Textbook of Rare Sexual Medicine Conditions

Yacov Reisman
Lior Lowenstein
Francesca Tripodi
Editors

Springer

Textbook of Rare Sexual Medicine Conditions

Yacov Reisman • Lior Lowenstein
Francesca Tripodi
Editors

Textbook of Rare Sexual Medicine Conditions

Springer

Editors
Yacov Reisman
Flare Health
Amstelveen, The Netherlands

Francesca Tripodi
Institute of Clinical Sexology
Rome, Italy

Lior Lowenstein
Department of Gynecology
Galilee Medical Center
Nahariya, Israel

ISBN 978-3-030-98262-1 ISBN 978-3-030-98263-8 (eBook)
https://doi.org/10.1007/978-3-030-98263-8

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

The *Textbook of Rare Sexual Medicine Conditions* represents an important and useful addition to our literature. While all of the conditions discussed are well known to the sexual medicine specialist, many of them are unknown to physicians in non-specialized practice.

The chapters covering a broad array of problems are written and edited by authorities in the field of sexual medicine. While it is true that the pathophysiology of most of these conditions is poorly elucidated, a thorough understanding of the prevalence, presentation, and possible management strategies will be very useful to all practitioners who see men and women in their practice. The book is particularly useful by including chapters on recently discovered sexual dysfunctions, such as persistent genital arousal disorder, post-SSRI sexual dysfunction, post-finasteride syndrome, post-orgasmic illness syndrome, post-orgasmic headache, and orgasmic anhedonia, all of which are likely to be unknown to most clinicians. It is my hope that in several years' time, for the next edition of this book, we will have a far greater understanding of the causes of these conditions, which cause so much distress for patients.

Sexual and Reproductive Medicine, Urology Service
Memorial Sloan Kettering Cancer Center
Manhattan, NY, USA

John P. Mulhall

Contents

1 Introduction 1
Yacov Reisman, Francesca Tripodi, and Lior Lowenstein

2 The Biopsychosocial Approach in Sexual Medicine Disorders 7
Francesca Tripodi, Yacov Reisman, and Lior Lowenstein

3 Penile Dysmorphic Disorder (PDD) 19
James Yianni and David Veale

4 Persistent Genital Arousal Disorder/Genitopelvic Dysesthesia 37
Caroline Pukall, Barry Komisaruk, and Irwin Goldstein

5 Post-SSRI Sexual Dysfunction (PSSD) 51
Yacov Reisman, James G. Pfaus, and Lior Lowenstein

6 Post-Finasteride Syndrome 65
Mary C. Fierro, Faysal A. Yafi, and Yacov Reisman

7 Orgasmic Anhedonia 81
R. J. Heruti, R. Kamin, and J. Bitzer

8 Headache Associated with Sexual Activity 97
Elena Colonnello, Massimiliano Toscano,
Tommaso B. Jannini, and Emmanuele A. Jannini

9 Post-Orgasmic Illness Syndrome (POIS) 111
Yacov Reisman and Francesca Tripodi

Contributors

J. Bitzer Obstetrics and Gynecology, University Hospital of Basel, Basel, Switzerland

Elena Colonnello Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

Mary C. Fierro Department of Urology, University of California, Newport Beach, CA, USA

Irwin Goldstein Sexual Medicine, Alvarado Hospital, San Diego, CA, USA

R. J. Heruti Department of Rehabilitation Medicine, Reuth Rehabilitation Hospital, Tel-Aviv University, Tel-Aviv, Israel

Emmanuele A. Jannini Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

Tommaso B. Jannini Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

R. Kamin Beer Sheva Mental Health Center, Beer Sheva, Israel

Barry Komisaruk Departments of Psychology and Radiology, Rutgers University, Newark, NJ, USA

Lior Lowenstein Department of Gynecology, Galilee Medical Center, Nahariya, Israel

James G. Pfaus Czech National Institute of Mental Health, Laboratory of Sexual Neuroscience, Klecany, Czech Republic

Caroline Pukall Department of Psychology, Queen's University, Kingston, ON, Canada

Yacov Reisman Flare Health, Amstelveen, The Netherlands

Massimiliano Toscano Department of Human Neurosciences, "Sapienza" University of Rome, Rome, Italy

Department of Neurology, Fatebenefratelli Hospital, Isola Tiberina, Rome, Italy

Francesca Tripodi Institute of Clinical Sexology, Rome, Italy

David Veale South London & Maudsley NHS Foundation Trust and King's College London, London, UK

Faysal A. Yafi Department of Urology, University of California, Newport Beach, CA, USA

James Yianni South London and Maudsley NHS Foundation Trust, London, UK

Chapter 1
Introduction

Yacov Reisman, Francesca Tripodi, and Lior Lowenstein

Learning Objective
After reading this chapter, the learners:

- will be familiar with the content of the book,
- will understand the selection criteria of the different subjects,
- will be familiar with the different aspects included in each chapter.

When someone sees the title of this book, they are instantly struck by an important question: "Rare Sexual Medicine Conditions, what are they, and how do you characterize them?" We will try to set up the situation and discuss the problem here.

With the rise of social media and instantaneous digital communication, it appears that many patients are suffering from undiagnosed conditions, many of which are sexually related. As sexuality carries a lot of stigma and taboo, these inexplicable situations remain largely unaddressed, unexpressed, and unspoken. Health care professionals are often unaware of these conditions and cannot find appropriate information to treat or assist their patients.

Y. Reisman (✉)
Flare Health, Amstelveen, The Netherlands
e-mail: reisman@flare-health.nl

F. Tripodi
Institute of Clinical Sexology, Rome, Italy

L. Lowenstein
Department of Gynecology, Galilee Medical Center, Nahariya, Israel

Y. Reisman et al. (eds.), *Textbook of Rare Sexual Medicine Conditions*,
https://doi.org/10.1007/978-3-030-98263-8_1

The prevalence of these conditions is unclear, and estimations are based on case reports or online platforms. Furthermore, there is still no consensus on the pathophysiological mechanism that underpins these diseases. The lack of a clear definition and diagnostic criteria for each of these conditions is one of the reasons for these consequences.

The majority of these conditions evolve to a chronic stage and have a detrimental influence on the patient's and partner's quality of life (and other family members). The impact harms the patients' level of performance and their ability to maintain intimacy and a healthy sex life with their partner. Because of the taboo, this might drag on for a long time.

Sexual dysfunctions and sexual impairments are the most common complaints of patients suffering from the conditions described in this book. These conditions also correlate with sexuality-related physical and mental problems. As a result, biological, psychological, and social factors need to be considered. Involvement of the central nervous system is common in many disorders, and neurotransmitters are frequently mentioned as possible pathophysiological explanations. This is not surprising given that the brain is the most significant sexual organ since it is where sexual desire, pleasure, and orgasm are established and where the genital response is induced or inhibited. As a result, any imbalance in neurotransmitters may have an impact on sexual function.

Sexuality may significantly impact an individual's overall wellbeing, social functioning, and quality of life. Sexual difficulties are frequently linked to feelings of failure, low self-esteem, rejection anxiety, and problems forming and maintaining relationships. Individuals who present with sexual dysfunction often show a depressed mood or performance anxiety. As a result, there is a definite connection between mental and sexual well-being. Every clinician should be aware of this interaction and apply knowledge and experience from their everyday work.

Although some disorders are iatrogenic, there is a great deal of inconsistency in the medical community's awareness of them. Patients have expressed emotions of abandonment and a perceived lack of consideration. More importantly, patients rarely receive adequate information on sexual function and sexual problems and possible support. Attempts to develop a treatment have resulted in a wide range of methods being tested, but none of them has been proven by large randomized trials or guided consensus. There is no effective therapy or cure. Medical acknowledgement of these disorders is critical for obtaining funding for additional research into their prevalence, pathophysiological mechanisms, and potential treatments.

The recognition of the patient's complaints and concerns, honesty about our limited understanding of the condition and treatment approaches can already make a difference in the patient's life. Education, knowledge, and emotional and physical care can help improve the patient–doctor relationship and the patient's quality of life.

The care process includes a multidisciplinary team of experts (physicians, psychologists, social workers, couple therapists, and sexologists) who work together to give up-to-date information and, if necessary, appropriate therapy concentrating on the patient's sexual and relational needs. Even after relationship and sex life have

significantly changed due to the circumstances, it is still possible to have a satisfying intimacy if persons adapt, accept, and receive the proper support.

Conditions with sexual complaints or dysfunctions with limited knowledge of their clinical and pathological features, who are still not recognized or defined by health authorities, have low awareness among health care professionals, and in which patients report significant discomfort and suffering have been selected for the various chapters. To our knowledge, this is the first hands-on book on these conditions. Due to a lack of practical knowledge and training, we opted to concentrate on what is known and what can be done, even if some evidence and clinical options have no clear consensus among the medical community. We want to provide the reader with information that they may utilize in their clinical practice.

The biopsychosocial model is a general theory affirming that biological, psychological, and social (e.g. socioeconomic, socioenvironmental, and cultural) elements all affect health and disease. The second chapter of this book discusses the bio-psycho-social paradigm of sexual complaints as determined and influenced by biological, psychological, and sociocultural factors. It also contains an outline of the evolution of modern sexual medicine and its connections to various disciplines. Rather than being understood solely in physical terms, health and sickness are best comprehended in the interaction of biological, psychological, and social elements. The reader will have a better understanding of each of the different disorders in Chaps. 3–9, where the pathophysiology, assessment, and management of the conditions and sexual dysfunction and related issues are presented using biological and psychological approaches.

Chapter 3 deals with the Penile Dysmorphic Disorder (PDD), a type of body dysmorphic disorder in which persons have a severe obsession and worry over their penis size and shape, even if it is within the normal range. Patients with PDD often have distressing concerns about their penis and exhibit repetitive and compulsive behaviours (medical seeking and obtaining procedures) in reaction to these concerns. Because there are no particular measures for distinguishing men with PDD from men who are concerned about the size of their penis but do not have PDD, understanding the condition is critical for management.

Persistent Genital Arousal Disorder (PGAD) is discussed in Chap. 4. PGAD is defined as a spontaneous, persistent, unwanted, and uncontrollable genital arousal in the absence of sexual stimulus or sexual desire that is not alleviated by orgasm. The literature disputes the nomenclature, and PGAD differs from hypersexuality, characterized by an increase in sexual desire. Due to an inability to carry out daily duties, PGAD might cause chronic physical stress and psychological problems. Some women have expressed suicidal ideas.

The next chapter is about Post-SSRI Sexual Dysfunction (PSSD). PSSD is a debilitating disorder in which individuals continue to have sexual side effects after discontinuing SSRI usage. It has a negative impact on sexual health, relationships, and quality of life. Because no precise and reproducible diagnostic criteria have been evaluated or agreed upon, it is difficult to diagnose the illness with certainty (which is characteristic of the other conditions in this book). Currently, diagnosis is based solely on symptoms, which vary significantly in severity and duration.

The sixth chapter is about Post-Finasteride Syndrome (PFS). PFS refers to a group of major side effects manifested in sexual and other clinical symptoms that develop and persist during and/or after finasteride treatment. Finasteride is prescribed to men with pattern hair loss (androgenetic alopecia) or benign prostatic hyperplasia. Although PFS is closely related to PSSD, it has distinct symptoms and, most likely, a different pathological aetiology.

Chapter 7 is about Orgasmic Anhedonia, also known as Pleasure Dissociative Orgasmic Dysfunction, or PDOD. Anhedonia is defined as the inability to get pleasure from a typically rewarding action. When people with orgasmic anhedonia climax, they cannot feel pleasure. Desire and arousal are still present in people with this unusual condition. Men continue to ejaculate, and women can achieve orgasm, but the pleasure is lacking. Couples may find the situation to be somewhat aggravating. Orgasmic anhedonia might make people feel embarrassed or as though they are missing out. Partners may feel inept as they are doing something incorrectly, while some partners are clueless about the issue. There are a variety of possible explanations for this illness, and treatment aims to address the underlying problem, but it is common to utilize a combination of physical and sexual therapies.

Post-Orgasmic Headache is discussed in Chap. 8, a rare but debilitating clinical phenomenon documented since Hippocrates' time. In contrast to other migraine disorders, males are three times more likely than females to be affected, with an average onset age of 30–40 years. This disorder is treated with pharmaceutical and non-pharmacological therapy with varying degrees of success.

The final chapter is on Post-Orgasmic Illness Syndrome (POIS), a rare disorder in which a person suffers flu-like symptoms as well as other symptoms like irritability, mood swings, and issues with concentration, memory, and attention following ejaculation/orgasm. The symptoms arise after the climax, whether with a partner, through masturbation, or spontaneously during sleep. POIS is most commonly reported in males (after ejaculation), but occasionally, females with POIS have been reported.

The book is intended to be a comprehensive and practical guide for physicians of various disciplines, specialists, and trainees in sexual medicine, clinical sexology, psychotherapists, and all other healthcare providers and students who want to improve their knowledge and skills to help patients suffering from sexual health problems. Based on the available scientific literature and the authors' clinical experience, recommendations for assessment and therapy approaches are provided.

This interdisciplinary effort would not be possible without a group of motivated individuals—excellent specialists from a variety of countries who have worked in the field and are here to review the available evidence and share their expertise and practical skills. They form a group with a wide diversity of specialities, approaches, and expertise. We owe a debt of gratitude to the authors of each chapter, and we appreciate their efforts, patience, and ongoing support for the project. We believe that readers will not only find this book valuable in their clinical practice but that it will also raise medical community awareness.

Key Messages

- Rare sexual medicine conditions described in this book are unrecognized, debilitating sexual complaints or dysfunctions with limited knowledge of their clinical and pathological features, and have low awareness among health care professionals.
- The book aims to provide useful information about these rare conditions to healthcare professionals in their clinical practice and increase awareness among the medical community.

Chapter 2
The Biopsychosocial Approach in Sexual Medicine Disorders

Francesca Tripodi, Yacov Reisman, and Lior Lowenstein

Learning Objectives
After reading this chapter, the learners will:

- Know about the historical development of the biopsychosocial model.
- Understand the essential elements of the model.
- Understand the connection of the model with sexual health and sexual dysfunction.
- Be able to emphasize the different components for a successful approach and treatment of the patient or the couple.

2.1 Introduction

Sexuality is a central aspect of being human throughout life encompasses sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy, and reproduction. Sexuality is experienced and expressed in thoughts, fantasies, desires, beliefs, attitudes, values, behaviours, practices, roles, and relationships. While

F. Tripodi (✉)
Institute of Clinical Sexology, Rome, Italy

Y. Reisman
Flare Health, Amstelveen, The Netherlands

L. Lowenstein
Department of Gynecology, Galilee Medical Center, Nahariya, Israel

Y. Reisman et al. (eds.), *Textbook of Rare Sexual Medicine Conditions*,
https://doi.org/10.1007/978-3-030-98263-8_2

sexuality can include all of these dimensions, not all of them are always experienced or expressed. Sexuality is influenced by the interaction of biological, psychological, social, economic, political, cultural, legal, historical, religious, and spiritual factors [1].

Interdependent to this definition, sexual health is understood as a state of physical, emotional, mental, and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction, or infirmity. Sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination, and violence. For sexual health to be attained and maintained, the sexual rights of all persons must be respected, protected, and fulfilled [1].

This means that sexuality should not be correlated exclusively with biology, so consideration of social, psychological, and environmental factors should be investigated.

In late 1970, George Engel introduced the biopsychosocial (BPS) model, mainly for psychiatry. He believed that clinicians must simultaneously attend to the biological, psychological, and social aspects of the disease to understand and respond adequately to the suffering of patients and give them a sense of being understood. The model was formulated as a dynamic, interactional view of human experience in which there is the mutual influence of mind, body, and culture. This holistic model is cross-disciplinary, contextual, and does not deny the biomedical objective importance but criticizes its exclusive focus, involving the patient's subjective experience [2, 3]. Actually, the earliest systematically written evidence on the knowledge about a holistic approach and the relation between soul and body, between physiological or organic and psychological, can be found in the writings of ancient Greek philosophers such as Hippocrates in the period from the year 500 to 300 B.C. The signs of the multifactorial disease model can be seen in these early writings, along with the significance of natural, extra-organic factors affecting health and disease development [4].

In later years, the BPS model was established as "psychiatric orthodoxy," attesting to the magnitude of its influence on modern psychiatry [5]. In our opinion, BPS is more of a paradigm asserting that all medical conditions are divided into the three components of BPS, but allows the clinician to examine if a particular disease can occur from a combination of biological, psychological, and social factors; and if so, whether the condition needs treatment in all three spheres, which is unlikely to be the case for all illnesses. The BPS guides the process of diagnosis, education, and treatment and should be evidence-based [6].

The conceptual effect of the BPS model has extended beyond the fields of psychiatry. This concept has been endorsed in several academic areas, such as health education, health psychology, public health, preventive medicine, chronic pain and chronic disease, rehabilitation medicine, and public opinion [7, 8]. Finally, it became the gold standard approach in sexual medicine and clinical sexology [9, 10].

2.2 The BPS Perspective

Clinical reality is far more complex than a linear cause-effect model. Structural causality is more precise and describes a hierarchy of unidirectional cause–effect relationships—the necessary causes, precipitants, sustaining forces, and associated events involved. While conventional biomedical models of clinical medicine concentrate on pathophysiology and other biological approaches to illness, the biopsychosocial approach stresses the value of understanding human well-being and disease in their fullest sense. The BPS model involves the patient's experience, objective data, and perspective on the patient–health care professional (HCP) relationship, with more power to the patients in the clinical process. This implies that biological, psychological, and social factors exist along a continuum of natural systems; systematic consideration of psychological and social factors requires applying relevant sciences, and humanistic qualities are highly valued complements to the approach.

The models suggest that disorder arises from an individual who is part of a whole system made up of "sub-personal levels" (i.e. nervous system, organs, tissues, cells, etc.) and "supra-personal levels (i.e. individuals living in a psychosocial context) [3]. The determinants and prognosis of health conditions result from an interaction between biological, psychological, and social influences without having a monopoly of any factors on the explanation and/or remedy [11]. The patient is acknowledged as an active participant in the recovery process and good health, rather than a mere passive victim of deviations in physiologic functioning [3]. This implies a patient/client-centred and relationship-centred approach, therefore arriving at a correct biomedical diagnosis is only part of the clinician's tasks. Other tasks are giving the patient the space to discuss their concerns, finding out the patient's expectations, and being kind and empathic to them, interpreting illness and health from an intersubjective perspective. This model suggests that the reality of each individual is not just interpreted by the HCP but created and recreated through the dialogue. The HCP's goal is to come to a shared understanding of the patient's narrative with the patient. Such understanding may not mean uncritical acceptance of something suspected or speculated by the patient. However, it does not encourage the uncritical negation of the patient's viewpoint, as it still happens too often, for instance, when patients complain of symptoms that doctors do not clarify [12, 13].

Application of the BPS model requires not only clinical skills but also building trust (a core skill, the achievement of an emotional tone conducive to a therapeutic relationship), having empathic curiosity (to maintain an open mind), the ability to recognize our own bias (using self-awareness as a tool), deciding which aspects are important to clarify, educate, and communicate with the patient (in the term that the patient can understand and according to the patient's need), and providing multimodal treatment [14]. Studies offer empirical support for the idea that clinician-patient dyadic factors—including clinician empathy—can influence the outcomes of various pathologies [15].

There are several detractors of the BPS model. It was reported that it is still a biomedical model, psychological and social factors are still superimposed on biological factors, the theoretical basis of the model is not clear enough, the model's drawback is the absence of a shared language/system of terms (i.e. there is parallel and unconnected psychological and medical terminology), and the complex relations between causes and effects of different BPS factors, influencing the state of health and occurrence of disease, are not properly known. Some report that it is time-consuming and expensive to apply as it requires more information gathering. Another criticism is the lack of research with clear, supportive results for the use of the model [16, 17].

Nevertheless, using a BPS lens to address sexual concerns is seen as essential in sexual medicine. It means developing an integration between clinical theories and techniques, working in a multidisciplinary team, and using all available resources—medical, pharmacological, psychological, relational, and psychosexual. Medical and psychological knowledge is often hard to be integrated, and this process costs efforts from both parts but reports a better impact on patients' outcomes [9, 10, 18–20].

2.3 BPS in Sexual Medicine

Sexual function and sexual pleasure are determined by age, gender, norms, experience, relationship quality, lifestyle, and overall health of the individual [21].

To diagnose a sexual dysfunction (SD) according to DSM-5, the symptoms must occur for at least 6 months, appear in all or almost all sexual episodes (more than 75% of the time) and cause personal distress. The SD should not be a direct consequence of a non-sexual mental disorder, severe relationship distress, or other significant stress factors and should not be attributable to the effects of a substance/drug or other medical condition; otherwise, the diagnosis cannot be made. The readers surely understand that many of these conditions are concurrent with sexual dysfunction in most patients: illness, mental disorders, drug intake, severe relationship conflicts, traumatic experiences, substance abuse, etc. That is why many physicians do not take the time to assess the sexual health of their patients, considering it as really secondary to all the other health issues and not that important for the overall well-being [22].

The ICD-11 expands inclusion criteria for the diagnosis of SD [23], including all those etiological factors that can contribute to the onset or maintenance of the symptom, and in fact, it is better suited to the BPS perspective [24]. First of all, the ICD-11 define the sexual response as "a complex interaction of psychological, interpersonal, social, cultural, physiological and gender-influenced processes." Any of these factors may contribute to the development of sexual dysfunctions, which are described as syndromes that comprise the various ways in which people may have difficulty experiencing personally satisfying, non-coercive sexual activities. Second, where possible, categories in the proposed classification of SD apply to

both men and women, emphasizing commonalities in sexual response rather than differences as assumed in the DSM-5. Third, "satisfactory" sexual functioning is defined as being satisfying to the individual. Suppose the individual is satisfied with their pattern of sexual experience and activity. In that case, even if it is different from what may be enjoyable to other people or what is considered normative in a given culture or subculture, a sexual dysfunction should not be diagnosed. Consequently, the diagnosis is not valid in the case of (a) unrealistic expectations on the part of a partner; (b) discrepancy in sexual desire between partners; (c) inadequate sexual stimulation. Last but not least, the ICD-11 classification uses a system of harmonized qualifiers that may be applied across categories to identify the critical clinical characteristics of sexual dysfunctions. These qualifiers are not mutually exclusive, and as many may be applied as are considered relevant and contributory in a particular case. Proposed qualifiers include the following:

(a) Associated with disorder or disease classified elsewhere, injury or surgical treatment (e.g. diabetes mellitus, depressive disorders, hypothyroidism, multiple sclerosis, female genital mutilation, radical prostatectomy);
(b) Associated with a medication or substance (e.g. selective serotonin reuptake inhibitors, histamine-2 receptor antagonists, alcohol, opiates, amphetamines);
(c) Associated with lack of knowledge (e.g. about the individual's own body, sexual functioning, and sexual response);
(d) Associated with psychological or behavioural factors (e.g. negative attitudes toward sexual activity, adverse past sexual experiences, poor sleep hygiene, overwork);
(e) Associated with relationship factors (e.g. relationship conflict, lack of romantic attachment);
(f) Associated with cultural factors (e.g. culturally based inhibitions about the expression of sexual pleasure, the belief that loss of semen can lead to weakness, disease, or death).

The literature shows a growing body of sex-focused research with a biopsychosocial orientation. Still, overall, studies provide evidential support for considering sexual behaviour, sexual functioning, and the treatment of sexual problems within the biopsychosocial framework [19]. The International Consultation on Sexual Medicine (ICSM) diagnostic and treatment standards provide a care process for applying biopsychosocial methods in sexual medicine, with specific recommendations for sexual history taking and diagnostic evaluation (Fig. 2.1) [25]. Standardized scales, checklists, and validated questionnaires are additional adjuncts that should be used routinely in sexual problem evaluation.

When addressing a new sexual complaint, a thorough history using a biopsychosocial approach should be undertaken, including assessment of the complaint and any current or past sexual experience, medication use and health problems, a history of emotional, physical, or sexual abuse, beliefs and attitudes regarding sex and body image concerns. Particular attention should be paid to symptoms of depression, anxiety, and sleep problems, all of which are common. HCP should inquire about

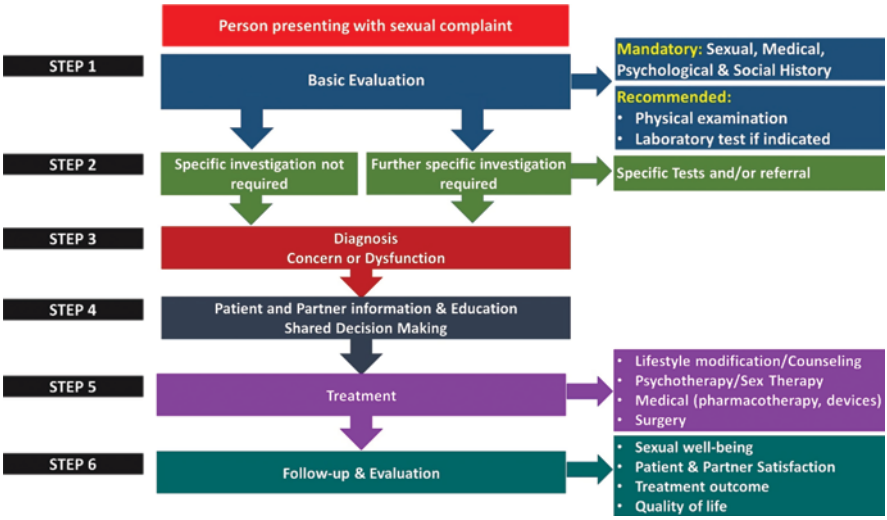

Fig. 2.1 Algorithm for the management of sexual dysfunctions based on the revised International Consultation on Sexual Medicine [25]

risk behaviour such as alcohol, drug, or substance use and may be associated with sexual dysfunction. Any health or sexual problems affecting the partner(s) should also be explored, and relationship discord or communication issues should be inquired. Furthermore, specific questioning directed toward the impact of disease on quality of life may help clinicians ascertain the extent of disease impact [25]. Validated patient questionnaires can facilitate the initial diagnoses and assist the diagnosing clinician in accounting for biological and psychosocial variables. Such tools may be of particular importance in light of research [26]. An emphasis on sexual satisfaction and complete assessment of the biopsychosocial contributors to sexual function may help avoid over-medicalization. Understanding longitudinal patterns in sexual function is essential to ensure that we can confidently educate our patients regarding what to expect and to tailor treatments for sexual dysfunctions optimally.

Assessment of sexual complaints and dysfunctions requires the HCP to overcome stereotypes, prejudices, and internalized distaste regarding diverse sexuality and relationships. Sexual history taking should always be conducted in a culturally sensitive manner, taking account of the individual's background and lifestyle, the status of the partner relationship, and the clinician's comfort and experience with the topic [24, 27]. Specifically, the sexual history aims to identify sexual problems, possible biological and psychosocial contributing factors, and the patient's and/ or couple's treatment goals. While exploring the presenting problem, the clinician should also:

– take note of information relevant to secondary gain,
– identify potential risk of the treatment, including understanding the client's value system, level of concern, cognition sensibilities/embarrassment,
– observe relational dynamics within the couple,
– define and acknowledge differences between partners' goals, priorities, and expectations.

Beyond history taking, a focused physical examination is strongly recommended, although not mandatory, and better if performed by specialists in urology, gynaecology, or sexual medicine. This can serve as an opportunity to identify possible contributing factors or comorbid conditions and/or a chance to reassure the patient of the absence of anatomic problems. In addition, laboratory tests are recommended only when there are indications of organic pathology or general medical conditions potentially affecting sexual function.

After collecting all the relevant information and outcomes from psychometric tools, lab tests, or other consultations, if any, the case leader should communicate with the health care providers who are already treating the patient for other problems that impact sexuality and with the other professionals of their networking that could help for the further steps. The aim is to confirm the diagnosis and evaluate the best options to propose to the client/couple.

After assessments are complete, the patient and/or couple should be given information and education on the sexual problem identified and the contributing factors and available treatment methods. Clinicians should be aware that a significant amount of sexual complaints could be solved "only" with patient/partner education. Generally, relevant topics here are the anatomy of the genitals, physiology of sexual response, sexual scripts and wrong beliefs, myths on performance, normality in a variety of orientations or preferences, simple exercise or devices that can help in experiencing body function and pleasure. If this is not enough, the health care provider ideally should engage in shared decision-making with the patient or couple to agree on the most appropriate approach or treatment method. The clinician needs to provide the patient with the necessary evidence-based information, clarify the patient's needs and preferences, and together select among the available treatment options [24]. The expert's competence and opinion orient the process and tailored treatment. In most cases, the treatment zone is related to maintaining and contextual factors. The predisposing and precipitating ones are often difficult to change (constitutional and prior life experiences or traumas, personality traits, chronic illness, mental illness and medications, etc.).

As sexuality is a multi-causal, multidimensional, complex phenomenon, the treatment of sexual dysfunction should be integrated into a multidisciplinary biopsychosocial framework [28]. The ICSM guidelines underline that treatment should be directed towards each causative factor and may involve different clinicians from multiple disciplines. Appropriate treatment should address all identified

contributing factors and involve education and counselling for patients and partners, while specific and directed medical treatment may be warranted [25]. A solid interdisciplinary referral network is required, and multidisciplinary treatment teams can provide highly integrated biopsychosocial therapy where possible. In addition, research points to the value of appropriate training of medical professionals with sexual history taking and clinical experience [29].

A variety of structured medical interventions have been suggested within a biopsychosocial framework to treat sexual disorders for a wide range of sexual and sex-related diagnoses, including male sexual dysfunction, female sexual dysfunction, urological and gynaecological conditions [30]. Sex-related pain disorders, especially among women, appear to be a specific area of focus in biopsychosocial treatment [31–34]. In addition to sexual pain, integrative and biopsychosocial models have been introduced to resolve the sexual effects of chronic pain [35]. The application of the BPS model has been examined in the context of directed pharmacotherapy of sexual and comorbid disorders [36, 37] and the biopsychosocial application of combined drug therapy and psychotherapy [38] and hormonal treatments [39]. One promising therapeutic effort to meet the diverse medical needs of biopsychosocial concerns is the combined use of pharmacotherapy and psychotherapy. This concept suggests that clinicians should be prepared to treat sexual dysfunctions as biopsychosocial phenomena that are etiologically and symptomatically complex.

Counselling (e.g. clarification, normalization, orientation, education, decision-making support) and lifestyle modification (e.g. diet, exercise, free time, privacy, stop drug/alcohol assumption), as well as medical and surgical prescriptions, will face the conscious, evident, concrete factors that maintain the SD. Generally, the patient/couple reach awareness easily on those aspects of the problem and show compliance on the targeted suggestions. Benefits can be achieved linearly if it is the right time for the patient. The clinician should ensure that the client(s) have enough knowledge, skills, and insight for subsequent self-management, developing evidence-based and appropriate interventions for the assessment findings and the client's context.

Psychosexual therapy is needed when the factors at play are more intricate and/or belong to the blind area of the patient. For example, it is common to see people complaining of SDs with concurrent psychological symptoms that they do not know to explain and even not a root. It is also common to see couples who declare no conflicts but great dissatisfaction with their sexual life. In complex cases, in which the SD is only one piece of a big puzzle of problems, psychotherapy could be the best treatment option.

According to the ICSM algorithm (Fig. 2.1) and other evidence-based clinical guidelines, follow-up and evaluation of treatment play a key role in successful management. Treatment outcome in terms of symptoms relief is not sufficient to evaluate the success. Particular attention should be given to the overall sexual well-being and sexual satisfaction of the patient and the partner. Follow-up can be continued at predefined intervals to assess whether the patient's and/or partner's needs are being met in the long term. Client responsibility for self-evaluation is encouraged, and

appropriate tools and outcome measures are defined. Many clinicians are comfortable not following up on their patients. This is understandable: it is nice to think that they do not need our help anymore because they are just fine, and everything is going desirably.

Nevertheless, it will be a big mistake not to follow up with our patients. First of all, we will never know if our interventions are effective, and this ignorance will leave us doing the same things all the time. Moreover, we will not compare what to us seemed achievements for that patient/couple, and what are in their opinion, that is what really counts. Second, follow-up sessions lead to better results in the treatment process. Even when the sexual function is restored, patients may want to discuss a few other issues connected to their sexual satisfaction or well-being. These "late adjustments" help in maintaining the results of the treatment and avoiding relapses. Last but not least, we will learn from our patients what is often not written in the books but allow us to improve our competence in managing complex cases.

2.4 Conclusion

The BPS approach to sexual dysfunction requires effective communication between HCPs from different disciplines, allowing the care to be adapted directly to the patient's needs, focusing first on a specific element (biological, psychological, or social) or different factors in combination. Some barriers to the implementation of the BPS include curriculum limitations, inadequate preparation of practitioners and insufficient awareness of sexual health issues, the discomfort of practitioners in addressing the sexual health of patients, privacy concerns, demographic factors (i.e. age and gender of both practitioners and patients), and personal sexual attitudes and mores of the practitioner (i.e. conservative vs liberal) [40].

Dedicated training programs can be beneficial in BPS research and practice. As a result of good training and professional expertise, knowledge and competence should lead to greater flexibility in adopting a patient-centred approach.

As described in this textbook, rare sexual medicine conditions lack clear evidence-based definitions, and their prevalence is unclear. The availability of validated measurements such as questionnaires for the distress or treatment outcomes are scarce. To explain these conditions, only hypothetical pathophysiological models are accessible at this time, while empirical evidence is absent. Consequently, the treatment modalities are only anectodical delineated in the current literature. Therefore, using a BPS approach is necessary to better understand the factors involved and at least tailor the treatments to the patient's well-being. Valuable steps in developing this BPS paradigm could be professional integration, scientific research, manualized biopsychosocial treatment models, dedicated training systems, updates of medical training curricula, tailored outreach initiatives, and social advocacy.

Key Messages

- The biopsychosocial approach stresses the value of understanding human well-being and disease in their fullest sense.
- Disorder in the individual arises and has an impact on a whole system made up of "sub-personal levels" (i.e. nervous system, organs, tissues, cells, etc.) and "supra-personal levels."
- The determinants and prognosis of health conditions are the product of an interaction between biological, psychological, and social influences.
- Application of the BPS model requires clinical skills, creating trust, having empathic curiosity, being able to recognize own bias, educate and communicate with the patient and providing multimodal treatment.
- Sexuality is a multi-causal, multidimensional, complex phenomenon, and therefore treatment of sexual dysfunction should be integrated into a multidisciplinary biopsychosocial framework.

References

1. World Health Organization. Defining sexual health: report of a technical consultation on sexual health, 28–31 January 2002, Geneva; 2006.
2. Engel G. The need for a new medical model: a challenge for biomedicine. Science. 1977;196:129–36.
3. Engel G. The clinical application of the biopsychosocial model. Am J Psychiatry. 1980;137:535–44.
4. Serafino EP, Smith TW. Health psychology—biopsychosocial interaction. New York: Wiley; 2016. ISBN: 978-1-119-29948-6
5. Pilgrim D. The biopsychosocial model in Anglo-American psychiatry: past, present, and future? J Ment Health. 2002;11:585–94.
6. Models in Science: Section 2.4 Descriptions. Stanford Encyclopedia of Philosophy. February 27, 2006. https://plato.stanford.edu/entries/models-science/#Des. Accessed December 19, 2020.
7. Alvarez AS, Pagani M, Meucci P. The clinical application of the biopsychosocial model in mental health: a research critique. Am J Phys Med Rehabil. 2012;91:S173-80.
8. Havelka M, Lucanin JD, Lucanin D. Biopsychosocial model—the integrated approach to health and disease. Coll Antropol. 2009;33(1):303–10.
9. Kirana PS, Tripodi F, Reisman Y, Porst H, editors. The EFS and ESSM syllabus of clinical sexology. Amsterdam: Medix; 2013.
10. Reisman Y, Porst H, Lowensten L, Tripodi F, Kirana PS, editors. The ESSM manual of sexual medicine. Amsterdam: Medix; 2015.
11. Deacon BJ. The biomedical model of mental disorder: a critical analysis of its validity, utility, and effects on psychotherapy research. Clin Psychol Rev. 2013;33:846–61.
12. Stewart M. Towards a global definition of patient centered care. BMJ. 2001;322:444–5.
13. Epstein RM. Mindful practice. JAMA. 1999;282:833–9.
14. Borrell-Carrió F, Epstein RM. Preventing clinical errors: a call for self-awareness. Ann Fam Med. 2004;2:310–6.

