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Vulvodynia

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Abstract | Vulvodynia is a condition that occurs in 8–10% of women of all ages and is characterized by pain at the vulva that is present during sexual and/or non-sexual situations. Diagnosis is established through careful medical history and pelvic examination, including the cotton-swab test. The onset and maintenance of vulvodynia involves a complex interplay of peripheral and central pain mechanisms, pelvic floor muscle and autonomic dysfunction, anxiety, depression and childhood maltreatment as well as cognitive–affective, behavioural and interpersonal factors. Given the absence of empirically supported treatment guidelines, a stepwise approach of pelvic floor physical therapy and cognitive behavioural therapy as well as medical management is suggested, with surgery as the last option. Vulvodynia has a negative effect on the quality of life of women and their partners, and imposes a profound personal and societal economic burden. In addition, women with vulvodynia are more likely to report other chronic pain conditions, which further alters their quality of life. Future efforts should aim to increase girls', women's and healthcare professionals' education and awareness of vulvodynia, phenotype different subgroups of women based on biopsychosocial characteristics among more diverse samples, conduct longitudinal studies and improve clinical trial designs.

Dyspareunia
Pain during sexual intercourse.

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Vulvodynia is characterized by pain of the vulva (FIG. 1), either spontaneous or upon touch, and can occur during attempted or successful penetration and sexual and/or non-sexual situations. The 2015 consensus terminology and classification of persistent vulvar pain and vulvodynia define vulvodynia as vulvar pain that occurs for >3 months without an identifiable cause, and with a number of potential associated factors. These include musculoskeletal and neurological factors, comorbid pain syndromes (such as fibromyalgia and irritable bowel syndrome) and psychosocial factors. The association of these factors with vulvodynia suggests that it is likely the endpoint of a constellation of symptoms and underlying pathophysiological processes[1]. This classification of vulvodynia also provides descriptors of the pain[2] (BOX 1), although whether these descriptors characterize distinct aetiological pathways and/or are predictive of women's pain trajectories is unclear. Overall, this new classification, which is the result of an interdisciplinary collaboration and consensus, addresses the multiple dimensions of vulvodynia and will facilitate future studies aimed at identifying phenotypes.

Vulvodynia is encompassed by the 'genito-pelvic pain/penetration disorder' diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, listed in the category of sexual dysfunctions[3]. This new diagnosis replaces the previous diagnoses of dyspareunia and vaginismus. Despite the overlap with vulvodynia, genito-pelvic pain/penetration disorder is a broader diagnostic category as it includes both vulvar pain and deep pain or pelvic pain during intercourse, whereas vulvodynia refers only to vulvar pain. The new International Association for the Study of Pain Classification of Chronic Pain for the International Classification of Diseases classifies vulvodynia within the 'chronic primary visceral pain' category[4,5] and will be based on the existing 2015 vulvodynia consensus terminology[1] (BOX 2). The 11th revision of the International Statistical Classification of Diseases and Related Health Problems was adopted by the WHO on 25 May 2019, to come into effect on 1 January 2022 (see Related links). It includes, for the first time, a new classification system for chronic pain syndromes, including vulvodynia (see Related links).

The Analgesic, Anaesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) and the American Pain Society (APS) (ACTTION-APS) Pain Taxonomy (AAPT) is a new taxonomy system that aims to expand existing diagnostic criteria by incorporating available knowledge about biopsychosocial pain mechanisms[6,7] and will also include vulvodynia (BOX 2). The most common subtype of vulvodynia is localized provoked vestibulodynia (PVD)[8].

Although pain is the characteristic symptom of vulvodynia, the effect of the disorder is far-reaching as it is associated with reduced sexual desire, arousal, sexual frequency and sexual satisfaction, and can adversely affect women's and their partners' psychological and relationship adjustment[9,10]. Given the deleterious consequences of vulvodynia on couples' sexuality and intimacy, this

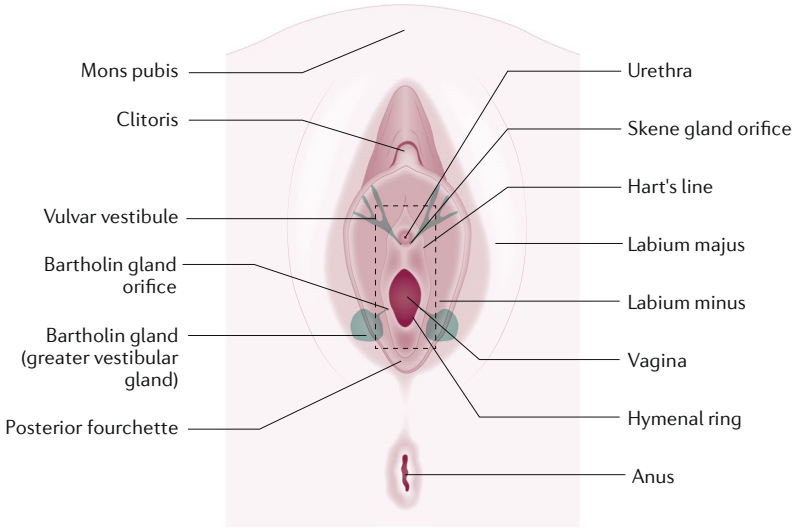

Fig. 1 | **Anatomy of the female lower genital tract.** Schematic of the female lower genital tract, illustrating the external vulva, vestibule and lower vaginal tract.

disorder might carry a heavier psychosocial burden than other pain conditions, with many women reporting feelings of shame, inadequacy as a sexual partner, lesser body appreciation and lower self-esteem[11]. Data from population-based studies have suggested that only 60% of women with symptoms of vulvodynia seek help, and 40% of these women are never diagnosed[12]. The quality of care available to these women and their partners is, therefore, less than optimal.

This Primer summarizes the epidemiology of vulvodynia and provides an overview of the biomedical, psychosocial and pelvic floor-related mechanisms as well as of diagnosis and screening. In addition, this Primer discusses management approaches for vulvodynia, which encompass psychosocial therapies, pelvic floor physical therapy (PFPT) and medical management, together with guidelines for future research and treatment, including quality of life issues.

Epidemiology

Although global epidemiological studies to evaluate the prevalence of vulvodynia worldwide have not been conducted, estimates of the lifetime prevalence from individual countries or regions suggest that vulvodynia is an important and neglected women's health condition. Indeed, one epidemiological study in the USA found that up to 16% of women experience vulvodynia during their lives[13] and that, by 40 years of age, 7–8% of women will have experienced symptoms consistent with vulvodynia at some point in time[14]. Another US-based survey found a lifetime prevalence of 9.9%, with 45% of women with vulvodynia reporting an adverse effect on their sexual life[15]. High prevalence rates have also been reported in a large-scale Spanish study, which demonstrated a lifetime prevalence of 13%[16], whereas a Portuguese study reported a lifetime prevalence of 16%[17]. By contrast, of 5,521 female patients attending a dermatology outpatient clinic in eastern Nepal, <1% had vulvodynia[18]. This relatively low prevalence rate could be due to a lack of knowledge of vulvodynia in women and health-care professionals in Nepal, which could lead to under-reporting and under-diagnosing. Additional population-based studies are needed to determine the prevalence of vulvodynia subtypes in low-income and middle-income countries.

Although vulvodynia occurs in women of all ages, prevalence estimates tend to vary by age group, depending on the criteria used. In a large Canadian study of 1,425 sexually active girls 13–19 years of age (with a median age of 15), 20% reported pain during intercourse for >6 months[19]. This pain was at the vaginal opening, inside the vagina or in the lower abdominal region, of which most girls identified the vaginal opening as the most painful site, which is suggestive of vulvodynia[11]. Similarly, in the National Health and Social Life Survey in the USA, 21% of sexually active women of 18–29 years of age complained of pain during sexual intercourse during the past 12 months[20], whereas rates were lower in women aged 30–49 years (13%) and 50–59 years (8%)[20]. A lack of intercourse, combined with cultural norms concerning the sexuality of ageing women, could have led postmenopausal women to under-report their pain. A British probability sample survey of 6,777 sexually active women 16–74 years of age demonstrated that the prevalence of pain during intercourse was highest among women aged 16–24 years (9.5%) and those aged 55–64 years (10.4%)[21]. The fact that this study included sexually active women exclusively could explain the higher prevalence in postmenopausal women, compared with rates in other studies. Another study of 3,017 Swedish women showed that 13% of those aged 20–29 years reported pain during intercourse for >6 months, compared with 6.5% of women aged 50–60 years[22]. However, it should be noted that several of the studies asked participants about the presence of 'pain during intercourse' and were not necessarily referring to vulvodynia in particular.

One study using vulvodynia-based criteria demonstrated a relatively stable prevalence of 9.4% in women aged 18–70 years, with lower rates in those >70 years of age overall (2.4%) but similar rates among those ≥70 years of age who were still sexually active[23]. Furthermore, a population-based study of sexual behaviour in 1,550 women aged 57–85 years in the USA indicated that 17% of women reported symptoms of postmenopausal vulvodynia[24]. Taken together, findings from epidemiological studies suggest that vulvodynia is a common gynaecological pain condition that is prevalent among women of all ages, including postmenopausal women.

By contrast, the incidence of vulvodynia is highest among younger women. Indeed, one study in the USA showed that 4% of women experience their first episode of vulvodynia before 25 years of age[14], whereas another longitudinal study reported an annual incidence of 7.6% at 20 years of age, decreasing to 5.0% at 40 years of age and 3.3% at 60 years of age[25]. Another study demonstrated a lower incidence in women in their late 20s and 30s, with a higher incidence as women enter their 40s, but ranged from 1.8% to 2.0% per year overall[13]. Furthermore, a Swedish population-based survey demonstrated an incidence of self-reported pain during sexual intercourse of 2.2% in women 20–29 years of age, compared with 0.8% in women 50–60 years of age[22].

Provoked vestibulodynia
Pain elicited via pressure to the vulvar vestibule or attempted vaginal penetration.

Allodynia
Pain due to a stimulus that does not normally provoke pain.

Hyperalgesia
Intensified pain from a stimulus that normally provokes pain.

One factor that may explain discrepancies between studies is that some estimate prevalence and incidence in women who are sexually active, whereas others do not consider the level of sexual activity. In addition, studies often fail to ask whether women stopped having sex due to intolerable provoked pain, which could bias results towards lower estimates. Another important caveat is that incidence can be confused with first recognition; if primary PVD is lifelong, first recognition might not accurately reflect the development of the condition, which could have been present from childhood but not yet provoked by touch. Moreover, studies do not always specify whether vulvodynia is primary or secondary. Other inconsistencies in findings could be attributable to the variability in the populations sampled and questions posed (for example, vulvodynia versus any type of pain during intercourse, the use of different definitions of vulvodynia (such as spontaneous pain versus pain on touch), time frame, distress experienced), and whether the study was longitudinal[26].

