Self-reported prevalence, description and management of pain in adults with haemophilia: methods, demographics and results from the Pain, Functional Impairment, and Quality of life (P-FiQ) study

M. WITKOP,* A. NEFF,† T. W. BUCKNER,‡ M. WANG,§ K. BATT,¶ D. QUON,** L. BOGGIO,†† M. RECHT,‡‡ K. BAUMANN,§§ R. Z. GUT,¶¶ D. L. COOPER¶¶ and C. L. KEMPTON***

* Munson Medical Center, Traverse City, MI; † Cleveland Clinic, Cleveland, OH; ‡ University of Colorado School of Medicine, Aurora, CO; § Wake Forest School of Medicine, Winston-Salem, NC; ¶ Georgetown University Hospital, Washington, DC; ** Orthopaedic Hemophilia Treatment Center, Orthopaedic Institute for Children, Los Angeles, CA; †† Rush University Medical Center, Chicago, IL; ‡‡ Oregon Health & Science University, Portland, OR; §§ University of Minnesota Health Center for Bleeding and Clotting Disorders, Minneapolis, MN; ¶¶ Clinical, Medical and Regulatory Affairs, Novo Nordisk Inc., Plainsboro, NJ; and *** Emory University School of Medicine, Atlanta, GA, USA

Introduction: Haemophilia is characterized by frequent haemarthrosis, leading to acute/chronic joint pain. **Aim:** To assess self-reported prevalence, description and management of pain in adult males with mild-to-severe haemophilia and history of joint pain/bleeding. **Methods:** Participants completed a pain survey and five patient-reported outcome instruments assessing pain, functional impairment and health-related quality of life (HRQoL). **Results:** Of 381 participants enrolled, median age was 34 years; 77% had haemophilia A, 71% had severe disease and 65% were overweight/obese. Many (56%) were not receiving routine infusions; 30% never received routine infusions. During the prior 6 months, 20% experienced acute pain, 34% chronic pain and 32% both acute/chronic pain. Subjects with both acute/chronic pain (vs. none, acute or chronic) were more likely to be depressed (30% vs. 0–15%), obese (35% vs. 20–29%) and have lower HRQoL (mean EQ-5D visual analog scale, 69 vs. 83–86) and function (median overall Hemophilia Activities List, 60 vs. 88–99). Most common analgesics used for acute/chronic pain during the prior 6 months were acetaminophen (62%/55%) and non-steroidal anti-inflammatory drugs (34%/49%); most common non-pharmacologic strategies were ice (65%/33%) and rest (51%/33%). Hydrocodone-acetaminophen was the most common opioid for both acute/chronic pain (30%); other long-acting opioids were infrequently used specifically for chronic but not acute pain (morphine, 7%; methadone, 6%; fentanyl patch, 2%). **Conclusion:** Patients with chronic pain, particularly those with both acute/chronic pain, frequently experience psychological issues, functional disability and reduced HRQoL. Treatment strategies for acute pain (e.g. routine infusions to prevent bleeding) and for chronic pain (e.g. long-acting opioids) may be underused.

Keywords: acute pain, chronic pain, haemophilia, pain, pain management, patient-reported outcome

Introduction

As the life expectancy of people with haemophilia (PWH) has increased, the management of comorbidities such as pain has become an area of greater focus within the haemophilia comprehensive care setting [1,2]. Joint pain is the most common type of pain observed in individuals with haemophilic arthropathy and is a major problem affecting adult PWH [3–6]. An assessment of pain in adult PWH was performed in the Hemophilia Experiences, Results and Opportunities (HERO) study, which demonstrated that 89% of participants experienced pain that interfered with activities during the prior 4 weeks [7].

