Trends in Andrology and Sexual Medicine
Series Editors: E.A. Jannini, C. Foresta, A. Lenzi, M. Maggi

Emmanuele A. Jannini
Alberto Siracusano *Editors*

Sexual Dysfunctions in Mentally Ill Patients

siams
Società Italiana di Andrologia
e Medicina della Sessualità

Springer

Trends in Andrology and Sexual Medicine

This series will serve as a comprehensive and authoritative resource that presents state of the art knowledge and practice within the fields of Andrology and Sexual Medicine, covering basic science and clinical and psychological aspects. Each volume will focus on a specific topic relating to reproductive or sexual health, such as male and female sexual disorders (from erectile dysfunction to vaginismus, and from hypoactive desire to ejaculatory disturbances), diagnostic issues in infertility and sexual dysfunction, and current and emerging therapies (from assisted reproduction techniques to testosterone supplementation, and from PDE5i to SSRIs for premature ejaculation). In addition, selected new topics not previously covered in a single monograph will be addressed, examples including male osteoporosis and the approach of traditional Chinese medicine to sexual medicine. Against the background of rapid progress in Andrology and Sexual Medicine, the series will meet the need of readers for detailed updates on new discoveries in physiology and pathophysiology and in the therapy of human sexual and reproductive disorders.

More information about this series at http://www.springer.com/series/13846

Emmanuele A. Jannini · Alberto Siracusano
Editors

Sexual Dysfunctions in Mentally Ill Patients

siams
Società Italiana di Andrologia e Medicina della Sessualità

Springer

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

Alberto Siracusano
Department of Systems Medicine
University of Rome Tor Vergata
Rome
Italy

ISSN 2367-0088 ISSN 2367-0096 (electronic)
Trends in Andrology and Sexual Medicine
ISBN 978-3-319-68305-8 ISBN 978-3-319-68306-5 (eBook)
https://doi.org/10.1007/978-3-319-68306-5

Library of Congress Control Number: 2018947578

Printed on acid-free paper

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

Contents

1 Introduction: The Need of Sexual Medicine in Contemporary Psychiatry and the Need of Psychiatry in the Growing Field of Sexual Medicine

Emmanuele A. Jannini and Alberto Siracusano

It is written in the annals of history: Sexology is born in the psychiatric land. In the modern era, the first great scholars dealing with the function—and dysfunction—of human sexuality were just the doctors of the mind. Two features characterized the first sexologists: being psychiatrists and working in a German milieu. This was the case of the noble Richard Freiherr von Krafft-Ebing (Fig. 1.1), who wrote the bible of the field, the *Psychopathia Sexualis* (Psychopathy of Sex), of Magnus Hirschfeld, who edited in 1908 the first scientific journal, *Zeitschrift für Sexualwissenschaft* (Journal for Sexual Research) [1], and it was the case of Felix Abraham, Iwan Bloch, Arthur Kronfeld, Albert Moll, and Bernard Schapiro, who together built a sexual theory which was universally considered a genuine part of psychiatry. That time was also the *belle époque* of the great psychodynamic theories and research of Sigmund Freud and his psychoanalysis [2]. This glorious period was well represented by the Berliner *Institut für Sexualwissenschaft* (Institute for Sexual Research), dramatically destroyed in 1933 by the collective folly of Nazism.

Unfortunately, not only for this latter reason, the psychiatric paternity did not last long. Psychiatrists, in fact, have gradually become less interested in treating the most common male and female sexual symptoms (from erectile dysfunction to anorexia, from ejaculatory dysfunction to vaginismus, from the hypoactive sexual desire disorder to anorgasmia), apart from, perhaps, some traditional interests for sexual dependencies and paraphilias. This decline in interest has probably been the basis of the controversial classification of the sexual dysfunctions published in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), edited by the American Psychiatric Association (APA) [3]. This poor outcome cannot exclusively be attributed to psychiatry; the lack of scientific

E. A. Jannini (✉) · A. Siracusano
Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
e-mail: eajannini@gmail.com

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*,
Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_1

Fig. 1.1 Richard Fridolin Joseph Freiherr Krafft von Festenberg auf Frohnberg, genannt von Ebing Krafft-Ebing (born in 1840 in Mannheim, Germany, died in Graz, Austria, in 1902), was a famous psychiatrist and author in 1886 of the foundational work *Psychopathia Sexualis*

knowledge on sexual pathophysiology and a typical psycho-reductionism that characterized sexology are not ancillary reasons [4].

Infant sexology, abandoned on the orphanage of science, was rapidly transformed in psychosexology, and the psychologist has become the (only) adoptive parent. Thus, in the face of excellent doctors, there have been so many—too many—psychologists who have rapidly destroyed the medical and scientific content to promote an opinion-based psychosexology grounded on improvisation and presumption. Even Virginia Johnson, the wife of the gynecologist Bill Masters, despite the undeniable merit of being the true thinking mind of the famous couple, was not graduated [5]. This self-referential arrogance of much (certainly not of all) psychosexologists has led to the lack of recognition of sexology as a science not only from the biomedical and psychiatric environment but also from the same academic psychology. The result was a long, deafening silence on the sexological themes that in many universities still lasts, giving room for the improvisation of "pseudo-sexologists" outside the official academy. This is also due to the existence of plenty of questionable private courses, grown as poisonous fungi, thanks to the relative absence of an official academic training in sexology in most of medical schools, as well as in several schools of psychology [6].

In the last 20 years (having a symbolic birth date of that virtuous process in marketing the first oral treatment of erectile dysfunction, the type 5 phosphodiesterase inhibitor [7]), a substantially opposite trend has become evident. In the same time frame, studies on the animal sexual behavior, psycho-neuro-endocrinological research, human brain imaging during the appetitive phase, excitation, coitus, ejaculation, and orgasm clearly demonstrated that sexual functioning is bound to the same neurobiological substrate which involves the psychiatric science. Despite that,

the birth of medical sexology—or sexual medicine—paradoxically happened in the less logical of possible cribs, that one of the genitourinary surgery. It was, in fact, the urologist who first understood the possibility to carry sexology within the medical field. Immediately after the dramatic success of sildenafil citrate and the consequent possibility to easily (but apparently) cure erectile dysfunction without a sexological background, sexual research was influenced by the pharmaceutical companies. Suddenly, industry realized the enormous potential economic outputs of sex-enhancing drugs for mass consumption [8, 9], carrying the obvious concerns about marketing-driven mechanisms potentially able to interfere or distort objective research [10].

Despite the obvious evidence that the sexual pathophysiology and symptoms are, in general, much more related to internal medicine, and in particular to endocrinology, when compared to surgical disciplines, the endocrinologist only recently (and yet incompletely) realized the responsibility of taking care of the sexual health of its patients [11]. But this late collaboration was crucial to rapidly transform the opinion-based (psycho)sexology into the new evidence-based (medical) sexology. Quickly and fairly, the key opinion leaders in psychosexology adapted to the Galilean method by designing a new psychosexology labeled as "holistic," but which could be now better renamed as *systems sexology* [12]. The new term systems sexology is based on the biopsychosocial model that does not admit ideological fences in the scientific exploration of the complex systems that impact human sexuality, its pathophysiology, and treatment [13].

The extensive and methodologically sound scientific production; the blossom of plenty of scientific journals with good impact factor; the large number of dedicated congresses, conferences, courses, and debates; and the fundamental call for qualified intervention from patients, i.e., the final users of the new systems sexology [14], are now generating in the psychiatrist a superb resumption of genuine interest in sexology [15]. That is why we are here, an endocrinologist-sexologist and a psychiatrist, to introduce, to present, and to edit this new collaborative book of the young but fortunate series *Trends in Andrology and Sexual Medicine*.

This text is devoted to the several aspects of systems sexology of cultural and practical interest of the psychiatrist dealing with mentally ill patients with sexual symptoms and sexual comorbidities. The large majority of sexological arguments of specific clinical interest for the psychiatrists are here discussed. The reader will find articles on the possible *sex toxicity* of (almost) all classes of drugs used in psychiatry or for illegal abuse, the comorbidity of sexual and psychiatric and personality disorders, the sexology of the eating behavior disorder, and the role of the psychiatrist in the treatment of gender dysphoria, sexual abusers, and paraphilic patients demonstrating that the space for a new collaboration between the doctors of the mind and those of the sex is vast and is revealing scientific products able to satisfy the most rosy and flattering expectations.

We are finally in debt with our coworkers Drs. Emanuela Bianciardi, Giacomo Ciocca, Erika Limoncin, and Daniele Mollaioli for their great and expert help in editing and reviewing the manuscripts before publication.

In conclusion, this book aims to stimulate the revival of medical sexology in the psychiatry of the twenty-first century and to demonstrate the need of a renaissance of the psychiatric science and culture in the growing, multifaceted field of sexual medicine.

References

1. Hirschfeld M, editor. Journal for Sexual Research. Leipzig: George H. Wigand's Verlag; 1908.
2. Freud S. Three essays on the theory of sexuality (Drei Abhandlungen zur Sexualtheorie). 1905. Strachey J, trans. New York: Basic Books; 1962.
3. American Psychiatric Association, editor. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC.
4. Derogatis LR, Laan E, Brauer M, Van Lunsen RHW, Jannini EA, Davis SR, et al. Responses to the proposed DSM-V changes. J Sex Med. 2010;7(6):1998–2014. https://doi.org/10.1111/j.1743-6109.2010.01865.x.
5. Masters WH, Johnson V. Human sexual response. New York: Bantam Books; 1966.
6. Pinchera A, Jannini EA, Lenzi A. Research and academic education in medical sexology. J Endocrinol Invest. 2003;26(3 Suppl):13–4.
7. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. N Engl J Med. 1998;338(20):1397–404. https://doi.org/10.1056/NEJM199805143382001.
8. Jannini EA, Sternbach N, Limoncin E, Ciocca G, Gravina GL, Tripodi F, Petruccelli I, Keijzer S, Isherwood G, Wiedemann B, Simonelli C. Health-related characteristics and unmet needs of men with erectile dysfunction: a survey in five European countries. J Sex Med. 2014;11(1):40–50. https://doi.org/10.1111/jsm.12344.
9. Corona G, Maggi M, Jannini EA. EDEUS, a real-life study on the users of phosphodiesterase type 5 inhibitors: prevalence, perceptions, and health care-seeking behavior among European men with a focus on 2nd-generation Avanafil. Sex Med. 2017;6(1):15–23. https://doi.org/10.1016/j.esxm.2017.10.003.
10. Jannini EA, Eardley I, Sand M, Hackett G. Clinical and basic science research in sexual medicine must rely, in part, on pharmaceutical funding? J Sex Med. 2010;7(7):2331–7. https://doi.org/10.1111/j.1743-6109.2010.01898.x.
11. Guay AT, Spark RF, Bansal S, Cunningham GR, Goodman NF, Nankin HR, American Association of Clinical Endocrinologists Male Sexual Dysfunction Task Force, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of male sexual dysfunction: a couple's problem – 2003 update. Endocr Pract. 2003;9(1):77–95. https://doi.org/10.4158/EP.9.1.77.
12. Jannini EA. SM = SM: the Interface of systems medicine and sexual medicine for facing non-communicable diseases in a gender-dependent manner. Sex Med Rev. 2017;5(3):349–64. https://doi.org/10.1016/j.sxmr.2017.04.002.
13. Jannini EA, McCabe MP, Salonia A, Montorsi F, Sachs BD. Organic vs. psychogenic? The Manichean diagnosis in sexual medicine. J Sex Med. 2010;7(5):1726–33. https://doi.org/10.1111/j.1743-6109.2010.01824.x.
14. Siracusano A, Bianciardi E, Niolu C. The new taxonomy of sexual disorders [It.] In: Jannini EA, Lenzi A, Maggi M, editors. Medical sexology: textbook of psychosexology, sexual medicine, and couple's sexual health. milan: EDRA; 2017.
15. Ciocca G, Ribolsi M, Limoncin E, Mollaioli D, Bianciardi E, Niolu C, Di Lorenzo G, Siracusano A, Jannini EA. Sexuality of patients with first episode psychosis [It.]. Noos. 2017;23(1):27–31. https://doi.org/10.1722/2780.28048.

Experimental Models in Sexual Medicine: Eight Best Practices

2

David L. Rowland and Ion G. Motofei

2.1 Introduction and Goals

This chapter is intended to help the clinician and/or researcher understand how experimental research models can be applied to the study of sexual medicine. We discuss several critical concepts that help ensure a research project meet its objectives and, as a convenience to the readership, elaborate these as a series of best practices for consideration when investigating parameters of sexual response in populations of the mentally ill. The chapter does not intend to provide a comprehensive review of experimental methodology; rather, for who have not had the benefit of a strong background in research methodology or who are seeking a brief refresher, we discuss a number of methodological issues frequently raised in the review/evaluation of research projects and papers. Although the ideas presented here may be elementary to more seasoned researchers, as new waves of cohorts throughout the world engage in the study of sexual medicine, it behooves them to understand and differentiate good from poor research, whether as an investigator, grant proposer, manuscript reviewer, or consumer of ideas. In this chapter, we briefly address the following key points:

- Exploring the interface between sexual response and mental illness
- Identifying research questions and variables
- Understanding the general paradigm for the experimental approach
- Defining and assessing study variables
- Understanding and minimizing errors and design flaws
- Analyzing data and drawing legitimate conclusions

D. L. Rowland (✉)
Department of Psychology, Valparaiso University, Valparaiso, IN, USA
e-mail: david.rowland@valpo.edu

I. G. Motofei
Department of Urology, Carola Davila University, Bucharest, Romania

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*,
Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_2

2.2 The Interface Between Sexuality and Mental Illness

Human sexual response and dysfunction have traditionally been conceptualized along the desire-arousal (psychological/physiological)-orgasm continuum first suggested by Kaplan [1] and Leif [2], with more recent distinction made between men's and women's models of sexual response and classification of problems [3]. Mental illness is usually broadly defined, encompassing problems in the emotional, cognitive, and/or behavioral realms. In some instances, a mental illness exists independent of the sexual problem (e.g., a drug addiction), although this does not preclude one from affecting the other. In others, the problems may be more intricately interwoven such that vulnerability to one heightens vulnerability to the other. A psychophysiological model recognizes that often brain systems and functions involving different psychological domains may be neurologically intertwined. For example, autonomic and somatic processes serve to link cognitive function and sexual function: somatic pathways serve as peripheral afferents for autonomic sexual centers, in order to generate within the brain sexual activation and response; the autonomic sexual centers process environmental (nonsexual) information autonomously, generating in this way cognition and mental experiences. As a working hypothesis, mental experiences and sexuality are supported within the brain by a common (somatic-autonomic) neurobiological substrate, which selects either a cognitive-mental or sexual commitment depending on context (e.g., external-social, mental-disposition, physical-hormonal, emotional and cultural) [4, 5].

This psychophysiological perspective integrating cognition and sexuality might help explain why multiple psychological disorders are often associated with sexuality and sexual dysfunctions [6, 7], why sexual dysfunctions are often accompanied by psychological impairments, and why sexual dysfunctions are often the consequence of psychotropic medications [8, 9]. For example, from a pathological perspective, the peak for schizophrenia incidence takes place during major sexual transition periods, namely, at puberty for both sexes, with a second peak for women following menopause [10]; bipolar disorder/mania induces not only elevated mental activities (mood, hyperactivity, etc.) but also hypersexuality [11]; depression is characterized by decreased mental/brain function and inhibited sexual function [12, 13]; and treatment with psychoactive drugs such as antidepressants not only activates cerebral areas, alleviates depression, and increases sexual arousal in women [14] but also proves useful for both depression and premature ejaculation in men [15], a condition sometimes associated with anxiety and attention deficit/hyperactive disorder [16, 17].

Such "apparent coincidences" suggest that sexual dysfunctions and associated psychological problems might represent a common vulnerability, that is, these associations may be more than mere coincidence, signifying common or overlapping pathways. Furthermore, given these associations, such problems might be addressed by taking a more holistic/integrated approach that combines pharmacological and neuroendocrine strategies [18]. In this regard, some authors suggest that sexual hormones might be integrated into the treatment of various psychiatric disorders [19, 20].[1]

[1] Interestingly, recent studies have suggested that an individual's handedness and sexual orientation may assume modulating roles in the links between psychological/cognitive problems and sexuality [21–26].

Such associations not only indicate the importance of carefully studying linkages between sexual problems and mental illness, but suggest studies dealing with sexual response should include mental health *and* mental illness parameters as covariates in the analyses. That is, most studies dealing with sexuality typically screen out individuals with mental health issues. In fact, a better approach might include both mentally healthy and mentally ill participants and, assuming sufficient numbers in the sample, treat these conditions as relevant covariates.

In the following sections, we discuss various issues in the implementation of experimental protocols and identify eight best practices to help investigators understand the process of transforming empirically based questions into successful studies that will help explain relationships between sexual response, sexual dysfunction, and mental illness.

Box 2.1 Studying Sexual Response in the Laboratory

Sexual response has physiological, psychological, and sociocultural elements. Over the past 40 years, substantial effort has been devoted to understanding men's and women's physiological and psychological experience of sexual response, for example, how it relates to their level of subjective sexual arousal, to their emotional and cognitive responses, and to their physiological response. Much of this research has been "psychophysiological" in nature, a term referring to any process that involves the interaction of psychological and physiological systems. Traditionally, the field of psychophysiology has referred to an approach investigating the relationship between particular psychological states or experiences (perceptive, affective, and cognitive) and concomitant or subsequent physiological responses. The range of physiological responses has been wide, usually tapping into autonomic response systems that include such measures as electrodermal response, event-related potentials, EEG, EMG, EKG, genital smooth muscle, and/or other direct or indirect measures of neurophysiological or neuromuscular response.

Psychophysiology as a discipline shares much in common with psychosomatic medicine, behavioral medicine, and health psychology. However, the "psychophysiological" approach is also defined in part by a laboratory methodology that supports the acquisition of knowledge within this setting and is characterized by the precise and (often) amplified measurement of subtle (often autonomic) physiological responses. These responses are measured during specific mental states (sensory-perceptive, affective, and/or cognitive) induced through the presentation of controlled stimuli.

With respect to the study of human sexual response, the psychophysiological approach typically attempts to understand mind (subjective/psychological)/body (various physiological responses) interactions that occur during sexual arousal, studied in a controlled laboratory environment. This approach not only makes it possible to control the stimulus conditions, but enables assessment of both outcome (response) and predictor (often stimulus or contextual) variables with substantial precision and reliability. Thus, sexual response—including

such measures as erection and ejaculation in men or vaginal lubrication and orgasm in women—can be investigated as a function of any number of covariates of presumed importance to this response. For example, with respect to one male sexual dysfunction, premature ejaculation (PE), such covariates may include the kinds of stimuli most likely to elicit the dysfunctional response (rapid ejaculation), the patient's self-reported levels of sexual arousal, the mitigating effects of anxiety and negative affect, various dyadic relationship factors, and so on [27].

Although the laboratory approach to the study of sexual response provides a tightly controlled environment under which to manipulate and study sexual response (e.g., performance demand), its use has waned over the past decades, presumably due to costs in terms of space, equipment, time, and labor. Nevertheless, this approach has yielded a wealth of understanding of sexual response, sexual dysfunction, and their covariates in both men and women (e.g., [27–29]).

2.3 Identifying the Research Questions and Hypotheses

Embedded in every research project are questions awaiting answers, often though not always stated as *research hypotheses* and typically ordered in terms of importance. In some instances, these hypotheses represent specific applications of larger, more general theories (i.e., general-to-specific, a deductive process); in others, they represent specific tests carried out on samples for the purpose of generalizing to broader populations (i.e., specific-to-general, an inductive process). Most research programs involve a combination, with theories spawning new hypotheses, and/or the results of hypothesis testing shaping new ideas and theories.

Furthermore, embedded within every research hypothesis are the variables that define the topic of the study. In most research, one or several variables are designated *outcome* or *dependent* variables—the ones the researcher is interested in measuring or understanding. The other variables are usually *predictor* or *independent* (also treatment) variables—the ones suspected of affecting the outcome variables. For example, in the statement "Treatment for depression improves sexual satisfaction," sexual satisfaction is the outcome or dependent variable, which is presumed to be affected by a certain treatment, the predictor or independent variable.

This simple hypothesis might be elaborated by introducing a second predictor variable:

> Treatment for depression improves sexual satisfaction more in women than men.

Two questions are now on the table, the effects of treatment and whether the treatment affects women more than men.[2]

[2] This second question is actually asking whether an interaction effect exists between the treatment and the sex of the recipient. Thus, there are actually three hypotheses being tested: (1) does the treatment have an effect on depression; (2) is one sex more depressed overall than the other; and (3) whether the effects of the treatment depend on the sex of the recipient.

Or multiple endpoints might be added by stating:

> Treatment for depression increases the likelihood of relationship engagement which in turn improves sexual satisfaction.

In this last statement, a *mediating variable*, relationship engagement, has been introduced to help explain the effects of the treatment on sexual satisfaction.

Although each of these statements seems simple enough, each calls for a different type of research design and, subsequently, statistical analysis.

2.3.1 The Problem of Defining Variables

Once one or more hypotheses have been formulated, these variables are defined procedurally with an *operational definition*. Although this is one of the most critical steps in the research preparation process, it is sometimes overlooked as a simple or self-evident process. Often the variables under scrutiny represent *constructs*—a phenomenon presumed to exist but which is not directly observable. Variables such as motivation, satisfaction, and arousal are examples of such constructs [30]. Therefore their assessment may require significant forethought, with no single measure being entirely adequate or accepted—in fact many different measurements may have been developed to assess the construct (think of the many ways to assess "motivation," a slippery and difficult construct to measure). Projects sometimes suffer because researchers choose measures that are not widely accepted or are even inappropriate for the constructs they are assessing. For example, if sexual satisfaction is being investigated, does a general question about the issue suffice or are multiple questions required? Should specific measures about sexual response be included (e.g., erection, lubrication, desire, orgasm)? Should assessments be taken during the non-depressed state and depressed state? And how might all these measures be interrelated? Are validated questionnaires available (see Chap. 4, Psychometry in Sexual Medicine), and if so, do these need to be modified or supplemented with questions that pertain more specifically to the research question at hand.

Often no single definition is completely satisfactory, so the key is to find previous research that relies on existing or standardized measures considered "passable" in the field. These measures can then be elaborated to address the specific goals of the study at hand. In using such a strategy, the researcher can cite successful studies using similar definitions, while simultaneously building the knowledge base of the field.

An adjunct strategy, becoming ever more common among researchers, is to take advantage of *focus groups* that serve as sounding boards for experimental procedures and assessment strategies [31]. Such groups, typically comprised of samples of about 10–30 individuals representative of the population of interest, can assist with such issues as item clarity and relevance, appropriate response categories, face validity of items, and perceived problems with measures (e.g., too invasive, too vague, too broad, etc.). For example, even when using standardized, validated instruments, we have found that potential participants are sometimes

confused by the wording of questions, leading us to tweak the wording or elaborate with more vernacular language.

2.3.2 Sensitivity and Specificity of the Outcome Variable

Sensitivity refers to the ability of the outcome measure to detect changes, a characteristic that partly depends on the *scale of measurement*. In some instances, the outcome measure need not be particularly sensitive or refined, and a simple "yes" or "no" categorization may suffice (referred to as a categorical or *nominal* variable). For example, did the patient recover sexual function? Is the woman with anorgasmia now able to reach orgasm? However, more often than not, "yes" or "no" outcomes represent endpoints along a continuum. For example, in answer to the question "did the patient recover sexual function?" the possible responses might be ordered from "no" to "mild improvement" to "great improvement" to "complete recovery." The categorical yes-no variable has now been transformed into an *ordinal* scale of improvement that yields substantially more sensitive information. While such rating scales may reflect global subjective judgments on the part of the patient or clinician, outcome measures may sometimes be more useful when based on objective criteria derived from continuously scaled *interval* or *ratio* measures. Using another sexual dysfunction, premature ejaculation, as an example, a subjective global judgment as to whether a treatment procedure is effective for delaying ejaculation in men with premature ejaculation may be supplemented with an actual measure of "seconds/minutes to ejaculation" following penetration. These interval or ratio measures can be very precise and yield numbers that have clearly defined relationships with one another. For example, the researcher can know precisely how an ejaculation latency of 20 s compares to one of 60 s. In contrast, the researcher cannot be so sure knowing how "great improvement" compares with "mild improvement," other than to state that the former represents the more desirable outcome [32, 33].

