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SOCIETY REPORT

International Society for the Study of Women's Sexual Health (ISSWSH) Review of Epidemiology and Pathophysiology, and a Consensus Nomenclature and Process of Care for the Management of Persistent Genital Arousal Disorder/Genito-Pelvic Dysesthesia (PGAD/GPD)

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ABSTRACT

Background: Persistent genital arousal disorder (PGAD), a condition of unwanted, unremitting sensations of genital arousal, is associated with a significant, negative psychosocial impact that may include emotional lability, catastrophization, and suicidal ideation. Despite being first reported in 2001, PGAD remains poorly understood.

Aim: To characterize this complex condition more accurately, review the epidemiology and pathophysiology, and provide new nomenclature and guidance for evidence-based management.

Methods: A panel of experts reviewed pertinent literature, discussed research and clinical experience, and used a modified Delphi method to reach consensus concerning nomenclature, etiology, and associated factors. Levels of evidence and grades of recommendation were assigned for diagnosis and treatment.

Outcomes: The nomenclature of PGAD was broadened to include genito-pelvic dysesthesia (GPD), and a new biopsychosocial diagnostic and treatment algorithm for PGAD/GPD was developed.

Results: The panel recognized that the term PGAD does not fully characterize the constellation of GPD symptoms experienced by patients. Therefore, the more inclusive term PGAD/GPD was adopted, which maintains the primacy of the distressing arousal symptoms and acknowledges associated bothersome GPD. While there are diverse biopsychosocial contributors, there is a common underlying neurologic basis attributable to spontaneous intense activity of the genito-pelvic region represented in the somatosensory cortex and its projections. A process of care diagnostic and treatment strategy was developed to guide the clinician, whenever possible, by localizing the symptoms as originating in any of five regions: (i) end organ, (ii) pelvis/perineum, (iii) cauda equina, (iv) spinal cord, and (v) brain. Psychological treatment strategies were considered critical and should be performed in conjunction with medical strategies. Pharmaceutical interventions may be used based on their site and mechanism of action to reduce patients' symptoms and the associated bother and distress.

Clinical Implications: The process of care for PGAD/GPD uses a personalized, biopsychosocial approach for diagnosis and treatment.

Strengths and Limitations: Strengths and Limitations: Strengths include characterization of the condition by consensus, analysis, and recommendation of a new nomenclature and a rational basis for diagnosis and treatment. Future investigations into etiology and treatment outcomes are recommended. The main limitations are the

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dearth of knowledge concerning this condition and that the current literature consists primarily of case reports and expert opinion.

Conclusion: We provide, for the first time, an expert consensus review of the epidemiology and pathophysiology and the development of a new nomenclature and rational algorithm for management of this extremely distressing sexual health condition that may be more prevalent than previously recognized. **Goldstein I, Komisaruk BR, Pukall CF, et al. International Society for the Study of Women's Sexual Health (ISSWSH) Review of Epidemiology and Pathophysiology, and a Consensus Nomenclature and Process of Care for the Management of Persistent Genital Arousal Disorder/Genito-Pelvic Dysesthesia (PGAD/GPD). J Sex Med 2021;18:665–697.**

Key Words: Paracentral Lobule; Cauda Equina; Tarlov Cyst; Suicidality; Overactive/Hypertonic Pelvic Floor Dysfunction; Cognitive Behavioral Therapy

INTRODUCTION

In 2001, Leiblum and Nathan first reported the condition of "persistent sexual arousal syndrome" (PSAS) in a case series of 5 women. The main features of PSAS were symptoms of unremitting genital arousal that were noted in "the absence of conscious feelings of sexual desire" where there were "no obvious hormonal, vascular, neurological, or psychological causes."[1] In 2006, Leiblum revised the name of this condition to persistent genital arousal disorder (PGAD),[2] in part, because "the condition was more a problem of *genital*, rather than *sexual*, arousal." Since PGAD was first described, management strategies for women with PGAD have often defied usual psychological and biological treatments, leaving many patients with high levels of bother and distress and sometimes suicidal ideation.[3] There has also been a broadening of the peer-reviewed literature concerning the epidemiology, pathophysiology, diagnosis, and treatment of PGAD.[4] However, most of the literature still consists of case studies and expert opinion. In 2016, for the first time, the International Society for the Study of Women's Sexual Health (ISSWSH) consensus nomenclature report defined PGAD and its associated risk factors.[5] What has been lacking until now is a critical consensus evaluation of the contemporary literature concerning PGAD and a comprehensive management strategy for this difficult-to-treat condition. To this end, ISSWSH assembled a panel of experts to review the epidemiology and pathophysiology of this condition and to provide guidance for evidence-based management.

METHODS

ISSWSH is a not-for-profit multidisciplinary academic and scientific organization dedicated to supporting the highest standards of ethics and professionalism in the research, education, and clinical practice of women's sexual health. The ISSWSH executive committee selected co-chairs to organize this PGAD consensus project. The co-chairs identified an expert multidisciplinary panel (ISSWSH members and nonmembers) consisting of one academic clinical psychologist, one graduate student in psychology, one sex therapist, one basic scientist, 2 neurophysiologists, one gynecologist, one internist, one urologist, one neuropsychiatrist, one spine surgeon, one sexual medicine physician, one sexual medicine nurse practitioner, one pelvic floor physical therapist, and one sexuality educator. After a series of planning conference calls, panelists were assigned topics for evidence-based literature reviews, identifying relevant publications. The panel convened in Atlanta, GA on March 6, 2019, to provide evidence and expert opinion on patient impact, epidemiology, psychosocial, and medical factors, and the diagnostic and treatment process for PGAD. Members were assigned to writing groups for the development of this article and periodically reconvened through video conferences to discuss manuscript content. Consensus at the original live in-person meeting and follow-up video conferences was achieved using a modified Delphi method. Levels of evidence (LOE) and grades of recommendation were assigned using the criteria of Shekelle et al,[6] based on the consensus of the panel (Table 1). If not specified, the level of evidence (LOE IV) and treatment recommendations (Grade D) are based on expert opinion. While PGAD can affect people of all gender identities, this report will focus on cisgender women (gender identity corresponds to sex assigned at birth), the main gender studied to date.

PATIENT IMPACT

In 2005, Leiblum et al conducted a survey of 103 women with PSAS, in which 75% of respondents rated their distress related to the condition as moderate to high.[7] The strongest predictors of distress associated with this condition were intrusive and persistent symptoms of genital arousal, unhappiness, shame, and worry about the symptoms, reduced sexual satisfaction, and negatively impacted relationship wellbeing.[7] In 2007 and 2009, Leiblum further reported that women who endorsed all 5 PGAD criteria (genital arousal that is persistent and involuntary, unrelated to sexual desire, not relieved with orgasm, intrusive and unwanted, and has an unidentified cause) compared to those who only endorsed some of these symptoms, reported lower desire, less sexual satisfaction, greater pain, and lower overall scores on the Female Sexual Function Index (FSFI).[11,17]

Table 1. Levels of evidence for associated/contributing factors and grades of recommendation for treatments for PGAD/GPD. Only treatments receiving a grade of C or higher are listed. All other treatments are based on expert opinion. Levels of evidence and recommendation grades were assigned as previously described[6]

Associated/Contributing factors	LOE	Citations
Psychosocial		
Symptom distress	IIA	2,7–10
Anxiety symptoms/panic*	IIA	2,3,8,9,11
Depressive symptoms/suicidality*	IIA	3,8,9,11
Obsessive-compulsive symptoms*	IV-III	2,8,12,13
Catastrophization/hypervigilance*	IIA	2,3,14
Sexual/emotional/other trauma*	III	2,15
Other psychiatric comorbidities*	III	2,8,16
Sexual functioning*	IIA	2,3,8,17
Relationship adjustment*	IIA	3,18
Other medical comorbidities*	IIA	2,3,8,11
Overactive/hypertonic pelvic floor muscle dysfunction	III	19
Pudendal neuropathy	III	20,21
Sacral Tarlov cyst	IIB	22
Lumbar disc disease		
Annular tear	IIB	23,24
Medications		
Trazodone	III	25
Use of or discontinuation of SSRIs/SNRIs	III	26–29
Treatment	**Grade† (recommendation)**	
Psychotherapy and other psychological strategies (eg, CBT [including decatastrophizing], mindfulness, breathwork, self-compassion, etc.)	C	2,3,7–11,13,15
Pelvic floor: sacral/pudendal neuromodulation	C	19
Tarlov cyst surgery or aspiration (with or without fibrin glue)	C	30
Lumbar disc disease surgery (eg, laminectomy, discectomy, annuloplasty)	C	23
Dose adjustment of SSRI/SNRIs	C	26–29
Electroconvulsive therapy (ECT)	C	31,32

*These factors have been associated with PGAD/GPD.
†Grade C recommendations are based on level III evidence (non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies) or extrapolated recommendations from Level I or II evidence.

In a survey of women experiencing symptoms of PGAD, 54% of women reported experiencing some degree of suicidal ideation, more than double that of the control group (25.0%).[3] Patients with PGAD who experience suicidality should be assessed for other risk factors such as severe depression, prior suicide attempts, comorbid history of a psychiatric or substance use disorder, recent severe interpersonal stressors, and prescription drug misuse.[3,11,14,33]

Women afflicted with PGAD experience difficulty with mental health issues such as depression, high rates of negative emotions, including worry and stress, and substantial difficulties with psychosocial adjustment.[3,7,8,34,35] They may also experience anxiety, including panic attacks and certain obsessive-compulsive symptoms.[11,36] The anxiety may reinforce, exacerbate, and maintain PGAD.[8]

PGAD is also associated with impairment of function, including activities of daily living, such as driving and housework, social activities, and employment.[10,14] PGAD sufferers may use online support groups to share experiences and information as they navigate the negative impact of PGAD.[37,38] In summary, PGAD negatively affects the quality of life factors such as mental health, sexual satisfaction, relationship wellbeing, and activities of daily living, and it is associated with high suicidality.

EPIDEMIOLOGY

Several studies have investigated the prevalence of PGAD.[39] Garvey and colleagues surveyed women attending a sexual health clinic in London, UK.[40] They found that 1.0% reported the criteria of Leiblum & Nathan (2001).[1] Of note, 3.1% reported persistent genital arousal in the absence of desire that was not distressing or intrusive. This finding emphasizes that the criterion of distress is necessary for the diagnosis. Jackowich and Pukall surveyed 1,634 first-year undergraduate students at a

Canadian university in Ontario.[41] A total of 0.6% of women reported experiencing symptoms consistent with PGAD, including persistent feelings of genital arousal with an unknown cause that was unwanted or intrusive and occurred in the absence of subjective arousal, persisted for hours to days, and did not go away after orgasm. Given that this sample was not representative of the general population, they also examined the presence of these symptoms in a separate representative U.S. sample consisting of 1,026 participants. They found that almost 3% of women endorsed experiencing these symptoms.[41] Another study of 679 university students in Italy that utilized the same questions as in Jackowich and Pukall[41] revealed that 1.6% of women reported experiencing symptoms consistent with PGAD.[39,41] Based on these limited epidemiological studies, there is a consistency of prevalence data, ranging from 0.6% to approximately 3%, suggesting that a substantial number of individuals may be affected by this condition worldwide.

In addition, PGAD symptoms may be continuously present[7,14] or intermittent (ie, symptom "flares" and symptom-free periods) and lifelong (10.4%) or acquired. Those with acquired symptoms develop them, on average, at around 37 years of age (range = 6−66 years), and symptoms started prior to the age of 18 in 25.2%.[14]

NOMENCLATURE

Historical Perspective

The 2016 ISSWSH consensus nomenclature panel defined PGAD as a condition "*characterized by persistent or recurrent, unwanted or intrusive, distressing feelings of genital arousal or being on the verge of orgasm (genital dysesthesia), not associated with concomitant sexual interest, thoughts, or fantasies for a minimum of 6 months. PGAD can be lifelong or acquired, generalized or situational, and associated with the following characteristics:*

- *limited resolution, no resolution, or aggravation of symptoms by sexual activity with or without aversive and/or compromised orgasm in terms of impaired orgasm frequency, intensity, timing, and/or pleasure;*
- *aggravation of genital symptoms by certain circumstances (sitting, car driving, listening to music, general anxiety, stress or nervousness);*
- *despair, emotional lability, catastrophization, and/or suicidality;*
- *inconsistent evidence of genital arousal on physical examination during symptoms (lubrication, swelling of clitoris or labia).*"[5]

In the International Classification of Diseases (ICD-11), the term PGAD is included for the first time for women and listed in the category "Other Specified Sexual Arousal Dysfunction."[19] However, as PGAD is not a named sexual dysfunction category, no diagnostic criteria are listed in the ICD-11 classification.[42]

At the ISSWSH PGAD consensus meeting in 2019, experts discussed a possible name change for the following reasons: (1) the term PGAD was descriptive rather than medical; (2) Pukall et al recommended that PGAD be considered a genito-pelvic dysesthesia characterized by distressing arousal, that is classified according to its primary sensation (eg, arousal) and that this overarching framework could include other distinct (but often overlapping) sensations (ie, pain, vulvodynia, itch)[43]; and (3) there are patients who have a distressing genital itch and/or pain symptoms[10,14,43] with or without genital symptoms of arousal, and a change in terminology would acknowledge the overlap among these dysesthesia symptoms. Further supporting the change in nomenclature is that common neural pathways (spinothalamic and/or spinoreticular tracts) convey genital sensations of arousal and orgasm, as well as dysesthesias such as itch and pain.[44−47] Recognition that the PGAD condition described by Leiblum should be broadened was originally based on Waldinger's association of PGAD symptoms with urinary urgency and frequency, and restless leg symptoms that led to the proposal of the term "restless genital syndrome."[48−52]

Given the interest in considering a conceptual shift and name change for PGAD to a broadened term such as genito-pelvic dysesthesia, a survey was conducted in patients and family members of patients with a history of PGAD (n = 98; 94% female, 3% male, 3% non-binary; mean age ± SD = 46.2 ± 14.5; range = 17−74). The majority (69%) agreed that the name of the condition should be changed, whereas 17% disagreed, and 6% were neutral or declined to respond.[53] The majority of survey respondents (>60%) also agreed that the term "arousal" in PGAD should be changed.

Based upon the discussion of the evidence and in consideration of patient perspectives, the ISSWSH consensus panelists voted to keep the ICD-11 term of PGAD as the primary condition but also introduce the term "genito-pelvic dysesthesia" (GPD) as an additional component to generate a more accurate diagnostic schema and inclusive nomenclature. GPD is defined as an unpleasant, atypical sensation in the genito-pelvic region that may also include lower extremity dysesthesia due to the involvement of common sacral nerve roots. Although GPD is an emerging condition in need of more research regarding its connection to and representation of the experience of women with distressing genital arousal sensations, the panel agreed to the term PGAD being newly referred to as PGAD/GPD. This shift represents the third name change for this condition from PSAS in 2001 to PGAD in 2006 and now to PGAD/GPD.