Despite the prevalence of joint pain in adult PWH, the assessment of pain and functional impairment in this population has been limited and inconsistent, even...
Haemophilia history and pain assessments

Prior to the start of their comprehensive care visit, all participants completed a survey adapted from national and regional pain surveys [6,11], capturing: (i) sociodemographic information; (ii) current actual haemophilia treatment information; (iii) bleeding history in the 6 months prior to enrolment; (iv) functional status (Centers for Disease Control and Prevention-Universal Data Collection [CDC-UDC] scale and questions); (v) acute haemophilia/joint-related pain characteristics/descriptors and treatments; (vi) chronic (persistent) haemophilia/joint-related pain characteristics/descriptors and treatments (see Table S1); and (vii) five PRO instruments (described below). Investigators completed a separate case report form during the comprehensive care visit capturing health-related patient demographics, haemophilia characteristics (diagnosis, haemophilia history including inhibitor history/status, current prescribed treatment, comorbidities including prescribed medications [antiviral, antidepressant, anxiolytic]), functional status (CDC-UDC scale and questions) and joint range of motion (CDC-UDC template). The sites optionally had a physical therapist complete Hemophilia Joint Health Score (HJHS). Initially enrolled patients were eligible to complete a retest consisting of the five PRO instruments to support assessment of reliability.

Patient-reported outcomes

The current analysis includes data from three PRO instruments: the EQ-5D-5L [13], Brief Pain Inventory v2 Short Form (BPI) [14] and Hemophilia Activities List (HAL) [15,16]; other instruments administered included the International Physical Activity Questionnaire (IPAQ) [17] and SF-36v2 [18]. PRO domain and total scores were calculated using established algorithms. EQ-5D-5L consists of a 100-point visual analog scale (VAS) measuring health status ‘today’, as well as five descriptive domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), from which an overall health index score is calculated. BPI includes a pain severity domain (derived from measures of current pain and worst, least and average pain experienced in the past 7 days) and a pain interference domain (derived from measures of effects of pain in the past 7 days on general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life). HAL consists of seven domains representing functional status over the past month (lying/sitting/kneeling/standing, functions of the legs, functions of the arms, use of transportation, self-care, household tasks and leisure activities and sports), and an overall score calculated from the domain scores.
Data analysis
Statistical analysis included descriptive statistics regarding participant demographics, pain history, pain characteristics and pain management strategies. Categorical variables are summarized by numbers and percentages of valid observations. Continuous variables are summarized by numbers of valid observations and quartiles (Q1, median, and Q3). Data entry was performed by contract research organization staff members using electronic edit checks and random sampling edit checks to assure data accuracy. Analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

Results
Participant characteristics
Overall, 381 adult males with haemophilia were enrolled, of a total of 543 identified as eligible by sites (70% participation rate). Reasons for not participating were not queried. Enrolment occurred between October 2013 and October 2014, and a mean (median) of 25.4 (28.0) subjects were recruited from each site. The median age of participants was 34 years, and most were white, non-Hispanic; a detailed description of subject demographics, haemophilia history and comorbidities is presented in Table 1, and an extended version of these data appear in Table S1.

Functional disability, as assessed over the 6 months prior to enrolment using the scale and questions from the CDC-UDC form [19], was reported both by site investigators and by participants themselves (Table 2). Participant/site reports indicated that only 33%/41% of individuals had unrestricted school or work and recreational activities, and the use of a cane, crutches, or walker (32%/26%) was more common than that of a wheelchair (11%/9%). Participant-reported vs. site-reported measures of functional disability consistently indicated higher levels of impairment, suggesting a potential underestimation of patients’ functional status by HTC staff, or potential discrepancies in the perception of function between patients and investigators. HAL was also used to assess functional status; mean (SD) HAL score (range: 0–100; higher scores indicating better function) was 73.3 (22.2; Table 1). Health status was assessed by EQ-5D-5L; mean (SD) EQ-5D-5L VAS (range: 0–100; higher scores indicating better QoL) was 75.3 (17.8) and health index (range: −0.011 to 1; higher scores indicating better QoL) was 0.776 (0.171).