Only 60% of women who report chronic vulvar pain seek treatment and approximately half of those women never receive a diagnosis[14]. Furthermore, women who do seek care are likely to report feeling stigmatized by physicians[27]; this finding is in line with those from a qualitative study suggesting that women with vulvodynia report many barriers to help-seeking[28]. Although vulvodynia occurs in women of all ethnicities and ages[29,30], such barriers could prevent specific subgroups of women from seeking care and/or may contribute to their greater stigmatization, particularly women from sexual and gender minorities and minority ethnic groups. Indeed, research in the USA indicated that Hispanic women have significantly higher rates of vulvodynia than non-Hispanic white women, including both higher incidence (9.5 cases per 100 person-years compared with 4.2 cases per 100 person-years in the overall sample)[25] and prevalence (Hispanic women are 1.4 times[25] to 1.8 times[23] more likely to develop vulvodynia than white women). In addition, Hispanic women are also 47% more likely to report primary vulvodynia, defined as pain with first intercourse, compared with white women[31]. This finding is particularly alarming as substantial gender and racial-ethnic inequities in pain treatment and sexual health have been reported, with North American women being undertreated for their chronic and acute pain compared with men[32–34]. By contrast, black women are 43% less likely to meet criteria for vulvodynia than white women, although the prevalence among this group is still substantial (4.2% in black women versus 9.3% in white women)[23]. The varied vulvodynia rates in women of different ethnicities could reflect true prevalence discrepancies or could be the result of varying sociocultural norms regarding how pain and sexuality are experienced.

Box 1 | **Vulvodynia characteristics — descriptors**

Descriptors of vulvodynia that can be used to classify the distribution, onset and timing of pain were developed in the 2015 International Society for the Study of Vulvovaginal Disease, the International Society for the Study of Women's Sexual Health, and the International Pelvic Pain Society consensus statement[2].

Localized versus generalized

- Localized: pain in the vestibule (at the vaginal opening within Hart's line) or at the clitoris
- Generalized: pain extending beyond Hart's line onto the labia minora or majora, upper legs, or lower abdomen

Provoked versus spontaneous

- Provoked: pain elicited by touch, for example, with intercourse, tampon use or tight clothing
- Spontaneous: pain occurring without any provocation
- Mixed: provoked and spontaneous pain

Primary or secondary onset

- Primary: pain present since the first intercourse or tampon use, or for those with spontaneous pain, no period of time without pain prior to pain being present
- Secondary: pain that started after a period of time without pain or after a time when these activities were not painful

Temporal pattern

- Persistent: pain present since onset, either constantly, in the case of spontaneous pain, or each time it is provoked in the case of provoked pain
- Intermittent: pain not present at all times or every time provoked
- Immediate: pain starts when provoked
- After provocation: pain is delayed or persists after provocation for minutes, hours or days (this delayed pain is sometimes the most distressing symptom)

Mechanisms/pathophysiology

Multiple pathophysiological mechanisms may have a role in the development and persistence of vulvodynia[35,36] and various mechanisms could contribute at different times during the course of disease (FIG. 2). Most mechanistic studies have focused on PVD, which is the most common subtype.

Vulvodynia has traditionally been conceptualized in a dualistic manner, resulting from either physical factors or psychological and sexual difficulties, despite research contrary to this concept as well as other hypotheses suggesting that these two perspectives should be combined. Indeed, more recent theorizing has focused on an integrated model considering the interdependency of biopsychosocial factors in vulvodynia and its associated impairments, whereby medical and psychosocial mechanisms are thought to contribute to the onset, chronicity and exacerbation of the pain and associated difficulties[37].

Biomedical

Genital pain and sexual responses are modulated by neural pathways, including autonomic–somatic communications (FIG. 3), and circulating levels of gonadal hormones[38]. Genital pain can lead to sexual dysfunction by reducing desire, decreasing arousal and increasing sexual inhibition.

Peripheral and central pain mechanisms. The neuropathophysiology of vulvodynia is multifaceted and is characterized by both peripheral and central sensory abnormalities[35,36]. Indeed, vulvodynia is characterized by mechanical allodynia and hyperalgesia localized to the vulvovaginal area and often occurs in the context of other chronic overlapping pain conditions[36,39,40] (BOX 3).

An increase in nerve fibre density in the vulvar vestibule has been positively correlated with the level of local inflammation but inconsistently with mucosal allodynia

Central sensitization
Also known as central pain mechanisms. Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input.

in women with vulvodynia[41–44]. The aetiology of this increased nerve fibre density and its role in the pathogenesis of vulvodynia remains to be further explored, although a study of vestibular biopsy specimens from women with vulvodynia and asymptomatic controls has provided evidence that local inflammation may lead to angiotensin II formation, which induces angiotensin AT2-receptor-mediated neuronal sprouting in cells cultured from dorsal root ganglia from neonatal rats, suggesting that a local inflammatory renin-angiotensin system might drive nociceptor axon sprouting in PVD[45]. Interestingly, the increased nerve fibre density in women with vulvodynia is in contrast with the observed reduction in intra-epidermal nerve fibre density in skin biopsies of patients with painful peripheral neuropathies[46]. Thus, the specific role of nerve fibre density in the pathogenesis of painful conditions needs further investigation and might differ between vulvodynia and painful peripheral neuropathies. An increased nerve fibre density has also been reported to be associated with the itch sensitization in atopic dermatitis[47], although the neurophysiological correlates of the neural proliferation that produces pain versus itch remain to be defined.

Numerous psychophysical studies, using different sensory modalities such as temperature, light touch, pinprick or pressure related to different peripheral and central somatosensory channels[48], have consistently demonstrated lower sensory and pain thresholds and increased pain sensitivity in the urogenital area in women with vulvodynia compared with healthy controls[36]. In addition, there is evidence of increased sensitivity to several sensory modalities at extra-genital sites in women with vulvodynia[49–51], suggesting central sensitization. This central sensitization could explain the observations of chronic overlapping pain conditions in women with vulvodynia[39] (BOX 3). Several studies have investigated the involvement of the endogenous pain modulatory system in vulvodynia using psychophysical assessments. However, results from these studies are conflicting, reporting either an intact pain inhibitory function in women with vulvodynia[52,53] or a dysfunctional inhibitory pain modulatory mechanism characterized by less efficient conditioned pain modulation, as has been reported in patients with other chronic pain conditions[54]. These differences might be due to the specific methods and stimuli used to study conditioned pain modulation or due to patient-related factors such as subtype of PVD, duration of disease or psychological characteristics. Specifically stronger perceptions of illness chronicity have been correlated with less efficient conditioned pain modulation in women with chronic pelvic pain syndrome[55].

Structural and functional MRI studies in women with provoked vulvar or distant/extra-genital pain have supported a role of central sensitization and dysregulation of endogenous pain modulatory systems in the central nervous system in the pathophysiology of vulvodynia[49,56–60]. In addition, structural MRI studies of women with vulvodynia have demonstrated an increased grey matter volume in the basal ganglia, sensorimotor cortices and the hippocampus compared with healthy controls[60,61]. By contrast, most structural MRI studies have found a reduction in grey matter volume in patients with chronic pain, either in total volume or regionally[60]. Reasons for this difference might be due to the varying characteristics of these populations. For example, women with vulvodynia are typically younger at pain onset than patients with other chronic pain syndromes[60] and the majority of patients with vulvodynia experience provoked pain only, with no ongoing or spontaneous

Box 2 | **Criteria for vulvodynia**

The IASP Classification of Chronic Pain for ICD-11 (REF.[4])

The International Association for the Study of Pain (IASP) classifies chronic pain in the International Classification of Diseases, 11th revision (ICD-11) as:

- Pain that persists or recurs for >3 months
- Chronic pain can be conceived as a disease in its own right; this subgroup is defined as 'chronic primary pain'
- Chronic pain is secondary to an underlying disease; this subgroup is defined as 'chronic secondary pain', in which pain may, at least initially, be conceived as a symptom

In the IASP Classification of Chronic Pain in the ICD-11, vulvodynia will be listed under 'Chronic primary visceral pain' (within the subcategories of 'Chronic primary pelvic pain' and 'Chronic primary pelvic pain in females')[5] and based on the existing vulvodynia classification[1]. The ICD-11 was adopted by the WHO on 25 May 2019 to come into effect on 1 January 2022.

The ACTTION-APS Pain Taxonomy[6]

In conjunction with the Analgesic, Anaesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) public–private partnership with the FDA and the American Pain Society (APS), the ACTTION-APS Pain Taxonomy (AAPT) initiative was launched in 2014 to provide an evidenced-based and multidimensional approach to classify chronic pain conditions[6]. This classification system classifies chronic pain along the following five dimensions:

- Core diagnostic criteria
- Common features
- Common medical comorbidities
- Neurobiological, psychosocial and functional consequences
- Putative neurobiological and psychosocial mechanisms, risk factors, and protective factors

The purpose of this classification is to expand existing diagnostic criteria by incorporating available knowledge about biopsychosocial pain mechanisms into the taxonomy[6]. AAPT diagnostic criteria have already been published for several chronic pain conditions[7], and the AAPT diagnostic criteria will also be applied to urogenital pain syndromes, including vulvodynia[6]. The vulvodynia AAPT taxonomy will be based on the existing vulvodynia classification[1].

DSM-5 criteria for genito-pelvic pain/penetration disorder[3]

- Criterion A: persistent or recurrent difficulties with one (or more) of the following:
  - Vaginal penetration during intercourse
  - Marked vulvovaginal or pelvic pain during vaginal intercourse or penetration attempts
  - Marked fear or anxiety about vulvovaginal or pelvic pain in anticipation of, during or as a result of vaginal penetration
  - Marked tensing or tightening of the pelvic floor muscles during attempted vaginal penetration
- Criterion B: the symptoms in criterion A have persisted for a minimum duration of ~6 months
- Criterion C: the symptoms in criterion A cause clinically significant distress in the individual
- Criterion D: the sexual dysfunction is not better explained by a non-sexual mental disorder or as a consequence of a severe relationship distress (for example, partner violence) or other significant stressors and is not attributable to the effects of a substance or medication, or another medical condition

DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.*

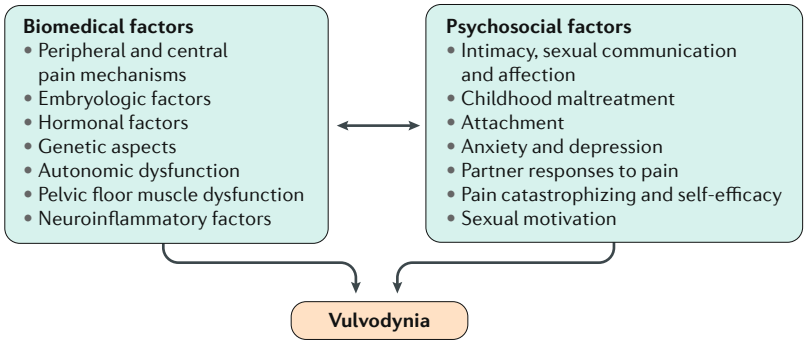

Fig. 2 | **Factors associated with the development and maintenance of vulvodynia.** The development and maintenance of vulvodynia is associated with the interplay of both biomedical factors and psychosocial factors. The level of evidence supporting a causal association between individual factors and vulvodynia varies between factors.

pain symptoms, which is in contrast to those with other pain conditions[60]. Resting state functional MRI studies in women with vulvodynia, irritable bowel syndrome and healthy controls have suggested that some alterations in functional connectivity might be disease specific; for example, women with vulvodynia have substantial alterations in the intrinsic connectivity of sensorimotor, salience and default mode networks, which exceed those observed in women with irritable bowel syndrome[57]. In addition, diffusion tensor MRI studies have further suggested disease-related microstructural differences in the brain, specifically in fibres associated with sensorimotor integration and pain processing that relay information between the thalamus, basal ganglia, and the sensorimotor cortex and insula in women with vulvodynia compared with women with irritable bowel syndrome[62].

