has been shown to be substantially lower among symptomatic individuals with UF compared with those who are asymptomatic.^{13–16} Disease burden may result in missed workdays and a decrease in work

productivity.^{14,17,18} Currently, longitudinal real-world evidence on the impact of UF symptoms on work and productivity, as well as the use of over-the-counter (OTC) medications to alleviate symptoms, is lacking. Although several cross-sectional studies focusing on the symptoms of UF and their impact on QoL and work and productivity have been conducted in UF, these studies did not examine symptoms and their impacts longitudinally.^{18,19} To date, no prospective observational study has been conducted assessing UF-associated pain and pain medication use during menstrual and non-menstrual days among individuals with UF.

This study characterized the burden of UF in individuals who experienced HMB and moderate-to-severe pain in the overall study population, as well as on menstrual versus non-menstrual days, and by groups determined based on most potent pain medication used. Outcome measures assessed daily included the presence and severity of menstrual bleeding, UF-associated pain severity, and pain medication use. In addition, impact on work and non-work activities was evaluated weekly.

Materials and Methods

Study Design and Objectives

This was a 16-week, prospective, observational study of 350 females aged 18–50 years from the USA recruited using an online digital health platform (Achievement, Evidation Health Inc., CA, USA), as well as other online sources such as social media. Participants self-reported via an online screener survey that they had UF diagnosed by a healthcare provider (HCP), HMB (assessed on a categorical scale), UF-associated moderate-to-severe pain (defined as worst pain ≥ 4 on an 11-point numerical rating scale [NRS]), and regular menstrual periods. Exclusion criteria included regularly taking pain medication to manage another chronic condition, such as migraine or endometriosis. Full inclusion and exclusion criteria are shown in Table 1.

The objectives of this study were to describe UF-associated pain severity and the use of pain medications on menstrual and non-menstrual days, and the impact of UF symptoms on work, productivity, and activity impairment on menstrual and non-menstrual weeks among individuals with UF, HMB, and moderate-to-severe pain.

Table 1 Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Premenopausal females between 18 and 50 years of age. • Self-reported history of healthcare provider-given diagnosis of UF. • Self-reported symptoms associated with UF, including both heavy menstrual bleeding^a and moderate-to-severe UF-associated pain, defined as worst pain greater than or equal to 4 on an 11-point numerical rating scale. • Currently experiencing regular menstrual periods of 2–14 days duration occurring every 21–35 days from the start of one menstrual period to the start of the next. • Living in the USA. • Able to speak, read, and understand English. • Willing to complete daily surveys online for 4 months.	• Self-reported history of healthcare provider-given diagnosis of endometriosis, adenomyosis, pelvic congestion syndrome, or interstitial cystitis. • Self-reported regular intake of pain medications to manage pain due to any of the following chronic conditions: chronic pain other than related to UF, diabetes, low back pain not related to UF, migraine or severe headaches, multiple sclerosis, neuropathy, neuropathic pain, nerve damage, osteoarthritis, rheumatoid arthritis, sickle cell disease, fibromyalgia, complex regional pain syndrome, central sensitization syndrome. • Currently enrolled or planning to participate in any clinical trial in the next 4 months. • Planning to have surgery or another medical procedure to treat their UF in the next 4 months. • Self-reported diagnosis of chronic kidney disease that requires dialysis. • Self-reported current diagnosis of cancer. • Self-reports currently being pregnant.

Notes: ^aBaseline HMB was defined as usually experiencing one of the following during a menstrual period: bleeding that lasts more than 7 days, needing to change your menstrual protection (pads, tampons, and/or menstrual cup) every 2 hours or more often, needing to use more than one type of protection at a time to control menstrual flow, needing to change menstrual protection during the night, or bleeding through clothes or onto bedding during the night, menstrual flow with blood clots that are as big as a quarter or larger, or your bleeding prevents you from doing normal activities, such as going out, working, or shopping.

Abbreviations: HMB, heavy menstrual bleeding; UF, uterine fibroids.

Data Collection and Outcome Assessment

Potential participants completed a screener survey to determine their eligibility based on inclusion and exclusion criteria for the study. If enrolled, participants completed a baseline survey collecting data on demographics, health characteristics, disease history, including age at first severe menstrual pain, age at first HMB, medications currently used for HMB, age at UF diagnosis, and history of medical procedures. Starting the day after completion of the baseline survey, participants received daily and weekly surveys assessing study outcomes, which participants completed online. Daily surveys included menstrual status and bleeding severity, UF-associated pain severity, and pain medication usage for UF (prescription medications and OTC products); while the weekly survey—the Work Productivity Activity Impairment – UF (WPAI-UF)—asked participants to report the impact of their UF on work and non-work activity.

Menstrual Bleeding Severity

Participants completed daily reports on the presence and severity of their menstrual bleeding the prior day, assessed using the following categories:

- None – “no bleeding and no spotting.”
- Spotting – “evidence of minimal blood loss that does not require the use of protection (except for panty liners).”
- Bleeding – “evidence of blood loss that requires the use of pads, tampons, or a menstrual cup.”
- Heavy bleeding – “more than normal bleeding that requires use of protection for heavy flow or very frequent pad/tampon/menstrual cup changes.”

In general, days with “bleeding” or “heavy bleeding” were classified as menstrual days, while days with “no bleeding” or “spotting” were classified as non-menstrual days. If days with “spotting” were contiguous with “bleeding” and/or “heavy bleeding” days, they were classified as menstrual days. Three or more contiguous days of “spotting” only were classified as menstrual days. A “menstrual week” was a week where $>30\%$ of the reported days (those with valid daily survey data) were menstrual days. A “non-menstrual week” was a week in which $\leq 30\%$ of the reported days were menstrual days.

UF-Associated Pain

Participants completed daily reports on the worst UF-associated pain experienced the prior day using an 11-point NRS, where 0 = “no pain” and 10 = “pain as bad as you can imagine”. Moderate-to-severe pain was defined as pain ≥ 4 on the NRS, which is an accepted threshold value²⁰ that has been used in previous studies of treatments for UF treatment-associated pain.^{9,21,22}

Pain Medication and Usage for UF

Each morning, participants reported the prior day’s medication use for UF-associated pain. Three categories of pain medication were assessed: OTC medications, non-opioid prescription medications, and opioid prescription medications. For OTC medications, participants reported the type of OTC medication and the number of tablets taken. For non-opioid prescription medications, no additional detail was collected. For opioids, three classes were defined ([Supplementary Table 1](#)) based on the morphine milligram equivalent from the Centers for Disease Control and Prevention: low, medium, and high potency.²³ Participants reported the number of tablets of an opioid of a given potency level taken on the given day.

