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Pain characteristics in people with Prader-Willi, Williams, and Fragile-X syndromes: an international survey of caregivers' perspective

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Abstract

Many people with intellectual disabilities (ID) depend on caregivers for pain identification and pain management decisions. Therefore, the aim was to explore caregivers' experience with pain in Prader-Willi syndrome (PWS), Williams syndrome (WS), and Fragile-X syndrome (FXS). A questionnaire was developed to gather third-party reporting of mainly pain presence, expression, and coping. Questions had single or multiple choice answers and open text fields, without verification of the putative information. The questionnaire was sent digitally to associations and interest groups for the syndromes and healthcare institutions for people with ID. After excluding absent, unknown, or uncertain genetic diagnoses and people without ID, the remaining 243 responses originated by caregivers (90.6% parents) of children and adults with PWS ($n=165$), WS ($n=53$), and FXS ($n=25$) in English, French, Dutch, and German speaking countries. More than half of all respondents reported the presence of known physical conditions that could be painful (58.4%) and pain observed during the past three months (54.3%, of which 70.9% chronic). Results reveal caregivers' barriers in identifying pain (e.g., interpreting pain expression and sensitivity). Respondents cope with pain mainly by seeking (para) medical help and observe both passive and active coping in people with the syndromes. Within limitations of the study's scope and design (e.g., used questionnaire), the results open a discussion about the validity of caregivers's perspective on pain. In-depth analysis in a more representative sample is recommended, as well as solutions for clinical practice such as training and education material about pain.

Keywords Prader-Willi syndrome · Williams syndrome · Fragile-X syndrome · pain characteristics · caregivers

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Over the last decades, knowledge has increased about pain characteristics in people with intellectual disabilities (ID) such as the presence, experience, treatment, expression, and coping of pain. The prevalence of health problems in people with ID is 2.5 to 3 times higher than in the general population (McMahon & Hatton, 2020; Van Schrojenstein Lantman-De Valk et al., 2000). People with ID have an increased risk of some potentially painful conditions such as injuries (Finlayson et al., 2010), migraine (Cooper et al., 2015), and diseases of the digestive system (McMahon & Hatton, 2020). Current researchers indicate that cognitive and communicative difficulties in people with ID cause misconceptions about a higher pain threshold (Barney et al., 2020; Doody & Bailey, 2017; MacDonald et al., 2021). Experimental evidence demonstrates that people with ID are sensitive to acute pain (Benromano et al., 2017; Defrin et al., 2021; McGuire & Defrin, 2015). Pain treatment is complicated by pharmacological factors (e.g., polypharmacy and genetic variability in metabolism) and indirect pain evaluation (e.g., proxy ratings and interpretation of behaviour) (Lonchampt et al., 2020; Symons et al., 2008). Some findings suggest a lack of pain treatment in people with ID (e.g., McGuire et al., 2010; Stallard, 2001). However, statements about undertreatment are often only based on analgesics (Axmon et al., 2018; Bernal-Celestino et al., 2021; Boerlage et al., 2013). A diverse, large number of behaviours are identified as indicators for pain expression (De Knegt et al., 2013; Weissman-Fogel et al., 2015; Zwakhalen et al., 2004). These include both typical indicators such as crying and atypical indicators such as 'hand in mouth' (Weissman-Fogel et al., 2015). People with ID use fewer pain coping strategies than people without ID (Breau & Burkitt, 2009; Valkenburg et al., 2015; Zabalia, 2013). The use of active coping strategies (e.g., cognitive self-instruction or refocusing, problem solving, information seeking) is related to a higher mental age (Breau & Burkitt, 2009; Burkitt et al., 2011; Valkenburg et al., 2015).

An integration of perspectives on pain in people with ID is needed for insight in clinical practice. Multifaceted pain research should include file research, medical examination, and information from people with ID themselves, but also tacit knowledge from caregivers. Although this rich experiential knowledge (Carter et al., 2002; Kruithof et al., 2020; Nieuwenhuijse et al., 2020) is a third-party perspective, many people with ID depend on caregivers for pain identification and pain management decisions. According to survey research, half of healthcare professionals base their pain assessment of people with ID on reporting by caregivers (Millard & de Knegt, 2019; Walsh et al., 2011). Some findings suggest that caregivers are able to recognize pain behaviours with high inter-rater reliability (Weissman-Fogel et al., 2015; Lotan et al., 2009) and to provide pain ratings similar to those of people with ID themselves (Hägglund et al., 2020; Voepel-Lewis et al., 2005). However, the Social Communication Model of Pain shows that psychosocial factors such as biases and experience influence a caregiver's appraisal of pain and subsequent actions (Craig, 2009). Barriers to accurate pain assessment of people with ID by caregivers include the influence of caregivers' pain-related beliefs on the perceived need for medical attention (Genik et al., 2017). Parents report that children with Down syndrome (Valkenburg et al., 2015) and Rett syndrome (Cappuccio et al., 2019) are less sensitive for pain than children without ID. It is unknown whether this appraisal is influenced by parents' difficulty to identify the presence and location of pain in children with Down syn-

drome (Hennequin et al., 2003) and the small number of pain expressions observed by parents of children with Rett syndrome (Cappuccio et al., 2019). Also little is known about pain assessment by caregivers of other specific subgroups of people with ID. Due to the heterogeneous population of people with ID, genetic syndromes are a starting point for research into pain management by caregivers of people with ID. The current study aims at Prader-Willi syndrome due to concerns about a possible high pain threshold and on both William syndrome and Fragile-X syndrome due to relatively unknown pain characteristics. These three syndromes will be described below.

Prader-Willi syndrome (PWS) has a prevalence of 1:16.000, according to the most recent findings (Lionti et al., 2015). PWS is caused by a reduced gene expression from the 15q11.2-q13 region on the paternal chromosome 15. This lack of gene expression is often caused by a deletion (70%), but can also be the result of maternal uniparental disomy (Mupd; 25%) and defects or translocations in the imprinting center (3%) (Bittel & Butler, 2005). Common and potentially painful conditions are scoliosis, fractures, and skin-picking (Sinnema et al., 2011). Caregivers have described many painful situations (e.g., bruises, toothache, burns) in which the person with PWS did not express pain (Butler et al., 2002; Sinnema et al., 2013). Absent pain expression could be related to cognitive impairments in expressive language, such as poor narrative skills (Ho & Dimitropoulos, 2010). Another explanation is a presumed high pain threshold, which is reported by 76–97% of caregivers (Butler et al., 2002; Sinnema et al., 2013). Possible causes for the increased pain threshold are: a decreased activity in the insula, neurotransmitter imbalance of the hypothalamus, reduced sensory neurons of the dorsal root ganglia, or nerve response amplitude dampened by a thicker subcutaneous layer (Klabunde et al., 2015; Priano et al., 2009). A quantitative sensory threshold (QST) experiment demonstrated in adults with PWS significantly higher thresholds for cold pain and heat pain compared to healthy adults without ID (Priano et al., 2009). Further research is needed to confirm this finding due to the the small sample size and the use of a reaction-time dependent method (McGuire & Defrin, 2015).

Williams syndrome (WS) occurs in 1:7.500 according to the most recent estimation (Strømme et al., 2002). WS is caused by a microdeletion of genes on chromosome 7q11.23 (Pérez Jurado et al., 1996). Some painful conditions are common, such as diverticulitis (Partsch et al., 2005) and constipation (Morris et al., 2020). According to parents, a lowered pain threshold for loud sounds occurs in 79.8% of people with WS and is more common than in people with Down syndrome or autism (Levitin et al., 2005). Examples of pain behaviour during sounds are covering ears with both hands, crying, whining, stating ‘It hurts my ears’, and cringing (e.g., arching back and bringing shoulders towards neck) (O’Reilly et al., 2000). Relevant for pain communication is the cognitive impairment in pragmatics: misinterpreting questions and providing little information when asked for information or clarification (Mervis & Velleman, 2012).