Of note, vulvodynia is one of the 'central sensitivity syndromes', a group of heterogeneous syndromes including fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome and temporomandibular joint disorder, characterized by distressing symptoms such as pain and fatigue in the absence of clinically obvious pathology[63]. These syndromes are characterized by central sensory augmentation in neuroimaging studies, which might be either a predisposing factor or a consequent effect. A defining 'neuroimaging signature' cannot be discerned for any of these syndromes based on the current literature[63].

Inflammatory factors. Similar to other chronic pain conditions, in which it has been hypothesized that chronic pain is associated with long-lasting central sensitization that persists after acute inflammation has resolved[64], an inflammatory pathogenesis has been hypothesized for vulvodynia[36]. Numerous studies have evaluated the association between vulvodynia and inflammation (see REF.[35] for the methods and approaches used), although results have been inconsistent. Indeed, one systematic review concluded that there is limited and contradictory evidence regarding the characteristics of local and systemic inflammation, including cytokine levels, prostaglandin E_2, T cells, B cells, mast cells, natural killer cells and macrophages, in women with localized provoked vulvodynia[65]. Pertinent findings were an increased number of mast cells in vestibular tissue in women with vulvodynia compared with healthy controls in several studies (see Table 4 in REF.[65]) and a reduced systemic number of natural killer cells in women with vulvodynia compared with controls[66]. In addition, some women with vulvodynia report recurrent yeast infections[67]; therefore, it has been hypothesized that a deficiency in natural killer cell numbers could be correlated with recurrent *Candida* infections in these women. To this end, a susceptibility to *Candida* infection associated with a reduced capacity to terminate the resulting inflammation has been described (see Genetics, below); however, a causal relationship between *Candida* infection and vulvodynia development cannot be concluded from these observations, and longitudinal studies are required to test this hypothesis.

Several groups have proposed the study of proinflammatory vaginal or plasma cytokine profiles as possible biomarkers of vulvodynia[68–70]. Interestingly, one detailed study of the vaginal microflora in patients with PVD demonstrated that women with the most severe pain scores suffered more from aerobic vaginitis and less from *Candida* vaginitis, with an inverse relationship between the presence of *Candida* in the vaginal smear and the pain score[71]. These data emphasize the importance of a detailed examination of the vaginal microflora in relation to the pain profile in women with vulvodynia.

Autonomic dysfunction. Similar to other chronic urogenital pain syndromes[72], vulvodynia can be accompanied by autonomic dysfunction, although whether it is a cause or a consequence of pain is unknown[36]. Reported autonomic dysfunction in women with vulvodynia includes higher resting pulse rates and lower systolic blood pressure compared with controls[50]. Furthermore, women with primary vulvodynia have lower systolic blood pressure than women with secondary vulvodynia[73]. In addition, data in rodents indicate that the autonomic nerve fibre density can be influenced by the gonadal hormonal milieu. Indeed, in rodents, oestrogen regulates vaginal autonomic nerve fibre density to a similar extent as unmyelinated sensory fibre density, and ovariectomy results in increased sympathetic innervation of the vagina, which can be reduced by subsequent oestrogen replacement[74]. Whether this association is similar in women with vulvodynia remains to be demonstrated.

Hormonal factors. As mentioned above, the extent of vaginal innervation as well as that of other regions of the reproductive tract is regulated by gonadal hormonal levels[74–76]. Indeed, a reciprocal relationship between oestrogen and reproductive tract innervation has been observed in histological studies in rodents[74], supporting the idea that low oestrogen levels could lead to increased vaginal innervation and vice versa. This finding is consistent with the results of clinical studies in women with vulvodynia, which found that tampon-induced vaginal pain is lowest during the periovulatory phase (corresponding to the phase that is characterized by oestradiol rising to its peak level before ovulation) compared with other phases of the menstrual cycle, and highest in the premenstrual phase (characterized by low oestrogen

levels)[77]. In addition, cross-sectional clinic-based studies have reported an association between oral contraceptive use and the risk of adult-onset vulvodynia, but this association has not been reported in population-based studies[78,79]. Prospective studies, including those containing subgroups with different risk profiles, are urgently needed to evaluate the effect of contraceptive use and of the postpartum and postmenopausal periods (associated with decreased oestrogen) on the onset and characteristics of vulvodynia, so that informed decisions regarding these clinical situations and the risk of vulvodynia can be made by women and health-care providers.

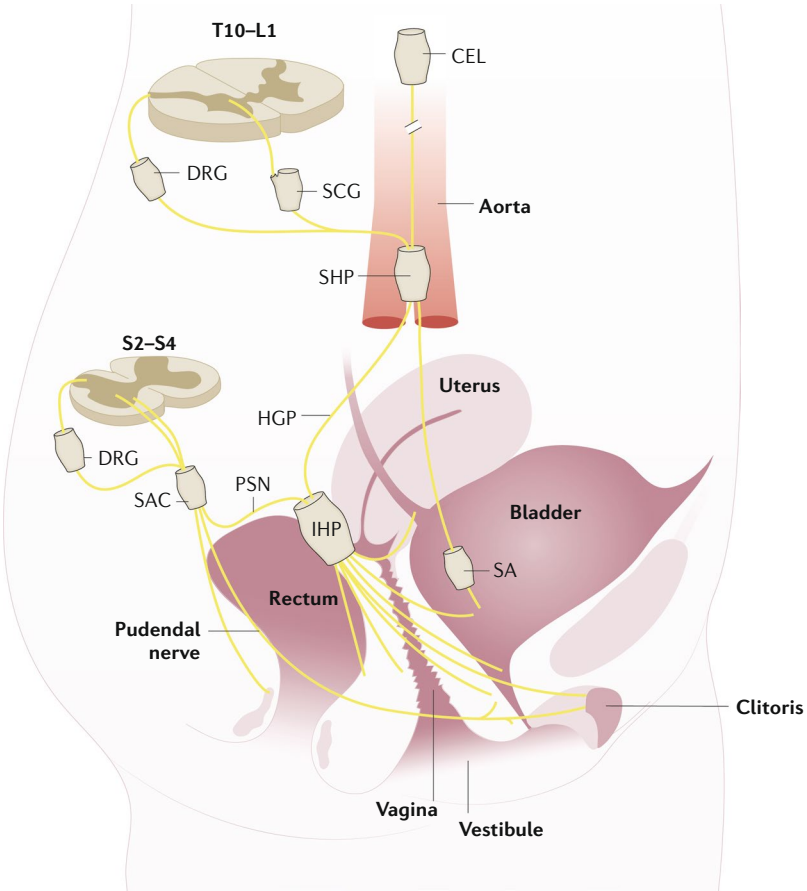

Fig. 3 | **Pelvic floor innervation in females.** The pelvic floor is innervated by both components of the autonomic nervous system (sympathetic and parasympathetic divisions) as well as by the somatic nervous system[226,227]. Projections from the thoracolumbar (between thoracic level 10 (T10) and lumbar level 1 (L1)) and sacral (between sacral levels 2 (S2) and 4 (S4)) segments of the spinal cord innervate the pelvic floor, converging primarily into peripheral neuronal plexuses before distributing nerve fibres throughout the pelvis and the pelvic floor. The pudendal nerve supplies the sensory and motor input to the pelvic floor. Within the pelvis, the inferior hypogastric plexus (IHP) is regarded as the major neuronal integrative centre innervating multiple pelvic organs as well as the genital and reproductive tract structures[227]. Although this schematic shows the innervation in humans, most of the anatomical information is derived from animal data. CEL, coeliac plexus; DRG, dorsal root ganglion; HGP, hypogastric plexus; PSN, pelvic splanchnic nerve; SA, short adrenergic projection; SAC, sacral plexus; SCG, sympathetic chain ganglion; SHP, superior hypogastric plexus. Adapted with permission from REF.[226], Wesselmann, U., Burnett, A. L. & Heinberg, L. J. The urogenital and rectal pain syndromes. *Pain* **73**(3), 269–294 (1997), The Journal of the International Association for the Study of Pain (https://journals.lww.com/pain/pages/default.aspx).

Muscle dysfunction. Vulvodynia is associated with some degree of pelvic floor muscle dysfunction, including increased tone and difficulties in contracting and controlling the musculature. Controlled studies using validated measurement (such as 4D ultrasonography or dynamometer) have demonstrated abnormalities of the pelvic floor musculature whilst at rest, including hypertonicity, poor muscle control, hypersensitivity and altered contractility[80,81]. Women may further exhibit a spontaneous contraction of the pelvic floor musculature during attempted vaginal penetration. Whether the observed muscle hypertonicity is causally related to the aetiology of vulvodynia or is a result of pain remains unclear given the cross-sectional designs of studies to date[35,36]. Further evidence supporting a role of muscle dysfunction in vulvodynia is the frequent co-occurrence with the musculoskeletal disorder fibromyalgia; it has been hypothesized that central sensitization is an overarching mechanism in these chronic overlapping pain conditions[40,82]. In addition, pain during intercourse in women with vulvodynia was associated with muscle sensitivity, suggesting that muscle sensitivity might have to be considered as an important aspect in the diagnostic work-up and treatment of vulvodynia. Further research exploring the role of muscle sensitivity in the development and maintenance of vulvodynia is needed[83]. However, to assess pelvic floor muscle dysfunction in clinical practice more accurately, validated measurement techniques, such as 4D transperineal ultrasonography or a dynamometric speculum, will have to be further developed[84].

Embryologic factors. Factors affecting the embryological development of the vulva could also contribute to the development of vulvodynia. Early in the fifth week of embryonic development the cloaca is divided by the urorectal septum, which gives rise to the perineum and folds of tissue that form on either side of the cloaca; the anterior folds form the urogenital sinus whereas the posterior folds form the anorectal canal. The urogenital sinus gives rise to the vaginal vestibule into which the urethra, vagina and greater vestibular glands open[85]. Case reports have described interstitial cystitis coexisting with vulvodynia in girls as young as 4 years of age, raising the question of whether it could be a disorder of urogenital sinus-derived endothelium[86], but further studies would be required to confirm this hypothesis.

Genetic aspects. A familiality analysis in women with PVD who underwent vestibulectomy has suggested a heritable component of vulvodynia[87]. This study used population-based genealogy and identified several families at high risk of PVD, suggesting a genetic predisposition. Further studies have suggested several potential mechanisms that could underlie a genetic predisposition for vulvodynia[36], including an influence on the risk of recurrent *Candida* or bacterial vaginosis infections or a prolonged response to infection or inflammation[88,89], an altered inflammatory response[90], or an increased risk to gonadal hormonal milieu changes associated with oral contraceptives[91].