Increasing sensitivity by using a higher scale of measurement means the researcher will be less likely to err by missing an effect that really exists between the variables in the population (this type of error is discussed later in this chapter). Thus, one common strategy is to choose more sensitive measures (assuming they are available) over less sensitive ones. A measure that ends up being overly sensitive can be reduced to lesser sensitivity; the opposite does not hold.

Although interval/ratio measures often improve objectivity and sensitivity, they sometimes have the disadvantage of being too sensitive, introducing so much noise in the experiment as to make it difficult for the researcher to distinguish a true effect from background noise. Furthermore, a high level of sensitivity may be less relevant from a clinical standpoint. An improvement from 20 s to 60 s may represent a statistically significant delay in ejaculatory latency but conveys little information regarding alleviation from a functional impairment or the patient's satisfaction level. In contrast, a global judgment such as "near normal" ejaculatory latency may provide extremely useful clinical information. The challenge is one of using objective and sensitive outcome measures, yet identifying endpoints that are also

clinically relevant. A pertinent example can be seen in the research on "sexual satisfaction" in men using a pharmacological treatment for erectile failure. Improvement in erectile capacity (e.g., measured in terms of mm increase in penile circumference) imparts little benefit if sufficient rigidity is lacking to enable vaginal penetration. One approach to this dilemma is to collect as sensitive data as possible using interval- or ratio-scaled variables and then construct ordinal categories or dichotomous outcomes from them. For example, the researcher might decide that any increase in penile circumference greater than 20 mm is clinically significant, since most men can achieve penetration under such conditions. Alternatively, the researcher might incorporate additional endpoints in the project, for example, whether the man is able to achieve vaginal penetration (a reasonably objective "yes-no" dichotomy) and how satisfied the man is with his erectile capacity (an important subjective measure that can be ordinally scaled from "not at all" to "complete"). Ultimately, the issue needs to be resolved by the researchers themselves as they consider the goals of their project and the population they are targeting.

As pharmacologists and most healthcare professionals well know, some measures may be adequately sensitive yet lack *specificity*, the ability to differentiate those with one "disease" or condition from those with another, including those without the disease or condition [34]. A measure of "ejaculatory control" is fairly specific to issues of premature ejaculation (PE). In contrast, "sexual satisfaction" lacks specificity when used in conjunction with treatment of sexual conditions such as premature ejaculation, erectile dysfunction, or anorgasmia.[3] For example, sexual satisfaction may change as the result of any number of factors unrelated to the specific sexual problem, such as increased intimacy with the partner, less routinized sex, higher levels of sexual excitement, and so on. Yet, the original concern of not getting a full erection, ejaculating too early, or not being able to reach orgasm may not necessarily have been fully or even partially ameliorated. Nevertheless, global assessments having less specificity often play an important role in broad-based outcome evaluation and establishing clinical significance.

2.3.3 The Dilemma of Using Multiple Outcome Measures

In generating multiple measures for the outcome variable, it's less likely that an important outcome measure will be omitted; in addition, issues of objectivity, sensitivity, and clinical relevance may all be addressed.

Since most research constructs such a "sexual satisfaction" (or from other health fields, "mental health" or "cardiovascular health") represent constellations of behavioral or physiological responses, often their definition defies a simple single-measure outcome. Equally likely, there may be no single accepted definition for the construct. In such instances, the researcher may decide to develop an *index* or

[3] Correlations between sexual satisfaction and improvement in a specific parameter of sexual response (e.g., ejaculatory control in men with premature ejaculation) tend to be around 0.30–0.50 [35].

composite that represents several measures simultaneously. Such indices may be derived from a combination of variables of differing levels of measurement (nominal, ordinal, interval), but each usually must first be reduced to the scale of the least refined measure. Using the example of sexual satisfaction, a researcher might construct a summary index indicating overall amount of "improvement" based on three measures, with each being transformed to a simple dichotomous outcome such that "improvement" = 1 and "no improvement" = 0. These three measures might include (1) a 20 mm or greater increase in penile circumference, (2) ability to achieve vaginal penetration, and (3) patient's yes-no indication of at least partial satisfaction of erectile function. The outcome variable now incorporates three components related to the construct and can be represented by an ordered three-point scale ranging from 0 to 2.

Such indices can be highly useful to developing clinically relevant endpoints, but they come with important caveats and can involve a complex process [36]. The researcher usually must provide a priori rationales for cutoff points that transform the continuous or ordinal variables to simple dichotomous outcomes. Second, the individual measures should not be assessing essentially identical phenomena (this would inflate outcome differences among individuals), although each measure should be relevant to the overall endpoint. Finally, the researcher will have to decide whether to weight the measures equally or to assign greater weights to specific measures on the assumption that they contribute more to the definition of the construct. These procedures are sometimes risky for new researchers entering the field, as such cutoffs and weighting often generate significant controversy and may easily become a target of criticism by reviewers (see [37]).

Thus, an important first best practice is to understand and clearly define the variables in the research question.

2.4 The General Paradigm of the Experimental Approach

In general, the outcome variable (e.g., sexual satisfaction) in a clinical research study related to sexual dysfunction depends upon one or more independent or predictor variables of interest and a host of extraneous variables, which may not be of initial interest but which potentially influence the outcome variable. The goal of the research study is to test the hypothesis by investigating the effect (or relationship) of the predictor or independent variable(s) on the outcome variable, controlling for the effects of extraneous variables. For example, in a study of the effects of depression treatment on sexual satisfaction, variables that measure baseline health status, demographic characteristics, and lifestyle factors would be considered extraneous variables.

Experimental data used in clinical research are typically generated by a randomized controlled study. In the ideal study, subjects are randomly assigned to treatment and control groups, with neither subject nor researcher aware of group membership. Random assignment ensures that groups are similar in terms of extraneous variables, with any difference attributable to chance. Therefore, control of extraneous

variables is achieved largely through randomization so that any statistically significant difference in the outcome variables between groups provides evidence that the independent variable caused the change in the outcome variable. Such designs are considered the gold standard in research because they allow causal inference between independent and dependent variables [33, 38, 39].

Box 2.2 Nomenclature of Variables

One of the challenges of research methodologies is that different fields and disciplines sometimes use different terminologies for the same idea. When referring to variables in studies using a correlational method, the variable of interest is typically called the outcome variable, and the variables used to account for variation in the outcome are called predictor variables or covariates. In studies using an experimental approach where participants are sampled in a methodical manner (e.g., randomization, stratification, etc.), the outcome variable is usually called the dependent variable, and the predictor variable is the independent variable. Of course, for every generalization, exceptions abound.

Correlational/observational data, on the other hand, are generated by a natural process rather than by random assignment. In such situations, the outcome variable is measured for groups of *nonrandomly* allocated subjects. For example, assume that the researcher does not randomly assign individuals to either a treatment group or nontreatment group, but rather simply identifies individuals falling into these two categories and then measures their sexual satisfaction. Because data on "sexual satisfaction" are not generated by a randomized process, the independent/predictor variable(s) of interest (treatment or not) is likely to be correlated with one or more extraneous variables. Specifically, individuals receiving treatment may also be more motivated to resolve their problem, may more likely be in a relationship where they have partner support, or may have more debilitating episodes of depression. Therefore, any observed difference in "sexual satisfaction" between subjects treated and not treated for depression may result from one or more of these uncontrolled extraneous factors [32, 33].

Such problems typically occur when predictor variables are *subject* variables, that is, variables that represent physical, psychological, or sociocultural characteristics inherent to the individuals in the study. Such variables—age, sex, depression, motivation, intelligence, and so on—are often used as grouping variables and therefore appear to simulate an experimental design (and thus are called *quasi-experimental* designs). But they are not true independent variables (as would be a condition imposed on the participants such as a particular treatment), as the critical process of random assignment is lacking. Because selecting and grouping individuals on the basis of sex, education level, being depressed, or other subject characteristics also selects for any number of unknown covariates, such designs do not allow for a straightforward causal inference between predictor and outcome variables and

may require the use of relatively sophisticated statistical procedures to control for extraneous variables and other problems that arise when data are not generated through a randomized process [39–41].

In summary, an important second best practice is knowing the nature of the study, whether experimental, quasi-experimental, or correlational.

2.5 The Logic Behind Hypothesis Testing: A Brief Recap

Hypothesis testing is *the essential power tool* of the empirical researcher, and understanding this power and its limitations is critical for anyone addressing research questions related to sexual response.

2.5.1 Testing the Null Hypothesis

Underlying every research question or hypothesis suggesting a relationship between two or more variables is a statement of the opposite (usually negated) condition or outcome. This statement, the *null hypothesis*, actually states that any change or variation in the outcome variable is the result of chance (as opposed to the predictor or independent variable). The null hypothesis serves an important function in that it is the *only* hypothesis in the study that can be tested directly.

Why? Because every outcome measure (e.g., sexual satisfaction) shows random variation, both among individuals and within individuals over time (called measurement error). The goal of most research is to show that variation in the outcome variable is related to variation in predictor or independent variables. But variation in the outcome variable can never exclusively be attributed to the predictor variable (as the research hypothesis states) since some of this variation results from random fluctuation. For example, variation or change in sexual satisfaction among participants results from:

1. Random variation (from sampling or measurement error)
2. Possibly, the independent variable, treatment of depression

The problem lies in the fact that the researcher never knows how much of the variation can be attributed to random fluctuation (some of it? all of it?) and how much to the predictor variable, thus meaning that the research hypothesis is untestable using conventional research tools.

So scientific methodology requires testing the null hypothesis—this hypothesis states that any changes in the outcome variable are the result of chance and therefore by implication *not* related to the predictor or independent variable. Inferential statistical tests, the kind used in most analyses and which lead to conclusions of "significance," allow the researcher to determine the probability that changes in the outcome variable occurred mainly from chance or random variation. If it is *not* likely that they occurred mainly by chance (usually considered 1 out of 20 times or less—or

≤0.05), then the researcher invokes another variable, namely, the predictor variable, to explain variation in the outcome variable. In research lingo, the researcher rejects the null hypothesis and, in doing so, accepts the alternative research hypothesis, which states that variation in the outcome is related to the predictor variable.

Thus, researchers either accept the null hypothesis or they reject it. In doing the latter, they turn to the research hypothesis as the next best explanation available. That is, if we believe (from statistical evidence) that the changes in the outcome are due to *more* than random fluctuation, then we're willing to attribute those changes to the independent or predictor variable. But, no *direct* evidence based on the scientific method exists to "prove" that the predictor or independent variable is affecting the outcome variable. The relevance of this point becomes apparent in the next section.

2.6 Design Flaws and Errors

Understanding the above process is critical to avoiding flaws in research design and minimizing errors in accepting the wrong hypothesis, each discussed briefly below.

2.6.1 Confounding Factors

One sometimes hears that a project has a "fatal flaw." Such flaws, which can lead to erroneous conclusions, sometimes refer to the fact that variables other than the predictor variable (known as *extraneous* variables) are likely to change along with predictor or independent variables in the study. Therefore, to conclude that variation in the outcome measure is due exclusively or even predominantly to the independent or predictor variable cannot be justified. For example, sexual satisfaction is known to be related to aging,[4] so unless age is controlled in such studies through randomized assignment, it may not be possible to make conclusions about a particular treatment on sexual satisfaction. A particularly vexing problem within sex studies is that the very nature of the study increases participants' awareness of and attention to their sexuality; that is, mere participation may increase the participant's sexual interest and/or discussions about sexual intimacy with his/her partner during the course of the study. When such extraneous variables are allowed to vary along with the independent variable, *confounding* occurs, a situation where changes in the outcome variable cannot be attributed exclusively to variation in the predictor variables because other variables are changing simultaneously [38]. Confounding greatly

[4] In some instances, sexual satisfaction increases with age, for example, as young women progress from their early 20s to their 30s, they tend to become more orgasmic, and their sexual satisfaction tends to increase. However, beyond the age of about 50, sexual satisfaction shows variability, presumably increasing in women but slightly decreasing in men, this latter finding probably the result of aging effects on general health as well as the physiological systems underlying sexual response [42–44].

weakens the researcher's capacity to draw conclusions of any strength and often leaves the researcher in the position of having to acknowledge a flaw that may render the findings inconclusive.

To avoid such problems, an important third best practice is to identify beforehand possible extraneous variables that might confound the study.

Avoiding confounding requires a review of similar studies on the topic as well as assuming a devil's advocate role regarding the tenability of any presumed (desired) relationship between predictor and outcome variables. For example, consider the fact that relationship quality might change as a function of participation in a sex study; that is, participation might increase sexual and thus emotional intimacy with the partner and therefore might represent a possible confounding variable. This extraneous variable may be handled in a variety of ways. It might be held constant by the researcher, although in this case, this strategy might be difficult to implement; for example, the researcher might measure baseline frequency of sexual interaction and attempt to limit sexual behavior during treatment to baseline frequency. It might be controlled through a process of randomization in treatment groups (for some, relationship quality might improve, for others remain the same, and for others actually get worse). It might be controlled through the sampling process (e.g., in a study on sexual satisfaction, limiting the sample only to participants who are in long-term, committed, high-quality relationships). Or it might simply be measured as part of the study so that any potential effect can be statistically controlled in the data analysis—clearly the most expedient option for this variable. Of course, each strategy has its own set of benefits and limitations.

Nevertheless, the "cost" of any of the procedures above for handling extraneous variables far outweighs the problems encountered when possible confounding variables have not been identified and adequately taken into account.

2.6.2 Making Errors by Accepting the Wrong Hypothesis

The researcher never actually knows which hypothesis—the research or null—represents the true state of affairs in the population. Research conclusions are based upon the *likelihood* of one of the hypotheses being true. As such, any research conclusion is subject to error, so understanding and minimizing these errors is important [32, 33, 45].

The researcher may reject the null hypothesis when it is true. This error, known as Type I, means that the researcher has erroneously attributed variation in the outcome variable to the predictor variable, when in fact the variation resulted simply from random fluctuation. This error might be viewed as "overestimating" of the effect of the predictor/independent variable, for example, concluding that sexual satisfaction improved from the treatment of depression when in fact the improvement was a chance outcome. The probability of a Type I error, known as *alpha* (α), is easily quantified, as it is equal to the significance level selected by the researcher. Scientific convention generally sets this probability at 0.05, or 1 out 20, meaning that if the outcome occurs 1 out of 20 times or less by chance alone ($p \leq 0.05$), then

the researcher attributes the variation to the independent variable, in this case the treatment of depression. The alpha level is also known as the "significance level," the criterion that must be met or exceeded to conclude a significant relationship between two or more variables.

How is it that the significance level represents the probability of a Type I error? Consider the following:

1. Whenever variation in the outcome occurs 1 out of 20 times or less ($p \leq 0.05$) from random fluctuation, the researcher rejects the null hypothesis and attributes the variation to the predictor variable.
2. But this amount of variation in the outcome variable can occur simply by chance (i.e., 1 out of 20 times or less) regardless of whether the independent variable was affecting the outcome variable.
3. Yet, because each and every time the outcome occurs 1 out of 20 times or less by chance the researcher attributes the variation to the predictor variable, on average the researcher errs 1 out of 20 times in his/her conclusion.

Although researchers can state precisely the probability of making a Type I error, unfortunately they never know in which specific situation or study they might have made that error.

An expedient way to decrease the probability of a Type I error is to change the significance level to something more stringent, say, 0.01 or 0.001. But this cannot be done without the consequence of increasing the likelihood of making a second type of error.

This second type of error, appropriately called Type II, occurs when the researcher accepts the null hypothesis when it is false, thereby rejecting the "true" research hypothesis, for example, attributing changes in sexual satisfaction to chance when in fact the treatment was exerting an effect. This kind of error, perhaps akin to "underestimating" the effect of the predictor/independent variable, is not as easy to quantify, as its probability, known as *beta* (β), is affected by a number of factors. In general, however, beta is related to how much "noise" (unexplained or random variation known as *error*[5]) exists in the data and, more specifically, the ratio of:

$$\frac{\text{Predictor / independent variable effect}\left(\text{explained variation}\right)}{\text{Noise}\left(\text{unexplained variation or error}\right).}$$

By examining the ratio above, it is apparent that the probability of a Type II error can be decreased by reducing noise or unexplained variation (the denominator), by increasing the effect or variation in the predictor or independent variable (the numerator), or by doing both. Stated simply, the stronger the predictor variable effect stands out against the background noise, the more likely the researcher will detect the effect and the lower the beta.

[5] Do not confuse Type I and Type II errors with statistical error which represents an estimate of sampling or measurement error (random variation) within the study.

2.6.3 The Limits of Hypothesis Testing

Hypothesis testing never reveals which of the hypotheses—research or null—is true, but only which of the two is probably true. Because conclusions in science reflect probabilistic outcomes, the term "proof" is generally reserved for mathematical, not scientific, conclusions. Specifically, research is aimed at generating support (rather than proof) for hypotheses, and because of the nature of hypothesis testing, a lack of support for the research hypothesis *does not refute* or *provide evidence against* the hypothesis. This, of course, explains the bias in the literature toward reporting significant outcomes rather than nonsignificant ones. It is far more difficult to conclude that certain factors are *not* related to the outcome variable than to identify factors that are related to it. In accepting the null hypothesis, the researcher merely attributes variation in the outcome variable to chance—indicating that he/she is unable to detect any effect. But there is no indication as to whether this conclusion might have resulted from a poorly designed study that failed to account for or control the level of random variation (noise) in the study. Only when the researcher provides strong evidence that conditions for detecting an effect were optimal (meaning a high level of "power" within the study) will a statement regarding a lack of relationship between two variables be given any credibility [32].

The above probability for making errors, coupled with the fact that researchers can never fully assume that variation in the outcome variable is attributable to only the predictor variables measured in his/her study (vs those that are not measured or controlled), means some degree of uncertainty regarding a research conclusion always exists. Researchers are generally aware of this limitation, qualifying their findings with the well-worn cliché that "more research is needed." Indeed, the post-positivist approach recognizes the critical need for multiple studies from independent groups in the process of theory development and hypothesis testing.

2.7 Minimizing Errors Regarding Hypotheses

An important fourth best practice is controlling and/or minimizing Type I and Type II errors.

Controlling and/or measuring extraneous variables does more than merely protect against confounding within the study. Controlling extraneous variables experimentally or sampling specific subpopulations can reduce the amount of unexplained variance in the study (the term in the denominator); and measuring an extraneous variable enables the researcher to move variance from the denominator (unexplained) to the numerator (explained). In the words of Cohen [46], "anything that reduces the variability of observations by the exclusion of sources of variability serves to increase power." And as discussed below, power is one way of ensuring a low level of beta within the study. Thus, the most valuable studies minimize levels of both alpha and beta.

2.7.1 Lowering Type I Error Rates by Increasing the Significance Level

Alpha, or the probability of a Type I error, is usually set at 0.05 or 5%. As mentioned earlier, alpha can be reduced by using a more stringent significance level such as 0.01 or 0.001. Although it makes sense to *report* statistical outcomes that reach significance at the 0.01 or 0.001 level, as this indicates a low alpha within the study, there is a consequence to actually moving the threshold criterion from 0.05 to 0.01. Doing so makes it five times more difficult to reject the null hypothesis or, conversely, to accept the research hypothesis and thus declare an outcome as significant. Assuming for the moment that the research hypothesis is actually true, that is, the phenomenon truly exists in the population, changing alpha to 0.01 makes it all the more difficult to accept it as true. Thus, the probability that the researcher might ignore a real effect of the predictor or independent variable (or make a Type II error) increases fivefold.

2.7.2 Keeping Type II Error Rates Low: The Concept of Power

Ensuring sufficient power within the study is critically important to maximizing the conditions for hypothesis testing. Power refers to the probability of rejecting the null hypothesis and ultimately concluding that a relationship between predictor and outcome variables exists in the population (is significant).

Power is defined as 1-β, indicating that as beta decreases, power increases. Although, as with alpha, there is no specific level of beta required in a study, Cohen [46] suggests 0.20 as a reasonable target, resulting in a power value of 0.80 ($1 - \beta$). Using $\beta = 0.20$ and $\alpha = 0.05$, one can see that the error rate for making a Type II error (over-interpreting the data) is four times that of making a Type I error (under-interpreting the data). So in a well-designed study, typically there is a 4-to-1 bias toward making a Type II error over a Type I error, i.e., accepting the null hypothesis over the research hypothesis.

How does the researcher achieve power of 0.80 (or beta = 0.20)? Within a research study, power is related to a multitude of factors, some of which have already been mentioned. These factors are invariably related to the relative amounts of explained and unexplained variance in the study, as well as to the assumptions that can be made about the distribution of those variances. Specifically, in the ratio of explained to unexplained variance noted previously, the higher the explained variance and the lower the unexplained variance, the higher the power. Procedures already discussed that affect power include:

- The level of measurement of the outcome variable, with higher levels (e.g., ratio data) typically providing greater sensitivity and more predictable structure within the data. Not surprisingly, statistical procedures that can assume such predictable structures can increase power.
- Use of control procedures and sampling techniques that reduce unexplained variance (measurement or sampling error).

Box 2.3 Making Errors About Errors

At times I have had a reviewer criticize an experiment, indicating that power was too low due to a small sample size (Box 2.4). However, power is related to the probability of making a Type II error (β), and if the results reach significance (e.g., due to a large effect), power is not an issue. Specifically, if the researcher rejects the null hypothesis and accepts the research hypothesis, the probability of making a Type II error is zero. That is, if the research hypothesis is in fact true (a situation unbeknownst to the researcher), there is no possibility of making an error if the research hypothesis is accepted. In a similar vein, if the null hypothesis is true and the researcher accepts the null hypothesis, the probability of making a Type I error (α) is zero.

2.7.3 Power as a Function of Sample Reliability and Effect Size

Two factors (beyond those mentioned above) that affect the ratio of explained to unexplained variance, and thus beta, are the *reliability of the sample* and the *effect size* of the predictor or independent variable. Sample reliability helps keep unexplained or random variance low within the study, while effect size helps increase explained variance.

Sample reliability refers to the degree to which the sample approximates the population, and this parameter can be statistically represented by the standard error of the mean. The standard error provides an estimate of the precision of the sample, and its value is always dependent on the size of the sample.[6] Specifically, as sample size increases, the smaller the standard error, and consequently, the greater the reliability or precision of the sample due to a reduction in measurement error (unexplained variation). Thus, a direct and positive relationship exists between sample size and power [46].

Effect size refers to the degree to which the independent or predictor variable is actually related to the outcome variable in the population. If the effect size is zero, indicating no relationship between predictor and outcome variables, then the null hypothesis is true. If the effect size is greater than zero, then technically the research hypothesis is true. Of course, the research hypothesis will be accepted by the researcher as being true only when the effect size (explained variance) stands out clearly against the background of noise (unexplained variance). As a result, the greater the effect size, the greater the explained variance relative to the unexplained variance, and the more likely the researcher will be able to detect the effect and thus accept the research hypothesis.

[6] The standard error is used to establish confidence intervals around the sample mean. In doing so, the researcher can determine a 95 or 99% confidence interval, that is, the researcher can be 95% or 99% confident that the population mean lies within the interval surrounding the sample mean.

Box 2.4 How Large Does the Sample Need to Be?