15. Kelley JM, Kraft-Todd G, Schapira L, Kossowsky J, Riess H. The influence of the patient-clinician relationship on healthcare outcomes: a systematic review and meta-analysis of randomized controlled trials. PLoS One. 2014;9(4):e94207.
16. Havelka M, et al. Biopsychosocial model. Coll Antropol. 2009;33(1):303–10.
17. Lane RD. Is it possible to bridge the biopsychosocial and biomedical models? Biopsychosoc Med. 2014;8:3.
18. Simonelli C, Fabrizi A, Rossi R, et al. Clinical sexology: an integrated approach between the psychosomatic and the somatopsychic. Theol Sex. 2010;19:3–7.
19. Berry MD, Berry PD. Contemporary treatment of sexual dysfunction: reexamining the biopsychosocial model. J Sex Med. 2013;10:2627–43.
20. Goldstein I. Sexual medicine reflects the light of knowledge. J Sex Med. 2012;9:2733–5.
21. Lodge AC, Umberson D. All shook up: sexuality of mid- to later life married couples. J Marriage Fam. 2012;74:428–43.
22. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM–5). American Psychiatric Association; 2013. p.Nov 25. ISBN 978-0-89042-555-8
23. Reed GM, Drescher J, Krueger RB, et al. Disorders related to sexuality and gender identity in the ICD-11: revising the ICD-10 classification based on current scientific evidence, best clinical practices, and human rights considerations. World Psychiatry. 2016;15(3):205–21.
24. Tripodi F. Counselling and psychotherapy in sexual medicine. In: Lew-Starowicz M, Giraldi A, Krüger T, editors. Psychiatry and sexual medicine. A comprehensive guide for clinical practitioners. Springer Nature Switzerland AG; 2021. ISBN 978-3-030-52298-8.
25. Hatzichristou D, Kirana PS, Banner L, Althof SE, Lonnee-Hoffmann RA, Dennerstein L, Rosen RC. Diagnosing sexual dysfunction in men and women: sexual history taking and the role of symptom scales and questionnaires. J Sex Med. 2016;13:1166–82.
26. Fisher WA, Gruenwald I, Jannini EA, Lev-Sagie A, Lowenstein L, Pyke RE, Reisman Y, Revicki DA, Rubio-Aurioles E. Standards for clinical trials in male and female sexual dysfunction:I. phase I to phase IV clinical trial design. J Sex Med. 2016;13:1805–17.
27. Althof SE, Rosen RC, Perelman MA, Rubio-Aurioles E. Standard operating procedures for taking a sexual history. J Sex Med. 2013;10:26–35.
28. McCarthy BW, McDonald DO. Psychobiosocial versus biomedical models of treatment: semantics or substance. Sex Relat Ther. 2009;24:30–7.
29. Reisman Y, Eardley I, Porst H, and the Multidisciplinary Joint Committee on Sexual Medicine (MJCSM). New developments in education and training in sexual medicine. J Sex Med. 2013;10:918–23.
30. Kirana PS, Papaharitou S, Athanasiadis L, Nakopoulou E, Salpiggidis G, Moysidis K, Pipilaki C, Hatzimouratidis K, Tzotstzis V, Portseli A, Iraklidou M, Apostolidis A, Bekos A, Hatzichristou D. A conceptual framework for the evolution of sexual medicine and a model for the development of alternative sexual health services: 10-year experience of the center for sexual and reproductive health. J Sex Med. 2009;6:2405–16.
31. Martin S, Atlantis E, Wilson D, Lange K, Haren MT, Taylor A, Wittert G. Clinical and biopsychosocial determinants of sexual dysfunction in middle-aged and older Australian men. J Sex Med. 2012;9:2093–103.
32. Giraldi A, Rellini AH, Pfaus J, Laan E. Female sexual arousal disorders. J Sex Med. 2013;10:58–73.
33. Smith KB, Tripp D, Pukall C, Nickel JC. Predictors of sexual and relationship functioning in couples with chronic prostatitis/chronic pelvic pain syndrome. J Sex Med. 2007;4:734–44.
34. Boyer SC, Goldfinger C, Thibault-Gagnon S, Pukall CF. Management of female sexual pain disorders. Adv Psychosom Med. 2011;31:83–104.
35. Breton A, Miller CM, Fisher K. Enhancing the sexual function of women living with chronic pain: a cognitive–behavioural treatment group. Pain Res Manag. 2008;13:219–24.
36. Basson R. Pharmacotherapy for sexual dysfunction in women. Expert Opin Pharmacother. 2004;5:1045–59.

37. Segraves RT. Pharmacologic management of sexual dysfunction: benefits and limitations. CNS Spectr. 2003;8:225–9.
38. Aubin S, Heiman J, Berger B, Murallo A, Liu Y. Comparing sildenafil alone vs. sildenafil plus brief couple sex therapy on erectile dysfunction and couple's sexual and marital quality of life: a pilot study. J Sex Marital Ther. 2009;35:122–43.
39. MacDonald K, Feifel D. Dramatic improvement in sexual function induced by intranasal oxytocin. J Sex Med. 2012;9:1407–10.
40. Eardley I, Reisman Y, Goldstein S, Kramer A, Dean J, Coleman E. Existing and future educational needs in graduate and postgraduate education. J Sex Med. 2017;14:475–85.

Chapter 3
Penile Dysmorphic Disorder (PDD)

James Yianni and David Veale

Learning Objective
To identify Penile Dysmorphic Disorder (PDD) as a manifestation of Body Dysmorphic Disorder (BDD) and gain an understanding of how the symptoms of PDD develop, are maintained and treated.

3.1 Introduction

Though this is a textbook of rare sexual medical conditions, the paradox is that anxiety about penis size is one of the most common sexual conditions. In an internet survey of over 52,000 heterosexual men and women, it was found that only 55% of men were satisfied with the size of their penis [1]. This contrasts with 85% of women being satisfied with the penis size of their partner. In this group, 66% of men rated their penis size as average, 22% as large and 12% as small. Many men wanted their penis to be larger. Over 9 out of 10 men who rated their penis as small wanted theirs to be larger, and even of those men who rated their penis as average in size, almost half wanted theirs to be bigger. To provide context, in the same sample, 38% of people were dissatisfied with their height and 41% with their weight. It is

J. Yianni
South London and Maudsley NHS Foundation Trust, London, UK

D. Veale (✉)
South London & Maudsley NHS Foundation Trust and King's College London, London, UK
e-mail: david.veale@kcl.ac.uk

Y. Reisman et al. (eds.), *Textbook of Rare Sexual Medicine Conditions*,
https://doi.org/10.1007/978-3-030-98263-8_3

therefore evident that men place considerable importance of the size of their penis, and significantly more so than their partners.

Men's dissatisfaction with their penis size has been implicated in broader patterns of body image discontent. Those with a large penis reported greater satisfaction with their face and body, as well as less concern about exposing their body during sexual activity. Whereas, men who rated their penis as small had the least satisfaction in these domains. Although one can question the directionality of this correlation or debate that self-esteem may play a causal role, it highlights that penis size can be a source of concern for men and could contribute to broader worries.

Before discussing Penile Dysmorphic Disorder (PDD), it is first necessary to describe Body Dysmorphic Disorder (BDD). Much of what we know about PDD is drawn from BDD and therefore, it is necessary to describe BDD in general. BDD is a common psychiatric disorder, often misdiagnosed or underdiagnosed and in need of serious attention. This is likely to be more pertinent for individuals suffering from PDD, who are likely to present in cosmetic settings, if at all, where there is little to no screening.

3.2 Definition of Disorder

BDD was first described by an Italian psychiatrist Morselli in 1886 as dysmorphophobia, from the Greek 'dysmorphia' referring to ugliness. If left untreated, BDD is often chronic and disabling. Given it has been over 100 years since inception, one may assume that BDD is now a well understood and recognised disorder. However, this is not yet the case, though progress is being made.

3.2.1 Body Dysmorphic Disorder: Diagnosis

BDD is classified under the Obsessive-Compulsive and Related Disorders (OCRDs) in both the DSM-5 and ICD-11. It is defined as a persistent preoccupation with one or more perceived flaws in one's own appearance, where the flaws are not noticeable or if slight, the resulting preoccupation and distress from said flaw are extremely marked. It is commonly associated with repetitive actions. Such behaviour may be overt, where individuals perform physical acts such as mirror checking, or covert, where individuals engage in mental activity such as comparing oneself with others. These behaviours, though intended to keep oneself safe, have the juxtaposed effect of crippling the functioning of the individual and further fuel the disorder. The preoccupation and behaviours must cause significant distress and impair the individuals functioning in professional, social or other important capacities (upwards of one

hour a day in terms of time consumed). In addition, the impairment and distress of the individual cannot be better explained by any other disorder.

During screening, it is important that clinicians specifically ask about BDD as individuals are unlikely to report such concerns due to feelings of shame [2]. Onset of BDD typically occurs during adolescence [3]. At this time, body image is an important aspect of interpersonal and psychological development, and social status is highly valued. These factors may contribute to the onset of BDD. Often these are mistaken as normal development concerns, emphasising the need for greater education around possible indicators of BDD. This is pertinent as early onset is associated with some increase in BDD severity, higher frequencies of suicide attempts and greater comorbidity.

3.2.2 Preoccupations

Preoccupation in BDD can focus on any body part. In fact, it can occur on many body parts simultaneously and the preoccupation(s) may change over time. Over the course of a lifetime, the average sufferer with BDD is occupied with 5–7 different body parts [4]. The most common preoccupations are of the face or head, particularly the hair, nose and skin [5]. Some individuals may not be worried about a specific area, but their body as a whole. For others, it can be more vague, amounting to a feeling of ugliness, being 'not right' or too masculine/feminine. Preoccupations can also differ by cultural ideas around beauty, such as a focus on eyelids in Japan (rare in Western Cultures) or muscle dysmorphia, which is more common in the West [5]. There are too some differences between men and women, but there are overwhelmingly more similarities. These concerns are intrusive and unwanted, accompanied by intense feelings of anxiety, disgust, sadness and shame.

There are some common themes in the way individuals with BDD worry about their perceived flaw. This includes symmetry, proportion and/or size of the feature [6]. Sometimes they are more specific and hence can differ between individuals. For example, one individual may worry about the symmetry of their nose, whilst another may focus on enlarged pores on their nose. The beliefs that the individual has about their appearance can be specific and personal too. Using the example of preoccupation around the nose again, one individual may fear that they look like a crook, whilst another may believe that they will end up alone and unloved.

Shame often seems to be a dominant emotion expressed by those with BDD and can be thought of in two components: internal and external. Internal shame is reflected in common worries of being an unattractive social agent or being undesirable. External shame is more related to fears of negative evaluation, rejection or humiliation by others. With high levels of shame, it is understandable that people with BDD find it particularly difficult to disclose their concerns.

3.2.3 Penile Dysmorphic Disorder: Defined

PDD is a presentation of BDD where the male's preoccupation is about their genitalia. It is therefore not distinct from BDD and is referred to as PDD for convenience. Only one other preoccupation in BDD has been given a subtype (muscle dysmorphia in DSM5 but not ICD11), and it perhaps would not be best practice to do so. One could predict a future where there would be countless variations, reflecting the same disorder, only differing in terms of locus of preoccupation. And as areas of concern are often multiple or often change over time, an unhelpful situation could result where an individual has various diagnoses all of which have the same essence.

A common misconception of PDD is that it solely relates to disruption in sexual function. Another is that individuals with PDD are just concerned with the size of their penis, that is the length and/or girth. However, as is the case for BDD, concerns often differ between people and are typically more complex. In PDD, concerns extend and are not limited to, symmetry and proportion, it being 'just so' or specific concerns about the testes.

Diagnosis of PDD is appropriate when the size of the penis falls in the range of what is considered 'normal' and the preoccupation is focused on size. It therefore excludes 2.28% of men whose penises are at least two standard deviations below the mean, which is less than 6 cm in flaccid length and 9.5 cm in stretched length [7].

Preoccupation with one's genitals in BDD is more common in men than in women. In men, body image concerns often relate to masculinity including worries about height, build, genital size, muscle definition, body hair, head hair and feature proportion. This may provide some explanation for this gender difference, where the penis may be considered a sign of masculinity and sexual prowess. These beliefs about masculinity, and others around a partners' sexual dissatisfaction seem to be two of the main driving forces for men to worry about the size of their penis. This is furthered as discussion of sex is a topic that is often avoided, so pornography is typically used as a benchmark for many men, reinforcing the notion that sexual fulfilment largely depends on size.

3.2.3.1 Beliefs about Penis Size Scale

The Beliefs about Penis Size Scale (BAPS) is 10 item self-report scale designed to measure beliefs about masculinity and shame about perceived penis size [8]. It can be used as part of a screening process as it can discriminate between those who have concerns about penis size and those who do not. It is significantly correlated to relevant psychological measures such as anxiety and body image as well as measures of erectile function and the importance attached to penis size. It may therefore be useful as part of the outcome measures for treatment. The BAPS is not correlated to penis size, supporting previous research which has found no relationship with objective unusualness of a body feature and psychological distress.

3.2.3.2 Penile Dysmorphic Disorder and Small Penis Anxiety

As PDD is a presentation of BDD, the diagnostic criteria are aligned. Therefore, the preoccupation and behaviours that the individual engages in due to shame around their penis must cause significant distress and cause impairment in the individuals functioning. The preoccupation should be upwards of 1 h a day. This is a necessary component and provides research with a useful group for comparison; men with Small Penis Anxiety (SPA). These men do have concerns around their penis, and thus may have shame about the size of their penis, but the extent of this is not severe enough to meet diagnostic criteria of BDD. It is important to recognise that men with SPA too may engage in unhelpful behaviours and seek cosmetic procedures.

Research has found that men with PDD hold stronger beliefs about masculinity, feel greater shame and more interference in relationships. An example of this is a study which looked at the sexual functioning of men with PDD relative to those with SPA and a control group with no concerns [9]. Though there were no differences in sexual desire, frequency of sexual intercourse and mean number of sexual partners, other areas varied significantly. Specifically, those with PDD and SPA reported lower intercourse satisfaction. The PDD group experienced significantly lower overall satisfaction and a lower orgasmic function. They also had higher erectile dysfunction than controls.

The phenomenology of these groups differs too. For example, a study looked at the characteristics of men with PDD (38% of whom had delusional beliefs) relative to an SPA group and a group with no concerns [10]. There were no significant differences in marital status, education or ethnicity between the groups but men with PDD were found to be significantly older. It is therefore likely that they have engaged in Safety-Seeking Behaviours (SSBs) and avoidance for a longer time. In turn, their behaviours are likely to be more engrained and so too will the beliefs these actions reinforce. Men with PDD were found to score higher on symptoms of general psychopathology (e.g., low mood, general anxiety and quality of life). Both individuals with PDD and SPA were more likely to report concern with their testes and other features, where 66% of these other feature concerns were related to masculinity. Men with PDD were more likely to be worried about both the flaccid and erect size of their penis than men with SPA, who were typically concerned with either flaccid or erect size. The PDD group were also more likely to have psychiatric comorbidity, with depression, social phobia or general anxiety disorder being the most common, respectively.

Research using a self-discrepancy theory framework has also highlighted significant differences between those with PDD, SPA and no worries [11] which have important implications for treatment. Those with PDD were suggested to have stronger beliefs that their penis should be bigger, reflecting a tougher inner critic and deeper shame, as well as less flexible beliefs and greater external shame. There was too evidence that one's ideals or demands and importance placed on penis size are more related to symptom severity and degree of distress than is actual size. Greater discrepancy between one's perceived and ideal size was associated with

increasing PDD symptomology. The cognitive processes underlying these various discrepancies should be targeted in treatment.

3.2.3.3 Muscle Dysmorphia

Muscle dysmorphic disorder is a subtype of BDD in the DSM-5 (but not ICD-11). This mainly occurs in men who are concerned predominantly about the size of their muscles. Despite these men often having a muscular physique, they consider themselves as too small or puny. These individuals may spend excessive time exercising, maintain strict and specific diets, use supplements as well as anabolic steroids and testosterone [12]. It has been suggested that this group is like those with PDD, in that if they have other areas of preoccupation, these seem to be related to features of masculinity. This implies that muscle dysmorphia is less about specific muscle size and more about masculinity.

3.2.4 Epidemiology

BDD is more common than obsessive-compulsive disorder (OCD), anorexia and schizophrenia with estimated prevalence of 1.9% [13].

The presence of BDD in different settings varies significantly. This is higher in cosmetic settings, where 5–15% of people in cosmetic surgery clinics could be considered to have BDD. In certain specialties, this disparity was more significant. The weighted prevalence of individuals with BDD was 20.1% in rhinoplasty surgery, 11.2% in orthodontist/cosmetic orthognathic surgery settings and 11.3% in dermatology outpatients. Screening for BDD specifically is important as individuals often present with symptoms of depression, social anxiety and OCD when BDD would be their main problem [14]. Many people with BDD will not mention their appearance concerns unless directly asked due to feelings of shame and that their clinician would not understand their concern.

It is hard to accurately measure the proportion of the male BDD population that have concerns around their penis. Given 45% of men in the aforementioned survey of 52,000 heterosexual men and women were dissatisfied with the size of their penis, one may predict the proportion is relatively high. This hypothesis seems reasonable when dissatisfaction with other typical concerns of masculinity, namely weight and height, was lower at 41% and 38%, respectively. What's more is the survey was only of heterosexual men who are at less risk of body dissatisfaction than homosexual men to whom penis aesthetics may have greater importance [8, 9]. In the homosexual male community, penis size is considered important in terms of how they construct their sense of self, masculinity and there seems to exist a narrative that 'bigger is better' when looking for a partner. It too relates to sexual positioning, where those with smaller penises often assume the submissive position.

Further research on the influence of sexual orientation on the importance placed on penis specifics is needed.

3.3 Clinical Presentation

3.3.1 Insight

The level of insight in individuals with BDD varies significantly. Delusional beliefs in BDD are common, with 32–38% with absent insight [5]. It is therefore no surprise that many see their problem as physical in nature and present more commonly in cosmetic settings.

3.3.2 Safety-Seeking Behaviours and Avoidance

Safety-Seeking Behaviours (SSBs) and avoidance capture the actions those with BDD carry out with the aim of protecting themselves. These are employed in response to the intense emotions which appearance preoccupations trigger. They may be specific to their preoccupation and seem intuitive. For example, those with concerns around their skin may 'camouflage' by applying copious layers of make-up to conceal their perceived flaw. Others are less intuitive and complex, such as mirror gazing (as will be discussed). Other SSBs include seeking reassurance to verify existence of the defect, comparing appearance with others or old photos of themselves, excessive grooming, surgery and treatments. Most SSBs in PDD can be divided into threat detection or monitoring (such measuring and comparing one's penis) and camouflage (such as changing posture to avoid penis being seen) [10]. On average, BDD sufferers spend 3–8 h occupied by their appearance, with 25% spending more than 8 h a day [5].

Given strong fears of judgement and social rejection combined with intense shame, it is no surprise extensive avoidance is typical. The degree of avoidance can depend on preoccupation and ability to conceal it. Sadly, avoidance often extends to the individual becoming housebound, and sometimes restricted to a single room, as they begin to fear the judgement of even from those closest to them. In PDD, anxiety provoking situations can be broadly categorised in two main forms; situations where one would display a flaccid penis in a public situation, such as changing rooms, and situations where one would display a flaccid or erect penis with a sexual partner [5].

In the study of the phenomenology of men with PDD, it was found PDD group exhibited significantly greater frequency of avoidance [10]. They also engaged in significantly more SSBs than the control group (in all but 1 of the 16 domains) as did those with SPA (in 12 of 16 domains). When questioned about the anxiety they

anticipated to experience in various situations, they described significantly greater anxiety relative to the other groups in all situations.

Both SSBs and avoidance fuel the disorder and do not allow one to test out what would happen if they did not employ these behaviours. In turn, they reinforce the individual's unhelpful beliefs, drastically reduce their quality of life as well as ability to seek treatment.

3.3.2.1 Mirror Gazing

Mirror gazing or taking selfies is considered as a type of checking behaviour. Others may also directly check with their fingers and hands by touch.

During mirror gazing, BDD patients typically experience a 'felt impression' of themselves. This is often in the visual modality of the view of an observer with attention focussed on an internal impression, physical sensations or feelings and not their reflection in the mirror. These are commonly related to memories with strong affect that bring about a current sense of threat as they have not been processed and have lost their context. In a study of the characteristics of those with PDD, a higher proportion of the PDD group experienced recurrent images relative to the SPA and control group [10]. These images could be considered as four distinct categories: flashbacks, flashforwards, images of their own penis and images of their partner being sexually intimate with a larger penis. Naturally, some of these would be informed by memories. Although there was no difference between the groups for the type of imagery experienced, those with PDD experienced them more frequently. Processing and cognitively appraising memories as being related to an experience or just an image form an important part of treatment.

3.3.3 Cosmetic Treatment

Often, through a combination of lack of awareness, education and insight in BDD, sufferers seek cosmetic procedures in the hope that it will remedy their concerns. They see their issue as physical rather than psychological in nature. Indeed, 76% of individuals with BDD undergo cosmetic treatment, either surgical or minimally invasive [15] and the prevalence of BDD sufferers as a proportion of those in cosmetic surgeries is high. Worrying rates have been found in cosmetic, orthodontic and dermatological settings, where 5%, 10% and 12% of individuals could be considered to have BDD symptomology up to a staggering 25% of the individuals seeking rhinoplasty [15].

It is considered rare that such intervention will help to relieve BDD symptoms. Sufferers often describe being dissatisfied with the outcome of the procedure and/or desire to alter it again. A review of 11 studies (6 retrospective and 5 prospective) of cosmetic treatment outcomes in BDD found that the weight of evidence indicated that this is an ineffective intervention for the majority of BDD sufferers [15].

Even for those without BDD, cosmetic treatment can have complex psychological outcome. A 5-year follow-up study of 24 individuals who requested cosmetic surgery included 12 who were diagnosed with BDD at baseline [16]. 15 of these individuals underwent a cosmetic procedure. At follow-up 6 of 7 with BDD still met the diagnostic criteria. Concerningly, 3 individuals who did not have BDD at baseline now met diagnostic criteria at follow-up.

Solutions to worries about one's penis, particularly size, are not difficult to come by. All internet search engines provide thousands of links to apparent solutions. There is a great variety of interventions, both surgical and non-surgical. Surgical procedures promising to alter length, such as suspensory ligament release and cartilage transplant, and adjust girth, such as dermal graft and injection of synthetic materials, have not been extensively research and are experimental at best. The case is the same for non-surgical procedures including exercises such as a massage technique called jelqing.

A systematic review of 17 studies looking at the efficacy of 21 interventions in 1192 men with penis concerns (773 followed up) concluded the offer of any such intervention is both unethical and negligent when assessment and counselling in a psychological setting are not conducted [17]. Most of these studies featured exclusively men with penises in the normal range in terms of length and girth dimensions (all but two studies) and only one study included 3 men with a micro-penis. Concerningly, far more men attempted surgical ($N = 525$) rather than non-surgical ($N = 248$) interventions. Even in instances when the same procedure was used, outcomes had high variability. Complications across all interventions were common ranging from bruising to wound dehiscence and the need for surgical revision. In some instances, penile length was reported to have reduced after surgery. When screening and/or patient counselling was given, most men were dissuaded from physical intervention with a range of 66.6–100% no longer seeking such procedures.

The majority of practitioners would refuse to treat someone if they had BDD [15]. Given this, more diligent screening would be expected to decrease the presence of BDD populations in cosmetic settings. Indeed, screening questionnaires for BDD designed for clinical settings have been developed such as the Cosmetic Procedure Screening Questionnaire for BDD (COPS), which has also been adapted for those with penis concerns (COPS-P). There needs to be a close liaison between professionals, so that these individuals can be provided with the appropriate education, treatment and support.

3.3.3.1 Cosmetic Procedure Screening Scale for PDD

The Cosmetic Procedure Screening Scale for PDD (COPS-P) is a 9-item self-report scale adapted to focus on concerns about one's penis and designed to screen for PDD [18]. It can discriminate between those with PDD, SPA or no concerns and therefore can be used to advise on where it is most suitable to refer the individual seeking cosmetic treatment. The COPS-P can assist to inform treatment, reducing unrealistic expectations and measuring outcomes after different interventions. Like

the BAPS, it is not related to girth or flaccid length and only weakly related to erect length, consistent with body image research suggesting no relationship between a physical feature and psychological distress.

3.3.3.2 Cosmetic Surgery in Women with Genital Concerns

Preoccupation in BDD around genitals can also occur in women, though it is less common, where concerns typically centre around the face. However, the incidence of labiaplasty (a surgical procedure which usually consists of reducing the degree of protrusion of the labia minora) is rising with 1726 women seeking labiaplasty in the NHS in 2010–11 [19].

Women often seek labiaplasty for aesthetic, functional or sexual reasons. A study comparing women seeking labiaplasty ($N = 55$, 10 of who met diagnostic criteria for BDD with concerns largely specific to their genitalia) to those who were not ($N = 70$), found these women had significantly greater interference in their life for all domains assessed [19]. The largest effect sizes were found for interference in sex life, discomfort and distress in general. These women also reported engaging in significantly more frequent avoidance and safety behaviours with a significantly greater dissatisfaction towards the appearance of their genital area. 38.6% of the labiaplasty group, relative to 5.13% of the comparison group, reported receiving negative comments or reactions about the appearance of their labia and the distress around these comments were also significantly greater. There was little difference in terms of many of the risk factors typically associated with BDD, such as abuse and neglect.

The outcomes of labiaplasty seem to contrast those of cosmetic procedural attempts to resolve other preoccupations in BDD. A prospective comparison study looking at the psychosexual outcomes after labiaplasty (N = 49) to a comparison group (N = 39) found surprising results [20]. 24 of 25 women in the labiaplasty group showed reliable and clinically significant improvement on the Genital Appearance Satisfaction (GAS) scale, which reflects attitudes towards one's genital appearance. 21 of 23 women showed an improvement at the long-term follow-up. 8 of 9 women in the labiaplasty group no longer met diagnostic criteria for BDD after the procedure at the 3-month follow-up. These results are promising but caution must be emphasised due to the small sample size. Larger scale studies are required before recommending such a procedure as an intervention for BDD in women where their genitalia is the preoccupation.

3.3.3.3 Cultural Considerations

As discussed, people with BDD have extensive fears surrounding rejection and/or humiliation. In some Asian cultures, they are also concerned with causing offense to others [6]. Further research on the characteristics of BDD in different cultures is required, as much is currently derived from North America and Western Europe.

Koro or suo-yang, also known as genital restriction syndrome, mainly occurs in Asia and, to a lesser extent in Africa, and some consider it a cultural variation of BDD and perhaps PDD [6]. It describes a fear or belief in men that the penis is shrinking/retracting into one's body or in women the same is occurring with respect to their labia and breasts. A main difference between Koro and BDD is that the anxiety and avoidance, though acute, are transient where the sufferer anticipates impotence, sterility or death. Additionally, others in the immediate family may share the same beliefs and participate in what may be considered SSBs of holding on to the genitalia of the individual, using special instruments or manually.

3.4 Possible Pathophysiological Mechanism

Research has proposed a diathesis stress model, where predisposing vulnerability factors (notably visual processing and greater aesthetic sensitivity) and environmental influences (notably experiences of bullying and neglect) result in the development of BDD.

Individuals with BDD often experience greater rates of teasing and bullying relative to clinical comparison groups and healthy controls. Sometimes, the nature of the bullying can differ too, with some reporting greater levels of teasing focussed on aesthetics and competency. As discussed, imagery plays an important role in BDD. Some individuals experience intrusive, appearance-related images which research has found are more negative, reoccurring and viewed from an observer perspective [21]. They are often associated with memories of being teased or bullied about their appearance in adolescence and therefore inform their 'felt impression'. A high proportion of individuals with BDD report childhood abuse and neglect which can result in poor attachment and body shame [22]. Certain types of abuse and neglect have also been implicated with BDD symptom severity and other comorbidities.

Those with PDD have been found to be more likely to have experienced abuse and neglect as a child relative those with SPA [9, 10]. As they got older, these men were also more likely to have experienced teasing about their appearance and competency by their peers. Both those with PDD and SPA report experiencing specific teasing about the size of their genitalia by peers in adolescence or early sexual experiences. This is compounded due to the abuse and neglect in childhood, where those with PDD may be more sensitive and likely to retain comments from others.

The visual perception, gaze and eye movements of individuals with BDD seem to play an important role and differ relative to individuals with other OCRDs. A systematic review of visual processing in BDD found specific abnormalities [23]. These pertained to face and object recognition, aesthetics, emotion identification and gestalt processing. Those with BDD were also found to exhibit a dominance of detailed, local processing over global processing relative to healthy controls, alongside the associated changes in brain activation in visual regions. This highlights a visual attention bias in BDD that leans to specific details or features, rather than

perception of an image as whole, in contrast to non-BDD populations who use an effective combination of both.

There is little evidence of saccades (abnormalities in basic eye movements) in those with BDD, which feature in individuals with certain other psychiatric disorders (such as OCD). The visual perception differences in BDD are likely to be the result of disruption in higher order processing. Research on face processing highlights this. BDD suffers usually demonstrate higher error rates and slower response times when recognising the identity and emotions of face stimuli. It seems an atypical strategy may be employed when viewing images reflected in a pattern of hyposcanning with significantly more blinks, fewer fixations of extended duration and higher mean saccade amplitudes [12, 24]. Less visual attention seems to be devoted to salient facial features and gaze may focus on or avoid the perceived area of concern [24]. These patterns also extend to somatoperception (the perception by which individuals formulate a sense of what they look like) as well as others' faces, which may reflect the compulsion to repeatedly check or avoid one's own appearance as well as engage in frequent comparison to others. There also appears to be a processing bias amongst those with BDD, where neutral faces and scenarios are interpreted as more threating. Aesthetic sensitivity also appears to be greater in people with BDD, who are more likely to be trained in art or design, and a genetic predisposition for a need for symmetry and order [25].

3.5 Clinical Management

There is insufficient existing data on PDD for a specific treatment protocol to be developed. Much of how PDD is treated relies on generalisations from, and adaptations to, the treatment of BDD. This comprised of Cognitive Behaviour Therapy (CBT) and pharmacotherapy, alone or in combination. The National Institute for Health and Clinical Excellence (NICE) recommends that adults should be offered either the choice of a course of a Selective Serotonergic Reuptake Inhibitor (SSRI) or specialised CBT. This recommendation is irrespective of insight, which seems to have no significant impact on the efficacy of the treatment.

Unfortunately, provision of such treatment is not widespread. For example, surveys have found that only between 19% and 34% of people with body dysmorphic concerns had received SSRI medication and 10–17% had received an empirically supported psychotherapy [2, 26]. Barriers to widespread provision of treatment include a lack of trained therapists, costs associated with treatment as well as geographical barriers.

An additional and significant barrier is that many with BDD believe their problem is physical rather than psychological in nature and therefore may present in cosmetic settings. Even in psychiatric settings, high levels of shame and grave fears of judgement and rejection make it tough for them to disclose their true concerns. Hence, they often present with symptoms of depression, social anxiety and

OCD. BDD-specific screening is needed as some may only disclose body dysmorphic concerns if asked directly.

3.5.1 Pharmacotherapy

Serotonergic reuptake inhibitors (SRIs) denote a class of anti-depressants (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline and clomipramine). The usual dose of SRIs to treat those with BDD is higher than that of depression. Typically, to determine if a medication is suitable, a trial of 12 weeks of an SRI is recommended, where 4 of these weeks are at the maximum tolerated dose.

Given the high proportion of those with delusional beliefs in BDD, the role of antipsychotic medication in treatment may seem logical, especially given its efficacy in OCD (a related OCRD).

This has not been extensively researched, with only one negative RCT [27]. Antipsychotic augmentation is not therefore recommended in routine treatment of BDD.

3.5.2 Psychological Therapies

The treatment recommended by the NICE guidelines is CBT adapted for BDD comprising of 16–24 sessions. This treatment aims to help patients build an alternative understanding of their problem, disengage from unhelpful coping strategies that fuel the disorder and expand their self-focussed attention. Through graded exposure and response prevention (ERP) and behavioural experiments, individuals test out their fears and challenge their beliefs. Often, due to a combination of poor insight, ambivalence towards psychological therapy and the high levels of anxiety that accompany testing out fears and beliefs, motivational interviewing techniques and extensive psychoeducation play an important role during treatment. As it is common for individuals with BDD to have psychiatric comorbidities, a hierarchical approach is often practiced, prioritising that which is causing most distress and impairment [12]. When CBT for BDD is employed, it can result in improvements in the comorbid disorders too. In addition, a commitment to not pursue cosmetic procedures during treatment is often necessary.

A meta-analysis of seven RCTs of CBT for BDD ($N = 299$) found that CBT was superior to waitlist or credible psychological placebo in reducing symptoms with large effect sizes [28]. There were also medium effect sizes for depressive symptoms and improvements in insight. In most trials, those with delusional beliefs responded with a similar effect size. These gains were maintained at least in the short term, specifically at the 2- to 4-month follow-up and are comparable to earlier meta-analysis of CBT for OCD. The results described are robust with similar

improvements found in the varying control groups, CBT specific techniques, delivery of treatment (individual, group or internet based) and age groups.

One study in the meta-analysis compared CBT for BDD against another psychological treatment. This was a comparison of Anxiety Management (AM) versus CBT for BDD [29]. 46 adults in the moderate to severe range were randomised to either CBT ($N = 21$) or AM ($N = 25$) where they would receive a weekly session of an hour for 12 weeks. The groups did not differ significantly in terms of baseline variables or demographics and CBT was found to be more effective after the treatment period. It was also found to be just as effective for those who were significantly depressed or had delusional beliefs (over half had delusional beliefs). Although AM did have a significant effect in reducing symptom severity (BDD-YBOCS scores), cognitive and behavioural aspects of BDD (Appearance Anxiety Inventory, AAI, scores) and depression. But, CBT had significantly larger effects sizes across these domains.

The most recent RCT ($N = 120$) looked at the efficacy of supportive psychotherapy ($N = 59$) in contrast to CBT for BDD ($N = 61$) [30]. This was conducted at two hospital sites in the US, where weekly treatment was administered for 24 weeks followed by a 3- and 6-month follow-up assessment. 84% of participants undergoing CBT for BDD met response criteria, with most maintaining these gains at the 6-month follow-up. Interestingly, the efficacy of SPT was site specific; one site had a response rate of 46% (a significant difference to CBT) and the other had a response rate of 64% (not a statistically significant difference to CBT). It has been suggested that this variance may reflect differences in the quality of the psychotherapy treatment at the two sites, where the latter provides predoctoral and postdoctoral training in supportive or integrative psychotherapy. As such, this site is likely to have provided superior psychotherapy and this psychotherapy is likely to be superior to that in other academic medical or community settings. This difference between the two sites may also be due to the nature of SPT, which emphasises common factors, in contrast to specific skills as in CBT, and therefore therapist factors may have a greater impact. It should be noted that the response rate of SPT in this trial may be inflated and not reflect the true efficacy of SPT in treating BDD. This is because it was delivered at a site that specialises in both SPT and BDD and the SPT was enhanced with BDD-specific psychoeducation and treatment rationale where there was a considerable patient contact time.

3.5.2.1 Internet-Based CBT

An emerging method of treatment that warrants further development and evaluation is the delivery of internet-based interventions for BDD. This could be valuable in a stepped care model, providing CBT which could be sufficient for less severe patients. It could also widen access to appropriate treatment by circumventing the barrier of geographical location and help those who are too afraid to leave their home. Research into the efficacy of a therapist guided internet-based CBT programme for BDD (BDD-NET) has yielded promising results. A 12-week single

blind parallel group RCT of 94 adults, with a BDD-YBOCS of at least 20, compared the efficacy of BDD-NET ($N = 47$) with online supportive therapy ($N = 47$) [12]. BDD-NET was found to be superior to supportive therapy. It was associated with significant improvements in BDD severity, depression and other secondary outcome measures including global functioning and quality of life. At the 3-month follow-up, 56% of individuals receiving BDD-NET were classed as responders, in contrast to 13% of those in supportive therapy. Later, patients who received supportive therapy were offered BDD-NET.

Future research should compare efficacy of internet-based interventions to face-to-face treatment and consider which facets indicate which treatment delivery method would be optimal. As CBT is often delivered as a combination of specific modules (such as imagery rescripting) with various adjuncts (such as compassion focussed therapy), it would be useful to compare the efficacy of these.