For data analysis, participants were categorized into medication-use subgroups according to the most potent type of pain medication used over the observational study period. The subgroups were: opioids, prescription non-opioids, OTC acetaminophen only, OTC non-steroidal anti-inflammatory drug (NSAID) only, OTC acetaminophen and NSAID, and no pain medication. Of note, participants could also receive other, less potent medication types (eg, individuals in the opioids group could also take OTC pain medications).

Work Productivity and Activity Impairment Questionnaire – Uterine Fibroids (WPAI-UF)

The WPAI-UF questionnaire is a validated instrument to assess work productivity and activity impairment related to UF.²⁴ The WPAI-UF questionnaire—which includes questions about hours of missed work, productivity loss, and activity impairment due to UF²⁴—was completed weekly by participants.

Analysis Population

The analysis population consisted of participants who had ≤ 5 consecutive missing days of daily survey responses over the study period, or $\geq 75\%$ completion rate of the daily surveys.

Work productivity and activity impairment outcomes were evaluated using participants in the analysis population who had also completed $\geq 75\%$ of the weekly WPAI-UF surveys.

Statistical Analysis

A sample of 350 individuals with UF, HMB, and moderate-to-severe pain was targeted. While no formal sample size determination was performed for this real-world study, sample size estimates were based on the primary outcome of self-reported pain medication use and centered on having a sufficient number of participants to make a population estimate of medication usage rates with a 5% precision. Referring to previous research indicating that 35% of patients with UF in the USA use pain medication,¹⁹ the Cochran formula for population-based sample size estimates determined that a sample size of 350 would provide this level of precision.

UF-associated pain and WPAI-UF responses were analyzed on a daily and weekly basis, respectively, with mean scores and standard deviation (SD) calculated for the overall population and medication-use subgroups. In addition, UF-associated pain mean scores and SD were calculated across all days, menstrual days, and non-menstrual days; mean WPAI-UF scores were determined for all weeks, menstrual weeks, and non-menstrual weeks. The following WPAI-UF subscale scores were calculated based on the developer's guidance:²⁵ hours of work missed due to UF (absenteeism), impairment due to UF while working (presenteeism), overall productivity impairment at work due to UF (work impairment), and non-work activity impairment due to UF (non-work impairment). Only descriptive statistics were performed.

Results

Participant Demographics

The number of individuals invited to participate in the study and who completed each of the steps up to enrollment are detailed in [Supplementary Figure 1](#). Of 350 enrolled participants, 307 (87.7%; the analysis population) met the data quality requirements imposed a priori for inclusion of their data in the analysis of daily survey results. No enrolled participants discontinued the study.

Participants had a mean (SD) age of 37.2 (6.3) years; 52.4% were White and 35.5% were Black or African American. Most reported having at least a college degree (71.7%), were in full-time employment (72.0%), and had health insurance (93.8%). Mean (SD) body mass index of participants was 30.3 (8.1) kg/m². Mean (SD) ages at time of first HMB and time of first severe menstrual pain were 20.0 (9.1) and 20.5 (8.7) years, respectively. The mean (SD) time between age at first HMB and age at UF diagnosis was 9.6 (9.3) years; the mean (SD) time between age at first severe menstrual pain and age at UF diagnosis was 9.1 (8.7) years. At baseline, around half of the participants (45.9%) reported receiving medications for HMB, of which oral contraceptives formed the largest group (27.7%).

Demographics and baseline characteristics for the analysis population are shown in [Table 2](#).

Pain Experience and Pain Medication Use

The most common medication-use subgroups—based on the most potent type of pain medication used in the observational study period—were combined OTC acetaminophen and NSAID (27.7% of participants), OTC NSAID only (20.5%), followed by prescription non-opioids (16.0%). The OTC acetaminophen only (8.8%) and opioids (6.2%) groups were less common. Approximately one-fifth of the participants (20.8%) were in the no pain medication group ([Figure 1](#)).

Table 2 Demographics, Baseline Characteristics, and Disease History of Analysis Population

Category	Description	N = 307
Age, Mean years (SD)		37.2 (6.3)
Race,^a n (%)	Black or African American	109 (35.5)
	White	161 (52.4)
	Other ^b /Prefer not to say	62 (20.2)
Health insurance, n (%)	Yes	288 (93.8)
Education, n (%)	Some High School, High School degree, or equivalent, or some College ^c	44 (14.3)
	Trade/technical/vocational training, Associate's or Bachelor's degree ^d	148 (48.2)
	Master's, Professional degree, or Doctorate ^e	115 (37.5)
Employment,^f n (%)	Employed full-time (40 or more hours per week)	221 (72.0)
	Employed part-time (39 or less hours per week)	35 (11.4)
Body mass index, Mean kg/m² (SD)		30.3 (8.1)
Comorbid disease^a (self-reported in >5% of participants)	Obesity or overweight	111 (36.2)
	Anxiety	99 (32.2)
	Depression	86 (28.0)
	Migraine/severe headaches	75 (24.4)
	Low back pain	51 (16.6)
	None of the above	83 (27.0)
Age at first HMB, Mean years (SD)		20.0 (9.1)
Age at first severe menstrual pain, Mean years (SD)		20.5 (8.7)
Age diagnosed with UF, Mean years (SD)		29.5 (7.9)
Time between age of UF diagnosis and age of first HMB, Mean years (SD)		9.6 (9.3)
Time between age of UF diagnosis and age of first severe menstrual pain, Mean years (SD)		9.1 (8.7)
Medications currently used for HMB^a	Oral contraceptives	85 (27.7)
	Hormonal IUD	27 (8.8)
	Other hormonal contraceptives	18 (5.9)
	Tranexamic acid	3 (1.0)
	Other	17 (5.5)
	None of the above	166 (54.1)

(Continued)

Table 2 (Continued).