Although polymorphisms in *GCH1* (encoding GPT cyclohydrolase 1) and *COMT* (encoding catechol

O-methyltransferase) have been associated with an increased sensitivity to pain, polymorphisms in these genes have not been identified in women with vulvodynia[92,93]. However, the A118G polymorphism in *OPRM1* (encoding the μ-opioid receptor) and levels of β-endorphin are associated with PVD and pressure pain sensitivity, and suggest a possible genetic predisposition that is related to endogenous pain modulation[94]. In addition, one study of Ashkenazi Jewish women with moderate to severe primary PVD (BOX 1) revealed a genetic susceptibility to primary PVD associated with specific alleles of *TRPV1* (encoding transient receptor potential cation channel subfamily V member 1) and *NGF* (encoding nerve growth factor)[90]. A comparison of pain conditions with frequent alleles (allele frequency refers here to the fraction of gene copies that are of a particular allele in a defined population) found the rs222747 'CC' genotype of *TRPV1* to be associated with temporomandibular symptoms, recurrent vaginitis and PVD, suggesting a genetic predisposition for the familial occurrences of overlapping chronic pain conditions with altered inflammatory aspects.

Psychosocial

Childhood maltreatment. Several studies have linked childhood maltreatment (physical, emotional or sexual abuse, or physical or emotional neglect that occurs during childhood) with subsequent health problems[95,96]. In two epidemiological studies, women with vulvodynia were more likely to have reported childhood sexual abuse and severe physical abuse than women without vulvodynia[97,98], and a large-scale survey of sexually active high school girls reported associations between pain during sexual intercourse and a history of sexual abuse[19]. In addition, childhood maltreatment might also complicate women and partners' adjustment to vulvodynia. Women who reported pain during sexual intercourse and had a history of childhood sexual abuse had significantly lower levels of sexual function and higher levels of psychological distress than women with pain during sexual intercourse without a history of sexual abuse[99]. Although the above findings suggest that childhood maltreatment could be a risk and maintenance factor for vulvodynia, these data warrant some caution, as differences between women with a history of maltreatment and controls tend to be small (13.1% of women with vulvodynia reporting sexual abuse versus 7.4% of controls in one study)[97], childhood maltreatment affects up to 30% of individuals in the general population[100], recall bias among symptomatic women may enhance the association[101], and it is a common pathway to many chronic illnesses, and, is therefore, not specific for vulvodynia.

Intimacy, sexual communication and affection. Studies have indicated that empathic responses and self-disclosure — two components of intimacy — are associated with pain-related sexual difficulties in women with vulvodynia and their partners. In one study, greater observed and self-reported empathic responses by both women with PVD and their partners were associated with higher sexual satisfaction and lower sexual distress[102]. Moreover, greater perceived self-disclosure by both women with PVD and their partners was associated with their higher sexual satisfaction and lower sexual distress[102], and women's greater observed empathic response and perceived self-disclosure was related to a higher quality of life[103]. In accordance with these data, another observational study of eight couples reported comparable associations between greater observed empathic responses and higher self-reported sexual and relationship satisfaction[104]. Similarly, another study (in which women kept a daily diary of affectionate behaviour) indicated that more physical affection (such as hugging and kissing) outside of a sexual context was associated with higher sexual and relationship satisfaction as well as higher sexual function (such as desire or arousal)[105]. Moreover, two cross-sectional studies found that couples' reports of lower sexual communication were linked to greater pain during intercourse for women and to lower sexual and relationship satisfaction for both women and their partners[106,107]. Overall, this body of evidence indicates that intimacy could act as a protective factor to mitigate the negative effects of vulvodynia on sexuality and relationship outcomes.

Attachment. Attachment is based on the stability and security of the infant–caregiver relationship and influences later adult romantic relationships[108]. Attachment insecurity involves two dimensions: attachment anxiety (fear of abandonment) and attachment avoidance (discomfort with emotional intimacy)[109,110]. In one study, women with vulvodynia had higher levels of attachment avoidance than women without vulvodynia, which in turn was associated with a greater probability for vulvodynia[111]. In addition, one cross-sectional dyadic study demonstrated that higher attachment anxiety and avoidance in women was associated with their own lower sexual function and satisfaction, whereas partners' higher attachment anxiety and avoidance were related to their own lower sexual function[112]. Women with attachment avoidance could find it challenging to ask for their partner's support and would, therefore, be left to manage their pain on their own. Moreover, owing to their greater fears of abandonment, women with attachment anxiety could experience more pain catastrophizing and lower pain self-efficacy than other women. Indeed, one prospective study has demonstrated that women's greater attachment anxiety predicted their lower pain self-efficacy and greater pain intensity 2 years later[113].

Box 3 | Overlapping chronic pain conditions[40]

- Chronic fatigue syndrome
- Chronic migraine
- Chronic low back pain
- Chronic tension-type headaches
- Endometriosis
- Fibromyalgia
- Interstitial cystitis (also known as painful bladder syndrome)
- Irritable bowel syndrome
- Temporomandibular disorders
- Vulvodynia

Pain catastrophizing
Tendency to hold exaggerated negative thoughts and feelings about the pain, that is, rumination, helplessness and magnification.

Pain self-efficacy
The degree to which a woman believes she can manage the pain effectively.

Pain catastrophizing and self-efficacy. Cognitive–affective factors have an important role in the sexuality and relationship outcomes of both women and their partners. Studies of women with PVD have suggested cross-sectional and prospective associations between greater pain catastrophizing, lower pain self-efficacy and higher levels of pain intensity[114,115]. By contrast, a 2-year prospective study of 222 women with PVD found that only increases in pain self-efficacy — not decreases in pain catastrophizing or anxiety — were associated with reductions in pain intensity[116].

Relationship factors. Among the relationship factors associated with vulvodynia, partner responses to women's pain have received the most scientific attention. Partner responses can be solicitous (such as attention or sympathy), negative (such as hostility or anger) and/or facilitative (such as adaptive coping). Cross-sectional and daily diary studies of women with vulvodynia and their partners have indicated that greater facilitative partner responses were associated with lower levels of pain[117] and greater sexual function[118] in women, in addition to their partners' greater relationship and sexual satisfaction[117,119]. By contrast, greater negative and solicitous partner responses were linked to women's higher levels of pain[117,120–122] and depressive symptoms[123], and women and partners' lower sexual function[118] as well as lower relationship and sexual satisfaction[119]. Solicitous and negative responses can interfere with the co-regulation of pain-related negative affect of women and their partners by reinforcing behavioural and experiential avoidance. In addition, one study found that lower pain catastrophizing in male partners was associated with lower pain in women[124]. In another study comprising 354 women with vulvodynia and their partners, greater partner pain catastrophizing and negative attributions were correlated with more negative partner responses and higher levels of pain in women. Moreover, greater partner pain catastrophizing was associated with greater solicitous partner responses, and these were associated with higher levels of pain and depression in women[116].

Mood. Anxiety, depression and post-traumatic stress disorder are associated with vulvodynia in clinical and community samples[125]. One study found that antecedent depression or anxiety disorders were associated with a fourfold increased risk of current vulvodynia[126]. In addition, vulvodynia was also correlated with new or recurrent onset of depression or anxiety, which could indicate the presence of bidirectional associations between anxiety, depression and vulvodynia or a common risk factor for both chronic pain and psychological disorders.

Beyond psychiatric diagnoses, subclinical daily mood variations can also affect vulvodynia severity. Indeed, a dyadic daily diary study showed that, on days of sexual activity, women's higher anxiety and depression levels were associated with their own greater pain and lower sexual function, whereas partners' higher anxiety and depression were associated with greater sexual distress for both women and their partners[127]. Moreover, a longitudinal study examining the predictors of pain trajectories in women with vulvodynia found that anxiety is one of the most robust prospective predictors of pain persistence[128]. In addition, a study of 218 sexually active adolescents showed that anxiety mediates the association between a history of childhood sexual abuse and the reporting of pain during sexual intercourse[129]. Anxiety and depression may act as precursors, consequences and maintenance factors in vulvodynia, suggesting there could be a common pathway for pain hypersensitivity and mood disorders.

Sexual motivation. Despite their pain, women with vulvodynia continue to engage in vaginal intercourse[130–133]; however, engaging in sexual activity when undesired could exacerbate pain. Interestingly, one dyadic daily diary study found that, on days when women with vulvodynia reported engaging in sexual activity to pursue positive relationship outcomes such as intimacy (that is, approach goals), they reported less pain and they and their partners reported greater sexual function and relationship satisfaction[134]. By contrast, when women reported having sex to avoid negative relationship outcomes (that is, avoidance goals) they had greater pain and poorer sexual function, and their partners reported poorer sexual function. Given that they are modifiable factors, sexual goals could be promising key clinical targets.

Models of genital pain

Several in vivo models, primarily rodent models, have been developed to study vulvovaginal hypersensitivity, genital pain and female sexual behaviour (reviewed previously[38,135–137]). These models have provided new information on the neural pathways, neurotransmitters and inflammatory mediators involved in the central and peripheral mechanisms of genital pain and sexual function, and have shown translational relevance to the clinical characteristics of vulvodynia in women.

These animal models have focused on several different mechanisms that are hypothesized to contribute to vulvodynia in humans: early life stress and injury[138,139], repeated *Candida* infections[88], vaginal hyper-innervation and nociceptor sensitization induced by proinflammatory agents[140–142], mast cell-mediated allergic responses in the context of vaginal hyperinnervation and tactile hypersensitivity[143], and central sensitization due to repeated pelvic and urogenital infections[144]. In addition, an in vitro model using human vulvar fibroblasts has been developed with the aim of improving the understanding of the inflammatory pathways affected during PVD[145–147]. The rationale for this model is that fibroblasts have been shown to contribute to pain through the production of proinflammatory cytokines in several animal models. In addition, PI16 (which is mainly produced by fibroblasts) has been recently identified to promote neuropathic pain in rodents[148], making it an attractive target to control pain. These in vivo and in vitro models of vulvovaginal hypersensitivity might provide validated platforms for drug screening and drug development for vulvodynia in the future.

Diagnosis, screening and prevention

Vulvodynia should be considered in all women (those of any age or ethnicity) who present with symptoms of vulvovaginal discomfort or dyspareunia[23], and should be differentiated from other common disorders to avoid misdiagnosis and lack of improvement. The diagnosis of vulvodynia can be summarized as a normal vulvar appearance (with or without local erythema) and normal vaginal walls and secretions, in association with introital sensitivity on cotton-swab testing. Pelvic floor muscle tenderness may also be present in some women. FIGURE 4 shows a schematic of the diagnostic work-up.

Medical history

The medical history often helps identify the probability of vulvodynia in women with suggestive symptoms[149–152]. The most helpful part of the history includes clarifying the characteristics and timing of the pain, as well as previous gynaecological diagnoses and treatments. The diagnosis can be further supported by the presence of comorbid pain conditions (BOX 3), psychological symptoms and relationship factors that could be associated with the pain.