Pain
Eighty-five percent of respondents reported experiencing pain during the 6 months preceding enrolment. Among those with severe haemophilia, 88% reported pain; among those with mild/moderate haemophilia, 79% reported pain. Participants also self-reported the type of pain experienced during the past 6 months: no pain (n = 55, 15%), acute pain only (n = 73, 20%), chronic pain only (n = 129, 34%) and acute and chronic pain (n = 118, 32%). People with severe haemophilia seemed to more frequently report both acute and chronic pain compared to other types of pain (acute pain only, 17%; chronic pain only, 33%; acute and chronic pain, 37%). Ankles were reported by 37% as the ‘joints with most pain’, compared to 24% indicating the knees, 19% the elbows, 12% the shoulders and 8% the hips. The most common descriptors of acute and chronic pain used by participants are shown in Fig. 1. Terms used more often to describe acute pain included ‘sharp’, ‘stabbing’ and ‘burning’, and terms used more often to describe chronic pain included ‘aching’, ‘nagging’ and ‘tiring’. Pain was also assessed using the BPI; mean (SD) pain severity (range: 0–10; lower scores indicating less pain) was 3.3 (2.3), and pain interference (range: 0–10; lower scores indicating less interference) was 3.2 (2.7; Table 1).

Pain categories and sociodemographic characteristics
Overall, participants who reported no pain in the past 6 months seemed to be younger than those with acute pain only or any chronic pain (median: 27.3, 32.9 and 35.3 years respectively; Table 3). Similar percentages of working and non-working participants reported having chronic pain only (31% and 33% respectively), although rates of having both acute and chronic pain appeared higher among those who were not working compared with those who were working (39% vs. 28%). Compared with individuals in other pain categories, participants with both acute and chronic pain seemed to more often be married or with a long-term partner (no pain, 42%; acute pain only, 40%; chronic pain only, 48%; acute and chronic pain, 53%) and more often live with others (no pain, 69%; acute pain only, 79%; chronic pain only, 68%; acute and chronic pain, 82%).

Pain categories and comorbid conditions
Median body mass index (BMI) was similar across pain categories; however, the proportion of participants who were obese increased numerically across categories (no pain, 20%; acute pain only, 25%; chronic pain only, 29%; acute and chronic pain, 35%; Table 3). The presence of psychological conditions also increased numerically across pain categories, with highest levels found in those with both acute and chronic pain (no pain, 5%; acute pain only, 22%; chronic pain only, 24%; acute and chronic pain, 44%).
Table 1. Participant characteristics (N = 381, unless otherwise indicated).

| Age, median (Q1, Q3), years | 34.0 (26.3, 47.2) |
| Race/ethnicity, n (%) | n = 380 |
| White, non-Hispanic | 263 (69.2) |
| Black | 50 (13.2) |
| White, Hispanic | 29 (7.6) |
| Other | 38 (10.0) |
| Body mass index, n (%) | 134 (35.2) |
| Normal/underweight (<25 kg m⁻²) | 134 (35.2) |
| Overweight (25–30 kg m⁻²) | 158 (36.2) |
| Obese (≥30 kg m⁻²) | 109 (28.6) |
| Education, n (%) | 230 (60.7) |
| Attended college | 230 (60.7) |
| Did not attend college | 149 (39.3) |
| Employment, n (%) | 190 (49.9) |
| Full-time | 163 (52.9) |
| Part-time | 45 (14.6) |
| Not working | 70 (22.7) |
| Student | 43 (14.0) |
| Current relationship status, n (%) | 190 (49.9) |
| Married or long-term partner | 179 (64.6) |
| Haemophilia type, n (%) | 295 (77.4) |
| Haemophilia A | 295 (77.4) |
| Haemophilia severity, n (%) | 62 (16.3) |
| Mild (FVIII/FIX 5–10%) | 62 (16.3) |
| Moderate (FVIII/FIX 1–5%) | 50 (13.2) |
| Severe (FVIII/FIX <1%) | 268 (70.5) |
| Presence of inhibitors, n (%) | 33 (8.7) |
| Current treatment regimen, n (%) | 33 (8.7) |
| Routine infusions to prevent bleeding | 165 (43.5) |
| On-demand treatment of bleeding | 143 (37.7) |
| Mostly on-demand treatment | 71 (18.7) |
| With infusions ahead of anticipated activities (n = 71) | 60 (84.5) |
| With occasional periods of prolonged treatment (n = 71) | 9 (12.7) |
| Extent of prophylaxis during lifetime, n (%) | 105 (30.3) |
| Never on prophylaxis | 105 (30.3) |
| 25–50% | 111 (32.1) |
| 50–99% | 72 (20.8) |
| Always on prophylaxis | 37 (10.7) |
| Viral illness, n (%) | 62 (16.3) |
| HIV | 62 (16.3) |
| HCV | 194 (50.9) |
| Arthritis/bone/joint problems, n (%) | 246 (64.6) |
| Psychological problems, n (%) | 73 (19.2) |
| Depression* | 73 (19.2) |
| On antidepressant treatment (n = 73) | 26 (35.6) |
| Stress* | 57 (15.0) |
| Anxiety* | 53 (13.9) |
| On anxiolytic treatment (n = 53) | 14 (26.4) |
| Other† | 17 (4.5) |
| History of joint procedures and surgeries, n (%) | 190 (49.9) |
| Reported | 190 (49.9) |
| Not reported | 184 (48.3) |
| Unknown | 7 (1.8) |
| Number of bleeds in past 6 months, n (%) | 380 |
| Median (Q1, Q3; n = 310) | 3 (1, 9) |