Category	Description	N = 307
Treatment procedures received to date for UF ^a	Myomectomy	33 (10.7)
	Endometrial ablation	12 (3.9)
	Uterine artery embolization	10 (3.3)
	MRI-guided focused ultrasound ablation	4 (1.3)
	None of the above	253 (82.4)

Notes: ^aParticipants could choose more than one option and percentages may add up to >100%. ^bOther includes: American Indian or Alaskan Native; Asian; Hispanic, Latino, or Spanish; Middle Eastern or North African; Native Hawaiian or Other Pacific Islander; Another race or ethnicity. ^cSome High School (no diploma or GED), High School degree or equivalent (eg, GED), some College (no degree). ^dAssociate's degree (eg, AA, AS), Bachelor's degree (eg, BA, BS). ^eMaster's (eg, MA, MS, MEd), Professional degree (eg, MD, DDS, DVM), Doctorate (eg, PhD, EdD). ^fData on other employment categories (working as a homemaker or caregiver [unpaid], not currently employed, currently looking for employment, receiving disability/governmental support, student, retired, and I prefer not to answer) were also collected, but are not shown in the table. Therefore, percentages do not add up to 100%.

Abbreviations: AA, associate of arts; AS, associate of science; BA, bachelor of arts; BS, bachelor of science; DDS, doctor of dental surgery; DVM, doctor of veterinary medicine; EdD, doctor of education; GED, general education development; HMB, heavy menstrual bleeding; IUD, intrauterine device; MA, master of arts; MEd, master of education; MRI, magnetic resonance imaging; MS, master of science; PhD, doctor of philosophy; SD, standard deviation; UF, uterine fibroids.

Overall, use of pain medications was reported on 9.2% of total person-days over the 16-week study period (Table 3). The most common medication used for UF-associated pain was OTC pain medications (65.8%), and these contributed most of the total person-days of pain medication use (84.3%); prescription non-opioids accounted for 10.1% and prescription opioids—which were mostly of medium potency—accounted for 4.4% of the total person-days of medication.

Mean ages of participants at baseline were similar across the different medication-use subgroups, as shown in Table 4, with the lowest mean age seen in the no pain medication group. Distribution of races across the medication use subgroups was also similar except for the prescription non-opioid user group, which had a numerically higher proportion

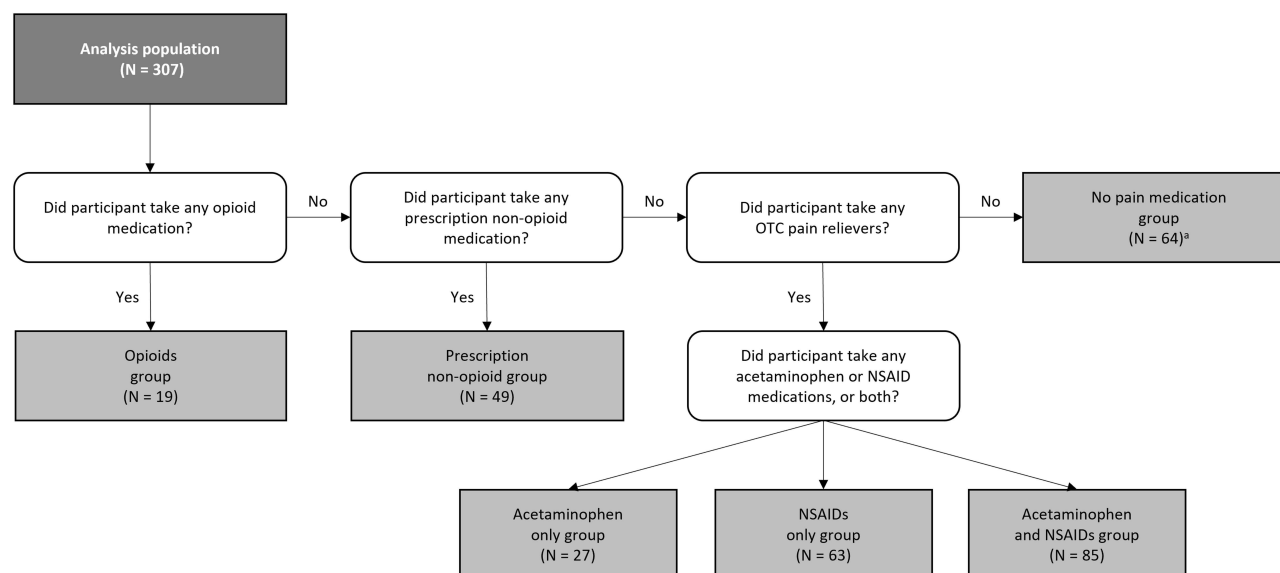


Figure 1 Participant flow into different pain medication use subgroups.

Notes: ^aThe no pain medication group included four participants who took medication not listed in the daily survey.

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; OTC, over-the-counter.

Table 3 Pain Medication Use for UF-Associated Pain

Description	Days used (%) ^a	Mean pills per day on days with medication use (SD)
Number of daily surveys completed by the analysis population N = 31,406		
Any pain medication	2879 (9.2)	4.2 (2.8)
Number of days any pain medication was taken N = 2879		
OTC pain relievers	2428 (84.3)	4.2 (2.9)
Prescription non-opioids	291 (10.1)	— ^b
Prescription opioids	127 (4.4)	2.3 (1.2)
Other pain medication	360 (12.5)	— ^b
Number of days any OTC pain relievers were taken N = 2428		
Acetaminophen	1123 (46.3)	3.2 (1.7)
NSAIDs	1506 (62.0)	4.1 (2.8)
Combination (Excedrin)	100 (4.1)	3.3 (1.8)
Number of days any prescription opioids were taken N = 127		
Low potency	38 (29.9)	1.7 (0.8)
Medium potency	90 (70.9)	2.4 (1.1)
High potency	0 (0.0)	— ^c

Notes: ^aPercentages for days (for each medication category) used are based on the numbers in the headings (pale blue rows) immediately above the percentages. ^bParticipants were not asked about number of pills taken for these pain medication subgroups. ^cHigh potency opioid use was not reported by any participant.