Key Messages

- BDD is a relatively common condition which incorporates PDD.
- PDD is a term used for convenience and refers to men with BDD whose primary or sole preoccupation is with their genitalia.
- Individuals with BDD may engage in extensive and complex safety seeking and avoidance behaviours.
- Cosmetic treatment for men with PDD without prior assessment and specific therapy is unlikely to be helpful.
- Bullying, neglect, visual processing and greater aesthetic sensitivity are pathophysiological mechanisms implicated in the development of BDD.
- Treatment for PDD is like to generalise from that of BDD.
- NICE guidelines recommend adults with BDD should be offered either the choice of a course of SSRIs or specialised CBT.

References

1. Lever J, Frederick D, Peplau L. Does size matter? Men's and women's views on penis size across the lifespan. Men Masculinities. 2006;7(3):129–43. https://www.researchgate.net/publication/232595653_Does_Size_Matter_Men's_and_Women's_Views_on_Penis_Size_Across_the_Lifespan. https://doi.org/10.1037/1524-9220.7.3.129f.
2. Buhlmann U. Treatment barriers for individuals with body dysmorphic disorder: an internet survey. J Nerv Ment Dis. 2011;199(4):268–71. https://pubmed.ncbi.nlm.nih.gov/21451352/. https://doi.org/10.1097/NMD.0b013e31821245ce.
3. Bjornsson AS, Didie ER, Grant JE, Menard W, Stalker E, Phillips KA. Age at onset and clinical correlates in body dysmorphic disorder. Compr Psychiatry. 2013;54(7):893–903. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3779493/. https://doi.org/10.1016/j.comppsych.2013.03.019.
4. Neziroglu F, Cash TF. Body dysmorphic disorder: causes, characteristics, and clinical treatments. Body Image. 2008;5(1):1–2. https://pubmed.ncbi.nlm.nih.gov/18358798/. https://doi.org/10.1016/j.bodyim.2008.03.001.

5. Singh AR, Veale D. Understanding and treating body dysmorphic disorder. Indian J Psychiatry. 2019;61(Suppl 1):S131–5. https://pubmed.ncbi.nlm.nih.gov/30745686/. https://doi.org/10.4103/psychiatry.IndianJPsychiatry_528_18.
6. Veale D, Matsunaga H. Body dysmorphic disorder and olfactory reference disorder: proposals for ICD-11. Braz J Psychiatry. 2014;36(Suppl 1):14–20. https://pubmed.ncbi.nlm.nih.gov/25388608/. https://doi.org/10.1590/1516-4446-2013-1238.
7. Veale D, Miles S, Bramley S, Muir G, Hodsoll J. Am I normal? A systematic review and construction of nomograms for flaccid and erect penis length and circumference in up to 15,521 men. BJU Int. 2015;115(6):978–86. https://pubmed.ncbi.nlm.nih.gov/25487360/. https://doi.org/10.1111/bju.13010.
8. Veale D, Eshkevari E, Read J, Miles S, Troglia A, Phillips R, et al. Beliefs about penis size: validation of a scale for men ashamed about their penis size. J Sex Med. 2014;11(1):84–92. https://pubmed.ncbi.nlm.nih.gov/24118940/. https://doi.org/10.1111/jsm.12294.
9. Veale D, Miles S, Read J, Troglia A, Wylie K, Muir G. Sexual functioning and behavior of men with body dysmorphic disorder concerning penis size compared with men anxious about penis size and with controls: a cohort study. Sex Med. 2015;3(3):147–55. https://pubmed.ncbi.nlm.nih.gov/26468378/. https://doi.org/10.1002/sm2.63.
10. Veale D, Miles S, Read J, Troglia A, Carmona L, Fiorito C, et al. Phenomenology of men with body dysmorphic disorder concerning penis size compared to men anxious about their penis size and to men without concerns: a cohort study. Body Image. 2015;13:53–61. https://pubmed.ncbi.nlm.nih.gov/25675864/. https://doi.org/10.1016/j.bodyim.2014.09.008.
11. Veale D, Miles S, Read J, Bramley S, Troglia A, Carmona L, et al. Relationship between self-discrepancy and worries about penis size in men with body dysmorphic disorder. Body Image. 2016;17:48–56. https://pubmed.ncbi.nlm.nih.gov/26952016/. https://doi.org/10.1016/j.bodyim.2016.02.004.
12. Castle D, Beilharz F, Phillips KA, Brakoulias V, Drummond LM, Hollander E, et al. Body dysmorphic disorder: a treatment synthesis and consensus on behalf of the International College of Obsessive-Compulsive Spectrum Disorders and the obsessive compulsive and related disorders network of the European College of Neuropsychopharmacology. Int Clin Psychopharmacol. 2021;36(2):61–75. https://pubmed.ncbi.nlm.nih.gov/33230025/. https://doi.org/10.1097/YIC.0000000000000342.
13. Veale D, Gledhill LJ, Christodoulou P, Hodsoll J. Body dysmorphic disorder in different settings: a systematic review and estimated weighted prevalence. Body Image. 2016;18:168–86. https://pubmed.ncbi.nlm.nih.gov/27498379/. https://doi.org/10.1016/j.bodyim.2016.07.003.
14. Phillips KA. Body dysmorphic disorder: diagnosis and treatment of imagined ugliness. J Clin Psychiatry. 1996;57(Suppl 8):61–4. discussion 65, https://pubmed.ncbi.nlm.nih.gov/8698683/
15. Bowyer L, Krebs G, Mataix-Cols D, Veale D, Monzani B. A critical review of cosmetic treatment outcomes in body dysmorphic disorder. Body Image. 2016;19:1–8. https://pubmed.ncbi.nlm.nih.gov/27517118/. https://doi.org/10.1016/j.bodyim.2016.07.001.
16. Tignol J, Biraben-Gotzamanis L, Martin-Guehl C, Grabot D, Aouizerate B. Body dysmorphic disorder and cosmetic surgery: evolution of 24 subjects with a minimal defect in appearance 5 years after their request for cosmetic surgery. Eur Psychiatry. 2007;22(8):520–4. https://pubmed.ncbi.nlm.nih.gov/17900876/. https://doi.org/10.1016/j.eurpsy.2007.05.003.
17. Marra G, Drury A, Tran L, Veale D, Muir GH. Systematic review of surgical and nonsurgical interventions in Normal men complaining of small penis size. Sex Med Rev. 2020;8(1):158–80. https://pubmed.ncbi.nlm.nih.gov/31027932/. https://doi.org/10.1016/j.sxmr.2019.01.004.
18. Veale D, Miles S, Read J, Troglia A, Carmona L, Fiorito C, Wells H, Wylie K, Muir G. Penile dysmorphic disorder: development of a screening scale. Arch Sex Behav. 2015;44(8):2311–21. https://pubmed.ncbi.nlm.nih.gov/25731908/. https://doi.org/10.1007/s10508-015-0484-6.
19. Veale D, Eshkevari E, Ellison N, Costa A, Robinson D, Kavouni A, Cardozo L. Psychological characteristics and motivation of women seeking labiaplasty. Psychol Med. 2014;44(3):555–66. https://pubmed.ncbi.nlm.nih.gov/23659496/. https://doi.org/10.1017/S0033291713001025.

20. Veale D, Naismith I, Eshkevari E, Ellison N, Costa A, Robinson D, et al. Psychosexual outcome after labiaplasty: a prospective case-comparison study. Int Urogynecol J. 2014;25(6):831–9. https://doi.org/10.1007/s00192-013-2297-2.
21. Wilhelm S, Phillips KA, Greenberg JL, O'Keefe SM, Hoeppner SS, Keshaviah A, et al. Efficacy and posttreatment effects of therapist-delivered cognitive behavioral therapy vs supportive psychotherapy for adults with body dysmorphic disorder: a randomized clinical trial. JAMA Psychiat. 2019;76(4):363–73. https://pubmed.ncbi.nlm.nih.gov/30785624/. https://doi.org/10.1001/jamapsychiatry.2018.4156.
22. Didie ER, Tortolani CC, Pope CG, Menard W, Fay C, Phillips KA. Childhood abuse and neglect in body dysmorphic disorder. Child Abuse Negl. 2006;30(10):1105–15. https://pubmed.ncbi.nlm.nih.gov/17005251/. https://doi.org/10.1016/j.chiabu.2006.03.007.
23. Beilharz F, Castle DJ, Grace S, Rossell SL. A systematic review of visual processing and associated treatments in body dysmorphic disorder. Acta Psychiatr Scand. 2017;136(1):16–36. https://pubmed.ncbi.nlm.nih.gov/28190269/. https://doi.org/10.1111/acps.12705.
24. Toh WL, Castle DJ, Rossell SL. Facial affect recognition in body dysmorphic disorder versus obsessive-compulsive disorder: an eye-tracking study. J Anxiety Disord. 2015;35:49–59. https://pubmed.ncbi.nlm.nih.gov/26363226/. https://doi.org/10.1016/j.janxdis.2015.08.003.
25. Veale D, Ennis M, Lambrou C. Possible association of body dysmorphic disorder with an occupation or education in art and design. Am J Psychiatry. 2002;159(10):1788–90. https://pubmed.ncbi.nlm.nih.gov/12359691/. https://doi.org/10.1176/appi.ajp.159.10.1788.
26. Marques L, Weingarden HM, Leblanc NJ, Wilhelm S. Treatment utilization and barriers to treatment engagement among people with body dysmorphic symptoms. J Psychosom Res. 2011;70(3):286–93. https://pubmed.ncbi.nlm.nih.gov/21334500/. https://doi.org/10.1016/j.jpsychores.2010.10.002.
27. Phillips KA. Placebo-controlled study of pimozide augmentation of fluoxetine in body dysmorphic disorder. Am J Psychiatry. 2005;162(2):377–9. https://pubmed.ncbi.nlm.nih.gov/15677604/. https://doi.org/10.1176/appi.ajp.162.2.377.
28. Harrison A, Fernández de la Cruz L, Enander J, Radua J, Mataix-Cols D. Cognitive-behavioral therapy for body dysmorphic disorder: a systematic review and meta-analysis of randomized controlled trials. Clin Psychol Rev. 2016;48:43–51. https://pubmed.ncbi.nlm.nih.gov/27393916/. https://doi.org/10.1016/j.cpr.2016.05.007.
29. Veale D, Anson M, Miles S, Pieta M, Costa A, Ellison N. Efficacy of cognitive behaviour therapy versus anxiety management for body dysmorphic disorder: a randomised controlled trial. Psychother Psychosom. 2014;83(6):341–53. https://pubmed.ncbi.nlm.nih.gov/25323062/. https://doi.org/10.1159/000360740.
30. Osman S, Cooper M, Hackmann A, Veale D. Spontaneously occurring images and early memories in people with body dysmorphic disorder. Memory. 2004;12(4):428–36. https://pubmed.ncbi.nlm.nih.gov/15487539/. https://doi.org/10.1080/09658210444000043.

Chapter 4
Persistent Genital Arousal Disorder/ Genitopelvic Dysesthesia

Caroline Pukall, Barry Komisaruk, and Irwin Goldstein

Learning Objectives
- To describe the definition, prevalence, and characteristics of Persistent Genital Arousal Disorder/Genitopelvic Dysesthesia (PGAD/GPD) to facilitate its understanding and aid in its efficient diagnosis.
- To illustrate the biopsychosocial influences involved in the expression of PGAD/GPD.
- To characterize PGAD/GPD as a multifactorial condition in which multiple, concurrent approaches are most likely to be effective in its management.

4.1 Introduction

Persistent Genital Arousal Disorder/Genitopelvic Dysesthesia (PGAD/GPD) is a highly distressing yet poorly understood condition affecting people of all ages and genders [1]. It is characterized by sensations of genital arousal (e.g., throbbing) that

C. Pukall
Department of Psychology, Queen's University, Kingston, ON, Canada

B. Komisaruk
Departments of Psychology and Radiology, Rutgers University, Newark, NJ, USA

I. Goldstein (✉)
Sexual Medicine, Alvarado Hospital, San Diego, CA, USA

Y. Reisman et al. (eds.), *Textbook of Rare Sexual Medicine Conditions*,
https://doi.org/10.1007/978-3-030-98263-8_4

are persistent, unwanted, and distressing. These sensations occur in the absence of subjective feelings of sexual desire/arousal or feeling "turned on" [1]. Part of the reason that PGAD/GPD is not well understood is that the experience of genital "arousal" is usually interpreted to be time limited, wanted, and pleasurable [2]. Adding to the complexity of PGAD/GPD is the belief that "arousal" is a unified construct: the physical aspects of arousal are assumed to act in concordant ways with the subjective aspects [2]. However, decades of sexual psychophysiological research examining the main components of sexual arousal (genital response and subjective ratings of arousal) in response to sexual stimuli have indicated that the physiological and subjective components are not perfectly concordant [3]. In fact, there is much variation in sexual concordance (i.e., the relationship between the physiological and subjective components of sexual arousal) both between and within participants given various parameters, such as genital arousal measurement device, scales used for arousal ratings, and types of sexual stimuli (e.g., films versus audio stories) [3]. Thus, the experience of arousal is best conceptualized on a continuum—from not at all pleasurable to extremely pleasurable, for example. Applying this same perspective to the experience of orgasm, which is also assumed to be wanted and pleasurable, is useful in conversations with patients with PGAD/GPD because some patients experience repetitive, disruptive, and unpleasant orgasms [1]. Interestingly, the experience of non-pleasurable orgasms has also been reported in nonclinical and clinical (e.g., those with anhedonic ejaculation) samples [4, 5]. It is therefore essential to focus on the patients' experiences of their symptoms, avoid making assumptions about the valence of these experiences, and recognize the complexity of PGAD/GPD symptoms.

4.2 Definition of PGAD/GPD

Various names referring to PGAD/GPD have existed over the past two decades. It was first called Persistent Sexual Arousal Syndrome by Leiblum and Nathan (2001) [6]; however, it was changed to Persistent Genital Arousal Disorder (PGAD) to clarify that it was only the sensations of *genital arousal* (not "sexual arousal," which includes both physiological and subjective components) that were persistent [7]. The term PGAD was adopted by most sexual medicine experts [8] and by the International Classification of Diseases-11 [9], although some referred to it as Restless Genital Syndrome, drawing a parallel between PGAD and Restless Legs Syndrome [10]. In 2021, a consensus and process of care paper formally reconceptualized PGAD as PGAD/GPD, given that the genitopelvic sensations of arousal were unpleasant and atypical (i.e., a dysesthesia) [1]. This landmark paper defined PGAD/GPD as "persistent or recurrent, unwanted or intrusive, distressing sensations of genital arousal (e.g., feelings of being on the verge of orgasm and of lubrication and swelling, tingling, throbbing, contractions) that persist for 3 months or more and may include other types of genitopelvic dysesthesia (e.g., buzzing, burning, twitching, itch, pain)" (p. 668). In addition, it specified that the sensations of

PGAD/GPD are not associated with sexual interest, thoughts, or fantasies; that they can occur in various genitopelvic areas (e.g., clitoris, vulva, bladder) in the absence of observable signs of genital arousal (e.g., vaginal lubrication, vulvar or clitoral swelling); and that some people with PGAD/GPD experience uncontrollable orgasms or have an excessive number of orgasms. Furthermore, it states that PGAD/GPD symptoms may be resolved partially, not at all resolved, or even aggravated by sexual activity; may include dysesthetic orgasms (e.g., experienced as aversive); and may be aggravated by various factors (e.g., vibrations from a moving vehicle, music or sounds, stress). PGAD/GPD is also associated with various psychological experiences, such as despair, emotional lability, catastrophization, and suicidality [1].

4.3 Known Epidemiology

Studies examining the prevalence of PGAD/GPD in clinical and nonclinical samples indicate that up to 4.3% of individuals may be affected. Garvey and colleagues found that 1% (1 of 96) of women presenting at a sexual health clinic in London, UK reported distressing sensations of genital arousal in the absence of sexual desire [11]. In a study of more than 1500 undergraduate students attending a Canadian university, Jackowich and Pukall (2020) [12] reported prevalence rates of 0.6% (7 of 1267) in women and 1.1% in men (4 of 360), similar to the rate of 1.6% (11 of 679) of undergraduate women attending an Italian university [13]; none of the seven nonbinary participants reported PGAD/GPD symptoms [12]. In a representative US sample, Jackowich and Pukall (2020) [12] reported somewhat higher rates: 2.7% of women (14 of 514) and 4.3% of men (22 of 506) reported symptoms consistent with PGAD/GPD; 2 of 6 nonbinary participants reported mild intensity PGAD/GPD symptoms, with none reporting moderate to high intensity. Despite the study's finding that participants of all educational and cultural backgrounds endorsed at least one PGAD/GPD symptom, individuals who completed a high school degree/general educational development (as compared to those with less than a high school degree and those who completed post-secondary education) and Non-Hispanic Black and Hispanic/Latinx (as compared to non-Hispanic white) participants endorsed significantly more symptoms. The latter finding is consistent with prevalence patterns of other forms of genitopelvic dysesthesia, such as vulvodynia [12].

4.4 Clinical Presentation and Contributing Factors

Given that the bulk of research and published case studies have focused on samples of women with PGAD/GPD, little is known about the clinical presentation and contributing factors in men and individuals with trans and nonbinary identities; however, based on the clinical experience of the authors, all people with PGAD/GPD

symptoms can present with symptoms similar to those experienced in women and patients with a penis may also experience unwanted spontaneous ejaculation [14].

Distress is a key component to diagnosing PGAD/GPD [1](Goldstein et al., 2021). It is important to note that some individuals with persistent sensations of genital arousal do not experience distress associated with their experience; therefore, the diagnosis of PGAD/GPD would not be made in these cases. Those with PGAD/GPD report moderate to high levels of distress; in addition, suicidal ideation and high levels of worry, stress, and depression have also been reported [15]. Those with PGAD/GPD may experience a variety of symptoms related to orgasm (e.g., spontaneous orgasm, feeling on the verge of orgasm), urination (e.g., urgency, frequency), and pain (e.g., pain in the clitoris at rest) [15]. Therefore, a comprehensive assessment is critical, and accessible mental health support is essential.

The average age of PGAD/GPD onset for women is in their mid-thirties, but the range is wide, and PGAD/GPD can start at any age; in addition, most people with PGAD/GPD will report that the symptoms started suddenly (versus gradually) and that they are constantly (versus intermittently) experienced [15]. Triggers for symptoms range widely and include sexual (e.g., feeling sexual desire), nonsexual (e.g., driving), emotional (e.g., stress), and physiological (e.g., full bladder) states; not surprisingly, most patients with PGAD/GPD will report that their symptoms interfere with activities of daily living, such as work and social activities [15]. Fortunately, those with PGAD/GPD report that engaging in distracting activities, relaxation exercises, and solitary and partnered sexual activity, as well as sleeping and other activities, can alleviate their symptoms temporarily, although others report that some of the same activities (e.g., sexual activity, sleep) can trigger their symptoms [15]. It is important to note that some individuals with PGAD/GPD may engage in frequent sexual activity (solitary, partnered) to alleviate their symptoms; because of this, and because of the lack of knowledge about PGAD/GPD and the complexities of arousal, many individuals with PGAD/GPD may be diagnosed with hypersexual disorder. It is important to fully understand the motivations for high frequency of sexual activity and the criteria for PGAD/GPD and any differentials before a definitive diagnosis is made.

4.5 Possible Pathophysiological Mechanisms

Based on recent multidisciplinary research, it has become evident that organic pathologies play a significant role in PGAD/GPD [1]. As demonstrated by functional magnetic resonance imaging (fMRI) in women, there is a common representation of the dysesthesia of PGAD/GPD as spontaneous intense hyperactivity in the genital sensory cortex (paracentral lobule). A review of PGAD/GPD management has recognized that this hyperactivity in the genital sensory cortex can emanate from five specific body regions, categorized as Regions 1–5. These regions are the following: end organ (Region 1), pelvis/perineum (Region 2), cauda equina (Region 3), spinal cord (Region 4), and brain (Region 5) [1].

Region 1 end organ pathologies involve the clitoris, penis, vestibule, vagina, scrotum, prostate, urinary bladder, and urethra (e.g., dermatoses such as lichen sclerosus, infections, GSM, and inflammation) [1].

Upon physical examination, for patients whose PGAD/GPD trigger is related to clitoral pathology, the following histories may be observed. They may have a history of hypersensitivity of glans (e.g., "grain of sand" sensation), discomfort wearing tight clothing or contact during sexual activity, inability to see the glans, or traumatic injury to the vulva/clitoris from a straddle injury. Patients whose PGAD/GPD trigger is related to vaginal pathology may have a history of copious yellow discharge, chronic infection, severe allergic reactions (sensitive skin), or genitourinary syndrome of menopause (GSM) symptoms (e.g., vaginal dryness and introital dyspareunia) [1].

Region 2 pelvis/perineum pathologies include pudendal and/or pelvic nerve pathology, high tone pelvic floor dysfunction, vascular pathologies, e.g., arteriovenous malformation and pelvic congestion syndrome, in addition to hypertonic pelvic floor muscle, and pudendal nerve entrapment [1]. Patients whose PGAD/GPD trigger is related to neuropathy of pelvic nerve may have previously undergone a Loop Electrosurgical Excision Procedure (LEEP) for cervical dysplasia or a mid-urethral sling surgery (MUS) for stress urinary incontinence. In this latter case, we have shown that the mesh in a cadaveric study lies close to critical pelvic nerves in the anterior vaginal wall/periurethral prostatic tissue [16].

The report that Tarlov cysts, which form on the genital sensory nerve roots of the cauda equina (Region 3), occurred in 12 of 16 (66.7%) of women with PGAD/GPD raised the awareness that PGAD/GPD perceptual symptoms can be generated by neuropathy that occurs distant from the genitopelvic region [17]. These Tarlov cysts are cerebrospinal fluid-filled meningeal "blisters" that contain aberrant sensory nerve fibers and form on the genitopelvic sacral nerve roots. Region 3 pathologies also include herniation of the lumbosacral intervertebral discs, resulting in extrusion of the nucleus pulposus through the tear in the annulus of the disc, which produces inflammation of the pudendal, pelvic, and sciatic nerve roots in the cauda equina, typically at L5-S1 and/or L4-L5 [1]. Region 4 spinal cord pathology may result from cervical/thoracic herniated intervertebral discs or medication changes. The latter could produce an imbalance in spinal cord serotonin and/or norepinephrine, resulting from initiation and/or discontinuation of SSRIs or SNRIs, which could alter the function of the pain-gate mechanism that utilizes these neurotransmitters, thereby provoking or exacerbating the dysesthesias [1]. Region 5 represents direct brain mediation of PGAD/GPD symptoms resulting from, for example, epileptic seizures [17], medication changes (e.g., SSRI or SNRI discontinuation and even initiation in some cases), and/or psychological factors (e.g., sexual/emotional trauma, anxiety, hypervigilance, catastrophization), which can trigger or exacerbate PGAD/GPD symptoms, leading to suicidality [1].

4.6 Clinical Management, Including Biological-Psychological-Social Contributing Factors

4.6.1 Diagnosis

An accurate diagnosis is essential to the process of clinical management and will likely involve a multidisciplinary team and ruling out differentials (e.g., hypersexual disorder). To this end, a comprehensive biopsychosocial diagnostic evaluation is recommended; this process consists of taking a detailed symptom, psychosocial, and medical history through an extensive clinical interview and a multi-stage physical examination of all relevant regions. It may also involve referrals to other health care providers for full assessment of relevant regions [1]. In line with recent recommendations by an expert consensus panel [1], we recommend that the physical examination begin with a careful evaluation of Regions 1 and 2 given that these regions are symptomatic and are accessible to physical examination by most medically trained clinicians. Additional details about the physical examination are included in this section after the clinical interview is described.

During the clinical interview, the clinician should gather detailed information about the PGAD/GPD symptoms (e.g., arousal, orgasm), such as their location/s, intensity, pattern, and onset. Additional questions on any triggers, alleviators, and past and current treatment or management strategies should also be asked. Importantly, the impact of the symptoms on one's overall quality of life, including their work, family, social, and sexual activities, should be documented [1]. Mood, distress, and suicide ideation should be carefully assessed, and if the patient needs immediate support for their mental health, access to appropriate providers should be offered. Medical history, including any comorbid genitopelvic or other conditions (e.g., medical, psychiatric), as well as trauma history, should be documented. All medications and any medical or other interventions undertaken for any health-related complaints, including PGAD/GPD, should also be carefully documented [1].

The physical assessment includes conducting a comprehensive physical examination, which may take one or several appointments. Conceptualizing pathologies in patients with PGAD/GPD that could occur in five distinct body regions has been found useful in developing a systematic approach for the examination [1]. Since the presumptive pathophysiology of PGAD/GPD is sensory hyperactivity, the purpose of the comprehensive physical assessment is to assist the clinician in localizing the origin of the trigger(s) of this hyperactivity. This will enable the clinician to perform appropriate differential diagnoses and thereby rationale-based treatment(s) of patients with PGAD/GPD.

Region 1 Region 1 end organ pathologies involve the clitoris, vestibule, vestibular bulbs, vagina, cervix, Bartholin's glands, the glans penis, penile shaft, scrotum, prostate, epididymis/vas deferens, urethra, prostate, urinary bladder, rectum, and/or umbilicus [1]. For patients with clitoral pathologies, physical examination may generate the following findings: clitoral phimosis using vulvoscopy, keratin "pearls"

associated with balanitis from clitoral adhesions, vulvar dermatoses, inability to fully retract the prepuce, and inability to visualize clitoral corona [1]. On physical examination, patients with vaginal pathology may show erythema, induration, tenderness of vestibule and vaginal mucosa, leukorrhea, or cervicitis. Additional Region 1 pathologies are lichen sclerosus, lichen planus, vulvar inflammatory conditions (e.g., candidiasis), desquamative inflammatory vaginosis, GSM, and/or neuropathies of sensory branches of the pudendal nerve (e.g., dorsal nerve, perineal nerve, inferior hemorrhoidal nerve), and/or sensory branches of the pelvic nerve (e.g., clitoris, vestibule, vagina, cervix, and/or prostate) [1]. For patients with female genital anatomy who have other end organ pathologies, please see Goldstein et al. [1]. Examples of Region 1 pathologies in patients with male genital anatomy are genital dermatoses, balanitis secondary to phimosis, penile/scrotal inflammatory conditions, candidiasis, and sensory neuropathies of the branches of the pudendal and pelvic nerves [1].

Region 2 Region 2 pathology involves skin dysesthesia overlying the perineum and perianal area and/or high tone pelvic floor muscle dysfunction. This latter condition in patients with female genital anatomy is suspected if palpation of the pelvic floor musculature is reported by the patient as feeling tender or painful, specifically at the 4, 6, and 8 o'clock positions of the introitus and/or of trigger points within the deeper muscles of the pelvis [1]. In such cases, a pelvic floor physical therapist should be involved to manage the pelvic floor dysfunction. Region 2 pathology may also result from direct injury to the pudendal nerve, which courses through the pelvis in proximity to the bony pelvic structures (i.e., ischial spine, ischial tuberosity, ischiopubic ramus). It can be injured by trauma with or without entrapment resulting from bicycle/motorcycle riding, from childbirth, or from bony spicules resulting from pelvic fracture. This possible involvement of pudendal nerve can be assessed if the symptoms are attenuated or blocked by injection of local anesthetic at the ischial spine near the pudendal nerve entry into the pelvis, or medial to the ischial tuberosity, or at Alcock's canal, where the pudendal nerve divides into its three branches. Region 2 may also involve pelvic nerve neuropathology resulting in internal pressure/distension dysesthesia following radical cancer surgery of the bladder (cystectomy) or uterus (hysterectomy) and/or following intense pelvic radiation therapy. Additional Region 2 pathologies may include pelvic arteriovenous malformation and/or pelvic congestion syndrome. These can be accessed via pelvic radiologic imaging (e.g., internal pudendal arteriography).

Hormone Blood Testing (Regions 1 and 2) In patients with PGAD/GPD, hormone blood testing should be considered. Specifically, patients with PGAD/GPD and a history of combined hormonal contraceptive use should have their androgen status evaluated for hormonally mediated vestibulodynia as a potential trigger [1]. Menopausal patients typically have low testosterone and low estradiol, as GSM is a potential contributor to PGAD/GPD. In addition, as hyperthyroidism is a recognized contributor to premature ejaculation, it could be considered an excitatory condition similar to PGAD/GPD. Thus, in patients with PGAD/GPD, the following

laboratory tests should be considered: testosterone, free testosterone, sex hormone binding globulin, estradiol, and thyroid stimulating hormone.

Neurogenital Testing (Regions 1 and 2) In patients with PGAD/GPD, neurogenital testing should be considered [1]. Assessment of afferent pudendal nerve integrity involves determining vibration (A-beta), cold (A-delta), and warm/hot (c-fiber) sensory thresholds in the genitals compared to a non-genital control location (pulp of index finger). Assessment of afferent sciatic nerve integrity involves determining vibration thresholds in buttocks, posterior thigh, posterior calf, and feet compared to a non-sciatic control location (pulp of index finger). Bulbocavernosus reflex latency is subsequently determined. If both afferent pudendal nerve testing and bulbocavernosus reflex latency are abnormal, but afferent sciatic nerve testing response is normal, this suggests that the PGAD/GPD symptoms (e.g., clitorodynia, vestibulodynia, pudendal neuralgia) are associated with neuropathy (i.e., of the pudendal nerve dorsal branch, perineal branch, and pudendal nerve proper, respectively) located in Regions 1 and 2. Neurogenital testing is also applicable to diagnosis of Regions 3–5 pathology (see below).

End Organ Anesthesia Testing (Regions 1 and 2) Local anesthetization of the end organ (i.e., clitoris, vulva, and/or vestibule, penis and/or scrotum) or the pudendal nerve can help localize the pathology of PGAD/GPD to Regions 1 and 2. If this procedure temporarily results in clinically significant reduction of the PGAD/GPD symptoms, then the suspected location of the trigger of the symptoms can be considered to be located in Region 1 and/or Region 2. Thus, appropriate management of the end organ/pelvis/perineum pathology may help to alleviate PGAD/GPD symptoms. However, if in the seemingly paradoxical case in which local anesthetization of the end organ produces numbness to tactile stimulation, but at the same time, the bothersome dysesthesia (e.g., pain, itching) persists, then a more proximal ("farther upstream") trigger for the symptoms is probable.

Region 3 PGAD/GPD can result from sacral radiculopathy indicative of pathology in the cauda equina. Sacral radiculopathy is suspected if the following criteria are met: a) PGAD/GPD triggers in Regions 1 and 2 are ruled out, typically by a local anesthesia test that does not eliminate the PGAD/GPD symptoms; b) Neurogenital testing shows abnormal pudendal and sacral nerve responses and a prolonged bulbocavernosus reflex response; c) A lumbosacral MRI demonstrates pathology of the cauda equina, e.g., Tarlov cyst and/or herniated intervertebral disc(s) due to annular tear, typically at L4-5 and/or L5-S1. Since physical examination cannot occur of the cauda equina, it is important to recognize and emphasize the nature of the lesions causing the sacral radiculopathy. Sacral Tarlov cysts contain aberrant pudendal and/or pelvic sensory nerve root fibers, and their occurrence is highly correlated with PGAD/GPD symptoms [17]. Annular tears, particularly at the lumbosacral level, are a second type of pathology highly correlated with the symptoms [1]. A tear in the annulus fibrosus of the disc(s), particularly at the L4-5 and L5-S1 levels, allows the nucleus pulposus of the disc to be extruded, which can physically and chemi-

cally irritate and inflame the dura mater and adjacent genital sensory nerve roots of the cauda equina.

Suspected sacral radiculopathy is confirmed by administering an anesthetic (e.g., lidocaine) either via Trans-Foraminal Epidural Spinal Injection (TFESI) or caudal epidural. This diagnostic injection is administered at the suspected vertebral level indicated by the MRI. Anesthetic spinal injections are associated with risks of epidural hematoma, infection, nerve root damage/sciatica, dural puncture leak/headache, vomiting, dizziness, leg weakness/numbness. A clinically significant reduction in any or all PGAD/GPD symptoms would confirm the role of the Tarlov cysts (caudal epidural) and/or one or more annular tears (TFESI) as the PGAD/GPD trigger.

Region 4 At present, we are aware of no case of PGAD/GPD that has been attributed to pathology of the spinal cord. We believe, though, that the diagnostic evaluation of Region 4 would be similar to that of Region 3 [1]. This would involve ruling out other triggers, having abnormal neurogenital test findings, and an abnormal MRI in the thoracic or cervical region. Pathology in Region 4 could emanate from the genitopelvic nerve roots of the cauda equina that synapse at the S2-4 levels of the spinal cord in the conus medullaris (which is typically located at lumbar vertebral levels L1-2), from which the spinothalamic tracts transmit the genitopelvic sensory activity to the brain. It is possible that injury could occur to the spinal cord at any level, from lumbar to cervical, that would compromise the integrity of these genitopelvic sensory pathways. Such injury could include annular tears, nucleus pulposus herniation, spinal stenosis, facet synovial cyst, and others. These possible pathologies could be assessed by lumbar, thoracic, and/or cervical MRI. Furthermore, since serotonin and norepinephrine neural pathways descend from the brainstem to the spinal cord and modulate aversive sensory activity (e.g., via the "pain-gate" mechanism), SSRI/SNRI administration or withdrawal could iatrogenically affect PGAD/GPD symptoms via their action on the spinal cord [1].

Region 5 Although PGAD/GPD inevitably involves the brain, there is little evidence that any *specific* brain pathology is the initiating factor, except perhaps in the case of epileptic seizure, which was reported to correlate temporally with PGAD/GPD symptoms [18]. However, extrinsic factors that affect brain function, such as withdrawal from SSRI/SNRI therapy, can certainly trigger the onset of PGAD/GPD symptoms [1]. While not necessarily a brain-generated "cause" of PGAD/GPD, the following types of brain-involving factors have been reported to be associated with the symptoms and/or therapies.

- *Psychological factors*: Stress, depression, anxiety, and loss have been reported as initial triggers of PGAD/GPD symptoms in some patients. Exacerbating psychological factors include hypervigilance and catastrophizing [1].
- *Pharmaco-therapeutic factors*: In addition to PGAD/GPD symptoms being triggered by SSRI/SNRI withdrawal, discontinuation of trazodone has been associated with clitoral and penile priapism (persistent genital engorgement). PGAD/

GPD symptoms have also been associated with initiation of treatment with certain CNS-active medications (e.g., lamotrigine) [1].

- *Organic brain pathologies*: These include traumatic brain injury, arteriovenous malformations (AVMs), aneurysms, and/or other space-occupying lesions, which can be assessed by MRI, electroencephalography, and magnetic electroencephalography. Procedures that directly modify brain activity have included electroconvulsive therapy and transcranial magnetic stimulation, with inconsistent efficacy.

4.6.2 Treatment

Psychosocial Treatment The primary roles of a mental health care provider in the management of PGAD/GPD are to help the client cope with and manage their PGAD/GPD symptoms, aid in reducing the amount of distress they are experiencing, and, if desired, assist with connecting the client to their sexuality. A cognitive-behavioral therapy (CBT) approach is recommended, given that CBT has been useful for the treatment of genitopelvic dysesthesias characterized by pain [15]. A CBT approach would initially involve providing patients with information about their symptoms, the effects of the symptoms on sexual and nonsexual activities, and the role of psychological factors in maintaining the symptoms. Among other strategies, patients would be encouraged to keep track of their symptoms and any factors that may increase or decrease them, to engage in relaxation and mindfulness strategies, and to engage in cognitive restricting exercises to reduce their tendency to catastrophize about their symptoms given that catastrophization has been associated with negative outcomes (e.g., symptom intensity) [15]. Partners of those with PGAD/GPD are also encouraged to attend sessions to educate and involve them in the process. Other patients may benefit from trauma-informed therapy if trauma is a significant part of their history and if other strategies are not suitable for the patient at that time, and if distress is the key presenting factor, then a CBT approach focused on reducing distress, increasing social support, and targeting other urgent priorities is recommended [1].

Region 1 Patients with PGAD/GPD symptoms associated with clitoral and/or penile pain may have balanitis and/or adhesions between the prepuce and glans [1]. Treatment of underlying balanitis can be accomplished with appropriate medical management. Should adhesions be identified, these may be released in an office setting under local anesthesia using microfine Jacobson mosquito forceps. Another strategy could be dorsal slit surgery. Patients with traumatic dorsal nerve neuropathy (e.g., straddle injury) may be managed by local anesthesia/steroid nerve blocks. For patients with vestibulodynia, the following strategies may be employed based on the underlying triggering pathology: physical therapy, hormonal therapy, derma-

tological therapy using ultra-potent corticosteroids, medical therapy with oral neuroleptics (e.g., gabapentin) and/or topical agents (e.g., capsaicin), and complete vestibulectomy if neuroproliferation is thought to be the main contributing factor.