(continued)

Most individuals with a history of joint procedures reported having either chronic pain only (38%) or both acute and chronic pain (41%); only 6% of those with a history of joint procedure reported no pain. The most commonly defined worst joints based on pain scores were the right ankle (n = 42), right knee (n = 23) and left ankle (n = 20); prior procedures

Table 1. (continued)

| Number of joint bleeds in past 6 months, n (%) | 3 (1, 8) |
| Site reported. | 2017, 556–565

Pain categories and functional disability, health status and pain severity/interference

Mean EQ-5D-5L VAS and health index seemed to be lowest (indicating lowest QoL) in subjects with both acute and chronic pain (VAS: no pain, 86; acute pain only, 83; chronic pain only, 86; acute and chronic pain, 69; health index: no pain, 0.93; acute pain only, 0.83; chronic pain only, 0.93; acute and chronic pain, 0.68). Median HAL overall score also appeared lowest (indicating lowest QoL) among those with both acute and chronic pain (no pain, 99; acute pain only, 88; chronic pain only, 99; acute and chronic pain, 60). Mean pain severity on BPI seemed greatest among those with any chronic pain (4.1), with only a small difference between those with chronic pain only or both acute and chronic pain (acute pain only, 1.0; chronic pain only, 4.0; acute and chronic pain, 4.3). Mean pain interference was also not substantially affected by the presence of both acute and chronic pain vs. chronic pain only (acute pain only, 2.0; chronic pain only, 3.7; acute and chronic pain, 4.4).

Pain management strategies

The most common medications and other substances used for acute and chronic pain during the 6 months prior to enrolment are shown in Fig. 2. Use of factor VIII/IX or bypassing agents for treatment of pain increased numerically across categories of pain experienced during the past 6 months (no pain, 35%; acute pain only, 59%; any chronic pain, 69%). Medications

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taken during the prior 6–8 h included routine (prophylactic) use of coagulation factor or other haemophilia treatments (29%) and prescription pain medications (28%); 38% reported taking no medications within this time.

The most common opioid medication for acute and chronic pain during the past 6 months was hydrocodone-acetaminophen (used by 27% for acute pain and 30% for chronic pain; Fig. 2). Any opioid use was reported by 14% of participants who reported acute pain only during the past 6 months, compared with 44% and 50% of those with chronic pain only and acute and chronic pain respectively (Table 3). Among individuals with an acute component of pain, higher use of opioids was reported in those treated on demand than in those treated with routine infusions (acute pain only: on demand, 21%; routine infusions, 4%; acute and chronic pain: on demand, 57%; routine infusions, 45%). Of the 74 participants who reported ‘burning’ pain (typically applied to chronic neuropathic pain) only seven (9%) reported using gabapentin/pregabalin, and only one (1%) reported using TCAs.