The issue of sample size is pertinent to the clinical researcher because access to patients or other participants may be *the* limiting factor of the study. How large does a sample need to be in order to achieve a power level of 0.80? This depends on the anticipated effect size of the predictor variable (explained variation), as well as other factors that may reduce unexplained variation. Consider an illustration based on Cohen's [46] power tables. Assuming a fairly strong effect size for the predictor variable, as might occur in a pharmacological study that investigates a physiological or behavioral outcome, the study would require about 20–25 participants per group (or condition) to maintain a power level of 0.70–0.80. In contrast, a researcher anticipating only a moderate effect, as might occur when a drug can be tested only at a low dose because of its adverse effects or when the study incorporates more "social" or "more subjective" variables, must consider a sample size 60–70 participants. And an anticipated weak effect may require over 100 participants. The differences between 25, 65, and 100 participants can be costly, both economically and in terms of the researcher's time. These examples indicate that in order to achieve a power level 0.80, there is a trade-off between sample size and effect size. As sample size gets larger, the effect size required for achieving a power level of 0.80 gets smaller and vice versa.

Conceptually, effect sizes range from small to large, with its statistical representation depending on the type of research design and analysis being employed. A large effect might be viewed as a difference of 0.80–1.00 standard deviation between groups or conditions, by an r-value from a correlational study of 0.50 or by an R^2 value in a multiple regression study of 0.25 (see Table 2.1). Whatever the case, understanding and anticipating an effect size for one's predictor variables is useful in determining the practicality of designing and carrying out a study. For example, if the researcher knows that the effect is likely to be small, she/he will either have to expect to use a large sample or look for other ways to reduce unexplained variance through control procedures, sampling techniques, and so on. Unfortunately, in much exploratory research, effect sizes are difficult to anticipate.

Table 2.1 Some examples of effect size[a]

	t-test (*d*)[b]	ANOVA (*f*)[c]	Pearson (*r*)	Regression (R^2)
Small	0.20	0.10	0.10	0.02
Medium	0.50	0.25	0.30	0.13
Large	0.80	0.40	0.50	0.26

[a]Based on Cohen [46]

[b]*d* is defined as the difference of the means divided by the population standard deviation or, alternatively, the *z* score difference between the means

[c]*f* is defined as the standard deviation of the means divided by the population standard deviation

2.8 Complex vs Simple Research Designs

In their enthusiasm to answer too many questions at once, novice researchers often design studies that are overly complex. Even initially very simple projects may quickly become complex for reasons beyond the investigator's immediate control, such as attempting to control for extraneous variables.

2.8.1 Reasons to Keep the Design Simple

Simple research designs having only a few outcome and predictor variables have several advantages.

- The more variables under investigation, the more complex the design must become in order to handle additional questions and to control extraneous variation (e.g., from order effects: does drug before placebo have the same effect as placebo before drug?).
- Given the same effect size, the number of participants required for simple designs is fewer—each added variable will necessitate an increase in the sample size in order to maintain a constant power level. For example, in statistical analyses of experimental or quasi-experimental designs that compare across cells, each new independent variable may cut the cell size in half. Thus, including sex of the participant as part of the hypothesis and thus comparing men's and women's sexual satisfaction following treatment of depression necessitates additional cells. In multiple regression analysis, an increase of 5–10 participants may be necessary with each added covariate, even when the variable is included simply as an attempt to control an extraneous variable.
- Related to the preceding point, a study with only one predictor variable tests for a single main effect, whereas one with three predictor variables will test for three main effects but may also test for four potential interaction effects among the predictor variables. Each new effect, whether main or interaction, consumes a "degree of freedom" in the numerator in the analysis, thereby making it more difficult to achieve a significant effect for any one variable.
- Simple designs often enable the researcher to draw conclusions with fewer qualifications.

2.8.2 Why Study Designs Become Complex

The advantages of simple designs must be balanced with the potential need for (and benefit of) more complex designs [32, 33]. As mentioned earlier, in the process of designing a study, potential confounding variables may require statistical control. For example, in the sexual satisfaction study, patients may be drawn from four to five different clinics, meaning the clinic site may contribute extraneous variation (measurement error) and thus must be treated as a "nested" variable in the

analysis. And other factors relevant to the outcome variable may need to be assessed: sexual satisfaction at pretesting, age of the participant, family history of depression, doses and types of antidepressant medication, and so on. By collecting information on each of these, the researcher may be able to move variance from the unexplained to the explained variance category. In doing so, however, each new variable adds to the complexity of the study design and to all the disadvantages inherent to those designs.

A second benefit of complexity is that it allows the researcher to investigate clusters of predictor variables both in relation to the outcome variable, as well as to one another. Such designs are often better at simulating real-life situations and permit the researcher to estimate the relative effect of each variable on the outcome in the context of other potentially relevant variables. For example, the researcher could assess the relative effects of various treatment types for depression on sexual satisfaction (e.g., medication, mindfulness, counseling, etc.), determining which might be more salient. Or she/he could include the sex of the participant as an interaction term in the statistical analysis to assess whether this variable has differential effects on sexual satisfaction. In sum, complex designs enable the researcher to answer a basic research question regarding sexual satisfaction in sophisticated and detailed ways that simple designs do not. On the downside, the write-up of such studies may become so involved and complex that the author is unable to present the study as a relatively straightforward and simple narrative.

A common procedure designed to test a research protocol and the feasibility of a particular research design is to run a pilot study. Pilot studies are typically simple in design and allow the researcher not only to test the protocol but also to get a handle on the effect size of the predictor variables. If after running a handful of subjects, the relationship between the predictor variable and outcome variable begins to emerge, the researcher might assume a moderate effect size and proceed with a more adequate and complex test of the hypothesis.

To estimate effect size and ensure feasibility of a study protocol, a fifth best practice involves running a pilot study before investing significant resources in a project.

2.9 Choosing Statistical Analyses

The heart of clinical research requires drawing conclusions about a population of subjects from evidence provided by a sample (subset) of those subjects. In brief, the research process involves stating the hypothesis that specifies the relationship between two or more well-defined variables, generating a sample of data, and selecting appropriate statistical procedures for drawing conclusions from the data. The conclusions rely heavily on the statistical tools of hypothesis testing and estimation. While the basic logic of hypothesis testing and estimation explained above is the same for any clinical research study, a wide variety of statistical techniques are used to implement this logic, depending upon the nature of the research questions addressed and the type of data used.

In the broadest terms, statistics can be used to:

- Describe the characteristics of the sample(s).
- Estimate population parameters from the sample (e.g., using the standard error of the mean).
- Determine degree and direction of relatedness between two or more variables using measures such as correlation or regression (these procedures often produce an estimate of effect size).
- Test and decide whether to accept or reject the null hypothesis.

Some or all of the above uses of statistics may come into play in any given project. The latter two rely on the concepts of explained and unexplained variances and typically involve some sort of hypothesis testing at some point in the process. But the goals of the study, the nature of the data, the process by which the data were generated, and the presumed nature of the relationship between the variables are all important factors in determining the best statistical procedures to be employed.

2.9.1 Knowing Enough About Statistics and Your Data to Avoid Pitfalls

A wide variety of statistical analyses are used in clinical research, some of which are quite sophisticated. In choosing the appropriate statistical analysis and interpreting the results, a clinical researcher may not be fully aware of the range of available statistical techniques and procedures. What is important is that the researcher has a thorough understanding of the data, how they were generated, a working knowledge of statistical reasoning, a familiarity with the more commonly used statistical procedures, the ability to recognize potential pitfalls, and, when necessary, a willingness to consult with or include a statistician in the study.

2.9.1.1 Know the Process that Generated the Data

The appropriate analytical methods to use and the interpretation of the statistical analysis depend in large part on how the research data are generated [33]. As discussed earlier, the two major types of data used in clinical research studies are *experimental* data and *correlational/observational* data. Case studies and single-subject designs, used sometimes in pilot research or situations where participants have unusual characteristics or where settings are rare, provide another strategy for clinical research. However, because they are less commonly used in major clinical studies, they are not included here.

When the researcher generates experimental data through a randomized process, choosing the appropriate statistical methods for hypothesis testing and interpreting the results is usually straightforward. Typically, it involves demonstrating differences among treatment groups or treatment conditions (explained variance) that stand out against an estimate of unexplained variance (e.g., the random variance occurring within the groups). To make these comparisons, the researcher should

have a working familiarity with simpler statistical procedures like the *t-test*, *chi-square test*, and *analysis of variance*. In some instances, these procedures allow for the inclusion of extraneous variables as controlled covariates. Statistically significant outcomes are usually given a causal interpretation—over the past decade, such "inferential" statistics have been increasingly supplemented with confidence intervals and measures of effect size between independent and outcome variables [38, 39]. Quasi-experimental designs (i.e., forming groups on the basis of subject variables) are often analyzed using the same statistical procedures used for experimental designs, but because the data are not generated through a randomized process, causal interpretation is limited.

Box 2.5 The Same Question but Answered Using Different Designs

Let's say we are interested in the question posed at the beginning of this chapter, "Does treatment for depression improve sexual satisfaction?" This and other such questions may often be addressed with *either* an experimental design or a quasi-experimental/correlational design. For example, if the researcher were able to identify 40 willing participants suffering from depression, she/he might randomly assign them to treatment vs nontreatment groups and then determine the effects on sexual satisfaction. This method represents a true experimental design that would support a fairly strong causal interpretation. But it would probably be a challenge for the researcher to find such willing participants (i.e., individuals suffering from depression but not undergoing some sort of treatment). On the other hand, a more expedient approach might be to identify a number of individuals already under treatment for depression and compare their sexual satisfaction with depressed individuals who are not currently undergoing treatment. This design does not incorporate random assignment to groups, so it would be considered a quasi-experimental or correlational design. Although undoubtedly easier to carry out, the researcher would be limited in the causal inferences he/she could draw.

Correlational data involving several variables are most often analyzed by a multivariate statistical procedure called regression, which statistically controls extraneous variables so that the separate effect of each predictor and/or covariate can be estimated and tested [38, 39]. Regression (or correlation) models vary but have a common structure, generally producing statistics that provide measures of relatedness or association (e.g., an r-value, R^2 value, odds ratio, etc.). The *linear regression* model assumes the outcome variable (typically at least ordinal but better if interval or ratio scaled) is a linear function of a set of predictor variables, which include both the variable(s) of interest and measurable extraneous variables (together providing measures of explained variance) and an assumed random error term that represents the net effect of omitted factors (unexplained variance). The coefficient attached to a predictor variable measures the effect of that variable on the outcome variable, while statistically controlling for the effects of all other covariates. Hypothesis

testing can then be applied to these coefficients to determine if the predictor variable of interest has a significant effect on (or relationship to) the outcome variable. The results are used to make predictions; and sometimes a causal interpretation is implicated, although evidence of causation is compromised by the ever present possibility that strong association between the outcome variable and the predictor variable might be attributable to one or more important extraneous variables that either could not be measured or were inadvertently omitted from the analysis and therefore were not statistically controlled. Nonetheless, regression analysis and its more sophisticated elaborations (e.g., structural equation modeling [40]) provide powerful statistical tools which when carefully applied can come close to simulating a randomized experiment. When working with nonexperimental data, the researcher should be acquainted with regression analysis.

2.9.1.2 Know Your Data by Generating Descriptive Statistics

Regardless of the design or type of study, before beginning an involved statistical analysis, it's worthwhile to generate basic descriptive statistics on all measures of interest [47]. This may include frequency distributions and measures of centrality (e.g., mean or median) and dispersion (e.g., range or standard deviation) for predictor and outcome variables, both overall and for subsets of groups or conditions. A careful review of these values can provide the researcher with a sense of whether problems might exist in the data set (e.g., missing data), whether overall expected patterns are evident (e.g., skew in the distribution of the variables), whether extraneous variables appear to be playing a role, and which, if any, relationships show promise for careful exploration and hypothesis confirmation.

2.9.1.3 Know About Other Factors Affecting the Choice of Statistical Analyses

Whether data are experimental or correlational, the specific choice of statistical tests is further driven by several other considerations. In experimental studies, for example, tests for differences among treatment groups are dictated partly by the scale of measurement of the outcome variable. Categorical data (and frequencies) may call for a chi-square test, ordinal data for a Mann-Whitney, and interval or higher data for a t-test or analysis of variance. All three tests generate statistics that enable evaluation of the null hypothesis. In correlational studies, logistic regression assumes a categorical outcome (e.g., did the women become orgasmic?) and generates an odds ratio, a measure of association that indicates the likelihood of one outcome (e.g., yes) to another (e.g., no). In contrast, linear regression generally assumes interval- or ratio-scaled outcome variable (e.g., by how much did the women's difficulty reaching orgasm decrease?) and generates an R^2 value, an overall measure of the proportion of variance in the outcome variable that can be explained by all the predictor variables together. Both statistics can be tested for their significance to determine whether the effect should be considered more than a chance event that can then be generalized to the population (i.e., a significant outcome).

Other factors also affect the specific choice of statistical test. For example, the distribution of the outcome variable may be bimodal or truncated at one tail or

assume other non-normal shapes. The variance across groups or conditions may not be homogenous, or the variance may change as values of the variable reach certain levels. The relationship between variables may be nonlinear or even parabolic. Or the outcome measure may occur partly as a function of time (e.g., compliance with treatment over extended periods of time). Statistical procedures have been devised for these and just about every other imaginable situation. Because many such procedures are beyond the understanding of most clinical researchers, the inclusion (or at least consultation) of a statistician may be an important consideration in project planning.

An important sixth best practice involves understanding and choosing appropriate statistical procedures: indeed, the kinds of statistical analyses should be anticipated prior to the outset of the study.

2.9.2 Understanding Bias

No matter how elegant the statistical analysis, no procedure is able to recognize potential sources of bias or *systematic* error. Hypothesis testing and estimation can deal only with situations in which sampling error is *random*. As such, bias of any type can invalidate hypothesis tests, lead to incorrect construction of confidence intervals, and thus threaten the validity of conclusions drawn from the data. Bias can arise from the research design, data generation process, or inappropriate statistical analysis. It is critically important that researchers recognize signs of possible bias.

Bias in experimental studies arises from factors that adversely affect randomization and measurement error. Examples include subjects who refuse to participate if assigned to a particular treatment, drop out of the study, or do not comply with the treatment regimen. In these cases, measured differences in outcomes between treatment and control groups may result from systematic factors (and thus variance) related to subject choice or errors in measurement, rather than the treatment itself. Important potential sources of bias in correlational/observational studies are measurement error, self-selection, and bias resulting from omitting relevant variables. For example, in a quasi-experimental/correlational study of the effects of treatment on sexual satisfaction, the researcher must identify, measure, and include in the analysis all important factors related to treatment that could influence sexual satisfaction. As an example, since relationship and partner factors play an important role in sexual expression and satisfaction, the effects of treatment are most likely not determined independently of factors affecting the relationship. Failure to account for any important extraneous factors, observable or unobservable, can result in a biased estimate of the effect of treatment and invalidate hypothesis tests.

Before carrying out the project, the researcher should be fairly confident that conditions that could produce bias in the data can be addressed. For example, in studies dealing with sexuality, self-selection is often a major concern. If the source of the bias is unavoidable, the problem can sometimes be mitigated using appropriate statistical techniques. Examples of such techniques include self-selection corrected regression models, fixed effects regression models, and instrumental variables

estimation procedures. Since these analyses tend to be more difficult to implement and interpret, consultation of a statistician may be required.

A seventh best practice is to understand, identify, and minimize sources of bias or systematic error.

2.10 Interpreting Data and Drawing Conclusions

Drawing conclusions from statistical outcomes is often, though not always, a straightforward (not necessarily simple) process. As statistical analyses become more complex, researchers may need the assistance of a statistician not only to understand the output but also to verify that the conclusions follow from the statistical results. Assuming they do, the researcher can recognize the value of the study's conclusions while not overstating them—they are, of course, only probabilistic outcomes subject to error. At the same time, the researcher acknowledges the limitations of the study and, in particular, exercises caution and qualification regarding statements of causality if the study is quasi-experimental, correlational, or observational in nature.

2.10.1 Clinical Versus Statistical Significance Revisited

As mentioned earlier, a major pitfall related to interpretation of statistical analysis is the failure to distinguish between statistical significance and clinical significance or practical importance [32]. Hypothesis testing leads to the conclusion of a statistically significant or nonsignificant effect of an independent variable on an outcome variable in the population of interest. Statistical significance indicates how likely it is that an observed effect might arise from chance variation and therefore provides information about the *strength of evidence* for the existence of an effect. It provides no guidance about what magnitude of the effect is *clinically* significant—for example, the finding that treatment of depression has a statistically significant effect on sexual satisfaction may be of little practical importance if the size of the effect is a mere 10% improvement.

As noted in the discussion on power, statistical significance depends strongly on sample size. If the sample size is sufficiently large, a statistically significant effect may result even when the magnitude of the effect is too small to be important. Such outcomes are becoming increasingly common as Internet studies capable of recruiting large sample sizes yield significant effects even though effect sizes are very small.[7] Alternatively, a clinical study may produce an effect large enough to be clinically important (e.g., a return to sexual engagement in 40% of the participants), but which is not statistically significant because of the relatively small sample used in the study. The researcher must be sure not to confuse the size of a test statistic (e.g., t-statistic, F-statistic) and its probability, which are directly related to the strength of evidence for an effect, with the size of the effect itself.

[7] Ironically, when sample sizes are very large, some might view power as being too great, that is, capable of detecting even the smallest of effects which may be clinically negligible.

Box 2.6 The Meaning (and Often Misinterpretation) of a "Highly Significant Effect"

Sometimes authors report correlations or differences among groups as being "highly significant." It is important to understand what a significant effect allows the researcher to conclude. A significant effect at the 0.05 level indicates that the evidence is sufficiently strong and reliable to conclude that a relationship exists between two or more variables—but it says nothing about effect size. If the significant effect is at the 0.001 level, this indicates that the *evidence* for the relationship is yet stronger, not necessarily the effect size. Furthermore, as the criterion moves from 0.05 to 0.001, this does *not* necessarily indicate that the effect size is getting stronger (remember, sample size may be getting larger). As an example, with large sample sizes, a researcher may find that an r-value (correlation) of 0.15 is significant at the 0.001 level, mistakenly interpreting this as a strong effect. In fact, an r-value of this magnitude indicates only 2.25% covariance (or explained variance, i.e., the r^2 value) between the two variables, meaning that 97.75% of the variance in the outcome variable remains unexplained! Thus even a "highly significant" correlation could be fairly meaningless because, although the difference is highly reliable, the effect size is yet negligible.

An eighth best practice is to demonstrate the clinical salience of the findings.

2.10.2 The Convention of Using 0.05

In hypothesis testing, convention dictates that outcomes greater than 0.05 lead to acceptance of the null hypothesis. However, a good researcher will not ignore probabilities falling between 0.05 and about 0.10. While researchers should adhere to the 0.05 criterion, there is no need to be rigid about it. One of the problems of rigidly implemented hypothesis testing is that it makes no differentiation between an outcome that is, say, 0.06 and one that is 0.35—both lead to acceptance of the null hypothesis. Yet the former strongly suggests an independent variable effect, whereas the latter does not. Sometimes outcomes that fall close to 0.05 are reported as "marginally" significant, and the thoughtful researcher will determine effect sizes for these independent variables to ascertain whether they might represent important variables that can guide future research projects [32, 48].

Conclusion

Sexual dysfunction in the mentally ill is an understudied yet critically important topic. Both mental and sexual health are vital to overall well-being, and understanding the relationship between the two has the potential to improve the lives of many people. Indeed, much of the research on sexual problems has viewed mental illness as an annoying variable—requiring control or screening—rather than as a variable of significance in its own right. However, the understanding of

such relationships must be based upon well-designed studies that minimize error and misinterpretation. Researchers adhering to the best practices in research increase the likelihood of meeting such a goal.

References

1. Kaplan HS. Hypoactive sexual desire. J Sex Marital Ther. 1977;3(1):3–9.
2. Leif H. Inhibited sexual desire. Med Aspects Hum Sex. 1977;7:94–5.
3. Basson R. The female sexual response: a different model. J Sex Marital Ther. 2000;26:51–65. https://doi.org/10.1080/009262300278641.
4. Motofei IG. A dual physiological character for cerebral mechanisms of sexuality and cognition: common somatic peripheral afferents. BJU Int. 2011;108(10):1634–9.
5. Motofei IG, Rowland DL. The ventral-hypothalamic input route: a common neural network for abstract cognition and sexuality. BJU Int. 2014;113(2):296–303.
6. Simiyon M, Chandra PS, Desai G. Sexual dysfunction among women with schizophrenia – a cross sectional study from India. Asian J Psychiatr. 2016;24:93–8.
7. Ghassemzadeh H, Raisi F, Firoozikhojastefar R, Meysamie A, Karamghadiri N, Nasehi AA, Fallah J, Sorayani M, Ebrahimkhani N. A study on sexual function in obsessive-compulsive disorder (OCD): patients with and without depressive symptoms. Perspect Psychiatr Care. 2016;53(3):208–13. https://doi.org/10.1111/ppc.12160.
8. Mourikis I, Antoniou M, Matsouka E, Vousoura E, Tzavara C, Ekizoglou C, Papadimitriou GN, Vaidakis N, Zervas IM. Anxiety and depression among Greek men with primary erectile dysfunction and premature ejaculation. Ann General Psychiatry. 2015;14:34. https://doi.org/10.1186/s12991-015-0074.
9. Clayton AH, Alkis AR, Parikh NB, Votta JG. Sexual dysfunction due to psychotropic medications. Psychiatr Clin North Am. 2016;39(3):427–63.
10. Markham JA. Sex steroids and schizophrenia. Rev Endocr Metab Dis. 2012;13(3):187–207.
11. Kendler KS. The clinical features of mania and their representation in modern diagnostic criteria. Psychol Med. 2016;47:1–17.
12. Soterio-Pires JH, Hirotsu C, Kim LJ, Bittencourt L, Tufik S, Andersen ML. The interaction between erectile dysfunction complaints and depression in men: a cross-sectional study about sleep, hormones and quality of life. Int J Impot Res. 2016;29(2):70–5. https://doi.org/10.1038/ijir.2016.49.
13. Yang JC, Park K, Eun SJ, Lee MS, Yoon JS, Shin IS, Kim YK, Chung TW, Kang HK, Jeong GW. Assessment of cerebrocortical areas associated with sexual arousal in depressive women using functional MR imaging. J Sex Med. 2008;5(3):602–9.
14. Yang JC, Park JI, Kim GW, Eun SJ, Lee MS, Han KL, Chae JH, Jeong GW. Effects of antidepressant treatment on sexual arousal in depressed women: a preliminary FMRI study. Psychiatry Investig. 2012;9(4):379–83.
15. Motofei IG. Treatment of premature ejaculation with paroxetine hydrochloride as needed: 2 single-blind placebo controlled crossover studies. J Urol. 2002;168(4):1508–9.
16. Motofei I. The etiology of premature ejaculation starting from a bihormonal model of normal sexual stimulation. Int J Impot Res. 2001;13(1):49–50.
17. Soydan H, Ates F, Adayener C, Akyol I, Semiz UB, Malkoc E, Yilmaz O, Basoglu C, Baykal KV. Attention-deficit hyperactivity disorder in patients with premature ejaculation: a pilot study. Int Urol Nephrol. 2013;45(1):77–81.
18. Motofei IG, Rowland DL. Solving the mind-body problem through two distinct concepts: internal-mental existence and internal mental reality. J Mind Med Sci. 2015;2(2):128–41.
19. Paba S, Frau R, Godar SC, Devoto P, Marrosu F, Bortolato M. Steroid 5α-reductase as a novel therapeutic target for schizophrenia and other neuropsychiatric disorders. Curr Pharm Des. 2011;17(2):151–67.