Region 2 In patients with PGAD/GPD, pelvic floor physical therapy may improve daily activity by treating overactive/hypertonic pelvic floor dysfunction and pudendal neuropathy [1]. Treatment consists of a combination of education, manual therapy, therapeutic exercises, and neuromuscular re-education. Symptom triggers include specific activities, positions, and movements (e.g., squatting, sitting), which can be modified/paced to reduce the severity of the dysesthesia. In addition, iatrogenic kinesiophobia and hypervigilant behavior are potential risks.

Pudendal nerve block (without patient sedation) may attenuate the PGAD/GPD symptoms and, if effective, can be used in conjunction with long-lasting steroid injection (e.g., triamcinolone acetonide 80 mg) [1]. This treatment may also improve voiding dysfunction and reduce pelvic pain. Other therapies for consideration are pudendal nerve entrapment surgery to release the nerve compression, and pudendal neuromodulation.

In patients suspected of having PGAD/GPD from pelvic congestion syndrome or pelvic arteriovenous malformation, referral to an interventional radiologist for diagnosis (i.e., pelvic MRI and selective venography/arteriography) and for treatment (i.e., embolization) [1].

Region 3 For patients with PGAD/GPD secondary to a lumbosacral annular tear, minimally invasive LESS (Lumbar Endoscopic Spine Surgery) procedure is optimal. During LESS, the extruded nucleus pulposus is morcellated via laser and removed by suction. For patients with PGAD/GPD secondary to a Tarlov Cyst, surgery involves laminectomy, draining, and imbricating the cyst(s) [1].

Region 4 If diagnostic procedures based on MRI and TFESI indicate pathology such as annular tear, the LESS procedure may be applied. In preliminary findings, administration of morphine to the conus medullaris has attenuated PGAD/GPD symptoms temporarily, suggesting that chronic dorsal root electrical stimulation may be indicated. In some cases of vertebral degenerative disc disease, however, the risk of surgical complications may be considered greater than the possible benefit [14].

Region 5 There are no medications approved for the treatment of PGAD/GPD. Off-label treatments that have shown inconsistent efficacy include varenicline, zolpidem, clonazepam, gabapentin, pregabalin, oxcarbazepine, topiramate, tramadol, hydrocodone, duloxetine, paroxetine, nortriptyline, amitriptyline, clomipramine, methocarbamol, cyclobenzaprine, baclofen, diazepam suppositories, and/or botulinum neurotoxin [1].

4.7 Conclusion

PGAD/GPD presents as a variable combination of abnormal sensations (dysesthesias: e.g., itching, burning, pain, "arousal") perceived as emanating from the clitoris/penis, vulva/scrotum, vestibule, vagina, urinary bladder, urethra, rectum, pelvic floor, buttocks, feet, legs, and/or lower back. In some cases, the condition results from pathology that is evident in the peripheral organs. However, many cases of PGAD/GPD are resistant to, and persist after, locally applied surgical, hormonal, and/or topical anesthetic therapy. In many of the persistent cases, pathology is found to originate in the pudendal, pelvic, and/or sciatic nerve roots, which originate in common at the S2 and S3 sacral foramina, where they join the cauda equina. There, they are subject to mechanical and/or chemical irritation, i.e., Tarlov cysts and/or herniated (annular tear) lumbosacral intervertebral discs. Thus, the PGAD/GPD sensations are perceived by the patient as emanating from the genitopelvic region, but are, in fact, due to radiculopathy remote from the perceived source. Psychosocial factors (e.g., depression, catastrophization) and iatrogenic factors (e.g., initiation or termination of anti-depression medication) can also initiate and/or exacerbate PGAD/GPD symptoms. Comprehensive biopsychosocial evaluation is recommended to optimize effective treatment of this complex condition.

Key Messages

- Because PGAD/GPD is relatively unknown by most health care providers, and because of the assumption that genital arousal experiences are pleasurable, PGAD/GPD is often misdiagnosed or undiagnosed.
- PGAD/GPD can affect up to 4.3% of the adult population, and it affects people of all gender identities even though most of the research focuses on women.
- A biopsychosocial, multidisciplinary approach is essential to the successful management of PGAD/GPD, and this process is complex, involving the careful and comprehensive assessment of symptomatology, and psychosocial, medical, and biological factors.
- Based on recent evidence, regional diagnostic and treatment approach to PGAD/GPD is suggested. This involves examining end organ pathologies (Region 1), pelvis/perineum pathologies (Region 2), pathologies affecting the lumbosacral region of the cauda equina (Region 3), pathologies affecting the spinal cord (Region 4), and factors affecting brain function and activity (Region 5).
- A multidisciplinary approach in the assessment, diagnosis, and treatment of PGAD/GPD is recommended.

References

1. Goldstein I, Komisaruk BR, Pukall CF, Kim NN, Goldstein AT, Goldstein SW, Hartzell-Cushanick R, Kellogg-Spadt S, Kim CW, Jackowich RA, Parish SJ, Patterson A, Peters KM, Pfaus JG. 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;8(4):665–97. https://doi.org/10.1016/j.jsxm.2021.01.172.
2. Pukall CF, Jackowich R, Mooney K, Chamberlain SM. Genital sensations in persistent genital arousal disorder: a case for an overarching nosology of genitopelvic dysesthesias? Sex Med Rev. 2019;7:2–12. https://doi.org/10.1016/j.sxmr.2018.08.001.
3. Chivers ML, Seto MC, Lalumière ML, Laan E, Trimbos T. Agreement of self-reported and genital measures of sexual arousal in men and women: a meta-analysis. Arch Sex Behav. 2010;39:5–56. https://doi.org/10.1007/s10508-009-9556-9.
4. Chadwick SB, Francisco M, van Anders SM. When orgasms do not equal pleasure: accounts of "bad" orgasm experiences during consensual sexual encounters. Arch Sex Behav. 2019;48(8):2435–59. https://doi.org/10.1007/s10508-019-01527-7.
5. Gray M, Zillioux J, Khourdaji I, Smith RP. Contemporary management of ejaculatory dysfunction. Transl Androl Urol. 2018;7(4):686–702. https://doi.org/10.21037/tau.2018.06.20.
6. Leiblum S, Nathan SG. Persistent sexual arousal syndrome: a newly discovered pattern of female sexuality. J Sex Marital Ther. 2001;27:365–80. https://doi.org/10.1080/009262301317081115.
7. Leiblum S. Persistent genital arousal disorder: what it is and what it isn't. In: Principles and practice of sex therapy. 4 th ed. Guilford Press; 2006.
8. Parish SJ, Goldstein AT, Goldstein SW, et al. Toward a more evidence-based nosology and nomenclature for female sexual dysfunctions—part II. J Sex Med. 2016;13:1888–906. https://doi.org/10.1016/j.jsxm.2016.09.020.
9. World Health Organization. International classification of diseases for mortality and morbidity statistics (11th Revision). 2021. https://icd.who.int/browse11/l-m/en
10. Waldinger M, Schweitzer DH. Persistent genital arousal disorder in 18 Dutch women: part II. A syndrome clustered with restless legs and overactive bladder. J Sex Med. 2009;6:482–97. https://doi.org/10.1111/j.1743-6109.2008.01114.x.
11. Garvey LJ, West C, Latch N, et al. Report of spontaneous and persistent genital arousal in women attending a sexual health clinic. Int J STD AIDS. 2009;20:519–21. https://doi.org/10.1258/ijsa.2008.008492.
12. Jackowich RA, Pukall CF. Prevalence of persistent genital arousal disorder in 2 north American samples. J Sex Med. 2020;17:2408–16. https://doi.org/10.1016/j.jsxm.2020.09.004.
13. Dèttore D, Pagnini G. Persistent genital arousal disorder: a study on an Italian group of female university students. J Sex Marital Ther. 2021;47:60–79. https://doi.org/10.1080/0092623X.2020.1804022.
14. Komisaruk BR, Goldstein I. Persistent genital arousal disorder: current conceptualizations and etiologic mechanisms. Curr Sex Health Rep. 2017;9:177–82. https://doi.org/10.1007/s11930-017-0122-5.
15. Pukall CF, Goldmeier D. Persistent genital arousal disorder. In: Binik YM, Hall K, editors. Principles and practice of sex therapy. 6th ed. New York: Guilford Press; 2020. p. 488–503.
16. Giovannetti O, Tomalty D, Gaudet D, Clohosey D, Forster A, Monaghan M, Harvey MA, Johnston S, Komisaruk B, Goldstein S, Hannan J, Goldstein I, Adams MA. Immunohistochemical investigation of autonomic and sensory innervation of anterior vaginal wall female periurethral tissue: a study of the surgical field of mid-urethral sling surgery using cadaveric simulation. J Sex Med. 2021;18(7):1167–80. https://doi.org/10.1016/j.jsxm.2021.05.002. Epub 2021 Jun 24
17. Komisaruk BR, Lee HJ. Prevalence of sacral spinal (Tarlov) cysts in persistent genital arousal disorder. J Sex Med. 2012;9:2047–56. https://doi.org/10.1111/j.1743-6109.2012.02765.x.
18. Anzellotti F, Franciotti R, Bonanni L, Tamburro G, Perrucci MG, Thomas A, Pizzella V, Romani GL, Onofrj M. Persistent genital arousal disorder associated with functional hyperconnectivity of an epileptic focus. Neuroscience. 2010;167(1):88–96. https://doi.org/10.1016/j.neuroscience.2010.01.050. Epub 2010 Feb 6

Chapter 5
Post-SSRI Sexual Dysfunction (PSSD)

Yacov Reisman, James G. Pfaus, and Lior Lowenstein

Learning Objectives
After reading this chapter, the reader:

- will be familiar with the variable clinical presentation of the PSSD and the bio-psycho-social and relational consequences of PSSD,
- will develop comprehensive assessment and monitoring skills,
- will gather knowledge about the possible pathophysiological mechanism related to this syndrome and the link between evidence-based and proposed pathophysiology and treatment,
- be able to deliver tailor-made and when needed multidisciplinary treatment modalities for the patient who suffers from PSSD,
- consider partner and relationship aspects in the treatment plan, including all bio-psycho-social components involved.

Y. Reisman (✉)
Flare Health, Amstelveen, The Netherlands
e-mail: reisman@flare-health.nl

J. G. Pfaus
Czech National Institute of Mental Health, Laboratory of Sexual Neuroscience, Klecany, Czech Republic

L. Lowenstein
Department of Gynecology, Galilee Medical Center, Nahariya, Israel

Y. Reisman et al. (eds.), *Textbook of Rare Sexual Medicine Conditions*,
https://doi.org/10.1007/978-3-030-98263-8_5

5.1 Introduction

Selective serotonin reuptake inhibitors (SSRIs) are a type of medication used widely to treat a variety of mental conditions, including depression, anxiety, panic disorders, and to a lesser extent obsessive-compulsive disorder, as well as off-label treatment for premature ejaculation, pre- and postmenopausal syndromes, hot flashes, chronic pain, and chronic fatigue. Serotonin and norepinephrine reuptake inhibitors (SNRIs) are similar to selective serotonin reuptake inhibitors (SSRIs) in that they inhibit both serotonin and norepinephrine reuptake, and both are commonly lumped together when discussing mechanism, precautions, and contraindications [1]. All stages of the sexual response cycle (desire, arousal, and orgasm) have been reported to be affected adversely by SSRIs and to a lesser extent SNRIs, with findings ranging from 58 to 73% among users [2].

While the sexual side effects of SSRIs are well-known and documented, it has long been assumed that these symptoms would disappear once the medication was withdrawn although there is little solid data to support this belief [1, 3]. Some SSRI and SNRI users report impairments in sexual functioning and sexual satisfaction that continue long after the medication is stopped. The sexual functioning of these individuals does not return to baseline levels, sometimes even years after the medication is withdrawn [1, 3, 4]. These findings have been established in the literature, and since 2006 the term "post-SSRI sexual dysfunctions" (PSSD) is used to describe this category of disorders [5–7].

In May 2019, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) declared PSSD a medical condition that can outlast the discontinuation of treatment with SSRIs and SNRIs, based on published literature and patient reports. A month later, the EMA recommended that the patient product information of all SSRIs and SNRIs should be updated to refer to reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRIs [8].

5.2 Definition of Disorder

Although the European Medical Agency (EMA PRAC) recognizes PSSD as a medical condition, and despite a body of research supporting this, there is no universally accepted definition or conceptualization of the disorder and its symptoms [4].

PSSD has been characterized as a "debilitating and under-recognized disorder" with symptoms such as reduced sexual arousal and desire, reduced pleasurable tactile sensations in the genitals, erectile dysfunction, failure to reach orgasm, pleasureless or weak orgasm, delayed or anejaculation, and, oddly, also premature ejaculation. The sensory alterations may extend beyond the genital area, resulting in a generalized reactivity dampening. Importantly, patients report that prior to the usage of SSRIs, there was no evidence of these sexual dysfunctions [7].

Symptoms unique to antidepressant use, such as genital numbness, nipple insensitivity, and orgasms without pleasure, have been identified as atypical symptoms of depression and anxiety that can aid in the diagnosis of PSSD. Significant sexual dysfunction can occur both during and after therapy with any SSRI [4]. It is not necessary to have a significant loss of function after discontinuing the medication to diagnose PSSD. Even if there may be some improvement, the overall symptomatology would still qualify as PSSD if it has not returned to what patients consider "normal" [9].

PSSD then refers to a common condition that occurs after the termination of any SSRI or SNRI. It is unrelated to any pre-existing or reactive mental health issue, medical condition, or substance abuse. It has some overlap with the Post-Finasteride Syndrome (PFS) [9].

5.3 Epidemiology

Post-marketing research studies reported a high incidence of patients who developed impairment of sexual function after the use of SSRIs and SNRIs [5]. However, the actual prevalence of persistent sexual side effects after discontinuing SSRIs is unknown, as is the risk of developing PSSD from taking either an SSRI or an SNRI.

When these medications are prescribed, patients are rarely cautioned about the possibility of long-term sexual side effects, and we lack reports from well-controlled studies. Another factor for the under-diagnosis of PSSD is a lack of knowledge and awareness in the medical community. Patients frequently are reluctant to discuss their sexual concerns with health care providers, and medical professionals often experience discomfort when discussing the sexual side effects of medications or treatments. As a consequence, when addressing health care providers, many PSSD patients have an unpleasant experience. Another challenge in making a diagnosis is that in some situations, the symptoms do not manifest until the antidepressant treatment is discontinued and patients are lost to subsequent follow-up [10].

In cases of depression, women outnumber men at a ratio of approximately 2:1; the lifetime prevalence of major depression is 21% in women and 12% in men [11]. Although depressed men have a higher overall rate of sexual dysfunction (62.4%) compared to women (56.9%), women have a higher intensity of decreased desire, delayed orgasm, and/or anorgasmia. Even 6 months after starting SSRI treatment, almost 80% of the patients did not experience any improvement in their sexual symptoms. About 40% of individuals reported that their sexual side effects were not well tolerated. In the case of PSSD, all publications are case reports (see Table 5.1), potential theoretical explanations, or reviews of the literature. As a result, there is no conclusive evidence of possible sex/gender disparities; however, recent data suggest that men outnumber women in PSSD by roughly 4:1 [12]. However, this may also be accounted for by social factors, including the relative ease with which men may report sexual problems compared to women.

Table 5.1 Published PSSD case reports (adapted from [12])

Author	No of cases	Gender	Age	Duration SSRI use	Symptoms duration after withdrawal
Bolton [13]	1	1♂	26	5 months	6 years
Csoka [6]	3	2♂ 1♀	27 (24–30)	3–35 days	7 months–3 years
Kauffman [14]	1	1♂	32	Few days	1 year
Csoka [15]	3	3♂	33 (18–44)	3 days-2 years	4–11 years
Ekhart [16]	19	13♂ 6♀	30 (20–59)	9 days–10 years	2 months–2 years
Stinson [17]	9	4♂ 5♀	35 (22–59)	4 months–1 year	2 months–3.9 years
Hogan [18]	90	75♂ 15♀	31 (15–65)	3 days–15 years	Up to 18 years
Waldinger [19]	1	1♂	43	1 week	2 years
Ben-Sheetrit [20]	183	143♂ 40♀	36 ± 11.4	1 day–15 years	1 month–19 years
Healy [3]	229	170♂ 49♀	31 (15–66)	1 day–16 years	Up to 20 years
Reisman [21]	12	12♂	31.3 ± 6.21	3–36 months	3–26 months

Age: median(range) or mean ± standard deviation

5.4 Clinical Presentation and Contributing Factors

PSSD affects people of all ages, sexes, genders, and ethnicities. It can appear after a few doses of treatment or manifest after years of exposure, and it can last for decades (Table 5.1). PSSD affects patients with varying degrees of severity and persistence. Genital anaesthesia (numbness and impaired sensation in the genital area) decreased nipple sensitivity, pleasureless or inadequate orgasm, decreased sex drive, erectile dysfunction or diminished lubrication, and even premature ejaculation may be signs of PSSD [3]. Genital anaesthesia, hypoactive desire, and erectile dysfunction form the most common triad among these symptoms [9]. Additional PSSD symptoms include reporting a "disconnection" between the brain and the genitals. Hogan et al. include reports of decreased penile size, reduced seminal volume, testicular atrophy in men, and pain and irregular menstruation in women [18]. Table 5.2 lists the most noticeable symptoms in 170 male cases and 49 female cases with PSSD, organized by frequency of complaints [3].

Men and women in internet groups commonly report symptoms of genital anaesthesia and pleasureless orgasm, which are part of a growing case report literature as chronic sexual dysfunction side effects, the majority related to a diminished capacity to experience sexual pleasure, following discontinuation of SSRI treatment [9]. Because genital skin sensitivity plays a role in the chain of events that drives and maintains sexual responsiveness, genital anaesthesia may result in arousal difficulties and ejaculatory anhedonia. Genital anaesthesia is well associated with SSRI but not with depression or anxiety. In the study by Ben-Sheetrit et al. [20] genital anaesthesia was a predictor of sexual dysfunction severity. The explanation could be that

Table 5.2 The most apparent symptoms according to the frequency of complaints of 170 male patients and 49 female patients with PSSD

170 male patients		49 female patients	
Complaints	%	Complaints	%
Erectile dysfunction	86	Loss of desire	72
Loss of desire	79	Genital anaesthesia	60
Genital anaesthesia	49	Difficulty achieving orgasm	60
Pleasureless orgasm	43	Emotional blunting	28
Difficulty in achieving orgasm	33	Pleasureless orgasm	26
Emotional blunting	20	Vaginal dryness	18
Loss of nocturnal erections	13	Other skin numbness	10
Reduced ejaculation volume	13	Reduced nipple sensitivity	10
Premature ejaculation	10		

anaesthesia by decreased sensation is likely to lead to decreased pleasure, which in turn can cause decreased lubrication or quality of an erection and subsequently loss of libido. These complaints, on the other hand, could lead to compulsive sexual behaviours, potentially exposing people to new sexual problems or triggering a relapse of depression [21]. It is critical to inquire about genital sensation and orgasm intensity alterations, as these sensory changes appear to be specific to PSSD and distinguish it from other types of persistent sexual dysfunction [9, 18].

PSSD symptoms are distressing for patients and have a significant negative impact on their quality of life [9]. Sexual dysfunctions are generally linked to a diminished quality of life and can have serious consequences for one's physical and mental health, interpersonal relationships, and recovery from mental illness [22]. Patients consistently report that PSSD made it difficult or impossible to engage in normal romantic relationships, that the condition had caused relationships to end, and that the condition had impacted their profession, including job loss [9]. In some cases, it appears that a degree of spontaneous recovery occurs over time (months to even several years), while others experience transient remissions (for days) that are commonly triggered by stopping a brief term of another medicine. As a result, there is reason to assume that these effects are not the result of long-term damage [9].

PSSD is a challenging condition to diagnose. Because no specific parameters are known, there are no standardized investigative procedures that allow a clear diagnosis. Decreased desire, arousal, and orgasm difficulties have been observed in more than half of depressive or anxious patients, and anxiety itself produces alterations in desire, arousal, and sexual enjoyment, as well as some forms of vaginismus [22]. The overlap of PSSD symptoms with the sexual dysfunctions that occur secondary to depression or anxiety is one challenge that leaves little room to conceptualize and distinguish PSSD symptoms from psychodynamic causes [7]. PSSD is diagnosed by examining all aspects of a patient's clinical presentation, including drug use history, symptom onset, and premorbid disorders. Ruling out other possible causes of sexual dysfunction assists in the diagnosis of PSSD. Genital anaesthesia has been

used as a predictor of the severity of sexual dysfunction induced by SSRIs in PSSD [9].

Suggested diagnostic criteria for the diagnosis of PSSD are as follows:

- Prerequisite:
  - Prior treatment with an SSRI/SNRI.
  - Long-lasting change in genital sensation after stops of SSRI/SNRI.
  - Sexual complaints (see Table 5.2).
- The problem should be present for more than 3 months after stopping treatment.
- Exclude any of the following: previous sexual dysfunction that matches the current profile before the use of SSRI and medical conditions, medication and substance abuse that could account for the symptoms.
- Possible additional non-sexual symptoms may include emotional numbing, sensory problems involving skin, smell, taste or vision, cognitive problems.

The first step in evaluating PSSD is to conduct a thorough examination to determine that the sexual side effects were truly caused by the discontinuation of SSRI use. This assessment might range from a physical examination to a formal sexual health examination. Other disorders that can influence sexual functions, such as diabetes, hypertension, and depression must be considered and ruled out [23]. Setting up a timeline of complaints, symptoms, and treatments can aid the diagnosis in most circumstances (differentiating sexual complaints or relationship problems that began with the medication versus those that appeared after withdrawing an SSRI/SNRI). The diagnosis of PSSD should be considered whenever the depression or anxiety is relieved, the medicine is stopped, and the sexual dysfunction remains or appears.

Hormonal laboratory tests can help rule out any related abnormalities, such as hypogonadism, hyperprolactinemia, or hypothyroidism, as well as any other evident neuroendocrine problem with the hypothalamus–pituitary peripheral gland axes, and can be treated as needed [7].

5.5 Possible Pathophysiological Mechanisms

There is currently no evidence-based pathophysiological explanation for PSSD, and as a result, no obvious therapeutic option or well-designed clinical studies exist.

SSRIs augment serotonin neurotransmission in both ascending and descending serotonin pathways from the brainstem Raphé nuclei by blocking reuptake proteins on presynaptic terminals. Increased activation of ascending serotonin pathways that innervate hypothalamic, limbic, and especially cortical structures is part of the general mechanism for behavioural inhibition and executive function and can inhibit sexual arousal and desire in the presence of competent sexual cues [22]. At the same time, increased activation of descending serotonin pathways from the brainstem to the spinal cord inhibits genital erection, ejaculation, and orgasm, providing

feedback that reinforces the central inhibitory state. However, SSRIs can delay ejaculation by maintaining a parasympathetic tone that inhibits the sympathetic threshold for the activation of orgasm [23, 24]. In fact, the ability of certain SSRIs like fluoxetine (FLU) to engage these mechanisms has led to their use as short-term treatments for premature ejaculation.

Preclinical animal studies show a similar pattern of disrupted sexual activity with both acute and chronic SSRI treatment. In male rats, acute FLU dose-dependently delays ejaculation and increases the total number of mounts before ejaculation and lengthens the post-ejaculatory refractory period. Furthermore, male rats that were chronically administered lower doses of FLU (e.g., 10 or 20 mg/kg) showed fewer ejaculations and a decrease in measures of sexual motivation relative to baseline [25]. In female rats, FLU decreased sexual solicitations and the motivation to interact with a male (quantified by the number of nose-pokes performed to gain access to a male counterpart). Also, FLU-treated females showed a decrease in the magnitude of the lordosis reflex and the number of hops and darts. Because the effect of SSRIs in rats successfully mimics two of the most prominent symptoms of sexual dysfunction observed among humans (anorgasmia and decreased sexual desire), rats have been used as preclinical models to delineate both the basic neuropharmacology of SSRI effects on sexual behaviour and as proof of concept in testing potential treatments. Lesions of the brainstem nucleus paragigantocellularis in males (which contains serotonin neurons that project from the brainstem to the spinal cord) reversed the effects of FLU on ejaculation.

In blocking serotonin reuptake, SSRIs keep serotonin in the synapse longer thus allowing it to act on a variety of serotonin receptor subtypes both pre- and postsynaptically. Because this creates an overabundance of serotonin, neurons engage homeostatic mechanisms to reinstate balance. For example, presynaptic 5-HT1a receptors found on axon terminals of serotonin neurons typically inhibit serotonin release. Chronic antidepressant treatment desensitizes 5-HT1a receptors [26], which leads to a decreased ability of serotonin neurons to regulate their own presynaptic release mechanisms for a period after the antidepressant treatment is terminated. Such an effect could result in a dysregulation of serotonin release patterns in the brain or spinal cord terminal regions. Although serotonin transporters are not affected significantly by chronic SSRI treatment, an isoform of the rate-limiting enzyme tryptophan hydroxylase 2 was found to be downregulated within serotonin cell bodies [27], giving rise to the idea that vesicular stores of serotonin may decrease with long-term SSRI treatment. Downstream mechanisms are also altered. For example, brain-derived neurotrophic factor was upregulated following many, but not all chronic SSRI treatment regimens in rats, and that genes related to GABA and glutamate transmission also showed heterogeneous changes, with a downregulation of the NMDA glutamate receptor in the striatum and amygdala, two regions that play important roles in emotion and motivation. An intriguing study by Alboni et al. [28] examined the nature–nurture interaction of SSRI treatment and the environment. They exposed C57BL/6 mice to chronic stress in order to induce a depression-like phenotype and, subsequently, treated them with FLU for 21 days in either an enriched environment, stressful environment, or a controlled environment

(their home cages). At the end of the treatment, mice were evaluated on a battery of molecular, cellular, electrophysiological, and behavioural endophenotypes of depression, including depression-like behaviour, neurogenesis, brain-derived neurotrophic factor levels, hypothalamic–pituitary–adrenal axis activity, and long-term potentiation. Compared to controls, mice that received FLU in the enriched environment showed marked amelioration of depression-like behaviour that corresponded to ameliorations of molecular and cellular dysregulations shown in the controls. Conversely, mice treated in the stressful environment showed a marked worsening of the depression-like behaviours along with a worsening of the associated molecular and cellular dysregulations. Given the individual variation in human susceptibility to treatment efficacy by different SSRIs or SNRIs, it is likely that a similar epigenetic interplay exists for those that suffer PSSD. In these cases, the very dysregulation of serotonin transmission that ameliorates the depression likely sensitizes somewhere in the sexual circuit (e.g., cortex, limbic, preoptic, hypothalamic, or spinal cord) to either maintain low sexual desire, disrupted orgasm, genital anaesthesia, etc., or to exacerbate those symptoms when the drug is discontinued. It is not yet clear if changes in hormone action, especially of oestradiol, testosterone, and/or cortisol, might alter the ability of SSRIs or SNRIs to induce long-term sensitization of inhibitory serotonin action on sexual desire, orgasm, and genital sensitivity.

Animal studies also suggest that SSRIs may cause future and irreversible sexual dysfunction if the exposure was at a young age [29]. Developmental exposure to SSRIs has been shown in preclinical studies to have a long-term impact on the sexual behaviour of male offspring. Regular prenatal exposure to a potent and highly selective SSRI causes substantial reductions in both the rate-limiting enzyme tryptophan hydroxylase within serotonin cell bodies and serotonin transporter expression in the cortex that last throughout adulthood [30, 31].

5.6 Clinical Management Including Biological-Psychological-Social Contributing Factors

PSSD, as previously stated, is a challenging disorder to diagnose. PSSD can be verified or ruled out based on the patient's medical and sexual history, as well as an assessment of the patient's symptoms. Although there are no PSSD-specific designed and validated questionnaires or patient-reported outcomes available, it is suggested to maintain follow-up information with questionnaires for sexual dysfunctions and satisfaction such as the IIEF for men, FSFI for women, and orgasmometer [21].

Although there is no actual and definitive treatment, efforts to control PSSD have concentrated on modulating the serotonergic and dopaminergic systems. 5HT1a agonists such as buspirone and 5HT-2 and 5HT-3 antagonists such as trazodone and mirtazapine have been used to blunt lingering serotonergic actions. Drugs with

predominant actions as dopamine agonists, including pramipexole and cabergoline, as well as bupropion, dexamphetamine, and other stimulants can be used to augment sympathetic tone. Patients have also used phosphodiesterase type 5 inhibitors and testosterone to try to treat symptoms of erectile dysfunction. Regrettably, these attempts at treatment offer little or no improvement [3, 18, 19]. On the other hand, a 5HT1A *antagonist* has been tried in rats and shown 70% improvement of penile erections that had been hampered by chronic fluoxetine [32]. In one case report, penile anaesthesia in PSSD responded to low-power laser irradiation [19]. Clinical improvements of 40% in glans penis sensitivity were observed, and it was hypothesized that low-power laser irradiation treatment reduced penile anaesthesia by restoring transient receptor potential ion channels in mechano-, thermo-, and chemosensitive nerve endings and receptors.

Patients were also given sildenafil, vardenafil, and other phosphodiesterase types 5 inhibitors (PDE5is), as well as testosterone, but no improvement was seen [18]. Patients may be able to switch to bupropion or nefazodone as an extra therapy option, as these antidepressants are not known to induce sexual side effects [33]. Bupropion does not have serotonergic activity and, hence, does not affect sexual function in patients [29]. Adjunct therapy with bupropion as an antidote demonstrated promising results in treating SSRI-related sexual dysfunction [33, 34]. Patients that had either switched to bupropion or had it added to their antidepressant treatment regimen documented recovery from their hypoactive sexual desire and infrequency of sexual activity. It is not yet known if such adjunct therapy lessens the incidence of PSSD.

Psychiatrists have also used cognitive behavioural therapy (CBT) to help patients have a better understanding of their condition and cope with their situation. CBT is effective for dealing with negative thoughts that many patients have, such as sexual inadequacy and low self-esteem [21].

Sex therapy and couples counselling should seek to educate partners on the fact that sexual dysfunction is a side effect of these medications rather than some indication of an intrinsic lack of interest. Furthermore, such therapies can promote positive couple experiences and provide patients and partners with emotional and psychological support [21].

PSSD patients' complaints and distress are influenced by biological, psychological, and social variables. An observational case study has described the clinical experience of patients treated using a newly developed method that included bio-psycho-social therapies. The treatment protocol entailed lifestyle recommendations (e.g. smoking cessation, dietary recommendations, physical activity), hormonal adjustment, the use of L-Arginine (3 g/day) and L-Carnitine (2 g/day) supplements, and PDE5is in cases of erectile dysfunction, and buspirone (15–60 mg/day) for delayed ejaculation or anorgasmia. Mindfulness training, CBT, sex therapy, and sensate focus were also offered to patients. The results were measured using the IIEF and orgasmometer, and the mean scores improved from baseline during the 6-month follow-up [21].

5.7 Conclusion

PSSD is an iatrogenic condition that is caused by antidepressant medication side effects. Some authors and physicians argue that taking SSRIs is typically associated with a mental disorder such as depression that might contribute to PSSD symptoms. These features could be revealed with more thorough research. The EMA's acknowledgement of PSSD and requests for informed consent will provide future SSRI/SNRI users with more information about the sexual side effects of SSRI/SNRI medications and the potential for PSSD to occur if the medications are discontinued. Medical recognition for PSSD is critical for obtaining the resources needed to investigate the true prevalence of the disorder, its pathophysiological mechanism(s), and potential treatments.

Commonly reported symptoms of PSSD include genital anaesthesia, erectile dysfunction, pleasureless orgasm, hypoactive sexual desire, decrease or absence of erection, premature ejaculation, vaginal lubrication issues, and nipple insensitivity in women.

PSSD is difficult to diagnose and should be done by analysing the patient's drug history, the onset of symptoms, and sexual function before starting such a medication. Furthermore, any concomitant disorders and conditions that can cause PSSD must be ruled out. PSSD symptoms appear after withdrawing an SSRI/SNRI, and patients say that the sexual compliant or relational problems did not exist before starting medication. When depression or anxiety is resolved, the medication is stopped, and the sexual dysfunction persists, PSSD should be considered.

To explain the pathophysiology of PSSD, various theories have been suggested: epigenetic gene expression, dopamine–serotonin interactions, serotonin neurotoxicity, downregulation of 5HT1A, and hormonal changes in the central and peripheral nervous systems.

There is no clear treatment for PSSD; nevertheless, certain management approaches have begun to be explored. Lowering SSRI dosage may reduce sexual adverse effects while weakening the drug's treatment efficacy. Adjunctive therapy, such as sildenafil and bupropion, provided little statistical advantage. CBT may be beneficial in the treatment of PSSD. PSSD treatments have included buspirone, trazodone, donepezil, ketamine, metformin, and mirtazapine, with varying degrees of efficacy.

Many patients with PSSD remain silent since it is difficult to discuss sexual dysfunction and some clinicians are sceptical that it is caused by SSRIs (thus downplaying potential mechanisms that SSRI treatment could sensitize). PSSD's emotional, social, and sexual implications are broad, and sufferers frequently feel estranged from their peers and loved ones as a result. With this in mind, SSRI prescribers must be aware of the possibility of PSSD and inform their patients about it. Before starting SSRIs, the patient's informed consent and the right to choose or reject SSRIs as a therapeutic option should be required. Clinicians must obtain baseline information from their patients and conduct regular follow-ups on sexual function before, during, and after SSRI treatment.

Finally, more research is needed to determine the aetiology and potential mechanism of PSSD, as well as to reach an accurate diagnosis and treatment. PSSD causes more complicated issues than traditional or even drug-induced sexual dysfunction, given that the drug used to ameliorate depressive symptoms has been removed and what appears to be a new and insidious baseline function established. There are still many unanswered questions about PSSD. It is therefore extremely important to investigate PSSD extensively to understand its pathophysiology and find appropriate treatments.

Key Messages

- PSSD has a variable clinical presentation with debilitating physical and psychological consequences.
- In the diagnostic process, the proposed criteria could be applied.
- PSSD has a profound negative influence on the quality of life and sexuality of the patient, partner, and their relationship.
- There is no clear consensus about the aetiology or treatment of PSSD.
- More research is necessary to determine the clear prevalence, optimal diagnostic criteria, pathophysiology, and effective treatment modality of PSSD .

References

1. Bala A, Nguyen HMT, Hellstrom WJG. Post-SSRI sexual dysfunction: a literature review. Sex Med Rev. 2018;6(1):29–34. https://doi.org/10.1016/j.sxmr.2017.07.002.
2. Clayton AH, Croft HA, Handiwala L. Antidepressants and sexual dysfunction: mechanisms and clinical implications. Postgrad Med. 2014;126(2):91–9. https://doi.org/10.3810/pgm.2014.03.2744.
3. Healy D, Le Nourya J, Mangin D. Enduring sexual dysfunction after treatment with antidepressants, 5α-reductase inhibitors and isotretinoin: 300 cases. Int J Risk Saf Med. 2018;29:125–34. https://doi.org/10.3233/JRS-180744.
4. Reisman Y. Post-SSRI sexual dysfunction. BMJ. 2020;368:m754. https://doi.org/10.1136/bmj.m754.
5. Bahrick A. Post SSRI sexual dysfunction. Am Soc Adv Pharmacother Tablet. 2006;163:1504–9.
6. Csoka AB, Shipko S. Persistent sexual side effects after SSRI discontinuation. Psychother Psychosom. 2006;75:187–8. https://doi.org/10.1159/000091777.
7. Reisman Y. Sexual consequences of post-SSRI syndrome. Sex Med Rev. 2017;5(4):429–33. https://doi.org/10.1016/j.sxmr.2017.05.002.
8. https://www.ema.europa.eu/en/documents/other/new-product-information-wording-extracts--prac-recommendations-signals-adopted-13-16-may-2019-prac_en.pdf.
9. Healy D, Bahrick A, Maarten B et al. Diagnostic criteria for enduring sexual dysfunction after treatment with antidepressants, finasteride and isotretinoin. Int J Risk Saf Med. 2022;33(1):65–76. https://doi.org/10.3233/JRS-210023.
10. Healy D, Le Nourya J, Mangin D. Post-SSRI sexual dysfunction: patient experiences of engagement with healthcare professionals. Int J Risk Saf Med. 2019;30:167–78. https://doi.org/10.3233/JRS-191005.
11. Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. JAMA Psychiat. 2018;75(4):336–46. https://doi.org/10.1001/jamapsychiatry.2017.4602.