Fragile-X syndrome (FXS) results from a full mutation in the Fragile-X Mental Retardation 1 (FMR1) gene on the X-chromosome and subsequent loss of its protein product (Krueger & Bear, 2010). A systematic review with meta-analysis indicates a prevalence of 1.4:10.000 males and 0.9:10.000 females (Hunter et al., 2014). Poten-

tially painful conditions such as gastro-intestinal problems and recurrent ear infections are common (Kidd et al., 2014; Lozano et al., 2016). Mutated FXS mice show a decreased response to ongoing harmful or painful stimuli (Price et al., 2007), but the implication of this finding for pain experience in humans with FXS remains unclear. Cognitive impairments in expressive speech such as syntactic complexity and lexical diversity (Shaffer et al., 2020) may hamper clear self-report of pain by people with FXS.

In conclusion, much remains unknown about pain characteristics in people with PWS, WS, and FXS. Especially in syndromes with specific language impairment or decreased response to injury, the experience of caregivers would provide valuable insight for pain management and detecting early pain signals. Despite their third-party and putative information, caregivers (i.e., both family and paid staff) are an essential part of multifaceted pain research on people with ID. Therefore, the aim of the current study was to explore in a large sample caregivers' experience with pain in people with PWS, WS, and FXS. As a first step, the current survey focused on both similarities and differences in pain characteristics between these syndromes as perceived by caregivers (i.e., presence, experience, treatment, expression, and coping). The ultimate goal is that the caregivers' perspective leads to further research and directions for clinical practice.

Method

Study design

The survey study had a cross-sectional design.

Respondents

Inclusion and exclusion criteria. Caregivers (i.e., family and paid staff) were included as respondents if: (1) they stated that the person under their care has a genetic diagnosis of PWS, WS, or FXS as well as the presence of ID and (2) they fully completed the questionnaire. The study was part of a larger pain study in PWS, WS, and FXS that involved neuropsychological assessment of Dutch participants. Due to the neuropsychological assessment, possible cognitive interference excluded other rare syndromes relevant for pain research, such as severe ID in Cornelia de Lange syndrome (Kline et al., 2018), delayed or absent speech in 22q13.3 deletion syndrome (Cusmano-Ozog et al., 2007), and high prevalence of seizures in Angelman syndrome (Raby et al., 2013).

Sample characteristics. Only data of the 355 fully completed questionnaires were used (48.3% of the 753 received responses). Based on respondents' statements that genetic diagnosis of the syndrome was absent, unknown, or uncertain ($n=103$) and that ID was absent in the person with the syndrome ($n=9$), a total of 112 responses were subsequently excluded. The remaining 243 responses had been collected with the English ($n=99$), French ($n=57$), Dutch ($n=46$), and German ($n=41$) versions of

the questionnaire. The questions were answered by respondents about people with PWS ($n=165$), WS ($n=53$), or FXS ($n=25$). Genetic PWS subtype was reported to be mainly paternal deletion (66.1%) and further to consist of Mupd (24.2%), chromosome 15 translocations (5.5%), imprinting defects (3.6%), and atypical deletions (0.6%). Of the people with PWS, 39.4% used growth hormones. The people with the syndromes were adults (i.e., ≥18y; 70%) or children (i.e., <18 year; 30%). The ID level according to the respondents was: moderate ID (38.7%), mild ID (33.3%), borderline ID (18.9%), severe ID (8.2%), and profound ID (0.8%).

All results were based on the caregivers' perspective rather than first-hand information (i.e., people with the syndromes). Respondents consisted of mothers (81.5%), fathers (9.1%), 'other' related people (4.9%), or personal support workers (4.5%). Respondents in the category 'other' were relatives (i.e., other than parents, 72.7%), health care workers (18.2%), or host families and acquaintances (9.1%). The people with the syndromes mainly lived at home with parents (66.7%): a minority lived in care centers for people with ID (28.8%) or other settings (4.5%) such as an apartment supported with care.

Material and procedure

Development of questionnaire. The questionnaire was developed by N. de Knegt and consisted of five parts: (1) background information, (2) medication, (3) presence of pain, (4) expression of pain, and (5) coping with pain. The original Dutch questionnaire was translated in a forward-backward manner by the VU University Language Center into English, Spanish, German, and French. The English version has been approved by the Prader-Willi Syndrome Association USA, but has not been examined with data on reliability or validity. There was lack of verifiability for all answers, including genetic and medical information. Online Resource 1 includes the English version of the questionnaire, therefore only a general description will be given below. The question about pain expressions across increasing pain intensity was based on the Individualized Numeric Rating Scale for people with ID (INRS; Solodiuk et al., 2010). INRS scores of parents and nurses about post-operative pain in non-verbal children with severe ID show high inter-rater agreement and reliability as well as moderate to strong convergent validity (Solodiuk et al., 2010). The questions about coping were based on the Pain Coping Questionnaire (PCQ; Reid et al., 1998). The PCQ has been validated for both healthy children and children with recurrent pain (Reid et al., 1998) and has been used in pain research on children with ID (i.e., Down syndrome; Valkenburg et al., 2015).

Questionnaire. Background information was gathered on the respondent's relationship to the person they cared for and the person's age (adult/child), genetic diagnosis, level of intellectual functioning, and type of living facility. Information about currently used medications and/or growth hormones (maximum of 10) was gathered in a table. The table required the name of each medication and the reason as well as time period of its use. Information about potentially painful or discomforting conditions (maximum of 10) were also gathered in a table. The table required the medical name, presence of a medical diagnosis, severity, chronic persistence, and treatment

of each physical condition. Information about the presence and location of pain during the past three months was gathered in a table with questions about the following aspects: the presence of chronic pain, the persistence and frequency of pain, the estimated pain intensity, the cause of pain (i.e., according to the physician and the respondent), and pain treatment. Information about expression and coping of pain was gathered for a general overview of experienced pain (i.e., instead of pain due to specific physical condition s or situations). Information about pain expression was gathered by a general question about pain indications and by specific questions about observed behavioural change after the use of a pain reliever (i.e., without specifying the time between the use and observation), verbal expressions, reduced pain sensitivity, possible underlying reasons for expressing pain, and caregivers' difficulties with identifying pain. In addition, a description of pain expression was asked for at least five different pain intensities on a numeric scale of 0 (no pain) to 10 (worst pain). Information about pain coping was gathered about strategies used by the person with the syndrome and strategies used by the respondents (i.e., to cope with the pain in the person they cared for). The multiple choice answers included pharmacological and non-pharmacological strategies as well as the possibility to add an own answer.

Procedure of data collection. Between 17 and 2017 and 16 May 2019, questionnaires were sent digitally without a priori sample size calculation. Respondents were recruited by distribution of the questionnaire through associations for families of individuals with the syndromes, interest groups by the families themselves, and health care institutions for people with ID (e.g., clinical genetic departments of hospitals and living or working facilities). Responses were received from countries with the following national languages: Dutch (Belgium, Netherlands), English (Australia, England, Ireland, New Zealand, United States), Spanish (Argentina, Colombia, Spain), French (France, Switzerland, Quebec Canada), and German (Austria, Germany, Switzerland). All Spanish responses were excluded after selection on genetic diagnosis. It was unknown how countries related to individual data, as country was not registered within the questionnaire.

Respondents received an invitation to the questionnaire by a link in an e-mail. The questionnaire was completely anonymous, as no name or date of birth was requested and IP addresses were unknown. Therefore, no informed consent was necessary. It took on average 25 min to complete the questionnaire ($Mdn = 25.5$, $IQR = 20.6$), which could be paused and continued at any time. To avoid missing data, it was set that no questions could be skipped. Data were collected using Qualtrics (Provo, Utah, USA).