20. Golightly L, Young A. Sex hormones and mental health. Adv Psychiatr Treat. 1999;5:126–34.
21. Motofei IG, Rowland DL, Popa F, Bratucu E, Straja D, Manea M, Georgescu SR, Paunica S, Bratucu M, Balalau C, Constantin VD. A pilot study on tamoxifen sexual side effects and hand preference in male breast cancer patients. Arch Sex Behav. 2015;44(6):1589–94.
22. Motofei IG, Rowland DL, Georgescu SR, Dimcevici P, Paunica S, Constantin V, Bălălău C. A pilot study on the sexual side effects of finasteride as related to hand preference for men undergoing treatment of male pattern baldness. BJU Int. 2013;111(4):E221–6.
23. Coull JT, Nobre AC, Frith CD. The noradrenergic alpha2 agonist clonidine modulates behavioural and neuroanatomical correlates of human attentional orienting and alerting. Cereb Cortex. 2001;11(1):73–84.
24. Shang CY, Yan CG, Lin HY, Tseng WY, Castellanos FX, Gau SS. Differential effects of methylphenidate and atomoxetine on intrinsic brain activity in children with attention deficit hyperactivity disorder. Psychol Med. 2016;46(15):3173–85.
25. Motofei IG, Rowland DL, Georgescu SR, Tampa M, Baconi D, Stefanescu E, Baleanu BC, Balalau C, Constantin V, Paunica S. Finasteride adverse effects in subjects with androgenic alopecia: a possible therapeutic approach according to the lateralization process of the brain. J Dermatolog Treat. 2016;27(6):495–7.
26. Motofei IG, Rowland DL, Georgescu SR, Tampa M, Baleanu BC, Paunica S. Are hand preference and sexual orientation possible predicting factors for finasteride adverse effects in male androgenic alopecia? Exp Dermatol. 2016;25(7):557–8. https://doi.org/10.1111/exd.13003.
27. Rowland DL. Issues in the laboratory study of human sexual response: an overview for the non-technical sexologist. J Sex Res. 1999;36:1–29.
28. Hamilton LD, Rellini AH, Meston CM. Cortisol, sexual arousal, and affect in response to sexual stimuli. J Sex Med. 2008;5:2111–8.
29. Meston CM, Heiman JR. Ephedrine-activated physiological sexual arousal in women. Arch Gen Psychiatry. 1998;55(7):652–6. https://doi.org/10.1001/archpsyc.55.7.652.
30. MacCorquodale K, Meehl PE. On a distinction between hypothetical constructs and intervening variables. Psychol Rev. 1948;55:95–107.
31. Marshall C, Rossman GB. Designing qualitative research. 3rd ed. London: Sage; 1999. p. 115.
32. Rowland DL, Thornton JA. Transforming ideas into research. In: Niebauer J, editor. The clinical research survival guide. London: Remedica; 2002. p. 43–78.
33. Gold JA. Principles of psychological research. Homewood: The Dorsey; 1984.
34. Altman DG, Bland JM. Diagnostic tests. 1: sensitivity and specificity. Brit Med J. 1994;308(6943):1552. https://doi.org/10.1136/bmj.308.6943.1552.
35. Rowland DL, Patrick DL, Rothman M, Gagnon DD. The psychological burden of premature ejaculation. J Urol. 2007;177:1065–70.
36. Nunnally J. Psychometric theory. 2nd ed. New York: McGraw Hill; 1978.
37. Rowland D, Cooper S, Schneider M. Defining premature ejaculation for experimental and clinical investigations. Arch Sex Behav. 2001;30:235–54.
38. Winer BJ. Statistical principles in experimental design. New York: McGraw Hill; 1962.
39. Lunneborg CE. Modeling experimental and observational data. Belmont: Duxbury (Wadsworth); 1994.
40. Schumacker RE, Lomax RG. A beginner's guide to structural equation modeling. Mahwah: Lawrence Erlbaum Associates; 1996.
41. Pedhazur EJ. Multiple regression in behavioral science: explanation and prediction. 2nd ed. Ft Worth: Holt, Rinehart & Winston; 1982.
42. Rowland D, Kolba T. Understanding orgasmic difficulty in women. J Sex Med. 2016;13(8):1246–54. https://doi.org/10.1016/j.jsxm.2016.05.014.
43. Woloski-Wruble AC, Oliel Y, Leefsma M, Hochner-Celnikier D. Sexual activities, sexual and life satisfaction, and successful aging in women. J Sex Med. 2010;7(7):2401–10. https://doi.org/10.1111/j.1743-6109.2010.01747.x
44. Bortz WM II, Wallace DH, Wiley D. Sexual function in 1,202 aging males: differentiating aspects. J Gerontol Med Sci. 1999;54A(5):M237–41.

45. Vogt P. Dictionary of statistics and methodology: a nontechnical guide for the social sciences. Newbury Park: Sage; 1993.
46. Cohen J. Statistical power analysis for the behavioral sciences. Revised ed. New York: Academic; 1977.
47. Rowland D, Arkkelin D, Crisler L. Computer based data analysis. Chicago: Nelson-Hall; 1991.
48. Nelson CJ, Schofield E. The seduction of P values. J Sex Med. 2016;13(12):1828–9.

Patient-Reported Outcomes in Sexual Medicine

3

Stanley E. Althof

3.1 Introduction

This book focuses on sexual dysfunction in mentally ill patients. Mental illness covers a broad spectrum of disorders from mood, trauma, obsessive compulsive symptoms, autism, anxiety, addictions, dementia, and schizophrenia to name a few. Also included in the *Diagnostic and Statistical Manual of Mental Disorders*-fifth edition, the officially sanctioned compilation of disorders from the American Psychiatric Association, is a section devoted to male and female sexual dysfunctions, paraphilias, and gender identity disorders [1]. Sexual problems can occur in patients whether they have no mental illness, whether afflicted with severe illness or the less severe disorders. Additionally, sexual dysfunctions can be caused by the pharmacological agents that are utilized to treat mental illness.

Psychological testing casts a wide net assessing intelligence, neuropsychological concerns, vocational aptitude, relationship satisfaction, personality issues, mood, suicidal ideation, diagnostic questions (i.e., reality testing impairments), quality of life, and impact of illness. In the history of psychology, there is a long and storied tradition of using psychological measures for screening, diagnostic questions, and prediction of treatment outcome.

Sexuality measures are but a small part of the spectrum of psychological tests. Over the past 30 years, sexuality measures have become a vital element to identify the presence or absence of sexual dysfunctions, assess the impact of treatment, and examine the impact of sexual dysfunctions on quality of life and relationship satisfaction. Were it not for sexuality questionnaires such as the International Index of

S. E. Althof
Case Western Reserve University School of Medicine, Cleveland, OH, USA

Center for Marital and Sexual Health of South Florida, West Palm Beach, FL, USA
e-mail: stanley.althof@case.edu

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*,
Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_3

Erectile Function (IIEF) [2], Sexual Encounter Profile (SEP) [3], Female Sexual Function Index (FSFI) [4], Female Sexual Distress Scale (FSDS) [5], Male Sexual Health Questionnaire (MSHQ) [6], and Peyronie's Disease Questionnaire (PDQ) [7], drugs such as sildenafil, flibanserin, alfuzosin, and collagenase clostridium histolyticum would not have received FDA approval.

Sexuality measures have been known by various names including self-report diaries, event logs, self-administered questionnaires, and clinician-administered rating scales. The term patient-reported outcome, abbreviated as PRO, was introduced by the US Food and Drug Administration (FDA) to include all the above designations. Sexuality PROs seek to capture the subjective perceptions of patients and/or partner's related to their specific symptoms, degree of bother, efficacy of a medication or psychotherapy intervention, and quality of life issues related to a specific condition.

This chapter will review the most relevant male and female sexuality PROs and discuss the process of psychometric validation. The constructs of reliability, various forms of validity, sensitivity, and specificity as well as concerns with translating a PRO into a different language are reviewed.

Although valuable in recognizing and identifying sexual dysfunction, PROs should **not** substitute for a thorough sexual, medical, and psychosocial history. Taken together, selected PROs combined with the patient's sexual, medical, psychosocial history provide a comprehensive assessment of the patient's sexual status.

3.2 Key Psychometric Concepts

In order to be considered psychometrically valid, PROs must possess the essential characteristics of reliability, validity, sensitivity, and specificity. The validation process is an iterative, ever evolving process that increases clinicians' and regulatory agencies confidence in the quality of the data [8].

There are two forms of reliability—test-retest and internal consistency. Test/retest reliability refers to the ability of the questionnaire to measure the same phenomenon in a similar fashion at two or more points in time. For instance, an ED questionnaire is deemed reliable, if holding all conditions constant, a subject's scores on a subscale or total score, are similar from week to week. Internal consistency measures the degree to which all questions are measuring the same phenomenon or construct (i.e., how all the questions on a distress subscale are related to one another).

There are several forms of validity that include face, construct, discriminant, known groups, and predictive validity. Face validity is the extent to which a measure is subjectively viewed as covering the construct it purports to measure. It refers to the transparency or relevance of the PRO as it is perceived by subjects responding to it. Simply stated a measure is said to have face validity if it appears to be assessing the construct under consideration (e.g., sexual desire) [9, 10].

Construct validity is composed of three aspects consisting of discriminant (known groups or convergent/discriminant), predictive (response to treatment), and

content (clarity, relevance, construct comprehensiveness) validity. To assess convergent and divergent validity, subjects complete questionnaires that evaluate similar symptoms (i.e., IIEF vs. MSHQ) and questionnaires that are unrelated to the focus of the PRO (i.e., SF-36, a measure of health status). One would expect to see different scores on the relevant scales from men or women with a sexual dysfunction versus those who do not have a dysfunction. A PRO sensitivity refers to the percentage of cases that are correctly classified by the PRO (i.e., 95% of cases with delayed ejaculation are classified as having the dysfunction), while specificity refers to the percentage of non-cases that are correctly identified (i.e., 87% of men with normal ejaculation are classified as not being dysfunctional).

Content validity is established through qualitative research in which focus are interviewed to identify all the entire set of relevant constructs generated by the subjects on a specific topic (i.e., female subjective arousal). Questions and response sets are developed based on the results of focus groups. An initial PRO is constructed knowing in advance that many of the questions will not be suitable to be brought forward. The measure is administered to subjects diagnosed with a specific disorder and subjected to factor analysis to determine the domain structure of the questionnaire and the relationship of specific questions to the domain(s) and other questions. Questions are removed from the draft PRO based on redundancy, poor psychometric performance, failing to fit into the factor structure, and subjects not understanding the intent of the question. After identification of initial constructs, a second round of qualitative research seeks to confirm the findings of the first round [11].

The next phase of validation concerns predictive validation or the PROs ability to measure treatment efficacy. Responses of subjects given placebo versus those receiving an active psychotherapeutic or psychopharmacologic intervention are examined expecting the active treatment groups to demonstrate superior statistical and clinical significance.

After the initial psychometric work on reliability and validity, further research can determine a PRO's cutoff score, the point at which one would classify a person as suffering from a sexual dysfunction. Cutoff scores are used in PROs such as the IIEF, FSFI, and Premature Ejaculation Diagnostic Tool (PEDT) which establish and classify individuals as having or not having a dysfunction.

Questionnaires developed in a specific language or cultural context cannot be assumed to be valid when translated to a different language or cultural setting. Specific procedures such as forward and back translation are used to assure that the intended meaning of a question appears in the translated item. Additionally, the translated questions are judged by focus group participants to confirm that all items have adequate content validity (i.e., have the same meaning and significance) [12].

Finally, an important distinction should be made between self-report measures of sexual function (e.g., IIEF) and validated, self-report measures of sexual satisfaction or quality of life (e.g., Self-Esteem and Relationship Questionnaire (SEAR), Sexual Quality of Life (SQOL)). Some measures (e.g., Erectile Dysfunction Inventory of Treatment Satisfaction) are designed to focus on treatment satisfaction, while others are directed at psychosocial outcomes of treatment (e.g., SEAR). It is important to

make distinctions between the conceptual focus and theoretical rationale for each of these outcome measures, in addition to the psychometric strengths and weaknesses of each scale. These measures differ also in the degree to which they are couple-oriented or more directed at the individual patient. Unfortunately, the majority of the PROs are heterosexually biased and generally not appropriate for individuals in same sex relationships.

3.3 PROs for Sexual Dysfunction

This section is devoted to reviewing and suggesting psychometrically validated PROs for male and female sexual dysfunction as well as quality of life concerns. Some questionnaires are multidimensional (IIEF, FSFI), that is, they assess more than one parameter of sexual function versus PROs that only examine one aspect of sexual function (i.e., Male Sexual Health Questionnaire-EjD). Two tables have been developed for this chapter. Table 3.1 reviews the male PROs, while Table 3.2 examines the female PROs. When selecting which PRO to employ, one needs to consider the psychometric characteristics, the population it was validated on, patient burden,

Table 3.1 PROs for male sexual dysfunction

Name	Number of questions	Domain names	Level of evidence/ grade
Multidimensional assessment			
International Index of Erectile Function (IIEF) [2]	15	Erectile function, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction	A-1
Male Sexual Health Questionnaire (MSHQ) [6]	29	Ejaculation, erection, and sexual satisfaction	B-2
Arizona Sexual Experiences Scale (ASEX) [13]	5	Sex drive, arousal, vaginal lubrication/ penile erection, ability to reach orgasm, and orgasm satisfaction	B-3
Erectile function			
Erection hardness scale [14]	1	One domain	B-2
Ejaculation difficulties			
Male Sexual Health Questionnaire-EjD short form [15]	4	Ejaculation, bother, and satisfaction	B-2
Premature ejaculation			
Premature Ejaculation Profile (PEP) [16]	4	Satisfaction with sexual intercourse, control over ejaculation, ejaculation-related distress, and interpersonal difficulty	B-2
International Index of Premature Ejaculation (IPE) [17]	10	Control, satisfaction, and distress	B-2
Premature Ejaculation Diagnostic Tool (PEDT) [18]	5	One domain	B-2

Table 3.1 (continued)

Name	Number of questions	Domain names	Level of evidence/ grade
Quality of life measures			
Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) [19]	29	Treatment satisfaction (men) and partner satisfaction (women)	A-1
Treatment Satisfaction Scale (TSS) [20]	40	Satisfaction with medication, ease with erections, satisfaction with erectile function, pleasure from sexual activity, satisfaction with orgasm, and sexual confidence	A-2
Self-Esteem and Relationship Questionnaire (SEAR) [21]	14	Self-esteem, confidence, and relationships	A-1
Sexual Quality of Life (SQOL-M) [22]	11	Sexual confidence, emotional well-being, and relationship issues	C-2
Peyronie's disease			
Peyronie's Disease Questionnaire [7]	15	Psychological and physical symptoms, Peyronie's symptom bother, penile pain	A-1
Special populations- cancer			
PROMIS Sexual Function and Satisfaction (SexFS) [23]	79	Interest in sexual activity, lubrication, vaginal discomfort, erectile function, global satisfaction with sexual life, orgasm, anal discomfort, therapeutic aids, sexual activities, interfering factors, and screener questions	A-1

Table 3.2 PROs for female sexual dysfunction

Name	Number of questions	Domain names	Level of evidence/ grade
Multidimensional assessment			
Female Sexual Function Index (FSFI) [4]	25	Desire, arousal, lubrication, orgasm, satisfaction, and pain	A-1
Sexual Functioning Questionnaire (SFQ) [24]	28	Desire, arousal, orgasm, pain, enjoyment, and partner relationship	B-3
Arizona Sexual Experiences Scale (ASEX) [13]	5	Sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and orgasm satisfaction	B-3
Sexual desire			
Sexual Interest and Desire Inventory (SIDI) [25]	15	Hypoactive sexual desire disorder	B-2
Distress			
Female Sexual Distress Scale-Revised (FSDS-R) [5]	14	Distress regarding sexual life	A-1

(continued)

Table 3.1 (continued)

Name	Number of questions	Domain names	Level of evidence/ grade
Pain			
McGill Pain Questionnaire (MPQ) [26]	28	What does your pain feel like, how does your pain change with time, how strong is your pain?	A-1
Postmenopausal symptoms			
McCoy Female Sexuality Questionnaire (MFSQ) [27]	19	?	B-2
Quality of life			
Sexual Quality of Life-Female (SQOL-F) [28]	18	Sexual confidence, emotional well-being, and relationship issues	C-2
Special populations-cancer			
PROMIS Sexual Function and Satisfaction (SexFS) [23]	79	Interest in sexual activity, lubrication, vaginal discomfort, erectile function, global satisfaction with sexual life, orgasm, anal discomfort, therapeutic aids, sexual activities, interfering factors, and screener questions	A-1

and changes in the nomenclature. For instance, the FSFI assesses sexual desire, genital lubrication, and subjective arousal but does not have a scale for female sexual interest/arousal disorder found in DSM-5. Similarly, some of the female pain questionnaires were developed based on DSM-IV-TR nomenclature; since then there have been further revisions to the female sexual dysfunction nomenclature.

In both Tables 3.1 and 3.2 for each PRO, the reader will find the PROs categorized by their specific purpose, i.e., multidimensional assessment versus assessment of a specific function. Additionally, the tables list the number of questions, domains, and the level of evidence. Included in these tables are PROs that assess both male and female sexual function (i.e., ASEX) and questionnaires focused on quality of life and special populations (i.e., cancer, menopause, Peyronie's disease).

Conclusion

PROs are valuable tools in the assessment of sexual function in both research and clinical settings. They serve as a useful adjunct to identify and detect treatment benefits in individuals with sexual problems. Also included in this chapter are PROs that assess quality of life concerns and sexual concerns with special populations of men and women (PROs for cancer, Peyronie's disease, menopause). This chapter reviewed the important psychometric features of PROs that insure that the measure will be consistent and accurate—reliability, validity, specificity, and sensitivity.

Development and refinement of existing PROs is an ongoing process that must keep pace with regulatory concerns and changes in the nomenclature. PROs offer clinicians and patients an efficient method of assessment and are a useful adjunct in the evaluation process.

References

1. American Psychiatric Association. The diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
2. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology. 1997;49(6):822–30.
3. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. N Engl J Med. 1998;338(20):1397–404. https://doi.org/10.1056/NEJM199805143382001.
4. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000;26(2):191–208.
5. Derogatis L, Clayton A, Lewis-D'Agostino D, Wunderlich G, Fu Y. Validation of the female sexual distress scale-revised for assessing distress in women with hypoactive sexual desire disorder. J Sex Med. 2008;5(2):357–64. https://doi.org/10.1111/j.1743-6109.2007.00672.x.
6. Rosen RC, Catania J, Pollack L, Althof S, O'Leary M, Seftel AD. Male Sexual Health Questionnaire (MSHQ): scale development and psychometric validation. Urology. 2004;64(4):777–82. https://doi.org/10.1016/j.urology.2004.04.056.
7. Hellstrom W, Feldman R, Rosen R, Smith T, Kaufman G, Tursi J. Bother and distress associated with Peyronie's disease: validation of the Peyronie's disease questionnaire. J Urol. 2013;190(2):627–34.
8. Althof S. Patient reported outcomes in the assessment of premature ejaculation. Transl Androl Urol. 2016;5(4):470–4.
9. Gravetter F, Forzano L. Research methods for the behavioral sciences. 4th ed. Belmont: Wadsworth; 2012.
10. Holden R. Face validity. In: Weiner I, Craighead E, editors. The corsini encyclopedia of psychology. 4th ed. New Jersey: Wiley; 2010. p. 637–8.
11. Hatzichristou D, Kirana P, Banner L, Althof S, Lonnee-Hoffmann R, Dennerstein L, et al. 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.
12. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, et al. Principles of good practice for the translation and cultural adaptation process for Patient-Reported Outcomes (PRO) measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005;8(2):94–104.
13. McGahuey C, Gelenberg A, Laukes C, Moreno R, Delgado P, McKnight K, et al. The Arizona Sexual Experience Scale (ASEX): reliability and validity. J Sex Marital Ther. 2000;26:25–40.
14. Mulhall J, Goldstein I, Bushmakin A, Cappelleri J, Hvidsten K. Validation of the erection hardness score. J Sex Med. 2007;4:1626–34.
15. Rosen RC, Catania J, Althof S, Pollack L, O'Leary M, Seftel AD, et al. Development and validaton of four-item version of male sexual health questionnaire to assess ejaculatory dysfunction. Urology. 2007;69:805–9.
16. Patrick DL, Giuliano F, Ho KF, Gagnon DD, McNulty P, Rothman M. The premature ejaculation profile: validation of self-reported outcome measures for research and practice. BJU Int. 2009;103(3):358–64. https://doi.org/10.1111/j.1464-410X.2008.08041.x.
17. Althof S, Rosen R, Symonds T, Mundayat R, May K, Abraham L. Development and validation of a new questionnaire to assess sexual satisfaction, control, and distress associated with premature ejaculation. J Sex Med. 2006;3(3):465–75. https://doi.org/10.1111/j.1743-6109.2006.00239.x.
18. Symonds T, Perelman M, Althof S, Giuliano F, Martin M, May K, et al. Development and validation of a premature ejaculation diagnostic tool. Eur Urol. 2007;52:565–73.
19. Althof S, Corty E, Levine S. EDITS: development of a quesitonnaire for evaluating satisfaction with treatment for erectile dysfunction. Urology. 1999;53:793–9.

20. DiBenedetti DB, Gondek K, Sagnier PP, Kubin M, Marquis P, Keininger D, et al. The treatment satisfaction scale: a multidimensional instrument for the assessment of treatment satisfaction for erectile dysfunction patients and their partners. Eur Urol. 2005;48(3):503–11. https://doi.org/10.1016/j.eururo.2005.05.008.
21. Althof S, Cappelleri JC, Shpilsky A. Treatment responsiveness of the self-esteem and relationship questionnaire in erectile dysfunction. Urology. 2003;61:888–92.
22. Abraham L, Symonds T, Morris MF. Psychometric validation of a sexual quality of life questionnaire for use in men with premature ejaculation or erectile dysfunction. J Sex Med. 2008;5(3):595–601. https://doi.org/10.1111/j.1743-6109.2007.00749.x.
23. Flynn K, Lin L, Cyranowski M. Development of the NIH PROMIS (R) sexual function and satisfaction measures in patients with cancer. J Sex Med. 2013;10(7):43–52.
24. Quirk F, Haughie S, Symonds T. The use of the sexual function questionnaire as a screening tool for women with sexual dysfunction. J Sex Med. 2005;2(4):469–77. https://doi.org/10.1111/j.1743-6109.2005.00076.x.
25. Clayton AH, Segraves RT, Leiblum S, Basson R, Pyke R, Cotton D, et al. Reliability and validity of the Sexual Interest and Desire Inventory-Female (SIDI-F), a scale designed to measure severity of female hypoactive sexual desire disorder. J Sex Marital Ther. 2006;32(2):115–35. https://doi.org/10.1080/00926230500442300.
26. Melzack R. The McGill pain questionnaire: major properties and scoring methods. Pain. 1975;1:277–99.
27. McCoy N. The McCoy female sexuality questionnaire. Qual Life Res. 2000;9:739–45.
28. Symonds T, Boolell M, Quirk F. Development of a questionnaire on sexual quality of life in women. J Sex Marital Ther. 2005;31(5):385–97. https://doi.org/10.1080/00926230591006502.

4 Epidemiology of Sexual Dysfunctions in Persons Suffering from Psychiatric Disorders

Giacomo Ciocca, Susana Ochoa, and Emmanuele A. Jannini

4.1 Introduction

Patients with mental disorders often can suffer from sexual dysfunction [1], and, in most cases, psychopharmacological treatment causes sexual dysfunction-related side effects [2].

Generally, in psychiatric patients, affective relationships and sexuality are seriously affected by psychopathology as well as by the related long-term pharmacological treatment [3]. Moreover, psychoses, anxiety, mood, and personality disorders have a negative effect on personal and sexual relationships. In fact, the prevalence of sexual dysfunctions in these patients is higher than in general population [4]. However, few literature evidences exist on the prevalence of sexual dysfunctions in people suffering from mental disorders. Therefore, this chapter describes the main knowledge regarding the epidemiology of sexual dysfunctions in female and male psychiatric patients (Table 4.1).