12. Reisman Y. Are there any sex/gender differences in post-selective serotonin reuptake inhibitors (SSRI) sexual dysfunction (PSDD)? Curr Sex Health Rep. 2019;11:237–42. https://doi.org/10.1007/s11930-019-00222-x.
13. Bolton JM, Sareen J, Reiss JP. Genital anesthesia persisting six years after sertraline discontinuation. J Sex Marital Ther. 2006;32(4):327–30. https://doi.org/10.1080/00926230600666410.
14. Kauffman RP, Murdock A. Prolonged post-treatment genital anesthesia and sexual dysfunction following discontinuation of citalopram and the atypical antidepressant nefazodone. Open Women' Health J. 2007;1:1–3. https://doi.org/10.1258/ijsa.2008.008402.
15. Csoka AB, Bahrick AS, Mehtonen OP. Persistent sexual dysfunction after discontinuation of selective serotonin reuptake inhibitors (SSRIs). J Sex Med. 2008;5:227–33. https://doi.org/10.1111/j.1743-6109.2007.00630.x.
16. Ekhart GC, Van Puijenbroek EP. Blijvende seksuele functiestoornissen na staken van een SSRI? Tijdschr Psychiatr. 2014;56:336–40.
17. Stinson RD. The impact of persistent sexual side effects of selective serotonin reuptake inhibitors after discontinuing treatment: a qualitative study. PhD (Doctor of Philosophy) thesis, University of Iowa, 2013. http://ir.uiowa.edu/etd/5061.
18. Hogan C, Le Noury J, Healy D, Mangin D. One hundred and twenty cases of enduring sexual dysfunction following treatment. Int J Risk Saf Med. 2014;26(2):109–16. https://doi.org/10.3233/JRS-140617.
19. Waldinger MD, van Coevorden RS, Schweitzer DH, Georgiadis J. Penile anesthesia in post SSRI sexual dysfunction (PSSD) responds to low-power laser irradiation: a case study and hypothesis about the role of transient receptor potential (TRP) ion channels. Eur J Pharmacol. 2015;753:263–8. https://doi.org/10.1016/j.ejphar.2014.11.031.
20. Ben-Sheetrit J, Aizenberg D, Csoka AB, et al. Post-SSRI sexual dysfunction clinical characterization and preliminary assessment of contributory factors and dose-response relationship. Clin Psychopharmacol. 2015;35:1–6. https://doi.org/10.1097/JCP.0000000000000300.
21. Reisman Y, Jannini TB, Jannini EA. Post-SSRI sexual dysfunctions (PSSD). Retrospective clinical experience with patients treated with a multimodal approach. J Men's Health 2022.
22. Higgins A, Nash M, Lynch AM. Antidepressant-associated sexual dysfunction: impact, effects, and treatment. Drug Healthc Patient Saf. 2010;2:141–50. https://doi.org/10.2147/DHPS.S7634.
23. Pfaus JG. Pathways of sexual desire. J Sex Med. 2009;6:1506–33. https://doi.org/10.1111/j.1743-6109.2009.01309.
24. Montejo AL, Montejo L, Navarro-Cremades F. Sexual side-effects of antidepressant and antipsychotic drugs. Curr Opin Psychiatry. 2015;28(6):418–23. https://doi.org/10.1097/YCO.0000000000000198.
25. González Catuela BV, Quintana GR, Ackerman J, et al. Acute caffeine reverses the disruptive effects of chronic fluoxetine on the sexual behavior of female and male rats. Psychopharmacology. 2021;238:755–64. https://doi.org/10.1007/s00213-020-05728-0.
26. Celada P, Bortolozzi A, Artigas F. Serotonin 5-HT1A receptors as targets for agents to treat psychiatric disorders: rationale and current status of research. CNS Drugs. 2013;27:703–16. https://doi.org/10.1007/s40263-013-0071-0.
27. Kumar A, Russell RM, Pifer R, et al. The serotonin neurotransmitter modulates virulence of enteric pathogens. Cell Host Microbe. 2020;28(1):41–53.e8. https://doi.org/10.1016/j.chom.2020.05.004.
28. Alboni S, van Dijk RM, Poggini S, et al. Fluoxetine effects on molecular, cellular and behavioral endophenotypes of depression are driven by the living environment. Mol Psychiatry. 2017;22:635. https://doi.org/10.1038/mp.2015.191.
29. Coskuner ER, Culha MG, Ozkan B, Kaleagasi EO. Post-SSRI sexual dysfunction: preclinical to clinical. Is it fact or fiction? Sex Med Rev. 2018;6(2):217–23. https://doi.org/10.1016/j.sxmr.2017.11.004.
30. Simonsen AL, Danborg PB, Gotzsche PC. Persistent sexual dysfunction after early exposure to SSRIs: systematic review of animal studies. Int J Risk Saf Med. 2016;28:1–12. https://doi.org/10.3233/JRS-160668.

31. Maciag D, Simpson KL, Coppinger D, et al. Neonatal antidepressant exposure has lasting effects on behavior and serotonin circuitry. Neuropsychopharmacology. 2006;31:47–57. https://doi.org/10.1038/sj.npp.1300823.
32. Sukoff Rizzo SJ, Pulicicchio C, Malberg JE, et al. 5-HT1A receptor antagonism reverses and prevents fluoxetine-induced sexual dysfunction in rats. Int J Neuropsychopharmacol. 2009;12:1045–53. https://doi.org/10.1017/S1461145709000406.
33. Coleman CC, Cunningham LA, Foster VJ. Sexual dysfunction associated with the treatment of depression: a placebo controlled comparison of bupropion sustained release and sertraline treatment. Ann Clin Psychiatry. 1999;11:205–15. https://doi.org/10.1023/a:1022309428886.
34. Clayton A, Warnock J, Kornstein S, et al. A placebo-controlled trial of bupropion SR as an antidote for selective serotonin reuptake inhibitor-induced sexual dysfunction. J Clin Psychiatry. 2004;65:62–7. https://doi.org/10.4088/jcp.v65n0110.

Chapter 6
Post-Finasteride Syndrome

Mary C. Fierro, Faysal A. Yafi, and Yacov Reisman

Learning Objectives
By the end of this chapter, the practising physician will:

- better understand the existing profile of post-finasteride syndrome,
- gain knowledge about what clinical presentations indicate PFS in patients treated for benign prostatic hyperplasia or androgenic alopecia,
- get information about current data regarding adverse events seen in 5α-reductase inhibitor users,
- acquire knowledge on possible clarification of the clinical diagnosis and management of this lesser-known condition.

6.1 Introduction

The continued controversy regarding possible adverse effects in finasteride users has caught the attention of clinicians, patients, and potential users alike. Post-finasteride syndrome (PFS) is a condition indicated by a mosaic of adverse effects that develop during usage and linger even after the discontinuation of finasteride or dutasteride, another 5α-reductase inhibitor. Reported symptoms include various

M. C. Fierro · F. A. Yafi (✉)
Department of Urology, University of California, Newport Beach, CA, USA
e-mail: fyafi@uci.edu

Y. Reisman
Flare Health, Amstelveen, The Netherlands

Y. Reisman et al. (eds.), *Textbook of Rare Sexual Medicine Conditions*,
https://doi.org/10.1007/978-3-030-98263-8_6

sexual dysfunction disorders, psychological effects such as depression, and physical or biological changes to skin and metabolism [1].

Finasteride is a 5α-reductase inhibitor medication commonly used to treat lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (prostate enlargement) as well as male androgenic alopecia, or male pattern hair loss (MPHL). Briefly put, finasteride acts as an inhibitor of the type-2 isoform of 5α-reductase, an enzyme found in prostate tissue, seminal vesicles, and the brain that converts testosterone to 5α-dihydrotestosterone (DHT). DHT levels decrease with finasteride use, therefore influencing androgen-responsive tissues associated with the prostate and hair follicles [1]. Treatment of both conditions with finasteride or dutasteride has been historically successful and well tolerated. However, the more recent influx of reported sexual, psychological, and physical adverse effects even after the discontinuation of 5ARIs has led to a demand for further research. Additionally, the available data regarding the authenticity of PFS is limited and relatively indecisive. Due to such significant knowledge gaps, PFS is not yet officially recognized as a true disorder by the medical community.

Finasteride gained approval by the Food and Drug Administration (FDA) in 1992 for the treatment of BPH at a dose of 5 mg and later in 1997 for the treatment of AGA at a lower dose of 1 mg. Reports of PFS symptoms were not common until 2012 when the FDA announced labeling changes for Propecia© (finasteride 1 mg) and Proscar© (finasteride 5 mg) to include persistent sexual dysfunction in the form of libido, ejaculation, and orgasm disorders as possible persisting side effects [2]. Later that same year, a non-profit organization known as the Post-Finasteride Syndrome Foundation was created with the primary mission to "facilitate research on the characterization, mechanisms and treatment of post-finasteride syndrome" in addition to increasing public awareness [3]. The magnified publicity of PFS and its symptoms led to a nearly quadrupled number of reported adverse events for this medication in a post-marketing database between 2011 and 2014 [4].

The establishment of post-finasteride syndrome began with the use of limited, low-quality evidence such as post-marketing reports, targeted case series, and inconsistent surveys of selected patient populations. Since then, attempts to fill the knowledge gap have still not provided definitive conclusions on PFS validity, and most studies focusing on specific adverse effects have found varying levels of statistical support. Although PFS is acknowledged as a possible 5α-reductase inhibitor adverse event in the US National Institute of Health's (NIH) Genetic and Rare Diseases database, it is still not recognized as a true condition by the NIH due to the great ambiguity [5]. Bearing the above elements in mind, the primary aim of this chapter is to provide a succinct and concise overview of current knowledge of PFS and aid in the understanding and demystification of this rare condition. As prescribers, proper patient education addressing what is known and unknown about PFS must be prioritized to better help the patient make well-informed decisions concerning their care.

6.1.1 Finasteride Treatment of BPH

The use of 5α-reductase inhibitors is approved for the treatment of symptomatic benign prostatic hyperplasia, an age-associated gland enlargement commonly seen in men >50 that often leads to lower urinary tract symptoms (LUTS) such as urgency, frequency, weak stream, and difficulty emptying. This medication type works to effectively control serum 5α-DHT levels that would otherwise stimulate gland tissue proliferation by inhibiting the conversion of testosterone to its reduced form DHT, shrinking the prostate size over time and decreasing bladder outlet obstruction [6]. Finasteride is known to improve urinary symptom scores consistently and decreases risks of BPH progression in men with large glands, especially when used in conjunction with an alpha-blocker [7]. Despite the established warning of possible adverse effects such as sexual dysfunction, finasteride and dutasteride remain common and effective treatments to reduce prostate volume, manage symptoms of BPH, and prevent BPH progression.

6.1.2 Finasteride Treatment of AGA

5α-reductase inhibitors are widely popular and effective drugs used in dermatology for the treatment of androgen-dependent hair disorders such as androgenic alopecia or male pattern hair loss. As briefly explained above, 5α-reductase enzymes present in hair follicles convert testosterone into 5α-DHT, which has been found to impair the absorption of nutrients necessary for hair growth. Men more sensitive to DHT are believed to be those most affected by MPHL [8]. Since finasteride and dutasteride function to decrease DHT levels, these medications effectively drop scalp and serum 5α-DHT levels and reduce hair loss in many patients with AGA. While finasteride dosage for BPH is recommended at 5 mg, usage for alopecia is found to be optimal at 1 mg, with no difference in efficacy between 1 and 5 mg [9]. Another difference is that patients may begin taking finasteride much earlier for AGA than for BPH, as symptoms of prostate enlargement typically emerge later in life while male-pattern balding can begin in early adulthood. It should be recognized that there is evidence suggesting daily use of finasteride for alopecia does increase hair count while also increasing the risk of sexual dysfunction [10]. Again, finasteride used for the treatment of AGA is historically well tolerated and considered safe for long-term use; however, the conflicting and limited data regarding persistent adverse events continue to create hesitation and influence medication compliance.

6.2 Definition of Disorder

Post-finasteride syndrome is a term that embodies the collection of sexual, psychological, and biological adverse effects that may arise during finasteride or dutasteride use and continue despite stopping the medication. Patients treated with 5α-reductase inhibitors for BPH or AGA have both reported such repercussions. Developing symptomatology has been predominantly composed of patient self-reports, and no past studies have directly justified finasteride responsibility for all reported symptoms, preventing this condition from being acknowledged as a genuine disorder.

6.3 Known Epidemiology

Due to debate regarding the authenticity of PFS itself and the lack of conclusive, direct investigation of finasteride association with reported adverse effects, the epidemiology of PFS is not known. Despite researchers encountering contrasting experimental findings, the uncertainty regarding the incidence and prevalence of this condition can at least be agreed upon. However, it has been estimated that greater than 1000 men globally are experiencing the conventional symptoms of PFS. This data was found by quantifying the number of registered users on the advocacy forum www.propeciahelp.com.

6.3.1 PFS in Women

Finasteride achieved FDA approval for the treatment of alopecia in male subjects only. Although not as common compared to male patients, this use of finasteride has been gradually increasing in women for the treatment of female pattern hair loss (FPHL) and symptoms of hyperandrogenism such as hirsutism [1]. Some success with this drug has been seen in female patients with FPHL, but the recommended dosage for maximum efficacy remains controversial and needs further scrutinization [9]. Although generally well tolerated in female patients, it is important to note that finasteride is not recommended for pregnant women due to teratogenicity, and reliable contraception is strongly encouraged for those of childbearing potential. Few studies investigated post-finasteride syndrome in women specifically; however, results remain fairly consistent in potential impact. Reported adverse effects in women treated for alopecia include headache, menstrual irregularities, and decreased libido, all of which were present during finasteride treatment but resolved after discontinuation [1]. Based on the guideline that requires symptom persistence, this finding suggests that PFS is present in males only.

6.4 Clinical Presentation and Contributing Factors

PFS remains a wide-ranging clinical phenotype, with most reported symptoms varying in severity and unconfirmed as significant by the past experimental investigation. Reported adverse effects such as sexual dysfunction and depressive mood are often more typical and suggestive of commonality but still remain uncertain and in need of further direct investigation. Due to the broad symptom profile of this condition, the literature consistently separates such clinical manifestations into these three categories or similar equivalents; sexual, psychological, and physical adverse effects.

6.4.1 Sexual Adverse Effects

Complaints of sexual dysfunction during and after 5ARI use are arguably the most publicized adverse effects of PFS. The most commonly reported sexual adverse effects include erectile dysfunction exhibited as decreased erection quality or impotence, ejaculatory disorders, orgasmic dysfunction and decreased or total loss of libido. These symptoms, however, have not been confirmed by current studies as a valid rationalization for PFS existence [11].

Meta-analyses have been conducted with conflicting results, some suggesting an increased risk of sexual dysfunction for certain subgroups, while others report no association. In a 2018 systematic review and meta-analysis, there was a 1.55-fold risk of sexual dysfunction issues such as ED, decreased libido, and ejaculatory dysfunction seen in patients treated with 5ARIs. This finding was statistically significant regarding finasteride 1 mg for alopecia and not 5 mg for BPH [12]. This study differentiated from the findings of a previous systematic review and meta-analysis that found significant increased sexual dysfunction in men treated for BPH and not in those treated for AGA [13]. Overall, the validity of most studies demonstrating a higher likelihood of association are typically limited by inadequate methodology, nocebo effect, and various biases, particularly reporting bias.

Studies have even explored impacts on male fertility and finasteride treatment. In two studies, the patient populations consisted of men seeking treatment at infertility clinics to assess the impact of finasteride on those predisposed to infertility. Less than 1% of men at the clinic were finasteride users, but among that population, there was an 11.6-fold mean increase in sperm concentration after medication cessation [14]. Researchers compared these study results to those with patient populations of healthy young men that demonstrated no spermatogenesis alterations, suggesting that finasteride may exacerbate infertility in those predisposed but not exclusively causing it in healthy users.

In a prospective case-control study on subjects with a history of 5ARI use for AGA, there was a significant difference in total International Index of Erectile Function (IIEF) scores of finasteride users compared to controls, further supporting

the sexual dysfunction claims as a result of finasteride use [15]. This study was also the first to evaluate vascular abnormalities and arterial insufficiency using penile duplex doppler ultrasound (PDDU) on finasteride subjects. Out of the twenty-five subjects with a history of finasteride use, seventeen (68%) of them had vascular abnormalities on PDDU, 32% had arterial insufficiency, and 16% had venous leak. It was also noted that two subjects committed suicide during or after the study, an outcome that was not seen among the twenty-eight control subjects [15].

6.4.2 Psychological Adverse Effects

Emerging clinical observations have suggested that treatment of BPH and AGA using Finasteride may not only be associated with sexual dysfunction as more commonly advertised, but also with an increased appearance of psychological effects such as impaired cognition, agitation and mood swings, anxiety, depression, and even suicidality [16]. In patients treated with finasteride 1 mg for alopecia specifically, increased self-harm, slowed cognition, insomnia, and changes in emotional affect were also reported. These findings were not as common in those taking 5 mg for prostate enlargement [4].

Multiple pharmacovigilance studies using disproportionality analysis have been performed to investigate the possible association of suicidality and psychological events with finasteride. Significant disproportionality signals for suicidality were found among younger patients taking finasteride for alopecia, indicated by increased reports of suicidal ideation, anxiety, and depression [16]. Such disproportionality was only present in this patient population and was not reflected in older patients taking finasteride for BPH, patients taking tamsulosin (another medication used to manage BPH), or patients using minoxidil (another drug used to manage alopecia). Comparable findings were seen in another study about 5 years prior using similar techniques, suggesting that persistent sexual dysfunction may contribute to an increased risk of suicidal ideation in young men taking finasteride for alopecia. Among adverse events reported by patients with either persistent sexual dysfunction or suicidal ideation, 87.2% of patients experiencing suicidal ideation also had persistent sexual dysfunction [17]. While having some limitations, these findings encourage continued investigation. Additionally, in a recently published systematic review on the risk of depression after finasteride treatment, significant association with high rates of sexual dysfunction was seen along with suggestive evidence of increased risk of suicidal behavior. Overall findings included a pooled suicidal risk rate of 21.2% in finasteride users versus 14% in non-users. One study used in this review reported a suicidal ideation rate of 44.3% for those exposed to finasteride versus 3.45% for those without exposure [18]. As always, reporting bias, pre-existing sexual and psychiatric conditions in patient populations, and insufficient data regarding suicidal ideation may limit the validity of these studies.

6.4.3 Biological Adverse Effects

The biological or physical effects of PFS are perhaps lesser known than the other two categories. Most studies tend to focus on sexual dysfunction and more recently psychological dysfunction, with physical repercussions briefly addressed. Among the physical effects that patients have reported, muscle atrophy, chronic fatigue, gynecomastia, decreased oil and sebum production, and metabolic changes are the most common [8].

Much like the other two categories, not all symptoms have been experimentally associated with finasteride use. In a 2018 review of the literature regarding PFS, conflicting data was seen concerning changes in muscle mass and fat deposition in finasteride users versus non-users. One study demonstrated a significant proportion of patients reporting muscle weakness and increased fat deposition, while another saw no experimental difference in body lean and fat mass or leg press strength [19]. Although ill-defined, there is also data suggesting an association between gynecomastia, an enlargement of male breast tissue, and patients treated with finasteride for AGA [20]. One study surveyed men experiencing PFS symptoms and found that 70% of participants reported enlarged breast tissue. Additionally, in an online forum post targeted at men experiencing PFS symptoms, 19% of posts included similar estrogenic side effects [19]. (Table 6.1).

6.4.4 Possible Risk Factors

At this time, there are no predictive factors for the development of PFS. However, it would seem appropriate to be mindful of pre-existing sexual dysfunction or mental health disorders prior to finasteride treatment consideration. There are observations suggesting an increased risk of mental health disorders in finasteride users with a history of such [21]. Of note, personality disorders in patients with AGA were significantly more common than in the general population. These patients were also observed to experience increased levels of distress from hair loss compared to non-disordered patients and may experience an increased likelihood of finasteride

Table 6.1 Reported symptoms of post-finasteride syndrome

Sexual	Psychological	Physical
Erectile dysfunction	Depression	Metabolic changes
Ejaculatory disorders	Anxiety	Skin changes
Orgasmic anhedonia	Suicidal ideation	Gynecomastia
Decreased or complete loss of libido	Agitation and mood swings	Muscle weakness and atrophy
Hypogonadism	Impaired memory recall	Chronic fatigue
Penile shrinkage and loss of sensation	Slowed cognition	

adverse effects [22]. Caution with finasteride treatment for male-to-female transgender patients is also suggested due to the increased prevalence of anxiety, depression, and suicidal ideations in patients with gender dysphoria [23]. All possible risk factors, including those of similar effect, should be considered and discussed with the patient prior to starting finasteride.

6.5 Possible Pathophysiological Mechanism

Like many other clinical trademarks of PFS, the established pathophysiology explaining symptom presence in patients treated with finasteride is unknown. However, there are a number of proposed theories regarding observed adverse effects, all of them building off of the finasteride mechanism of action itself. Again, finasteride is an inhibitor of 5α-reductase, an enzyme that converts testosterone into its active form, DHT. DHT is a much more potent androgen than testosterone that binds with a higher affinity to androgen receptors and plays a key role in the development and function of the male reproductive system and processes. This near-irreversible variety of inhibition and slow dissociation rate has been thought to lead to epigenetic changes such as DNA methylation and upregulation of androgen receptor genes or 5α-reductase genes themselves. As a result, this drug may act as an endocrine disruptor that impacts several mechanisms and leads to undesirable sexual, psychological, and biological adverse effects [24].

The 5α-reductases themselves are a family of isoenzymes found throughout the body that contribute to hormone functionality and activation of neuroactive steroids from gonadal, adrenal, and CNS precursors. They are able to regulate the development and physiology of metabolic processes and are active in a wide variety of biochemical pathways involving libido, mood, and cognition [24]. The inhibiting properties that finasteride has towards 5ARs is what decreases DHT levels in the body and achieves the desired effects of androgenic alopecia improvement and decreased prostate volume. The high affinity and slow rate of dissociation between finasteride and 5ARs can also explain the lasting effects of this medication and lack of dose-dependency on its pharmacokinetics [25]. Unsurprisingly, it is believed that the inhibition of these enzymes leads to the adverse effects seen in patients with PFS.

6.5.1 Possible Mechanism for Sexual Dysfunction

There is some evidence in the literature regarding the physiologic responsibility of 5α-reductases in the central and peripheral nervous system. Again, these enzymes act as vital biological mediators in the CNS that manage functions such as libido. This finding led to the belief that inhibitors of such enzymes cause endocrine disruption in a wide variety of biochemical processes, including those regarding sexual function [24].

A recent prospective case-control study used penile tissue samples to investigate possible etiologies of sexual dysfunction secondary to finasteride, adding to the belief that genes influencing neurosteroid levels and androgen receptor (AR) expression differences are distinctions in PFS patients. This study was one of the first to explore and demonstrate significant gene expression differences of relevant biological pathways in patients with PFS symptoms compared to controls. Although the evidence of gene overexpression and under-expression correlates with observed biologic differences in patients with PFS, the study limitations and lack of mechanistic data to assert causality were acknowledged [26]. Using similar thought processes, another study investigated penile tissue in animal models to assess differences in 5α-dihydrotestosterone levels since 5α-DHT plays a key role in erectile physiology [27]. Pathophysiologic changes from finasteride's inhibitory properties demonstrated possible contributors to erectile dysfunction in patients using 5α-reductases.

6.5.2 Possible Mechanism for Psychological Dysfunction

The neurobehavioral effects of finasteride on those treated for AGA or BPH are hypothesized to result from changes in metabolism and the presence of neuroactive steroids such as testosterone and progesterone [18]. Synthesized in the brain and peripheral tissues, these neurosteroids can govern vital neurologic functional processes such as neurotransmission, myelination, and stress response. Since finasteride inhibits enzymes involved in the conversion of testosterone to DHT and progesterone into allopregnanolone and isoprenanolone, there were decreased concentrations of these neuroactive metabolites found in the cerebrospinal fluid and plasma in patients with depression and anxiety [18]. Allopregnanolone and isoprenanolone themselves have been found to have antidepressant and anxiolytic properties. Evidence of 5α-reductase downregulation in the prefrontal cortex of patients with depression helps support this belief that the risk of depression and suicide in PFS patients is due to the inhibitory capabilities of finasteride on neuroactive steroid availability [19].

6.5.3 Possible Mechanism for Biological Dysfunction

As touched on above, biological changes possibly resulting from the use of finasteride are less reported than sexual or psychological effects and have not been confirmed as associated. As a result, investigation of possible pathophysiology of such changes is limited and undetermined by current literature. Gynecomastia in male patients taking finasteride is believed to be influenced by testosterone metabolism into estradiol, a form of estrogen traditionally thought to be a "female hormone" that also exists in men for regulation of erectile function, libido, and spermatogenesis. It is due to this shift in estrogen to androgen ratio that is speculated to result in

breast tissue proliferation [20]. Regarding skin changes such as increased dryness and thinning reported by patients, again, no mechanism explaining dysfunction is confirmed. Considering finasteride inhibits 5α-reductases in the scalp to drop 5α-DHT levels and improve alopecia, additional unwanted skin effects are not anticipated with the use of 5α-reductase inhibitors but cannot be entirely unexpected. Overall, there is a scarce investigation of biological or physical changes in PFS patients that require additional inquiry.

6.6 Clinical Management Including Biological-Psychological-Social Contributing Factors

There remains a wide-ranging clinical phenotype for PFS, with most reported symptoms unconfirmed as significant by the past experimental investigation. The limited amount of information in the literature regarding the treatment of these adverse effects continues to be an obstacle for those affected. Frequently reported adverse effects such as sexual dysfunction are suggestive of commonality but still remain too broad and in need of further direct investigation to determine causality. Considering 50% of men between the ages of 51 and 60 will be affected by BPH, and 50% of Caucasian men will be affected by alopecia by age 40, much of the population will have an indication for finasteride use at some point in their lives [19]. This only further reveals the pressing need for exploration of PFS and management of its adverse effects.

At this time, there is no curative treatment of PFS due to the diversity of symptoms and unestablished causative pathophysiology of such symptoms. Current management of PFS focuses on the improvement of patient wellness by appropriately treating undesired symptoms. Like many other sexual medicine conditions, PFS with its reported symptoms is favorably evaluated and managed using the biopsychosocial approach, as these three domains of distinction encompass PFS symptoms as a whole.

With the development of the biopsychosocial (BPS) model in 1977, psychiatrist George Engel demonstrated how the intersection of three distinct domains of a person's life might better elucidate a patient's ailment than using a one-dimensional approach [28]. The BPS model expanded past the biomedical model of understanding illness that exclusively analyzed physiological or biological elements, an augmentation that would also include psychological or mental health components as well as social and cultural components. This dynamic, interdisciplinary approach, also known as the "mind-body" connection in mainstream society, has been increasingly utilized in the field of sexual medicine and can therefore be implemented in the evaluation and management of the controversial mosaic that is PFS. For a more in-depth exposition of this methodology, see Chap. 2 on the bio-psycho-social approach to sexual medicine disorders.

6.6.1 Diagnostic Criteria for PFS

Although a widely accepted diagnostic criterion for post-finasteride syndrome remains in the preliminary stage, some necessary characteristics are required for a PFS diagnosis. Such factors include prior treatment with a 5α-reductase inhibitor, such as finasteride or dutasteride, and the perseverance of sexual dysfunction symptoms after stopping this treatment. Additional specific indications include the reduction or loss of libido, erectile dysfunction, and the reduction in genital and orgasmic sensation, all of which must be present for at least 3 months after treatment discontinuation [29]. In order to confirm PFS, affected candidates cannot have evidence of sexual dysfunction of the same profile prior to medication use, medical conditions that may explain symptoms, current medication or substance misuse that may explain symptoms, or even prior medication that may explain symptoms [29]. Considering the vague profile of finasteride's adverse effects and the likelihood of sexual dysfunction exacerbated by various other medications, only after abiding by these qualifications can a patient be eligible for PFS diagnosis. Possible related effects of finasteride use, such as gynecomastia and changes in semen production, may be related to finasteride use but are not required as diagnostic determinants. Depression, suicidality, and cognitive impairment may occur alongside sexual dysfunction or be present independent of other effects [29].

6.6.2 Management of Adverse Effects

While knowledge gaps regarding PFS continue to fill, management of adverse effects impacting quality of life in patients is of great priority as a medical provider. The BPS model provides reason to doubt that a single factor exclusively causes conditions such as PFS, and the wide symptom profile of this condition further validates that. Patient treatment must be personalized and dependent on the identification and severity of symptoms experienced.

Management of sexual dysfunction conditions seen in patients with finasteride exposure is perhaps more straightforward than the psychological repercussions also seen. Erectile dysfunction is commonly reported and can be exacerbated by risk factors such as increased age, conditions such as diabetes or hypertension, endocrine disease, or neurological disorders [30]. In any case, treatment with phosphodiesterase type 5 inhibitors such as sildenafil and tadalafil, in addition to cognitive therapy, can be considered. Anxiety, depression, and other mood changes that have been reported are potentially more difficult to maneuver. In addition to antidepressant and anxiolytic medication, psychotherapy, sex therapy, cognitive behavioral therapy, and healthy lifestyle changes may also be beneficial for those suffering from psychological adverse effects. The coexistence of sexual dysfunction and major depressive disorder (MDD) is well established, with sexual dysfunction

increasing the risk of depression by 130–200% and depression increasing the risk of sexual dysfunction by about 50–70% [30]. Selective serotonin reuptake inhibitors (SSRIs) are generally utilized in depressed patients as an efficient treatment option for not only depression but also premature ejaculation. Again, there is no confirmed curative treatment for PFS and treatment of bothersome or even debilitating symptoms is highly recommended.

6.6.3 Alternatives to Oral Finasteride

Although finasteride is still considered a safe medication for the treatment of AGA, alternatives continue to be explored to avoid possible adverse events. The use of topical 5α-reductase inhibitors has been recently displayed as a possible solution to avoid PFS while still receiving benefit for alopecia. In one systematic review that included seven articles, every study reported a significant decrease in hair loss, increased hair counts, and positive patient hair assessment with the use of topical finasteride [31]. Serum testosterone levels remained constant, and there was a significant decrease in scalp and plasma DHT levels with application. One randomized, double-blind controlled study investigated the efficacy and safety of topical finasteride 0.25% mixed with 3% minoxidil versus the 3% minoxidil solution alone in men with AGA. It was found that the combined solution was significantly more effective than the sole minoxidil solution, with improvement in hair density and assessment without reported systemic adverse events [32]. Studies such as these are encouraging amongst the uncertainty of PFS and call for additional investigation of oral finasteride alternatives.

6.7 Conclusion

Finasteride is a commonly prescribed 5α-reductase inhibitor used in the treatment of benign prostatic hyperplasia (BPH) and androgenic alopecia (AGA). This medication works by preventing the conversion of testosterone into dihydrotestosterone (DHT), reducing scalp and serum levels of DHT and subsequently shrinking the prostate gland and preventing hair loss. Although this medication has been generally well tolerated by most users, the recent increase in reported adverse effects that persist even after discontinuation led to labeling these sexual, psychological, and biological symptoms as post-finasteride syndrome. As of now, the knowledge gap regarding this newer condition is significant, with the long-term safety profile of finasteride unconfirmed and disorder authenticity not yet fully accepted due to pathophysiological and epidemiological ambiguity. For patients experiencing severe adverse events, this continued uncertainty has the capability of significantly impacting their quality of life. Reported adverse effects include sexual dysfunction in the form of erectile or ejaculatory disorders, psychological effects manifesting as

increased anxiety, depression, and even suicidality, and biological effects seen as gynecomastia and skin dryness.

There are no confirmed mechanisms of action that encompass the wide symptom profile of PFS, and there is also no known treatment. Management of symptoms and severity specific to each patient are ultimately recommended, and prevention of PFS with the use of alternatives such as topical finasteride may be considered until further investigation elucidates the safety of long-term oral 5α-reductase inhibitor use.

Considering the spike in public recognition of post-finasteride syndrome and the unanswered questions remaining, research geared towards filling such a knowledge gap is necessary, especially since such a large portion of the population will develop an indication for finasteride usage. Patients with a history of sexual dysfunction, psychiatric disorders, or fertility issues should especially be informed of current literature prior to finasteride prescription as they may be at higher risk of developing adverse effects. As of now, PFS remains enigmatic, and until the association is confirmed or denied, it is recommended to reflect on possible undesirable outcomes that may come with finasteride in patients treated for either BPH or AGA.

Key Messages

- Post-finasteride syndrome is characterized by a collection of sexual, psychological, and physical adverse effects that persist in patients previously treated with 5α-reductase inhibitors like finasteride for benign prostatic hyperplasia or androgenic alopecia.
- The long-term safety profile of finasteride remains incomplete after nearly three decades of market use.
- The medical community does not officially recognize this disorder due to its ambiguous symptom presentation, unconfirmed pathophysiology, and inconclusive association from the past investigations.
- As a medical provider treating a patient with an indication for finasteride usage, one should consider the personal history of pre-existing conditions such as sexual dysfunction, infertility, and mood disorders before the prescription.

References

1. Diviccaro S, Melcangi RC, Giatti S. Post-finasteride syndrome: an emerging clinical problem. Neurobiol Stress. 2020;12:100209. https://doi.org/10.1016/j.ynstr.2019.100209.
2. Propecia. Letters, reviews, labels, patient package insert. Merck; 1997. Accessed June 6, 2021. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020788.
3. Post-Finasteride Syndrome Foundation. https://www.pfsfoundation.org. Accessed 3 Jun 2021.
4. Baas WR, Butcher MJ, Lwin A, Holland B, Herberts M, Clemons J, et al. A review of the FAERS data on 5-alpha reductase inhibitors: implications for postfinasteride syndrome. Urology. 2018;120:143–9. https://doi.org/10.1016/j.urology.2018.06.022.