New Consensus Nomenclature

Thus, the 2019 ISSWSH consensus panel recommends that PGAD/GPD be characterized by persistent or recurrent, unwanted or intrusive, distressing sensations of genital arousal (eg, feelings of being on the verge of orgasm and of lubrication and swelling,[2,7,14,54] tingling, throbbing, contractions) that persist for ≥3 months and may include other types of genito-pelvic dysesthesia (eg, buzzing, burning, twitching, itch, pain) (Table 2). The criterion for the duration of bothersome symptoms from

Table 2. ISSWSH consensus expert opinion on criteria and characteristics of persistent genital arousal disorder/genito-pelvic dysesthesia (PGAD/GPD)

Criteria	persistent or recurrent, unwanted or intrusive, distressing sensations of genital arousal
	duration of ≥3 months
	may include other types of **genito-pelvic dysesthesia** (eg, buzzing, tingling, burning, twitching, itch, pain)
	most commonly experienced in the clitoris but also in other genito-pelvic regions (eg, mons pubis, vulva, vestibule, vagina, urethra, perineal region, bladder, and/or rectum)
	may include being on the verge of orgasm, experiencing uncontrollable orgasms, and/or having an excessive number of orgasms
	not associated with concomitant sexual interest, thoughts, or fantasies
Associations	limited resolution, no resolution, or aggravation of symptoms by sexual activity
	compromised orgasm quality (eg, aversive, impaired, altered frequency, intensity, timing, and/or pleasure)
	aggravation of genito-pelvic dysesthesia by certain circumstances (eg, sitting, car driving, music or sounds, general anxiety, stress, or nervousness)
	despair, emotional lability, catastrophization, and/or suicidality
	on physical examination, absent evidence of genital arousal (genital lubrication, swelling of clitoris or labia)

6 months to 3 months was shortened based on unanimous agreement by the panel that PGAD/GPD is a highly distressing condition, and in a subgroup of women, waiting 6 months would unnecessarily delay management. Furthermore, other genito-pelvic dysesthesias (eg, vulvodynia) also use the criterion of consistent symptom duration to be a 3 months period.[55] The symptoms of PGAD/GPD are most commonly experienced in the clitoris but also in other genito-pelvic regions (eg, mons pubis, vulva, vestibule, vagina, urethra, perineum, bladder, and/or rectum). These sensations may be accompanied by the experience of uncontrollable orgasms and/or having an excessive number of orgasms. These sensations are not associated with concomitant sexual interest, thoughts, or fantasies. Furthermore, PGAD/GPD could be associated with: (i) limited resolution, no resolution, or aggravation of symptoms by sexual activity; (ii) compromised orgasm quality (eg, aversive; impaired; altered frequency, intensity, timing, and/or pleasure); (iii) aggravation by certain circumstances (eg, sitting, car driving, music or sounds, general anxiety, stress, or nervousness); (iv) despair, emotional lability, catastrophization, and/or suicidality; and (v) on physical examination, absent overt evidence of genital arousal (eg, genital lubrication, swelling of clitoris or labia).

PATHOPHYSIOLOGY

The expert panel concluded that there are many different specific etiologies contributing to PGAD/GPD. The panel agreed that a complex combination of biopsychosocial factors likely contributes to the development and maintenance of this condition. Psychological aspects (especially catastrophization) and medical aspects (eg, pudendal neuropathy, cauda equina pathology), as well as pharmacological factors (for example, selective serotonin reuptake inhibitor (SSRI) discontinuation), may all be contributing factors to PGAD/GPD. Psychosocial factors could include lack of awareness of PGAD by clinicians and the lay public, shame and embarrassment associated with PGAD, and fewer accessible treatment options.[7,56]

There is limited information on the pathophysiology of PGAD/GPD, in part, because there are no animal models to study this condition. However, in clinical studies, it has become appreciated that the diverse biopsychosocial etiologies likely have a common underlying neurological basis, as evidenced by the findings by Komisaruk and others.[22,30,57] Using functional MRI in women without PGAD (n = 12), clitoral self-stimulation activated the paracentral lobule in the somatosensory cortex of the brain.[58] In women with PGAD when symptomatic (n = 3), preliminary evidence revealed spontaneous, intense, and more extensive activation of the paracentral lobule even in the absence of any overt physical genital stimulation (Figure 1). The figure contrasts the PGAD activation with that in women who did not have PGAD and who just *imagined* clitoral stimulation.[59]

Based on anecdotal reports, it is possible that catastrophization is related more to distressing dysesthesia of the genitals than of other pelvic regions (eg, bladder or legs), suggesting the existence of a neurological process that may be unique to the genitals rather than to generalized emotional distress. Further research is needed to map the projections to and from the paracentral lobule and other brain regions that are likely involved in various genito-pelvic sensations of PGAD/GPD (eg, arousal, awareness, discomfort, itch, pain) and the associated emotional distress (eg, catastrophization, suicidality).

MANAGEMENT ALGORITHM

Based on expert opinion and case report evidence, the panel agreed to introduce a new algorithm to better understand the multiple triggers that may lead to an intense activation of the paracentral lobule and related projections as originating in one or more of 5 regions in a given patient with PGAD/GPD: (1) end organ; (2) pelvis/perineum; (3) cauda equina; (4) spinal cord; (5) brain (see Figure 2). In this classification, we include within the "cauda equina" the sacral spinal nerve roots at the level of the dorsal root ganglia. Relevant neural pathways from these 5 regions involve somatic and visceral afferent nerves in the periphery (Regions 1 and 2)

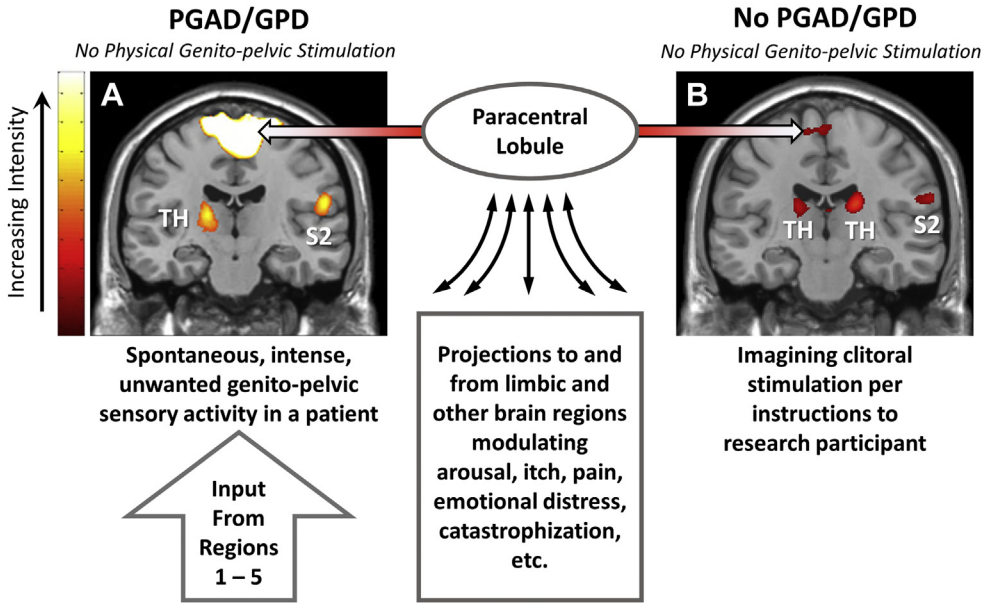

Figure 1. Comparison of brain activity in patients experiencing PGAD/GPD symptoms and those with no PGAD/GPD. While varying biopsychosocial etiologies may contribute to PGAD/GPD, there is likely a common underlying neurobiological basis within the brain that accounts for symptoms associated with an intense, unwanted genito-pelvic sensory activity. Panel A: Functional magnetic resonance image (fMRI) acquired in a human volunteer who was experiencing active PGAD/GPD symptoms. Panel B: fMRI in a healthy human volunteer without PGAD/GPD who was thinking about clitoral stimulation in the absence of any physical stimulation. Relative intensity of activation is shown by a representative pseudo-color hot metal analog scale, where dark red is least intense, orange/yellow is intermediate, and white is most intense. The sensory thalamus (TH) and secondary sensory cortex (S2), unilaterally or bilaterally, are also activated under these conditions, as shown in the fMRI images.[40]

and more centrally, sacral spinal nerve roots, cauda equina (Region 3),[57,58,60] spinal cord, spinothalamic and spinoreticular tracts (Region 4),[46,47] and brain pathways (Region 5).[61] For the remainder of this discussion, the various biopsychosocial contributors will be included within these 5 regions. It is important to emphasize that in certain cases, specific contributors may not be identified; thus, these patients would be considered as having an idiopathic form of PGAD/GPD. This classification of PGAD/GPD is consistent with the classification used for vulvodynia, where there are known versus idiopathic etiologies.[55]

DIAGNOSIS

The clinician should first establish if the patient meets the criteria for PGAD/GPD (Table 2). For those who meet the criteria, the clinician should then identify, whenever possible, the biopsychosocial triggers of the PGAD/GPD symptoms. The identification of these triggers allows rational psychological, medical, and other treatments to follow. Due to the multifactorial etiology of PGAD/GPD, it is important that the clinician perform a comprehensive biopsychosocial diagnostic evaluation, which includes taking a detailed psychosocial and medical history and conducting a comprehensive physical examination (Figures 3 and 4). This process should be tailored to each patient, and appropriate referrals should be made to specialists depending on the findings of the patient's history and examination, including their genital anatomy (eg, intersex) and identity (eg, transgender, nonbinary). This comprehensive approach enables the identification, assessment, management and/or referral, based on the comfort and expertise of the clinician.[33]

The panel agreed that the varying symptoms of PGAD/GPD may have a common underlying neuropathology involving intense activation of the genital sensory cortex. We recommend that the physical examination should begin with a detailed assessment of Regions 1 and 2 because these are the regions of the presenting genito-pelvic symptoms and they are accessible to a physical examination by the clinician.

Documenting Symptom Characteristics and Psychosocial and Medical History Taking

When assessing an individual presenting with PGAD/GPD symptoms, the clinician should gather detailed information about the symptoms (eg, location, degree of association with feelings of sexual desire and pleasure, intensity, distress, temporal pattern, whether orgasm symptoms are present, previous treatment attempts and outcomes, and family history) and document the onset of the patient's symptoms, triggers, exacerbating/relieving factors, the patient's assessment regarding inciting event(s), and how the symptoms impact the patient's sexuality, relationships, mental health,[62] and daily functioning.[8,12,18,33,63,64] The clinician should consider how the patient's symptoms developed over time (ie, the "natural history" of the PGAD/GPD) (Figure 5).[65]

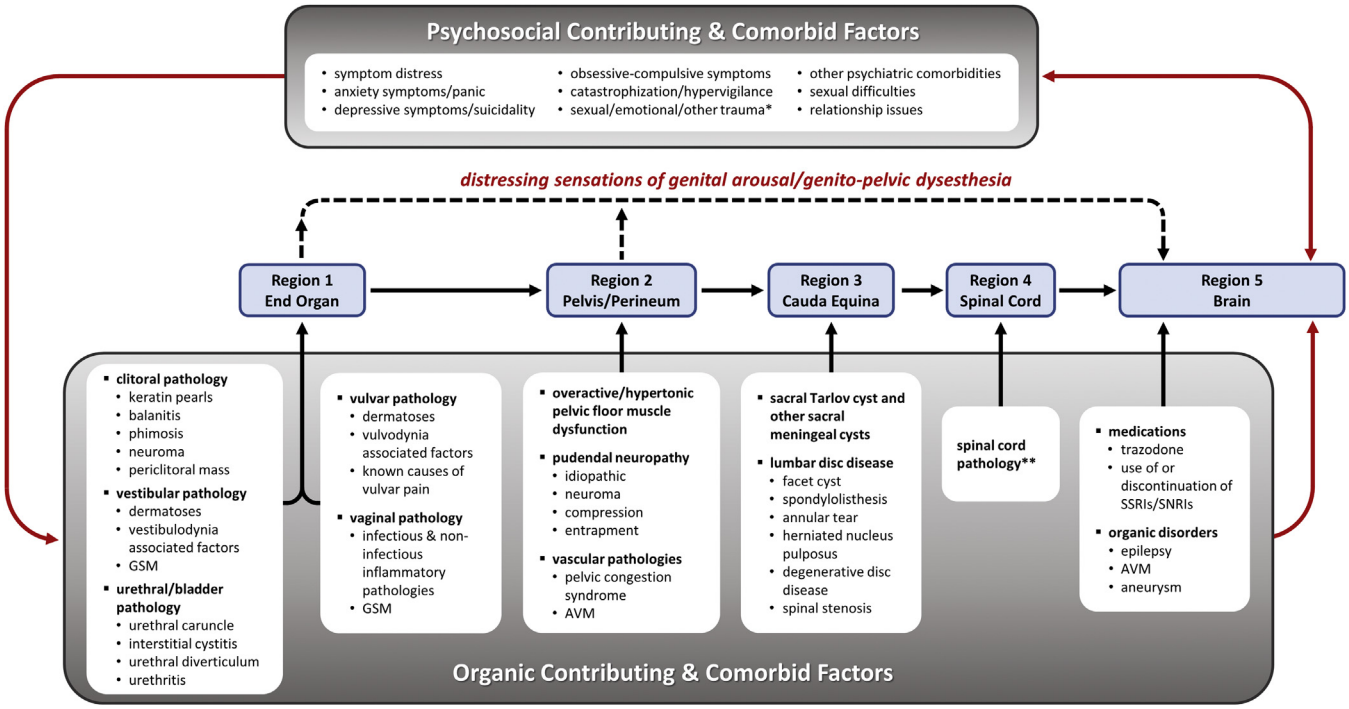

Figure 2. Biopsychosocial contributors and comorbid factors to PGAD/GPD. Factors are categorized as originating from 5 separate regions that may be successively modified through afferent nerve pathways. Pathology in Regions 3–5 may ultimately be interpreted by the brain as distressing sensations originating in Region 1 and/or Region 2 (dashed black arrows). Both psychosocial and organic factors modulate the nature and intensity of genito-pelvic sensations in the brain. Psychosocial factors may also influence organic factors in any of the 5 regions. AVM = arteriovenous malformation; GSM = genitourinary syndrome of menopause. *Sexual trauma may also include physical trauma related to Regions 1–4. **Spinal cord pathology may be a contributory factor, but cases associated with PGAD/GPD have yet to be reported in the peer-reviewed literature. Figure 2 is available in color online at www.jsm.jsexmed.org.

Early symptoms of PGAD/GPD may include genital awareness that is noticed but non-aversive. More intense dysesthesia symptoms (eg, genital/perineal pain,[10,15,22,55] itch,[43] clitorodynia,[66,67] vulvodynia,[51,68,69] vestibulodynia,[70] dyspareunia,[68] interstitial cystitis,[71] bladder/bowel dysfunction,[22,48,71,72] rectal,[72] leg, and/or back pain,[22] or restless legs),[48,73,74] with possible spontaneous orgasms/ejaculations, may represent a progression of the condition. Protracted neuropathy could result in damage to the nerves or nerve roots, changing the symptoms from "hyperfunction" (eg, genital arousal, pain, and/or itch) to "hypofunction" (eg, genital numbness, anorgasmia, and/or anejaculation).[65] However, other patients may report the sudden, spontaneous onset of their distressing symptoms, and some with comorbid pain may report that the pain preceded the onset of the PGAD/GPD symptoms.[14] This heterogeneity in onset underscores the importance of carefully detailing all aspects of PGAD/GPD. In addition, an accurate timeline of the onset of symptoms needs to be established since PGAD/GPD can be lifelong or acquired, its symptoms can be persistent or episodic, and the intensity of the symptoms can fluctuate. Those with lifelong PGAD/GPD may report a history of frequent masturbation at a very young age.[75] Reactions from the family and community to this behavior, punitive or supportive, should be documented. The onset of symptoms of acquired PGAD/GPD can be related to a specific occurrence (eg, fall, car accident). A medication history is especially important, as certain drugs are highly associated with acquired PGAD/GPD, especially initiation or discontinuation of SSRIs.[16,76,77] Other medications associated with PGAD/PGD include the use of trazodone, dopaminergic agents for Parkinson's disease, atypical tricyclic antidepressants, and histaminergic agents.[25,26,78–81] In addition, inquiring about family history is relevant as there is evidence of genetic susceptibility for connective tissue and/or mast cell disorders associated with PGAD/GPD.[82–85]

The clinician should pose questions about the patient's history of childhood or adult sexual trauma, messages about sex while growing up, and any strongly held sexual beliefs or sources of shame (eg, "masturbation is bad").[11] These questions are relevant because PGAD/GPD is uniquely associated with high suicidality.[3] Positive responses to these questions should direct clinicians to encourage patients to seek professional mental health care to provide strategies to prevent unnecessary patient demise.