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; OTC, over the counter; SD, standard deviation; UF, uterine fibroids.

of Black or African American participants (51.0% for prescription non-opioids versus 22.2–38.1% for the other medication use subgroups). With respect to other demographic and socio-economic characteristics, the proportions across medication use subgroups were generally in line with the overall cohort. Of note, the highest proportion of oral contraceptive users for HMB at baseline (37.5%) was observed in the no pain medication group. This was numerically higher than the proportion of participants using oral contraceptives for HMB at baseline in other medication use subgroups (range 23.8–26.5%). The highest proportion of intrauterine device (IUD) users for HMB at baseline (15.6%) was also observed in the no pain medication subgroup, with 4.8–10.2% of IUD users in the other medication-use subgroups.

Self-reported worst pain and pain medication use for each medication group over the entire study cohort period, non-menstrual days only, and menstrual days only are shown in Table 5. Overall, mean worst UF-associated pain scores were higher on menstrual days compared with non-menstrual days (mean [SD] NRS pain score 3.5 [2.73] versus 1.0 [1.78], respectively). A higher proportion of days with moderate-to-severe pain was reported during menstrual days (47.2% of menstrual days) compared with non-menstrual days (10.4% of non-menstrual days), and this was consistent across medication use subgroups. Pain medication use occurred on more menstrual days than non-menstrual days (22.9% versus 3.7%, respectively). Over the entire study cohort period, the highest mean worst pain score was in the no pain medication group during menstrual days (mean [SD] NRS pain score 4.89 [2.93]).

Table 4 Demographics and Baseline Clinical Characteristics by Pain Medication Use Subgroups

Category	Description	Acetaminophen only N = 27	NSAIDs only N = 63	Acetaminophen and NSAIDs N = 85	Prescription non-opioids N = 49	Opioid medication N = 19	No pain medication ^h N = 64
Age, Mean years (SD)		36.9 (5.4)	39.3 (5.9)	36.7 (5.9)	37.8 (6.7)	39.3 (5.0)	35.0 (7.1)
Race,^a n (%)	Black or African American	6 (22.2)	24 (38.1)	29 (34.1)	25 (51.0)	7 (36.8)	18 (28.1)
	White	15 (55.6)	33 (52.4)	45 (52.9)	22 (44.9)	9 (47.4)	37 (57.8)
	Other ^b /Prefer not to say	8 (29.6)	12 (19.0)	14 (16.5)	9 (18.4)	4 (21.1)	15 (23.4)
Health insurance, n (%)	Yes	26 (96.3)	58 (92.1)	78 (91.8)	47 (95.9)	18 (94.7)	61 (95.3)
Education, n (%)	Some High School, High School degree or equivalent or some College ^c	7 (25.9)	9 (14.3)	14 (16.5)	3 (6.1)	4 (21.1)	7 (10.9)
	Trade/technical/vocational training, Associate's or Bachelor's degree ^d	10 (37.0)	32 (50.8)	41 (48.2)	30 (61.2)	10 (52.6)	25 (39.1)
	Master's, Professional degree or Doctorate ^e	10 (37.0)	22 (34.9)	30 (35.3)	16 (32.7)	5 (26.3)	32 (50.0)
Employment, n (%)^f	Employed full-time (40 or more hours per week)	18 (66.7)	43 (68.3)	64 (75.3)	35 (71.4)	11 (57.9)	50 (78.1)
	Employed part-time (39 or less hours per week)	3 (11.1)	7 (11.1)	12 (14.1)	5 (10.2)	2 (10.5)	6 (9.4)
Medications for heavy menstrual bleeding^{a,g}	Oral contraceptives	7 (25.9)	15 (23.8)	21 (24.7)	13 (26.5)	5 (26.3)	24 (37.5)
	Hormonal IUD	2 (7.4)	3 (4.8)	6 (7.1)	5 (10.2)	1 (5.3)	10 (15.6)
	Other hormonal contraceptives	2 (7.4)	2 (3.2)	6 (7.1)	3 (6.1)	3 (15.8)	2 (3.1)
	Tranexamic acid	0 (0.0)	1 (1.6)	1 (1.2)	1 (2.0)	0 (0.0)	0 (0.0)
	Other	2 (7.4)	5 (7.9)	4 (4.7)	4 (8.2)	1 (5.3)	1 (1.6)
	None of the above	17 (63.0)	39 (61.9)	47 (55.3)	26 (53.1)	9 (47.4)	28 (43.8)

Notes: ^aParticipants could choose more than one option and percentages may add up to > 100%. ^bOther includes: American Indian or Alaskan Native; Asian; Hispanic, Latino, or Spanish; Middle Eastern or North African; Native Hawaiian or Other Pacific Islander; Another race or ethnicity. ^cSome High School (no diploma or GED), High School degree or equivalent (eg, GED), some College (no degree). ^dAssociate's degree (eg, AA, AS), Bachelor's degree (eg, BA, BS). ^eMaster's (eg, MA, MS, Med), Professional degree (eg, MD, DDS, DVM), Doctorate (eg, PhD, EdD). ^fData on other employment categories (working as a homemaker or caregiver [unpaid], not currently employed, currently looking for employment, receiving disability/governmental support, student, retired, and I prefer not to answer) were also collected, but are not shown in the table. Therefore, percentages do not add up to 100%. ^gParticipants could be taking contraceptives for other reasons. ^hThe no pain medication group included four participants who took medication not listed in the daily survey.

Abbreviations: AA, associate of arts; AS, associate of science; BA, bachelor of arts; BS, bachelor of science; DDS, doctor of dental surgery; DVM, doctor of veterinary medicine; EdD, doctor of education; GED, general educational development; IUD, intrauterine device; MA, master of arts; Med, master of education; MS, master of science; NSAID, non-steroidal anti-inflammatory drug; PhD, doctor of philosophy; SD, standard deviation.