Alcohol and marijuana were infrequently reported as pain treatments, although alcohol seemed to be used more often for patients with acute pain vs. chronic pain, and marijuana more often for patients with chronic pain vs. acute pain. Participants also reported use of non-pharmacologic strategies, including physical approaches (e.g. ice, rest, elevation, compression) and spiritual/mindfulness approaches (Fig. 3). While non-pharmacologic strategies were commonly used for individuals without pain (47%), nearly all of those with any acute pain only (90%), chronic pain only (93%) and both acute and chronic pain (94%) reported use of non-pharmacologic strategies for pain currently or in the past 6 months.

Discussion

Despite the high prevalence and impact of pain, recent studies have demonstrated a need for improved assessment of pain and functional impairment and better understanding of effective pain management strategies in PWH [6,8–11]. This analysis of P-FiQ illustrates the link between pain and functional capacity, psychological well-being and health-related QoL.

A majority of respondents (66%) reported experiencing chronic pain during the 6 months prior to enrolment, and nearly half of those also experienced acute pain. Interestingly, a low rate of prophylaxis was observed, considering the prevalence of severe haemophilia (71%); 30% had never received prophylaxis, an additional 32% had received prophylaxis for less than half of their lives and only 47% of those with both acute and chronic pain were currently receiving prophylaxis. The lack of prophylaxis, particularly if it occurred during childhood and adolescence, may have affected participants’ development of joint damage and chronic pain. Additionally, the presence of acute pain (typically attributed to bleeding) may indicate a need for greater use of tertiary prophylaxis (i.e. that initiated after the onset of joint disease [20]), particularly among those who experience both acute and chronic pain.

Associations of acute and chronic pain with comorbidities, treatments, bleeding symptoms and QoL measures suggest the greatest level of impairment in PWH who experience both acute and chronic pain. The

| Table 2. Assessment of functional disability in the past 6 months. |
|---------------------------------------------------------------|
| **Assessment of functional disability**                       |
| **Patient-reported**                                    | **Site-reported** |
| Observed, n                                                | 374               |
| Unrestricted school/work and recreational activities, n (%) | 125 (33.4)        |
| Full school/work with limited recreational activity levels  | 118 (31.6)        |
| due to plw, n (%)                                           | 101 (26.8)        |
| Limited school/work and recreational activity levels due  | 70 (18.7)         |
| to plw, n (%)                                               | 77 (20.4)         |
| Limited school/work, recreational activity levels and     | 34 (9.1)          |
| self-care levels due to plw, n (%)                         | 32 (8.5)          |
| Requires assistance from another person for school/work/self-care; no recreation due to plw, n (%) | 27 (7.2)          |
|                                                                 | 14 (3.7)          |
| **Use of cane/crutches/walker**                             |
| Observed, n                                                | 374               |
| Intermittent, n (%)                                         | 108 (28.9)        |
| Always, n (%)                                               | 13 (3.5)          |
|                                                                 | 18 (4.7)          |
| **Use of wheelchair**                                       |
| Observed, n                                                | 368               |
| Intermittent, n (%)                                         | 34 (9.2)          |
| Always, n (%)                                               | 8 (2.2)           |
|                                                                 | 9 (2.4)           |
| **School days/workdays missed due to lower extremity problems** |
| Observed, n                                                | 162               |
| Mean                                                       | 5.1               |
| Median (Q1, Q3)                                             | 1.0 (0.0, 4.0)    |
| **School days/workdays missed due to upper extremity problems** |
| Observed, n                                                | 140               |
| Mean                                                       | 2.6               |
| Median (Q1, Q3)                                             | 0.0 (0.0, 1.5)    |

Plw, pain, loss of motion, or weakness.
The prevalence of obesity and psychological conditions seemed to be higher among individuals who experienced pain in the previous 6 months vs. those who experienced none, and highest in those who experienced both acute and chronic pain. QoL outcomes similarly seemed to show the lowest measures of health status (measured via EQ-5D-5L VAS and health index) and functional abilities (measured via HAL) among individuals with both acute and chronic pain. Interestingly, BPI pain severity and interference scores appeared highest in those with chronic pain, with little difference between those with both acute and chronic pain vs. those with chronic pain only.