The clinician should also assess how the patient's cognitions (eg, catastrophizing) and emotions (eg, level of anxiety) may impact symptoms and how the symptoms interfere with daily activities.[3] Due to the high level of distress associated with symptoms, it is imperative that the clinician also assess the patient's social support network and explicitly ask about suicidal ideation, intent, and plans.[62]

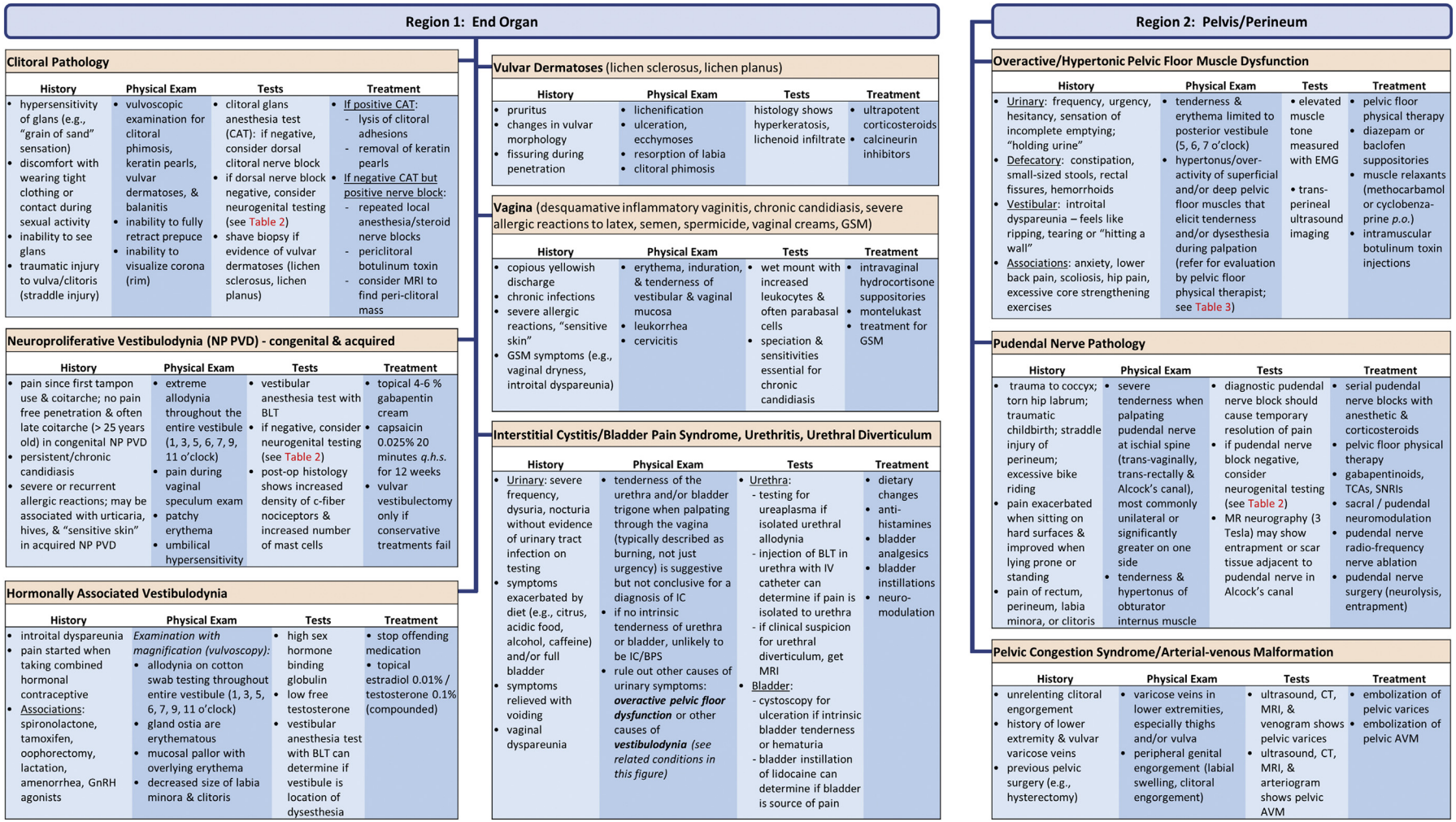

Figure 3. Diagnosis and treatment algorithm for PGAD/GPD: Regions 1 and 2. Figure 3 is available in color online at www.jsm.jsexmed.org.

Region 3: Cauda Equina

Tarlov Cyst/Lumbar Disc Disease

History	Physical Exam	Tests	Treatment
• Trauma: back injury, heavy lifting, fall on coccyx region, motor vehicle accident, childbirth • pain in lower back • history of connective tissue disorder (Ehlers-Danlos or Marfan's syndrome) • spine problems: scoliosis, disc disease (e.g., annular tear, herniated nucleus pulposus), previous spine treatments (surgery, chiropractic) • unilateral or bilateral lower extremity dysesthesia involving the buttocks, legs, and/or feet • lower extremity motor weakness (e.g., foot drop) • restless leg syndrome • neurogenic bladder and/or bowel	• abnormal sensation in genito-pelvic area • abnormal findings on lumbosacral dermatome, myotome, and/or reflex exam • Straight Leg Raise (SLR) test and Slump test	• consider neuro-genital testing (see Table 2) • sacral (with Tarlov cyst protocol) & lumbar MRI without contrast (with contrast if patient had previous spine surgery) • transforaminal epidural spinal injection (TFESI) in lumbar region; caudal epidural or perineural spinal injection in sacral region, depending on size/number of Tarlov cyst	• physical therapy ± pain management • TENS unit • lumbosacral shock wave therapy • neuromodulation • Tarlov cyst surgery or aspiration (with or without fibrin glue) • lumbar disc disease surgery (e.g., laminectomy, discectomy, annuloplasty)

Region 4: Spinal Cord

Spinal Cord

History	Physical Exam	Tests	Treatment
• back injury; heavy lifting; motor vehicle accident • history of connective tissue disorder (Ehlers-Danlos or Marfan's syndrome) • spine problems (scoliosis, disc disease, previous spine surgery) • dysesthesia and/or motor weakness in upper and lower extremities; • changes in muscle tone/stiffness • decreased coordination, balance • previous treatments for back problems (e.g., physical therapy) • neurogenic bladder and/or bowel	• abnormal findings on dermatome, myotome, and/or reflex exam of cervical and/or thoracic through lumbosacral levels • changes in muscle tone and/or spasticity	• consider neuro-genital testing (see Table 2) • thoracic & cervical MRI without contrast (with contrast if patient had previous spine surgery)	• physical therapy ± pain management • TENS unit • thoracic/cervical shock wave therapy • neuro-modulation

Region 5: Brain

CNS Medications & Organic Disorders

History	Physical Exam	Tests	Treatment
• Medications: initiation, termination, or dose changes of antidepressants, antipsychotics, insomnia drugs (e.g., trazodone), dopaminergic agents for treatment of Parkinson's disease • Associations: head injury, concussion, brain surgery, seizures, Tourette's syndrome, hyperthyroidism, iodine supplementation, misophonia	relevance not yet determined	• consider neurogenital testing (see Table 2) • MRI imaging • EEG recording of brain activity	Pharmacological (see Tables 3 & 4): • dose adjustment of SSRI/SNRIs • symptoms primarily genito-pelvic arousal: GABA activators, ion channel inhibitors (clonazepam, gabapentin, pregabalin, lamotrigine, oxcarbazepine, topiramate) • symptoms associated with leg/back pain: combination SNRI & baclofen suppository • symptoms associated with pelvic floor dysfunction: baclofen and/or diazepam suppositories; botulinum toxin (*i.m.*) Non-pharmacological: • neurological/neurosurgical consultation for organic brain pathology (traumatic brain injury, epileptic seizures, AVMs, or space occupying lesions) • electroconvulsive therapy (ECT) • transcranial magnetic stimulation (TMS)

Regions 1- 5

Psychosocial

History	Physical Exam	Assessments	Treatment
• symptom distress • Associations: - anxiety symptoms/panic - depressive symptoms/suicidality - obsessive-compulsive symptoms - catastrophization/ hypervigilance - sexual/emotional/other trauma - other psychiatric comorbidities - sexual difficulties - relationship issues	• results of any physical exam to be shared with the mental health care provider • plan of care & treatment progression for each patient to be shared among all health care providers	• at a minimum, validated instruments assessing depressive & anxiety symptoms as well as suicidality & catastrophizing, & numerical rating scales for symptom distress & intensity (at intake, as well as regularly throughout treatment sessions) • Recommended Instruments: - Beck Depression Inventory-II (BDI-II) - Patient Health Questionnaire (PHQ-9/PHQ-2) - Beck Anxiety Inventory (BAI) - Pain Catastrophizing Scale (PCS, with the term "pain" changed to "PGAD/GPD symptoms") - symptom distress ratings from 0 (no distress) to 10 (extremely high distress) - symptom intensity ratings from 0 (no sensation at all) to 10 (extremely intense sensations) • prescription drug/substance use/misuse/abuse • suicide risk/self-harm assessment should be undertaken	• psychotherapy (cognitive behavioral therapy targeting symptom management, mood, catastrophization is recommended) • other psychological strategies (e.g., mindfulness, breath work, and self-compassion) should be integrated into the psychotherapeutic approach when indicated • empirically-informed therapeutic strategies for trauma • therapeutic strategies for other psychiatric comorbidities • therapeutic strategies for sex and/or relationship therapy

Figure 4. Diagnosis and treatment algorithm for PGAD/GPD: Regions 3 - 5. Figure 4 is available in color online at www.jsm.jsexmed.org.

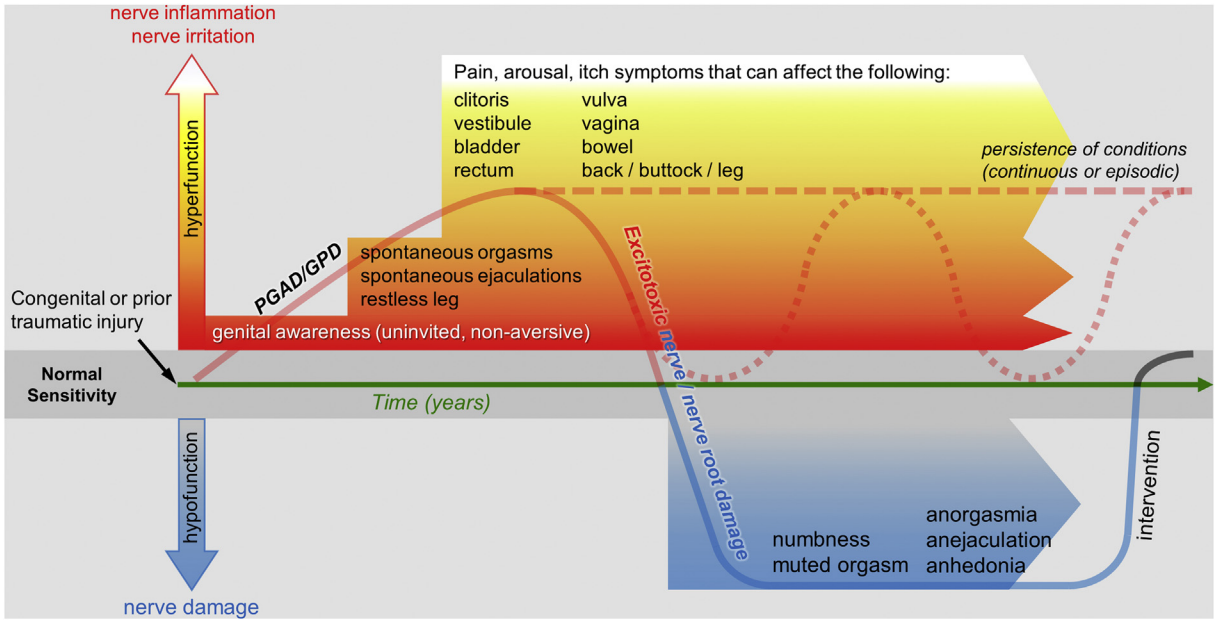

Figure 5. Hypothetical model of the natural history of PGAD/GPD due to neuropathy (eg, pudendal neuropathy) or radiculopathy (eg, Tarlov cyst, annular tear). The onset of symptoms over time is shown in relation to intensity of nerve or nerve root irritation, inflammation (increased neuronal activity), or damage (decreased neuronal activity). PGAD/GPD symptoms may increase, decrease, persist unchanged or be episodic. In some cases, "excitotoxic nerve damage" (declining nerve function secondary to a period of hyperstimulation) may occur and may be reversible after prolonged periods (eg, surgical intervention). Figure 5 is available in color online at www.jsm.jsexmed.org.

Differential conditions/diagnoses must be considered.[62] Some patients may present with persistent genital arousal symptoms but no distress; these patients would not be diagnosed with PGAD/GPD. In addition, in order to ensure that an appropriate diagnosis is made, the clinician should understand the differences between PGAD/GPD (unwanted, persistent arousal symptoms in the absence of sexual desire) and "hypersexuality" or Compulsive Sexual Behavior Disorder (CSBD; defined in the ICD-11 as "…a persistent pattern of failure to control intense, repetitive sexual impulses or urges resulting in repetitive sexual behavior", which can include disruptive, intense, difficult to control sexual fantasies, urges, or behaviors often in response to stress or negative emotions).[86] PGAD/GPD is often misdiagnosed as "hypersexuality" (CSBD) if clinicians are not aware of the complexities of PGAD/GPD symptoms.[17,62] Comorbid medical conditions should also be carefully assessed, given that patients with PGAD/GPD report significantly more medical and genito-pelvic conditions than those without PGAD/GPD.[3,15] These comorbid medical conditions are discussed below, by region, and include clitorodynia and vestibulodynia for Region 1, high tone pelvic floor dysfunction and pudendal nerve neuropathy for Region 2, and lumbar annular tear and sacral Tarlov cyst for Region 3.

Regional Diagnosis Algorithm

The presumptive pathophysiology of PGAD/GPD is sensory hyperactivity originating in any of the 5 regions. The purpose of this diagnostic algorithm is to assist the clinician in localizing the origin of the trigger(s).

Region 1: End Organ

Figure 3 describes multiple aspects of a patient's medical history and physical examination that may lead the clinician to suspect that the PGAD/GPD is related to Region 1. The physical examination of Region 1 should, if possible, be performed under magnification. Areas to be examined include the clitoris, vulva (labia majora, interlabial sulci, labia minora), vestibule, vagina, urethra, bladder, perineum, and perianal area. Engaging patients, partners, and/or family members by allowing them to see, if they agree, the various end organs using a hand-held mirror or vulvoscopic imaging displayed on a monitor can promote their understanding of the condition. Unilateral changes in sensation (either increased or decreased) in Region 1 can be evidence of neurologic pathology. While it is common for those with PGAD/GPD to complain of a sensation of unremitting genital engorgement, the genital tissue usually does not show genital arousal signs on physical examination, such as clitoral or labial engorgement.