Importantly, asking a woman about 'pain' in the vulvar region might not elicit the needed information as some women might not consider the sensation as pain but rather as discomfort, irritation, stabbing, a sharp sensation or even itching. Thus, using these other descriptors when asking women about their symptoms might increase the probability of making a correct diagnosis. The consensus definition of vulvodynia[1] is augmented by a set of descriptors that are used to characterize the disorder and can vary over time; these descriptors include location, provocation, onset and temporal patterns[2] (BOX 1). Descriptors help to clarify the presentation of vulvodynia and can be useful in clarifying which treatments might be most effective for different presentations.

As previously discussed, some women with vulvodynia have other, potentially related, pain or hypersensitivity conditions[39,153], and asking women with symptoms suggestive of vulvodynia about symptoms of these disorders can improve the change of diagnosis and may affect treatment choice. Indeed, women with vulvodynia are more likely to have one or more of the 'chronic overlapping pain conditions' (BOX 3) than women without vulvodynia[39,40]. In addition, psychological disorders, such as depression and anxiety, are more common in women with vulvodynia than in women without vulvodynia[125,154]. From a clinical standpoint, assessing these comorbid pain and psychological conditions is important as treatment of one comorbid condition might improve the symptoms of the other disorder[155].

In addition to comorbid pain and psychiatric disorders, higher rates of sexual difficulties have been reported among women with vulvodynia[35] and should be assessed during the initial evaluation. For some women, central themes above and beyond the pain itself are key in describing life with vulvodynia, including how vulvar pain affects their femininity or sexual identity, the centrality of sex within their relationships, and the prolonged uncertainty of the diagnosis[156] (BOX 4). Attention to the coexisting emotional burden of the presence of these rarely discussed and often discounted symptoms can be helpful as treatment options are considered[133].

The use of inventories such as the Vulvar Pain Assessment Questionnaire (VPAQ) can be a useful way to collect information about some of these varied components of the diagnostic history[157] (supplemental digital content available, see Related links). The VPAQ consists of several subscales of pain severity, emotional response, cognitive response, interference with life, sexual function and self-stimulation or penetration, plus supplementary scales of pain quality characteristics, coping skills and the effect on romantic relationships. The VPAQ is available in two versions — the full form and the screening form — and has been validated and correlates well with other pain, physical functioning and relationship functioning scales, placing specific emphasis on items relevant to vulvar pain.

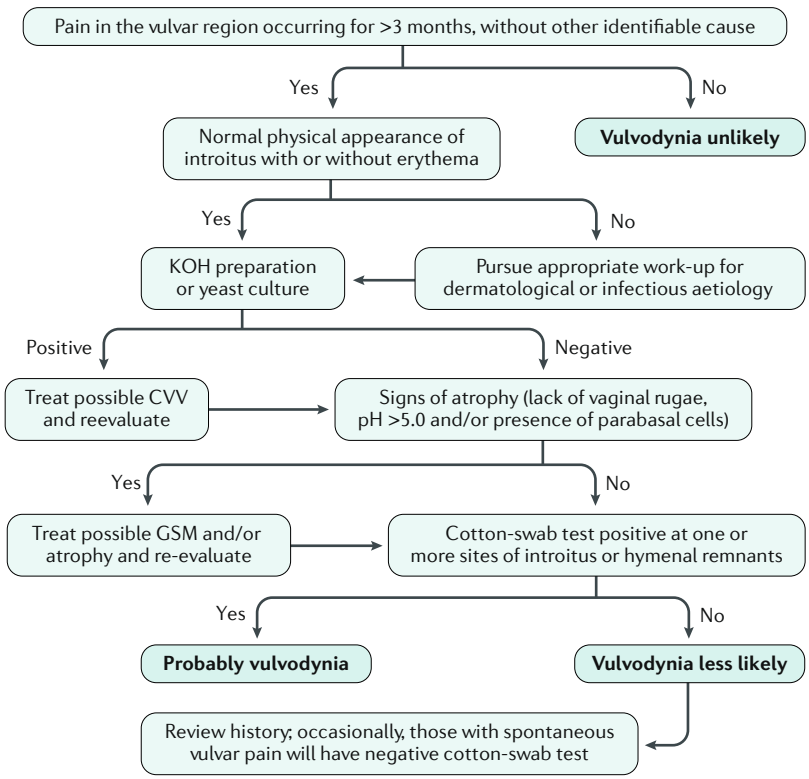

Fig. 4 | **Diagnostic algorithm for vulvodynia.** Diagnosis of vulvodynia involves medical history taking, pelvic examination (to rule out dermatological conditions affecting the vulvar region and to assess vulvar sensitivity using the cotton-swab test) and laboratory assessment (to assess pH, background flora and vaginal yeast). Results from these examinations can help to exclude other potential causes of vulvar pain, such as infectious disease or genital symptomatology of menopause (GSM). CVV, *Candida* vulvovaginitis.

Pelvic examination

Although the medical history alone is helpful in making a diagnosis of vulvodynia, a pelvic examination can both support the diagnosis and differentiate vulvodynia from other vulvar pain disorders such as *Candida* vulvovaginitis and atrophic vaginitis. Several specific helpful aspects of the examination are emphasized here.

Box 4 | **Psychosocial effects of vulvar pain**

A meta-ethnography of women's subjective experiences in living with vulvodynia identified four key concepts[156]

- Negative consequences of social narratives around womanhood, sexuality and femininity, emphasizing penetrative sex, the role of women to provide sex for men, and portrayals of sex as easy and normal
- Experiencing the health-care community as dismissive and at times uninformed
- Feeling shame and guilt associated with psychological distress, low mood, anxiety, low self-esteem and social isolation
- Positivity about the availability of changing narratives elucidating a way forward such as empowerment, self-efficacy, and group and individual multidisciplinary approaches

These constructs elucidate various issues of women with vulvodynia that extend far beyond that caused by the pain alone; they deserve attention and treatment in addition to pain-focused care.

External appearance. Typically, women with vulvodynia have a normal appearing vulva. Erythema (redness of the skin or mucosa) localized to the vulvar vestibule near the Skene and Bartholin gland openings is often observed, although this finding is no longer required for diagnosis[158]. The presence of other dermatological changes, such as lichenification, excoriations, ulcerations or masses, suggest an alternative or concomitant diagnosis that should be further addressed with cultures or biopsies as indicated.

Vulvar sensitivity. The cotton-swab test is commonly used to assess sensitivity at the vestibule, labia and hymenal remnants. This test involves exerting light pressure to several regions of the vulvar vestibule with the tip of a cotton swab. A variety of techniques have been described for this test, without consensus. One such method includes indenting the tissue by 3–5 mm at the 2, 5, 6, 7 and 10 o'clock positions of the vulvar vestibule, together with bilateral pressure on the hymenal remnants. This test will typically elicit tenderness at one or more points in most women with vulvodynia but will only rarely elicit tenderness in women without vulvar pain[51,159]. Although the test is positive (that is, at least one site of mild or greater tenderness) in the majority of women with provoked pain and in a substantial percentage of women with spontaneous pain, occasionally, some women with vulvodynia will have a negative test[159]. If it is unclear whether the discomfort is in the vulvar vestibule or further within the vagina, application of topical lidocaine to the vestibule can help to clarify this issue[160].

Pelvic floor muscles. Tenderness and/or spasm of the pelvic floor muscles is associated with sexual dysfunction[161] and pain intensity[162,163]. Various methods for evaluating pelvic floor muscle tenderness have been described, without a final consensus reached[164]. However, some appreciation for pelvic floor tenderness can be ascertained by inserting one finger in the vaginal introitus and exerting mild to moderate pressure on the pelvic floor muscles posteriorly and lateral to the vaginal opening (to assess the superficial transverse perineal muscles), bilaterally to the opening (to assess the bulbospongiosus muscles more medially and the ischiocavernosus muscles more laterally), and deeper in the pelvis (to assess the levator ani muscles). Asking the patient to contract and then relax the pelvic floor muscles will often identify a lack of control of this function in women with vulvodynia.

Vaginal examination. Gentle insertion of a speculum (if tolerated by the patient) can be used to assess the vaginal wall and any present vaginal secretions. A specimen of discharge or vaginal wall moisture obtained with a swab (either after the speculum is inserted or without use of the speculum if not tolerated) can be used for laboratory assessment (see Laboratory assessment, below). In addition, bimanual vaginal palpation (when tolerated) can assess whether deep (cervical or uterine) or adnexal (fallopian tubes, ovaries or bowel) tenderness is present, which can suggest an alternative or additional diagnosis if the medical history suggests deeper discomfort. An abdominal or rectal examination might be substituted if the vaginal examination is too painful. The application of a small amount of topical lidocaine to the vulvar vestibule can allow both speculum insertion and a bimanual examination in women who are otherwise unable to tolerate these procedures[165].

Laboratory assessment

Specimens of vaginal discharge or wall moisture can be used to examine vaginal yeast, pH and cytology in the laboratory to assess the possibility of alternative or concomitant diagnoses. Vaginal yeast assessment is carried out either via microscopic KOH preparation evaluation or yeast culture, which can confirm or exclude the presence of yeast as the likely cause or contributor to symptoms. An increased vaginal pH of ≥5 is suggestive of concomitant infection (such as bacterial vaginosis or *Trichomonas*) or a hypoestrogenic state (which can occur after menopause, in some women who have recently given birth or, occasionally, with use of some oral contraceptives)[166]. Microscopic assessment of the specimen using a normal saline preparation is used to evaluate vaginal cytology; a normal saline preparation may demonstrate parabasal cells (rounded epithelial cells) that suggest oestrogen deficiency, which could cause symptoms.

Differential diagnosis

The differential diagnosis of vulvodynia includes infections, inflammatory dermatological disorders, vulvar neoplasms, neurological disorders, trauma, iatrogenic pain following medical treatments to the area or hormonal deficiencies[1]. Two conditions in particular are often misdiagnosed as causing symptoms in the presence of vulvodynia and deserve special mention: *Candida* vulvovaginitis and genital symptomatology of menopause (GSM; including atrophic vaginitis). Women with vulvar pain often self-treat using over-the-counter medications for a *Candida* infection or are treated for presumed infection by their medical providers. In women with

persistent vulvar symptoms after treatment of a supposed yeast infection, a yeast culture as described above can help confirm the presence or absence of *Candida*. By comparison, perimenopausal or menopausal women with vulvar pain are frequently presumed to have symptoms related to GSM owing to oestrogen deficiency, although it is possible that these women have vulvodynia[23]. Differentiation of these conditions can be difficult, particularly in women with a high vaginal pH and/or the presence of parabasal cells[167]. Often, a trial of oestrogen treatment is a reasonable first course of action if the examination and/or laboratory data suggest oestrogen deficiency, with a plan to treat further for vulvodynia if the oestrogen treatment does not resolve symptoms. Similar clinical findings of high pH and the presence of parabasal cells can be found in some women using oral contraceptives or in postpartum, and a trial of oestrogen therapy may also be useful in these women.

Of note, all three diagnoses — vulvodynia, *Candida* vulvovaginitis and GSM — are relatively common, and, therefore, two or more may occur concomitantly. Thus, women should be informed that a treatment trial (for yeast infection or atrophic changes) will help differentiate whether that diagnosis is causing the discomfort and, if improvement does not occur, that further discussion and treatment for vulvodynia will be pursued.