Table 5 Mean UF-Associated Worst Pain, Days with Pain, and Medication Use by Pain Medication Use Subgroups

	All	Acetaminophen only	NSAIDs only	Acetaminophen and NSAIDs	Prescription non-opioids	Opioid medication	No pain medication ^b
All days							
N (days)	31,406	2721	6665	8781	4915	2021	6303
Worst pain score, mean (SD)	1.72 (2.38)	1.76 (2.30)	1.03 (1.76)	1.63 (2.07)	2.09 (2.64)	1.97 (2.45)	2.17 (2.92)
Percentage of days with moderate or severe pain, %^a	20.9	20.3	11.3	18.4	27.1	25.4	28.7
Percentage of days with pain medication use, %	9.2	7.2	6.1	11.9	4.0	6.0	—
Menstrual days							
N (days)	9014	608	1648	2554	1411	570	2223
Worst pain score, mean (SD)	3.50 (2.73)	3.16 (2.41)	2.24 (2.34)	2.95 (2.29)	3.82 (2.70)	3.70 (2.70)	4.89 (2.93)
Percentage of days with moderate or severe pain, %^a	47.2	40.6	27.8	37.9	53.6	52.5	68.4
Percentage of days with medication use, %	22.9	27.8	20.9	27.7	11.3	16.5	—
Non-menstrual days							
N (days)	22,392	2113	5017	6227	3504	1451	4080
Worst pain score, mean (SD)	1.00 (1.78)	1.36 (2.10)	0.63 (1.29)	1.09 (1.70)	1.40 (2.27)	1.29 (1.97)	0.70 (1.51)
Percentage of days with moderate or severe pain, %^a	10.4	14.4	5.8	10.4	16.4	14.7	7.0
Percentage of days of medication use, %	3.7	1.3	1.3	5.4	1.0	1.9	—

Notes: ^aDays with moderate or severe pain are defined as days with a pain score of 4 or greater. ^bThe no pain medication group included four participants who took medication not listed in the daily survey.

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; UF, uterine fibroids.

Work Productivity Impact

Of the 307 participants included in the analysis of daily survey results, two participants completed less than 75% of the weekly surveys and were excluded from the work and non-work activity impairment analyses. Of the remaining 305 participants, 223 were employed and had worked in the 7 days prior to baseline and were, therefore, included in the work impairment analyses. In this population, UF were associated with work impairment, absenteeism, presenteeism, and non-work impairment (Table 6). Work impairment was higher during menstrual weeks than non-menstrual weeks (31.5% versus 12.7% impairment), which was observed across medication use subgroups (19.2–43.2% impairment during menstrual weeks; 6.9–21.6% impairment during non-menstrual weeks). The highest work impairment (43.2%) was observed in the no pain medication group during menstrual weeks, while the highest non-work impairment (41.6%) was observed in the opioids group during menstrual weeks. Absenteeism during both menstrual and non-menstrual weeks was highest in the opioids group (9.3% and 6.2% of missed work time, respectively). The highest presenteeism was observed in the no pain medication group during menstrual weeks (40.0% impairment) and in the opioids group during non-menstrual weeks (17.7% impairment).

Discussion

This was the first prospective, observational study of individuals with UF, HMB, and moderate-to-severe pain, assessing UF symptom severity and pain medication use alongside an assessment of work and non-work activity impairment in a longitudinal real-world setting.

Participants reported a gap between their age at first UF symptoms and age at first diagnosis of UF. This gap in diagnosis may result from challenges in diagnosing UF before the appearance of obvious morphological symptoms that can be easily confirmed by imaging.²⁶ It may also result from individuals with UF believing that their symptoms are “normal”.^{27–29} There can also be difficulties for the physician in diagnosing UF, which may be due to the similarity of UF symptoms with those of other gynecological diseases,^{30–32} or possible physician misconceptions around UF, for example, that pain is not a UF symptom.²⁷

Over the study period, participants reported more pain and pain medication use during menstrual days than on non-menstrual days, which is consistent with previous publications, including an interview study of the burden of UF in individuals with HMB associated with UF¹⁴ and a study assessing the level of menstrual distress—including pain—experienced by individuals with UF versus those without UF.³³ In the present study, the highest pain scores were reported by participants in the no pain medication subgroup on menstrual days, despite this subgroup having the highest proportion of participants receiving hormonal contraception for HMB at baseline. It may, therefore, be important for physicians to consider that pre-existing treatment may not fully address a patient’s UF-associated pain, and that additional interventions may be needed.

While few studies document the real-world use of specific analgesics for treatment of pain associated with UF, those that do report that NSAIDs^{34–36} and opioids^{34,35} are the most frequently used. This partially corresponds with the findings of the present study, in which OTC medications—particularly NSAIDs—accounted for most pain medications taken by participants.^{36,37} However, only a small proportion of participants in the present study reported regular opioid use, which may be a result of restrictive opioid prescribing laws and practices in the USA, which were well established at the time of the present study.³⁸

UF interfered with work, in terms of impairment, absenteeism, and presenteeism. This is in line with published literature describing that individuals with UF had greater work and non-work activity impairment, reduced productivity, increased absence,^{14,18,39} and extended periods of unemployment.¹⁴ The impact of menstrual symptoms on an individual’s career has been previously reported, with discomfort—experienced to a similar or more severe degree in UF—noted as having a particular impact at work, exacerbated by the taboo nature of menstruation and women’s health in general.⁴⁰ Of particular concern are the participants who did not take pain medication, who made up a sizeable proportion (20.8%) of the study cohort. Participants in the no pain medication subgroup had high levels of work impairment during menstrual weeks. This may indicate a need in individuals with UF for further care to address pain and allow full participation in professional life. Work impairment may also have been exacerbated by the well-documented impact of UF on mental health.^{10,14,41,42} There was a high prevalence of self-reported anxiety and depression among the