Clitorodynia, including clitoral hypersensitivity and/or discomfort, a risk factor for PGAD/GPD, may be reflective of various pathologies. Clitorodynia can be caused by dorsal nerve neuropathy (eg, resulting from previous perineal trauma). Additional end-organ pathology such as clitoral phimosis can be identified by an inability to retract the prepuce. Examples of clitoral pathology are shown in Figure 6.[60,68,87]

Vestibulodynia, either hormonally-mediated or neuroproliferative, may be associated with PGAD/GPD.[88] Congenital neuroproliferative vestibulodynia may be a contributor to lifelong

PGAD/GPD. The vestibule may receive sensory innervation from branches of the somatic pudendal nerve and the visceral pelvic nerve. This exam should focus on sensory changes (eg, allodynia) as well as physical findings, such as atrophy, and combined erythema and pallor, a surprising but common vulvoscopic finding (Figure 6). A thorough description for the evaluation of vestibulodynia and its associated factors can be found in the Fourth International Consultation on Sexual Medicine's vulvodynia consensus paper.[69]

When examining the vestibule, the urethral meatus is readily visualized. The most common pathology of the urethral meatus possibly associated with PGAD/GPD is a urethral caruncle (prolapse of the urethral mucosa at the meatus; Figure 6). An examination of the vagina should be performed for evidence of atrophy and infection, as inflammation related to such vaginal disorders may contribute to PGAD/GPD symptoms. Additionally, the urethra, trigone, and bladder should be gently palpated. Tenderness is suggestive of a urethral diverticulum, bladder pain syndrome/interstitial cystitis, or urethritis; all are potential contributors to PGAD/GPD.[71]

Hormone Blood Testing

There are 3 embryologic tissues that comprise the introitus: the vulva is ectodermal, the vestibule is endodermal, and the vagina is mesodermal. Among these, the endoderm has strong androgen dependency. In women with PGAD/GPD who have a history of combined hormonal contraceptive use, infertility treatments, or hormone-modifying treatments for endometriosis or acne, determination of the androgen status may be important since hormonally mediated vestibulodynia is a potential contributor. Menopausal women typically have low testosterone values, and the condition known as genitourinary syndrome of menopause (GSM) is another potential contributor to PGAD. Laboratory tests that assess the androgen milieu (ie, testosterone, free testosterone, sex hormone-binding globulin) have been discussed in a recent ISSWSH consensus clinical practice guideline.[89] In perimenopausal and menopausal women, estradiol (E_2) level should also be tested.

Another potential hormonal contributor to PGAD/GPD is hyperthyroidism. Hyperthyroidism is a recognized contributor to premature ejaculation in men, considered to be an excitatory condition similar to PGAD/GPD. Hyperthyroidism is also associated with decreased peripheral vascular resistance and an increase in cardiac output due to an increase in heart rate. Thus, in patients with PGAD/GPD, thyroid function may be assessed, in part, by measuring for a decrease in blood levels of thyroid-stimulating hormone.

Anesthesia Testing

End-organ anesthesia testing (eg, of glans clitoris, vestibule, urethra, bladder) can be performed in those end organs involved in the symptoms of the dysesthesia (Figure 7). This approach is standard procedure in the diagnosis of the location of neuropathy in other organs.[90] As applied to PGAD/GPD, the panel reached a consensus that the diagnostic use of anesthesia testing is appropriate (expert opinion). If symptoms are clinically significantly reduced ("very much better" or "much better"), the implication is that pathology in the end organ contributes to the

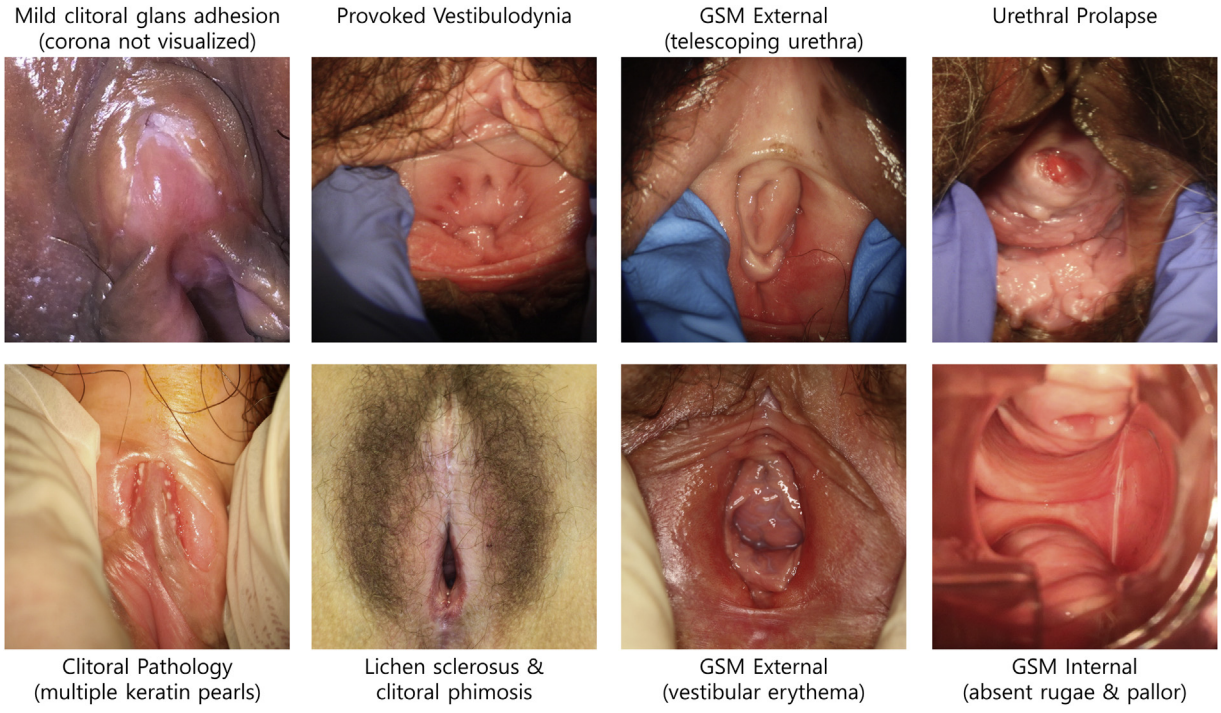

Figure 6. Contributing factors to PGAD/GPD in Region 1. Various pathological findings are shown.

PGAD/GPD. For example, if clitorodynia is the result of trauma to the glans clitoris, it would be expected that the clitoral anesthesia test would be positive, consistent with clinically significant symptom reduction. For performing end-organ anesthesia testing, a topical anesthetic may be carefully applied to the end organ until complete anesthesia to cotton swab testing is achieved. A commonly used topical anesthetic compound consists of benzocaine 20%, lidocaine 8%, and tetracaine 6% (BLT). If end-organ anesthesia cannot be achieved with a topical anesthetic, then subcutaneous lidocaine 1% should be considered. For achieving clitoral anesthesia testing with subcutaneous lidocaine, a 31-gauge needle, 5/16″ length, attached to a 1 ml syringe filled with 1% lidocaine is directed to the clitoral shaft above the glans and subcutaneously administered. To achieve vestibular anesthesia testing with subcutaneous lidocaine, a 27-gauge needle, $^{1}/_{2}$ ″ length, attached to a 10 ml syringe filled with 1% lidocaine, is directed to the right and left anterior and posterior regions of the vestibule. If, however, symptoms persist despite end-organ anesthesia through topical or subcutaneous administration, the etiology is consistent with originating in other Regions (2–5) or may be idiopathic.

Neurological Testing

The somatic neurological pathways in Region 1 include the 3 branches of the pudendal nerve (S2–S4) innervating the clitoris (dorsal nerve), urethra,[91] vulva and/or vestibule (perineal nerve), and perianal region (inferior hemorrhoidal nerve). The visceral afferent neurological pathways in Region 1 include the distal branches of the pelvic nerve that convey sensory activity originating in the vagina, urethra, bladder, and rectum.[92,93] Neurologic pathologies in the somatic (pudendal nerve) and/or visceral (pelvic nerve) afferent pathways are recognized risk factors for PGAD/GPD.

There are 3 office-based somatic neurologic testing procedures that are used for ascertaining neurologic pathology in Regions 1–5. These procedures are currently performed in highly specialized sexual medicine clinics as non-invasive strategies to assess the integrity of the neurologic pathways and are not considered required for the generalized clinician (Figure 8). One procedure is genital quantitative sensory testing (QST) of the nerves of the clitoris, vestibule, and perianal regions (S2–S4), which consists of vibration perception threshold testing for large myelinated Aβ fibers and temperature perception threshold testing for small myelinated Aδ fibers (cold) and for unmyelinated c fibers (warm).[94–98] The second procedure is non-genital sacral dermatome testing in which the patient is asked to lie in the prone position, and vibration perception threshold values are obtained separately on the left and right sides in sacral innervated regions, including S1–S4 gluteal dermatomes, S1–S2 posterior thigh dermatomes, and S1–S2 posterior calf dermatomes. The third procedure is bulbocavernosus reflex latency testing, which involves

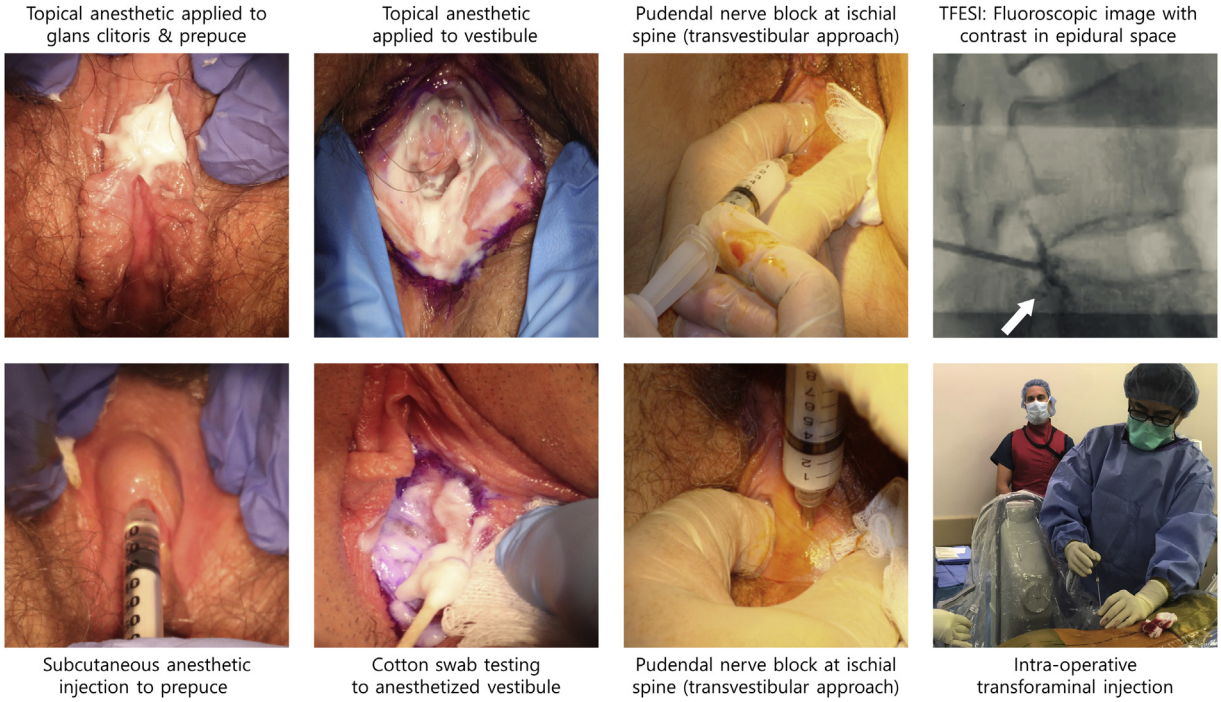

Figure 7. Anesthesia testing in Regions 1–3. Positive anesthesia testing, where symptoms are clinically significantly reduced, is helpful to localize the site of the contributing factors. For Region 1, panels depict clitoral and vestibular anesthesia testing. For Region 2, panels depict pudendal nerve block. For Region 3, diagnostic transforaminal epidural steroid injection (TFESI) is depicted. The goal is to bathe the annular tear with an anesthetic (white arrow). The flow of contrast media should be carefully followed to ensure the anesthetic remains predominantly at the desired disc level. Figure 7 is available in color online at www.jsm.jsexmed.org.

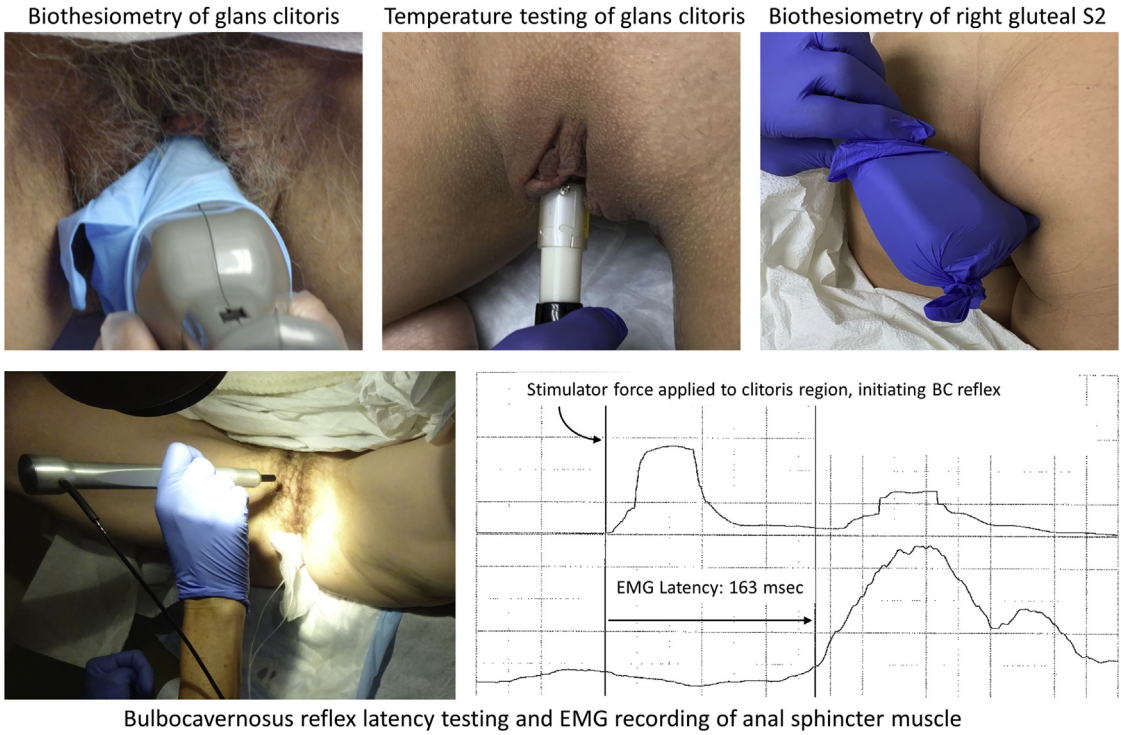

Figure 8. Quantitative sensory testing (QST) of the genital region, non-genital sacral dermatome testing (gluteal, posterior thigh, and posterior calf regions; control for each study is QST of index finger), and bulbocavernosus reflex latency testing (normal = 30–50 msec).[87] These tests will help localize suspected localized neurological pathology (see Table 2). Figure 8 is available in color online at www.jsm.jsexmed.org.