Statistical and qualitative analyses

The 15 datasets from the three syndrome-specific questionnaire versions in the five languages were exported and merged into one file, using IBM SPSS Statistics 26. Subsequently, respondents were excluded based on (1) incomplete questionnaires, (2) absent, unknown, or uncertain genetic diagnosis, and 2) absence of ID. Textual answers of the final dataset were classified in categories of similar responses (e.g., psychological cause of stomach ache) based on the data instead of a priori theoretical

categories. Variables were added to count the number of medications per category across the maximum of 10 medications. Data of all physical condition s were gathered in separate Excel tabs per pain aspect (e.g., type of condition and treatment) for the total sample and separately per syndrome. Additional variables were created in both SPSS and Excel to classify answers that consisted of combined categories (e.g., analgesics and massage): these frequencies in SPSS output were subsequently added to the main categories in Excel for a final count. The same procedure in Excel was used for pain during the past three months (i.e., to calculate pain frequencies and average pain intensities across locations and to categorize cause and treatment per pain location) and for all questions related to pain expression and pain coping. Besides qualitative data analyses, descriptive statistics were performed (i.e., frequencies, means, and Chi-squared tests). Aggregated results were presented to describe similarities between syndromes for a more coherent caregivers' perspective (i.e., also in line with the relative small total sample size and the unequal number respondents per syndrome). Differences between syndromes were based on salient results per syndrome (e.g., the highest and/or lowest percentages of response categories were cautiously interpreted for uniformity, without providing a characterisation that applies to each individual respondent).

Results

Presence of pain

Physical conditions potentially causing pain or discomfort. The presence of potentially painful or discomforting physical conditions (from now on referred to as 'physical conditions') was reported in 58.4% of the sample ($n=142$). This included injury caused by self-injurious behaviour. The presence of physical conditions was not statistically significantly associated with syndrome (χ^2 (2)=5.73, $p=0.057$, Cramer's V=0.15). On average, one physical condition was reported in the sample ($Mdn=1$, $IQR=2$, range=0–6). As shown in Table 1, the most frequently reported known locations of physical conditions, injury, or pain were: (1) the spine, rib, and chest, (2) the digestive system, (3) skin and nails, and (4) hips and lower joints/limbs. Table 2 shows the most prevalent categories of known treatment: 1) gastrointestinal,2) massage, weight loss, exercise, physiotherapy, different sitting or lying position, and 3) treatment for skin, nails, ears, eyes, teeth, or mucous membranes. No other current treatment than rest was reported for 13.8% of the sample.

Analgesics were reported in 4.5% of the sample and consisted of paracetamol, unspecified analgesics (i.e., 'pain relievers' or 'pain medication'), ibuprofen, aspirin, and gabapentin (i.e., anticonvulsant that reduces neuropathic pain). As shown in Tables 2, other treatment categories contain reported medication that could have an indirect pain relieving effect such as laxatives, antacids, and antibiotics.

In each syndrome (see Table 3), the presence of a physical condition was reported by approximately half of the respondents (48–64.8%). Almost all of these conditions were stated to be chronic (78.2–85.1%). Syndromes differed in the most prevalent known physical condition (i.e., spine and rib/chest pain in PWS, digestive system

Table 1 Percentage of people with the syndromes within categories of potentially painful physical conditions

Category (vertical) and percentage (horizontal) of physical conditions	Total	PWS	WS	FXS
Spine (scoliosis, kyphosis, lordosis, back pain), rib pain, chest pain	31.2	39.3	12.5	15.4
Digestive system (e.g., reflux, diverticulosis, constipation, stomach inflammation)	27.2	24.3	29.2	53.8
Skin (e.g., wounds, eczema, ulcers, hemorrhoids, fungus), nails (e.g., biting or scratching)	18.8	20.7	12.5	15.4
Hips (e.g., arthrosis), lower joints (knee, ankle: e.g., luxation), lower limbs (legs, feet: e.g., fracture)	16.8	16.4	14.6	23.1
Self-injurious behaviour (e.g., skin picking, scratching, finger biting, nail removal, ear lobe piercing)	10.4	14.3	0.0	7.7
Mouth (teeth, gums), eyes (dry), ears (inflammation, hyperacusis), nose (polyp), headache, migraine	9.9	10.0	8.3	15.4
Indirect or unlocalized pain (e.g., Lyme disease, heart disease, previous surgeries, braces)	4.0	3.6	6.3	0.0
Unlocalized pain in muscles (cramp), joints, bones (arthrosis, arthritis, sprains, gout, osteoporosis)	4.0	3.6	6.3	0.0
Regulation of blood pressure (high/low), fluid (lymph oedema), or hormones (thyroid)	3.0	2.9	4.2	0.0
Urinary tract (infection) and reproductive organs (menstrual cramps, ovarian cyst, balanitis)	2.5	2.1	0.0	15.4
Other intestines (e.g., abdominal hernia, cholecystitis, kidney stone, liver disease)	1.5	0.0	4.2	7.7
Respiratory tract (asthma, apnea, aerophagia, sore throat, sarcoidosis)	1.5	1.4	2.1	0.0
Shoulders and arms (e.g., burn, muscle pain)	0.5	0.7	0.0	0.0
Total	100	100	100	100

Note. Potentially painful' refers to physical conditions that could cause pain (including injury caused by self–injurious behaviour), regardless of whether the participant is complaining of them. Total = total group of people with the syndromes, PWS = Prader–Willi syndrome, WS = Williams syndrome, FXS = Fragile–X syndrome. Rows are coloured grey alternately to increase readability

conditions in WS and FXS) and in the most prevalent known treatment (i.e., massage and movement-related treatment in PWS, gastrointestinal treatment in WS, (para) medical devices and gastrointestinal treatment in FXS).

Reported by the respondents. More than half of the people with the syndromes (54.3%, $n=132$) were reported by the respondents to have had pain in the past three months. The average observed pain intensity over all body areas was mild to moderate ($M=5.2$, range 4.14–5.94). On average, pain was observed in two body areas ($Mdn=2$, $IQR=3$, range = 1–9 areas). The most prevalent observed pain locations were 54.5% head, 45.5% back, 44.7% abdomen, and 40.9% legs (see Online Resource 2). Chronic pain was common, with a observed prevalence exceeding 50% for five out of nine body areas.

The observed presence of pain in the past three months was not statistically significantly associated with syndrome (χ^2 (2) = 1.63, $p=0.44$). However, the most prevalent observed pain location differed between syndromes (see Table 4): back in PWS (52.9%), abdomen in WS (65.6%), and head in FXS (66.7%). Remarkably, respondents identified a psychological cause of abdominal pain in WS (i.e., stress or anxiety) besides the physical cause (e.g., constipation) that physicians had informed them about. Pain was observed to occur mainly 2–3 times per month in PWS and WS,

Table 2 Number of people with the syndromes within categories of treatment for potentially painful physical conditions

Category (vertical) and percentage (horizontal) of physical conditions	Total	PWS	WS	FXS
Rest or without treatment (e.g., wait for it to pass, no compliance, relaxation)	13.9	14.1	12.3	12.5
Gastrointestinal (e.g., adjusted diet, laxative, antacid, enema, probiotics)	12.9	11.0	17.5	20.8
Massage, weight loss, exercise, physiotherapy, different sitting or lying position	12.9	13.2	14.0	8.3
Skin (e.g., ointment), nails (e.g., clipping), ears (e.g., removing earwax), eyes (i.e., drops), teeth (e.g., root canal), or mucous membranes (i.e., mouth ulcers gel)	10.6	12.3	7.0	4.2
(Para)medical devices (e.g., brace, orthopaedic shoes, ear tubes, stent, cast, splint)	9.4	7.9	8.8	20.8
Unclear or general (e.g., 'medication', 'therapy', 'over the counter', 'pain relief')	8.4	7.0	12.3	12.5
Combination of categories	8.4	7.9	10.5	8.3
Other (para)medical monitoring/involvement (e.g., diagnostics, follow-up, scans, referral, visit to doctor/specialist, 'in observation', aftercare, adjusted medication)	6.5	7.0	5.3	4.2
Surgery, visit to Accident and Emergency department, hospital admission	6.1	6.6	5.3	4.2
Analgesics (e.g., over the counter pain relievers and gabapentin)	4.5	4.8	5.3	0.0
Behavioural/psychological interventions (e.g., distraction, reminders, instructions)	3.5	4.4	0.0	4.2
Other medication[a] (e.g., antibiotics), supplements, or homeopathy	2.3	3.1	0.0	0.0
Other non-pharmacological interventions (heat, cold, aromatherapy)	0.6	0.4	1.8	0.0
Total	100	100	100	100

Note. Total = total group of people with the syndromes, PWS = Prader–Willi syndrome, WS = Williams syndrome, FXS = Fragile–X syndrome. a = not directly related to other categories (e.g., no gastrointestinal medication or analgesics), b = no (medical) device, massage, or movement related treatment. Rows are coloured grey alternately to increase readability

but less than once per month in FXS. Across the syndromes, pain was reported to be mainly chronic (M=70.9%, range 68.8–73.3%) and to occur daily in 11.1 to 20%.