Table 6 WPAI-UF Metrics for Work Productivity Impact of UF

	All	Acetaminophen only	NSAIDs only	Acetaminophen and NSAIDs	Prescription non-opioids	Opioid medication	No pain medication ^a
All weeks							
N (weeks)	4754	405	984	1330	745	302	988
Work Impairment, % (SD)	19.65 (24.58)	22.71 (24.60)	10.94 (18.08)	19.99 (22.46)	21.59 (25.25)	28.10 (27.66)	23.23 (28.91)
Absenteeism, % (SD)	3.09 (9.78)	3.14 (10.65)	1.06 (6.91)	2.77 (9.68)	2.96 (9.34)	7.27 (15.35)	4.53 (10.00)
Presenteeism, % (SD)	18.07 (22.96)	20.55 (23.01)	10.38 (17.27)	18.58 (21.13)	20.09 (23.65)	24.34 (25.56)	21.10 (26.91)
Non-Work Impairment, % (SD)	21.67 (24.38)	23.60 (22.28)	13.91 (19.58)	22.77 (23.37)	25.36 (25.52)	30.33 (26.98)	21.68 (27.05)
All menstrual weeks							
N (weeks)	1750	127	323	495	274	113	418
Work Impairment, % (SD)	31.46 (27.54)	30.78 (26.27)	19.15 (22.48)	27.81 (23.47)	30.42 (26.32)	40.31 (30.88)	43.16 (30.09)
Absenteeism, % (SD)	4.94 (11.16)	3.89 (11.23)	1.44 (7.52)	4.06 (11.67)	3.92 (10.15)	9.33 (17.19)	8.32 (10.78)
Presenteeism, % (SD)	29.42 (26.03)	28.28 (25.11)	18.51 (21.88)	25.96 (22.30)	28.87 (24.82)	36.90 (29.45)	40.03 (28.37)
Non-Work Impairment, % (SD)	33.35 (26.30)	30.00 (22.29)	23.41 (23.32)	30.69 (23.96)	36.75 (26.35)	41.59 (27.31)	40.74 (28.76)
All non-menstrual weeks							
N (weeks)	3004	278	661	835	471	189	570
Work Impairment, % (SD)	12.74 (19.62)	19.27 (23.07)	6.87 (13.75)	15.55 (20.60)	16.56 (23.19)	21.63 (23.46)	6.87 (13.64)
Absenteeism, % (SD)	2.01 (8.70)	2.82 (10.41)	0.88 (6.59)	2.03 (8.25)	2.42 (8.81)	6.17 (14.23)	1.40 (8.07)
Presenteeism, % (SD)	11.42 (17.88)	17.25 (21.27)	6.35 (12.65)	14.40 (19.23)	15.08 (21.43)	17.69 (20.41)	5.59 (11.16)
Non-Work Impairment, % (SD)	14.86 (20.29)	20.68 (21.69)	9.27 (15.49)	18.07 (21.71)	18.73 (22.53)	23.60 (24.49)	7.70 (14.16)

Notes: Data are for 305 participants who had ≤5 consecutive missing days of daily survey responses over the study period or ≥75% completion rate of the daily surveys (ie, the analysis population) and who had also completed ≥75% of the weekly WPAI-UF surveys. ^aThe no pain medication group included four participants who took medication not listed in the daily survey.

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; UF, uterine fibroids; WPAI-UF, Work Productivity and Activity Impairment Questionnaire – Uterine Fibroid.

participants, and these conditions have been associated with increased use of pain medications, decreased QoL, and reduced workplace functioning.^{43–45} There is also a well-established relationship between pain and mental health symptoms such as anxiety and depression, in which one can exacerbate the other.^{46–48}

There were several limitations to this study. Firstly, it is possible that the cohort did not adequately represent less advantaged individuals, as evidenced by the skew towards employment and higher education. Secondly, the reliance on participant self-reports via surveys introduced several constraints. While symptom experience is best self-reported by the participants, the subjective nature of self-assessments may have had an impact on the accuracy of medical information gathered, such as comorbidities or medical history. Additionally, to reduce the complexity of study participation for the participants, the study protocol did not include the collection of detailed clinical information about participants' diagnoses, including factors known to have an impact on the severity of pain, such as the size, location and number of UF, or whether the participants had other diagnoses, such as adenomyosis. Additionally, daily surveys of medication use may have led to recency bias, in which the participant response is influenced by their most recent memory of prior responses.

The exclusion of participants with endometriosis was necessary to ensure that pain measured was due to UF. However, it may have limited the study population to those with less severe pain symptoms, potentially leading to an underestimation of the impact of UF-associated pain.

Finally, the study provided descriptive statistics only and was not designed to look for causal associations or relationships. Therefore, any explanations given in this discussion are hypothetical.

Conclusion

This study demonstrated that pain and pain medication use intensified on menstrual days compared with non-menstrual days in individuals with UF-associated HMB, which was consistent across different groups of pain medication use. Furthermore, UF symptoms reduced participants' ability to take part in both work- and non-work-related activities; impairment was more prevalent during menstrual weeks than non-menstrual weeks. There is a need to increase public and HCP awareness of UF symptoms to improve diagnosis and facilitate effective management of symptoms, including pain, which could greatly improve QoL among individuals with UF.

Abbreviations

AA, associate of arts; AS, associate of science; BA, bachelor of arts; BS, bachelor of science; DDS, doctor of dental surgery; DVM, doctor of veterinary medicine; EdD, doctor of education; GED, general education development; HCP, healthcare provider; HMB, heavy menstrual bleeding; IUD, intrauterine device; MA, master of arts; MEd, master of education; MRI, magnetic resonance imaging; MS, master of science; NRS, numerical rating scale; NSAID, non-steroidal anti-inflammatory drug; OTC, over-the-counter; PhD, doctor of philosophy; QoL, quality of life; SD, standard deviation; UF, uterine fibroids; WPAI-UF, Work Productivity and Activity Impairment Questionnaire – Uterine Fibroids.

Data Sharing Statement

The data underlying this article are available in the article and its online supplementary material.

Ethics Approval and Informed Consent

The protocol, informed consent form, recruitment materials, and all participant-facing materials were submitted to the Western Institutional Review Board (WIRB; now WIRB-Copernicus Group IRB) for review and approval, which was obtained before any participant was enrolled. Any amendments to the protocol or consent form were reviewed and approved by WIRB before the respective changes were implemented to the study. Participants provided written informed consent prior to performance of study-related procedures. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines⁴⁹—which are consistent with the Declaration of Helsinki—and was approved by the Western Institutional Review Board (WIRB; now WIRB-Copernicus Group IRB). Additionally, FDA guidelines for “Digital health technologies for remote data acquisition in clinical investigations” were followed.

Acknowledgments

The authors would like to thank the individuals who participated in this study. The authors would also like to acknowledge editorial support and medical writing from AXON Communications (London, UK), which was sponsored by Sumitomo Pharma Switzerland GmbH, in collaboration with Pfizer, in accordance with Good Publication Practice guidelines.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Funding for the analysis and medical writing of the article was provided by Sumitomo Pharma Switzerland GmbH and Pfizer.

Disclosure

EH and VR are employed by Sumitomo Pharma Switzerland GmbH (formerly Myovant Sciences GmbH). NM and JS are employees of Evidation, which was compensated by Sumitomo Pharma Switzerland GmbH (formerly Myovant Sciences GmbH) to conduct this research. BL reports personal fees from Myovant, outside the submitted work.