electromyographic monitoring of the bulbocavernosus muscle or external anal sphincter muscle contraction in response to mechanical stimulation of the left and right sides of the glans clitoris. Table 3 describes the location(s) of suspected neurologic pathology based on the outcomes of neurogenital testing.[99]

Region 2: Pelvis and Perineum

Figure 3 describes multiple aspects of history-taking and physical examination that may lead the clinician to suspect that the PGAD/GPD is related to Region 2. Referral to a pelvic floor physical therapist for an evaluation of the pelvic floor (pelvic girdle, muscles, connective tissue) and extra-pelvic regions (eg, abdomen, spine, hips) is important to determine which soft tissues are potential generators and/or contributors to PGAD/GPD. Pelvic floor dysfunction may be due to visceral-somatic and/or somato-visceral contributions to the patient's dysesthesia;[100–102] for example, palpation of muscles of the abdominal wall may reproduce the patient's symptoms of pain or other dysesthesia of the bladder (ie, somato-visceral).[103,104] In addition, palpation at the obturator internus muscle may reproduce the patient's dysesthesia near the urethra (somato-visceral) and/or ipsilateral hip (somato-somatic) (see Table 4).[100–102,104,105]

Overactive/hypertonic pelvic floor dysfunction, potential contributors to PGAD/GPD, may be defined as the muscles of the pelvic floor having increased contractile activity at rest,[114,115] leading to impairment in the ability for the pelvic floor muscles to relax and/or lengthen. These terms are often used

Table 3. A proposed neurogenital testing schema to assist in trigger localization by region

Region of pathology	Genital quantitative sensory testing (QST)*	Non-genital sacral dermatome testing	Bulbocavernosus (BC) reflex latency Testing†
End organ – Region 1	abnormal	normal	abnormal
Perineum/Pelvis – Region 2	abnormal	normal	abnormal
Cauda Equina – Region 3	abnormal	abnormal	abnormal
Spinal cord‡– Region 4	abnormal	abnormal	normal
Brain – Region 5	abnormal	abnormal	normal

*Control for each study is QST of index finger.
†Normal = 30–50 msec.
‡Above conus medullaris.

Table 4. Research shows variability in regard to pudendal nerve anatomy and muscle innervation.[106–108] With sacral or sacrospinal nerve root neuropathies, any of the below muscles and/or functions could be affected.

Pelvic floor & vulvar-vaginal anatomy	Innervation	Potential clinical relevance to PGAD/GPD
Ischiocavernosus	Motor perineal nerve branch of the pudendal nerve. Assists with maintaining a clitoral erection.[102]	Sexual dysfunction, lower urinary tract symptoms (LUTS).
Bulbocavernosus	Perineal nerve branch of the pudendal nerve. Contraction reduces the size of the introitus, contributes to clitoral erection.[102,109] Sensory to the skin of labia majora, minora.	Sexual dysfunction; pain, itching, burning sensations at labia and perineum. Dyspareunia at distal $^1/_3$ of vagina. LUTS
Superficial Transverse Perineal (STP)	Perineal nerve branch of the pudendal nerve	Pain, Itching and/or burning sensation at perineum, LUTS
External Anal Sphincter (EAS)	Inferior rectal nerve branch of the pudendal nerve (motor to EAS and sensory to the distal portion of the anal canal)	Bowel voiding dysfunctions: constipation/ pain or burning with bowel movements/ reduced awareness of defecation/feeling of "golf ball" in the rectum, etc.
Urogenital Diaphragm (Sphincter urethrae, compressor urethrae, urethrovaginal sphincter, and deep transverse perineal)	Perineal branch of the pudendal nerve. External urethral sphincter allows for voluntary control of micturition.[102,110]	LUTS
Anterior Vaginal Wall/Pubic Region	Dorsal branch of the pudendal nerve provides sensory innervation to the clitoral body and glans	Sexual dysfunction, clitorodynia
Obturator Internus	Nerve to obturator internus. Externally rotates and abducts hip. Alcock's canal formed by obturator fascia. Perineal and dorsal nerve to clitoris, and sometimes inferior rectal branches of the pudendal nerve, travel through Alcock's canal before exiting the pelvis.	May potentially affect up to all 3 pudendal nerve branches, as well as referred dysesthesia to urethra, and ipsilateral hip.
Levator Ani Muscles (Puborectalis, Pubococcygeus, Illiococcygeus)	Motor branch of the pudendal nerve[106,110–112] or nerve to levator ani[100,102] or inferior rectal nerve[111]	May contribute to constipation/voiding dysfunction/pain with bowel movement, hemorrhoids, anal fissures, dyspareunia, may be affected with injury to the coccyx
Coccygeus	Nerve to levator ani. Extends coccyx during bowel movement, and flexes coccyx with pelvic floor contraction.	May be affected with injury to the coccyx. May present with coccydynia, gluteal pain with sitting; may contribute to bowel voiding dysfunctions, pain with bowel movement, constipation, deep dyspareunia
Piriformis	Nerve to piriformis. Externally and internally rotates and abducts hip.	Hypertrophy of muscle may occur with certain athletics and compress the pudendal and/or sciatic nerve.[110,113] Along with PGAD/GPD, may present with gluteal and/or hip pain with sitting and sciatica into lower extremity.

synonymously with descriptions of the pelvic floor muscles being "tight," "tense," and/or in "spasm." Note, however, that there can be a hypertonic pelvic floor that is "short" and usually does not demonstrate an increase in contractile activity and therefore can be electrically silent on surface electromyography (SEMG) biofeedback.[116]

A pelvic floor examination includes palpation of the superficial to deep layers of the pelvic floor muscles and associated connective tissue, externally and internally (vaginal and/or rectal). It also includes evaluating the ability of the pelvic floor muscles to contract, relax, lengthen, and their strength, endurance, and coordination.

SEMG or transperineal ultrasound imaging may also be used to confirm overactivity of the pelvic floor muscles. These tools may also be used as a type of biofeedback for patients to learn how to relax their overactive/hypertonic pelvic floor muscles during physical therapy treatment. The advantages of transperineal ultrasound imaging are that it is not painful as there is

no internal sensor required, and as opposed to SEMG, is not associated with interference from other non-pelvic floor muscles. Measurement of the anorectal angle has been shown to correlate with the degree of overactivity/hypertonicity (Figure 9).[117] SEMG or ultrasound imaging should not be a substitute, however, for performing a thorough examination of the pelvic floor and extra-pelvic regions, which will guide pelvic floor physical therapy treatment interventions.

Overactive/hypertonic pelvic floor muscles are typically weak with tender points identified upon examination. Overactive/hypertonic pelvic floor dysfunction can occur asymmetrically and/or in specific individual muscles of the pelvic floor. Overactive/hypertonic pelvic floor muscle dysfunction is also associated with pudendal neuropathy,[110,118] persistent pelvic pain, and vulvodynia,[119,120] as well as musculoskeletal conditions of the lumbosacral spine, pelvic girdle, coccyx, and hips,[121] which may all be associated with PGAD/GPD.

The pudendal nerve is a mixed somatic sensory and motor nerve (S2−S4); pathology in the sensory component may be implicated in chronic pelvic pain disorders, while pathology in the motor component could contribute to pelvic floor dysfunction. Pudendal neuropathy may result from trauma, entrapment, neuroma, or compression.[21,122]

Vascular pathologies such as pelvic congestion syndrome and pelvic arteriovenous malformation (AVM) are risk factors for genito-pelvic dysesthesia. A congenital pelvic AVM may be a contributor to lifelong PGAD/GPD. Examples of diagnostic testing of Region 2 vasculature using color Doppler ultrasound and arteriograms are shown in Figure 9.

Pathology in the abdominal wall somatic afferent nerves, which include the ilioinguinal (L1), iliohypogastric (T12−L1), and/or genitofemoral nerves (L1−2), are potential contributors to PGAD/GPD.[21,123] This pathology may result from abdominal wall nerve injury at lateral laparoscopic or robotic port insertion sites, as has been reported for ilioinguinal and iliohypogastric neuralgia associated with bladder pain syndrome.[21,124]

The pelvic, hypogastric, and vagus nerves innervate the uterus and cervix.[44] Damage to these nerves, as can occur with radical hysterectomy, may be a potential contributor to PGAD/GPD. Pink et al[15] reported that hysterectomy was an aggravating factor for PGAD symptoms.

Anesthesia Testing

If end-organ (Region 1) anesthesia testing is negative, pudendal nerve blocks at Alcock's canal or the ischial spine can be performed with local anesthesia (Figure 7). If symptoms are clinically significantly reduced ("very much better" or "much better"), the implication is that the pudendal neuropathy contributes to the PGAD/GPD. For example, if clitorodynia is a result of a bicycle trauma to Alcock's canal, a clitoral anesthesia test would be negative, and a pudendal nerve block would be positive. If the pudendal nerve block fails to provide clinically significant symptom reduction, pathology further "upstream" is likely (eg, Regions 3, 4, 5) or may be idiopathic.

Neurologic and Vascular Testing

Another strategy to assess for the involvement of the pudendal nerve in PGAD/GPD is to perform a trial with pudendal neuromodulation.[20,66] Abdominal wall nerve blocks of the ilioinguinal, iliohypogastric, or genitofemoral nerves can be performed. If clinically significant symptom reduction is observed, an abdominal wall nerve neuroma should be suspected. If an injury to the pudendal nerve is suspected, then neurogenital testing should be considered (Table 3). For testing the possibility of vascular pathology as the cause of PGAD/GPD, appropriate vascular imaging should be considered. Examples of diagnostic testing of Region 2 vasculature using color Doppler ultrasound and arteriograms are shown in Figure 9.

Region 3: Cauda Equina

Figure 4 describes multiple aspects of history-taking and physical examination that may lead the clinician to suspect that the PGAD/GPD is related to Region 3. Radiculopathy of sacral spinal nerve roots within the cauda equina or sacrum are contributors to PGAD/GPD.[23,24,125] Temporary iatrogenic radiculopathy producing PGAD/GPD symptoms has been noted after sacral neuromodulation.[126]

In 2012, Komisaruk and Lee first reported the occurrence of sacral Tarlov cysts in women with PGAD symptoms, which were previously thought to be incidental radiologic findings.[22,127] Risk factors for Tarlov cysts include a family history of connective tissue disorders (eg, Ehlers-Danlos syndrome)[128] and physical trauma to the pelvic region or lower back. Lifelong PGAD/GPD may be associated with a Tarlov cyst resulting from physical trauma in young patients. Tarlov cysts associated with PGAD/GPD typically form at S2−S3, distal to the dorsal root ganglia and near the internal surface of the foramina, where the dura mater transitions into the weaker perineurium; they are aneurysm-like structures filled with cerebrospinal fluid that contain aberrant S2−S3 fibers from the pudendal, pelvic, and sciatic nerve roots (see Figure 10). Thus, a Tarlov cyst can contribute to clitoral, vaginal, and urethral dysesthesia, including pain. As the S2−S3 component of the sciatic nerve (L4−S3) conveys afferent activity from the buttock, back of the leg, and side of the foot, a Tarlov cyst at S2−S3 can result in dysesthesia and pain in all these regions. Even a relatively small Tarlov cyst irritates some, but not all, of the fibers of the S2−S3 nerve root, resulting in variations of these symptoms. The pressure exerted by the Tarlov cyst against the sacral foramina can result in bone erosion and localized pain (coccygeal pain).[22] A second type of cyst, termed "meningeal diverticulum," forms proximal to the dorsal root ganglia and nerve roots, where the wall of the aneurysm-like structure is dura mater rather than perineurium.[129] Both Tarlov cysts and meningeal diverticula are fluid-filled spaces that are indistinguishable from each other in

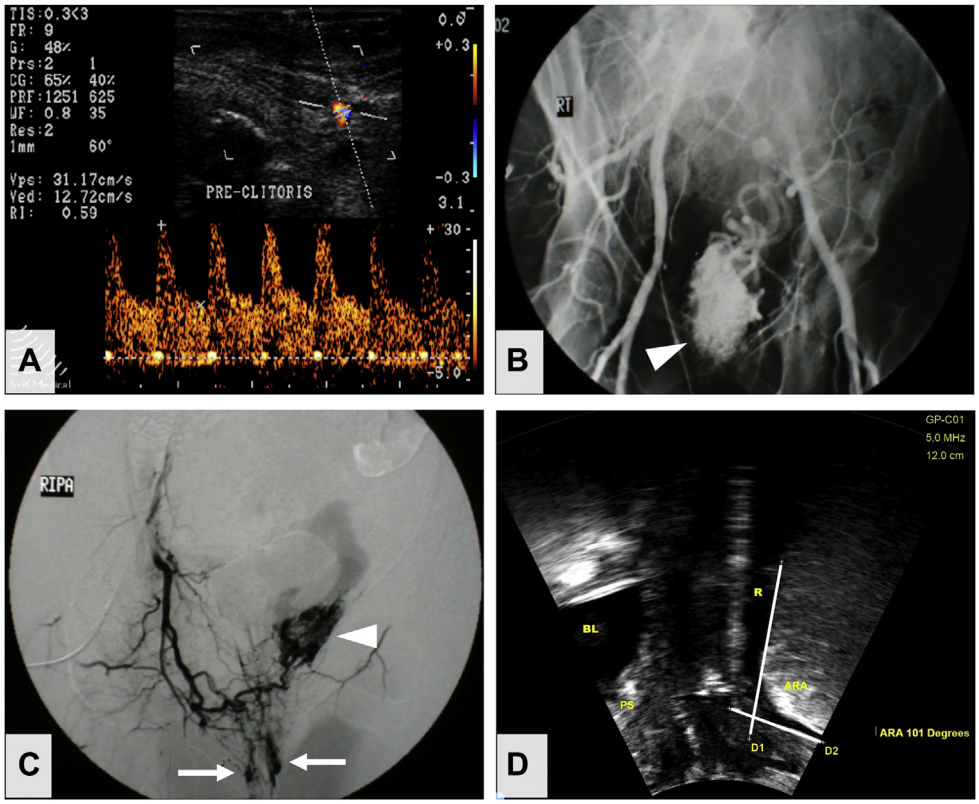

Figure 9. Diagnostic testing in Region 2. A, Color Doppler ultrasound of clitoral cavernosal artery in a woman with lifelong PGAD and left pelvic arteriovenous malformation. B, Aortic arteriogram showing left internal iliac arteriovenous malformation (white arrowhead). C, Selective right internal pudendal arteriogram with visualization of the arteriovenous malformation (white arrowhead) directly communicating with the left and right clitoral corpus cavernosum (white arrows). Visualization of contrast within the clitoral corpora cavernosa, indicating engorgement, is consistent with PGAD symptoms. D, Transperineal ultrasound image showing anorectal angle of 101°, consistent with overactive/hypertonic pelvic floor dysfunction (Image provided by Ramona Horton, PT, DPT). Figure 9 is available in color online at www.jsm.jsexmed.org.

T2-weighted MRIs. Despite these differences, both types of cysts may irritate the passing nerve root fibers, thereby triggering the PGAD/GPD symptoms.