Expression of pain

In the total sample and for each syndrome, respondents mainly recognized pain by verbal expression, a combination of various expressions, and physiological indicators (see Table 5). Prominent pain expressions in people with PWS were atypical indicators (e.g., hiding, trivializing, or denying pain) and an increase or decreae in interaction and activities, while physiological and facial pain indicators were relatively less often observed. Physiological indicators and non-verbal indicators (i.e., communication and vocalisation) were dominant in people with WS, while body posture or movement and facial indicators were relatively often observed in people with FXS. The change in prevalence of observed pain expression categories with increasing pain intensity did not reveal a clear pattern (see Table 6), but some trends were visible: (1) a shift into more diverse and more physiological indicators with higher pain intensity, (2) the use of verbal expression increases until a pain level of 4 and then slowly decreases, while the use of vocalization steadily increases until the high-

Table 3 Presence of pain per syndrome: potentially painful physical conditions and treatment

Syndrome	Presence of physical conditions within syndrome	Number of physical conditions within syndrome	Percentage of adults and children with physical conditions [a]	Most prevalent physical condition [a,b]	Presence of medical diagnosis [a,b]	Severity of physical condition [a,b]	Chronic physical condition (>3 months) [a,b]	Most prevalent treatment (not necessarily related to the most prevalent physical condition) [a,b]
	% (*n*)	*Mdn* (*IQR*) or *M* (*SD*), range	% (*n*)	Name: %	%	%	%	Name: %
PWS	64.8 (107)	*Mdn* = 1 (2), 0–6	Adults 83.8 (88), children 16.2 (17)	Spine and rib/chest pain: 39.3	79.5	Mild 27.9, Moderate 48.0, Severe 24.0	85.1	Massage, weight loss, exercise, physiotherapy, different sitting/lying position: 13.1
WS	50.9 (27)	*Mdn* = 1 (2), 0–6	Adults 32.0 (8), children 68.0 (17)	Digestive system: 29.2	79.2	Mild 23.5, Moderate 52.9, Severe 23.5	79.2	Gastrointestinal: 17.5
FXS	48.0 (12)	*M* = 0.80 (1), 0–3	Adults 66.7 (8), children 33.3 (4)	Digestive system: 53.8	80.0	Mild 30.0, Moderate 50.0, Severe 20.0	80.0	(Para)medical devices and Gastrointestinal: each 20.8

Note. PWS = Prader–Willi syndrome, WS = Williams syndrome, FXS = Fragile–X syndrome. a = within people with both the syndrome and presence of physical conditions, b = calculated over all categories of all physical conditions per participant. 'Severity' refers to the physical condition (e.g., degree of injury or stage of disease), not to the intensity of experienced pain. Rows are coloured grey alternately to increase readability

Table 4 Pain during past three months per syndrome and over all pain locations

Syndrome	Presence of pain during past 3 months within syndrome	Chronic pain (> 3 months) [a]	Persistent pain [a]	Frequency of pain [b]	Pain intensity [c]	Most prevalent pain location	Most prevalent cause of pain (doctor) in this pain location [d]	Most prevalent cause of pain (respondent) in this pain location [d]	Most prevalent pain treatment for this pain location [d]
	% (*n*)	% (*n*)	% (*n*)	%	*M*, range	Name, % (*n*)	Name, %	Name, %	Name, %
PWS	51.5 (85)	70.6 (60)	90.6 (77)	Most prevalent: 2-3x per month, 23.3 Daily: 20.0	5.2, 1–10	Back, 52.9 (45)	Spine or hips, 63.0	Spine or hips, 56.9	Massage, weight loss, exercise, physiotherapy, different sitting or lying position, 33.9
WS	60.4 (32)	68.8 (22)	100 (32)	Most prevalent: 2-3x per month, 28.0 Daily: 13.0	5.4, 2–10	Abdomen, 65.6 (21)	Constipation, Crohn's disease, narrowing / tenderness / slowness of bowel, cramps, diarrhea, 30.0	Psychological, 25.0	Gastrointestinal (i.e., adjusted diet or laxative), 30.4
FXS	60.0 (15)	73.3 (11)	86.7 (13)	Most prevalent: < 1x per month, 36.1 Daily: 11.1	4.8, 1–9	Head, 66.7 (10)	Teeth or oral health, 50.0	• Ears or eyes, 33.3 • Teeth or oral health, 33.3	Analgesics, 41.7

Note. PWS = Prader-Willi syndrome, WS = Williams syndrome, FXS = Fragile-X syndrome. a = people with ≥ 1 location of chronic or persistent pain, respectively, b = % as average of the total number pain locations per syndrome, c = adding the pain intensity product (*M* * *n*) of each pain location and dividing this total by the total number of people with a pain location (i.e., which exceeded the total number of people per syndrome, because each person could have several pain locations), d = % prevalence per category of most prevalent pain location per syndrome, after coding the textual answers and correcting for combined answers per location. Rows are coloured grey alternately to increase readability

est pain intensity, (3) facial expression is mainly described for the least severe pain levels, and (4) the reporting of the mood category increases quickly from the lowest pain levels and remains relatively prevalent throughout higher pain levels.

The most commonly observed change after using pain medication by all people with syndromes and in each syndrome was relaxation in behaviour, facial expression, or physiology (see Table 7). This category was the highest prevalence of observed positive change (22.3% of the total sample and up to 30.6% of people with WS). An absent, instable, or even negative change were reported for 13.7% in the total sample (up to 23.8% within people with FXS). About one quarter of all people with syndromes was reported as being able to give a clear verbal expression of pain and to mention pain locations or conditions (27.6% of all people and 13.6–27.3% per syndrome, see Table 8). However, respondents commented that the expressed information is not always helpful. For example, some people with syndromes were stated to lack understanding of pain intensity, to mention only severe pain, or to localize pain incorrectly. Knowing the person seemed important in 12.8% of the sample (up to 36.4% in caregivers of people with FXS) due to the use of synonyms or unique descriptions to report the presence of pain.

According to respondents, an apparent high pain threshold or pain tolerance was the main reason for difficult pain recognition (see Table 9), with many examples of absent pain indicators in potentially painful situations (e.g., appendicitis). The prevalence of other reasons for difficult pain recognition differed between syndromes. Especially prevalent in PWS was an assumed delayed pain expression or recognition (e.g., an unnoticed fracture for four months). Reasons that were especially prevalent in WS included pain indicators without (specific) complaints, difficult report on pain characteristics, and no distinctive pain behaviour. The recognition of internal injuries was stated to be especially difficult in FXS, in which people tended to express pain only for visible injury (e.g., crying for a scraped knee but having a severe ear infection only accidentally discovered during medical examination).