Table 4.1 Prevalence ranges of sexual dysfunctions in people suffering from psychiatric disorders according to the main studies examined in this chapter

	Sexual dysfunctions	
Psychiatric disorders	Men	Women
Anxiety	7–47.3%	22–64%
Mood disorders	5.1–36.4%	40–65%
Personality disorders	5.8%	n.f.
Psychotic disorders	6.9–94%	37–50%
Eating disorders	n.f.	40%

n.f. not found

G. Ciocca (✉) · E. A. Jannini
Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
e-mail: giacomo.ciocca@libero.it; eajannini@gmail.com

S. Ochoa
Parc Sanitari Sant Joan de Déu, Institut de Recerca Sant Joan de Déu. CIBERSAM, Barcelona, Spain

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*, Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_4

4.2 Sexual Dysfunctions in Men with Mental Disorders

The most common male sexual dysfunctions are certainly represented by erectile dysfunction (ED) and premature ejaculation (PE), although also disorders of sexual desire and other orgasmic or ejaculatory disorders equally occur in men. The Fourth International Consultation on Sexual Medicine calculated the prevalence of ED according to the age in the general population, i.e., from 1–15% before 50 years to 20–40% after 60 years and a higher prevalence after 70 years of age [5]. The prevalence of PE varies from 8% to 30% for all age groups among the general male population [5].

The prevalence of sexual dysfunctions changes in cases of people suffering from mental disorders, where there are several implications, also due to pharmacological treatment.

4.2.1 Anxiety

Anxiety disorders can occur in men with sexual dysfunction, above all in cases of ED and PE. Some authors interestingly found that the 23.4% of patients suffer from a comorbidity between sexual dysfunction (SD) and anxiety [6]. In another study, PE, sexual avoidance, and decreased sexual desire were found in 21%, 36%, and 14% of male patients with panic disorders (PD), respectively. In these, only 7% had erectile difficulties [7]. Premature ejaculation was the most common sexual dysfunction in male social phobia patients (47.4%) [7]. Other researchers have instead investigated the relationship between sexual dysfunction and obsessive-compulsive disorder (OCD). They found that the 57.1% of male PCD patients had sexual infrequency, as evaluated using the Golombok Rust Inventory of Sexual Satisfaction (GRISS) [8]. Finally, in a study on outpatients seeking help for sexual problems, the 52% suffered from PE. Among these, 25.5% had social phobia disorder as a comorbidity, 13.7% had obsessive-compulsive disorder, and 17.3% had a panic disorder, although a significant difference with other sexual problems was found only for social phobia [9].

4.2.2 Mood Disorders

A controversial clinical issue exists regarding cases of male depression with possible comorbidity of sexual dysfunction, although this relationship is often bidirectional, because it is possible that ED could be a cause or an effect of depressive symptomatology.

On the other hand, a recent study on males with ED and PE revealed that 12.5% of cases suffering from depressive disorders were also at risk of suicidal ideation, while 23.4% of males with sexual dysfunction were also diagnosed with anxiety disorders [6]. Moreover, the Massachusetts Male Aging Study revealed that moderate to complete ED is 1.82 times more likely in patients showing depressive

symptomatology [10]. Another American epidemiological study showed that, in the general population, the prevalence of moderate or complete ED was 36.4%, while the prevalence of current depression was 12.1% and the prevalence of concomitant ED and depression was 5.1%; this type of comorbidity was higher in males after 50 and 70 years of age, 6.3% and 7.5%, respectively [11]. The authors used well-validated psychometric tools for their assessment. This study revealed no statistically significant correlation between the severity of ED and the severity of depression.

Another important study investigated the bidirectional association between depression and ED, showing that the prevalence of depressive mood was 19% in patients with ED and 11% in those without ED. The authors found that the incidence of ED was 39/1000 person years; in particular, 59/1000 person years of men with depressive mood disorders declared to suffer from sexual dysfunctions, while the incidence of sexual dysfunctions among people who suffered from mood disorders was 37/1000 person years [12].

4.2.3 Personality Disorders

Sexual functioning and sexual behavior strongly depend on personality organization, and dysfunctional traits could differently influence sexual life. This relationship is clear, and it assumes clinical relevance when we study and assess sexuality in personality disorders (PD). A recent review article discussed sexual functioning and mating strategies in people with personality disorders, highlighting some evidence, particularly regarding sexuality. However, the history of sexual abuse plays a role in borderline disorder with consequences for sexual functioning [13]. In fact, one study demonstrated that schizoid personalities are characterized by sexual retire and in some cases by real asexuality, i.e., a reduction or absence of interest in sexual activities [14], while another investigation revealed the prevalence of 5.8% of erectile difficulties in people with PD [15]. However, epidemiological data about sexual problems in PD are still lacking.

4.2.4 Psychotic Disorders

In male psychotic patients, sexuality is seriously affected by psychopathological disorders and by the related long-term pharmacological treatment [3]. Moreover, psychosis has a negative effect on personal and sexual relationships, and the prevalence of sexual dysfunction in psychotic patients is higher than in the nonpsychotic population [4]. Our recent study on the first 2 years of this psychopathology, called first-episode psychosis (FEP), established that 42.5% of males suffer from SD [16]. Also, the EUFEST group studied SD in FEP, showing that before treatment in males, 17.7% had ED, 15.7% had ejaculatory problems, and 30.8% had a decreased libido. These SDs did not significantly improve after 12 months of treatment [17]. In the study regarding the role of drugs on sexuality, it was found that 50% of psychotic

patients had SD [1]. Instead, in a dated study by Finn et al. (1990), a prevalence of 34% for erectile dysfunction in schizophrenic males was found, while an important meta-analysis revealed that 7–46% of patients using antipsychotics had erectile dysfunction [18, 19]. Interestingly, Italian researchers analyzed the prevalence of SD according to pharmacological treatment on desire (12.6–43.4%), arousal (7.5–29.2%), and orgasm (6.9–29%) [18]. However, the percentage increased to 74% if the presence of at least one SD was considered, as revealed in a cross-sectional survey [20]. In their investigation, Fan et al. found higher percentages of male SD, as follows: impairment of desire/frequency (81%), arousal disorder (87%), orgasmic disorder (94%), and impairment in pleasure (68%) [21]. Finally, according to the data of an important British study on males taking antipsychotic drugs, it was found that these patients complained of SD 6.3 times more often than healthy subjects [22].

4.2.5 Eating Disorders

Although there is a considerable body of work on eating disorders and female sexuality, in males with eating disorders, sexual functioning has been little explored. However, an important but old study found that male patients with eating disorders reported experiencing sexual isolation, sexual inactivity, and conflicted homosexuality [23].

4.3 Sexual Dysfunctions in Women with Mental Disorders

Sexual dysfunctions are more common in women suffering from a psychiatric illness than in the general population [24]. The Fourth International Consultation on Sexual Medicine estimated in 2015 that 5.8% of women report symptoms that constitute a diagnosis of female sexual dysfunction (FSD) and 15.5% reported lifelong FSD. Particular attention is dedicated to disorders of sexual desire, with a prevalence around 20%; this increases significantly in older women (45–80%) [5].

The assessment of sexual dysfunction in women should include in the evaluation an assessment of the impact on the patient's mental health.

4.3.1 Anxiety

The literature shows that anxiety is more prevalent in women than in men, being diagnosed at least twice [25]. Anxiety disorders include several diagnoses such as anxiety, phobias, social anxiety, panic disorders, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (DSM-5). Sexual function is altered in people with anxiety disorders in several ways.

Regarding panic disorder, women show more problems related to sexual desire [26]. Moreover, some researchers assessed the presence of SD comparing patients

with panic disorders and social phobia, and they found that women with panic disorders presented more problems than social phobia, such as sexual aversion disorder [7]. On the other hand, in another study it was found that the 64% of women with panic disorder also presented sexual avoidance [8]. It is also well known that association between sexual dysfunctions (SDs) and social phobia is mostly gender-specific. Women, in fact, present more problems in areas such as desire, arousal, sexual activity, and subjective satisfaction [27].

Moreover, several studies have assessed the relationship between OCD and sexual dysfunction with a large range of prevalence and percentage values. An old study found that 22% of women presented sexual arousal problems, while 9% had anorgasmia [28]. The prevalence of anorgasmia in a more recent investigation was higher than 24% [8]. In addition, Van Minnen and Kampman (2000) found that women with OCD have more problems regarding sexual desire than control subjects [26]. In the same line, other authors found that sexual satisfaction is reduced in these patients, showing that 62% of patients experienced reduced sexual desire, 33% had orgasmic-phase dysfunction, and 29% had reduced sexual arousal [29].

The sexual problems related to women with post-traumatic stress disorder are sometimes associated with sexual trauma [30]. However, also the post-traumatic stress disorder is mediated by a variety of daily stresses and it affects sexual arousal in women with a history of childhood abuse [31]. If alexithymia cannot be considered related to only anxiety disorders, it was found related to the 26.8% of women with vaginismus [32]. On the other hand, anxiety disorders were also found in 24.9% of women suffering from vaginismus [33].

4.3.2 Mood Disorders

The prevalence of sexual dysfunctions in people with mood disorders ranges from 40% to 65% [34, 35]. It is interesting to note that there is a bidirectional association between depression and sexual dysfunction [36]. Loss of sexual interest and libido are the most prevalent dysfunctions in women with depression, although difficulties with arousal are also reported [37]. The relationship between several diagnoses of depression and sexual problems assessed in a large sample of women revealed that women with recurrent depression presented more problems regarding sexual arousal, physical pleasure, and emotional satisfaction within their current sexual relationships [38]. Moreover, the severity of sexual dysfunction was related to the severity of the depressive dimension [39].

The use of antidepressants is related to sexual dysfunction in women. While some authors suggest that the use of antidepressants negatively affects the sexuality of women [40], others suggest that the use of antidepressants improves their sexual problems [41, 38]. More research is clearly needed in this area.

Women with bipolar disorder have an increased risk of sexually transmitted diseases and unplanned pregnancies during the mania phase [42].

4.3.3 Personality Disorders

Personality disorders, mainly borderline and histrionic personality disorders, are associated with sexual dysfunction [43, 44]. In the case of borderline personality disorder, the problem is related to promiscuity in their sexual relations, unstable relationships, and experiences of sexual aggression [45–47]. Moreover, women with borderline personality disorder experience a greater prevalence of sexual aggression since childhood [47, 48]. In this line, borderline patients often avoid sexual relationships. Histrionic personality disorder is more frequent in women. In this line, several studies have suggested that women with histrionic personality disorder are more often preoccupied with appearing attractive and sexually seductive, tend to have fantasies about sex, are impulsive, and express dissatisfaction with their sexual relationships [49, 50]. Regarding sexual dysfunctions, Apt and Hurlbert found that women with histrionic personality disorder have greater sexual preoccupation, lower sexual desire, and greater orgasmic dysfunction with respect to unaffected population [51].

4.3.4 Psychotic Disorders

The presence of sexual dysfunction in women with psychotic disorders is little studied. In an interesting study, the 50% of institutionalized and noninstitutionalized women with schizophrenia referred sexual dysfunctions compared with only 12.7% of women in the control group [52]. However, another but controversial study found that women with schizophrenia presented problems related to sexual desire in the same proportion as the general population, although assessed women had less sexual practice and less satisfaction [53]. Moreover, other authors found that there were no gender differences in schizophrenic patients about the relationship between SDs and the iatrogenic effect of hyperprolactinemia [54].

In this regard, Malik et al. (2011) suggested that psychopharmacological treatment affects the hormonal system related to sexual dysfunction, causing an increase in prolactin and some types of endocrinological dysregulation such as amenorrhea, galactorrhea, and gynecomastia [17].

However, in a small sample of women with FEP, the prevalence of sexual dysfunctions was found around 37% [16].

The most frequent sexual dysfunctions in women with schizophrenia or at the first-episode psychosis are hypolubrication, anorgasmia, and decreased sexual desire and libido [1, 16, 21]. It is important to consider that sexual dysfunctions are very frequently intercorrelated between each other. Problems with vaginal lubrication are related to decreased libido and orgasmic alteration, while decreased libido could be related to orgasmic alteration. Moreover, sexual dysfunction in terms of vaginal lubrication and orgasm is related to higher scores of positive and affective psychotic symptoms [16].

4.3.5 Eating Disorders

Eating disorders (anorexia, bulimia nervosa, and binge eating disorder) are more prevalent in women than in men [55]. A systematic review showed that sexual dysfunction is highly prevalent in this group [56]. Hence, it is very important to consider the sexual dysfunction during treatment of these disorders [57].

Eating disorders are characterized by concerns regarding body shape and body image disturbances, especially in women with anorexia. In this line, several researchers found that women with anorexia presented with decreased libido [57–59]. It is interesting to note that, following weight restoration, women increase their sexual activity [60]. On the other hand, in patients with bulimia, the 40% also suffers from sexual impairment [61]. Binge eating disorder is also associated with problems in sexual function [62]. In an interesting review, obstetric and gynecologic problems associated with eating disorders were described. Moreover, the authors highlighted the importance of multidisciplinary teams to provide care to women with these disorders [63]. Another important issue described in the literature is that women with eating disorders present with higher rates of sexual trauma [64]. In this line, it is interesting to assess the role of sexual trauma in the disorder and in the treatment of the associated sexual dysfunction.

Conclusion

In conclusion, the overview of current literature demonstrates a relative scarcity of epidemiological data on the relationship between psychiatric diseases and sexual dysfunctions.

We found large ranges of percentage values in different studies about the prevalence of sexual deficit in people suffering from mental disorders. In many cases the high presence of SD is considered as a comorbidity factor related to a primary diagnosis of mental suffering. This is the case of mood and anxiety disorders. On the other hand, sexual dysfunctions in psychotic diseases are often due to the side effects of pharmacological treatment. More controversial and also interesting is, instead, the relationship between sexuality and eating disorders, above all in women. Further studies concerning this fundamental topic are necessary through large survey protocols also considering the gender perspective.

References

1. Montejo AL, Majadas S, Rico-Villademoros F, Llorca G, De La Gandara J, Franco M, et al. Frequency of sexual dysfunction in patients with a psychotic disorder receiving antipsychotics. J Sex Med. 2010;7(10):3404–13. https://doi.org/10.1111/j.1743-6109.2010.01709.x.
2. Serretti A, Chiesa A. Sexual side effects of pharmacological treatment of psychiatric diseases. Clin Pharmacol Ther. 2011;89(1):142–7. https://doi.org/10.1038/clpt.2010.70.
3. Nunes LV, Moreira HC, Razzouk D, Nunes SO, Mari JJ. Strategies for the treatment of antipsychotic-induced sexual dysfunction and/or hyperprolactinemia among patients of the

schizophrenia spectrum: a review. J Sex Marital Ther. 2012;38(3):281–301. https://doi.org/10.1080/0092623X.2011.606883.
4. Bourdeau G, Masse M, Lecomte T. Social functioning in early psychosis: are all the domains predicted by the same variables? Early Interv Psychiatry. 2012;6(3):317–a. https://doi.org/10.1111/j.1751-7893.2011.00337.x.
5. McCabe MP, Sharlip ID, Lewis R, Atalla E, Balon R, Fisher AD, et al. Incidence and prevalence of sexual dysfunction in women and men: a consensus statement from the fourth international consultation on sexual medicine 2015. J Sex Med. 2016;13(2):144–52. https://doi.org/10.1016/j.jsxm.2015.12.034.
6. Rajkumar RP, Kumaran AK. Depression and anxiety in men with sexual dysfunction: a retrospective study. Compr Psychiatry. 2015;60:114–8. https://doi.org/10.1016/j.comppsych.2015.03.001.
7. Figueira I, Possidente E, Marques C, Hayes K. Sexual dysfunction: a neglected complication of panic disorder and social phobia. Arch Sex Behav. 2001;30(4):369–77.
8. Aksoy UM, Aksoy SG, Maner F, Gokalp P, Yanik M. Sexual dysfunction in obsessive compulsive disorder and panic disorder. Psychiatr Danub. 2012;24(4):381–5.
9. Corretti G, Pierucci S, De Scisciolo M, Nisita C. Comorbidity between social phobia and premature ejaculation: study on 242 males affected by sexual disorders. J Sex Marital Ther. 2006;32(2):183–7. https://doi.org/10.1080/00926230500442342.
10. Araujo AB, Durante R, Feldman HA, Goldstein I, McKinlay JB. The relationship between depressive symptoms and male erectile dysfunction: cross-sectional results from the Massachusetts male aging study. Psychosom Med. 1998;60(4):458–65.
11. Kantor J, Bilker WB, Glasser DB, Margolis DJ. Prevalence of erectile dysfunction and active depression: an analytic cross-sectional study of general medical patients. Am J Epidemiol. 2002;156(11):1035–42.
12. Shiri R, Koskimaki J, Tammela TL, Hakkinen J, Auvinen A, Hakama M. Bidirectional relationship between depression and erectile dysfunction. J Urol. 2007;177(2):669–73. https://doi.org/10.1016/j.juro.2006.09.030.
13. Collazzoni A, Ciocca G, Limoncin E, Marucci C, Mollaioli D, Di Sante D, Di Lorenzo G, Niolu C, Siracusano A, Maggi M, Castellini G, Rossi A, Jannini EA. Mating strategies and sexual functioning in personality disorders: a comprehensive review of literature. Sex Med Rev. 2017;5(4):414–28. https://doi.org/10.1016/j.sxmr.2017.03.009.
14. Brotto LA, Knudson G, Inskip J, Rhodes K, Erskine Y. Asexuality: a mixed-methods approach. Arch Sex Behav. 2010;39(3):599–618. https://doi.org/10.1007/s10508-008-9434-x.
15. Mallis D, Moysidis K, Nakopoulou E, Papaharitou S, Hatzimouratidis K, Hatzichristou D. Psychiatric morbidity is frequently undetected in patients with erectile dysfunction. J Urol. 2005;174(5):1913–6. https://doi.org/10.1097/01.ju.0000176746.73667.3c.
16. Ciocca G, Usall J, Dolz M, Limoncin E, Gravina GL, Carosa E, et al. Sexual dysfunctions in people with first-episode psychosis assessed according to a gender perspective. Riv Psichiatr. 2015;50(5):239–44. https://doi.org/10.1708/2040.22166.
17. Malik P, Kemmler G, Hummer M, Riecher-Roessler A, Kahn RS, Fleischhacker WW. Sexual dysfunction in first-episode schizophrenia patients: results from European first episode schizophrenia trial. J Clin Psychopharmacol. 2011;31(3):274–80. https://doi.org/10.1097/JCP.0b013e3182199bcc.
18. Serretti A, Chiesa A. A meta-analysis of sexual dysfunction in psychiatric patients taking antipsychotics. Int Clin Psychopharmacol. 2011;26(3):130–40. https://doi.org/10.1097/YIC.0b013e328341e434.
19. de Boer MK, Castelein S, Wiersma D, Schoevers RA, Knegtering H. The facts about sexual (Dys)function in schizophrenia: an overview of clinically relevant findings. Schizophr Bull. 2015;41(3):674–86. https://doi.org/10.1093/schbul/sbv001.
20. Harley EW, Boardman J, Craig T. Sexual problems in schizophrenia: prevalence and characteristics. A cross sectional survey. Soc Psychiatry Psychiatr Epidemiol. 2010;45(7):759–66. https://doi.org/10.1007/s00127-009-0119-0.

21. Fan X, Henderson DC, Chiang E, Briggs LB, Freudenreich O, Evins AE, et al. Sexual functioning, psychopathology and quality of life in patients with schizophrenia. Schizophr Res. 2007;94(1–3):119–27. https://doi.org/10.1016/j.schres.2007.04.033.
22. Smith SM, O'Keane V, Murray R. Sexual dysfunction in patients taking conventional antipsychotic medication. Br J Psychiatry. 2002;181:49–55.
23. Herzog DB, Norman DK, Gordon C, Pepose M. Sexual conflict and eating disorders in 27 males. Am J Psychiatry. 1984;141(8):989–90. https://doi.org/10.1176/ajp.141.8.989.
24. Waldinger MD. Psychiatric disorders and sexual dysfunction. Handb Clin Neurol. 2015;130:469–89. https://doi.org/10.1016/B978-0-444-63247-0.00027-4.
25. Li SH, Graham BM. Why are women so vulnerable to anxiety, trauma-related and stress-related disorders? The potential role of sex hormones. Lancet Psychiatry. 2017;4(1):73–82. https://doi.org/10.1016/S2215-0366(16)30358-3.
26. Van Minnen A, Kampman M. Interaction between anxiety and sexual functioning: a controlled study of sexual functioning in women with anxiety disorders. Sex Relation Ther. 2000;15:47–57.
27. Bodinger L, Hermesh H, Aizenberg D, Valevski A, Marom S, Shiloh R, et al. Sexual function and behavior in social phobia. J Clin Psychiatry. 2002;63(10):874–9.
28. Monteiro WO, Noshirvani HF, Marks IM, Lelliott PT. Anorgasmia from clomipramine in obsessive-compulsive disorder. A controlled trial. Br J Psychiatry. 1987;151:107–12.
29. Vulink NC, Denys D, Bus L, Westenberg HG. Sexual pleasure in women with obsessive-compulsive disorder? J Affect Disord. 2006;91(1):19–25. https://doi.org/10.1016/j.jad.2005.12.006.
30. Moser DA, Aue T, Suardi F, Kutlikova H, Cordero MI, Rossignol AS, et al. Violence-related PTSD and neural activation when seeing emotionally charged male-female interactions. Soc Cogn Affect Neurosci. 2015;10(5):645–53. https://doi.org/10.1093/scan/nsu099.
31. Zollman G, Rellini A, Desrocher D. The mediating effect of daily stress on the sexual arousal function of women with a history of childhood sexual abuse. J Sex Marital Ther. 2013;39(2):176–92. https://doi.org/10.1080/0092623X.2012.691950.
32. Ciocca G, Limoncin E, Di Tommaso S, Gravina GL, Di Sante S, Carosa E, et al. Alexithymia and vaginismus: a preliminary correlation perspective. Int J Impot Res. 2013;25(3):113–6. https://doi.org/10.1038/ijir.2013.5.
33. Watts G, Nettle D. The role of anxiety in vaginismus: a case-control study. J Sex Med. 2010;7(1 Pt 1):143–8. https://doi.org/10.1111/j.1743-6109.2009.01365.x.
34. Lewis RW, Fugl-Meyer KS, Corona G, Hayes RD, Laumann EO, Moreira ED Jr, et al. Definitions/epidemiology/risk factors for sexual dysfunction. J Sex Med. 2010;7(4 Pt 2):1598–607. https://doi.org/10.1111/j.1743-6109.2010.01778.x.
35. Lee TI, Issac J, Lin SH, Yeh TL, Lee IH, Chen PS, et al. Gender difference in antidepressant-related sexual dysfunction in Taiwan. Gen Hosp Psychiatry. 2013;35(4):407–11. https://doi.org/10.1016/j.genhosppsych.2013.03.015.
36. Atlantis E, Sullivan T. Bidirectional association between depression and sexual dysfunction: a systematic review and meta-analysis. J Sex Med. 2012;9(6):1497–507. https://doi.org/10.1111/j.1743-6109.2012.02709.x.
37. Kennedy SH, Rizvi S. Sexual dysfunction, depression, and the impact of antidepressants. J Clin Psychopharmacol. 2009;29(2):157–64. https://doi.org/10.1097/JCP.0b013e31819c76e9.
38. Cyranowski JM, Bromberger J, Youk A, Matthews K, Kravitz HM, Powell LH. Lifetime depression history and sexual function in women at midlife. Arch Sex Behav. 2004;33(6):539–48. https://doi.org/10.1023/B:ASEB.0000044738.84813.3b.
39. Lin C, Juang YY, Wen JK, Liu CY, Hung CI. Correlations between sexual dysfunction, depression, anxiety, and somatic symptoms among patients with major depressive disorder. Chang Gung Med J. 2012;35(4):323–31.
40. Lorenz T, Rullo J, Faubion S. Antidepressant-induced female sexual dysfunction. Mayo Clin Proc. 2016;91(9):1280–6. https://doi.org/10.1016/j.mayocp.2016.04.033.