PGAD/GPD symptoms can also be generated by lumbar and lumbosacral intervertebral disc pathologies.[24,60,65,130] These pathologies, best visualized on MRI (using T2-weighted imaging), can include annular tears appearing as high-intensity zones on MRI, nucleus pulposus herniation, spinal stenosis, spondylolisthesis, facet synovial cyst, and others. These intervertebral disc pathologies can be mechanical (disc bulge or herniation impinging against the dura and the nerve roots) or chemical due to annular tear.[125] Annular tears involve extrusion of nucleus pulposus material through the annulus into the epidural space and produce irritation, through the dura, of the nerve roots by inflammatory modulators such as tumor necrosis factor-alpha.[131] The disc herniations and/or annular tears related to these symptoms often appear at L5—S1 and/or L4—L5 spinal levels. Their effect on genital and urinary symptoms is likely mediated by the S2—4 afferent fibers in their course ascending in the cauda equina. In order to optimize the diagnosis of these intervertebral disc pathologies, correlation of the pathology on sagittal and axial and/or coronal views by MRI is essential.

If radiculopathy of the lumbosacral nerve roots is suspected, then neurogenital testing should be considered (Table 3). When appropriate, highly targeted, diagnostic injections[132] can be performed with local anesthetic (eg, 1 cc of 0.25% bupivacaine, preservative-free) at the levels of pathology identified on the MRI. For those with PGAD/GPD with specific lumbar pathology (eg, annular tear), targeted injections into the appropriate location(s) can be performed via transforaminal epidural spinal injections (TFESI). For those with PGAD/GPD with specific sacral pathology (eg, Tarlov cyst), injections are targeted via caudal epidural or perineural spinal injection. These are traditionally performed by pain management specialists.

Surgical treatment of spinal abnormalities can be considered in patients who have a significant clinical response to targeted diagnostic injections (Table 3). If symptoms are clinically significantly reduced within approximately 4 hours after the anesthetic injection ("very much better" or "much better"), the implication is that the cauda equina and/or sacral nerve root

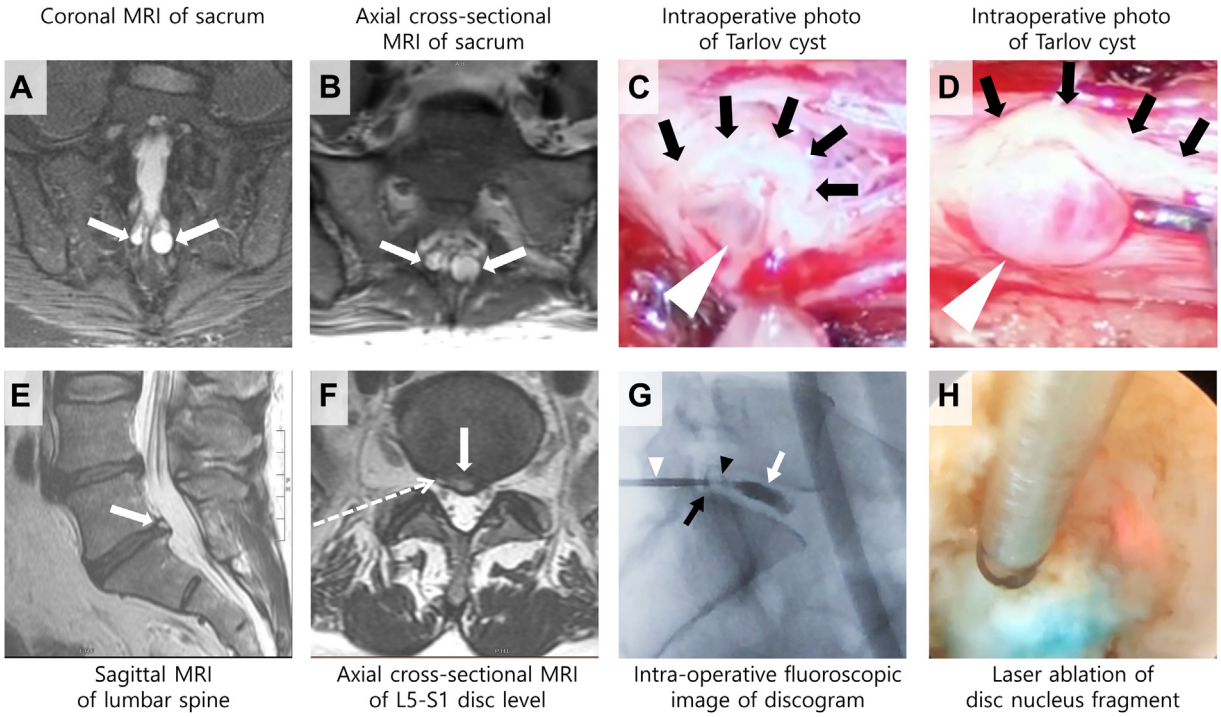

Figure 10. Contributing factors to PGAD/GPD in Region 3. **Tarlov Cysts:** T2-weighted coronal (A) and axial (B) magnetic resonance images (MRI) showing 2 distinct Tarlov cysts (white arrows) at S3. In intraoperative photos, a Tarlov cyst (white arrowhead) is seen emanating from behind the S3 nerve root (black arrows) before (C) and after (D) being released from intradural adhesions. **Annular Tears:** T2-weighted sagittal (E) and axial (F) MRIs showing a high-intensity zone (lighter gray) consistent with an annular tear (white arrows) on the right side of the L5-S1 disc. The route of a diagnostic injection using a targeted, transforaminal epidural approach is indicated by a dashed arrow in panel F. Intraoperative discogram (G) showing dilator (white arrowhead) docked at the posterior aspect of the disc. A fine needle is inserted into the center of the disc (nucleus) to inject contrast media-methylene blue into the nucleus (white arrow), and sequential intraoperative fluoroscopic imaging is used to monitor for leakages through the annular tears and defects. An annular tear is indicated by the thin streak of contrast media (black arrowhead), projecting posteriorly and outlining the outer ring of the annulus (faint darker gray streak perpendicular to the dilator at the black arrow in panel G). Intraoperative photo (H) showing a side-firing YAG-holmium laser (indicated by red area) used to ablate the disc nucleus fragment stained with methylene blue. Figure 10 is available in color online at www.jsm.jsexmed.org.

pathology contribute to the PGAD/GPD. In patients with a positive diagnostic response, surgery may be indicated.

Region 4: Spinal Cord

Figure 4 describes multiple aspects of history-taking and physical examination that may lead the clinician to suspect that the PGAD/GPD is related to Region 4. Spinal cord neurological pathologies are potential contributors to PGAD/GPD[133]; however, to our knowledge, cases associated with PGAD/GPD have yet to be reported in the peer-reviewed literature. The spinal cord extends from the brainstem to the conus medullaris at thoracolumbar level T12—L1. The ascending neural pathways from the genitals through the spinal cord to the brain include the lateral and ventral spinothalamic and spinoreticular tracts.[46,47] As in the case of cauda equina pathologies, we postulate that PGAD/GPD symptoms may also be associated with thoracic and cervical spine pathologies, including annular tears, nucleus pulposus herniation, spinal stenosis, facet synovial cyst, and others. It is suspected that inflammation of the neural pathways in the spinal cord generates the intense sensory activity of PGAD/GPD.[133] Serotonin and norepinephrine neural pathways descend from the brainstem to the spinal cord and modulate aversive sensory activity (eg, the "pain-gate" mechanism). Therefore, SSRI/SNRI administration or withdrawal may affect PGAD/GPD via action on the spinal cord.[134,135]

Neurogenital testing can be performed in those who have PGAD/GPD from lesions in Region 4. MRI imaging of the thoracic and cervical spine can confirm the location of the suspected spinal cord abnormality (eg, herniated disc).

Region 5: Brain

Figure 4 describes multiple aspects of history-taking and physical examination that may lead the clinician to suspect that the PGAD/GPD is related to Region 5. The sensory pathways from the genito-pelvic region to the paracentral lobule and related brain regions include: (1) first-order neurons that convey temperature, pressure, itch, pain, arousal-inducing stimuli from the genito-pelvic region, synapsing at the conus medullaris, or first-order neurons that convey

vibration or light touch that pass in the dorsal column and synapse at the medulla; (2) second-order neurons conveying temperature, pressure, itch, pain and arousal-inducing stimuli, passing in lateral and ventral spinothalamic and spinoreticular tracts, and spinohypothalamic tract, synapsing in the reticular formation, hypothalamus and/or thalamus, or second-order neurons that convey vibration or light touch that pass from the medulla to the thalamus; (3) third-order neurons that convey all this sensory neural activity, synapsing in the paracentral gyrus, insula, cingulate cortex, amygdala, hippocampus, medial preoptic area, ventral tegmental area, and the mesolimbic/mesostriatal systems.[46,58,136–138] Organic brain pathologies associated with PGAD/GPD include traumatic brain injury, epileptic seizures, AVMs, aneurysms, or other space-occupying lesions.[61] These can be assessed by MRI, electroencephalography, and magnetic electroencephalography. Anzellotti et al reported PGAD/GPD symptoms associated with epileptic seizures in a woman.[139] The epileptic focus was in the posterior insular gyrus, a region activated during orgasm in women.[140] Neurogenital testing may be performed in those who have PGAD/GPD from lesions in Region 5 (see Table 3).

Since patients have reported worsening of PGAD/GPD symptoms with exposure to certain sounds (ie, misophonia), other brain pathways may be involved. For example, abnormal sounds (eg, clicking, buzzing, hissing, ringing) and tinnitus have been reported as a corollary of Tarlov cysts.[141] Since Tarlov cysts are filled with fluctuating amounts of cerebrospinal fluid that is in communication with the cochlea via the cochlear aqueduct,[142] it is possible that the anomalous auditory sensations are due to variable flow of cerebrospinal fluid around the auditory nerve endings in the cochlea. Spinal pathologies (eg, bulging intervertebral discs) might also disrupt the flow of cerebrospinal fluid and thereby generate abnormal sounds.

Relevant Medications

In women with PGAD/GPD symptoms, exposure to or withdrawal from SSRIs and/or selective serotonin-norepinephrine reuptake inhibitors (SNRIs) and other central nervous system (CNS)-active medications (eg, lamotrigine) commonly initiates the clinical presentation of the disorder and, in many, further diagnostic studies also reveal contributing pathologies in any of the 5 regions.[15,26–29,76,143–145] This may be explained, in part, by disruption of the serotonergic "pain-gate" system in the brain and/or spinal cord, which could contribute iatrogenically to the disorder. There is a descending serotoninergic/noradrenergic system that originates in the lower brain stem and descends to lower levels of the spinal cord, where the serotonin and norepinephrine activate opioid interneurons that attenuate incoming pain signals.[134] Disruption of this signaling by SSRIs/SNRIs could potentially exacerbate PGAD/GPD symptoms.

Another medication that commonly triggers the disorder is trazodone, a widely used treatment for conditions such as depression and insomnia. Trazodone is associated with priapism (persistent genital engorgement) in both women (clitoral) and men (penile), in part, due to its alpha-1 adrenergic antagonism.[25,146–148] In addition, trazodone's inhibitory effects on histamine transmission in the brain would be expected to increase dopamine-mediated processing of genito-pelvic sensations, leading to intensified genital arousal. Discontinuation of trazodone has been associated with the cessation of PGAD/GPD symptoms. Use of these and other psychiatric medications that contribute to priapism in women and men should be considered as potential contributors to PGAD/GPD.

Relevant Psychologic Factors

Psychologic factors contribute to the development, maintenance, and consequences of PGAD/GPD. In 2007, Leiblum and Chivers proposed a psychological model of the development of PGAD/GPD.[149] They noted that negative appraisals of spontaneous genital arousal may lead to increased anxiety and sympathetic nervous system activity, which in turn increases genital arousal sensitization and narrows attention to these sensations. A small number of studies have noted high rates of past sexual abuse in samples of women with PGAD/GPD (46.7–52.6% report childhood sexual abuse).[11,15] Such experiences may negatively influence evaluations of arousal or emotional response to normative or dysfunctional spontaneous feelings of genital arousal. Carvalho and colleagues found that individuals with PGAD/GPD report more negative thoughts, increased negative affect, and decreased positive affect during sexual activity than women without PGAD/GPD.[8] Other studies have found high rates of pre-existing difficulties with mood, anxiety, and stress.[3,11] Indeed, many women with PGAD/GPD self-report that stress (33.98%), anxiety (29.13%), and loss (13.59%) were the initial triggers of their symptoms.[11]

In addition, psychological factors may mediate or maintain PGAD/GPD symptoms and associated distress. Such factors may include personality traits (greater neuroticism and lower openness) or sexually conservative beliefs,[8] as well as catastrophizing of the arousal sensations[3,10] and hypervigilance to genital arousal sensations.[11] These findings may lend some initial support to the utility of the fear-avoidance model[150] in understanding PGAD/GPD symptoms (Figure 11).[41]

This model suggests that if distressing sensations of arousal are interpreted as threatening (via catastrophizing, fear),[3] as indicated in Figure 11 by the loop on the left (in pink), one may start avoiding triggers or behaviors related to arousal and develop increased hypervigilance to arousal sensations.[11] This avoidance and hypervigilance may lead to negative psychosocial outcomes (eg, anxiety, depression, interference with work, and socializing),[3,10] which may contribute further to the experience and awareness of arousal sensations, maintaining the cycle. Note that catastrophizing is assumed to be influenced by negative affectivity and threatening arousal/illness information (eg, "there is no cure"'). Individuals with lower levels of fear and catastrophizing (right side of the model in Figure 11, in blue) would theoretically be able to quickly engage in symptom confrontation and re-engage in daily activities with lower levels of symptom severity and higher

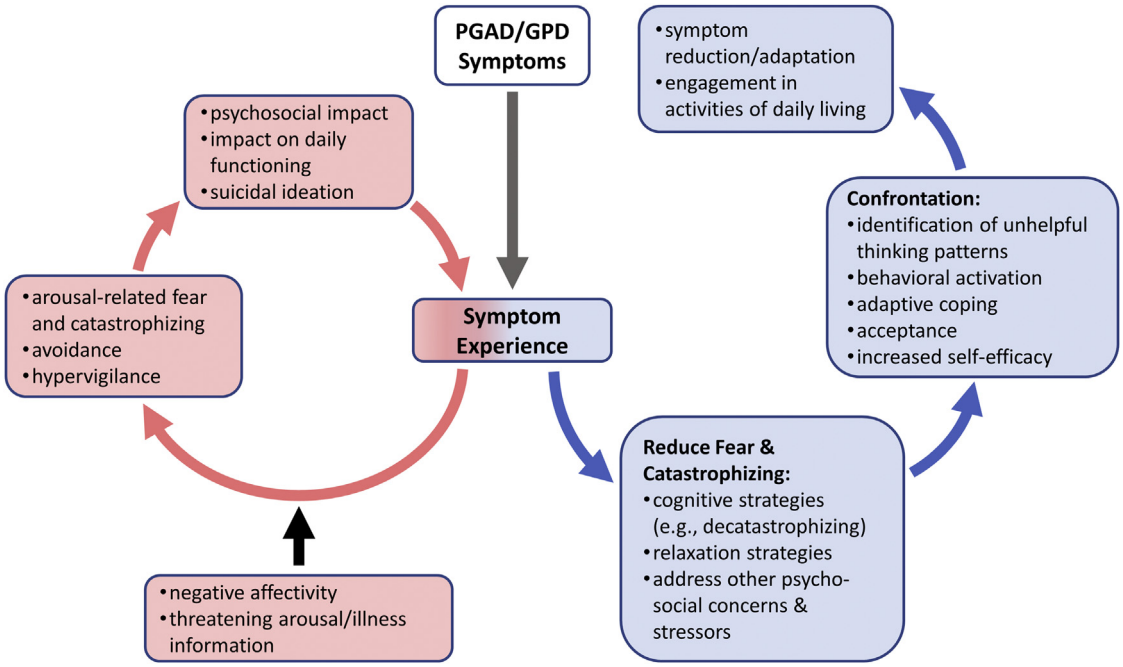

Figure 11. The fear-avoidance model, modified for PGAD/GPD. The left side of the model (pink) describes factors that maintain the fear-avoidance cycle, and in turn, PGAD symptoms. The right side of the model (blue) describes factors that move one out of the cycle, promoting symptom reduction and adaptation. Figure 11 is available in color online at www.jsm.jsexmed.org.

adaptation. In the context of this model, fear reduction may be facilitated by cognitive and behavioral strategies, such as decatastrophizing of arousal-related thoughts, reduction of hypervigilance and anxiety through graded exposure exercises, relaxation, and cognitive restructuring. In addition, addressing other psychosocial concerns and stressors is recommended. This process could, in turn, help with symptom confrontation, which includes changing unhelpful thinking strategies and increasing behavioral activation, adaptive coping, acceptance, and self-efficacy.