Table 10 shows that about one third of respondents (36%) based their statement of reduced pain sensitivity on two aspects. These were: (1) the presence of pain indicators such as crying without (many) complaints or with an observed quick recovery, and (2) potentially painful situations without (many) observed pain indicators. Arguments against reduced pain sensitivity were also mentioned, such as an assumed hiding of pain (e.g., an observed fear of the doctor, with a relatively high prevalence of 8.3% in WS) and a possible overestimated high pain threshold by physicians (0.5%). Respondents stated that these physicians do not take pain complaints seriously in the absence of other pain indicators. Difficulties with pain report were also apparent in various underlying reasons that respondents attributed to pain expression (see Table 11): mainly seeking attention (30.9%), but also avoidance (especially in WS: 31.6%), loving to take medication or receiving food in the hospital (especially PWS: 14.5%), and confusing pain with other feelings (especially in FXS: 13.9%).

Table 5 Percentage of people with the syndromes within categories of pain expression

Category (vertical) and syndrome (horizontal)	Total	PWS	WS	FXS
Verbal expression (e.g., asks for medication / doctor, incoherent speech, complains) [a]	31.3	33.4	26.8	24.5
Combination of categories	20.3	19.9	21.6	20.8
Physiological indicators (e.g., tears, appetite, sleep, breath, facial colour, pupil dilation)	11.9	9.7	18.6	15.1
Mood, panic, (increase in) physical aggression, or restless	7.1	7.0	7.2	7.5
Body posture or movement (e.g., rocks, places hands over ears, refuses to walk, limps)	6.9	6.7	6.2	9.4
Interaction and activities (increase or decrease)	5.8	6.7	2.1	5.7
Unclear answers	4.0	4.3	4.1	1.9
No pain indicators or presence of pain is difficult to detect / evaluate (e.g., lies, excuses)	2.7	2.4	2.1	5.7
Facial expression (e.g., grim, sad, grimaces, frowns, pinched / parted lips, winces)	2.1	1.6	2.1	5.7
Pain expression differs per pain location (e.g., abdomen: poor sleep, back: poor walking)	2.1	2.2	2.1	1.9
Atypical expression: too long / short, delayed, variable [b], hides / trivializes / denies pain	1.7	2.2	1.0	0.0
Non-verbal communication: demonstration, showing / pointing, or sign language	1.5	1.6	2.1	0.0
Non-verbal expression: vocalization (e.g., moans, wails, screams, whines, sharp sounds)	1.3	0.8	3.1	1.9
Seeking help (self or through caregivers) without referring to verbal expression [c]	0.6	0.5	1.0	0.0
Self-injurious behaviour, increased obsession (e.g., on pain / doctor), or compulsion (e.g., rubs hands)	0.4	0.5	0.0	0.0
Pain expression varies per intensity, type (e.g., needle versus fall), or duration of pain	0.2	0.3	0.0	0.0
Total	100	100	100	100

Note. Total = total group of people with the syndromes, PWS = Prader–Willi syndrome, WS = Williams syndrome, FXS = Fragile–X syndrome. Frequencies from the combination of categories were added to the frequencies of separate categories before percentages were calculated. a = respondents mention expressions of incorrect pain locations, too low pain intensities, or 'high pain thresholds' (e.g., only complains with severe pain). b = e.g., withdrawing but needing others for certainty at the same time. c = e.g., 'is looking for people who can help him', 'seeking intervention', or 'looks for solutions'. Rows are coloured grey alternately to increase readability

Coping of pain

According to respondents (see Table 12), people with the syndromes mainly cope with pain by withdrawing to rest (highest: 22.9% PWS and 25% FXS) and asking for reassurance, pain relief, or a doctor visit (highest: 22.9% PWS). Passive coping reactions were observed in two thirds of people with WS (i.e., moaning, complaining, crying, being passive, refusing pain medication, and expecting or needing help from others). In FXS, addressing oneself or the pain and an assumed hiding of the pain were often used (both 25%).

Table 13 shows that respondents themselves cope with pain in the people under their care mainly by seeking (para) medical help (28.4%) and applying paramedical treatment (16.2%) such as cold or heat. Advise (e.g., to have a rest), mental support

Table 6 Percentage of people with the syndromes within categories of pain expression across increasing pain intensity

Category (vertical) and pain intensity (horizontal)	0	1	2	3	4	5	6	7	8	9	10
Verbal expression	5.1	9.6	15.7[b]	20.6[c]	20.0[c]	19.8[b]	16.3[b]	14.4[a]	17.5[b]	11.8[a]	10.6[a]
Combination of categories	18.5[b]	9.6	9.4	12.1[a]	12.9[a]	14.8[a]	12.0[a]	16.5[b]	14.0[a]	15.1[b]	21.8[c]
Physiological indicators	0.3	1.2	2.4	4.7	7.1	10.6[a]	17.4[b]	15.8[b]	14.9[a]	16.1[b]	21.0[c]
Mood, panic, (increase in) physical aggression, or restless	17.3[b]	15.7[b]	25.2[d]	17.8[b]	25.9[d]	20.8[c]	15.2[b]	19.4[b]	21.9[c]	26.9[d]	17.8[b]
Body posture or movement	0.6	7.2	3.1	4.7	2.4	5.3	4.3	5.8	3.5	5.4	7.8
Interaction and activities (increase or decrease)	16.0[b]	12.0[a]	14.2[a]	8.4	12.9[a]	13.8[a]	17.4[b]	13.7[a]	17.5[b]	11.8[a]	8.0
Unclear answers	1.0	2.4	3.1	1.9	1.2	1.1	2.2	1.4	0.9	0.0	0.9
No pain indicators or presence is difficult to detect / evaluate	23.3[c]	27.7[d]	15.7[b]	14.0[a]	9.4	3.2	2.2	1.4	0.0	1.1	0.0
Facial expression	17.9[b]	10.8[a]	7.9	8.4	4.7	4.2	6.5	6.5	2.6	2.2	3.7
Non-verbal communication	0.0	0.0	1.6	0.9	0.0	1.1	1.1	0.0	0.0	1.1	0.0
Atypical expression	0.0	0.0	0.0	1.9	0.0	1.1	0.0	0.0	0.9	0.0	0.9
Non-verbal expression: vocalization	0.0	1.2	0.0	1.9	2.4	2.5	3.3	3.6	6.1	7.5	7.2
Seeking help without referring to verbal expression [a]	0.0	0.0	0.8	1.9	0.0	0.0	1.1	0.7	0.0	1.1	0.3
Self-injurious behaviour, attention for pain, or compulsion	0.0	2.4	0.8	0.9	1.2	1.8	1.1	0.7	0.0	0.0	0.0
Total	100	100	100	100	100	100	100	100	100	100	100

Note. A higher alphabetical code indicates a larger percentage of people: first degree ≥10% (a), second degree ≥15% (b), third degree ≥20% (c), fourth degree ≥25% (d). Frequencies from the combination of categories were added to the frequencies of separate categories before percentages were calculated

(e.g., comforting), and strategy (e.g., distraction) were also given (10.8%, 6.8%, and 1.4%, respectively). Medicines were only provided to people with PWS (8.2%).