References

1. Stewart EA, Cookson CL, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. *BJOG*. 2017;124(10):1501–1512. doi:10.1111/1471-0528.14640
2. De La Cruz MS, Buchanan EM. Uterine fibroids: diagnosis and treatment. *Am Fam Physician*. 2017;95(2):100–107.
3. American College of Obstetricians and Gynecologists. Management of symptomatic uterine leiomyomas: ACOG Practice Bulletin, Number 228. *Obstet Gynecol*. 2021;137(6):e100–e115. doi:10.1097/AOG.0000000000004401
4. Giuliani E, As-Sanie S, Marsh EE. Epidemiology and management of uterine fibroids. *Int J Gynaecol Obstet*. 2020;149(1):3–9. doi:10.1002/ijgo.13102
5. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *Am J Obstet Gynecol*. 2003;188(1):100–107. doi:10.1067/mob.2003.99
6. Vilos GA, Allaire C, Laberge PY, Leyland N. The management of uterine leiomyomas. *J Obstet Gynaecol Can*. 2015;37(2):157–178. doi:10.1016/S1701-2163(15)30338-8
7. Stewart EA, Solomon CG. Clinical practice. Uterine fibroids. *N Engl J Med*. 2015;372(17):1646–1655. doi:10.1056/NEJMc1411029
8. Nguyen PN, Nguyen VT. Evaluating clinical features in intracavitary uterine pathologies among Vietnamese women presenting with peri- and postmenopausal bleeding: a bicentric observational descriptive analysis. *J Midlife Health*. 2022;13(3):225–232. doi:10.4103/jmh.jmh_81_22
9. Al-Hendy A, Lukes AS, Poindexter AN, et al. Treatment of uterine fibroid symptoms with relugolix combination therapy. *N Engl J Med*. 2021;384(7):630–642. doi:10.1056/NEJMoa2008283
10. Marsh EE, Al-Hendy A, Kappus D, Galitsky A, Stewart EA, Burden KM. prevalence, and treatment of uterine fibroids: a survey of U.S. women. *J Womens Health*. 2018;27(11):1359–1367. doi:10.1089/jwh.2018.7076
11. David M, Pitz CM, Mihaylova A, Siedentopf F. Myoma-associated pain frequency and intensity: a retrospective evaluation of 1548 myoma patients. *Eur J Obstet Gynecol Reprod Biol*. 2016;199:137–140. doi:10.1016/j.ejogrb.2016.02.026
12. McKenna KA, Fogleman CD. Dysmenorrhea. *Am Fam Physician*. 2021;104(2):164–170.
13. Koga K, Fukui M, Fujisawa M, Suzukamo Y. Impact of diagnosis and treatment of uterine fibroids on quality of life and labor productivity: the Japanese online survey for uterine fibroids and quality of life (JOYFUL survey). *J Obstet Gynaecol Res*. 2023;49(10):2528–2537. doi:10.1111/jog.15758
14. Hunsche E, Rakov V, Scippa K, Witherspoon B, McKain L. The burden of uterine fibroids from the perspective of US women participating in open-ended interviews. *Womens Health Rep*. 2022;3(1):286–296. doi:10.1089/whr.2021.0086
15. Coyne KS, Harrington A, Currie BM, Chen J, Gillard P, Spies JB. Psychometric validation of the 1-month recall Uterine Fibroid Symptom and Health-Related Quality of Life questionnaire (UFS-QOL). *J Patient Rep Outcomes*. 2019;3(1):57. doi:10.1186/s41687-019-0146-x
16. Soliman AM, Margolis MK, Castelli-Haley J, Fuldeore MJ, Owens CD, Coyne KS. Impact of uterine fibroid symptoms on health-related quality of life of US women: evidence from a cross-sectional survey. *Curr Med Res Opin*. 2017;33(11):1971–1978. doi:10.1080/03007995.2017.1372107
17. Downes E, Sikirica V, Gilabert-Estelles J, et al. The burden of uterine fibroids in five European countries. *Eur J Obstet Gynecol Reprod Biol*. 2010;152(1):96–102. doi:10.1016/j.ejogrb.2010.05.012
18. Hasselrot K, Lindeberg M, Konings P, Kopp Kallner H, Hawkins SM. Investigating the loss of work productivity due to symptomatic leiomyoma. *PLoS One*. 2018;13(6):e0197958. doi:10.1371/journal.pone.0197958