41. Clayton AH, Gommoll C, Chen D, Nunez R, Mathews M. Sexual dysfunction during treatment of major depressive disorder with vilazodone, citalopram, or placebo: results from a phase IV clinical trial. Int Clin Psychopharmacol. 2015;30(4):216–23. https://doi.org/10.1097/YIC.0000000000000075.
42. Miller LJ, Ghadiali NY, Larusso EM, Wahlen KJ, Avni-Barron O, Mittal L, et al. Bipolar disorder in women. Health Care Women Int. 2015;36(4):475–98. https://doi.org/10.1080/07399332.2014.962138.
43. Zanarini MC, Parachini EA, Frankenburg FR, Holman JB, Hennen J, Reich DB, et al. Sexual relationship difficulties among borderline patients and axis II comparison subjects. J Nerv Ment Dis. 2003;191(7):479–82. https://doi.org/10.1097/01.NMD.0000081628.93982.1D.
44. Zemishlany Z, Weizman A. The impact of mental illness on sexual dysfunction. Adv Psychosom Med. 2008;29:89–106. https://doi.org/10.1159/000126626.
45. Sansone RA, Wiederman MW. Borderline personality symptomatology, casual sexual relationships, and promiscuity. Psychiatry (Edgmont). 2009;6(3):36–40.
46. Sansone RA, Chu JW, Wiederman MW. Sexual behaviour and borderline personality disorder among female psychiatric inpatients. Int J Psychiatry Clin Pract. 2011;15(1):69–73. https://doi.org/10.3109/13651501.2010.507871.
47. Schulte-Herbruggen O, Ahlers CJ, Kronsbein JM, Ruter A, Bahri S, Vater A, et al. Impaired sexual function in patients with borderline personality disorder is determined by history of sexual abuse. J Sex Med. 2009;6(12):3356–63. https://doi.org/10.1111/j.1743-6109.2009.01422.x.
48. Reich DB, Zanarini MC. Sexual orientation and relationship choice in borderline personality disorder over ten years of prospective follow-up. J Personal Disord. 2008;22(6):564–72. https://doi.org/10.1521/pedi.2008.22.6.564.
49. Gorton G, Akhtar S. The literature on personality disorders, 1985-88: trends, issues, and controversies. Hosp Community Psychiatry. 1990;41(1):39–51.
50. Jonusiene G, Griffioen T. Psychiatric disorders and sexual dysfunctions. In: Kirana PS, Tripodi F, Reisman Y, Porst H, editors. The EFS and ESSM syllabus of clinical sexology. Amsterdam: ESSM Educational Committee; 2013. p. 380–927.
51. Apt C, Hurlbert DF. The sexual attitudes, behavior, and relationships of women with histrionic personality disorder. J Sex Marital Ther. 1994;20(2):125–33. https://doi.org/10.1080/00926239408403423.
52. Acuna MJ, Martin JC, Graciani M, Cruces A, Gotor F. A comparative study of the sexual function of institutionalized patients with schizophrenia. J Sex Med. 2010;7(10):3414–23. https://doi.org/10.1111/j.1743-6109.2010.01832.x.
53. Huguelet P, Mohr S, Boucherie M, Yaron M, Perroud N, Bianchi-Demicheli F. An exploration of sexual desire and sexual activities of women with psychosis. Rev Med Suisse. 2015;11(486):1691–5.
54. Rubio-Abadal E, Del Cacho N, Saenz-Navarrete G, Arranz B, Cambra RM, Cuadras D, et al. How hyperprolactinemia affects sexual function in patients under antipsychotic treatment. J Clin Psychopharmacol. 2016;36(5):422–8. https://doi.org/10.1097/JCP.0000000000000539.
55. Mitchison D, Hay PJ. The epidemiology of eating disorders: genetic, environmental, and societal factors. Clin Epidemiol. 2014;6:89–97. https://doi.org/10.2147/CLEP.S40841.
56. Castellini G, Lelli L, Ricca V, Maggi M. Sexuality in eating disorders patients: etiological factors, sexual dysfunction and identity issues. A systematic review. Horm Mol Biol Clin Invest. 2016;25(2):71–90. https://doi.org/10.1515/hmbci-2015-0055.
57. Pinheiro AP, Raney TJ, Thornton LM, Fichter MM, Berrettini WH, Goldman D, et al. Sexual functioning in women with eating disorders. Int J Eat Disord. 2010;43(2):123–9. https://doi.org/10.1002/eat.20671.
58. Castellini G, Lelli L, Lo Sauro C, Fioravanti G, Vignozzi L, Maggi M, et al. Anorectic and bulimic patients suffer from relevant sexual dysfunctions. J Sex Med. 2012;9(10):2590–9. https://doi.org/10.1111/j.1743-6109.2012.02888.x.
59. Raboch J, Faltus F. Sexuality of women with anorexia nervosa. Acta Psychiatr Scand. 1991;84(1):9–11.

60. Morgan JF, Lacey JH, Reid F. Anorexia nervosa: changes in sexuality during weight restoration. Psychosom Med. 1999;61(4):541–5.
61. Quadflieg N, Fichter MM. The course and outcome of bulimia nervosa. Eur Child Adolesc Psychiatry. 2003;12(Suppl 1):I99–109. https://doi.org/10.1007/s00787-003-1113-9.
62. Castellini G, Mannucci E, Mazzei C, Lo Sauro C, Faravelli C, Rotella CM, et al. Sexual function in obese women with and without binge eating disorder. J Sex Med. 2010;7(12):3969–78. https://doi.org/10.1111/j.1743-6109.2010.01990.x.
63. Kimmel MC, Ferguson EH, Zerwas S, Bulik CM, Meltzer-Brody S. Obstetric and gynecologic problems associated with eating disorders. Int J Eat Disord. 2016;49(3):260–75. https://doi.org/10.1002/eat.22483.
64. Madowitz J, Matheson BE, Liang J. The relationship between eating disorders and sexual trauma. Eat Weight Disord. 2015;20(3):281–93. https://doi.org/10.1007/s40519-015-0195-y.

5 Diagnosis of Sexual Dysfunctions in Psychiatric Population: Lights and Shadows of DSM-5 Taxonomy of Sexual Disorders

Alberto Siracusano and Emanuela Bianciardi

5.1 Introduction

Among the scientific community, the transition from the *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition, text revision [1] to the fifth edition [2] has yielded a heated debate on its applicability and reliability. In the aftermath of these controversies, it is crucial that clinicians comprehend what empirical data supported the pathways of these changes [3].

The aim of this chapter was to review the new taxonomy of sexual disorders highlighting lights and shadows of DSM-5.

The first change of DSM-5 was to divide sexual disorders into three separate sections: sexual dysfunctions, gender dysphoria, and paraphilic disorders (Table 5.1).

Sexual dysfunctions and gender dysphoria were placed beside each other, but paraphilic disorders were five sections after gender dysphoria, suggesting that they were not strongly interconnected.

5.2 Sexual Dysfunctions

The World Health Organization (WHO) declared that the definition of "sexual dysfunction" (SD) is a problematic field. According to the International Classification of Diseases, human sexual dysfunction is "the various ways in which an individual is unable to participate in a sexual relationship as he or she would wish" [4]. The DSM-IV classified sexual dysfunctions on the basis of the four phases of human sexual response that were extrapolated from the theory of Masters and Johnson: excitement, plateau, orgasm, and resolution [5]. Then, Kaplan reduced the phases of

A. Siracusano · E. Bianciardi (✉)
Psychiatry, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
e-mail: siracusano@med.uniroma2.it; bianciardi@med.uniroma2.it

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*,
Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_5

Table 5.1 Changes from DSM-IV TR to DSM-5

DSM-IV TR diagnoses	DSM-5 diagnoses
Sexual dysfunctions and gender identity disorder	
Gender identity disorder	*Gender dysphoria*
Gender identity disorder	Gender dysphoria
Gender identity disorder NOS	Other specified gender dysphoria
	Unspecified gender dysphoria
Sexual dysfunctions	*Sexual dysfunctions*
Male orgasm disorder	Delayed ejaculation
Male erectile disorder	Erectile disorder
Female orgasm disorder	Female orgasm disorder
Female hypoactive desire disorder	Female sexual interest/arousal disorder
Female arousal disorder	
Dyspareunia	Genito-pelvic pain/penetration disorder
Hypoactive sexual desire disorder	Male hypoactive sexual desire disorder
Premature (early) ejaculation	Premature (early) ejaculation
Sexual aversion disorder	
Medication-induced sexual dysfunctions	Substance/medication-induced sexual dysfunctions
Substance-induced sexual dysfunctions	
Sexual dysfunctions NOS	Other specified sexual dysfunctions
	Unspecified sexual dysfunctions
Paraphilia	*Paraphilic disorder*
Voyeurism	Voyeuristic disorder
Exhibitionism	Exhibitionistic disorder
Frotteurism	Frotteuristic disorder
Sadism	Sexual sadism disorder
Masochism	Sexual masochism disorder
Pedophilia	Pedophilic disorder
Fetishism	Fetishistic disorder
Transvestic fetishism	Transvestic disorder
Paraphilia NOS	Other specified paraphilic disorder
	Unspecified paraphilic disorder

sexual response into three, desire, arousal and orgasm, assuming that sexual response would be linear rather than complex, as in the case of women [6]. In fact, it was argued that the cycle of sexual experience is more complex than linear, with several gender differences [7]. Therefore, in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, sexual disorder diagnostic criteria were revised abandoning the Masters and Johnson conceptual model.

Moreover, there was the need to establish what set a sexual problem into the area of psychiatric disorders [8, 9]. Accordingly, consistent with the diagnostic criteria that define the classification of many other mental disorders, the DSM-5 claims a minimum duration of 6 months together with a frequent presentation (sexual dysfunction occurring at least 75% of sexual encounters) in order to differentiate sexual disorders from other transient conditions.

Although this change was made to improve the diagnostic system, adding the standard of duration criteria may delay the treatment especially in those suffering from vaginism where a shorter period may be sufficient for diagnosis to be made. Further, this change may lead to a delayed treatment.

Another change from DSM-IV was to replace the global dysfunction criterion, "marked distress or interpersonal difficulty," with the DSM-5 criterion "clinically significant distress in the individual." Since a sexual disorder may negatively influence one's intimate relationship, it is creditable that the individual may experience clinically significant distress either in absence of a partner or intentionally avoiding sexual activities. Moreover, this latter change may help in reducing stigma that was associated with sexual disorders. In fact, it is now possible to make a diagnosis of sexual disorder in a person only when the disorder cause personal distress. By contrast, in DSM-IV it was stated than sexual disorder was present when it produced interpersonal difficulties [10].

Given the difficulty in attributing the cause of sexual disorders to psychological or combined factor, it was decided to remove these specifiers recommending the "V" or "Z" code when a relationship discord or a stressful/traumatic life event is recognized.

However, despite the advances of the new DSM, some critical issues are still wide open. Some clinicians believe that gender differences were not adequately cleared up with specific criteria [11, 12]. For example, criteria for early ejaculation and genito-pelvic pain/penetration disorder (GPPD) are applicable only to those experiencing vaginal intercourse rather than including homosexual orientation and non-penetrative sexual activities. The DSM-IV-TR terms "dyspareunia" and "vaginismus" were merged into the single disorder GPPD in DSM-5. Although some researches agreed with the elimination of the term "vaginismus" that was considered as labeling, and ignored women's anxiety and fear of pain referring only to muscle contractions, others underlined the uselessness of grouping together superficial dyspareunia and vaginismus in clinical practice where painful intercourse may require different treatment in respect to high anxiety and avoidance associated with fear of pain [13, 14]. Another issue is that it is possible to diagnose dyspareunia in men with the same criteria of women. Regarding the decision to combine "hypoactive sexual disorder" (HSDD) and "female sexual arousal disorder" (FSAD) into the "female sexual interest and arousal disorder" (FSIAD), it was argued that some women might have low sexual arousal without the impairment of sexual response and interest [15–17]. In the new classification of sexual disorders, one more controversy that needed to be elicited is about the diagnosis of "premature ejaculation" (PE). DSM-5 introduced the operational criterion, namely, "ejaculation occurring within approximately 1 min of vaginal penetration or sooner than"; some concerns regarding the absence of precise duration criteria for non-vaginal sexual activities and the cutoff of 1-min duration of "intravaginal ejaculation latency time" (IELT) were advanced. Moreover, the International Society for Sexual Medicine (ISSM) statement as "inability to delay ejaculation" was not clearly made explicit in DSM-5 [18].

Finally, the new released DSM-5 codes "sexual aversion disorder" as "other specified sexual disorder, this decision of not including sexual aversion disorder in the DSM-5 was supported by the lack of empirical data and the similarity of sexual aversion to phobias. Nevertheless, because sexual aversion rarely reverses spontaneously, the exclusion from the classification of mental disorders may worsen its recognition and treatment, underestimating the clinical presentation [19, 20].

5.3 Gender Dysphoria

Although the discordance between the personal sense of one' own gender, that is, "gender identity," and the sex assigned at birth, that is, "assigned gender" (Fig. 5.1), may cause discomfort or dysphoria in transgender people, there is an ongoing problematic debate about gender diagnosis that arises mostly from the controversial relationship between psychiatric disorder and stigma existing in this field [20–22]. In fact, whether the psychiatric diagnosis is necessary to engage in a gender reassignment protocol, it was debated about the unnecessary psycho-pathologization of transgender people [23, 24].

Accordingly, some members of the trans community concerned that the removal of gender dysphoria (GD) from the DSM would lead to denied access to public healthcare for those who seek medical and surgical treatment [25]. Perpetuating the gender identity disorder diagnosis in the psychiatric classification systems would further label transgender individuals, who are at high risk of lifetime bullying, stigmatization, and discrimination from peers and society [26]. Moving from these points, in the DSM-5 developed several changes in the gender diagnoses. With the challenge of reducing stigma, the gender identity disorder was renamed as gender dysphoria, which was placed in an independent section of DSM-5 and separated from paraphilias and sexual dysfunction. In this way, psychiatric diagnosis emerged as a transient condition and was restricted to individual who are, in a certain moment

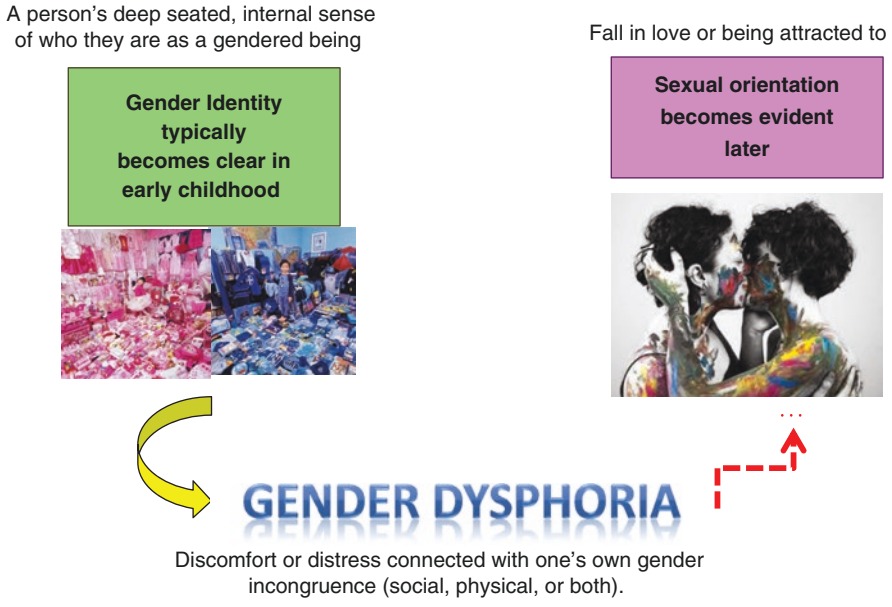

Fig. 5.1 Differences between gender identity, gender dysphoria, and sexual orientation

of their lives, distressed about their incongruence between gender assignment and gender identity. The revised nomenclature evidenced that gender identity is not synonyms of disorder [27]. In fact, dysphoria is a clinical symptom describing a mixing of discomfort, dissatisfaction, depression, anxiety, or agitation that regards, in this case, one's gender or physical sex.

An additional matter of controversies was that the criterion of distress and impairment was not universally present albeit it was required for the diagnosis [28]. However, the diagnostic criteria were simplified to reduce false positives. The specifier of "post-transition" was added to help individuals with no-longer dysphoria but still attending medical therapies with the aim to ensure the continuing treatment procedures. An important controversy related to the DSM-5 gender dysphoria was the retention of the diagnoses in children and in adolescents [29, 30]. It was debated that the diagnosis might label children as mentally disordered and may constitute a basis to obtain precautionary treatments for gender incongruence in childhood. On the other hand, even if gender identity disorder of childhood may not persist into adulthood, little is known about the factors that predict the persistency [31]. Thus, the diagnosis of childhood gender dysphoria was not removed from DSM-5 in order to guarantee access to medical care either for the future gender reassignment or to support the child in coping with the potential social risk factors such as bullying and stigmatization.

5.4 Paraphilic Disorders

The DSM-5 revision introduced many changes in the paraphilic disorders section, addressing some of the concerns that were proposed. The field was complicated by the problematic relationship existing between civil, criminal, and psychiatric judgments, ethics and moral points, and the variability of sexual norms across time and cultures [32, 33].

Another issue was the paucity of clinical data leading to a prevalence of forensic reviews to be considered by the Paraphilia Subworkgroup panel for the revision of paraphilic disorders rather than clinical studies carried out from psychiatrists or experts in the field of sexology [34, 35]. In fact, there was no evidence of trials funded by the American Psychiatric Association (APA) with the result of a lack of empirical support, uncertain reliability, and doubtful prevalence estimates [36]. The first advance of DSM-5 was to provide the definition of "normal" sexual behavior giving an elucidation of what paraphilic interests are not, namely, "an intense and persistent sexual interest other than sexual interest in genital stimulation or preparatory fondling with phenotypically normal, physically mature, consenting human partners." Further, in the text was clarified that paraphilic interests may be preferential rather than intense [37, 38].

A significant change was the distinction between paraphilias and paraphilic disorders, more consistently with the point of view of sexologists and researches.

Originally the term paraphilia was used to describe inverted erotic interests and, lately, with the DSM-III was used as a scientific expression characterizing atypical sexual arousal to objects, situations, or non-consenting individuals [39]. It is important to note that adult sexual fantasy and role-play are not correspondent to paraphilia because they may represent a continuum of phenomenon with qualitative and significant differences as in the case of sadism. However, there is relatively little agreement on when an unusual sexual interest becomes a paraphilia, especially considering the forensic implications [40, 41]. Voyeuristic, exhibitionistic, frotteuristic, and pedophilic paraphilias are legally classified as sexual offenses [42]. Thus, the presence or absence of mental disorders strongly influences civil and criminal judgments [43]. Moreover, there are some evidences about the risk of recidivism of paraphilic behaviors, and some sexual offenders had more than one paraphilia [44]. With the aim of make a distinction between the paraphilia and a psychiatric disorder the DSM specified that it is necessary to meet criteria A and B. In other words, one must display the paraphilia together with a clinically significant distress or impairment [45].

The criterion A of DSM-IV-TR for paraphilias was "over a period of at least 6 months, recurrent, intense sexually arousal fantasies, sexual urges or behaviors…." The statement generated ambiguity due to the possibility to assume that a behavior corresponds to a mental disorder, the paraphilia, with forensic consequences as a mitigated judgment.

Although it was cleared that the underlying arousal pattern, not the behavior, individuates the paraphilia, DSM-5 declared that recurrent patterns of relevant sexual behaviors may allow the diagnosis when the offender reneges the arousal, leading to many controversies regarding what relevant recurrent sexual behaviors means and how objectively measures arousal in someone who rejects it.

For all the paraphilic disorders, with the exception of pedophilia, the DSM-5 added a specifier indicating if paraphilic disorder is in remission either "in a controlled environment" or "in full remission." Two main arguments were opposed. The first was that paraphilic interest seems to be enduring, and the second regarded the paucity of empirical supporting data. However, according to the DSM-5, the paraphilic arousal may discontinue to cause dysfunction at some points in the lifespan leading clinicians to capture the ameliorations of patients [46].

Another disputation of the new taxonomy was a discrepancy between the age criteria of the different disorders. DSM-5 established an age criterion that was at least 18 years of age, only for voyeuristic disorder, and for pedophilic disorder indicating that the individual must be at least 16 years of age or at 5 years older than the victim. This assumption may suggest that voyeurism is not a disorder prior to age 18. Moreover, this cut-off did not reflect a particular neurodevelopmental changes but representing the age of majority in legal terms.

Furthermore, it was proposed to differentiate individuals with pedophilic disorders in two groups, those with interest in prepubertal children and those with pedohebephile disorder focusing on pubertal (ages 10–13) victims. Although there was no consensus about the utility of such differentiation, it was well recognized that victim age is an imperfect proxy of hebephilia and pedophilia. In fact, there are

important diversities in being sexually interested in pubertal or prepubertal young people [47, 48].

Finally, two paraphilia disorders, paraphilic coercive disorder and hypersexual disorder, were rejected from the revised DSM-5.

The exclusion of paraphilic coercive disorder was mainly motivated by the fear of medicalization of criminal behavior and by the inclination of DSM to conceptualize mental disorders with categories compared to dimensions of symptoms [49]. Accordingly, paraphilic coercive disorder was considered as a mitigated form of sadism. Even though, in DSM-5 there were not included specifies of severity simptoms to the sexual sadism disorder criteria [50, 51].

The concerns about hypersexual disorder regarded the insufficient psychometric instruments with the result of overdiagnosis and the poverty of scientific researches [52]. In particular there is no unanimity on the etiologic theory of the disorder with some pushing for a paraphilic disorder and others relying more on the addiction model [53]. One probable consequence, as expected, may be the inconsistency of treatments [53].

In conclusion, endorsing additions of DSM-5 were the notion of paraphilia, the distinction between paraphilias and disorders, and the inclusion of the remission specifier. Nevertheless, the lack of empirical supports about the aetiology and the biological correlates of the disorders resulted in poor reliability of diagnoses, with the second most frequent paraphilic disorder for civil commitment in the United States being the paraphilic disorders Not Otherwise Specified (NOS).

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Washington: American Psychiatric Association; 2000.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. Washington: American Psychiatric Association; 2013.
3. Campbell MM, Artz L, Stein DJ. Sexual disorders in DSM-5 and ICD-11: a conceptual framework. Curr Opin Psychiatry. 2015;28(6):435–9.
4. World Health Organisation. Defining sexual health. Report of a technical consultation on sexual health. Geneva: World Health Organisation; 2002. p. 2006.
5. Masters WH, Johnson VE. Human sexual response. New York: Bantam; 1966.
6. Kaplan HS. The new sex therapy. New York: Brunner/Mazel; 1974.
7. DeFeo J. Understanding sexual, paraphilic, and gender dysphoria disorders in DSM-5. J Child Sex Abus. 2015;24:210–5.
8. McCabe MP, Sharlip ID, Atalla E, Balon R, Fisher AD, Laumann E, 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. Navarro-Cremades F, Simonelli C, Montejo AL. Sexual disorders beyond DSM-5: the unfinished affaire. Curr Opin Psychiatry. 2017;30(6):417–22.
10. Sungur MZ, Gündüz A. A comparison of DSM-IV-TR and DSM-5 definitions for sexual dysfunctions: critiques and challenges. J Sex Med. 2014;11(2):364–73.
11. Derogatis LR, Sand M, Balon R, Rosen R, Parish SJ. Toward a more evidence-based nosology and nomenclature for female sexual dysfunctions – part I. Sex Med. 2016;13(12):1881–7.