Screening

Most women and girls with vulvodynia have not sought treatment for the disorder[14] and many women assume that discomfort with intercourse is normal; therefore, many women with vulvodynia may not mention their symptoms during a routine office visit. Accordingly, asking women and girls of all ages whether they experience discomfort at the vaginal opening, or during intercourse, can begin the discussion of potential diagnoses.

At least two studies have demonstrated the value of a very brief screening survey in identifying vulvodynia in adult women. In one study, participants reporting 'introital pain that had lasted ≥3 months' at the opening of the vagina were very likely (96%) to be diagnosed with vulvodynia in the office[152]. Although the screening questions differed, another study found that participants reporting '>10 episodes of pain on contact' led to 74% of women being identified as having vulvodynia, whereas women reporting that 'pain on contact prevented or limited intercourse' led to 83% of women being identified with vulvodynia; in each case, reporting the lack of those symptoms identified >94% of those without vulvodynia[150]. Based on these data, a very brief discussion would identify most women with symptoms consistent with vulvodynia. In addition to the question-based screening, applying an abbreviated cotton-swab test (at the 5–7 o'clock positions of the vulvar vestibule and at the hymenal remnants) during each pelvic examination will also identify unrecognized tenderness, which will then prompt further discussion (B.D.R., unpublished observations).

Management

Internationally, there is no general consensus on treatment algorithms for vulvodynia, and recommended guidelines are mainly based on expert opinion, case series and a limited number of placebo controlled randomized clinical trials (RCTs)[1,168]. Approximately 25 RCTs have been carried out for localized PVD compared with none for generalized unprovoked vulvodynia, which reflects the higher prevalence of PVD[169]. No standardized protocols or outcome measures have been used systematically in these RCTs. However, recommendations for self-reported outcome measures for clinical trials have now been proposed[170]. The use of consistent outcome measures and an improved understanding of whether subgroups of vulvodynia respond differently to various treatments will make it easier to compare future treatment studies.

A step-by-step approach of modalities addressing pelvic floor dysfunction and psychosexual health, together with medical management in various doses and combinations, is suggested for the treatment of vulvodynia. Women with less severe vulvodynia can benefit from the provision of information on pain mechanisms and psychosexual consequences, general care measures and support. In some cases, when patients have not responded to the initial treatment, a team of several health-care professionals, including gynaecologists or dermatologists, physical therapists and/or psychologists or sex therapists, might be needed to deal with the complex components involved in vulvodynia[171]. Clinically, this model provides the opportunity to target multiple dimensions of vulvodynia simultaneously, such that the treatment process may be more efficient and coherent. This efficiency can generate increased hope and engagement in the woman and her partner, in addition to the treatment team. However, the lack of RCTs makes it unclear whether multimodal approaches are more effective than single treatments. Importantly, treatment choice will likely depend, in part, on the local resources for skilled sex therapy or cognitive behavioural therapy (CBT), PFPT, and medical or surgical management. Only some geographical areas have access to all therapeutic modalities.

Psychosocial interventions

Consensus-based guidelines from the Fourth International Consultation on Sexual Medicine recommend PFPT and psychosocial interventions as potential first-line treatments for vulvodynia[172]. Psychosocial interventions include CBT, pain management, sex therapy and psychoeducation, either offered individually or in combination. CBT and pain management/sex therapy aim to reduce pain and improve women and partners' sexual function, sexual wellbeing, and relationship satisfaction by targeting the thoughts, emotions, behaviours and couple interactions associated with vulvodynia. These interventions offer the advantage of targeting multiple dimensions of vulvodynia beyond the pain itself, including sexual, relationship and psychological distress, and can be delivered in group, couple or individual therapy formats.

The first stage of psychosocial treatment involves psychoeducation. The second stage focuses on engaging women and their partners in more adaptive emotion co-regulation and sexual communication, whilst reconnecting through non-sexual physical and emotional

intimacy, expanding the sexual repertoire to steer the focus away from intercourse alone and optimizing pleasurable sexual activities, as well as sharing experiences of desire, arousal and sexual intimacy. Issues such as childhood maltreatment, mood and/or anxiety disturbances, and relationship conflict might need to be addressed via more intensive, trauma-informed CBT if they are thought to be related to vulvodynia and interfere with the targeted work on pain and sexuality.

The efficacy of group CBT has been investigated in three different randomized studies of women with PVD. In the first study, women with PVD were randomized to CBT, electromyography (EMG) biofeedback or vestibulectomy. Women who received CBT reported significant improvement in pain at a 6-month follow-up[173] and had similar pain levels during intercourse as women who received vestibulectomy at the 2.5-year follow-up period, whereas women in the EMG biofeedback arm fared as well as those in the CBT arm at the 6-month follow-up but not at the 2.5-year follow-up[174]. In the second study, women with PVD were randomized to receive either a topical corticosteroid or group CBT for 13 weeks of treatment. In this study, women who received group CBT reported significantly higher treatment satisfaction, less severe pain and pain catastrophizing, and better global improvements in pain and sexual function than women who received the topical corticosteroid[35]; therefore group CBT resulted in changes on more domains of PVD than topical corticosteroids. In another randomized trial, individual CBT yielded significantly greater improvements in pain and sexual function than individual supportive psychotherapy, and these improvements were maintained at the 1-year follow-up point[175].

Two new third-generation acceptance-based approaches of CBT also show promising results for the treatment of vulvodynia. The first approach targets relationship factors that have a role in vulvodynia and comprises a 12-week couple's therapy intervention, and has been tested in an open trial, prospective pilot study. This approach was associated with significant post-treatment improvements in pain and sexual function for women and in sexual satisfaction for both women and their partners, supporting the potential benefit of this therapy for vulvodynia treatment[176]. The second approach is a mindfulness-based group CBT programme that is delivered over four 2-hour sessions and consists of education about PVD and pain, CBT skills aimed at increasing awareness and acceptance of problematic thoughts, progressive muscle relaxation and mindfulness exercises as well as sex therapy. In one study that used a quasi-experimental design and a wait-list control comparison group, significant improvements in pain catastrophizing and hypervigilance, sexual distress, and pain during the cotton-swab test but not during intercourse were associated with the group mindfulness-based programme compared with the wait-list control[177]. In addition, a more recent study comparing this mindfulness-based group CBT programme to standard group CBT in 130 women with PVD found that mindfulness was as effective as group CBT in improving pain catastrophizing, hypervigilance and acceptance, in addition to sexual function and distress[178]. In a subset of 64 women who reported engaging in vaginal intercourse 4 weeks before the post-treatment and 6-month follow-up assessments, mindfulness was superior to CBT in reducing pain during intercourse[178], whereas the two groups were equivalent on this outcome at the 1-year follow-up[179]. Taken together, these findings suggest that CBT is an empirically validated, non-invasive therapeutic option that can be offered in different formats for the treatment of vulvodynia.

Box 5 | **Physical therapy techniques**

Electromyography (EMG) biofeedback: an EMG vaginal sensor is inserted in the woman's vagina as she learns to retrain her pelvic floor musculature via the feedback on the video screen about the quality of her contractions and relaxations.

Manual therapy: with the woman in the gynaecological position, the physiotherapist uses hands-on stretching and massaging of the pelvic floor to facilitate muscle relaxation and tissue mobility.

Education: instructions concerning avoidance of irritants (such as perfumed soaps), chronic pain management, sexual function and urogynaecological health.

Electrotherapy: a low-voltage electrical current to help women increase pelvic floor muscle proprioception.

Dilators and insertion techniques: use of vaginal dilators during in-office treatment and home exercises with a view to desensitize the vulvovaginal area and reduce the fear of pain and vaginal penetration.

Pelvic floor physical therapy

PFPT aims to rehabilitate the pelvic floor musculature by enhancing muscle proprioception, relaxation, discrimination and elasticity, normalizing muscle tone, desensitizing the painful vulvar tissue and, although not targeted directly, reducing fear of pain and vaginal penetration[180]. PFPT encompasses several techniques that can be delivered in combination or isolation, the most common of which are EMG biofeedback, manual therapy, education (about the removal of irritants, sexual function, pain management and urogynaecological health), electrotherapy, and dilators and insertion techniques[181] (BOX 5). Despite methodological shortcomings in many studies, such as a lack of control or comparison groups, small sample sizes, unstandardized treatment protocols, and a lack of randomized trials, one systematic review of PFPT for PVD found a consistent effectiveness of PFPT across studies, with a significant improvement in pain in 71–80% of women[180]. In terms of predictors of treatment outcome, only greater pretreatment pain was associated with higher pain severity at a 2.5-year follow-up point for EMG biofeedback[174]. Further, the overall effectiveness of the combination of PFPT techniques was greater than the effectiveness of isolated techniques (such as EMG biofeedback alone)[180]. In this regard, it is important to note that one large randomized multicentre trial of myofascial PFPT in women with interstitial cystitis or bladder pain syndrome demonstrated significant improvement[182], supporting the use of PFPT for the treatment of chronic pelvic pain disorders.

Similar trials are urgently needed to study the effectiveness of PFPT for subgroups of vulvodynia. Only one

Tampon test
Standardized research technique of insertion of a tampon of standardized size by the patient to assess discomfort. Can be used repetitively over time to assess changes.

randomized clinical trial has examined the efficacy of PFPT, in which PFPT was compared to overnight topical lidocaine treatment in 212 women with PVD. In this trial, women who received PFPT had a significantly larger improvement in pain intensity during intercourse, sexual function and distress from pre-treatment to post-treatment compared with those who received lidocaine, and the beneficial effects of PFPT were maintained at the 6-month follow-up[183]. These findings provide strong evidence that physical therapy warrants consideration as a first-line treatment for PVD.

Medical therapies

In terms of specific treatments for vulvodynia, medications for pain management are a cornerstone of medical therapies. The categories of medications differ in mode of action and administration.

Topical creams. Topical lidocaine 2–5% gel or cream is often tried in women with vulvodynia with the aim to reduce mucosal pain sensitivity and desensitize the vestibular nerves[184]. In one uncontrolled study, lidocaine was applied overnight[184]; however, in clinical practice, it is used several times per day or when needed. In a double-blinded RCT, no difference in pain response to the tampon test was found in women with PVD who received topical lidocaine compared with those who received placebo (each applied four times daily)[185]. Moreover, one study reported a greater benefit with PFPT than with overnight topical lidocaine use[183] (see Pelvic floor physical therapy, above). Despite the results of these studies, intermittent topical lidocaine use might be beneficial in women with intensive pain to vestibular touch[1] and can be used prior to vaginal penetration (TABLE 1).