Discussion

The results of the current study provide insight into caregivers' experience with pain in people with PWS, WS, and FXS. Potentially painful known conditions were reported by more than half of all caregivers and observations of chronic pain in the past three months were highly prevalent. Analgesics were used relatively seldom, possibly related to the assumed relief of symptoms by other medicines (e.g., laxatives or antibiotics) and the predominantly used paramedical treatment. Barriers for

Table 7 Percentage of people with the syndromes within categories of change after use of pain medication

Category (vertical) and syndrome (horizontal)	Total	PWS	WS	FXS
Calms down in behaviour, facial expression, or physiology (e.g., stops trembling)	22.3	19.5	30.6	23.8
Unspecific answers	15.1	13.8	19.4	14.3
No, small, temporary, variable, or negative change (e.g., more unrest)	13.7	14.9	6.5	23.8
Combination of categories	11.9	12.8	12.9	0.0
Sedation (i.e., becomes tired / sleepy) or difficulty with speaking	9.7	10.3	6.5	14.3
Improved mood or behaviour (e.g., less irritated, regains control over behaviour)	9.4	8.7	9.7	14.3
More alert, interaction, or activities (e.g., can think / speak about other things again)	7.6	8.2	6.5	4.8
Reports / inquires about pain relief, or stops complaining about pain	5.0	5.1	6.5	0.0
Expects / reports immediate pain relief (e.g., assumed placebo effect), wants more pain medication, or effect dependents on resistance against taking pain medication	2.9	3.6	1.6	0.0
Physiological improvement (i.e., vitality: e.g., facial colour, hungry, gets out of bed)	1.8	2.1	0.0	4.8
Improved movement (e.g., walking or swimming)	0.7	1.0	0.0	0.0
Total	100	100	100	100

Note. Total = total group of people with the syndromes, PWS = Prader-Willi syndrome, WS = Williams syndrome, FXS = Fragile-X syndrome. Frequencies from the combination of categories were added to the frequencies of separate categories before percentages were calculated. Rows are coloured grey alternately to increase readability

Table 8 Percentage of people with the syndromes within categories of verbal pain expression

Category (vertical) and syndrome (horizontal)	Total	PWS	WS	FXS
Mentions location or condition of pain (e.g., 'my head hurts', 'I have a heartburn') [a]	27.6	23.8	27.3	13.6
Combination of categories	19.7	15.8	10.9	9.1
Clear verbal expression (e.g., 'pain', 'hurts', 'sore') [b]	19.2	25.7	27.3	27.3
Different words than 'pain' (i.e., synonyms or descriptions, e.g., 'feels like a rock')	12.8	10.9	14.5	36.4
Unclear answers	5.4	3.5	5.5	4.5
Does not say it / cannot (clearly) express it, one must really know the person	4.9	2.5	7.3	9.1
Asks for advice, pain medication, doctor, or emergency room	4.9	4.5	1.8	0.0
Describes pain in detail (e.g., pain intensity, since when it hurts, precise location)	4.4	4.5	1.8	0.0
Simple verbal expression (e.g., 'ouch', 'help'), sometimes with screaming / crying	0.5	5.4	1.8	0.0
Non-verbal communication (e.g., gestures)	0.5	3.5	1.8	0.0
Total	100	100	100	100

Note. Total = total group of people with the syndromes, PWS = Prader-Willi syndrome, WS = Williams syndrome, FXS = Fragile-X syndrome. Frequencies from the combination of categories were added to the frequencies of separate categories before percentages were calculated. a = although not always correct or clear. b = e.g., without understanding pain intensity, mentioning only severe pain, or trivializing pain. Rows are coloured grey alternately to increase readability

interpreting pain expression by caregivers included reports of: atypical indicators, a

Table 9 Percentage of people with the syndromes within categories of reasons for difficult pain recognition

Category (vertical) and syndrome (horizontal)	Total	PWS	WS	FXS
Apparent high pain threshold [a] or pain tolerance [b]	23.3	24.3	12.5	20.0
Pain indicators, but no / few / unspecific complaints or does not ask for medication	12.4	10.8	18.8	8.6
Unclear answers	11.9	11.5	9.4	11.4
Combination of categories	10.9	10.8	12.5	5.7
No distinctive pain behaviour or difficult to determine (e.g., complains always)	8.9	8.1	12.5	5.7
Difficult reports on pain characteristics (e.g., unclear pain location or intensity)	7.4	6.8	15.6	0.0
Delayed pain expression (e.g., after fracture) or recognition (e.g., ear infection)	6.9	8.8	3.1	0.0
Unclear verbal reports of pain presence (i.e., hides, denies, trivializes, blames)	6.4	6.1	9.4	2.9
Pain perception sometimes seems exaggerated, unreal, or for gain	6.4	6.8	6.3	2.9
(Partially) atypical pain indicators (e.g., smiles due to medical attention)	2.5	3.4	0.0	0.0
No difficult pain recognition	1.5	1.4	0.0	2.9
Pain symptoms depend on visible injuries (e.g., severe internal injury is noted late)	1.5	1.4	0.0	40.0
Total	100	100	100	100

Note. Total = total group of people with the syndromes. PWS = Prader–Willi syndrome, WS = Williams syndrome, FXS = Fragile–X syndrome. Frequencies from the combination of categories were added to the frequencies of separate categories before percentages were calculated. a = e.g., no pain indicator in potentially painful situation. 'high threshold'. b = e.g., 'large endurance for pain', 'ability to endure pain'. Rows are coloured grey alternately to increase readability

larger variety in expression with increasing pain intensity, assumed misunderstanding about pain intensity or pain locations by people with the syndromes, the use of unique descriptions for pain, inconsistent evidence for reduced pain sensitivity, and assumed underlying reasons for pain expression such as attention. People with the three syndromes seem to cope with pain both passively (e.g., resting) and actively (e.g., asking for pain relief or doctor visit). Although caregivers mainly seek (para) medical help, they offer paramedical treatment and mental coping pain strategies as well. Findings will be discussed below. Differences in reported pain characteristics between syndromes should be cautiously interpreted due to the unequal and sometimes small sample sizes of the syndromes.

Presence and recognition of pain

The reported presence of physical conditions by 58.4% of all caregivers is high compared to the prevalence of 9–50% found in most of the related studies (Boerlage et al., 2013; Cooper et al., 2015; De Knegt et al., 2017; McGuire et al., 2010) and the reported prevalence of pain in the past three months (54.3%) is high compared to an 18–49% prevalence of pain in related literature (Bernal-Celestino et al., 2021; Boerlage et al., 2013, 2021; Weissman-Fogel et al., 2015). Two possible explanations for these findings are: either an actual high prevalence (i.e., selection bias by caregivers motivated to complete the survey and a wide time window of 3 months in the ques-

Table 10 Percentage of people with the syndromes within categories of assumed reduced pain sensitivity

Category (vertical) and syndrome (horizontal)	Total	PWS	WS	FXS
Yes: pain indicators (e.g., cry, behaviour change) but no / few complaints or quick recovery, or pain situations (e.g., fracture) but no / few pain indicators	36.0	36.6	29.2	39.1
Yes: reduced pain sensitivity (e.g., 'high pain threshold') or pain response	22.1	21.7	20.8	26.1
Unknown: no distinctive pain behaviour or difficult to determine	10.8	12.0	8.3	4.3
Unclear / incomplete answer	9.5	8.6	8.3	17.4
Combination of categories	8.1	8.0	8.3	8.7
Yes: delayed expression or pain recognition (>1 day or with advanced problems)	4.5	5.7	0.0	0.0
Yes: high pain tolerance (e.g., 'brave', 'hard on herself', accepts / endures pain)	4.1	4.0	8.3	0.0
No: hiding pain (e.g., not to miss recreational activities or fear of the doctor)	1.4	0.6	8.3	0.0
No: adequate pain indicators (e.g., holds his head and says that he has aches)	0.9	0.6	4.2	0.0
Yes: atypical pain indicators (e.g., crying due to constipation stops in hospital)	0.9	1.1	0.0	0.0
No: pain seems unreal (e.g., complaining ceases after 'stop!') or for attention	0.9	0.6	0.0	4.3
No: increased pain sensitivity or low pain tolerance	0.5	0.0	4.2	0.0
No: doctors do not take pain complaints seriously in a 'stoic' individual [a]	0.5	0.6	0.0	0.0
Total	100	100	100	100

Note. Total=total group of people with the syndromes, PWS=Prader-Willi syndrome, WS=Williams syndrome, FXS=Fragile-X syndrome. Frequencies from the combination of categories were added to the frequencies of separate categories before percentages were calculated. a=by which, according to the respondent, a high pain threshold is overestimated. Rows are coloured grey alternately to increase readability

tion about presence of experienced pain) or mere attribution of the presence of pain by respondents (i.e., based on the presence of physical conditions, perhaps influenced by barriers in interpretating pain expression). The third hand and putative information of survey respondents cannot validate which explanation is true. However, pain management in people with ID is too complex to view results regarding treatment as an argument for a low presence of pain. The little use of analgesics could be related to healthcare professionals' concerns about the increased risk of side effects (Barney et al., 2020) and about finding the cause of pain during analgesics use (Petigas & Newman, 2021). The little use of analgesics may further be explained by the absent, temporary, variable, or negative effect of pain medication reported by more than 10% of the caregivers, corresponding to the low effectivity of pain medication according to people with ID themselves (Findlay et al., 2014). The diversity of treatment (i.e., other medication than analgesics such as laxatives, and mainly non-pharmacological interventions) and 13.8% absent treatment could also be related to the large proportion of parents in the sample, who may try different interventions in the case of an unclear cause or effect measurement of pain (Carter et al., 2002; Clarke et al., 2007).