12. Parish SJ, Goldstein AT, Goldstein SW, Goldstein I, Pfaus J, Clayton AH, et al. Toward a more evidence-based nosology and nomenclature for female sexual dysfunctions – part II. J Sex Med. 2016;13(12):1888–906.
13. Brauer M, Lakeman M, van Lunsen R, Laan E. Predictors of task-persistent and fear-avoiding behaviors in women with sexual pain disorders. J Sex Med. 2014;11(12):3051–63.
14. Both S, Brauer M, Weijenborg P, Laan E. Effects of aversive classical conditioning on sexual response in women with dyspareunia and sexually functional controls. J Sex Med. 2017;14:687–701.
15. Derogatis LR, Laan E, Brauer M, Van Lunsen RHW, Jannini EA, Davis SR, et al. Responses to the proposed DSM-V changes. J Sex Med. 2010;7(6):1998–2014.
16. O'Loughlin JI, Basson R, Brotto LA. Women with hypoactive sexual desire disorder versus sexual interest/arousal disorder: an empirical test of raising the bar. J Sex Res. 2017:1–13.
17. Sarin S, Amsel R, Binik YM. A streetcar named "Derousal"? A psychophysiological examination of the desire-arousal distinction in sexually functional and dysfunctional women. J Sex Res. 2016;53(6):711–29.
18. McMahon CG, Althof SE, Waldinger MD, Porst H, Dean J, Sharlip ID, et al. An evidence-based definition of lifelong premature ejaculation: report of the International Society for Sexual Medicine (ISSM) ad hoc committee for the definition of premature ejaculation. J Sex Med. 2008;5(7):1590–606.
19. Borg C, de Jong PJ, Elgersma H. Sexual aversion and the DSM-5: an excluded disorder with unabated relevance as a trans-diagnostic symptom. Arch Sex Behav. 2014;43(7):1219–23.
20. Beek TF, Cohen-Kettenis PT, Kreukels BP. Gender incongruence/gender dysphoria and its classification history. Int Rev Psychiatry. 2016;28(1):5–12.
21. Zucker KJ. Epidemiology of gender dysphoria and transgender identity. Sex Health. 2017;14(5):404–11.
22. Davy Z. The DSM-5 and the politics of diagnosing transpeople. Arch Sex Behav. 2015;44(5):1165–76.
23. Zucker KJ. DSM-5: call for commentaries on gender dysphoria, sexual dysfunctions, and paraphilic disorders. Arch Sex Behav. 2013;42:669–74.
24. Lawrence AA. Gender assignment dysphoria in the DSM-5. Arch Sex Behav. 2014;43(7):1263–6.
25. Ault A, Brzuzy S. Removing gender identity disorder from the diagnostic and statistical manual of mental disorders: a call for action. Soc Work. 2009;54:187–9.
26. Winter S, Diamond M, Green J, Karasic D, Reed T, Whittle S, Wylie K. Transgender people: health at the margins of society. Lancet. 2016;388(10042):390–400.
27. Mueller SC, De Cuypere G, T'Sjoen G. Transgender research in the 21st century: a selective critical review from a neurocognitive perspective. Am J Psychiatry. 2017;174(12):1155–62.
28. Drescher J. Controversies in gender diagnoses. LGBT Health. 2014;1:10–4.
29. Drescher J, Cohen-Kettenis PT, Reed GM. Gender incongruence of childhood in the ICD-11: controversies, proposal, and rationale. Lancet Psychiatry. 2016;3:297–304.
30. Steensma TD, Biemond R, de Boer F, Cohen-Kettenis PT. Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study. Clin Child Psychol Psychiatry. 2011;16(4):499–516.
31. Kraus C. Classifying intersex in DSM-5: critical reflections on gender Dysphoria. Arch Sex Behav. 2015;44(5):1147–63.
32. Downing L. Heteronormativity and repronormativity in sexological "perversion theory" and the DSM-5's "paraphilic disorder" diagnoses. Arch Sex Behav. 2015;44:1139–45.
33. Potter NN. Philosophical issues in the paraphilias. Curr Opin Psychiatry. 2013;26:586–92.
34. Seto MC, Fedoroff JP, Bradford JM, Knack N, Rodrigues NC, Curry S, et al. Reliability and validity of the DSM-IV-TR and proposed DSM-5 criteria for pedophilia: implications for the ICD-11 and the next DSM. Int J Law Psychiatry. 2016;49(Pt A):98–106.
35. Moser C. DSM-5 and the paraphilic disorders: conceptual issues. Arch Sex Behav. 2016;45(8):2181–6.

36. Beech AR, Miner MH, Thornton D. Paraphilias in the DSM-5. Annu Rev Clin Psychol. 2016;12:383–406.
37. Ross CA. Commentary: problems with the sexual disorders sections of DSM-5. J Child Sex Abus. 2015;24:195–201.
38. Blanchard R. A dissenting opinion on DSM-5 pedophilic disorder. Arch Sex Behav. 2013;42:675–8.
39. De Block A, Adriaens PR. Pathologizing sexual deviance: a history. J Sex Res. 2013;50(3–4):276–98.
40. First MB, Frances A. Issues for DSM-V: unintended consequences of small changes: the case of paraphilias. Am J Psychiatry. 2008;165:1240–1.
41. Ryan EP, Otonichar JM. Juvenile sex offenders. Curr Psychiatry Rep. 2016;18(7):67.
42. Chan HC, Beauregard E, Myers WC. Single-victim and serial sexual homicide offenders: differences in crime, paraphilias and personality traits. Crim Behav Ment Health. 2015;25(1):66–78.
43. Turner D, Petermann J, Harrison K, Krueger R, Briken P. Pharmacological treatment of patients with paraphilic disorders and risk of sexual offending: an international perspective. World J Biol Psychiatry. 2017;23:1–25.
44. Joyal CC. Linking crime to paraphilia: be careful with label. Arch Sex Behav. 2017;46(4):865–6.
45. Wright S. Kinky parents and child custody: the effect of the DSM-5 differentiation between the paraphilias and paraphilic disorders. Arch Sex Behav. 2014;43:1257–8.
46. Federoff JP, Di Giacchino L, Murphy L. Problems with the paraphilias in DSM-5. Curr Psychiatry Rep. 2013;15:363.
47. Good P, Burstein J. Hebephilia and the construction of a fictitious diagnosis. J Nerv Ment Dis. 2012;200:492–4.
48. Stephens S, Seto MC, Goodwill AM, Cantor JM. Evidence of construct validity in the assessment of hebephilia. Arch Sex Behav. 2017;46(1):301–9.
49. Knight RA. Is a diagnostic category for paraphilic coercive disorder defensible? Arch Sex Behav. 2010;39:419–26.
50. Briken P, Bourget D, Dufour M. Sexual sadism in sexual offenders and sexually motivated homicide. Psychiatr Clin North Am. 2014;37(2):215–30.
51. Mokros A, Schilling F, Weiss K, Nitschke J, Eher R. Sadism in sexual offenders: evidence for dimensionality. Psychol Assess. 2014;26(1):138–47.
52. Montgomery-Graham S. Conceptualization and assessment of hypersexual disorder: a systematic review of the literature. Sex Med Rev. 2017;5(2):146–62.
53. Kingston DA, Graham FJ, Knight RA. Relations between self-reported adverse events in childhood and hypersexuality in adult male sexual offenders. Arch Sex Behav. 2017;46(3):707–20.

6 Aspects of Sexuality During Development in Autism Spectrum Disorder

Valentina Postorino, Martina Siracusano, Giulia Giovagnoli, and Luigi Mazzone

6.1 Introduction

Sexuality is a central dimension of a person's physical and psychological development, and it plays a fundamental role in shaping the individual's self-identity [1, 2]. In the past few years there has been an increased attempt to support people with developmental disabilities (e.g., autism spectrum disorder (ASD), Down syndrome, etc.) to experience all areas of their lives as normal as possible [3–5]. However, little attention has been paid to aspects of sexuality and romantic relationships in these populations [6].

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in two core domains: persistent deficits in social communication and social interaction across multiple contexts, and restricted and repetitive patterns of behavior, interests, or activities [7].

Although individuals with ASD experience the same aspects of sexuality (e.g., needs, desires, sex driven) as their peers, core symptoms of autism (i.e., deficits in social communication and social interaction) may impact on their ability to develop romantic and sexual relationships [8–12]. This implies that they may be not provided with the opportunity to achieve several developmental stages of their sexuality, which, in turn, can affect later well-being. For example, it is known that individuals with ASD are at an increased risk of sexual abuse or that they are more concerned with finding a partner [13, 14].

V. Postorino
Brain and Body Integration Mental Health Clinic, Denver, CO, USA

M. Siracusano · L. Mazzone (✉)
Department of Neurosciences, Child Neurology and Psychiatry Unit, Tor Vergata University Hospital of Rome, Rome, Italy
e-mail: gigimazzone@yahoo.it

G. Giovagnoli
Scientific Neuropsychiatric Center "Aita", Rome, Italy

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*, Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_6

Given the impact on long-term outcomes and well-being, understanding sexual development and sexual functioning in individuals with ASD is important in order to develop future research designs and interventions. To date, however, there has been little research on this topic in this clinical population.

In this chapter we examine characteristics of sexual development in ASD. Examination of the relationship between core symptoms of ASD and sexual relationships in children and adolescents with ASD may help clinicians disentangle factors likely associated with sexual well-being of individuals with ASD, in order to plan proactive prevention and intervention.

6.2 Sexual Development in ASD: The Role of Sex Hormones

Studies in nonhuman animals have demonstrated that the levels of sex hormones during early development have long-term effects on a variety of behaviors (e.g., learning, memory, play) [15]. Moreover, these studies have reported that hormones present during the prenatal period, including androgens (e.g., testosterone), act on the brain to induce sex differences in brain structure and influence human behavior [16]. Recent evidences have suggested that the brain is also sensitive to the effect of sex hormones during adolescence. These effects are relevant for the sexual development for several reasons. First, given that sex hormones refine neural circuits from early development to late development, adult sexual behaviors depend on appropriate exposure to these hormones during all stages of development. Second, if the brain is also sensitive to the effect of sex hormones during late development, pubertal timing can vary depending on the exposure to these hormones, and this can have different consequences on the behavior development (e.g., adverse behavioral outcomes of early puberty in girl). Finally, hormone deficiencies may be compensated only in part by social experiences.

Gender is the product of the interaction between an individual's biological sex and gender identity. Children start to be conscious about their gender between the ages of 18 months and 3 years [17]. The majority of children achieve their gender identity by the time they start to go to school, and, at that point, they start to be aware that their identity cannot change by the clothes they wear or the toys they play with.

Physical sexual maturation follows the normal developmental stages in individuals with ASD [18]. However, core symptoms of ASD, such as difficulties to develop and maintain relationships, lack of social insight, impaired theory of mind, reduced ability to empathize with others, or reduced social awareness, may delay or affect the achievement of gender identity [19]. Accordingly, studies have suggested that gay male or female sexual interest and bisexual sexual interest is more frequent in individuals with ASD [17, 20, 21]. Similarly, gender dysphoria is also common in individuals with ASD (see Sect. 6.4).

It has been speculated that fetal or perinatal exposure to elevated levels of male hormones may increase the risk for ASD. Specifically, the "extreme male brain" theory suggests that prenatal testosterone shapes the brain during fetal life toward masculinized cognition and behavior [22]. Auyeung et al. reported that fetal

testosterone measured from amniotic fluid relates positively to sexually differentiated play behavior in both girls and boys [23].

In line with this data, exposure to high levels of prenatal testosterone might be a risk factor for autism given that individuals with ASD demonstrate characteristics associated with masculinity, such as low empathy and high logical thinking [22].

Support for the influence of fetal sex hormones and later behaviors derives from a large body of research on women with congenital adrenal hyperplasia (CAH). CAH is a family of genetic disorders resulting from mutations of genes for enzymes mediating the biochemical steps of production of mineralocorticoids, glucocorticoids, or sex steroids from cholesterol by the adrenal glands (steroidogenesis) [24]. In the majority of these conditions, there is an excessive or deficient production of sex steroids that can affect the development of sex characteristics. If exposure to high levels of prenatal testosterone influences sexual development, women with this disorder should have masculinized cognition and behavior. In line with this thinking, studies on this population have reported that girls with CAH show increased preferences for male toys and activities and homosexual and/or bisexual orientations [25, 26].

Speculating, this pattern could also provide an explanation regarding the high rate of gender dysphoria found in females with ASD [17]. In more detail, exposure to prenatal testosterone in females with ASD could lead to masculine self-perception and, in turn, to perceive themselves as more masculine than their peers.

6.3 Sexuality and Romantic Relationships in Children and Adolescents with ASD

Early studies on sexuality in ASD heavily focused on the description of behavioral problems and difficulties in this field [27]. However, recently it has been always more accepted that sexuality is a part of the normal development, and there has been a growing interest toward psychosexual functioning in adolescents with ASD [3, 28, 29]. In the past, it was thought that people with ASD were indifferent to relationships with others, except for the necessity to satisfy their needs. This belief was disconfirmed by recent research, which has shown that individuals with ASD are interested to communicate and socialize with others, and in social, affective and romantic relationships [29–32].

As previously suggested, individuals with ASD go through the same sexual development as their peers. However, social communication and interaction deficits may affect their ability to develop romantic and sexual relationships [8–12]. For example, individuals with ASD have a reduced ability to understand rules of social interaction and difficulties in understanding people's behavior and feelings, which are necessary to establish sexual and romantic relationships.

This imbalance between physical and social maturation becomes particularly clear during adolescence, when individuals start to develop friendships and start to have their first romantic and sexual relationships. It is worth noting that

among the other barriers that affect sexual development in individuals with ASD, there is the fact that parents are commonly overprotective, and this can limit the already limited opportunities that people with ASD have to interact with peers [33].

Furthermore, psychosexual functioning may also be affected by other autistic features, such as sensory sensitivity. For example, people with ASD can be both hypersensitive and hyposensitive to sensory stimuli. Hypersensitivity can make the physical contact unpleasant, thus making the sexual experience unbearable. On the other hand, hyposensitivity may result in difficulty to became aroused or reach the orgasm which, in the worst cases, can lead females to experience a female orgasmic disorder or a female sexual interest/arousal disorder and males to have a delayed ejaculation or an erectile disorder [7, 34].

Overall, studies on sexuality and romantic relationships in individuals with ASD have reported contrasting results [13, 28, 30, 35]. For example, Dewinter et al. explored self-reported sexual behaviors, interests, and attitudes of 50 high-functioning adolescent boys with ASD compared with a control group of 90 boys [30]. Results of this study showed that the two groups were remarkably similar in terms of sexual behaviors: they fell in love, started to masturbate, and experienced their first orgasm in the same period. However, boys with ASD were more tolerant toward homosexuality compared to the control group. Moreover, a substantial part of boys with ASD reported to had experienced other partnered sexual behaviors. Similarly, Strunz et al., evaluating interest and experience in romantic relationships in 229 high-functioning adults with ASD, found that the majority of them (73%) were both interested and engaged in a romantic relationship [35]. In addition, individuals with ASD whose partner had a diagnosis of ASD, were also more satisfied with their relationship.

On the other hand, a recent study found that adolescents with ASD engaged in fewer social behaviors, had less sex education, fewer sexual experiences, and more pronounced concerns for the future compared to typically developing peers [13]. Accordingly, Dewinter et al. comparing a sample of 30 adolescent boys with ASD to 60 boys in the general population found that the proportion of boys with ASD that had no partnered sexual experience was larger than in the control group [28]. In addition, half of the ASD sample indicated some regrets about their first experience with sexual intercourse, and the majority of them did not use protections.

As a general consideration, it has to be noticed that severity of autism symptoms has been reported to be associated with problematic aspects of psychosocial sexual functioning in individuals with ASD, such as excessively thinking about sex, public masturbation, stalking, and sexual offenses. However, all of these studies involved only high-functioning participants [32, 36–40].

Taken all together, these findings suggest that people with ASD, and in particular during adolescence, could benefit from specialized sex education programs [13] (see Sect. 6.5).

6.4 Inappropriate Sexual Behaviors, Paraphilic Behaviors, Gender Dysphoria, and Risk of Sexual Abuse in ASD

Inappropriate sexual behaviors (e.g., public masturbation, excessive masturbation, stalking), paraphilic behaviors (e.g., pedophilia, frotteurism, etc.), sexual dysfunctions, gender dysphoria (GD), and higher risk of sexual abuse are often described in adolescents with ASD [18, 32, 36–40]. These inappropriate sexual behaviors can cause significant distress in individuals with ASD, may became a significant stressor for families, have a negative impact on quality of life, and can put this population in danger of experiencing sexual victimization with all the negative impact that it can have on the individual's mental health and well-being.

6.4.1 Inappropriate Sexual Behaviors

Inappropriate sexual behaviors often reported in adolescents with ASD are mainly related to public masturbation, excessive masturbation, and stalking [18, 27, 41, 42].

These behaviors may be explained by the fact that even if adolescents with ASD have the same sexual needs as their peers, lack of social awareness and skills, and deficits in theory of mind can lead these individuals to not always act suitably to the social setting. For example, the normal physical changes that occur during puberty can cause a sexual urge, and multiple stimuli can become sexually exciting; however, the lack of social awareness can bring these individuals to undress in presence of others and to engage in public masturbation [27, 41, 42]. In general, it has to be noted that public masturbation has been described mainly in low-functioning adolescents with autism. Instead, it seems that high-functioning individuals with ASD practice masturbatory behaviors, but not in public [39].

Excessive masturbation has also been described in adolescents with ASD [27]. Several things can be hypothesized to cause this inappropriate behavior. First, it can be possible that excessive masturbation might be related to hyposensitivity often present in individuals with ASD: these individuals may perseverate in masturbation due to altered tactile sensitivities that may result in low pleasure's perception and difficulty in reaching the orgasm [39]. Second, excessive masturbation can be a self-stimulatory behavior caused by the lack of other alternatives for sexual tension [27]. Finally, sexual knowledge, such as masturbatory techniques, is also acquired interacting with peers. However, deficits in social interaction lead adolescents with ASD to have less opportunities to interact with other adolescents. Therefore, excessive masturbation, caused by poor masturbatory technique, can be due by a limited sex education.

Another inappropriate social behavior that is often described in individuals with ASD is stalking. This behavior can be explained by some characteristic impairments present in individuals with ASD. Specifically, deficits in theory of mind (i.e., the ability to understand what someone else is thinking) or difficulty to interpret

correctly interpersonal cues (e.g., verbal or nonverbal cues from other people to communicate that the individual is unwanted) may lead these individuals to misunderstand social relationships. Repetitive interests and insistence on sameness can be expressed as a perseverative focus on a desired person. This behavior can also put individuals with ASD at risk to engage in stalking behavior.

6.4.2 Paraphilic Behaviors

Knowledge on paraphilic and/or unusual sexual behaviors, (e.g., pedophilia, fetishism, transvestism, exhibitionism, voyeurism), in individuals with ASD, comes largely from case studies [18, 39, 43–48]. Therefore, there is a lack of information regarding the prevalence of paraphilic disorders in this clinical population.

Hellemans et al., investigating sexual behaviors in 24 institutionalized, male, high-functioning adolescents and young adults with ASD, found that two participants involved in the study were primarily attracted to young, prepubescent girls [39]. In more detail, one had a platonic interest in young girls, whereas the other one met diagnostic criteria for pedophilia. Moreover, another participant included in this study met criteria for a diagnosis of fetishistic disorder.

Dozier et al. described a case of a 36-year-old man with ASD displaying foo-shoe fetishistic behaviors who responded to treatment using a response-interruption/time-out procedure [47].

Similarly, Coskun et al. presented a case of a 13-year-old male with ASD and fetishistic behavior successfully treated using mirtazapine [48].

Some hypothesis has been suggested to explain the relationship between paraphilic behaviors and ASD. In particular, restricted and repetitive interests, attention to details, different sensitivity to sensory inputs, or unusual interest in sensory aspects of the environment may contribute to these behaviors in individuals with ASD [49]. However, further researches on this topic are needed.

6.4.3 Gender Dysphoria

Gender dysphoria is defined as a marked incongruence between one's biologic sex and current gender identity that cause significant distress and impairment [7].

Several case reports have described the presence of a comorbid gender dysphoria in individuals with ASD [45, 50–53].

A recent study assessing the presence of ASD in a sample of 204 children and adolescents referred to a gender identity clinic found a surprisingly high rate (7.8%) of comorbid occurrence of ASD and gender dysphoria [54].

It has been speculated that several factors may contribute to the high rate of gender dysphoria in individuals with ASD. First, the exposure to high levels of prenatal testosterone (see Sect. 6.2). Second, sensory issues characteristic of ASD can play a role for these individuals in the development this disorder. Specifically, individuals with ASD may perceive sensory stimulus differently from the general population.

They might have preferences for specific sensory inputs, or tactile sensations, and can chose, for example, their clothes basing on these preferences and independently from the social norms [17]. Finally, core symptoms of ASD may interfere with the development of gender identity (see Sect. 6.2) [17, 20, 21].

However, literature on the connection between these disorders is scarce, and more systemic researches are needed.

6.4.4 Sexual Victimization

It has been reported that individuals with ASD are at increased risk of sexual victimization [13, 55]. However, studies on this topic are still limited. Lower levels of sexual knowledge may contribute to unsafe sexual relationships (e.g., not using the condom) and eventually to sexual victimization, sexual violence, and sexual abuse.

For example, Brown-Lavoie et al. found that individuals with ASD had less perceived and actual knowledge and experienced more sexual victimization than individuals without ASD [55]. Of interest is that individuals with ASD obtained more sexual knowledge from nonsocial sources, such as television and Internet, compared to their peers. Moreover, a concerning rate of individuals with ASD (70%) reported to have experienced sexual contact victimization and sexual coercion victimization.

Again, possible explanations for the relationship between poor sexual knowledge and high rate of sexual victimization can be found in the communication and social deficits characteristic of ASD. For example, individuals with ASD may have restricted opportunities to interact with peers, which, in turn, can impact on their lower perceived and actual sexual knowledge. In the same way, deficits in theory of mind can lead an individual with ASD to be less able to understand others' negative intentions, or what is safe and unsafe.

Given the relationship between sexual knowledge and victimization, sex education seems of particular importance in this clinical population (see Sect. 6.5).

6.5 Psychosexual Education and Sex Interventions for Children and Adolescents with ASD

Several studies have highlighted the need and importance of psychosexual educational programs for individuals with ASD [3, 38, 55]. To date, interventions that focus on the psychosexual development of children and adolescents with ASD are, however, limited [56, 57].

Although numerous educational programs on sexuality have been developed for people with developmental delay (e.g., intellectual disability, psychomotor retardation), these programs are not generally appropriate for individuals with ASD due to the fact that they do not take in consideration the communication and social impairments that are characteristic of this clinical population [58].

Until a few years ago, only three educational programs on sexuality were specifically developed for individuals with ASD [58]. In more detail, the Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH) program includes a specific sexual education curriculum concerning how to (1) develop appropriate behaviors and habits, (2) address issues of personal hygiene, (3) understand sexual anatomy and functioning, and (4) explain different kind of social relationships [59]. The Devereux Center proposed a model that included in its curriculum a wide variety of topics (ranging from personal hygiene to marriage) [8]. Finally, the Benhaven School focused mainly on personal care and appropriate behaviors as it is directed to people with very severe symptoms [58].

It has to be noticed, however, that none of these programs had been systematically and quantitatively investigated.

Only recently, the first randomized controlled trial investigating the effects of a psychosexual training program (i.e., Tackling Teenage Training (TTT) program) for adolescents with ASD has been published [56]. In this trial, 189 adolescents with ASD were randomized to an intervention condition ($n = 95$) or a waiting-list control condition ($n = 94$). The intervention has been developed for adolescents with ASD from 12 to 18-years-old with a normal or high-functioning cognitive ability, and includes 18 weekly individual core sessions, in which adolescents with ASD receive information regarding several topics (i.e., psycho-education), alternated with exercises (e.g., behavioral rehearsals, and knowledge and insight quizzes). The results of this study provided evidences that the TTT program is effective in increasing social responsiveness and in decreasing problematic sexual behaviors in adolescents with ASD.