P-FiQ demonstrated a high amount of overlap in descriptors and treatments used for acute and chronic pain, highlighting similarities between how PWH experience and manage both types of pain. This lack of discrimination may also reflect potential difficulties in distinguishing between acute and chronic pain or in identifying a new bleed. In some cases, PWH may not know whether their pain is caused by acute bleeding or is simply an exacerbation of chronic pain, and may not consider this information when determining how to manage their pain. These issues are consistent with observations in the DOSE (Dosing Observational Study in Hemophilia) diary study, during which significant day-to-day variability in pain was observed for adults with arthropathy, although pain was significantly higher on bleed than non-bleed days [21]. Furthermore, specific descriptors used in the current analysis that may be characteristic of neuropathic pain (i.e. ‘burning’) were not associated with antiepileptic or TCA use. This finding suggests that the term ‘burning’ may have a different connotation in the context of haemophilic arthropathy as opposed to its use in describing pain in neuropathic disorders such as complex regional pain syndrome, but also indicates that opportunities may exist for improved dialogue to explore established pain treatment strategies not commonly reported in US PWH.

Consistent with a lack of discrimination between pain caused by arthropathy vs. acute bleeding, only
51% of participants with acute pain reported using coagulation factor replacement as a strategy for acute pain management, a significantly lower proportion than the 84% reported in the large National Pain Study [6]. In addition, even within the group of PWH with any chronic pain, the use of factor VIII/IX or bypassing agents as a pain treatment was reported by 78% of those receiving routine infusions and 55% of those treated on demand. These observations suggest that PWH may associate the use of factor VIII/IX or bypassing agents with pain reduction, by both treating and preventing bleeding episodes.

Another important observation from this study is the high rate of acetaminophen use and relatively low rate of opioid use, considering the high prevalence of pain. Of note, at the time of data collection, hydrocodone was not a schedule II drug (i.e. a drug with a high potential for abuse, with use

| Age, median (Q1, Q3), years | 27.3 (22.3, 38.4) | 32.9 (24.7, 44.6) | 34.1 (27.8, 52.5) | 35.8 (28.2, 48.5) |
| Race, n (%) | | | | |
| White, non-Hispanic | 39 (71) | 49 (67) | 83 (64) | 88 (75) |
| Black | 5 (9) | 6 (8) | 11 (9) | 6 (5) |
| White, Hispanic | 5 (9) | 10 (14) | 22 (17) | 11 (9) |

Table 3. Participant characteristics by pain type.

| | No Pain (n = 55) | Acute Pain only (n = 73) | Chronic Pain only (n = 129) | Acute and chronic pain (n = 118) |
| | | | | |
| Median (Q1, Q3), kg m⁻² | 26.4 (23.2, 29.4) | 26.4 (23.2, 29.7) | 26.9 (23.8, 30.4) | 27.2 (23.4, 31.9) |
| Normal/underweight (<25 kg m⁻²), n (%) | 18 (33) | 51 (42) | 46 (36) | 37 (31) |
| Overweight (25<30 kg m⁻²), n (%) | 26 (47) | 24 (33) | 46 (36) | 40 (34) |
| Obese (≥30 kg m⁻²), n (%) | 11 (20) | 18 (25) | 37 (29) | 41 (35) |

Education, n (%) | | | | |
Attended college | 36 (65) | 47 (64) | 69 (53) | 76 (64) |
Did not attend college | 19 (35) | 24 (33) | 60 (47) | 42 (36) |

Haemophilia type, n (%) | | | | |
Haemophilia A | 40 (73) | 54 (74) | 101 (78) | 96 (81) |
Haemophilia B | 15 (27) | 19 (26) | 28 (22) | 21 (18) |

Haemophilia severity, n (%) | | | | |
Mild (FVIII/FIX ≥5–10%) | 16 (29) | 14 (19) | 22 (17) | 10 (8) |
Moderate (FVIII/FIX 1<5%) | 7 (13) | 13 (18) | 19 (15) | 10 (8) |
Severe (FVIII/FIX <1%), n (%) | 32 (58) | 46 (63) | 88 (68) | 97 (82) |