The first possible explanation for the reported high prevalence of pain (i.e., pain is actually present) is supported by the most prevalent known physical condition and location per syndrome that are in line with previous findings. In PWS, spinal and rib/

Table 11 Percentage of people with the syndromes within categories of underlying reasons for pain report

Category (vertical) and syndrome (horizontal)	Total	PWS	WS	FXS
Attention (unspecified or specific example, e.g., doctor or direct support staff)	30.9	28.9	42.1	29.1
Avoids something that the person does not want (e.g., work, school, wearing brace)	18.2	16.9	31.6	5.1
Loves / obsessed to take medication (e.g., analgesics, cough drops, heartburn tablet)	11.8	14.5	5.3	6.3
Combination of categories	10.0	10.8	10.5	0.0
Confused by other feelings (i.e., anxious, stress, uncertain, unsafe, overstimulated)	8.2	4.8	10.5	13.9
Unclear / incomplete answer	6.4	7.2	0.0	10.1
Pain complaint depends on the situation [a] or pain experience [b]	4.5	6.0	0.0	16.5
Receives food / drink (e.g., calls ambulance due to unlimited food in hospital)	3.6	4.8	0.0	10.1
Wishes to visit hospital / Accident and Emergency department (unspecified why)	3.6	4.8	0.0	5.1
No / rarely (e.g., person is non-verbal or does not complain about pain)	2.7	1.2	0.0	3.8
Total	100	100	100	100

Note. Total = total group of people with the syndromes, PWS = Prader-Willi syndrome, WS = Williams syndrome, FXS = Fragile-X syndrome. Frequencies from the combination of categories were added to the frequencies of separate categories before percentages were calculated. a = i.e., visible injury or family members are ill (especially if they use medication). b = i.e., variable ideas about how a headache feels and what helps against the pain. Rows are coloured grey alternately to increase readability

chest pain as physical condition and back pain in the past three months seem related to highly prevalent scoliosis and kyphosis (Shim et al., 2010). In WS, digestive conditions and abdominal pain during the past three months are consistent with the increased risk of gastro-intestinal conditions (Morris et al., 2020). The psychological cause of abdominal pain reported by the respondents may be anxiety (Cherniske et al., 2004). In FXS, digestive conditions could relate to the increased risk of gastro-esophageal reflux (Kidd et al., 2014). Headache in the past three months could be explained by common ear infections due to an increased risk of sinus inflammation and head banging (Kidd et al., 2014). Dental and oral causes of headache according to respondents may relate to teeth grinding (Montez et al., 2021) and poor oral health (Amaral et al., 2017).

The second possible explanation for the reported high prevalence of pain (i.e., attributed to physical conditions due to difficult pain recognition) is supported by barriers in interpretating verbal expression of pain. It is alarming that respondents mainly use verbal expression to recognize pain, while more than a quarter of the respondents report that clear verbal expression is not always useful and deficits in expressive speech are known for the three syndromes (Ho & Dimitropoulos, 2010; Mervis & Velleman, 2012; Shaffer et al., 2020). The use of synonyms or unique descriptions of pain (see Table 8) is consistent with unusual descriptions (Stone Pearn, 2002) and descriptions of pain as emotion (Beacroft & Dodd, 2010a). The barrier in pain recognition through verbal expression is further complicated by the reported hiding, denying, or trivializing pain. Although people with ID may have reasons for doing so (Beacroft & Dodd, 2010a), this may also be misinterpreted as a result of the above-mentioned difficulty with describing pain (Findlay et al., 2015).

Table 12 Percentage of people with the syndromes within categories of pain coping

Category (vertical) and syndrome (horizontal)	Total	PWS	WS	FXS
Sleeps, rests, or withdraws (e.g., for stereotype activity such as picking on clothes)	20.0	22.9	0.0	25.0
Asks for reassurance, ice pack, pain medication, massage, or doctor visit	20.0	22.9	16.7	0.0
Is passive, refuses pain medication, expects / needs help from others	13.3	11.4	33.3	0.0
Does not feel pain, has never indicated pain	8.9	11.4	0.0	0.0
Moans, complains, cries repeatedly	6.7	2.9	33.3	0.0
Panic / fear or 'challenging behavior' (e.g., aggressive, agitated, insistent questions)	6.7	8.6	0.0	0.0
Applies bandages, ointments, or compresses	4.4	5.7	0.0	0.0
Addresses oneself or the pain (i.e., 'go away') combined with deep breathing	4.4	2.9	0.0	25.0
Hiding pain for fear of the doctor or hospital	2.2	0.0	0.0	25.0
Unclear	4.4	2.9	0.0	25.0
Takes a drink (i.e., tea with honey)	2.2	2.9	0.0	0.0
Goes to the toilet more often (i.e., stomach ache)	2.2	0.0	16.7	0.0
Ambivalent behavior: indication of pain or something else (e.g., depression)	2.2	2.9	0.0	0.0
Combination of categories	2.2	2.9	0.0	0.0
Total	100	100	100	100

Note. Total = total group of people with the syndromes, PWS = Prader-Willi syndrome, WS = Williams syndrome, FXS = Fragile-X syndrome. Frequencies from the combination of categories were added to the frequencies of separate categories before percentages were calculated. Rows are coloured grey alternately to increase readability

Although parents can name individual pain expressions of their child (Clarke et al., 2008), even caregivers who know the person well can have difficulty to distinguish pain from other inner states (Barney et al., 2020). This could become even more difficult if, according to the current finding, the behavioural pattern shifts with higher pain intensity towards more diversity and emphasis on mood rather than verbal expression. Difficult distinction contributes to the reported assumption of underlying reasons for pain expression such as attention, in line with previous findings (Beacroft & Dodd, 2010b; Findlay et al., 2014). Barriers in recognizing the presence and location of pain by caregivers could have serious consequences in the timely identification of life-threatening situations (Mencap, 2007), such as cancer (Hogg & Tuffrey-Wijne, 2008) and intestinal obstruction (Jancar & Speller, 1994).