This model has been applied to other forms of genito-pelvic dysesthesia[151,152] which is not surprising, given that some have noted similarities between PGAD/GPD and other forms of chronic vulvar dysesthesia characterized by pain.[51]

TREATMENT

In a comprehensive treatment approach to PGAD/GPD, the overall role of the clinician is to use a biopsychosocial management model, including psychological, interpersonal, sociocultural, neurological, vascular, and/or endocrinological aspects of reducing the PGAD/GPD and alleviate the bother and distress (Figures 3 and 4). Levels of evidence for associated/contributing factors III or higher, and grades of recommendation for treatments C or higher are provided in Table 1. All other associated/contributing factors and treatments discussed in this consensus report and not included in this table are based on expert opinion.

While the diagnostic algorithm begins with a detailed assessment of Regions 1 and 2 due to the usual location of the presenting genito-pelvic symptoms, the panel agreed that the treatment algorithm should begin with Region 5, especially since psychological strategies have minimal risk and are beneficial.[62] In some patients, the clinician may initiate treatment for a specific trigger for the PGAD/GPD that was identified within regions 1–4 during the diagnostic process. Nevertheless, the panel agreed that psychological interventions should be used in parallel with medical/surgical interventions throughout the treatment process.

For treatment strategies that involve more than minimal risk, the risks and benefits of the procedures, anticipated recovery time, realistic outcomes (based on empirical research when available), and costs should be discussed, and the patient's informed consent should be obtained. The clinician should be prepared to discuss alternative options and make appropriate referrals based on the patient's wishes.

Psychological Treatment Strategies

Biologically-focused clinicians should encourage patients to seek professional mental health care to provide coping and other strategies to prevent unnecessary patient demise, as PGAD/GPD is uniquely associated with high suicidality. Psychological treatment strategies for Region 5 can be utilized to help the patient manage and cope with the symptoms of PGAD/GPD and its associated distress.[62] Cognitive-behavioral therapy (CBT) has been found to be successful in reducing pain intensity and distress in women with genito-pelvic pain[70]; therefore, its use should be considered for reducing arousal levels and distress in those with PGAD/GPD. CBT involves providing the patient

with information on the biopsychosocial nature of persistent arousal symptoms, the effects of the symptoms on sexual and nonsexual activities, and the role of psychological factors (eg, symptom catastrophizing) in the maintenance of symptoms. Patients can be advised to keep a symptom diary based on individual factors (eg, thoughts, feelings, behaviors, context, menstrual cycle phase) that may play a role in increasing or decreasing their symptoms, which can, in turn, promote self-efficacy and perceived control over the symptoms. CBT also teaches skills related to thoughts and includes targeting existing coping strategies that lead to increased symptom severity (eg, catastrophizing, hypervigilance). Although CBT may be useful for some patients, for others, support, such as decreasing external stressors, addressing any past history of trauma, and exploring other psychosocial concerns can help the patient manage their symptoms while they are searching for medical help for their symptoms. Relaxation exercises (eg, deep breathing, progressive muscle relaxation) are often practiced in session with the goal of the patient engaging in these exercises in their daily life. Furthermore, strategies that focus on defusing negative emotions, thoughts, and self-blame should be incorporated into the therapy. Mindfulness practice may also be beneficial in teaching the patient to "sit" with the distressing sensations through acceptance and self-compassion.[62]

It is important to allow the patient to define their own goals in therapy. Many of those with PGAD/GPD are solely interested in symptom reduction and not in restoring their sexuality. If sexuality is a goal, then exploring the differences between their distressing and pleasurable instances of sexual response is key. If the patient is in a relationship, involving their partner in therapy can be beneficial in, at the very least, ensuring that their partner understands the nature of PGAD/GPD. The partner should appreciate that PGAD/GPD is not hypersexuality, arousal sensations can be distressing, and the partner is not the cause of the symptoms. In the relationship context, the effects of the PGAD symptoms on the partner should be explored, and relationship dynamics that play a role in increasing symptom-related distress should be addressed.[62]

There are cases in which distress is central in the presentation of the patient. In these cases, this distress should be targeted via CBT and components of other therapeutic modalities (eg, distress tolerance). Therapy would focus on the reasons for the heightened distress (eg, trauma) while also addressing other potential contributing factors[70] and integrating the skills mentioned above for symptom reduction. In addition, conservative strategies may include yoga, acupuncture, hypnotherapy, and other alternative medicine approaches.[153]

Region 5: Brain

Pharmacologic treatment strategies for Region 5 (Tables 5 and 6) can be utilized, if appropriate, in parallel with psychological treatment strategies to help the patient manage and cope with the symptoms of PGAD/GPD and its associated distress.[154]

As there are no medications approved for the safe and efficacious management of PGAD/GPD, these are all off-label treatments. However, based on case reports and expert opinion, symptom reduction may be associated with their judicious use, with attention to adverse effects, toxicity, drug interactions, potential for abuse, and medical and psychiatric comorbidities. For example, efficacy in reducing symptoms has been reported using medications, including varenicline and zolpidem,[168] that suppress dopaminergic tone in the medial preoptic area based on animal studies.[161,169] Since dopamine in the medial preoptic area is the main driver of autonomic switching between sympathetic and parasympathetic tone in the regulation of genital blood flow, dopamine-suppressing medications appear to blunt further processing of genito-pelvic sensations in other regions of the brain.[136,137]

Depending on specific combinations of PGAD/GPD symptoms (eg, arousal, itch, pain, mood problems, pelvic floor hypertonicity, leg/back pain, and/or restless legs), it may be possible to develop an empirical strategy guiding which medication(s) to use. For example, if PGAD/GPD symptoms are primarily genito-pelvic arousal, consider agents that activate GABA and/or inhibit ion channels, such as clonazepam, gabapentin, pregabalin, lamotrigine, oxcarbazepine, or topiramate.[155] If restless legs are associated with genito-pelvic arousal, consider varenicline.

In women with PGAD, there are case reports of use of weak GnRH receptor agonists (eg, leuprolide) that desensitize the receptors and thereby inhibit gonadotropin secretion.[155,170] These agents, which indirectly induce sex steroid hormone deprivation, may act by reducing feelings of genital arousal, but there are numerous side effects to this therapy, especially in younger women. These side effects include hot flashes, headaches, osteoporosis, vaginal atrophy, and suppression of ovulation and menses in reproductive-age women. These agents should not be used for more than 1 year, given the risk of osteoporosis.

If PGAD/GPD symptoms are primarily genito-pelvic pain, consider opioid agonists such as tramadol or hydrocodone, as opioids are effective analgesics, and based on expert opinion, are effective in reducing PGAD/GPD symptoms. However, concern for opioid addiction needs to be considered. If symptoms include genito-pelvic pain and mood problems, consider SNRIs such as duloxetine or paroxetine and/or tricyclic antidepressants such as nortriptyline, amitriptyline, or clomipramine.[82,158,171] If PGAD/GPD symptoms are associated with leg and back pain, implying a spinal cord site of action (Regions 3 and 4), a combination of an SNRI (eg, duloxetine) and baclofen suppository could activate the pain gate mechanism plus GABAergic inhibition in the conus medullaris of the spinal cord. If PGAD/GPD symptoms are associated with pelvic floor dysfunction, consider oral muscle relaxants such as methocarbamol or cyclobenzaprine, baclofen and/or diazepam suppositories, and/or botulinum neurotoxin A intramuscular injection as strategies to temporarily reduce symptoms.[172] Although a rare presentation, should hyperthyroidism be considered associated with the PGAD/GPD, one

Table 5. Off-label pharmacological treatment strategies for symptom control of PGAD/GPD based on expert opinion. See package insert for dose ranges, adverse events, toxicity, drug interactions, contraindications, potential for abuse, and other safety information.

Category	References	Hypothesized Region of action	Commonly Prescribed medications	Potential Dosing Regimen
Anticonvulsants and non-opioid inhibitors of neurotransmission	122,139,155,156	5	carbamazepine gabapentin pregabalin topiramate lamotrigine oxcarbazepine	100 mg po, bid 100 mg po, tid; (maximum dose of 3,600 mg/d) 50 mg po, tid (maximum dose of 300 mg/d) 100 mg po, bid 50 mg po, qd; increase as needed 300 mg po, bid
Benzodiazepine GABA-ergic activators	157	5	clonazepam	0.25 mg bid
Non-benzodiazepine GABA-ergic activators	68	5	zolpidem	1 mg (compounded) tid or qid
Opioid Inhibitors of neurotransmission		4 - 5	tramadol hydrocodone	50 mg po, bid or tid 5–10 mg po, qd (in combination with acetaminophen, 325 mg)
Tricyclic antidepressants	82	5	amitryptiline clomipramine desipramine nortriptyline	10 mg po qd (maximum dose of 150 mg/d) 25 mg po, qd (maximum dose of 250 mg/d) 100 mg po, qd (maximum dose of 300 mg/d) 25 mg po, tid (maximum dose of 150 mg/d)
SSRI/SNRI	156,158,159	5	duloxetine paroxetine	20 mg po, bid (maximum dose of 60 mg/d) 12.5 mg po, qd (maximum dose of 50 mg/d)
Dopamine antagonists or lowering agents	22,79,160,161	5	paliperidone risperidone varenicline	6 mg po, qd (maximum dose of 12 mg/d) 2 mg po, qd (maximum dose of 16 mg/d) 0.5 mg po, qd (maximum dose of 2 mg/d)
Specific Indications				
Hyperthyroidism		5 N/A	methimazole propranolol	5 mg po, tid 40 mg po, bid (starting dose)
Restless leg syndrome				
Dopamine agonist	162	3–5	pramipexole	0.125 mg po, tid
Pelvic floor dysfunction		2		
Benzodiazepine			diazepam	2.5–10 mg, qd, vaginal/rectal suppository; in conjunction with physical therapy
GABA agonist	163,164		baclofen	20 mg, qd, vaginal/rectal suppository; in conjunction with physical therapy
Anti-cholinergic (neurotoxin)	165–167		botulinum toxin A	50–200 units, im, every 3 months

(continued)

Table 5. Continued

Category	References	Hypothesized Region of action	Commonly Prescribed medications	Potential Dosing Regimen
Menopause		1		
Sex steroid hormone receptor agonists			systemic estradiol	biologically identical estradiol
			systemic testosterone	biologically identical testosterone at one-tenth approved dose for men
			systemic progesterone	biologically identical progesterone
			systemic estradiol & progesterone	biologically identical estradiol and progesterone
			local vestibular/vaginal	compounded estradiol (0.01–0.03%)/testosterone (0.1%), topical to vestibule, qd
				local estradiol
				local DHEA suppository

option would be to consider methimazole (a thyroid hormone synthesis inhibitor), as this has been reported to treat premature ejaculation[173] (an excitatory condition in men similar to PGAD/GPD in women). In addition, hyperthyroidism can be associated with adrenergic hyperstimulation of the cardiovascular system that may result in persistent genital arousal. Thus, this condition may also be treated with beta-adrenergic receptor antagonists, a long-established and widely used strategy to manage hyperthyroidism.[174]

Non-surgical/non-pharmacologic strategies for this region include electroconvulsive therapy[31,32] and transcranial magnetic stimulation.[161,175,176] For PGAD/GPD patients with traumatic brain injury, epileptic seizures, arteriovenous malformations, aneurysms, or other lesions, neurological and neurosurgical consultation is recommended.

Regions 3 and 4: Cauda Equina/Spinal Cord

Non-surgical, non-pharmacologic strategies for pathologies in these regions are shown in Figure 4.[177,178] For patients who do not improve with non-operative treatment, spinal surgery consultation should be considered. In patients with symptomatic Tarlov cysts, a type of spinal meningeal cyst, neurosurgical intervention has been reported to be beneficial in 10 of 11 patients.[30] Independent of the type of meningeal cyst, the presence of nerve root compression appeared to be the underlying pathophysiology of the PGAD.[30]

In patients with symptomatic intervertebral disc pathologies (eg, annular tears, nucleus pulposus herniation), a preliminary study of 14 patients with PGAD treated via transforaminal endoscopic discectomy surgery, 12 patients had improvement and 8 experienced marked improvement based on the patient global impression of improvement (very much better or much better).[23] In these cases, surgery of even subtle, relatively mild abnormalities such as annular tears and small Tarlov cysts resulted in significant improvement of PGAD/GPD symptoms.[23]

Region 2: Pelvis and Perineum

Pelvic Floor

Pelvic floor physical therapy can help to improve pelvic floor muscle function in patients with PGAD/GPD and improve their daily activity (Figure 12).[19] Pelvic floor physical therapy is considered a treatment standard for those with overactive/hypertonic pelvic floor dysfunction and pudendal neuropathy,[118] one of the possible contributors to PGAD/GPD. Treatment consists of a combination of education, manual therapy, therapeutic exercises, and neuromuscular re-education (Figure 12). Initially, specific activities, positions, and movements that are found to be symptom triggers (ie, squatting, sitting) should be avoided, modified and/or paced in order to reduce the severity of the dysesthesia. Care should be taken not to promote kinesiophobia and hypervigilant behavior to avoid exacerbating the PGAD/GPD. Movements, exercises, and activities that are found

Table 6. Off-label medications, targeted symptoms, and primary mechanisms of action

	Symptoms associated with PGAD/GPD*					Primary mechanism of Action†						
Commonly used medications	Genito-pelvic arousal	Genito-pelvic Itch/Pain	Mood problems	Restless legs	Pelvic floor dysfunction	GABA (Inhibitory)	Opioid	5-HT	NE	DA	ACh	Ion channels
Gabapentin	+	+				+						
Pregabalin	+	+				+						
Clonazepam	+					+						
Carbamazepine	+	+										−
Zolpidem	+					+				−		
Lamotrigine	+											−
Oxcarbazepine	+											−
Topiramate	+					+						−
Tramadol		+					+					
Hydrocodone		+					+					
Duloxetine		+	+					+	+			
Paroxetine		+	+					+	+			
Nortriptyline		+	+					+	+			
Clomipramine		+	+					+	+			
Amitriptyline			+					+	+			
Desipramine			+						+			
Varenicline	+			+						+/−	+	
Paliperidone			+							−		
Risperidone			+							−		
Pramipexole				+						+/−		
Baclofen Suppository					+	+						
Diazepam Suppository					+	+						
Botulinum Toxin A					+						−	

*Symptoms: Drug is effective against symptom (+).
†Drug action: Drug increases neurotransmitter (+); drug decreases neurotransmitter or channel (−).

to be symptom reducers (ie, walking, diaphragmatic breathing, relaxation exercises), should be performed regularly, as well as other symptom self-management tools [ie, home transcutaneous electrical nerve stimulation (TENS) unit, cryotherapy, heat].