Presence of inhibitors, n (%) | | | | |
0 | 11 (20) | 27 (37) | 71 (55) | 77 (65) |

Viral illness, n (%) | | | | |
HIV and/or HCV | 16 (29) | 37 (51) | 69 (53) | 75 (64) |
HIV | 5 (9) | 11 (15) | 20 (16) | 24 (20) |
HCV | 16 (29) | 35 (48) | 67 (52) | 71 (60) |

Self-reported arthritis/bone/joint problems, n (%) | | | | |
11 (20) | 33 (45) | 100 (78) | 97 (82) |

Self-reported psychological condition, n (%) | | | | |
Any | 3 (5) | 16 (22) | 31 (24) | 52 (44) |
Stress | 1 (2) | 6 (8) | 17 (13) | 32 (27) |
Anxiety | 1 (2) | 7 (10) | 15 (12) | 29 (25) |
Depression | 0 (0) | 11 (15) | 16 (12) | 35 (30) |
Other | 2 (4) | 4 (5) | 5 (4) | 6 (5) |

Treatment regimen, n (%) | | | | |
On-demand treatment of bleeding | 24 (44) | 34 (59) | 42 (33) | 42 (36) |
Routine infusions to prevent bleeding | 21 (38) | 24 (33) | 61 (47) | 55 (47) |
Mostly on demand with infusions ahead of activities | 5 (9) | 9 (12) | 17 (13) | 13 (11) |
Mostly on demand with occasional periods of prolonged treatment | 3 (5) | 2 (3) | 2 (2) | 2 (2) |

Extent of prophylaxis during lifetime, n (%) | | | | |
Never on prophylaxis | 23 (42) | 29 (40) | 31 (24) | 21 (18) |
25–49% | 5 (9) | 12 (16) | 37 (29) | 55 (47) |
50–99% | 7 (13) | 16 (22) | 28 (22) | 21 (18) |
Always on prophylaxis | 12 (22) | 8 (11) | 10 (8) | 7 (6) |

Number of bleeds in the last 6 months | | | | |
Mean | 2.4 | 5.6 | 7.4 | 9.7 |
Median (Q1, Q3) | 1.0 (0.0, 2.5) | 4.0 (1.0, 10.0) | 3.0 (1.0, 7.0) | 5.0 (3.0, 11.0) |

Pain treatment, n (%) | | | | |
Any use of acetaminophen* | 26 (47) | 41 (56) | 69 (53) | 70 (59) |
Any use of alcohol* | 4 (7) | 10 (14) | 12 (9) | 13 (11) |
Any use of FVIII/FIX or bypassing agents* | 19 (35) | 43 (59) | 74 (57) | 97 (82) |
Any use of marijuana* | 4 (7) | 8 (11) | 22 (17) | 20 (17) |
Any use of NSAIDs* | 16 (29) | 29 (40) | 58 (45) | 54 (46) |
Any use of opioids for chronic pain | 3 (5) | 10 (14) | 57 (44) | 59 (50) |

FVIII, factor VIII; FIX, factor IX; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NSAIDs, non-steroidal anti-inflammatory drugs.
*Current or within the 6 months prior to enrolment.
potentially leading to severe psychological or physical dependence, as defined by the United States Controlled Substances Act), as it is presently; therefore, the rate of hydrocodone use may be expected to continue to decrease in PWH to levels similar to those observed for oxycodone. Furthermore, while chronic pain was a marker for higher opioid use in general, the presence of an acute (and presumably bleed-related) component to pain seemed to drive increased opioid use, particularly among individuals treated on demand.