Antidepressants. Tricyclic antidepressants (TCAs) are the first-line treatments for neuropathic pain conditions[186]. Although the precise anti-analgesic mechanism of TCAs is not fully understood, it has been suggested that it is due to repeated stimulation of β2-adrenoceptors by increased levels of noradrenaline in the synaptic cleft[186]. Amitriptyline is often used for generalized unprovoked vulvodynia in clinical practice and has been associated with favourable outcomes regarding pain in retrospective and non-controlled trials[187,188]. Amitriptyline is also frequently used for PVD, although it lacks strong evidence from RCTs[189]. The only RCT assessing TCAs in women with PVD was conducted with low-dose oral desipramine, and this trial found no superior effect of desipramine compared with placebo[185]. Topical 2% amitriptyline has been used in one uncontrolled study reporting improvement of dyspareunia[190]. Other types of antidepressants that are used for neuropathic pain have not yet shown proven efficacy for vulvodynia. For example, a small open-label trial of milnacipran (a serotonin and noradrenaline reuptake inhibitor) showed promising results for PVD, although larger trials are required before the efficacy of this treatment for PVD can be confirmed[186,191] (TABLE 1).

Anticonvulsants. Anticonvulsants, such as gabapentin and pregabalin, have been used for vulvodynia treatment and have been assessed in a limited number of studies of PVD. Gabapentin and pregabalin are thought to affect voltage-gated sodium channel function at nerve terminals, attenuating depolarization and the release of pain-promoting neurotransmitters such as glutamate and substance P[189]. In the first of two RTCs, a double-blind, crossover trial found no difference in pain associated with the tampon test in women who received gabapentin compared with those who received placebo[192]. However, the second RCT found improved sexual function with the same dose of gabapentin compared with placebo[193]. Although some women with vulvodynia obtain symptom relief with the use of various neuromodulating agents, larger and better designed studies are needed that consider comorbid pain conditions and analyse subgroups of vulvodynia[6], particularly for generalized unprovoked vulvodynia and subgroups of PVD.

Anti-inflammatory therapies. Whether inflammation has a substantial role in PVD onset and/or symptomatology is debated. According to patients' experience, the use of oral over-the-counter NSAIDs, such as ibuprofen, are not effective for vulvodynia (N.B.-S., unpublished observations). Similarly, attempts to treat PVD with topical corticosteroids have been made without convincing results[194], although intramucosal methylprednisolone injections in combination with lidocaine have been associated with some improvement of symptoms in one small uncontrolled study[195].

Future immune-targeting therapies for vulvodynia could target different components of the immune system. For example, one study found a significantly higher Toll-like receptor-mediated proinflammatory response in vestibular fibroblasts from women with PVD compared with pain-free controls, indicating that an upregulated innate immune response could be involved in the pathophysiology of vulvodynia and could be targeted therapeutically[146]. In addition, studies in animal models have suggested that the neuronal hypersensitivity in PVD may be caused by nociceptor axon proliferation associated with inflammatory cell-derived angiotensin II acting on neuronal AT2 receptors. This effect could be blocked in a rat model of PVD and could be a potential future therapeutic possibility[45,141].

Hormones. The role of hormonal contraceptives in increasing the risk of vulvodynia is another controversial topic. Two small RCTs in women with secondary vulvodynia tested the efficacy of topical oestrogen and reported conflicting results[196,197]. In a non-controlled case series study, the combination of topical oestrogen and testosterone and discontinuation of oral contraceptives was associated with reduced vestibular pain sensitivity[198]. Hormonal therapies are not recommended for vulvodynia treatment, although future studies might reveal a subgroup of patients who improve following cessation of hormonal contraceptive use in combination with topical hormonal treatment.

Neurotoxic agents. Several studies have assessed the use of botulinum toxin A (BTA) to decrease pelvic floor hypertonicity and pain in women in whom PFPT did

Table 1 | **Medical management for localized provoked vulvodynia**

Intervention	Study design (*n*)	Regimen	Outcome measures and efficacy	Refs
Anti-nociceptive agents				
Lidocaine	Non-controlled (*n* = 61)	Topical 5% ointment, every night for 7 weeks	Significant daily pain reduction and increase in the number of patients able to resume intercourse post-treatment	184
Lidocaine	Non-blinded RCT comparing lidocaine (*n* = 23) with EMG biofeedback as control (*n* = 23)	Topical 2% lidocaine gel, 5 times per day for 12 weeks	Vulvalgesiometer[a], significant improvement, but no difference compared to 12-week EMG biofeedback	214
Lidocaine	Double-blind, placebo controlled RCT comparing lidocaine (*n* = 28) with placebo cream (*n* = 31)	5% cream, 4 times per day for 12 weeks	NRS 0–10 tampon test, no difference in pain reduction compared with placebo	185
Tricyclic anti-depressives	Double-blind, placebo controlled RCT comparing desipramine (*n* = 27) with placebo tablets (*n* = 31)	Oral desipramine, administered daily, increasing dose from 25 mg to 150 mg (6 weeks) for 12 weeks	NRS 0–10 tampon test, no difference from placebo	185
Tricyclic anti-depressives	Prospective, non-controlled (*n* = 150)	Topical 2% amitriptyline cream, twice per day for 12 weeks	Slight to excellent improvement in 56%	190
Serotonin-norepinephrine reuptake inhibitors	Open label, uncontrolled (*n* = 18)	Oral milnacipran, 50–200 mg per day for 12 weeks	NRS 0–10 coital pain, significant improvement	191
Capsaicin	Retrospective, non-controlled (*n* = 52)	Topical 0.025% cream, 20 min application (then removed) per day for 8 weeks	Sensitivity to touch and Marinoff dyspareunia scale[b], significant improvement	215
Capsaicin	Non-controlled (*n* = 33)	Topical 0.05% cream, decreasing dose from twice per day to twice per week for 4 months	Partial response	216
Anti-convulsant agents				
Gabapentin[c]	Retrospective GV (*n* = 11), PVD (*n* = 24)	2–6% topical cream, 8 weeks	VAS 0–10, reduction in pain for all patients	217
Gabapentin	Double-blind, crossover, placebo controlled RCT (*n* = 45 gabapentin, *n* = 44 placebo)	Highest tolerable oral dose between 1,200 and 3,000 mg per day for 8 weeks	NRS 0–10 tampon test, no difference from placebo	192
Gabapentin	Double-blind, crossover, placebo controlled RCT (*n* = 45 gabapentin, *n* = 44 placebo)	Oral gabapentin, 1200–3000 mg per day for 8 weeks	FSFI, improved sexual function	193
Anti-inflammatory agents				
Corticosteroids	Non-controlled (*n* = 22)	Submucosal methylprednisolone (1, 0.5, 0.3 ml) once per week for 3 weeks	32% absence of symptoms, 36% with marked improvement at 24–36-month follow-up	195
Corticosteroids	Double-blind, crossover RCT (*n* = 14 in total)	0.05% Clobetasol propionate or 0.5% topical hydrocortisone ointment for 28 nights	Score of pain, tenderness and erythema; no significant improvement compared with hydrocortisone	218
Corticosteroids	Non-blinded RCT comparing hydrocortisone (*n* = 45) with CBT as control arm (*n* = 52)	Topical 1% hydrocortisone cream, twice per day for 13 weeks	Less pain reduction compared with group CBT	194
Neurotoxic agents				
Botulinum toxin A	Double-blind, placebo controlled RCT (*n* = 32 in each arm)	20 U, single injection into the bulbocavernosus muscle	NRS 0–10 for pain, no difference in pain compared to placebo at 6-month follow-up	199
Botulinum toxin A	Non-controlled 3 and 6 months of follow-up (*n* = 20) or 24 months of follow-up (*n* = 19)	100 U, single injection into the bulbocavernosus muscle	NRS 0–10 for pain, significant improvement of pain at 3, 6 and 24 months of follow-up	219,200
Botulinum toxin A	Retrospective, non-controlled (*n* = 79)	100 U, single injection into the levator ani muscle	NRS 0–10 for pain, cotton-swab test, significant improvement	220
Botulinum toxin A	Double-blind, placebo controlled RCT (*n* = 12 for 50 U, *n* = 9 for 100 U, *n* = 12 for placebo)	50 U (single injection), 100 U (single injection, repeated after 3 months)	NRS 0–10 for mucosal pain sensitivity; no difference compared to placebo at 3-month follow-up; repeated 100 U injection showed significant pain reduction	201

Table 1 (cont.) | **Medical management for localized provoked vulvodynia**

Intervention	Study design (*n*)	Regimen	Outcome measures and efficacy	Refs
Surgery				
Vestibulectomy	Retrospective (*n* = 54)	Vestibulectomy with vaginal advancement	Moderate to excellent improvement at 6-month follow-up	221
Vestibulectomy	Non-blinded RCT comparing surgery (*n* = 19), group CBT (*n* = 26) and EMG biofeedback (*n* = 26)	Vestibulectomy with vaginal advancement	McGill pain questionnaire, significant pain reduction compared to group CBT or EMG biofeedback at 6-month follow-up; significant pain reduction at 24-month follow-up with no differences between groups	173,174
Vestibulectomy	Retrospective, non-controlled (*n* = 126)	Vestibulectomy with vaginal advancement	Significant increase in patients able to have intercourse 1–4 years after surgery	222
Vestibulectomy	Retrospective, non-controlled (*n* = 104)	Vestibulectomy with vaginal advancement	93% were satisfied with the surgery, median 26-month follow-up	223
Posterior vestibulectomy	Retrospective, non-controlled (*n* = 67)	Posterior vestibulectomy with vaginal advancement	NRS 0–10, coital pain, significant pain reduction at 6 months and median 41-month follow-up	224
Posterior vestibulectomy	Retrospective (*n* = 57)	Posterior vestibulectomy with vaginal advancement	NRS 0–10, dyspareunia, significant pain reduction, median 36-month follow-up	225
Posterior vestibulectomy[d]	Observational case–control study comparing surgery (*n* = 39) with conservative treatment (*n* = 27)	Posterior vestibulectomy with vaginal advancement in non-responders to conservative management	NRS 0–10, dyspareunia, significant pain reduction in both groups, median 47-month follow-up	204

CBT, cognitive behavioural therapy; EMG, electromyography; FSFI, female sexual function index (19-item questionnaire generating a score for evaluation of sexual function); GV, generalized vulvodynia; NRS, numeric rating scale (a numeric rating scale for assessing pain); PVD, provoked vestibulodynia; RCT, randomized controlled trial; VAS, visual analogue scale. [a]A device that contains metal springs of varying compression rates, calibrated to exert a range of forces from 3 to 1,000 g, through a disposable cotton swab fitted at one end. [b]Scores are from 0–3: 0 refers to no pain with intercourse, 1 refers to pain with intercourse that does not prevent the completion, 2 refers to pain with intercourse requiring interruption or discontinuance, and 3 refers to pain with intercourse preventing any intercourse. [c]The study also includes women with generalized vulvodynia. [d]Conservative treatment includes combinations of topical and oral medications, physiotherapy for pelvic floor muscle dysfunction and sexual counselling. The table includes a restricted selection of studies with a major focus on monotherapies, the highest possible level of evidence and more recent studies.

not improve pelvic floor dysfunction. Although BTA has been evaluated in several studies, it has not yet proven to be effective for vulvodynia. In the one published RCT in women with PVD, a low dose (20 U) injection into the bulbocavernosus muscles resulted in the same improvement of dyspareunia as placebo[199]. Despite these results, BTA injection is an easy office procedure and an uncontrolled study reported favourable outcomes with injections of up to 100 U (REF.[200]). However, one small RCT using 50 U and 100 U BTA reported no difference in mucosal pain sensitivity at 3 months after treatment between women who received BTA or those who received placebo, although results indicate that repeated high-dose injections could reduce pain over 6 months[201]. Additional placebo-controlled RCTs for BTA are in progress and, hopefully, results from these studies will clarify what doses and injection techniques to use, and what subgroups of patients might benefit from this treatment.