Pain sensitivity

Within the scope of the current qualitative survey, no quantitative conclusions (i.e., based on physiological data) can be drawn about pain sensitivity of people with the syndromes. Results are rather respondents' interpretation of their observations and do not provide an entirely coherent view within the sample. For example, many examples of absent pain indicators in potentially painful situations and reports of a large ability to endure pain were given as a reason for difficult pain recognition, including

Table 13 Percentage of respondents within categories of coping with the pain of people with the syndromes

Category (vertical) and syndrome (horizontal)	Total	PWS	WS	FXS
Seeking (para) medical help: taking complaint seriously due to 'high pain threshold'	28.4	29.5	0.0	60.0
Paramedical treatment: cold / heat (e.g., compress, tea, bath), specific food (e.g., prunes), massage, adjusting brace, stimulating to drink water	16.2	16.4	12.5	20.0
Advising sleep, rest, breathe, or mindfulness	10.8	6.6	50.0	0.0
Person does not / rarely feel pain or respondent does not take any action	8.1	8.2	0.0	20.0
Searching for cause (e.g., asking direct support staff) or 'preventive measures'	8.1	9.8	0.0	0.0
Combination of categories	8.1	8.2	12.5	0.0
Medicines (e.g., paracetamol) or aids (e.g., homeopathy, over-the-counter laxative)	6.8	8.2	0.0	0.0
Mental help (e.g., listening, comforting, offering solutions / assurance / structure)	6.8	6.6	12.5	0.0
Providing loving care (e.g., wounds)	5.4	4.9	12.5	0.0
Mental strategy: distracting (e.g., going out) or inventing imaginary helping friends	1.4	1.6	0.0	0.0
Total	100	100	100	100

Note. Total = total group of people with the syndromes, PWS = Prader-Willi syndrome, WS = Williams syndrome, FXS = Fragile-X syndrome. Frequencies from the combination of categories were added to the frequencies of separate categories before percentages were calculated. Rows are coloured grey alternately to increase readability

literal statements of a 'high pain threshold' and 'high pain tolerance'. However, other results offer a more balanced explanation of the barriers in pain recognition, such as: absent complaints in the presence of other pain indicators or difficult report on pain characteristics (i.e., both confirming that the respondents rely mainly on verbal expression), impaired identification of internal injuries or hiding pain by people with the syndromes, and an overestimated high pain threshold by physicians. Besides, Table 10 illustrates perceived arguments in favour and against a reduced pain sensitivity. Therefore, the actual pain sensitivity remains uncertain. Still, attributions of absent or different pain behaviour to a high pain threshold or pain tolerance are alarming due to consequences for potentially painful procedures and adequate treatment of injury (Findlay et al., 2014). Regardless of the degree of actual and assumed pain sensitivity, the results provide evidence for the many challenges that caregivers are confronted with in recognizing pain and convincing health professionals of that pain.

The delayed pain expression or recognition in PWS corresponds to previous observations (Butler et al., 2002; Sinnema et al., 2013). In WS, the difficult reporting on pain characteristics is in line with the little informative responses due to impaired pragmatics (Mervis & Velleman, 2012) and hiding pain corresponds to the common phobia for medical procedures and doctors (Leyfer et al., 2006). The difficulty in recognizing internal injury and confusing pain with other feelings by people with FXS may be in line with sensory integration deficits (Lozano et al., 2016) and impaired emotion recognition (Shaw & Porter, 2013; Williams et al., 2014).

Coping of pain

Asking for confirmation by people with PWS could be in line with repeated questioning as a possible precursor for problem behaviour in situations that require coping (Oliver et al., 2009). The passive coping responses by people with WS may be caused by catastrophizing pain from a predisposition to fear (Meyer-Lindenberg et al., 2005) and worry (Leyfer et al., 2006). In addition, emotion-focused coping strategies in WS such as a need for confirmation are reported by parents (Royston et al., 2021). Frequently used coping strategies by people with FXS (i.e., addressing themselves or the pain and hiding the pain) appear to range from strong to weak self-control, respectively. This spectrum of adaptive functioning may be explained by the dependence of self-control on age and anxiety in FXS (Reisinger & Roberts, 2017). However, coping research on the three syndromes has not yet been performed regarding pain. Moreover, results should be interpreted cautiously due to the unknown influence of the multiple choice answers in the questionnaire (e.g., possibly explaining the discrepancy between providing analgesics only to people with PWS according to the question about coping, but also to people with WS according to the question about treatment: see Table 13 versus Table 2).

Limitations

Data were missing for country, gender, and specific age. Although not within scope of this explorative study, future studies that will elaborate on the current findings should take these factors into account. For example, the country in which caregivers live may influence their perspectives on pain and access to healthcare. Moreover, the unequal representation of the syndromes (i.e., 67.9% PWS, 21.8% WS, 10.3% FXS) limits the generalization of the results. More importantly, genetic diagnoses and medical information could not been verified. However, this limitation should be considered in light of three perspectives: (1) it was expected that the recruitment via associations for families of individuals with the syndromes, interest groups by the families themselves, and health care institutions for people with ID would have resulted in people with at least a probable diagnosis of the syndrome, (2) people with absent, unknown, or uncertain genetic diagnosis were excluded, and (3) the current study's aim was to retrieve the experience of as many caregivers as possible instead of an international dataset validated by medical files, which would not have been not feasible within the scope of the project. Still, all results should be interpreted cautiously as the information was received third-hand via caregivers and was not validated. Further, the questionnaire contained questions that were possibly suggestive (e.g., 'self-injurious behaviour' also has different causes or functions than pain expression) or ambiguous (e.g., not specifying the time between the use of a pain reliever and observed behavioural change) and was not validated for research on the three syndromes (i.e., including the questions inspired by the PCQ and INRS).

Recommendations

Especially two findings imply a responsible role of caregivers in pain management for people with the three syndromes: (1) the delayed discovery of injury and (2) withdrawing to rest and asking for reassurance, pain relief, or a doctor visit as predominantly coping strategies by people with the syndromes. Caregivers are thus required to recognize and monitor the pain but also to respond to needs (e.g., by rating the severity of the pain). The reported barriers in identifying, evaluating, and treating pain combined with the high potential presence of pain and injury that could impact quality of life necessitate action.

First, health care professionals should use caregiver's tacit knowledge about pain to create together individual health action plans with risks, expression, coping, and treatment of pain (Beacroft & Dodd, 2010a). A Functional Analysis by a skilled professional may help to interpretate for a specific individual with a syndrome whether behaviour reported in the current study (e.g., self-injurious behaviour) is actually caused by pain and what the function could be of atypical pain expression (e.g., hiding, trivializing, or denying pain). Booklets and communication aids could be used to teach people with the syndromes who function at a certain cognitive level about pain experience and expression (Beacroft & Dodd, 2010a; Dodd & Brunker, 1999; Fitzpatrick et al., 2022).

Second, associations and interest groups for the three syndromes worldwide should develop educational material with a balanced perspective on pain (e.g., possible causes for a seemingly high pain threshold) to increase awareness of caregivers and health care professionals. This could include the dissemination of training materials for staff and family carers about pain recognition and management in people with ID (Beacroft & Dodd, 2008, 2010a; Genik, Aerts, Barata, et al., 2021; Genik, Aerts, Nauman, et al., 2021).

Third, researchers should extend the current study with focus groups (i.e., caregivers and people with the syndromes) and by examining underlying mechanisms (e.g., the relationship between pain self-report and cognitive functioning or the influence of caregivers' characteristics such as the own pain coping style on their perspectives). Future research could also explore caregivers' perceptions about the effectiveness of the treatment methods for pain that were reported in the current study.

Conclusion

The findings add to existing knowledge and pain management practice regarding the three syndromes by highlighting similarities in: (1) the high potential presence of pain, (2) caregivers' barriers in identifying pain, and (3) caregiver's tacit knowledge of pain expression as well as treatment. Within limitations of the study's scope and design (i.e., sample and questionnaire), the results open a discussion about the validity of caregivers's perspective on pain. Although in-depth analysis in a more representative sample is needed to validate the putative information from the third-party perspective, the current study is the first large-scale study that focuses on caregivers' experience with pain in people with PWS, WS, and FXS. The results could stim-

ulate caregivers into dialogue with healthcare professionals and researchers about experienced barriers, including any possible misattributions of observed behaviour. This could be a starting point for solutions, such as Functional Analysis of assumed pain-related behaviour, health action plans with individual pain characteristics, and training/ education material about pain to improve communication in people with the syndromes and awareness in caregivers.

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Data Availability Due to ethical issues (i.e., respondents were not informed at the moment of completion that their answers could be made public), the data used in this study are not available.

Declarations

Ethical Approval All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. Approval was received by the Medical Ethical Committee of VU Medical Center in Amsterdam (file number 2016.478).

Informed Consent No informed consent was necessary: the questionnaire was completed voluntarily and anonymously (distribution via other organizations and no personal data collected).

Competing Interests The author declares to have no conflict of interest.

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