5. National Institutes of Health. National Center for Advancing Translational Sciences. Genetic and Rare Diseases Information Center. https://rarediseases.info.nih.gov/diseases/12407/post-finasteride-syndrome Accessed 2 June 2021.
6. Smith AB, Carson CC. Finasteride in the treatment of patients with benign prostatic hyperplasia: a review. Ther Clin Risk Manag. 2009;5(3):535–45. https://doi.org/10.2147/tcrm.s6195.
7. McVary KT, Roehrborn CG, Avins AL, Barry MJ, Bruskewitz RC, Donnell RF, et al. American Urological Association guideline: management of benign prostatic hyperplasia (BPH). Published 2010; reviewed and validity confirmed 2014. http://www.auanet.org/guidelines/benign-prostatic-hyperplasia-(2010-reviewed-and-validity-confirmed-2014).
8. Ganzer CA, Jacobs AR, Iqbal F. Persistent sexual, emotional, and cognitive impairment post-finasteride: a survey of men reporting symptoms. Am J Mens Health. 2015:222–8.
9. Mysore V, Shashikumar BM. Guidelines on the use of finasteride in androgenic alopecia. Indian J Dermatol Venereol Leprol. 2016;82:128–34.
10. Mella J, Perret M, Manzotti M, Catalano H, Guyatt G. Efficacy and safety of finasteride therapy for androgenetic alopecia. JAMA Dermatol. 2010;146(10):1141–50. https://doi.org/10.1007/s1193-018-0161-6.
11. Pereira AF, Coelho TO. Post-finasteride syndrome. An Bras Dermatol. 2020;95(3):271–7. https://doi.org/10.1016/j.abd.2020.02.001.
12. Lee S, Lee YB, Choe SJ, Lee WS. Adverse sexual effects of treatment with finasteride or dutasteride for male androgenetic alopecia: a systematic review and meta-analysis. Acta Derm Venereol. 2019;99(1):12–7. https://doi.org/10.2340/00015555-3035.
13. Liu L, Zhao S, Li F, Li E, Kang R, Luo L, et al. Effect of 5α-reductase inhibitors on sexual function: a meta-analysis and systematic review of randomized controlled trials. J Sex Med. 2016;13(9):1297–310. https://doi.org/10.1016/j.jsxm.2016.07.006.
14. Samplaski MK, Lo K, Grober E, Jarvi K. Finasteride use in the male infertility population: effects on semen and hormone parameters. Fertil Steril. 2013;100(6):1542–6. https://doi.org/10.1016/j.fertnstert.2013.07.2000.
15. Khera M, Than JK, Anaissie J, Antar A, Song W, Losso B, et al. Penile vascular abnormalities in young men with persistent side effects after finasteride use for treatment of androgenic alopecia. Transl Androl Urol. 2020;9(3):1201–9. https://doi.org/10.21037/tau.2020.03.21.
16. Nguyen D, Marchese M, Cone E, Paciotti M, Basaria S, Bhojani N, et al. Investigation of suicidality and psychological adverse events in patients treated with finasteride. JAMA Dermatol. 2021;157(1):35–42. https://doi.org/10.1001/jamadermatol.2020.3385.
17. Ali AK, Heran BS, Etminan M. Persistent sexual dysfunction and suicidal ideation in young men treated with low-dose finasteride: a pharmacovigilance study. Pharmacotherapy. 2015;35:687–95. https://doi.org/10.1002/phar.1612.
18. Pompili M, Magistri C, Maddalena S, Mellina C, Persechino S, Baldessarini RJ. Risk of depression associated with finasteride treatment. J Clin Psychopharmacol. 2021;41(3):304–9. https://doi.org/10.1097/JCP.0000000000001379.
19. Than J, Rodriguez K, Khera M. Post-finasteride syndrome: a review of current literature. Curr Sex Health Rep. 2018;10(3):152–7. https://doi.org/10.1007/s11930-018-0163-4.
20. Traish AM, Hassani J, Guay AT, Zitzmann M, Hansen ML. Adverse side effects of α-reductase inhibitors therapy: persistent diminished libido and erectile dysfunction and depression in a subset of patients. J Sex Med. 2011;8(3):872–84. https://doi.org/10.1111/j.1743-6109.2010.02157.x.
21. Ganzer CA, Jacobs AR. Emotional consequences of finasteride: fool's gold. Am J Mens Health. 2018;12(1):90–5. https://doi.org/10.1177/1557988316631624.
22. Maffei C, Fossati A, Rinaldi F, Riva E. Personality disorders and psychopathologic symptoms in patients with androgenic alopecia. Arch Dermatol. 1994;130(7):868–72. https://doi.org/10.1001/archderm.1994.01690070062009.
23. Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. J Psychosom Res. 2005;58:259–61. https://doi.org/10.1016/j.jpsychores.2004.08.010.

24. Traish A. The post-finasteride syndrome: clinical manifestation of drug-induced epigenetics due to endocrine disruption. Curr Sex Health Rep. 2018;10(3):88–103.
25. Traish AM. Post-finasteride syndrome: a surmountable challenge for clinicians. Fertil Steril. 2020;113(1):21–50. https://doi.org/10.1016/j.fertnstert.2019.11.030.
26. Howell S, Song W, Pastuszak A, et al. Differential gene expression in post-finasteride syndrome patients. J Sex Med. 2021; https://doi.org/10.1016/j.jsxm.2021.05.009.
27. Pinsky MR, Gur S, Tracey AJ, Harbin A, Hellstrom WJ. The effects of chronic 5α-reductase inhibitor (dutasteride) treatment on rat erectile function. J Sex Med. 2011;8:3066–74. https://doi.org/10.1111/j.1743-6109.2011.02425.x.
28. Engel GL. The need for a new medical model: a challenge for biomedicine. Science. 1977;196:129–33.
29. Healy D, Bahrick A, Bak M, Barbato A, Calabro RS, Chubak BM, et al. Diagnostic criteria for enduring sexual dysfunction after treatment with antidepressants, finasteride and isotretinoin. Publication in process. Int J Risk Saf Med. 2022;33(1):65–76.
30. Chokka PR, Hankey JR. Assessment and management of sexual dysfunction in the context of depression. Ther Adv Psychopharmacol. 2018;8(1):13–23. https://doi.org/10.1177/2045125317720642.
31. Lee SW, Juhasz M, Mobasher P, Ekelem C, Mesinkovska NA. A systematic review of topical finasteride in the treatment of androgenetic alopecia in men and women. J Drugs Dermatol. 2018;17:457–63.
32. Suchonwanit P, Srisuwanwattana P, Chalermroj N, Khunkhet S. A randomized, double-blind controlled study of the efficacy and safety of topical solution of 0.25% finasteride admixed with 3% minoxidil vs. 3% minoxidil solution in the treatment of male androgenetic alopecia. J Eur Acad Dermatol Venereol. 2018;32(12):2257–63. https://doi.org/10.1111/jdv.15171.

Chapter 7
Orgasmic Anhedonia

R. J. Heruti, R. Kamin, and J. Bitzer

Learning Objectives
- To know about the definition of Orgasmic Anhedonia or Pleasure Dissociative Orgasmic Dysfunction.
- To understand orgasm as a specific physiological process associated with the subjective experience of intensive pleasure.
- To understand the specificity of the disorder as a dissociation between physical reactions taking place during the orgasm reflex and the subjective experience of intensive pleasure, resulting in a loss of the positive emotional response.

7.1 Introduction

The term Orgasmic Anhedonia (OA) describes the lack of sexual climax, sexual pleasure, or any good sensation at the peak of the sexual response cycle in males and females. Although orgasm, or the subjective mental pleasant sensation, cannot be

R. J. Heruti (✉)
Department of Rehabilitation Medicine, Reuth Rehabilitation Hospital, Tel-Aviv University, Tel-Aviv, Israel
e-mail: heroti@reuth.org.il

R. Kamin
Beer Sheva Mental Health Center, Beer Sheva, Israel

J. Bitzer
Obstetrics and Gynecology, University Hospital of Basel, Basel, Switzerland

Y. Reisman et al. (eds.), *Textbook of Rare Sexual Medicine Conditions*,
https://doi.org/10.1007/978-3-030-98263-8_7

measured or compared between people and genders, it is considered for many as the "highlight" of the sexual act. The absence of that feeling (which was experienced before or not) is the topic at hand [1].

OA is also called Pleasure Dissociative Orgasmic Dysfunction (PDOD). The data on the disorder is scarce, and the aetiology is not yet clear enough. There are psychological causes, as well as many physical or iatrogenic causes. A comprehensive evaluation directed to possible aetiology is needed. The therapist needs to understand the differential diagnosis of the disorder, in order not to miss a reversible and /or treatable cause. It is essential to refer these complex patients for assessment and management by a specialist. Therapy should address causes that are diagnosed, as well as biological, psychological issues and couple aspects [2].

7.2 Definition of the Disorder

The sexual response cycle, introduced by Masters and Johnson, is an important cornerstone in understanding sexuality. Learning of sexual dysfunctions is easier using a model of phases, but because of some differences between men and women, many address those issues separately and use several terms to describe a dysfunction.

Anhedonia is the inability to experience pleasure from an activity that is normally considered pleasurable. Orgasmic Anhedonia (OA) is the inability to feel pleasure during the sexual climax. There is a dissociation between body and mind, therefore the disorder is also called pleasure dissociative orgasmic dysfunction (PDOD). For women, the common term used is anorgasmia, which is wrong, because anorgasmia is the absence of orgasm in general, including the bodily reactions during orgasm, whereas orgasmic anhedonia is the dissociation between the physical and cognitive appraisal of the experience.

This disorder can cause significant distress to both the patient and the partner [1]. Although this complaint was described and for a long time known, it did not get enough attention in the literature and there is no clear definition in medical classification systems (DSM or ICD) [1, 3]. Since OA is a disorder in the orgasmic phase, it was termed accordingly, but it was addressed separately for men and women. In men, orgasm usually occurs during erection and accompanied by ejaculation, so its absence is clearer to describe. The Diagnostic and Statistical Manual of Mental Disorders (DSM–5) classification for sexual dysfunctions defines the reduced intensity of orgasmic sensations or their absence only in women. The ICD-11 and DSM-5 have no particular definition for the lack of pleasurable sensation at the peak of the sexual climax in men [1, 3].

Primary OA is when the disorder presents from the first sexual experience. Usually, it occurs with other sexual dysfunctions. Most cases of OA are *secondary*, meaning that the individual had experienced a good orgasm in the past and later began to feel a less satisfying sensation.

7.2.1 Male Orgasmic Disorder

In men, the absence of orgasm might be with or without ejaculation. When both ejaculation and orgasm are missing, it is important to differentiate between anorgasmia and absence of ejaculation (including retrograde ejaculation and aspermia) [4].

For men, an older definition of "male orgasmic disorder" was changed to "delayed ejaculation". DSM-5 adds "*It is important in the history taking to ascertain whether the complaint concerns delayed ejaculation or the sensation of orgasm*". The complaint of decreased pleasure (i.e. OA, anhedonic ejaculation/anaesthetic ejaculation) would not be coded as delayed ejaculation, but could be coded as other specified sexual dysfunction or unspecified sexual dysfunction [1].

7.2.2 Female Orgasmic Disorder

The "Female orgasmic disorder" (FOD) is characterized by difficulty to experience orgasm and/or markedly reduced intensity of orgasmic sensations (Criterion A), but it does not state whether "absence of orgasm" is "lost", "not achieved" or "missing". The symptoms have to persist for a minimum duration of 6 months and cause clinically significant distress in order to fulfil the criteria [1]. It makes, female OA a complex diagnostic construct—combining objective physiological processes and subjective mental experience (Body and Mind interaction). The diagnosis must relate to its two constituents–**anhedonia** (Mind) and **orgasm–**the neurovascular and neuromuscular reflex with measurable changes (prospective, actual, and retrospective signs different); and a subjective highly pleasurable experience (with sensory, evaluative, and affective components) (Body and Mind) [5].

In men, the absence of the physical orgasmic response is easy to observe. In women, this is much more difficult. A scientific experimental approach would be to have women in a laboratory, measuring their vaginal blood flow, vaginal and pelvic muscle contractions, and other physical signs of orgasm, and ask them to record their feelings and thoughts (subjective response). Until now there have been no such studies on orgasm. It has only been done establishing the diagnosis of mental arousal disorder showing that in some women there is a dissociation between increased vaginal blood flow and pleasurable subjective response. The clinical "diagnostic case" would be the woman who reports having desire feeling aroused and observing lubrication. Her body produces the actual signs of orgasms (such as pelvic floor contractions), but there is no subjective pleasurable response (Body Mind Dissociation) [6, 7]. This seems to be a rare situation.

In clinical practice, it seems that there is considerable overlap between PDOD and a subtype of FOD. According to DSM 5 (302.73), FOD is the presence of either marked delay or marked reduced intensity of orgasmic sensations in most (75–100%) occasions of sexual activity [1]. This marked reduced intensity of sensations is not well described and might include the subjective experience which is not quantified.

So in clinical practice, OA in women seems to be on a continuum from reduced intensity to the absence of orgasm associated pleasure.

This is also reflected in the ISSWSH and ICSM statement, where FOD is defined by the persistent or recurrent, distressing compromise of orgasm frequency, intensity, timing, or pleasure associated with sexual activity, for a minimum of 6 months [8]:

(a) Frequency: orgasm occurs with reduced frequency (diminished frequency of orgasm) or is absent (anorgasmia).
(b) Intensity: orgasm occurs with reduced intensity (muted orgasm).
(c) Timing: orgasm occurs either too late (delayed orgasm) or too early (spontaneous or premature orgasm) than desired by the woman.
(d) Pleasure: orgasm occurs with absent or reduced pleasure (anhedonic orgasm, pleasure dissociative orgasm disorder).

7.3 Epidemiology

7.3.1 Men

Most research on sexual dysfunction in men have been conducted on erectile dysfunction (ED) and premature ejaculation (PE), so data on other disorders is limited. It is difficult to assess the prevalence of OA due to several reasons. Most researchers who use the term orgasmic dysfunction or anorgasmia in their research do not distinguish between ejaculation and orgasm. Other reasons include lack of unity in criteria used, different research methods, different inclusion criteria, and the difficulty of many men to distinguish between ejaculation and orgasm [9].

Epidemiological studies performed in the US and Europe estimate that up to 30% of males have experienced ejaculatory dysfunction. The most commonly reported orgasmic disorder experienced by men is PE followed by delayed and painful ejaculation. In the United States, difficulties in reaching orgasm were reported by 8% of men between 18 and 24 years and up to 14% of men aged 55 years and older [10]. A worldwide report showed a prevalence of 5% to 8% for all areas of the world except for East and Southeast Asia, where the prevalence was 10% to 15%. Other surveys have reported lower rates, ranging from 1.8% to 5.6%. Trouble reaching orgasm was commonly reported by men in at least half of sexual situations (9% to 17% in men below the age 55, and 30% in men aged 55 years and older). Orgasm difficulty was the second most common additional sexual complaint and was found among 63.2% of men presenting with low sexual desire and 36.4% with ED. Orgasm difficulties and ED were frequently reported by men experiencing low sexual desire (63.2% for each sexual problem [8].

Approximately one-quarter of men reported erection problems (23.8%) and ejaculation problems (24.7%). The data is not clear about special orgasmic/ejaculation

problems (Quinn-Nilas, 2018). In other studies, the prevalence of orgasmic dysfunction was much lower (11%–16%), whereas that of mild orgasmic dysfunction was remarkably higher (approximately 60%). Educational level was a significant predictor of orgasm difficulties, with the less literate reporting significantly more orgasm difficulties compared to the higher educated (0–9 years of school attendance, OR = 14.71, 95% CI: 1.94 to 111.37; 10 to 12 years of school attendance, OR = 10.35, 95% CI: 1.64 to 92.10) [11].

7.3.2 Women

As described above, PDOD in women is a clinical entity which in its pure form seems to be very rare (normal desire, normal arousal–mental and physical, normal orgasmic reflex), meaning that there is a dissociation between body and mind specifically during the orgasm phase. Taking into account the concept of a continuum of dissociation, the basic mechanisms may occur in different types of female orgasmic disorders. Therefore, the pathogenic mechanisms underlying the disorder may be more frequent than reported in studies about female PDOD [5].

The Prevalence of Female Sexual Problems Associated With distress and Determinants of Treatment Seeking (PRESIDE) study involving 31,581 US women aged 18–102 years found that, overall, 44% reported any sexual problem (desire, arousal, orgasm). Low desire was the most common problem reported by 39% of women, low arousal by 26%, and orgasm problems by 21%. When distress was combined with a sexual problem, 12% experienced any distressing sexual problem (10% low desire, 5.5% low arousal, 4.7% orgasm problems). A distressing sexual problem was more common in women aged 45–64 years (14.8%) than in younger (10.8%) or older (8.9%) women. Similar patterns have been shown in other larger-scale studies [7].

In a national survey in Canada, it was found that the rates of women's orgasm difficulty, vaginal pain, and vaginal dryness were 14.5%, 17.1%, and 28.8%, respectively. More than 80% of all sexually active women 18–74 years old reported some degree of orgasmic dysfunction. The prevalence of inability to have an orgasm in the Global Study of Sexual Attitudes and Behavior ranged from 10% in Northern Europe to 34% in Southeast Asia. A much higher prevalence was found in a recent study conducted in Ghana, with 72.4% of women experiencing orgasmic problems, but these were severe in only 8% of participants [8].

7.4 Clinical Presentation and Contributing Factors

Sexual function has four phases: (1) drive, (2) arousal, (3) orgasm (marked in men by emission and ejaculation), and (4) resolution. Emission, ejaculation, and orgasm are distinct events that might occur separately. Orgasm may vary in intensity and

duration, depending on many biopsychosocial factors such as duration of arousal, muscular tone of the pelvic floor, time-lapse from the last orgasm, general health, and drug or alcohol consumption, intensity of arousal, and emotional intimacy and/or comfort with the partner [12].

7.4.1 Men

As mentioned above, OA is the experience of normal ejaculation without pleasure or orgasm. Patients experience sexual stimulation and achieve an erection, but the connection in the brain which registers these sensations as pleasure is missing. Having once experienced orgasm, one knows when it is missing or weak. A man who reached ejaculation and then "fade" into the resolution phase without the pleasurable sensation that he expected, or a woman who feels ready to climax but "stuck" on the plateau stage and then find herself in "resolution" are the patients we are dealing with. Proposed aetiologies include diminished libido, hormonal, or metabolic imbalances (e.g. pituitary, thyroid, or testicular dysfunction), psychological disturbances, or medications [2].

The evaluation of the disorder is based on the patient's self-report of the intensity of orgasmic sensation. The pleasurable sensation itself is a combination of subjective sensory, cognitive and emotional experience, which any of them could be altered and make the individual feel "something is missing" [13]. To fulfil the diagnosis criteria by the DSM, the symptoms have to persist for a minimum duration of approximately 6 months and cause clinically significant distress in the individual [1].

Many men who present with the complaint of OA will describe a general feeling of anhedonia as well. Typically these men are clinically depressed, experiencing significant relationship distress or some other existential crisis. It may be a presenting symptom of depression since sexual dysfunction is diagnosed in 63% of depressed patients receiving medication and 45% of unmedicated depressed patients. When any of these situations exist, treatment of the larger symptom picture will often result in improved sexual functioning. Yet, like many "chicken and egg phenomena", it is critical to identify whether the depression is secondary to OA or instead of a precipitant to it. In addition, the mental health clinician must also be mindful of the effects it may have on the couple's relationship. Sexual dysfunction that presents in any coupled individual will likely have an impact on their partner and their relationship [12].

Many men, as a natural consequence of the ageing process, may experience diminished orgasmic sensations. This might be distressing but is not due to a pathological condition. The development of ED medication could confuse men to expect the same improvement in ejaculation amount and orgasm sensation, which usually do not improve as well as erection [14].

7.4.2 Women

Women with PDOD present usually with the complaint of not having an orgasm which is expected to be a highly pleasurable experience. This symptom or complaint can represent 4 different clinical conditions:

(a) The woman is not mentally aroused and her body does not react (increased blood flow in the vulvovaginal region, pelvic floor contractions (arousal and orgasmic disorder combined).
(b) The woman is aroused and her body produces the signals of excitement but she feels like a blockage to get to the point of orgasmic release (isolated inability to reach orgasmic phase with normal arousal -excitement phase- up to plateau phase).
(c) The woman is not sure whether what she feels during sex is an orgasm. How should an orgasm feel? (insecurity about quality of the orgasmic experience).
(d) The woman's body shows all the signs of excitement and orgasmic release but she "does not feel it", there is no emotional and cognitive correlation.

Most women complaining about "not having an orgasm" belong to groups a, b, and c. Women in group D are those who suffer from orgasmic anhedonia, a mismatch between the signals sent by the body and the subjective experience [6].

7.5 Possible Pathophysiological Mechanism

The main pathophysiological mechanism is the dissociation between the objective bodily signs of orgasm and the subjective experience as a highly pleasurable event. Given the low prevalence of male orgasmic disorder, studying this disorder is difficult, especially when little is known about the particular pathway to orgasm. Many studies were done on men since in men orgasm is normally conjugated to ejaculation.

Orgasm is a neurologic response to sexual stimulation. Autonomic innervation via the cavernous nerves mediates both erection and ejaculatory functions. Sympathetic fibres arising from T11–L2 travel to the penis via inferior mesenteric, hypogastric, and pelvic nerve plexuses to promote emission and ejaculation via contractions of the vas deferens, ampulla, seminal vesicles, prostate, and bladder neck [4]. The dorsal nerve branches from the pudendal nerve provide somatic innervation to the penis. It also mediates contraction of the pelvic floor muscles to achieve rigidity and plays a role in discharging ejaculatory fluid. It has been noted that conscious sexual arousal does not occur usually with damage to the pudendal nerve [15].

Emission involves smooth muscle contraction and seminal fluid secretion from the seminal vesicles and prostate, and rising pressure in the seminal bolus, which

cause the sensation of ejaculatory inevitability. Orgasm is the cognitive experience of pleasure that coincides with ejaculation [16]. During orgasm, there are downward motor signals that result in quick cycles of muscle contraction in the pelvic muscles that surround the pelvic floor (bulbospongiosus and ischiocavernosus muscles). This contraction of accessory sexual organs and the urethral bulb probably cause the pudendal nerve to transmit sensory stimuli to the cerebrum resulting in orgasm [15].

In men and women, it seems that the same brain centres and neurotransmitter messages are involved in processing the body signals.

If we look at the female PDOD from a psychophysiological perspective, we can understand the disorder as the result of the interplay between the bodily processes characteristic of orgasm and the subjective pleasurable experience. These mechanisms are the same in males and females (see above). This interplay can become dysfunctional by:

(a) Physical and endocrine factors disrupt arousal and the orgasmic reflex (neurological and other diseases, lack of testosterone).
(b) Central nervous factors disrupt or block the processing of the peripheral physical signals (such as depression and anxiety). A central aspect in anhedonia is the disorder of the central nervous reward system in the nucleus accumbens. Anhedonia seems to be associated with a deficit of activity of the ventral striatum (including the nucleus accumbens) and an excess of activity of the ventral region of the prefrontal cortex (including the ventromedial prefrontal cortex and the orbitofrontal cortex), with a pivotal, but not exclusive, the role of dopamine.

The limbic system is highly interconnected with the brain's emotion, behaviour, and pleasure centres, all of which play a role in sexual function. When sufficient input messages are received in the limbic system, in particular the thalamus, there is a release of a large number of neurochemicals that induce an orgasm. Brain scans during orgasm show a temporary deactivation in the metabolic activity of a large part of the left cerebral cortex with increased metabolic activity in the right brain, in particular the limbic area. In addition, during orgasm, there are upward neurologic signals to the cerebral cortex. These signals result in a general euphoric sensation that is characterized by intense pleasure.

Hormones and neurotransmitters are also involved in a very complex way. Positron emission tomography studies during orgasm have shown brain activations mainly in the anterior lobe of the cerebellar vermis and deep cerebellar nuclei and deactivations in the left ventromedial and orbitofrontal cortex. While these are similar between genders, in men there is additional activation in the periaqueductal grey matter. Oxytocin levels have been shown to increase in association with orgasm in both genders. Prolactin secretion similarly increases after orgasm and has been proposed as a marker for male orgasm [13].

Dopamine and serotonin have emerged as essential neurochemical factors, with dopamine facilitating ejaculation and serotonin inhibiting it. Dopamine release in the medial preoptic area (MPOA) appears to increase the copulatory rate in rats.

Dopamine antagonists inhibit sexual functioning, particularly orgasm. One theory speculates that dysfunction in the regulation of dopamine in the nucleus accumbens (the region of the brain's reward centre) is responsible for orgasm loss. This nucleus is thought to play an important role in reward, laughter, pleasure, addiction, and music. Serotonin tends to inhibit sexual behaviour. In monkeys, serotonin agonists inhibit sexual behaviour. In male rats, activation of the 5HT-1A receptor lowers the threshold for ejaculation, whereas activation of 5HT-1B and 5HT-1C and antagonism of 5HT-2 all inhibit sexual behaviour [16]. Sexual arousal without orgasm resulted in increased blood pressure and plasma norepinephrine, but without concomitant increases in other catecholamines or prolactin. Prolactin levels increased after orgasm in both genders for at least 1 h, suggesting it could contribute to the refractory period after orgasm. Intriguingly, in men who report short or absent refractory periods, a prolactin surge might not occur after orgasm [17].

Patients may receive sexual stimulation, but there is a disconnection between the sensation and the part of the brain that recognizes that sensation as pleasurable. Anatomically, damage to pelvic nerves (following prostatectomy, RPLND, TURP, bladder neck incision, or other colorectal or pelvic surgery) and spinal cord injuries may interfere with ejaculation and orgasm. Medical diseases including diabetic or alcoholic neuropathy, hypothyroidism, low testosterone, and even strokes have also been linked to impairment of orgasm. From a medication standpoint, the most well-known cause is the anti-depressant class (SSRIs) which increase the amount of circulating serotonin, an ejaculatory inhibitor. Medications, including MAO-inhibitors, tricyclic antidepressants, antipsychotics with alpha antagonist activity (chlorpromazine, haloperidol), opioids, benzodiazepines, ethanol, alpha antagonists (doxazosin, prazosin) have all been implicated in delayed and anejaculation. They also might affect the quality of orgasm itself [12, 16].

Psychosocial variables are also important in the setting of OA. Approximately 75% of affected males can achieve ejaculation through solitary masturbation. Relationship stress, feuding, and conflict may all compromise sexual responses and inhibit the achievement of orgasm. Primary disorders may indicate serious pathological dysfunctions like obsessive ruminations (of guilt, filth, and so on) causing difficulty in achieving sufficient excitement to trigger the sexual climax. The inhibition theory model describes a man who does not receive enough stimulation to reach his orgasmic threshold and/or a man who deprives his partner of something they desire. In secondary OA, one can find unresolved interpersonal and couple problems, of which the subject is less or more aware of or even clear hostility toward potential sexual partners [12].

A new cause of OA was discovered recently with the COVID-19 outbreak. One study presented two male patients with COVID-19 who developed anorgasmia, following recovery from the infection. Although no evidence of viral replication or inflammatory involvement could be identified in these patients, a lack of other known risk factors for anorgasmia points to the role of COVID-19 as the contributing factor [18].

7.6 Clinical Management Including Biological-Psychological-Social Contributing Factors

Evaluation and treatment of OA in men and women require thorough examination and evaluation of potential variables, including the possible sexual side effects of medications. Given the medical implications of OA, an initial assessment is best performed by a physician with expertise in sexual medicine. Oftentimes, the medical evaluation is unremarkable, and the patient will then be referred for psychosexual evaluation.

Physical examination is necessary to rule out obvious anatomical and organic contributions.

In women, the focus is on the examination of the vulvovaginal region to exclude conditions that may contribute to a diminished sensation from erotic zones.

Sometimes it is therapeutically beneficial, legitimizing the orgasmic concern as a medical problem, and addresses concerns about sexually transmitted diseases and genital appearance. In men patency of the urethral meatus, size and firmness of the testicles, presence or absence of spermatic cord structures, and foreskin retractability are examined. A rectal examination is done to rule out prostatitis and other pathological conditions. Additional hypogonadal body signs include the loss of body hair and muscle bulk, softening of the skin and gynecomastia. A neurological genital assessment is necessary if a neurological cause is suspected.

In men sensory evaluation of the genital dermatomes, pinprick sensitivity of the glans, and rectal determination of anal tone and voluntary anal contraction are necessary. A positive bulbocavernosus reflex signifies an intact sacral reflex, which bodes well for ejaculation (and reflex erection) potential. Other signs of peripheral neuropathy or general cardiovascular compromise should be looked for [12].

Blood testing should be considered if OA is associated with diminished desire, to assess testicular (ovarian) function, pituitary function, and thyroid function, such as testosterone, sex hormone-binding globulin, LH, FSH, oestradiol, prolactin, and TSH.

The sexual interview should explore psychosexual factors such as hypoactive sexual desire disorder, depression, difficulties with sexual arousal, anxiety, fatigue, past trauma/abuse, cultural/religious views on sex, partner's sexual difficulties/concerns, and other emotionally based concerns. People's level of stress and whether or not they have time to engage in sexual activity in a relaxed atmosphere will be important aspect to consider when assessing orgasmic capacity [14].

7.7 Treatment

There is limited data on any therapies, including pharmacologic agents for the treatment of OA. It is reasonable to use a combination of medical treatment and sex therapy.

As OA is on the one hand, a distinct orgasmic disorder in which there is a disconnect between body and mind it is nonetheless in clinical practice often associated with physical and mental health problems which have an influence on orgasmic function as a whole.

Treatment is therefore often along the lines of the general treatment options available for orgasmic disorders in general.

When a definite medical problem is thought to be the cause for OA, the first step would be to try and treat it, like a presumed side effect of a prescribed drug. If it appears to be related to addiction (e.g. opioids, alcohol, heroin), it seeks appropriate treatment. If due to psychological issues (depression, addiction), consider a referral to a psychiatrist. If a medical cause cannot be elucidated, the referral to psychosexual therapy may provide benefit [2].

As the effect on orgasm may be dose-dependent, strategies that involve reducing the serum level of SSRI below an individual's threshold for orgasmic dysfunction can be effective. Such strategies include "drug holidays"—in which a patient stops SSRIs with the shortest half-lives (such as sertraline or paroxetine) for 48 hours before planned sexual activity. Other strategies include switching within the SSRI class (which is generally effective only when the absolute serotonergic 5HT-2 activity is lowered) and lowering the SSRI dose. Most dose-reduction strategies entail some risk of depressive relapse. When patients who had SSRI-associated sexual dysfunction were switched to a non-SSRI, 65–80% of patients improved, whereas only 10% who were switched to paroxetine improved. Because data were not reported for male orgasmic disorder specifically, it is difficult to extrapolate from these data specifically to OA [13, 19].

Medications that may help with orgasm function include dopamine agonists, oxytocin, PDE −5 inhibitors, and alpha 2 receptors blockers such as yohimbine hydrochloride. Medications that partially help with delayed ejaculation might also be of interest. Cabergoline and bupropion are the two most commonly trialled medications, though neither has been approved by the FDA for those indications. Cabergoline is a potent dopamine receptor agonist. By increasing dopamine neurotransmission, it is thought to promote ejaculation. Some studies found that cabergoline (0.5 mg twice/week) in the treatment of men with orgasmic disorders (OA among them) showed improvement in 66% to 69% of men, and this was regardless of testosterone status [20]. Bupropion, which blocks the reuptake of both norepinephrine and dopamine, and buspirone which is primarily used to treat anxiety disorders, are used as an agent when SSRIs cause delayed or anejaculation [2].

In cases of concomitant ED, treatment will reduce anxiety and might improve OA. Testosterone replacement has been evaluated as a potential treatment for different sexual disorders. Not only does testosterone play a large role in male desire, but also testosterone deficiency was shown to decrease dopamine in rat models. Yet, testosterone replacement was not correlated with improvement in orgasmic disorders. Different psychological approaches may be used to address negative issues for sexual activity and orgasm especially [13].

Psychosexual approaches focus on body awareness to help patients focus on the here and now of the sexual experience and thus become more open to letting the "body take over". These interventions are based on the principles of mindfulness in its different forms including adapted sensate focus. Psychosexual therapy can include masturbation training starting with self-exploration, eventually regaining the pleasure of orgasm. It may include teaching stimulation techniques to men and their partners, mindfulness techniques (focus on any sensations that were felt like part of the orgasmic climax and then interpreting them positively), yoga exercises, Kegel exercises, and challenging/realigning men's expectations of the orgasmic experience. It might also emphasize enhancing greater immersion in sexual ideation/ fantasy (sexual cognitions) and minimizing self-monitoring, which inhibits awareness of both subjective pleasure and physical sensation [21].

7.8 Conclusion

Orgasmic anhedonia (also called pleasure dissociative orgasmic dysfunction) is a complicated and rare sexual disorder. In this chapter, we discuss the dissociation process resulting in the loss of the positive orgasmic emotional response. In males, this dissociation is easier to diagnose, because of the observable physical changes during the orgasmic phase. In women, it is more difficult, as there is a continuum reaching from decreased intensity of pleasurable feelings to complete loss of pleasure. In both, the main pathogenic mechanism is the pathologic processing of the bodily reaction during the orgasmic phase and the central nervous processing. The diagnosis includes the assessment of the different phases of the sexual response involving multi-disciplinary team.

Appendix

Step-by-step assessment of sexual functioning and contextual factors: (Regev, 2006).

- Medical evaluation.
- Genital functioning.
- Health problems/conditions.
- Medications.
- Psychological factors.
- Life situation.

Assess the following areas:

- Relationship status.
- Children.

- Living situation.
- Work.
- Current stressors.
- Comorbid mental disorders, such as:
  - Depression—Especially anhedonia/loss of interest in sexual activity that predates the orgasmic dysfunction.
  - Anxiety—Especially performance anxiety or PTSD resulting from sexual assault.
  - Substance use.
- Sexual functioning in the past month:
  - Desire—Frequency of sexual interest, thoughts, urges, feelings; frequency of engaging in sexual activity (including masturbation); contextual factors that enhance or inhibit desire.
  - Arousal—Erection/lubrication–swelling response, typically and maximally, with a partner and in masturbation (for male patients, also assess morning erections).
  - Orgasm.
  - Does the patient experience orgasm? Ask to describe the experience and ask about the specific physiological changes.
  - How often?
  - During which sexual activity(s) (intercourse, oral sex, masturbation, etc.)?
  - With what kind(s) of stimulation (manual, vibrator, visual, auditory, etc.)?
  - How much time is spent in foreplay?
  - Genital pain—Presence, intensity, during which type of sexual activity, the response of partner.
- Baseline sexual functioning (prior to time sexual difficulties began):
  - Desire. Frequency of sexual interest, thoughts, urges, feelings; frequency of engaging in sexual activity (including masturbation).
  - Arousal—Erection/lubrication–swelling response typically and maximally, with a partner and in masturbation (for male patients, assess morning erections).
  - Orgasm—Presence, timing, amount of foreplay, with a partner and during masturbation.
  - Genital pain—Presence, intensity, during which type of sexual activity, the response of partner.
- Onset—When did the sexual problem begin?
  - Did the problem develop gradually or abruptly?
  - Did the problem start around the same time as any of the psychological factors assessed above (e.g. life stressors, mental disorders)?
  - Did the problem start around the time of beginning a new medication, giving birth, or other events that could have led to biological changes?

- Context—global versus situational.
- Does the person experience low desire with all partners and during all sexual activities (e.g. intercourse, masturbation) or does it only occur in certain situations (e.g. with a specific partner or a specific sexual activity)?
- Are there thoughts/fears related to sexual activity that might be affecting orgasmic capacity? E.g. fears of STDs, pregnancy, loss of control, failure, closeness, feeling of vulnerability, disgust or that sex is morally wrong.
- Relationship issues.
- Quality of emotional intimacy/communication.
- Do the sexual difficulties adversely affect the overall relationship?
- Communication patterns regarding sex in general and sexual difficulties.
- Causal beliefs.
- What does the patient think is causing the problem?
- Goals for treatment.
- Are the stated goals realistic?
- What should be ruled out?
  - Another Axis I disorder (except another sexual dysfunction) that better accounts for the problem, such as depression or PTSD resulting from sexual assault.
  - Physiological effects of a substance that exclusively accounts for the problem, including prescription and street drugs.
  - Physiological effects of a medical disorder that reduces genital sensation to a degree incompatible with building arousal.
  - Unrealistic expectations regarding how often or during which sexual activity a person "should" reach orgasm.
- According to DSM-5[1}, specify:
  - Onset.
  - Whether the person never experienced an orgasm ("lifelong") or the disorder was "acquired" at some point.
  - Context.
  - Whether the orgasmic difficulty is true in all situations ("generalized") or only some situations ("situational"). E.g. experiences orgasmic difficulties with all sexual activities or only intercourse; experiences orgasmic difficulties with all potential sexual partners or only with a specific partner.
- Etiological factors.
  - Whether the orgasmic difficulty is due to "psychological factors" (e.g. relationship distress, anxiety, depression), "physiological factors," or "combined factors" (including both psychological and physiological factors).
  - According to DSM-5 [1], when the orgasmic difficulty is due exclusively to physiological effects of a general medical condition, the appropriate diagnosis is "Sexual dysfunction due to a general medical condition".

Key Messages

- In males and females, the common feature of the dysfunction is the loss of the subjective experience of pleasure during orgasm.
- In males, dissociation is easier to diagnose because of the observable physical changes during the orgasmic phase.
- In women, this is more difficult and there is a continuum reaching from decreased intensity of pleasurable feelings to anhedonia as complete loss of pleasure.
- In men and women, the main pathogenic mechanism is the processing of the bodily reaction during the orgasmic phase and the central nervous processing involving dysfunctions of parts of the limbic system especially the nucleus accumbens and dysregulation of neurotransmitter systems.
- Diagnosis includes the assessment of the different phases of the sexual response (desire, arousal, orgasm, resolution).