Combination approaches. The efficacy of various medical management options has been studied using monotherapy only, even though a multi-modal approach is commonly recommended. Indeed, in clinical practice, it is evident that physicians and health-care providers are using a wide variety of medications, often in combinations[151,202]. Many of these combined treatments have not been studied in women with vulvodynia but might be promising. For instance, combining antidepressants and anticonvulsants might be effective for some patients owing to the high comorbidity of vulvodynia with mood disorders or other pain disorders.

Surgery

Women with PVD that is refractory to conservative treatments may benefit from surgery. Surgery is usually performed after several other treatments have been tried with no or little observed benefit and the time interval from start of treatment to the surgical procedure may differ between individuals.

Of all treatments for PVD, surgery has been the most extensively studied. It seems that the variations in procedures for vestibulectomy are of minor importance and that surgery often improves symptoms[203]. Indeed, the type of vestibulectomy carried out varies between studies (see REF.[203] for a review of surgical procedures for vulvodynia, including a discussion of short-term and long-term adverse effects). Posterior vestibulectomy was performed in some studies with removal of the sensitive vestibular mucosa, from approximately 2 to 10 o'clock posteriorly, whereas in other studies, full vestibulectomy was carried out. Both techniques include excision of the hymenal ring and advancement of the posterior vaginal wall to cover the tissue defect. In addition, the openings of the Bartholin ducts are removed, although they normally regenerate[203].

The only RCT including surgery for PVD found the greatest short-term pain reduction after vestibulectomy

compared with EMG biofeedback or group CBT[173]. However, no differences in pain during intercourse were observed between the surgery group versus the CBT group at the 2.5-year follow-up point[174]. In another study, women with severe PVD who did not respond to conservative treatment subsequently underwent posterior vestibulectomy. At the post-surgical follow-up a median of 44 months after surgery, similar reductions on visual analogue scales for dyspareunia were reported for the surgical group compared with the conservatively treated group[204], suggesting that surgery could be effective in women who do not respond to conservative therapies. However, studies on surgery are often of inadequate quality, with poorly defined outcome measures and a lack of follow-up. Indeed, these studies generally lack detailed descriptions of patient selection, including details on local findings of mucosal hypersensitivity and whether hypertonicity of the pelvic floor muscles is present. Thus, further studies are needed to optimize patient selection and identify predictors of successful outcome.

Quality of life

The quality of life of women with vulvodynia varies substantially[9]. Women with spontaneous pain or pain provoked with everyday activities of daily living (such as sitting, exercising or sweating) can experience a marked effect on their lifestyle, including work restriction or avoidance, altered social and interpersonal activities, and impaired sleep[205]. Women with provoked pain may only experience discomfort primarily during and after certain activities (such as sexual intercourse, tampon use, wearing tight clothing, horseback riding and bicycle riding). For many women, the emotional effect of vulvodynia can greatly enhance its morbidity, including the distress associated with missed and erroneous diagnoses, lack of useful medical assistance and understanding, lower feelings of self-worth, self-blame, role as a sexual partner, response of the sexual partner, and altered interpersonal communication with partner, friends and colleagues[133,156]. In addition, the perceived effect of vulvodynia on the partner is often very distressing for the patient[133], and the consequences for the partner can vary greatly, from guilt and frustration, lower sexual satisfaction and erectile difficulties[206], to increased empathy and improved sexual health[207], suggesting that including the partner in discussions and treatment could be advantageous. As previously discussed, women with vulvodynia are more likely to report other pain syndromes, which can further affect their quality of life[39,153].

In addition to effects on quality of life, living with vulvodynia results in a profound personal and societal economic burden owing to long-term medical costs as well as to vulvodynia-related reduced productivity and disability in the work environment and in the personal domain. Indeed, one estimate suggests a cost per individual approaching US$9,000 in a 6-month period, and a cost to the US economy of US$31–72 billion dollars annually[208]. Furthermore, emerging data suggests that financial insecurity increases physical pain[209].

Outlook

Education and awareness

Although little is known about effective ways to prevent the onset of vulvodynia, early diagnosis and treatment are thought to be preferable to delayed diagnosis and treatment to minimize the cumulative burden of this condition[210]. As most women with vulvar pain have not sought treatment[14,23], educating girls and women about symptoms associated with vulvodynia is urgently needed. This education might include routine questions about vulvovaginal symptoms during medical visits as well as broader school-based and clinic-based strategies discussing which genital symptoms are suggestive of a disorder, the various diagnoses that can occur and their available treatments. These initiatives should be inclusive of sexual/gender and ethnic minority women, non-binary individuals and men, and focus on both the patient and partner perspectives. In particular, adolescence is a developmentally sensitive time period characterized by family, peer and health behaviour transitions that can positively or negatively modify childhood trajectories[211] and shape future adult health outcomes. Indeed, the strong association between adolescent and adult health suggests that evidence-based investments in healthy adolescent development have long-ranging implications for the future health of populations[212]. Accordingly, although often considered taboo, educating adolescents about pain during sexual intercourse or other penetrative activities and even by touch alone could decrease unnecessary suffering and increase timely treatment in women with vulvodynia. Although educational materials should be adapted to the targeted age groups, the current strong focus on negative factors in sex education (for example, risky sexual behaviour) should be counterbalanced with an emphasis on protective factors (such as safe vulvovaginal health behaviours and sexual communication in romantic relationships) that could be promoted in prevention initiatives and multimodal treatment protocols for all age groups. Of note, a social media campaign on vulvodynia (#ItsNotInYourHead) is aimed at breaking the stigma surrounding vulvar pain and to let women know that their pain is real. National public health initiatives and education programmes implemented in schools, such as the ongoing initiative for endometriosis spearheaded by the Australian Government, might also serve as a role model.

In addition to a lack of vulvodynia knowledge in the general population, there is also a lack of training and awareness among physicians and mental health professionals who diagnose and treat women and their partners. This point is not surprising as vulvodynia involves two health areas that have been generally neglected in graduate training programmes worldwide, and that tend to make most health-care professionals uncomfortable, independent of their professional background and allegiance: chronic pain and sexual health. Accordingly, medical residents and mental health doctoral interns should be exposed to these two broad areas and learn about the complex biopsychosocial aspects of pain and sexual health. Their uneasiness concerning these central dimensions of health and quality of life requires

special attention given studies indicating that women with vulvodynia often feel stigmatized and dismissed by the health-care community (BOX 4). In addition, there is an urgent need for national and international sexual medicine, gynaecology and pain medicine organizations to collaborate on developing such curricula to be implemented in health-care education.

Aetiological complexity

Several questions concerning the aetiological pathways of vulvodynia remain. For example, the role of various biomedical associations with vulvodynia, such as the link between PVD and infections, most importantly recurrent *Candida* vulvovaginitis, with extensive mucosal inflammation[88,147], the iatrogenic role of various repeated topical treatments in the context of mucosal inflammatory response and preventive measures, and the involvement of proinflammatory responses[146], remains unclear. Further study of these associations in women with vulvodynia as a whole and in specific subgroups of patients is needed.

In addition, some of the most frequently proposed psychosocial associations, such as childhood maltreatment and mood disorders, are not specific to vulvodynia. Nevertheless, these factors are often considered as such in the clinic, leading to relatively simplistic explanations for the pain and to treatment recommendations that may be less than optimal such as in cases whereby a health-care provider suggests that a patient's vulvodynia is caused by past sexual abuse. By contrast, the current evidence base suggests the existence of multiple aetiological pathways leading to the development and persistence of vulvodynia. For example, initial biomedical or mechanical trauma to the vulvovaginal area could trigger inflammation, pelvic floor muscle dysfunction and other local changes leading to nociceptor sensitization and to further peripheral and central alterations in pain processing[37]. More complex models integrating biomedical, cognitive, affective, behavioural and interpersonal factors need to be developed, empirically validated, and disseminated to researchers and clinicians. These models will require intensified interdisciplinary collaborations that are presently lacking. Forming a global multidisciplinary consortium for vulvodynia research could be a first step in this direction.

One large caveat of the research conducted to date lies in the lack of longitudinal studies that would allow clarity regarding the directionality of associations between purported mechanisms and vulvodynia. Indeed, following cohorts of adolescents into adulthood could identify prospective associations between biomedical and psychosocial factors emerging during this developmental period and potentially leading to vulvodynia in adulthood. Important barriers to conducting this research include the lack of funding for vulvodynia, the scarcity of interdisciplinary collaborations and challenges therein, and ethical issues surrounding medical testing in asymptomatic youths. Another important limitation of studies to date concerns the lack of ethnic, socioeconomic, gender and sexual orientation diversity among cohorts. Most epidemiological studies have focused on white women in North America, Europe and Australia, and studies from other countries are sparse[213]. Oversampling for sexual and gender minorities and members of minority ethnic groups may be the only way to overcome this shortcoming.

Clinical trial design

The evaluation of treatment outcomes in vulvodynia has met with multiple limitations that must be addressed if treatment recommendations are to be valid and evidence based. The lack of agreed-upon treatment outcomes has been a substantial barrier to comparisons of treatments and consensus on use of multidimensional, standardized endpoints is critical. To this end, one study[170] has recommended outcome measures for inclusion in vulvodynia clinical trials based on IMMPACT domains. The core measures suggested for use include pain intensity, pain quality and affect, the temporality of pain, physical function or health-related quality of life, sexual function, satisfaction, distress and interference, emotional function (such as depression or anxiety), participant ratings of global improvement and satisfaction with treatment, adverse events, and participant disposition. Adherence to these recommendations will likely move the field forward substantially.

In addition, if vulvodynia subgroups originate from multiple aetiological pathways, an RCT that does not evaluate outcomes in differing subgroups is likely to miss subgroup-specific treatment responses. Controlling and assessing for differences between subgroups in analyses will help limit the lack of appreciation for treatment effects that involve specific subgroups. To inform clinical trial design, pathophysiological studies need to focus on larger samples of women and include testing of specific subsamples in the clinic and the laboratory. This approach could facilitate the phenotyping of different subgroups of women with vulvodynia based on biopsychosocial characteristics and contribute to improving not only the rigor of future clinical trials but also the quality of clinical management[6].

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Competing interests
U.W. serves on the External Consultant Board for the NIH Preclinical Screening Platform for Pain, a novel preclinical pain therapy screening platform that has been launched at the National Institute for Neurological Disorders and Stroke as part of the NIH Helping to End Addiction Long-term Initiative. In her capacity as a special government employee of the FDA, U.W. has served as a voting member of the FDA Anaesthetic and Analgesic Drug Products Advisory Committee. U.W. has served as a consultant for Grünenthal GmbH and Ironwood Pharmaceuticals, Inc. All other authors declare no competing interests.

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