19. Zimmermann A, Bernuit D, Gerlinger C, Schaefers M, Geppert K. Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of 21,746 women. *BMC Womens Health*. 2012;12:6. doi:10.1186/1472-6874-12-6
20. Baranidharan G, Williams A, Wilson S, et al. Outcome Measures. 2019; Available from: https://www.britishpainsociety.org/static/uploads/resources/files/Outcome_Measures_January_2019.pdf. Accessed March 2024.
21. Wu Q, Zhou Y, Sun S, Li H, Cao S, Shou H. Clinical analysis of acute postoperative pain after total laparoscopic hysterectomy for adenomyosis and uterine fibroids - A prospective observational study. *Ann Med*. 2023;55(2):2281510. doi:10.1080/07853890.2023.2281510
22. Lan CF, Lin BH, Nie CL, Guo XL, Zhou DH, Lin YJ. Investigation and analysis of influencing factors of moderate to severe pain after uterine artery embolization in patients with cesarean scar pregnancy. *Int J Gen Med*. 2021;14:9023–9029. doi:10.2147/IJGM.S342735
23. Centers for Disease Control and Prevention. Calculating total daily dose of opioids for safer dosage. 2021; Available from: <https://www.cdc.gov/opioids/providers/prescribing/pdf/calculating-total-daily-dose.pdf>. Accessed February 2024.
24. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics*. 1993;4(5):353–365. doi:10.2165/00019053-199304050-00006
25. Reilly Associates. WPAI scoring; Available from: http://www.reillyassociates.net/wpai_scoring.html. Accessed March 2024.
26. Leyland N, Leonardi M, Murji A, Singh SS, Al-Hendy A, Bradley L. A call-to-action for clinicians to implement evidence-based best practices when caring for women with uterine fibroids. *Reprod Sci*. 2022;29(4):1188–1196. doi:10.1007/s43032-022-00877-3
27. Riggan KA, Stewart EA, Balls-Berry JE, Venable S, Allyse MA. Patient recommendations for shared decision-making in uterine fibroid treatment decisions. *J Patient Exp*. 2021;8:23743735211049655. doi:10.1177/23743735211049655
28. Orellana M, KN DS, Yap JQ, et al. “In our community, we normalize pain”: discussions around menstruation and uterine fibroids with Black women and Latinas. *BMC Womens Health*. 2024;24(1):233. doi:10.1186/s12905-024-03008-z
29. Evans J. The impact of health literacy on uterine fibroid awareness, diagnosis, and treatment in the United States: a mini literature review. *Front Reprod Health*. 2024;6:1335412. doi:10.3389/frph.2024.1335412
30. Aninye IO, Laitner MH. Uterine fibroids: assessing unmet needs from bench to bedside. *J Womens Health*. 2021;30(8):1060–1067. doi:10.1089/jwh.2021.0280
31. Uimari O, Nazri H, Tapmeier T. Endometriosis and uterine fibroids (leiomyomata): comorbidity, risks and implications. *Front Reprod Health*. 2021;3:750018. doi:10.3389/frph.2021.750018
32. Yang Q, Ciebiera M, Bariani MV, et al. Comprehensive review of uterine fibroids: developmental origin, pathogenesis, and treatment. *Endocr Rev*. 2022;43(4):678–719. doi:10.1210/edrv/bnab039
33. Vannuccini S, Clemenza S, Cassioli E, et al. Uterine fibroids, perceived stress, and menstrual distress: a key role of heavy menstrual bleeding. *Reprod Sci*. 2023;30(5):1608–1615. doi:10.1007/s43032-022-01126-3
34. Agarwal SK, Stokes M, Kung T, Tilney R, Lickert C. Describing the patient journey of women with claims for uterine fibroids and heavy menstrual bleeding using a commercial database (2011–2020). *Int J Womens Health*. 2023;15:1561–1575. doi:10.2147/IJWH.S420612
35. Arjona Ferreira JC, Migoya E. Development of relugolix combination therapy as a medical treatment option for women with uterine fibroids or endometriosis. *F S Rep*. 2023;4(Suppl 2):73–82. doi:10.1016/j.xfre.2022.11.010
36. Bonine NG, Banks E, Harrington A, Vlahiotis A, Moore-Schiltz L, Gillard P. Contemporary treatment utilization among women diagnosed with symptomatic uterine fibroids in the United States. *BMC Womens Health*. 2020;20(1):174. doi:10.1186/s12905-020-01005-6
37. National Institute for Health and Care Excellence. Heavy menstrual bleeding: assessment and management; Available from: <https://www.nice.org.uk/guidance/ng88> Accessed December 2024
38. Davis CS, Lieberman AJ, Hernandez-Delgado H, Suba C. Laws limiting the prescribing or dispensing of opioids for acute pain in the United States: a national systematic legal review. *Drug Alcohol Depend*. 2019;194:166–172. doi:10.1016/j.drugalcdep.2018.09.022
39. Soliman AM, Anand SB, Coyne KS, Castelli-Haley J, Snabes M, Owens CD. Examining the relationship between symptomatic burden and self-reported productivity losses among patients with uterine fibroids in the United States. *J Occup Environ Med*. 2017;59(10):974–981. doi:10.1097/JOM.0000000000001105
40. Grandey AA, Gabriel AS, King EB. Tackling taboo topics: a review of the three Ms in working women’s lives. *J Manage*. 2020;46(1):7–35. doi:10.1177/0149206319857144
41. Chiuve SE, Kilpatrick RD, Hornstein MD, et al. Chronic opioid use and complication risks in women with endometriosis: a cohort study in US administrative claims. *Pharmacoepidemiol Drug Saf*. 2021;30(6):787–796. doi:10.1002/pds.5209
42. Ghant MS, Sengoba KS, Recht H, Cameron KA, Lawson AK, Marsh EE. Beyond the physical: a qualitative assessment of the burden of symptomatic uterine fibroids on women’s emotional and psychosocial health. *J Psychosom Res*. 2015;78(5):499–503. doi:10.1016/j.jpsychores.2014.12.016
43. Fergusson DM, McLeod GF, Horwood LJ, Swain NR, Chapple S, Poulton R. Life satisfaction and mental health problems (18 to 35 years). *Psychol Med*. 2015;45(11):2427–2436. doi:10.1017/S0033291715000422
44. Skadberg RM, Moore TM, Elledge LC. A 20-year study of the bidirectional relationship between anxious and depressive symptomology and pain medication usage. *Pain Manag*. 2020;10(1):13–22. doi:10.2217/pmt-2019-0037
45. Deady M, Collins DAJ, Johnston DA, et al. The impact of depression, anxiety and comorbidity on occupational outcomes. *Occup Med*. 2022;72(1):17–24. doi:10.1093/occmed/kqab142
46. Feingold D, Brill S, Goor-Aryeh I, Delayahu Y, Lev-Ran S. Depression and anxiety among chronic pain patients receiving prescription opioids and medical marijuana. *J Affect Disord*. 2017;218:1–7. doi:10.1016/j.jad.2017.04.026
47. Magni G, Moreschi C, Rigatti-Luchini S, Merskey H. Prospective study on the relationship between depressive symptoms and chronic musculoskeletal pain. *Pain*. 1994;56(3):289–297. doi:10.1016/0304-3959(94)90167-8
48. Mental Health America. Early, equitable and trauma responsive care for chronic pain and mental health. 2020. Available from: <https://www.mhanational.org/sites/default/files/Early%2C%20Equitable%20and%20Trauma%20Responsive%20Care%20for%20Chronic%20Pain%20and%20Mental%20Health.pdf> Accessed December 2024.
49. European Medicines Agency. ICH Topic E 6 (R1) Guideline for Good Clinical Practice. 2002; Available from: <https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline>. Accessed October 2024.

International Journal of Women's Health**Dovepress****Publish your work in this journal**

The International Journal of Women's Health is an international, peer-reviewed open-access journal publishing original research, reports, editorials, reviews and commentaries on all aspects of women's healthcare including gynecology, obstetrics, and breast cancer. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/international-journal-of-womens-health-journal>