Physical therapists who treat patients with pudendal neuropathy, persistent pelvic pain, and other chronic pain-related diagnoses routinely provide pain education based on current neuroscience literature [14–20].[74,179–184] Based on shared sensory pathways (see Pathophysiology section), this same treatment strategy may be implemented for the patient with PGAD/GPD. Empowering the patient with knowledge about why the dysesthesia may occur, and how it can be modulated, helps to facilitate self-efficacy in symptom management and can reduce the patient's anxiety around the symptoms. This includes understanding that a flare in symptoms is not necessarily indicative of actual tissue damage or worsening of the condition and how other factors (previous experiences, psychosocial issues, poor sleep, stress) can contribute to the dysesthesia.[74,179,183] The patient with overactive/hypertonic pelvic floor dysfunction and pudendal neuropathy may have chronic constipation and chronic straining during toileting, which can further exacerbate PGAD/GPD symptoms.[72,113,185] Pelvic floor physical therapists can instruct in toileting positioning and breathing techniques to promote pelvic floor relaxation for improved bowel emptying. Education on diet/fiber/water intake and self-abdominal massage may also be provided.

Effective communication between the clinician and patient is essential throughout physical therapy treatments, so that non-threatening/non-noxious stimuli are introduced to the patient's nervous system, and treatment does not elicit a muscle guarding response or increase the patient's anxiety. Manual therapy techniques (Figure 12) should focus on the pelvic and extra-pelvic tissues found on the physical exam that generated the patient's dysesthesia.

Therapeutic exercises and neuromuscular re-education (Figure 12) should focus on relaxation/lengthening of the overactive/hypertonic pelvic floor[104,179,186] and improving any extra-pelvic impairments in stability, strength and/or endurance that may be contributing to the patient's pelvic floor dysfunction and limiting functional activities. Care should be taken to monitor symptoms (eg, during stretching interventions), as sustained holds or deeper ranges of motion could exacerbate the dysesthesia.

Concomitant therapy could include the use of trigger point injections, dry needling, vaginal or rectal suppositories of diazepam and/or baclofen, and/or pelvic floor muscle injection of botulinum neurotoxin A. These, along with pelvic floor physical therapy, can result in the reduction of the high tone pelvic floor dysfunction and resolution of PGAD/GPD symptoms.

Pudendal Nerve

Non-surgical and surgical treatments for pudendal neuropathy are shown in Figure 3.[177,178] Pudendal nerve blocks without patient sedation can assess the ability of the nerve block to achieve clinically significant symptom reduction in real time. Should local anesthesia pudendal nerve block reduce symptoms, a long-lasting steroid injection (eg, triamcinolone acetonide 80 mg) may then be administered.[187,188] Peters et al suggest that modulating the pudendal nerve can improve voiding dysfunction, pelvic pain, and symptoms of PGAD/GPD.[66,189] In a case series reported in 2018, 6 patients with PGAD/GPD were treated with pudendal neuromodulation, and 3 had clinical improvement. Historically, prior to pudendal nerve modulation, a case report in 2016 showed improvement in PGAD/GPD in a patient using sacral neuromodulation.[190] In appropriate cases, based on magnetic resonance neurography, pudendal nerve entrapment surgery may be considered to release the nerve compression and thereby reduce symptoms.[191,192]

Pelvic Congestion/AVM

Treatment for vascular pathophysiologies such as pelvic varices or pelvic arteriovenous malformations are performed by vascular interventionalists using therapeutic embolization strategies.[133,193,194]

Abdominal Wall Nerves

If the provider suspects that abdominal wall nerves (eg, ilioinguinal, iliohypogastric, and genitofemoral nerves)[195] are a source of the PGAD/GPD pathology, neurolysis of the damaged nerve may be considered.

Region 1: End Organ

Therapies involving region 1 are summarized in Figure 3.

Clitoral Pathology

Patients with PGAD/GPD symptoms associated with clitorodynia may have balanitis and/or clitoral adhesions between the prepuce and glans.[196] Treatment of underlying balanitis can be accomplished with antifungal, antibacterial and/or local steroid therapy. The balanitis may recur if there are underlying clitoral adhesions present. Such adhesions may be released in an office setting under local anesthesia using microfine Jacobson mosquito forceps, allowing the removal of any foreign bodies and/or keratin pearls. Clitoral adhesion release may also be accomplished in the operating room through dorsal slit surgery in appropriate cases.[67,196] For women with suspected clitorodynia associated with dorsal nerve neuropathy, treatment strategies may include repeated local anesthesia/steroid nerve blocks. There are several reports of success using peri-clitoral subcutaneous administration of botulinum neurotoxin A in women with PGAD/GPD.[165,197] The mechanism has not been elucidated but may be primarily neurological (eg, inhibition of the release of pain neurotransmitters at the first synapse in the conus medullaris).[198] Should all conservative strategies fail, lysis of the dorsal nerve of the clitoris may be considered.[21,123]

Although some desperate patients with PGAD/GPD may request clitoridectomy, we emphasize that there are no data

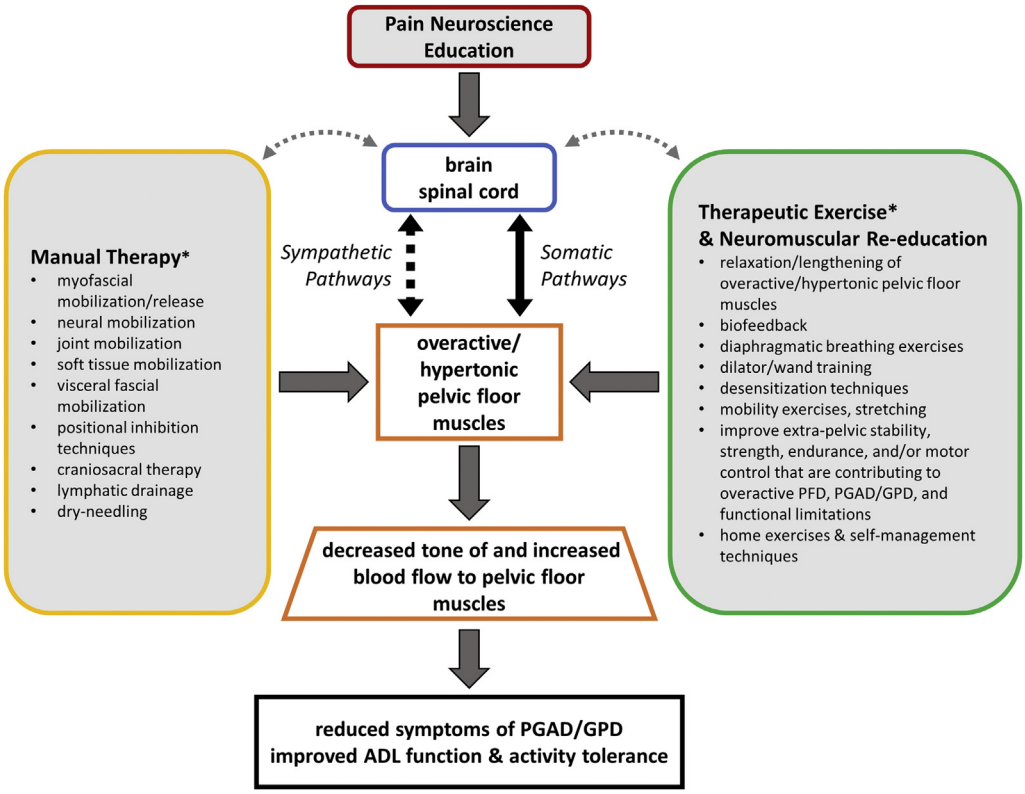

Figure 12. Overview of pelvic floor physical therapy treatment for PGAD/GPD. Manual therapy is targeted to tissues that contribute to and reproduce PGAD/GPD on physical exam in pelvic and extra-pelvic regions and/or are along the pathway of peripheral nerves that correlate with the patient's dysesthesia. Manual therapy, therapeutic exercise, and neuromuscular re-education impact the CNS through proprioceptive feedback and may have additive or synergistic effects on the reduction of PGAD/GPD symptoms and increased ADL function. ADL = activities of daily living. *Use techniques that introduce non-threatening/non-noxious stimuli to the patient's nervous system. Figure 12 is available in color online at www.jsm.jsexmed.org.

supporting this therapy as safe or effective.[49,57] It is also likely that the dysesthetic symptoms may persist or be exacerbated.

Vulva, Vestibule, Vagina, Urethra, and Bladder

The treatment of pathology within the vulva, vestibule, vagina, urethra, and/or bladder associated with PGAD/GPD should be focused on their specific underlying pathophysiology. For example, for the treatment of vestibulodynia, the recent consensus nomenclature emphasizes that *"treatment should be chosen according to the characteristics of the individual case and the possible associated factors, rather than as a 'one size fits all' approach."*[55] For example, physical therapy could be recommended if musculoskeletal factors are suspected, hormonal therapy may be recommended if endocrinological factors are suspected, ultrapotent corticosteroids may be recommended if dermatological factors are suspected, and surgery could be recommended if neuroproliferation is thought to be the main contributing factor. Concerning neuroproliferative vestibulodynia, Bornstein has characterized this disorder histologically by observing a significantly increased density of mast cells and nerves concentrated at the junction between the basal cells of the vestibular stroma when compared to a control population.[85] Although the etiology of the mast cell accumulation and sensory nerve ending proliferation is not known, it may involve genetic, immunological, or other factors.[84,199] Hypothetically, this high density of mast cells may release and/or activate growth factors that result in the proliferation of supernumerary sensory nerve endings throughout the vestibular stroma. Activation of these nerve endings (eg, by otherwise innocuous pressure from sitting) may lead to aversive intensity of sensory activation leading to PGAD/GPD. Medical therapy for this condition may include topical agents (eg, capsaicin, gabapentin). Surgical therapy may include complete vestibulectomy utilizing right and left anterior repair and posterior repair with a vaginal advancement flap to eliminate all the vestibular tissue containing the excessive mast cell accumulation and sensory nerve ending proliferation.[200] Current diagnostic criteria and up-to-date treatment recommendations for vestibulodynia and other urogenital disorders of the vagina, urethra, and bladder are described elsewhere.[69,201]

CONCLUSION

PGAD/GPD is associated with significant morbidity, including impaired activities of daily living, impaired cognitive-emotional states, and high rates of catastrophization, depression, anxiety, and suicidal ideation. Multinational

epidemiological data suggest a substantial number of women worldwide (approximately 0.6−3%) may be affected by PGAD/GPD. However, PGAD/GPD remains largely unrecognized by both healthcare practitioners and the lay public. Although there is a lack of research concerning the underlying pathophysiology of PGAD/GPD, there is accumulating clinical evidence that patients can be safely and effectively managed.

The ISSWSH expert consensus panel recommended: (1) maintaining the term PGAD as the primary condition and also introducing the term "genito-pelvic dysesthesia" (GPD) to provide a more inclusive nomenclature and management strategy; (2) reducing the criterion for the duration of bothersome symptoms from 6 months to 3 months; (3) classifying risk factors into 5 contributing regions (end organ, pelvis/perineum, cauda equina, spinal cord, and brain); (4) a process of care diagnostic algorithm that begins with the end organ (Region 1) and systematically examines Regions 2− 5 to localize the origin of the dysesthesia through strategies that elicit and/or clinically significantly reduce symptoms; and (5) a process of care treatment algorithm that emphasizes the overall guiding principle in which both psychological and medical interventions (and others, as appropriate) should be used in parallel throughout the process.

The primary strength of this ISSWSH consensus review and process of care is the characterization of PGAD/GPD by a multidisciplinary expert panel, directed by a society whose primary focus is women's sexual health. Additional strengths include a thorough analysis of existing international literature and the incorporation of the clinical experience of these experts through extensive interactive sessions utilizing the modified Delphi method.

The main limitations are the dearth of knowledge concerning many aspects of this condition and that the current literature consists primarily of case series and expert opinion. There are a lack of randomized, controlled studies, rationally-based pharmacotherapy (mainly empirically-based), understanding of specific brain mechanisms involved, understanding of the various etiologies, long-term follow-up studies of various therapies, and knowledge of sensory neurotransmitters (eg, as targets of pharmacotherapy).

Future research directions for investigation and management of PGAD/GPD include: (a) large-scale studies of symptom prevalence from different cohorts, countries, and cultures; (b) development of validated instruments for diagnosing subtypes of PGAD and assessment of treatment outcomes; (c) longitudinal studies to understand the natural history of how PGAD/GPD changes over time and the factors that predict these changes; (d) investigation using brain imaging to understand how pleasurable genital sensations become aversive; (e) clinical and laboratory investigation (eg, investigation of pharmacological mechanisms, development of animal models) examining the neurological pathophysiology of the 5 regions; (f) examination of the fear-avoidance model and other psychological factors related to PGAD/GPD that might provide cost-effective, accessible, and minimally invasive treatment options (eg, perceived control, self-efficacy, coping strategies, partner factors, cultural factors); (g) systematic studies of biopsychosocial treatment efficacy and safety (eg, randomized, controlled trials, with long-term follow-up); and (h) extending the investigation and management of PGAD/GPD to patients of diverse sexes and genders.

Since PGAD was first reported in 2001, clinical treatment strategies have vastly expanded, providing a rational basis for managing this condition in many patients. Yet, it should be emphasized that this process of care for PGAD/GPD is limited to consensus expert opinion, in part, due to the lack of awareness of the condition and its impact, the paucity of research, absence of large scale studies on any given therapy, and inadequate research support. Multiple and varied etiologies also preclude the development of a single treatment strategy and necessitate an individualized, biopsychosocial approach. Increasing awareness of this condition, combined with expanding clinical experience and research efforts stand to improve patient outcomes, may enable affected individuals to have an improved quality of life.

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This consensus guideline is dedicated to both Dr Sandra Leiblum and Dr Marcel Waldinger. Dr Leiblum died tragically on January 28, 2010, after sustaining injuries from an accident. Dr Leiblum was the first president of ISSWSH and the first to characterize PGAD. Dr Leiblum was the voice and the body of research and clinical expertise that defined ISSWSH. She also provided ISSWSH with the experience of a pioneer who entered the field of sexual medicine at a pivotal time in its history. Dr Marcel Waldinger passed away on May 1, 2019. Dr Waldinger published numerous critical papers in this area and was an active participant at the PGAD consensus panel meeting in March 2019 in Atlanta. He was an enthusiastic scientist/clinician dedicated to the treatment of PGAD, passionate about helping his patients and working cooperatively to further knowledge in the field. Dr Waldinger was a member of ISSWSH since its inception in 1998. We are indebted to and inspired by the work and lives of both Dr Leiblum and Dr Waldinger (Figure 13).

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Dr. Sandra Leiblum Dr. Marcel Waldinger

Figure 13. Dr Sandra Leiblum and Dr Marcel Waldinger. Figure 13 is available in color online at www.jsm.jsexmed.org.

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