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, D.C: American Psychiatric Association; 2013.
2. Gray M, Zillioux J, Khourdaji I, Smith RP. Contemporary management of ejaculatory dysfunction. Transl Androl Urol. 2018;7(4):686–702.
3. World Health Organization. The ICD-11 classification of mental and behavioural disorders–diagnostic criteria for research. Geneva: World Health Organization; 2020.
4. Alwaal A, Breyer BN, Lue TF. Normal male sexual function: emphasis on orgasm and ejaculation. Fertil Steril. 2015;104:1051–60.
5. Mayo Foundation for Medical Education and Research. Published by Elsevier Inc. This is an open-access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). Mayo Clin Proc. 2019;94(5):842–856.
6. Parish SJ, Goldstein AT, Goldstein SW, et al. Toward a more evidence-based nosology and nomenclature for female sexual dysfunctions: part II. J Sex Med. 2016;13(12):1888–906.
7. Parish SJ, Meston CM, Althof SE, et al. Toward a more evidence-based nosology and nomenclature for female sexual dysfunctions part III. J Sex Med. 2019;16(3):452–62.
8. McCabe M, et al. Definitions of sexual dysfunctions in women and men: a consensus statement from the Fourth International Consultation on Sexual Medicine 2015. J Sex Med. 2016;13(2):135–43.
9. McCabe M, et al. Incidence and prevalence of sexual dysfunction in women and men: a consensus statement from the fourth international consultation on sexual medicine. J Sex Med. 2015;13(2):144–52.
10. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA. 1999;281:537–44. https://doi.org/10.1001/jama.281.6.537.
11. Quinn-Nilas C, Milhausen RR, McKay A, Holzapfel S. Prevalence and predictors of sexual problems among midlife Canadian adults: results from a National Survey. J Sex Med. 2018;15(6):873–9.
12. Elliott S. Orgasmic and ejaculatory problems in clinical practice. J Sex Reprod Med. 2002;2(2):67–73.

13. Lipshultz LI, Pastuszak AW, Goldstein AT, Giraldi A, Perelman MA, editors. Management of sexual dysfunction in men and women: an interdisciplinary approach. New York, NY: Springer; 2016.
14. Regev LG, Zeiss A, Zeiss R. Orgasmic disorders. In: Fisher JE, O'Donohue WT, editors. Practitioner's guide to evidence-based psychotherapy. New York: Springer; 2006.
15. Kandeel FR, Koussa VKT, Swerdloff RS. Male sexual function and its disorders: physiology, pathophysiology, clinical investigation, and treatment. Endocr Rev. 2001;22:342–88.
16. Seidman S. Ejaculatory dysfunction and depression: pharmacological and psychobiological interactions. Int J Impot Res. 2006;18:S33–8.
17. Exton NG, Truong TC, Exton MS, et al. Neuroendocrine response to film-induced sexual arousal in men and women. Psychoneuroendocrinology. 2000;25:187.
18. Shoar S, Khavandi S, Tabibzadeh E, et al. A late COVID-19 complication: male sexual dysfunction. Prehosp Disaster Med. 2020;35(6):688–9. https://doi.org/10.1017/S1049023X20001223.
19. Healy D. Citizen petition: sexual side effects of SSRIs and SNRIs. Int J Risk Saf Med. 2018;29(3–4):135–47.
20. Hollander AB, Pastuszak AW, Hsieh TC, et al. Cabergoline in the treatment of male orgasmic disorder-a retrospective pilot analysis. Sex Med. 2016;4(1):e28–33.
21. IsHak WW, editor. The textbook of clinical sexual medicine. Switzerland: Springer International Publishing; 2017.

Chapter 8
Headache Associated with Sexual Activity

Elena Colonnello, Massimiliano Toscano, Tommaso B. Jannini, and Emmanuele A. Jannini

Learning Objectives

- To recognize the existence of a particular type of headache associated with sexual activity (HSA), distinct from other headaches disorders and neurological conditions.
- To acknowledge its main characteristics (key symptoms, quality, onset, duration, course) in order to ask correct questions when drawing the patient's medical history.
- To identify signs and symptoms suggestive of secondary headaches, which need immediate assessment, and to know the related clinical and diagnostic workup.
- To recognize the psychological impact, HSA may have on the individual and the couple, and to consider this aspect when building an adequate therapeutical strategy.
- To learn the main treatment lines and their possible side effects.

E. Colonnello · T. B. Jannini · E. A. Jannini (✉)
Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

M. Toscano
Department of Human Neurosciences, "Sapienza" University of Rome, Rome, Italy

Department of Neurology, Fatebenefratelli Hospital, Isola Tiberina, Rome, Italy

Y. Reisman et al. (eds.), *Textbook of Rare Sexual Medicine Conditions*,
https://doi.org/10.1007/978-3-030-98263-8_8

8.1 Introduction

One should be able to recognize those who have a headache from gymnastic exercises, or running, or walking or hunting, or any other unseasonable labour, or from immoderate venery; On Regimen in Acute Diseases, Hippocrates, Written 400 B.C.E, Translated by Francis Adams [1].

8.1.1 Definition, Epidemiology, Taxonomy

Through the archaic term of "venery", Hippocrates mentions, for the first time in the literature documented so far, a headache associated with sexual activity (HSA) [1]. This entity has had different names throughout history, such as benign sex headache, benign vascular sexual headache, coital cephalalgia, coital headache, intercourse headache, sexual headache [2]. Initially, such disorder was also called benign orgasmic cephalgia, which refers to a benign condition (i.e. not related to structural brain lesions) whose onset was precipitated by orgasms [3]. However, since this term did not include patients whose headache developed before orgasm, it was later replaced by HSA. Following the most recent definition of the III International Classification of Headache Disorders (or ICHD-3) [4], HSA is a headache precipitated by sexual activity, usually starting as a dull bilateral ache as sexual excitement increases and suddenly becoming intense at orgasm. A primary form occurs in the absence of any intracranial disorder and is usually benign, while the secondary can disclose potentially life-threatening causes such as subarachnoid or intracerebral haemorrhage, subdural hematoma, ruptured aneurysms, and so on. For this reason, it is demanding to differentiate these two forms, as will be discussed in Sect. 8.3. However, since around 80% of cases are primary [5] when discussing HSA, usually it is implicitly referred to the primary form, coded in ICHD-3 as 4.3 *Primary headaches associated with sexual activity.*

HSA is included in the fourth group of primary headaches of the ICHD-3, among the "Other Primary Headache Disorders", a clinically heterogeneous group of headaches that are not caused by any intracranial abnormalities. It has been subclassified as a "headache associated with physical exertion", a group which also includes: 4.1 *Primary cough headache*, 4.2 *Primary exercise headache,* and 4.4 *Primary thunderclap headache*. These entities share some features with HSA, for instance, they may be triggered by Valsalva manoeuvres, however, they are substantially different in terms of age groups, gender distributions, and treatment [6]. HSA, whose criteria are reported in Table 8.1, has a reported prevalence in the general population of 1–1.6% although it may be underreported as patients often feel too embarrassed to discuss sexual matters. From a gender perspective, anecdotal evidence suggests that headache attributed to sexual activity is more common among females, but interestingly, there seems to be a marked male preponderance for HSA, with a male-to-female ratio of 3:1. The mean age of onset is of 30–40 years, with two age periods

Table 8.1 Definition and criteria of primary headache associated with sexual activity, as coded in the International Classification of Headache Disorders—3rd Edition (ICHD-3)

4.3 Primary headache associated with sexual activity
Description:
Headache precipitated by sexual activity, usually starting as a dull bilateral ache as sexual excitement increases and suddenly becoming intense at orgasm, in the absence of any intracranial disorder.
Diagnostic criteria:
A. At least two episodes of pain in the head and/or neck fulfilling criteria B-D
B. Brought on by and occurring only during sexual activity
C. Either or both of the following:
1. Increasing in intensity with increasing sexual excitement
2. Abrupt explosive intensity just before or with orgasm
D. Lasting from 1 min to 24 h with severe intensity and/or up to 72 h with mild intensity
E. Not better accounted for by another ICHD-3 diagnosis.

at high risk to develop HSA occurring between 20 and 24 years and between 35 and 44 years [7, 8].

8.2 Clinical Features

In ICHD-I and ICHD-II, two subtypes of HSA were included, i.e. a *pre-orgasmic headache* and an *orgasmic headache*, because they appear to have a different presentation, pathophysiology, and clinical course, as discussed later. However, since there is quite an overlap between them, from a taxonomic point of view they are still regarded as different presentations of a single entity (i.e. HSA).

A third type was also included in the previous taxonomy, the postural sexual headache, a low cerebrospinal fluid (CSF) pressure-type headache resulting from a tear of the dura during sexual intercourse [2], this third type is now regarded as a secondary type headache and separately coded as 7.2.3 *Headache attributed to spontaneous intracranial hypotension.*

About 20% of patients experiencing HSA have the pre-orgasmic variant, or type 1, while the remaining 80% have the orgasmic one, or type 2 [9]. The two types, indeed, may differ in terms of presentation.

Type 1, or pre-orgasmic, headaches usually start before orgasm, have mild intensity, and resemble muscle-contraction headaches. In a retrospective study that evaluates the onset time of headache with respect to orgasm in 51 patients, a significant difference between type 1 and type 2 (median onset time in HSA type 1 of 150 s before orgasm vs onset exactly with orgasm in type 2, $p < 0.001$) was found [8]. These results suggest that more patients with HSA type 1 could relieve the pain by early termination of sexual activity (73% vs 30% in HSA type 2).

Type 2, or orgasmic, headaches instead are precipitated by orgasm, more explosive, shorter, often unilateral, pulsating, accompanied by vegetative symptoms, and associated with migraine in 30% of cases as opposed to 9% of those with type 1.

Comorbid primary exertional headaches are also seen in 35% of type 2 cases, differently from the 9% of type 1.

The typical pain occurring with HSA is predominantly bilateral (67%), being either diffuse or occipital (76%) [8], and can be dull, throbbing, or stabbing in quality. The attacks usually last from a few minutes to 24 h, with a mean duration of 30 min. The duration of pain is longer in HSA type 2 than in type 1 (4 vs. 1 h) [7]. Usually, after remission of severe acute pain, patients experience a milder one that can last up to 72 h. Accompanying symptoms such as nausea, photophobia, phonophobia, dizziness, and mood disturbance can occur, especially in type 2.

HSA most commonly occurs during sexual activity with the usual partner (94%, as found by a retrospective study [8]), but also during masturbation (35%) and presenting low rates with a new partner (14%). However, these headaches are not recurrent, but a relapse of symptoms has been reported when patients resumed sexual activity in the days after an attack; this justifies the recommendation, often given to the patients, of sexual abstinence until a complete resolution of pain occurs (see Sect. 8.5). In any case, the experience of pain and/or dullness that accompanies sexual activity may severely affect sexual pleasure and orgasm, both in the patient and in the couple. In fact, the patient may want to delay the time of orgasm, or to avoid it at all, and, in most cases, he/she refrain from sexual activity to avoid further attacks. Either the fear of experiencing another attack of HSA when engaging in sexual activity and the recommendation of abstinence may cause significant bother and distress. This may contribute to the onset of an overt sexual dysfunction, either of the libido (i.e. hypoactive sexual desire disorder) or the orgasmic (i.e. anorgasmia) type, both in the patient and in his/her partner(s).

8.3 Pathophysiology

Several theories have been proposed to explain the underlying mechanism of HSA, but the exact pathophysiology is still unknown. However, both a muscular component and impaired cerebrovascular autoregulation have been suggested [2]. In particular, type 1 has been compared to a muscle-contraction headache due to tension accumulated during sexual intercourse, while type 2 seems to be more related to the hemodynamic changes occurring at the time of orgasm (Fig. 8.1).

Indeed, from the studies of Masters and Johnson in 1966 [10], it is clear that sexual activity brings about changes in the body which encompass almost every system: genital, cardiovascular, neuroendocrine, hormonal. However, coitus is considered a moderate activity from an energy expenditure point of view. In terms of metabolic equivalent (MET), if running at 10 km/h is equivalent to 6–7 METs, sexual activity in the pre-orgasmic phase is 2–3 METs, almost like walking up to 3.5 km/h, with a small rise during the orgasmic phase [11]. Studies also showed that this metabolic activity does not change much among the various types of sexual activity (man-on-top, woman-on-top, self-stimulation, etc), making them almost

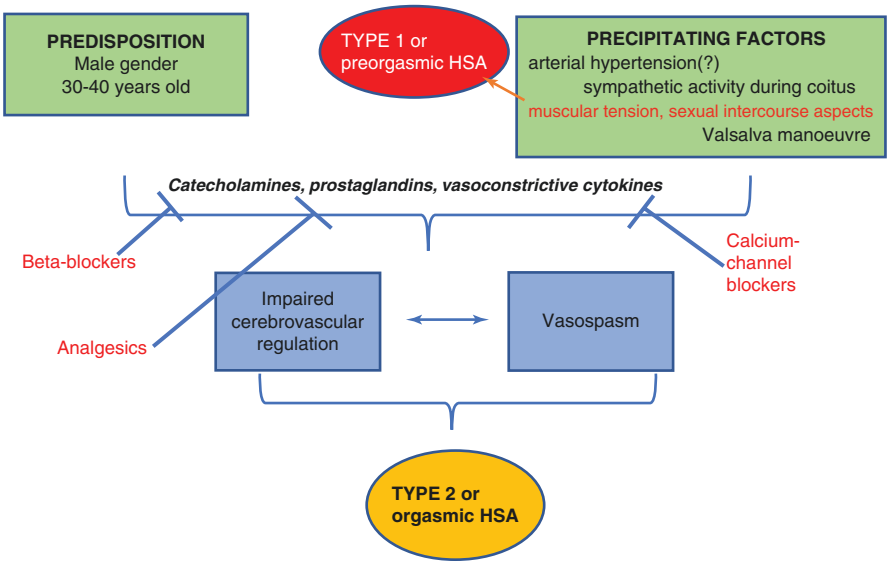

Fig. 8.1 Schematic representation of the main hypotheses regarding the pathophysiology of the headache associated with sexual activity (HSA) and the mechanism of action of the related pharmacological treatments. The role of arterial hypertension as precipitating factor is still controversial

equivalent [12]. Thus, overall, the energy spent during the sexual act may be considered low. What happens mainly is the high activation of sympathetic activity that elicits an increase in blood pressure and heart rate, which is maximal in the 10–15 s of orgasm and return to baseline following it. Catecholamines-driven emotional tension can accumulate in the climax phase, and patients reporting pre-orgasmic headaches often implicate the role of an excessive muscle contraction, particularly involving the neck and jaw muscles. By deliberately relaxing those muscles while continuing intercourse or masturbation, these patients often can ease the pain (see Sect. 8.4), and this corroborates the idea that type 1 HSA is similar to muscle-contraction headache or tension-type headache. As a matter of fact, this type of headache often seems to be related to the degree of sexual excitement and tension, other than the amount of physical exertion that, as said before, is on average moderately low.

On the other hand, physical exertion during coitus can transiently raise intracranial pressure through a Valsalva manoeuvre and, similarly as it occurs with primary exertional headache and primary cough headache, cause pain [2, 6, 9]. Since there is a relationship between the central venous system and intracranial pressure, some authors performed magnetic resonance venography in 36 patients with either primary cough headache, primary exertional headache or HSA and 16 controls [6]. Stenosis was observed in around half of the patients, especially in the transverse sinus or jugular veins, but in none of the control group. In particular, it was found in 12/19 patients with HSA, suggesting a possible role for venous abnormalities in the

pathogenesis of this type of headache, although there is still a debate on whether such abnormalities are the cause or, rather, the consequence, of a raised intracranial pressure. In all cases, such explanation places HSA along a continuum with primary exertional headache, and the similarity is consistent with the fact that patients with HSA often report headaches provoked also by physical efforts or sport, suggesting some degree of overlap.

It has been suggested that extramarital sexual activity may be associated with a higher risk of cardiovascular events, likely due to the increased activation of sympathetic activity, which augments the heart rate and therefore represents a trigger for malignant arrhythmias [13]. Although HSA is subclassified among the "exertional" headache, with the extramarital setting possibly suggesting increased activation of the "fight or flight" reaction, such setting is not a precipitant of the symptomatology of HSA, which otherwise most commonly occurs during sexual activity with the usual partner (see the previous section).

Neuroimaging suggested also another explanation for type 2 HSA. Specifically, MRI and digital angiographic studies performed before, during, and after episodes of HSA reporting reversible cerebral artery narrowing in these patients suggested a role of vasospasm in the pathophysiology of this type of headache [14]. This hypothesis justified the use of calcium-channel blockers such as nimodipine or nifedipine, which in several cases (also without ascertained cerebral vasoconstriction) relieved the symptomatology and prevented recurrence [15]. This reversible cerebral vasospasm is somewhat similar to a condition known as reversible cerebral vasoconstriction syndrome (RCVS) [16], which comes into play in the differential diagnosis workup of HSA (see Sect. 8.3).

Some authors sustained that impaired cerebrovascular autoregulation is responsible for the explosive, type 2 HAS [2]. During coitus, and particularly at orgasm, there is a massive release of vasoactive substances such as catecholamines, serotonin, neurokinin, which contributes to the hyperdynamic state associated with sexual arousal and intercourse. The intracranial haemodynamics of 12 patients with HSA was tested by analysing the cerebrovascular vasodilator reserve by means of transcranial doppler during two different provocation tests: physical exercise and acetazolamide [17]. Specifically, systolic blood pressure, cerebral blood flow velocity (CBFV), and pulsatility index (PI) were recorded. Results showed that patients with HSA had a higher increase of systolic blood pressure during physical exercise compared to 14 healthy controls and 12 migraine-patient without aura. Moreover, after 1 g of acetazolamide (i.e. stimulation of hypercapnia), patients with sexual headache showed a significantly higher increase of CBFV and a significantly lower decrease of PI as compared to controls, which can be explained by an increase of the cerebral blood flow without major changes in the diameter of the large pial vessels, therefore impaired vasodilation. According to the authors, since this did not occur with exercise but only with acetazolamide, the metabolic rather than the myogenic component of the cerebral autoregulation mechanism may be impaired in these patients [17].

Other authors emphasize a pathophysiological relationship between type 2 HSA and migraine, motivated by the fact that patients with type 2 HSA have a similar loss of cognitive habituation to patients with migraine with respect to controls [18]. In

particular, during visual event-related potential testing, both are characterized by potentiation instead of habituation of stimulation-evoked cortical responses [19]. An interictal habituation deficit of cortical evoked potentials to repeated monotonous stimuli according to different sensory modalities (be it visual, auditory, or somatosensory) has been usually detected in episodic migraineurs so that it is considered as a biomarker of interictal status [20]. This pattern was not found in any other primary headache disorders such as tension-type headache, which reinforces the idea that migraine and type 2 HSA may share a similar pathophysiology. Anyway, in our opinion, this association is yet quite speculative, firstly because, from a clinical point of view, this is in contrast with the fact that migraine shows a female predominance, unlike HSA. Then, HSA frequently occurs in patients with migraines, with a prevalence ranging from 25% to 45% [7], so that finding a link between them may be tricky due to the wide overlapping.

Secondly, from a neurological point of view, the habituation deficit is not widely accepted as a neurophysiological hallmark in migraines [21]. Moreover, this pattern differs according to migraine frequency, being quite normalized in a chronic phenotype similar to ictal EM recordings, so that CM was hypothesized to be like a "never-ending attack" [20].

Finally, the abnormal increase of blood pressure may also contribute to the development of pain. This hypothesis was coherent with the fact that beta-blockers and other antihypertensive agents have proven to be effective at least in the prevention of HSA (see Sect. 8.4). However, being intracranial pressure determined by a cerebral autoregulation mechanism, other authors have ruled out arterial hypertension as a major risk factor, since it was reported in only 18% of patients experiencing HAS [8].

8.4 Diagnosis Workup and Differential Diagnosis

HSA is a rare clinical entity in the general population, but due to its specific characteristics and clinical course, it should be always considered in the differential diagnosis with other headache disorders. In particular, the specific coital setting should be investigated when patients report episodic headaches apparently unrelated to major triggers, especially if comorbid with physical exertion headache and/or migraine. HSA may contribute to generating overt sexual dysfunction in the individual affected as well as in the partner, as they may enjoy the experience of sexual activity less than before, up to avoid it at all, due to the fear of experiencing another attack. Therefore, whenever HSA is suspected, a thorough medical history is demanding, because the patient may feel embarrassed to report a symptom occurring in such context. In any case, when the occurrence of headache is associated with sexual activity, it is mandatory to rule out secondary causes. Even though HSA is usually benign, it can be a symptom of underlying intra- or extracranial pathologies. Thus, a careful clinical examination should be performed for differential diagnosis. When performing the neurological examination, it is important to keep in mind a series of "red flags" which may indicate a more serious underlying

condition. For instance, vomiting, decreased level of consciousness, meningism, motor, sensory or visual disturbances, or severe pain persisting for more than 24 h are not typical features of HSA and therefore demand an immediate assessment. Overall, besides these "red flags", there are some clues to take into account when considering the differential diagnosis of primary vs. secondary HSA [5]. Secondary HSA is more frequent in females, with older age (>40 years) and should be suspected in the case of a single episode (i.e. not recurrent), and other neurological signs or symptoms.

Anyway, besides these clues, the neurological examination must be followed by a neuroimaging study in the presence of warning signs (i.e. "red flags") or patients presenting with headache's atypical features, change of headache type or frequency. This mainly consists of cerebral computed tomography (CT), brain magnetic resonance (MR), and CT/MR-Angiography. In doubt or selected cases, the digital subtraction angiography, the epiaortic and transcranial vessel Doppler sonography, and a lumbar puncture could be considered.

This diagnostic workup allows to exclude secondary HSA due to subarachnoid haemorrhage (whether *"sine materia"* or due to ruptured aneurysm, arteriovenous malformation, or traumatic head injury), intracerebral haemorrhage, subdural hematoma, intra- and extracranial artery dissection, cerebral venous sinus thrombosis, and reversible cerebral vasoconstriction syndrome (RCVS).

Subarachnoid haemorrhage (SAH) is bleeding in the subarachnoid space between the arachnoid membrane and the pia mater that surrounds the brain. Ruptured intracranial aneurysm accounts for 85% of SAH cases so that the abovementioned diagnostic workup is mandatory when SAH is suspected. SAH is among the first differential diagnoses to be considered, firstly because it is potentially life-threatening and disabling (nearly half of patients presenting with a subarachnoid haemorrhage caused by an underlying aneurysm die within 30 days, and a third of those who survive have complications) [22]. Then, because it occurs during sexual activity in about 4–12% of all cases with saccular aneurysms and in 4.1% of patients with arteriovenous malformations. Moreover, from a clinical point of view, both SAH and primary HSA patients typically present complaining of a sudden, "explosive like a thunderclap", severe and rapidly increasing pain. Anyway, patients presenting with a SAH classically present also with neck stiffness, vomiting, decreased level of consciousness, hemiparesis, and occasionally, seizures.

Blood products released from the SAH stimulate the tyrosine kinase pathway, which results in smooth muscle contraction of the cerebral arteries leading to vasospasm. Cerebral vasospasm typically occurs after the third day of onset and typically reaches its peak on the fifth to the seventh day [23]. Thus, it is worth noting that patients with SAH may complain of HSA-like pain even in the sub-acute phase of diseases. This is usually due to rebleeding and/or cerebral vasospasm, two of the most frequent complications of SAH.

In this regard, both the vasospasm and the thunderclap headache (TCH) are also indicative, as well as SAH, of the reversible cerebral vasoconstriction syndrome (RCVS), a syndrome characterized by a reversible segmental cerebral arterial narrowing, which then comes into play in the differential diagnosis workup [16]. This syndrome has had different names, such as Call–Fleming syndrome, TCH with

reversible vasospasm, benign angiopathy of the CNS, postpartum angiopathy, migrainous vasospasm or migraine angiitis, or drug-induced cerebral arteritis or angiopathy, depending on the context it was diagnosed. TCH is usually the initial symptom of RCVS, and up to 82–100% of patients with RCVS have repeated attacks of TCH during the clinical course. RCVS has a female predominance and can be primary, usually idiopathic, and secondary, most associated with puerperium or vasoactive substances such as illicit drugs (cannabis, ecstasy, cocaine, or amphetamine), selective serotonin-reuptake inhibitors [24], and over-the-counter agents such as nasal decongestants or diet pills. The pathophysiology is mainly explained by dysregulation of cerebral vascular tone and an angiographic study documenting multifocal segmental cerebral artery vasoconstriction and their reversibility within 12 weeks of onset is essential for diagnosing RCVS and to differentiate it, eventually, from HSA. Moreover, although most patients recover well, RCVS should be treated immediately, due to the risk of cerebral infarction and haemorrhagic complications.

8.5 Clinical Course and Treatment Strategies

Due to its relative rarity, treatment of HSA is based on case series, rather than randomized trials, and no meta-analyses on the therapies are currently available [7]. Although positive results have been gathered so far, data on pharmacotherapy as a valid option in the management of HSA remain scarce. Other than low cohort numerosity, ranging from one [15] up to only 60 patients [25], a lack of standardized approaches with validated outcome measures does not allow to draw consistent conclusions.

HSA may appear suddenly, last for many months or years, and stop abruptly, or occur in bouts that recur over weeks to months before resolving. In all cases, since the clinical course is usually self-limiting and benign, the primary treatment given to the patient should consist of explanation and reassurance, as these headaches usually represent a source of distress.

In general, most patients present an episodic course with remitting bouts [25], which are defined as at least two sex-induced headaches occurring in the acute stage, without further attacks for ≥4 weeks despite continuing sexual activity [26]. Otherwise, approximately one-quarter of patients present a chronic course, which consists of HSA lasting for ≥12 months with no remission longer than ≥4 weeks [25]. Prognostically, there is no significant difference between types 1 and 2, and recurrence rates of 33–50% have been reported after follow-up periods of approximately 6 years [25], and even higher (i.e. close to 70%) after a 3-year observation period [7]. Patient education and information include behavioural recommendations for sexual activity. For instance, regarding sexual abstinence, there is no evidence that it can cure HSA, but often patients are advised to refrain from engaging in sexual activity until a complete resolution of symptoms occurs, in order to prevent another attack from occur [2]. Interestingly, in a series of 45 patients with HSA, all of them experienced their sexual headaches whilst undertaking an “active” role in

sexual activity [2]. Similar case reports corroborate the idea that adopting a more "passive" role could prevent the onset of HSA or mitigate it. However, this seems not to be supported by compelling evidence, as explained in Sect. 8.2. In fact, studies have shown that there is no difference in peak coital heart rates, blood pressures, and their product (heart rate × systolic blood pressure) for the male subjects in the "man-on-top" or "woman-on-top" position [12]. However, behavioural measures [7], such as changing position and keeping the neck lower than the trunk, working the lower limbs less, losing weight, and avoiding engaging in close, more than one, sexual intercourses could help reduce HSA's frequency and recurrence.

This seems to be more true for patients with type 1 HSA, due to earlier onset and ability to "control" the muscular tension [8].

Drug management of HSA can be offered, and the treatment can be divided into acute, pre-emptive, and prophylactic.

- **Acute** (or **symptomatic**) **treatment**: unfortunately, the majority of analgesics (ibuprofen, paracetamol, acetylsalicylic acid, etc.) given after the onset of headache are of limited or no value in nearly all patients with HSA. Of all non-steroidal anti-inflammatory agents (NSAIDs), only indomethacin showed positive results in acute treatment [25]. Due to their fast-acting action, sumatriptan s.c. and zolmitriptan i.n. have been proposed as acute treatment with inconstant results [25].
- **Pre-emptive treatment**: since HSA attacks are usually short-lasting, taking therapy 30–60 min before sexual activity is reasonable. Indomethacin (25–100 mg) 30–60 min before intercourse is the most effective therapy, showing good results in 90% of patients [25]. Other NSAIDs, such as ibuprofen and diclofenac, have been used with poor efficacy [25]. Naratriptan 2.5 mg 2 h before sexual activity has been reported as effective and could be considered, as well as other triptans (i.e. rizatriptan, almotriptan, and sumatriptan) when attacks usually last longer than 2 h [9].
- **Prophylactic treatment**: for patients with a chronic debilitating course of HSA, or in patients with longer-lasting bouts, prophylactic treatment can be indicated. In all cases, prophylactic treatment should be tapered off after 3 months maximum to check for spontaneous remission [27]. The most consistent case series supports the use of beta-blockers such as propranolol 40–240 mg a day or metoprolol 100–200 mg/day [25]. Caution must be paid to beta-blockers side effects, such as depression inducing or increase and erectile dysfunction, two aspects that deserve particular attention when treating pathology of the sexual sphere such as HSA. Indomethacin can be given also regularly 25–50 mg/day. Calcium-channel blockers (i.e. diltiazem 60 mg 3/day, nifedipine 10 mg twice a day) can be employed, especially where cerebral vasoconstriction is suspected (nimodipine 30–60 mg to be taken every 4–8 h depending on vasospasm detection) [15]. Other prophylactic therapies have been anecdotally reported, such as lamotrigine 100 mg daily, which has been successfully used in one case of migraine with aura occurring after sexual intercourse [28]. Topiramate (50 g daily) may be another useful option but is contraindicated in women and girls of childbearing

potential. One study reported a role for triptans in the prophylaxis of headache associated with sexual activity in patients who do not respond to or tolerate indomethacin [29]. Finally, a promising perspective seems to be offered by greater occipital nerve (GON) blockade with the injection of steroid and local anaesthetic combination. GON injection is thought to modulate brain excitability acting on the input gate at the brainstem level [30]. Given its long-lasting action and the poor side effects, GON injection is well tolerated even for a long-time therapy. Considering the well-known beta-blockers sexual side effects (e.g. the erectile dysfunction), which could also increase the distress already experienced by these patients, GON injection may represent a valid add-on prophylactic therapy, allowing to reduce beta-blockers dosage in case of chronic headache with or without medication overuse. Moreover, GON injection could also represent an alternative treatment in case of contraindication to beta-blockers or indomethacin, so that further research is needed to better evaluate this promising therapy.

Regarding patients who cannot benefit from pharmacotherapy, such as those allergic to these active principles and pregnant or lactating patients, psychological treatment could be very useful. Moreover, psychotherapy could represent a valid supportive therapy in those chronic patients for whom HSA could represent a source of great discomfort. Although no specific evidence on HSA has been reported so far, a recent systematic review and meta-analysis showed how a psychological treatment seems to be good at treating headaches, regardless of the type [31]. Lee and colleagues [31] reported how headache indices, such as headache frequency and disability due to headache, were either statistically different or presented a favourable trend of the active group over the control group. The most used psychotherapies were cognitive behavioural therapy (CBT), mindful-based therapy (MBT), relaxation training, and biofeedback.

CBT and MBT might help to cope with HSA. Indeed, they act on psychological factors, such as temperament, personality traits, psychiatric conditions, stress, insomnia that have been reported to be comorbid with or to enhance headache episodes [32]. Furthermore, they allow patients to reach a better understanding of such conditions, providing also emotional support.

Recent evidence has also highlighted how psychological therapy might have physiological effects on the central nervous system. These span from changes in brain neuroplasticity, changes in sympathetic activity, and modulations in the endogenous opioid system [33].

In conclusion, both pharmacotherapy and psychotherapy seem to promise encouraging results. Furthermore, except in limited cases, the one does not exclude the other. To date, the most effective treatment is indomethacin (25–100 mg) 30–60 min before intercourse (i.e. pre-emptive treatment), with propranolol 40–240 mg a day as prophylactic therapy in case of chronic course or longer-lasting bouts. Psychotherapy should be taken into account as supportive therapy. More randomized clinical trials, with larger populations, control groups, and testing different treatment options are needed to shed a brighter light on this topic.

8.6 Conclusion

Headache associated with sexual activity (HSA) is a rare but debilitating clinical entity that has been described since Hippocrates' time, and it is formally classified as other primary headaches in the third International Classification of Headache Disorders (ICHD-3). In contrast to other migrainous disorders, males are three times more likely than females to be affected, with a mean age of onset of 30–40 years. There is a clinical and pathophysiological distinction between type 1, or pre-orgasmic, and type 2, or orgasmic, form, with type 2 being the most common. Both types are typically bilateral (67%), diffuse or occipital in nature, and can be dull, throbbing, or stabbing in magnitude. The attacks can last anywhere from a few minutes to 24 h with severe intensity (mean duration of 30 min) and/or up to 72 h with mild intensity. Several etiological causes, including muscular tension (for type 1) and vasospasm (for type 2), have been thought to play a role, though secondary causes, particularly subarachnoid haemorrhage, must be ruled out first. Patients should be reassured that the primary form of HSA is usually self-limiting and benign. Treatment includes both pharmacological (analgesics, beta-blockers, calcium-channel blockers, etc.) and nonpharmacological (cognitive behavioural therapy, mindful-based therapy) treatment strategies.

Key Messages

- Headache associated with sexual activity (HSA) is a rare and benign, but also debilitating, clinical entity that can lead patients to avoid sexual intercourse.
- Males are three times more likely to be affected than females, especially at 30–40 years old.
- HSA can be of two types: type 1, or pre-orgasmic (20%), and type 2, or orgasmic (80%).
- Pain is usually bilateral (67%), can be dull, throbbing, or stabbing in quality, and the attacks usually last from a few minutes to 24 h (mean duration of 30 min). The clinical course is chronic in ¼ of cases.
- Secondary causes, such as subarachnoid haemorrhage, should be always excluded. A careful neurological exam and neuroimaging work up (cerebral CT, brain MRI, CT/MR-Angiography, DSA, etc.) are mandatory in case of headache modification and/or presence of "red flags" (thunderclap headache, decreased level of consciousness, meningism, motor, sensory or visual disturbances, or severe pain persisting for more than 24 h).
- Treatment can be acute, pre-emptive, or prophylactic, and either pharmacological (analgesics, beta-blockers) or nonpharmacological (cognitive behavioural therapy, behavioural therapy) strategies can be employed.
- To date, the most effective treatment is indomethacin (25–100 mg) 30–60 min before intercourse, with propranolol 40–240 mg a day as prophylactic therapy in case of chronic course or longer-lasting bouts.

References

1. Hippocrates AF. The genuine works of Hippocrates; translated from the Greek by Francis Adams. Bailliere: Tindall & Cox; 1939.
2. Silbert PL, Edis RH, Stewart-Wynne EG, Gubbay SS. Benign vascular sexual headache and exertional headache: interrelationships and long term prognosis. J Neurol Neurosurg Psychiatry. 1991;54(5):417–21.
3. Paulson GKH. Benign orgasmic cephalalgia. Headache. 1974;13:7.
4. Arnold M. Headache classification committee of the international headache society (IHS) the international classification of headache disorders. Cephalalgia. 2018;38(1):1–211.
5. Alvarez R, Ramón C, Pascual J. Clues in the differential diagnosis of primary vs secondary cough, exercise, and sexual headaches. Headache. 2014;54(9):1560–2.
6. Donnet A, Valade D, Houdart E, Lanteri-Minet M, Raffaelli C, Demarquay G, et al. Primary cough headache, primary exertional headache, and primary headache associated with sexual activity: a clinical and radiological study. Neuroradiology. 2013;55(3):297–305.
7. Allena M, Rossi P, Tassorelli C, Ferrante E, Lisotto C, Nappi G. Focus on therapy of the chapter IV headaches provoked by exertional factors: primary cough headache, primary exertional headache and primary headache associated with sexual activity. J Headache Pain. 2010;11(6):525–30.
8. Frese A, Eikermann A, Frese K, Schwaag S, Husstedt IW, Evers S. Headache associated with sexual activity: demography, clinical features, and comorbidity. Neurology. 2003;61(6):796–800.
9. Bahra A. Other primary headaches—thunderclap-, cough-, exertional-, and sexual headache. J Neurol. 2020;267(5):1554–66.
10. Masters WH, Johnson VE. Human sexual response. Boston: Little, Brown; 1966.
11. Bispo GS, de Lima LJ, de Barros ALBL. Cardiovascular changes resulting from sexual activity and sexual dysfunction after myocardial infarction: integrative review. J Clin Nurs. 2013;22(23–24):3522–31.
12. Stein RA. Cardiovascular response to sexual activity. Am J Cardiol. 2000;86(2a):27f–9f.
13. Parzeller M, Bux R, Raschka C, Bratzke H. Sudden cardiovascular death associated with sexual activity. Forensic Sci Med Pathol. 2006;2(2):109–14.
14. Valença MM, Valença LPAA, Bordini CA, Da Silva WF, Leite JP, Antunes-Rodrigues J, et al. Cerebral vasospasm and headache during sexual intercourse and masturbatory orgasms. Headache. 2004;44(3):244–8.
15. Lee JW, Ha YS, Park SC, Seo IY, Lee HS. Orgasmic headache treated with nimodipine. J Sex Med. 2013;10(7):1893–6.
16. Chen S-P, Fuh J-L, Wang S-J. Reversible cerebral vasoconstriction syndrome: current and future perspectives. Expert Rev Neurother. 2011;11(9):1265–76.
17. Evers S, Schmidt O, Frese A, Husstedt I-W, Ringelstein EB. The cerebral hemodynamics of headache associated with sexual activity. Pain. 2003;102(1–2):73–8.
18. Frese A, Frese K, Ringelstein EB, Husstedt IW, Evers S. Cognitive processing in headache associated with sexual activity. Cephalalgia. 2003;23(7):545–51.
19. Biehl K, Evers S, Frese A. Comorbidity of migraine and headache associated with sexual activity. Cephalalgia. 2007;27(11):1271–3.
20. Viganò A, Toscano M, Puledda F, Di Piero V. Treating chronic migraine with neuromodulation: the role of neurophysiological abnormalities and maladaptive plasticity. Front Pharmacol. 2019;10:32.
21. Omland PM, Uglem M, Hagen K, Linde M, Tronvik E, Sand T. Visual evoked potentials in migraine: is the "neurophysiological hallmark" concept still valid? Clin Neurophysiol. 2016;127(1):810–6.
22. Kairys N, Das JM, Garg M. Acute subarachnoid Hemorrhage. StatPearls; 2021.
23. Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES Jr, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. Neurosurgery. 2006;59(1):21–7. discussion -7

24. Jannini TB, Di Lorenzo G, Bianciardi E, Niolu C, Toscano M, Ciocca G, et al. Off-label uses of selective serotonin reuptake inhibitors (SSRIs). Curr Neuropharmacol. 2021;19:1.
25. Frese A, Rahmann A, Gregor N, Biehl K, Husstedt IW, Evers S. Headache associated with sexual activity: prognosis and treatment options. Cephalalgia. 2007;27(11):1265–70.
26. Yeh Y-C, Fuh J-L, Chen S-P, Wang S-J. Clinical features, imaging findings and outcomes of headache associated with sexual activity. Cephalalgia. 2010;30(11):1329–35.
27. Frese A, Evers S. Primary headache syndromes associated with sexual activity. Pract Neurol. 2005;5(6):350–5.
28. D'Andrea G, Granella F, Verdelli F. Migraine with aura triggered by orgasm. Cephalalgia. 2002;22:485–6. England
29. Frese A, Gantenbein A, Marziniak M, Husstedt I-W, Goadsby PJ, Evers S. Triptans in orgasmic headache. Cephalalgia. 2006;26(12):1458–61.
30. Viganò A, Torrieri MC, Toscano M, Puledda F, Petolicchio B, Sasso D'Elia T, et al. Neurophysiological correlates of clinical improvement after greater occipital nerve (GON) block in chronic migraine: relevance for chronic migraine pathophysiology. J Headache Pain. 2018;19(1):73.
31. Lee HJ, Lee JH, Cho EY, Kim SM, Yoon S. Efficacy of psychological treatment for headache disorder: a systematic review and meta-analysis. J Headache Pain. 2019;20(1):17.
32. Altamura C, Corbelli I, de Tommaso M, Di Lorenzo C, Di Lorenzo G, Di Renzo A, et al. Pathophysiological bases of comorbidity in migraine. Front Hum Neurosci. 2021;15:131.
33. Tajerian M, Clark JD. Nonpharmacological interventions in targeting pain-related brain plasticity. Neural Plast. 2017;2017:2038573.