This analysis also presents one of the earliest documentations of marijuana for medicinal use among PWH. Interestingly, the rate of marijuana use was higher than or similar to that of most opioid drugs except for hydrocodone, and was also similar to the rate of physical therapy as an adjunctive therapy. These findings suggest that PWH may be finding avenues to ‘self-treat’ their pain, as purchasing medical marijuana does not require a provider’s approval, and obtaining certification for medical marijuana does not require individuals to involve their HTC. Given the role of

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### Table 1: Pain Medications and Other Substances Used for Acute and Chronic Pain

| Nonprescription Medications | Respondents (%) | Prescription Medications | Respondents (%) | Other Substances | Respondents (%) |
|-----------------------------|-----------------|--------------------------|-----------------|-----------------|-----------------|
| Acetaminophen               | 62              | Factor VIII/IX or bypassing agent | 51              | Medical marijuana | 12              |
| NSAIDs                      | 49              | Hydrocodone-acetaminophen | 30              | Alcohol         | 11              |
| Oxycodone                   | 13              | Oxycodone-acetaminophen | 10              |                 |                 |
| Hydromorphone               | 7               | Hydromorphone             | 7               |                 |                 |
| Codeine-acetaminophen       | 8               | Codeine-acetaminophen    | 6               |                 |                 |
| Tramadol                    | 7               | Morphine                 | 7               |                 |                 |
| Morphine                    | 7               | Fentanyl patch           | 3               |                 |                 |
| Gabapentin/pregabalin       | 7               | Gabapentin/pregabalin    | 2               |                 |                 |
| Methadone                   | 6               | Methadone                | 2               |                 |                 |
| Codeine                     | 2               | Codeine                  | 1               |                 |                 |
| Amitryptiline/nortryptiline | 0               | Amitryptiline/nortryptiline | 1               |                 |                 |
| Hydrocodone-acetaminophen   | 30              |                         |                 |                 |                 |

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Fig. 2. Pain medications and other substances used for acute (n=191) and chronic (n=247) pain in the past six months.

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marijuana in the treatment of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) [22,23], there may also be opportunities to explore marijuana use in pain management of older adult PWH. Alcohol use has also been reported in the past as a self-medication for pain in PWH, with one UK Hemophilia Society survey reporting 13% of respondents taking 15 or more units of alcohol per week [24]. A national study in the US found that 13% of those with acute pain and 15% of those with chronic pain reported alcohol as a non-pharmacologic treatment strategy [6], prompting inclusion of alcohol in this study; here, P-FiQ respondents with acute and chronic pain reported similar rates of alcohol use (14% and 9%).

Overall, the lack of discrimination between acute and chronic pain suggests that refined clinical assessments and focused dialogue may be needed to personalize pain management in PWH. A greater understanding among haemophilia providers of the nuances in identifying and managing acute and chronic pain may enable them to more effectively guide PWH towards appropriate management strategies. Additionally, greater use of pain management specialists may help PWH to appropriately select pain medications and set realistic pain management goals. The demonstrated associations between pain, joint status and bleeding and psychological conditions highlight the importance of addressing ongoing bleeding through appropriate use of tertiary prophylaxis, pain management including opioids where indicated, and treatment of psychological comorbidities in adult PWH.

Important limitations of this analysis include potential sampling bias due to the inclusion criteria of a history of joint pain or bleeding which limits any assessment of the epidemiology of pain prevalence, enrolment and participation of patients at routine or comprehensive care visits in a non-bleeding state and potential use of prescription and non-prescription medications ahead of the visit. While the inclusion criteria further the study objectives of capturing data on pain and its impact on function and health-related quality of life by focusing on patients with pain and/or arthropathy, every attempt was made to capture as covariates previsit medications and any treatments taken during the visit before the ‘retest’ with PROs was completed. Additionally, the P-FiQ study was not powered for statistical analysis, and therefore only descriptive analyses were performed.

Conclusion
Pain affects the daily lives of PWH, and while the description of pain and management strategies may be similar in those with acute and chronic pain, the impact of pain on QoL differs among those with acute pain, chronic pain, or both. These differences reflect a need to individualize pain management in PWH and suggest that a deeper understanding of pain associated with haemophilia may help guide more effective pain management strategies for PWH.

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Authorship contributions
All authors designed/perform the research and contributed to the writing/review of the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Extended participant characteristics (N = 381, unless otherwise indicated).

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