Chapter 9
Post-Orgasmic Illness Syndrome (POIS)

Yacov Reisman and Francesca Tripodi

Learning Objectives
After reading this chapter, the learners will:

- Be familiar with the variable clinical presentation of the post-orgasmic illness syndrome (POIS) and the bio-psycho-social and relational consequences of it.
- Develop comprehensive assessment and monitoring skills.
- Improve the understanding of the possible pathophysiological mechanism related to this syndrome and the link between evidence-based knowledge and treatment.
- Be able to deliver tailor-made and, when needed, multidisciplinary treatment modalities for the patient who suffers from POIS.
- Consider partner and relationships aspects in the treatment plan, including all the bio-psycho-social components involved.

9.1 Introduction

The Post-Orgasmic Illness Syndrome (POIS) describes a cluster of symptoms that occur soon after orgasm and cause debilitating physical and psychological implications [1–2]. The term POIS was first used in 2002 by Waldinger and Schweitzer for this uncommon sex-related illness, describing two otherwise healthy men aged 43 and 52 who suffer from flu-like symptoms after ejaculation [3]. Each time they

Y. Reisman (✉)
Flare Health, Amstelveen, The Netherlands
e-mail: reisman@flare-health.nl

F. Tripodi
Institute of Clinical Sexology, Rome, Italy

Y. Reisman et al. (eds.), *Textbook of Rare Sexual Medicine Conditions*,
https://doi.org/10.1007/978-3-030-98263-8_9

ejaculated, their symptoms will happen, regardless of whether they ejaculated during partnered sex, solo masturbation, or spontaneously at night. There were rapidly severe fatigue, intense warmth, and a flu-like state with generalized myalgia. The first patient reported the onset of symptoms at puberty, and the second patient reported the onset of symptoms at 45 years of age. These recurring after ejaculation symptoms were accompanied by a mental sequela of disturbances, including decreased concentration and irritability. After 4–7 days, the symptoms disappeared. According to Waldinger [1], this condition can also affect women, but most published case reports and patient's series consider males only.

In 2016, the International Society for the Study of Women's Sexual Health (ISSWSH) listed the female orgasmic illness syndrome (FOIS) among the new nomenclature of female sexual dysfunctions [3]. According to the expert panel, FOIS is characterized by peripheral and/or central aversive symptoms that occur before, during, or after orgasm and are not related, per se, to a compromise of orgasm quality. Central aversive symptoms can include disorientation, confusion, impaired judgement, decreased verbal memory, anxiety, insomnia, depression (post-coital tristesse), seizures (orgasmic epilepsy), and/or headache (coital cephalalgia). Peripheral aversive symptoms can include diarrhoea, constipation, muscle aches, abdominal pain, diaphoresis, chills, hot flashes, fatigue, akathisia, and genital pain. Such orgasm-associated symptoms can last for minutes, hours, or days after orgasm and vary widely among women. Although the syndrome has been defined, the conditions of FOIS are based on expert opinion. It should be considered provisional diagnosis until future research determines the validity of the diagnostic category. Therefore, in this chapter, we will refer only to the male syndrome.

After Waldinger and Schweitzer's report, other case series and surveys have been published, as well as internet-based patients' platforms [2] with similar complaints and clinical pictures.

This chapter aims to provide a closer look at the syndrome, update the current available POIS literature, revise the information on possible POIS pathophysiology, and discuss potential management options for biological, psychological, and social/contextual approaches. As the signs and symptoms are well characterized, more patients are expected to seek evaluation and treatment. This will undoubtedly ease the anxieties and fears of many patients with POIS symptoms, who have been unsuccessfully treated for psychiatric or factual somatic symptom disorders [4]. As more data become available on POIS, this may increase awareness among healthcare professionals and recognition by medical organizations about this syndrome, increasing research support.

9.2 Definition of Disorder

The National Institutes of Health Office of Rare Disease Research recognizes POIS as a rare disorder [5]; however, there is no available clear evidence-based definition of the syndrome.

Waldinger et al. [6] suggested five preliminary diagnostic criteria for assessing the variety of this condition. Strashny [7] conducted a self-report study to evaluate the validity of these criteria and proposed changes to criteria 2 and 5. Natale et al. more explicitly defined the criteria and combined their survey results with the findings of Strashny's publication [7, 8]. Although the presentation of POIS is highly variable, recent studies conclude that the five criteria captured the majority of cases [8]. The most recent criteria are presented in Table 9.1.

Criterion 1 states that at least one of the symptoms, classified according to 7 clusters of symptoms (general, flu-like, head, eyes, nose, throat, muscles), occur after ejaculation/orgasm. Adding severity degree to these symptoms was also recommended [6].

Table 9.1 POIS diagnostic criteria and 7 clusters reported symptomatology. According to [6–10]

Criterion number	Description	Cluster Symptoms	
1	At least 1 of the symptoms which are classified according to 7 clusters of symptoms	General	Extreme fatigue/exhausted, palpitations, problems finding words/incoherent speech, dysarthria, concentration difficulties, quickly irritated, cannot stand noise, photophobia, depressed mood
		Flu-like	Feverish, extreme warmth, perspiration, shivery/chills, ill with flu, feeling sick, feeling cold
		Head	Headache, foggy feeling in the head, heavy feeling in the head
		Eyes	Burning, red-injected eyes, blurred vision, watery, irritating, itching eyes, painful eyes
		Nose	Congested nose, watery-runny nose, sneezing
		Throat	Dirty taste in the mouth, dry mouth, sore throat, tickling cough, hoarse voice
		Muscle	Muscle tension in back or neck, muscle weakness, painful muscles, heavy legs, stiffness in muscles
2	Symptoms occur up to 6 h or less of orgasm from sexual intercourse, masturbation, and/or nocturnal emission		
3	Symptoms occur in more than 90% of all ejaculatory/orgasm settings (sex, masturbation, or nocturnal emission)	At least in one ejaculatory setting	
4	Symptoms last for 2–7 days		
5	Symptoms disappear spontaneously and last no longer than 21 days		

Criterion 2 states that symptoms occur immediately or within a few hours of orgasm from sexual intercourse, masturbation, or nocturnal emission. Waldinger proposed symptoms occurrence as immediately, soon, or within a few hours. The recent studies set this time within 6 h or less [7, 8].

Criterion 3 states that symptoms occur after all or almost all ejaculations in at least one ejaculatory setting (intercourse, masturbation, or nocturnal emission). Recently, it has been modified to symptoms occurrence in more than 90% of orgasm events.

Criterion 4 states that symptoms last for 2–7 days.

Criterion 5 states that symptoms disappear spontaneously. In a recent survey, a high rate of participants responded that they were "not sure" of the item related to this criterion [9]. The criterion may therefore have limited usefulness. Strashny suggested that POIS symptoms would not last longer than 21 days to distinguish POIS from other chronic conditions [7]. Considering that criterion 5 explores the possibility of allergic aetiology, perhaps it should be regarded as of lesser importance until the pathophysiology of POIS is better clarified [9].

Although not all the patients satisfied each of the five criteria, most patients met three or more [7, 8, 10]. To achieve a higher probability that patients suffer from POIS, we suggest applying the three or more criteria. Prognostically, the available results indicate that these diagnostic criteria may not be independently helpful in predicting outcomes [8].

9.3 Epidemiology

The prevalence and incidence of POIS are unknown and difficult to determine, owing to a paucity of studies. It is also likely that many affected individuals do not seek medical attention, and most physicians are unaware of the syndrome [2]. Due to a lack of awareness of POIS as a medical entity and its component symptoms of anxiety, distress, and depressed mood, men with POIS may first be referred to a mental health professional who may also be unfamiliar with the condition [10]. Since POIS was first described in 2002, the literature contains only 74 physician-diagnosed cases from different parts of the world [4, 6, 9–21], while studies with self-reported cases included 429 participants [7, 8]. More recently, there has been an increasing number of self-reported cases of POIS in internet forums, with approximately 1500 members [22–24], suggesting that POIS is under-diagnosed and under-reported [5]. In addition, case reports and editorials on similar symptoms that do not use the term "POIS" are also reported [25–27]. In an online survey to assess post-coital symptoms, with a sample of 223 women and 76 men, 94.3% reported any post-coital symptoms since they had been sexually active. The most common symptoms in women were mood swings, while men reported unhappiness and low energy. About 52% suffer from flu-like symptoms, 34% stated that they only experienced the symptoms after orgasm [28].

9.4 Clinical Presentation and Contributing Factors

According to Kinsey [29], "the only universal in human sexuality is variability itself", which certainly applies to the clinical presentation of POIS. We found a variable manifestation of the symptoms, order of appearance, duration, intensity, and type (primary or secondary) using the case reports and series data. Patients who are suffering from POIS are faced with the prospect of a distressing condition.

The age at presentation is highly variable; in the largest published surveys, the average age was at the beginning of their thirties [7, 8]. This is in accordance with the Reisman case series finding [10], while the Waldinger patients were on average 10 years older [6]. About half of the patients suffer from POIS from their first ejaculation, while others later in adulthood, reflecting primary and secondary disease presentation.

Some patients complain about symptoms from 1 cluster, whereas others display symptoms from several clusters. Fatigue, concentration difficulties, and irritability were among the most-reported symptoms in most of the studies. In the study of Waldinger, feverishness, and muscle weakness and/or myalgia were common symptoms [6–8, 10]. Flu-like complaints were the most apparent cluster mentioned in all the reports.

The majority of the patients described in different publications fulfil three or more diagnostic criteria, making the clinical diagnosis more reliable. The modification proposed in Table 9.1, concerning criteria 3 and 5, will probably increase the reliability. The number of diagnostic criteria that the respondents satisfied showed limited correlation to disease burden items, but categorizing patients according to symptom clusters may provide prognostic value [8]. Patients with general, head, and throat clusters are more likely to experience severe disease while the number of fellfield disease criteria could not independently predict disease course [8].

The most-reported comorbidity is premature ejaculation (14–56%) [5, 7, 9]. In a study by Waldinger, 56% of the men reported lifelong premature ejaculation (PE) with an intravaginal ejaculation latency time shorter than 1 min [6]. According to Waldinger et al., POIS bears a 22.5-fold risk for lifelong PE. Jiang et al. and Asby et al. also reported lifelong PE in their patients with POIS [11, 14]. PE shows a high correlation with muscle cluster complaints [8].

Other comorbidities include depression and anxiety disorder. Given that POIS is a distressing condition, it is still not known whether patients with POIS develop anxiety or depression as a result of their syndrome or whether patients with depression or anxiety are more likely to be diagnosed with POIS.

The physical and psychological effects of POIS can significantly affect the quality of life of patients. To reduce symptomatology, most POIS patients try to decrease sexual activity, such as abstinence from masturbation or intercourse, as much as possible, despite their normal urge to engage in sex and intimacy. This leads to internal struggles between enjoying and avoiding erotic activities for fear of ejaculation and associated symptoms. Moreover, because ejaculation can reduce concentration, alertness, and physical capacity, many patients need to plan ejaculations

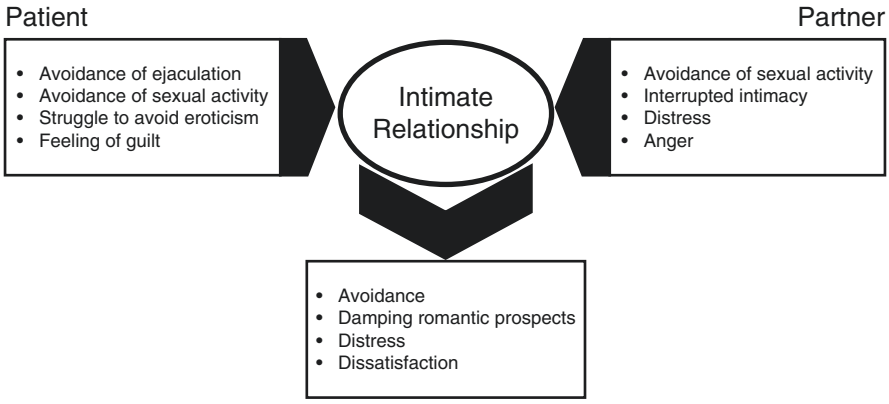

Fig. 9.1 The impact of POIS on patient, partner and their relationship

ahead of time to avoid inconvenience during everyday activities such as work or study [4, 6, 8, 10, 11]. Many single men with POIS may be reluctant to seek a romantic partnership due to the fear of stigma and lack of acceptance of intercourse abstention. It should be emphasized that POIS affected not only men but also their partners [2, 6, 22]. Men are also concerned about their relationship with their sexual partner and express feelings of guilt for having the disorder [1, 2, 6]. In one study, 10% of the patients divorced during follow-up due to patients' abstinence strategy or avoidance of sexual activity [6]. This finding sheds light on the severe mental and psychosocial burden POIS can place on men affected by this disorder (Fig. 9.1). Still, more studies are needed to understand the dyadic factors involved in the relationships.

9.5 Possible Pathophysiological Mechanism

Owing to the rarity of POIS in the general population, few studies have tried to study the aetiology of this condition, and there are several hypotheses on pathogenesis. However, there is no consensus on the underlying aetiology and, consequently, on the optimal treatment of POIS.

9.5.1 Immune Modulated Mechanism

The most challenged hypothesis was brought forward by Waldinger et al. [6] Based on the rapid onset and the generalized nature of the symptoms, they argued that POIS is an auto-immune or allergic disorder that causes an inflammatory reaction to a substance in the human seminal fluid. To test this theory, they performed Skin

Prick Tests (SPT) with extremely diluted autologous semen in patients with POIS. A protocolized intracutaneous (IC) skin prick test with male autologous semen was performed to quantify the skin reaction after inoculation of the semen. Semen was collected at home, and the samples were diluted with 0.9% saline to a concentration of 1:40,000. One-half millilitres of the different dilutions were IC injected into the volar side of the left forearm, and the skin reactions were recorded at 15 minutes after IC injections. Of 33 men who consented to skin prick testing, 29 (88%) had a positive SPT with their semen [6, 9]. The authors speculated that a Type I (immediate-type, related to antigen cross-linking with membrane-bound IgE antibody of a mast cell or basophil) and Type IV (delayed-type, cell-mediated response involving the interaction of T-cells, monocytes, and macrophages) allergy to autologous semen might act as the primary driver of POIS. Limitations of the studies by Waldinger et al. include a lack of healthy control men for the autologous semen SPT results and the observational study design. In addition, patients did not show elevated IgE levels; however, a similar study in Korean men showed that control subjects with no POIS symptoms had a more vigorous response to skin prick tests with autologous semen than the test subjects [16]. Arata et al. describe a patient with a positive SPT reaction and a negative level of serum seminal fluid specific IgE [20]. Also, 14 patients in the other study did not show elevated IgE levels or a significant increase of IgE 24 h after ejaculation [10].

To further explore the hypothesis that POIS is related to an allergic reaction, Waldinger et al. [9] investigated whether hyposensitization therapy with autologous semen would reduce the symptoms of POIS. Hyposensitization was performed with gradually increasing concentrations of autologous semen aimed at target whaling and 3+ flare response. Both patients reported decreased POIS burden after 15 and 31 months of injections [9]. One patient also reported PE improvement as his POIS symptoms decreased. Lack of local skin reactions after ejaculation and findings from hyposensitization therapy suggests that POIS immunological reactions occur due to repeated close contact during ejaculation between seminal peptides and circulating T-lymphocytes [6]. This leads to systemic reactions with multiple physical and cognitive complaints. In addition, to support the theory, the case report by Nguyen et al. showed that their POIS patient had positive SPT and intradermal semen test reactions [30].

Further information on the potential allergen source, Waldinger et al. [1] reported POIS occurrence in three men before and after sterilization. There was no change in symptoms after sterilization. They also noted the first case of a woman complaining about POIS and speculated that the antigen triggering POIS symptoms might be caused by prostatic tissue in males or prostatic-like tissue in females located around the upper wall of the vagina [1].

Of note, 58% of the cohort in Waldinger et al.'s study had many forms of allergies. However, the mean serum total immunoglobulin E (IgE) in men without atopy in the study was 27 kU/L (range 1.46–78), suggesting that IgE is normal in these patients. This shows that POIS is not associated with IgE-related disorders. POIS also occurs in men without any known allergy [6, 9, 11].

Kim et al. detected the existence of serum semen-specific IgE through Western blotting and ELISA in a Korean man with POIS [16]. The patient's POIS-related symptoms were alleviated after Intralymphatic immune therapy (ILIT), 3 to 6 injections of autologous semen at dilution of 1:40,000 into the inguinal lymph nodes at 4-week intervals, which indicates that POIS might be associated with an allergic Type I hypersensitivity reaction. Sneezing completely disappeared 15 months after ILIT, but the sore throat and urinary symptoms (residual urine sensation, voiding difficulty, weak stream, dribbling) remained unchanged after ILIT. A shortcoming of this study was that it did not include controls.

9.5.2 Opioid Withdrawal

Jiang et al. argued that POIS patients might suffer from a disorder of their endogenous opioid receptors as symptoms mimic opioid withdrawal [14]. They postulated that chemical imbalances in the brain could be the biochemical basis for POIS with psychological conditions that are risk factors. Using a different grading system and an SPT procedure according to Waldinger et al., SPTs and intracutaneous tests (ICTs) were performed with autologous semen in patients with POIS complaining about insomnia, anxiety, mild obsessive-compulsive disorder, and three healthy volunteers. Serum-specific IgE for semen was also measured in the affected patient and two healthy volunteers. In the POIS patient, the SPT response was mildly positive at 1:10 dilution, and the ICT response was positive at 1:100 dilution. In three healthy volunteers, SPT reactions were adverse, and ICT reactions were positive at 1:10 and 1:100. These results have shown that healthy controls may have positive skin reactions to autologous semen, possibly due to inflammatory cytokines and chemokines in the seminal fluid. Seminal fluid-specific IgE, which is detected in women with semen allergies, was undetectable in the serum of the POIS patient [14]. According to these findings, they concluded that there was less likelihood of an IgE-mediated mechanism in POIS. Instead, POIS symptoms were compared with opioid withdrawal, which includes similar physical and psychological manifestations. They argued that patients with POIS may have a disorder involving endogenous opioid receptors because the orgasm mechanism consumes large amounts of endogenous opioids in these patients, resulting in symptoms similar to opioid withdrawal.

9.5.3 Disordered Cytokine or Neuroendocrine Response

Ashby and Goldmeier described a POIS patient without any anxiety or depression. According to the neuropsychologist's opinion, the post-orgasm symptoms the patient experienced could be either wholly physical or had assumed a particular significance in the patient's life, leading him to become more alert to post-orgasm symptoms. The patient was treated with prophylactic non-steroidal anti-inflammatory drugs, which show a consistent improvement in the severity of symptoms.

Their second patient also showed cognitive and motor changes during the pre-and post-ejaculation examination but was less clearly suffering from POIS. Based on the findings of other studies showing that after orgasm, there is a surge in prolactin release, an increase in sympathetic activity, with the release of noradrenaline, as well as other catecholamines and neurotransmitters, POIS symptoms are likely to be caused by a disordered cytokine or neuroendocrine response [11].

9.5.4 Lack of Progesterone

Dexter [25] postulated that a lack of progesterone could cause POIS. He describes a 43-year-old man presented with a 27-year history of mental debility, fatigue, and headache, among other symptoms associated with ejaculation and orgasm during any form of sexual activity. The symptoms occurred 20 min after sexual activity and lasted for 72 h. The condition was spontaneously relieved during his partner's pregnancy, returning only after the birth of their child. The patient was successfully treated with norethisterone 5 mg 30 min before sexual activity.

9.6 Clinical Management Including Biological-Psychological-Social Contributing Factors

In clinical practice, patients suspected of having POIS should be interviewed about their complaints and sexual function, with attention paid to ejaculation disorders. As an essential factor in the diagnosis, the onset, course, and length of symptoms must be well noted. It is crucial to have a complete medical history, including current allergies, potential neurological or mental conditions, and address the POIS's effect on the patient and the relationship. As patients can suffer from their symptoms with a considerable emotional and psychosocial strain, these factors should also be addressed. Non-specific symptoms can often be dismissed as psychogenic. In the absence of obvious physical causes, it is reasonable to explore psychological issues triggered by sexual activity, such as guilt, religiosity, prior sexual abuse, or unrecognized feelings of uncertainty about sexual orientation or gender identification. Patients should be carefully examined and screened for other diseases with POIS-like symptoms (e.g. post-orgasmic cataplexy, orgasm-associated headaches, post-coital asthma and rhinitis). Health care professionals should bear in mind that a man may feel embarrassed and ashamed to discuss his symptoms in an open conversation. Although little is known about this syndrome, formally recognizing the symptoms with the terminology POIS reassures patients that they are not suffering from a psychiatric, psychosomatic, or other unknown disorder [31].

Males who are clinically diagnosed as having POIS should undergo routine tests, including a full blood count and hormonal laboratory tests (follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, testosterone) [6, 9, 10, 32]. As mentioned above, Waldinger et al. [6] performed a protocolized intracutaneous SPT

with extremely diluted autologous semen to demonstrate allergic reactions, with a potential risk of causing symptoms of POIS and even a generalized anaphylactic shock requiring an intensive care unit. Therefore, this investigation should only be carried out after an explicit explanation to the patient about the procedure and the risks and providing the necessary conditions before the performance.

Currently, there are no recognized treatment options for POIS. Patients with POIS-like symptoms have been treated with antihistamines, non-steroidal anti-inflammatory medication, immune suppressants, selective serotonin reuptake inhibitors, benzodiazepines, and alpha blockers. Hyposensitization therapy was also suggested.

9.6.1 Hyposensitization Therapy

Hyposensitization with autologous semen was used in two Dutchmen with POIS according to the protocol developed by Meinardi [6]. Hyposensitization began with extremely diluted autologous semen and gradually increased concentrations, with 60% and 90% improvement in POIS complaints at 31 and 15 months, respectively. However, this was not a randomized placebo-controlled clinical trial, so the efficacy of treatment remains unconfirmed [9].

Kim et al. [16] presented a POIS patient with allergic resembling symptoms who received ILIT with autologous semen instead of subcutaneous delivery. This is a novel method of allergen-specific immunotherapy used in allergic diseases. Autologous semen was aseptically injected into the inguinal lymph node with a 1:40,000 dilution using ultrasound guidance and a needle [16]. The concentration was then increased by three-fold. After 8 and 15 months of the first injection, all POIS-related symptoms except sore throat and urinary symptoms were relieved. The authors recommended that hyposensitization therapy may have therapeutic effects in patients with POIS who are thought to have allergies as a main etiological factor. The mechanism of ILIT is not sufficiently understood, and it was a single case report, so spontaneous remission cannot be excluded. The actual efficacy remains unconfirmed.

9.6.2 Non-steroidal Anti-Inflammatory Medication (NSAIDs)

Successful treatment with non-steroidal anti-inflammatory drugs (diclofenac), 75 mg 1–2 hours before sexual activity, continued twice daily for 24–48 hours, succeeded in alleviating symptoms (up to 80 percent improvement) and allowed in a single case report to increase his sexual frequency from 2 to 4 times a month [11, 14, 26]. In another case report, diclofenac 25 mg twice daily was prescribed. Post-ejaculation symptoms of the patient completely disappeared, and skin reactions to autologous semen decreased 90 min after oral administration of diclofenac [19]. In

one case report of a young patient with POIS, NSAID helped relieve headache and muscular pain [21]. However, non-steroidal anti-inflammatory drug therapy failed in other patients highlighting the need for further investigation into the nature and treatment of POIS [10, 12].

9.6.3 Testosterone Therapy

In a POIS patient with low total and free serum testosterone concentration, successful treatment of POIS complaints was achieved by elevating serum testosterone through subcutaneous injections of human chorionic gonadotropin (hCG 1500 IU injected subcutaneously three times a week). The choice of hCG to raise serum testosterone was based on a young man's desire to preserve fertility and testicular volume. After 6 weeks of follow-up, the symptoms were completely resolved. This treatment with hCG gives rise to the possibility that testosterone deficiency may be an underlying aetiology in some cases [17].

Takeshima et al. also administered testosterone enanthate every 2 weeks in patients with POIS and patients' free serum testosterone levels lower than 70% of the mean value in young adult males. This treatment was continued for up to 4 weeks and then replaced with a testosterone ointment preparation. The symptoms of general fatigue significantly improved, and he could ejaculate every day [21].

9.6.4 Alpha Blockers

Recently published literature indicates that treatment with alpha blockers, such as silodosin [10] or terazosin [32], may improve POIS symptoms. As POIS-related symptoms are thought to be caused by ejaculation, inhibiting ejaculation will prevent arising of symptoms. A highly selective alpha1A-blocker such as silodosin, which is registered for the treatment of lower urinary tract symptoms, often has anejaculation as a side effect without causing anorgasmia. In a case series of 14 POIS patients, silodosin 8 mg was prescribed 2 h before sexual activity. Eight of them were satisfied with the treatment and relief of POIS complaints [10]. Terazosin (non-selective alpha blocker) in combination with probiotics had POIS symptoms improvement in one patient. The authors suggested that terazosin blocks the autonomic hyperreflexia following orgasm as a potential mechanism for POIS [33].

9.6.5 Other Treatments

Prednisone, an immune modulator that reduces inflammatory reaction, has also been reported as a possible treatment [10, 22].

There is a wide variety of reported treatments on patients' platforms on the internet, non-have been confirmed in controlled trials. These treatments include selective serotonin reuptake inhibitors that may also improve mood, antihistamines, benzodiazepines, and niacin [8]. In addition, many alternative therapies, like vitamins, supplements, and herbal remedies, have been suggested to be effective in improving POIS symptoms, including niacin, olive leaf, fenugreek, saw palmetto, and Wobenzym [33].

9.7 Conclusion

POIS remains a challenging diagnosis causing disabling symptoms with no straightforward treatment. It has a variable clinical presentation but is consistently distressing and affects the patient's quality of life, their partner and their relationship.

The clinical evaluation should include the physical and psychological complaints with attention to the burden of the disease. To provide patients with an indicator of disease severity, clinicians may consider characterizing the disease following one or more symptom clusters. Symptom clusters may provide prognostic value to determine the burden of disease. Clinically, patients satisfying some or all of the diagnostic criteria should merit suspicion for POIS. Most POIS sufferers meet multiple diagnostic criteria, and patients who fulfil three or more diagnostic criteria have a more reliable diagnosis. For practitioners unfamiliar with the syndrome, developing an in-office tool will aid in the diagnosis of POIS.

As all proposed etiological factors are not sufficiently evidence based, the authors of this chapter do not support any pathophysiological aetiology. Probably multiple contributing factors are involved. An improved understanding of the pathophysiology behind POIS could likely guide future treatment. There are no recognized treatment modalities for POIS. Patients with POIS-like symptoms have been treated with antihistamines, non-steroidal anti-inflammatory medication, immune suppressants, selective serotonin reuptake inhibitors, benzodiazepines, and alpha blockers. Hyposensitization therapy was also suggested. The choice of treatment should be guided according to the symptoms and in a shared decision process. Future research is necessary to guide optimal clinical management.

Key Messages

- POIS has a variable clinical presentation with debilitating physical and psychological consequences.
- In the diagnostic process, the proposed criteria should be applied.
- POIS has a profound impact on the patient, partner and their relationship.
- There is no clear consensus about the aetiology, nor the treatment of POIS.
- More research is necessary to determine the clear prevalence, optimal diagnostic criteria, pathophysiology, and effective treatment options of POIS.

References

1. Waldinger MD. Post orgasmic illness syndrome (POIS). Transl Androl Urol. 2016;5:602–6.
2. Nguyen HMT, Bala A, Andrew T, Gabrielson AT, Hellstrom WJG. Post-orgasmic illness syndrome: a review. Sex Med Rev. 2018;6(1):11–5.
3. Parish SJ, Goldstein AT, Goldstein SW, Goldstein I, Pfaus J, Clayton AH, Giraldi A, Simon JA, Althof SE, Bachmann G, Komisaruk B, Levin R, Spadt SK, Kingsberg SA, Perelman MA, Waldinger MD, Whipple B. Toward a more evidence-based nosology and nomenclature for female sexual dysfunctions-part II. J Sex Med. 2016;13(12):1888–906.
4. Waldinger MD, Schweitzer DH. Post orgasmic illness syndrome: two cases. J Sex Marital Ther. 2002;28(3):251–5.
5. U.S. Department of Health & Human Services. National Institutes of Health. Genetic and rare diseases information center. https://rarediseases.info.nih.gov/diseases/10809/postorgasmic-illness-syndrome, 2020.
6. Waldinger MD, Meinardi MM, Zwinderman AH, et al. Postorgasmic illness syndrome (POIS) in 45 Dutch Caucasian males: clinical characteristics and evidence for an immunogenic pathogenesis (part 1). J Sex Med. 2011;8:1164–70.
7. Strashny A. First assessment of the validity of the only diagnostic criteria for postorgasmic illness syndrome (POIS). Int J Impot Res. 2019;31:369–73.
8. Natale C, Gabrielson A, Tue Nguyen HM, et al. Analysis of the symptomatology, disease course, and treatment of postorgasmic illness syndrome in a large sample. J Sex Med. 2020;17:2229–35.
9. Waldinger MD, Meinardi MMHM, Schweitzer DH. Hyposensitization therapy with autologous semen in two Dutch Caucasian males: beneficial effects in postorgasmic illness syndrome (POIS; part 2). J Sex Med. 2011;8:1171–6.
10. Reisman Y. Clinical experience with post-orgasmic illness syndrome (POIS) patients-characteristics and possible treatment modality. Int J Impot Res. 2021;33(5):556–562.
11. Ashby J, Goldmeier D. Postorgasm illness syndrome–a spectrum of illnesses. J Sex Med. 2010;7:1976–81.
12. Attia AM, Yasien HA, Al-Ziny MH. Post-orgasmic illness syndrome: a case report. F1000Research. 2013;2:113.
13. Desai G, Sharma M, Chaturvedi SK. Medically unexplained symptoms explained!!!! A case of post-orgasmic illness syndrome. Indian J Med Case Rep. 2013;2:18–20.
14. Jiang N, Xi G, Li H, Yin J. Postorgasmic illness syndrome (POIS) in a Chinese man: no proof for IgE-mediated allergy to semen. J Sex Med. 2015;12:840–5.
15. Depreux N, Basagaña M, Pascal M. Negative allergy study in a case of postorgasmic illness syndrome (POIS). Rev Int Androl. 2018;16:42–4.
16. Kim TB, Shim YS, Lee SM, Son ES, Shim JW, Lee SP. Intralymphatic immunotherapy with autologous semen in a Korean man with post-orgasmic illness syndrome. Sex Med. 2018;6:174–9.
17. Bolanos J, Morgentaler A. Successful treatment of post-orgasmic illness syndrome with human chorionic gonadotropin. Urol Case Rep. 2019;29:101078.
18. Stafie SC, Stafie II. Post coital allergy—a case report of post orgasmic illness syndrome. Med Surg J. 2019;123:258–61.
19. De Amicis K, Costa PR, Figo DD, De Lima CMF, Castro FFM, Kalil J, Santos KS, Galvão CES. Immunophenotypical characterization of a Brazilian POIS (post-orgasmic illness syndrome) patient: adding more pieces to puzzle. J Sex Marital Ther. 2020;46(3):227–33.
20. Arata K, Tamagawa-Mineoka R, Ohshita A, Masuda K, Katoh N. Nonsteroidal anti-inflammatory drugs are effective against postorgasmic illness syndrome: a case report. J Cutan Immunol Allergy. 2020:1–2.
21. Takeshima T, Kuroda S, Yumura Y. Case of post-orgasmic illness syndrome associated with hypogonadism. IJU Case Rep. 2020;3:189–91.

22. POIS Center.com. Post Orgasmic Illness Syndrome (P.O.I.S.) statistics center. https://poiscenter.com/forums/index.php?action¼stats. Accessed January 10, 2021.
23. The Naked Scientists.com. Post Orgasmic Illness syndrome (POIS). https://www.thenakedscientists.com/forum/index.php?topic¼46576.0; Accessed January 10, 2021.
24. Facebook.com. Post Orgasmic Illness Syndrome (POIS). https://www.facebook.com/groups/1457009341209480/; Accessed January 10, 2021.
25. Dexter S. Benign coital headache relieved by partner's pregnancies with implications for future treatment. BMJ Case Rep. 2010;2010:bcr10.2009.2359.
26. Angus-Leppan H, Caulfield A. Orgasmic migraine aura: report of two cases. Cephalalgia. 2018;39:153–6.
27. Shah A. Asthma and sex. Indian J Chest Dis Allied Sci. 2001;43:135–7. –15
28. Burri A, Hilpert P. Postcoital symptoms in a convenience sample of men and women. J Sex Med. 2020;17:556–9.
29. Kinsey A. Sexual report in human male. Indiana University Press; 1948.
30. Nguyen T, Dimov V, Bewtra A. Seminal fluid hypersensitivity in a man with postorgasmic illness syndrome (POIS). Ann Allergy Asthma Immunol. 2011;107:A48.
31. Paulos MR, Avelliino GJ. Post-orgasmic illness syndrome: history and current perspectives. Fertil Steril. 2020;113(1):13–5.
32. Abdessater M, Elias S, Mikhael E, Alhammadi A, Beley S. Post orgasmic illness syndrome: what do we know till now? Basic Clin Androl. 2019;29:13.
33. Fainberg J, Gaffney C, Pierce H, et al. Post-orgasmic illness syndrome: a case report and literature review with contemporary treatment considerations. J Sex Med. 2020;17(Suppl 1):S41–2.