Overall, these results suggest that further longitudinal research is needed to investigate how an increased sexual knowledge can improve subsequent well-being in individuals with ASD.

Conclusion

Sexuality is a central aspect of a person's physical and psychological development [1, 2]. In the past decade, there has been an increased interest on this topic. However, studies on sexual development and sexual functioning in individuals with ASD are still scarce. Given the impact of these aspects on long-term outcomes and well-being, further researches are needed to determine best practices for prevention and treatment.

References

1. Ailey SH, Marks B, Crisp C, Hahn JE. Promoting sexuality across the life span for individuals with intellectual and developmental disabilities. Nurs Clin North Am. 2003;38:229–52.
2. Duncan PMD, Dixon RR, Carlson JMD. Childhood and adolescent sexuality. Pediatr Clin North Am. 2003;50:765–80.
3. Ginevra MC, Nota L, Stokes MA. The differential effects of Autism and Down's syndrome on sexual behavior. Autism Res. 2016;9(1):131–40.

4. Cuskelly M, Bryde R. Attitudes towards the sexuality of adults with an intellectual disability: parents, support staff, and a community sample. J Intellect Dev Disabil. 2004;29(3):255–64.
5. Gilmore L, Chambers B. Intellectual disability and sexuality: attitudes of disability support staff and leisure industry employees. J Intellect Dev Disabil. 2010;35(1):1–22.
6. Bazzo G, Nota L, Soresi S, Ferrari L, Minnes P. Attitudes of social service providers towards the sexuality of individuals with intellectual disability. J Appl Res Intellect Disabil. 2007;20(2):110–5.
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders-5. Washington, DC: American Psychiatric Association; 2013.
8. Koller R. Sexuality and adolescents with autism. Sex Disabil. 2000;18(2):125–35.
9. Lawson W. Sex, sexuality and the autism spectrum. London: Jessica Kingsley; 2005.
10. Murphy NA, Elias ER. Sexuality of children and adolescents with developmental disabilities. Pediatrics. 2006;118(1):398–403.
11. Van Son-Schoones N, van Bilsen P. Sexuality and autism. A pilot-study of parents, health care workers and autistic persons. Int J Adolesc Med Health. 1995;8(2):87–101.
12. Seltzer MM, Krauss MW, Shattuck PT, Orsmond G, Swe A, Lord C. The symptoms of autism spectrum disorders in adolescence and adulthood. J Autism Dev Disord. 2003;33(6):565–81.
13. Mehzabin P, Stokes MA. Self-assessed sexuality in young adults with high-functioning autism. Res Autism Spectr Disord. 2001;5(1):614–21.
14. Edelson MG. Sexual abuse of children with autism: factors that increase risk and interfere with recognition of abuse. Disabil Stud Q. 2010;30(1):1041–5718.
15. Berenbaum SA, Beltz AM. Sexual differentiation of human behavior: effects of prenatal and pubertal organizational hormones. Front Neuroendocrinol. 2011;32:183–200.
16. Sisk CL, Zehr JL. Pubertal hormones organize the adolescent brain and behavior. Front Neuroendocrinol. 2005;26(3–4):163–74.
17. George R, Stokes M. Gender is not on my agenda!: gender dysphoria and autism spectrum disorder. In: Mazzone L, Vitiello B, editors. Psychiatric symptoms and comorbidities in autism spectrum disorder. Berlin: Springer; 2016.
18. Beddows N, Brooks R. Inappropriate sexual behaviour in adolescents with autism Spectrum disorder: what education is recommended and why. Early Interv Psychiatry. 2016;10(4): 282–9.
19. Fernandes LC, Gillberg CI, Cederlund M, Hagberg B, Gillberg C, Billstedt E. Aspects of sexuality in adolescents and adults diagnosed with autism spectrum disorders in childhood. J Autism Dev Disord. 2016;46(9):3155–65.
20. Byers ES, Nichols S, Voyer SD. Challenging stereotypes: sexual functioning of single adults with high functioning autism spectrum disorder. J Autism Dev Disord. 2013;43(11):2617–27.
21. Byers ES, Nichols S, Voyer SD, Reilly G. Sexual well-being of a community sample of high-functioning adults on the autism spectrum who have been in a romantic relationship. Autism. 2013;17(4):418–33.
22. Knickmeyer RC, Baron-Cohen S. Fetal testosterone and sex differences in typical social development and in autism. J Child Neurol. 2006;21(10):825–45.
23. Auyeung B, Baron-Cohen S, Ashwin E, Knickmeyer R, Taylor K, Hackett G, et al. Fetal testosterone predicts sexually differentiated childhood behavior in girls and in boys. Psychol Sci. 2009;20(2):144–8.
24. Warrell DA. Oxford textbook of medicine: sections 18–33. Oxford: Oxford University Press; 2005.
25. Hines M. Prenatal endocrine influences on sexual orientation and on sexually differentiated childhood behavior. Front Neuroendocrinol. 2011;32:170–82.
26. Meyer-Bahlburg HF, Dolezal C, Baker SW, New MI. Sexual orientation in women with classical or non-classical congenital adrenal hyperplasia as a function of degree of prenatal androgen excess. Arch Sex Behav. 2008;37(1):85–99.
27. Realmuto GM, Ruble LA. Sexual behaviors in autism: problems of definition and management. J Autism Dev Disord. 1999;29(2):121–7.

28. Dewinter J, Vermeiren R, Vanwesenbeeck I, Van Nieuwenhuizen C. Adolescent boys with autism spectrum disorder growing up: follow-up of self-reported sexual experience. Eur Child Adolesc Psychiatry. 2016;25(9):969–78.
29. Kellaher DC. Sexual behavior and autism spectrum disorders: an update and discussion. Curr Psychiatry Rep. 2015;17(4):562.
30. Dewinter J, Vermeiren R, Vanwesenbeeck I, Lobbestael J, Van Nieuwenhuizen C. Sexuality in adolescent boys with autism spectrum disorder: self-reported behaviours and attitudes. J Autism Dev Disord. 2014;45(3):731–41.
31. Gilmour L, Schalomon PM, Smith V. Sexuality in a community based sample of adults with autism spectrum disorder. Res Autism Spectr Disord. 2012;6(1):313–8.
32. Stokes M, Newton N, Kaur A. Stalking, and social and romantic functioning among adolescents and adults with autism spectrum disorder. J Autism Dev Disord. 2007;37(10):1969–86.
33. Dewinter J, Vermeiren RRJM, Vanwesenbeeck I, Van Nieuwenhuizen C. Parental awareness of sexual experience in adolescent boys with autism spectrum disorder. J Autism Dev Disord. 2016;46(2):713–9.
34. Hénault I. Sexual relationships. In: Welkowitz LA, editor. Asperger's syndrome: intervening in schools, clinics, and communities. Mahwah: Lawrence Erlbaum Associates; 2005. p. 243–55.
35. Strunz S, Schermuck C, Ballerstein S, Ahlers CJ, Dziobek I, Roepke S. Romantic relationships and relationship satisfaction among adults with Asperger syndrome and high-functioning autism. J Clin Psychol. 2017;73(1):113–25.
36. Dekker LP, van der Vegt EJM, van der Ende J, Tick N, Louwerse A, Maras A, et al. Psychosexual functioning of cognitively-able adolescents with autism spectrum disorder compared to typically developing peers: the development and testing of the teen transition inventory- a self- and parent report questionnaire on psychosexual functioning. J Autism Dev Disord. 2017;47(6):1716–38.
37. Dekker LP, van der Vegt EJ, Visser K, Tick N, Boudesteijn F, Verhulst FC, et al. Improving psychosexual knowledge in adolescents with autism spectrum disorder: pilot of the tackling teenage training program. J Autism Dev Disord. 2015;45(6):1532–40.
38. Dewinter J, Vermeiren R, Vanwesenbeeck I, van Nieuwenhuizen C. Autism and normative sexual development: a narrative review. J Clin Nurs. 2013;22(23–24):3467–83.
39. Hellemans H, Colson K, Verbraeken C, Vermeiren R, Deboutte D. Sexual behavior in high-functioning male adolescents and young adults with autism spectrum disorder. J Autism Dev Disord. 2007;37:260–9.
40. Sevlever M, Roth ME, Gillis JM. Sexual abuse and offending in autism spectrum disorders. Sex Disabil. 2013;31(2):189–200.
41. Haracopos D, Pedersen L. Sexuality and autism: Danish report. 1992. www.autismuk.com.
42. Ruble LA, Dalrymple NJ. Social/sexual awareness of persons with autism: a parental perspective. Arch Sex Behav. 1993;22(3):229–40.
43. Murrie DC, Warren JI, Kristiansson M, Dietz PE. Asperger's syndrome in forensic settings. Int J Forensic Ment Health. 2002;1(1):59–70.
44. Robinow O. Paraphilia and transgenderism: a connection with Asperger's disorder? Sex Relation Ther. 2009;24(2):143–51.
45. Landen M, Rasmussen P. Gender identity disorder in a girl with autism – a case report. Eur Child Adolesc Psychiatry. 1997;6(3):170–3.
46. Milton J, Duggan C, Latham A, Egan V, Tantam D. Case history of co-morbid Asperger's syndrome and paraphilic behavior. Med Sci Law. 2002;42(3):237–44.
47. Dozier CL, Iwata BA, Worsdell AS. Assessment and treatment of foot-shoe fetish displayed by a man with autism. J Appl Behav Anal. 2011;44(1):133–7.
48. Coskun M, Mukaddes NM. Mirtazapine treatment in a subject with autistic disorder and fetishism. J Child Adolesc Psychopharmacol. 2008;18(2):206–9.
49. Silva JA, Ferrari MM, Leong GB. The case of Jeffrey Dahmer: sexual serial homicide from a neuropsychiatric developmental perspective. J Forensic Sci. 2002;47(6):1347–59.
50. Tateno M, Tateno Y, Saito T. Comorbid childhood gender identity disorder in a boy with Asperger syndrome. Psychiatry Clin Neurosci. 2008;62(2):238.

51. Mukaddes NM. Gender identity problems in autistic children. Child Care Health Dev. 2002;28(6):529–32.
52. Gallucci G, Hackerman F, Schmidt CW Jr. Gender identity disorder in an adult male with Asperger's syndrome. Sex Disabil. 2005;23(1):35–40.
53. Kraemer B, Delsignore A, Gundelfinger R, Schnyder U, Hepp U. Comorbidity of Asperger syndrome and gender identity disorder. Eur Child Adolesc Psychiatry. 2005;14(5):292–6.
54. de Vries AL, Noens IL, Cohen-Kettenis PT, van Berckelaer-Onnes IA, Doreleijers TA. Autism spectrum disorders in gender dysphoric children and adolescents. J Autism Dev Disord. 2010;40:930–6.
55. Brown-Lavoie SM, Viecili MA, Weiss JA. Sexual knowledge and victimization in adults with autism spectrum disorders. J Autism Dev Disord. 2014;44(9):2185–96.
56. Visser K, Greaves-Lord K, Tick NT, Verhulst FC, Maras A, van der Vegt EJ. A randomized controlled trial to examine the effects of the tackling teenage psychosexual training program for adolescents with autism spectrum disorder. J Child Psychol Psychiatry. 2017;58(7):840–50.
57. Hénault I. Asperger's syndrome and sexuality: from adolescence through adulthood. London: Jessica Kingsley; 2006.
58. Sullivan A, Caterino LC. Addressing the sexuality and sex education of individuals with autism spectrum disorders. Educ Treat Child. 2008;31(3):381–94.
59. Schopler E. Implementation of TEACCH philosophy. In: Cohen DJ, Volkmar FR, editors. Handbook of autism and pervasive developmental disorders, vol. 35. 2nd ed. New York: Wiley; 1997. p. 767–95.

Attention-Deficit Hyperactivity Disorder (ADHD), Intimate Relationships and Sexuality

7

J. J. Sandra Kooij

7.1 About ADHD

ADHD is a neurobiological disorder that starts in childhood and persists in the majority of cases into adulthood, and even old age [1, 2]. Besides polygenetic factors, the environment may play a role in the background of ADHD, though little is known on the gene-environment interactions that bring ADHD to expression. We know that ADHD runs in families however. In ADHD, a smaller brain volume, later maturation, less connectivity and impaired brain functioning have been shown compared to controls [3]. Low dopamine levels in brain areas involved in impulse control and executive functioning are thought to be responsible for many clinical manifestations of the syndrome. Dopaminergic medication indeed improves the symptoms in the majority of cases [4].

The prevalence of ADHD is 2.5–5% in children, adults and older people [2, 5]. The clinical symptoms are hyperactivity or restlessness (difficulty to sit still, talkativeness, fidgeting), inattentiveness (forgetfulness, being late, difficulty organising, distractedness, difficulty to finish tasks) and impulsivity (acting and talking before thinking, spending too much, sensation seeking, binge eating). In addition, many people with ADHD have mood swings 4–5×/day and anger outburst that may be part of the syndrome as well. The core problem of ADHD seems an inhibition deficit in these four domains: movement, action, attention and cognition and mood.

Comorbidity with other psychiatric disorders is the rule in about 75%. Main comorbid disorders are addiction, sleep, mood, anxiety, bipolar, autism spectrum and personality disorders [6]. People with ADHD may also suffer from obesity and chronic physical conditions [7]. In psychiatry and clinics for substance abuse disorders, the prevalence of ADHD is much higher (around 20%), due to selection on

J. J. Sandra Kooij
PsyQ Expertise Center Adult ADHD, The Hague, The Netherlands
e-mail: s.kooij@psyq.nl

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*,
Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_7

severity, based on comorbidity. ADHD can be treated effectively in children and adults and even older people with psychoeducation, medication, coaching, cognitive behaviour therapy and relationship therapy, among others [8].

7.2 ADHD and Relationships

In adults with ADHD, intimate relationships may be problematic. Due to the lifetime symptoms of ADHD like inattentiveness, forgetfulness, mood swings and anger outbursts, as well as sensation seeking, impulsive and aggressive behaviour, some do not manage to start, others not to maintain relationships. The characteristics of relationships in adults with ADHD, including sexual relationships, will be discussed in this chapter.

7.3 Duration and Number of Relationships

In a study of 54 adults between the ages of 18 and 56, 70% had a relationship (n = 38), of which almost all (n = 30) experienced difficulties [8]. In 68% the relationship lasted longer than 5 years. The relationship was described as being 'good' by 45% of patients and as 'mediocre to (very) bad' by 55% of patients. The partner was a bit more pessimistic still about the relationship. The reasons given for the difficulties were conflicts about insufficient communication, a lack of intimacy; conflicts on not living up to agreements, not taking responsibility for family and household; conflicts regarding alcohol or drug abuse; and conflicts regarding aggressive behaviour. Most relationship problems were related to a combination of the above-mentioned conflicts. Before the current partner, patients with ADHD had often had several other relationships. Thirteen patients had not had a partner yet (24%), 16 had had 1–4 partners (30%), eight patients had had 5–10 partners (14%), but 17 had had more than ten partners (32%). Thirty to forty short relationships (including one night stands) were no exception in this last group. The duration of most relationships (excluding the last one) fits a pattern of short relationships with fast fluctuations (Table 7.1).

The duration of most previous relationships was less than a year in almost half of patients and less than 6 months in more than 35%. This pattern of short and quickly changing relationships is common in adolescents, who tend to experiment with relationships during this time in their life. It does however become a problem when people start to settle and when adults with ADHD are still not able to find

Table 7.1 Duration of relationships in 53 adults with ADHD

Duration of most previous relationships	*N* = 53	%
<6 months	19	35.8
1/2–1 year	7	13.2
1–5 years	6	11.3
5–10 years	9	17
n/a	12	23.6

and keep a steady relationship. This may be related to the tendency of impulsivity and sensation seeking in people with ADHD: looking for a challenge, somebody new, that may help increase dopamine levels temporarily in the brain, thereby diminishing the severity of ADHD itself but limiting the chance of stability in relationships.

7.4 Quality of ADHD Relationships

The influence of ADHD on intimate relationships is not limited to a short duration and in a subgroup, frequent changing of partners. The quality of the relationship also suffers when one of the partners has ADHD. Robin [9] performed a study with the 'Marital Impact Checklist' in 80 couples, of which one partner had ADHD. He interviewed 35 men (44%) and 45 women with ADHD (56%) and their partners. The average age was 42 years.

The problems from which both partners suffered most were:

- Communication problems/problems with time management and self-regulation of emotions
- Forgetting things that have been discussed
- Saying things without thinking
- Not sustaining attention on conversations
- Difficulty dealing with frustrations
- Difficulty starting tasks
- Wrongly estimating time it takes to complete tasks
- Leaving a mess
- Not finishing things

The questions that were answered were:

1. How many items do both partners indicate as being burdensome?
2. How unloved/unimportant do the partners feel because of this?
3. The negative impact of this behaviour on the relationship according to both partners.

The ADHD partner scored higher on the number of items, on feeling unloved and on the negative impact of the behaviour on the relationship. There was no difference between men and women with ADHD. The correlation between the scores of both partners was moderate to high. Of the partners without ADHD, men scored higher than women on the number of items, on feeling unloved and on the negative impact of the behaviour on the relationship. In summary this research showed that:

- The ADHD partners experienced most problems and impact.
- Partners of a woman with ADHD were a lot more dissatisfied with the relationship than partners of a man with ADHD.

7.5 ADHD and Sexuality

Sexual maturation in adolescents with ADHD aged 10–14 years has been compared with age-matched controls in the Multimodal Treatment study (MTA study). There was no difference in sexual maturation between both groups nor between groups that were and were not treated with stimulants [10].

Adolescents with ADHD are generally sexually active a year before their peers (15 as opposed to 16 years) and show more risky sexual behaviour: more partners, more one-night stands and less use of contraceptives. This leads to more sexually transmitted diseases (17% versus 4%) and a higher percentage of teenage pregnancies (38% versus 4%) compared to peers without ADHD [11, 12]. In studies in adults, those with the combined type ADHD indicated that they were bisexual slightly more often compared to controls, but not homosexual. There was no greater occurrence of sexual problems or disorders in ADHD compared to control groups. Adults with ADHD did indicate more often that they do not want sex (49% versus 25%) [11].

Clinical practice has learned that certain sexual problems may be associated with the ADHD symptoms: for instance, inattention, poor concentration, being easily distracted or thinking of other things while having sex can create problems with having an orgasm. Partners having different bedtimes is another common problem for having sex. This can be caused by poor planning, but also by a delayed sleep phase, which occurs in the majority of adults with ADHD, causing both partners to have a smaller chance of going to bed at the same time [13]. There are also indications that some have an increased need for sex. Frequent masturbation in someone with ADHD could, for instance, be a way of fighting off inner unrest. Other biological aspects may also play a role.

In Dutch research among 120 adults with ADHD (55% men), more than half had sexual problems (n = 64) [8]. There was no difference in the number of problems between the genders. The sexual problems were registered and afterwards divided into categories. The following categories of sexual problems could be distinguished (Table 7.2).

Most of the problems dealt with too much or too little sex drive or both alternating. Too much sex drive or not enough sex drive occurred almost equally. The difference in sexual desire between men and women was significant: men more

Table 7.2 Sexual problems in 64 adults with ADHD

Sexual problems in 64 adults with ADHD	*N*
Too much sex drive/obsessed	24
Not enough sex drive	20
Fluctuating between too much sex drive/not enough sex drive	4
Other	17
Pain during sex/physical complaints/use of antidepressants /relationship problems/doubts about being gay or straight	9
Problems associated with ADHD: concentration problems in sex or orgasm/too restless/difficulty relaxing/impatient/poor planning	8
Total number of problems	65

often had too much sex drive compared to women who lacked enough sex drive. A relationship with the subtype of ADHD could not be established, because almost all patients had the combined type ADHD. Scientific literature however shows indications that the combined type ADHD may have a larger sex drive than the inattentive type [14]. The sexual problems that appear to be directly related to ADHD (n = 8), such as unrest, tension, impatience, being easily distracted and poor planning, can also lead to less (desire for) sex; these problems were equally divided between the sexes.

Questionnaire research, comparing sexual disfunctions and sexual disorders in 136 adults with ADHD with the general Dutch population, found increased rates of sexual disfunctions in around 40% of men and women with ADHD and other sexual disorders in 17% of men and 5% of women. The reported disfunctions were sexual aversion, negative emotions during sex, too little excitement and difficulty reaching an orgasm. These disfunctions may stem from a history of unpleasant sexual experiences but also be related to the ADHD symptoms itself: inattentiveness and distractability does not help keeping focus of sexual excitement. The sexual disorders comprised hypersexuality, sado-masochistic desire, travestic desire and activity, pedofilic desire and ambivalent gender identity, the latter one remarkably especially in women [15]. Similar gender identity difficulties were found in children with autism and ADHD: around 5% of parents reported gender identity problems in their child, while this percentage is only 1.7% in control children [16]. Future research must determine whether the background of these findings is merely biological or psychological.

7.6 Sexual Abuse

Little research has been done into the relationship between ADHD and sexual abuse in adults. It is conceivable that ADHD and the often associated behavioural disorders in the family together can increase the chances of aggression and violence, among them sexual violence. Here we are dealing with impulsivity, need for sensation, lack of consideration, irritability, defiant and aggressive behaviour and, in the case of an associated bipolar disorder, possible also sexual disinhibition. Such comorbidity could lead to an explosive mixture. Because of the hereditary nature of these disorders, both perpetrator and victim could have characteristics that increase the chance of abuse. This is however merely a hypothesis which needs to be researched further.

However, research in children has shown that children who are sexually abused have a 14–46% chance of ADHD. Conduct disorder (CD) also occurs more in this group [17, 18]. Research among more than 14,000 adolescents shows that children with ADHD inattentive type have a 2.6 times increased chance of sexual abuse and twice as high a chance of physical neglect [19]. Sexual abuse occurred more often in a group of 144 girls with ADHD (14.3%) than in a matched control group (4.5%). In this research sexual abuse occurred more in the combined type ADHD than in the inattentive type [20].

In initial research into sexual abuse in adults with ADHD compared to controls, a questionnaire on traumas in childhood was used. Emotional neglect and abuse occurred more often in ADHD patients than in controls. Sexual abuse and physical neglect occurred more often in women than in men with ADHD (23% versus 12.5%). Sexual abuse was associated with anxiety and depression later on in life, but ADHD turned out to be an even better predictor of severe psychosocial disfunctioning in adulthood [21].

In Dutch research among 54 adults with ADHD, a history of sexual abuse in childhood was found in 18.5% of the total group but in 30% of the women. This number is similar to that of the previous study on ADHD and to the percentage of sexual abuse in other psychiatric disorders [22, 23]. Women with ADHD and sexual abuse in their history more often had bulimia nervosa and more aggressive behaviour throughout life; they less often had paid work and had more characteristics of the borderline personality disorder than women with ADHD without a history of abuse [23]. These two studies therefore indicate a higher frequency of sexual abuse in the history of adults with ADHD, in particular women. It was already known from literature that a history of sexual abuse leads to an increased chance of the development of a borderline personality disorder [24, 25]; a similar history in adults with ADHD can help to establish comorbidity with a cluster B personality disorder.

Recently, more research on intimate partner violence has become available in young adults with ADHD. Young women with ADHD have a higher chance of becoming a victim of this type of violence [26, 27]. Young men may behave more often verbally and physically aggressive towards their partners, especially in case of a comorbid conduct disorder [28, 29]. Preventive or treatment interventions for these problems in young people with ADHD have not yet been developed.

7.7 ADHD in Sexual Delinquents

ADHD also occurs more in sexual delinquents compared to controls. Research showed that 65% of sexual delinquents had psychiatric disorders. It is notable that the criminality started 10 years earlier in those with ADHD in childhood and that they had been convicted more often [30]. In other research into sexual delinquents, out of all psychiatric disorders, only childhood ADHD turns out to be associated with paraphilia and with socially deviant and aggressive forms of sexually impulsive behaviour [31]. In other research ADHD occurred in 43% of men with paraphilia. The comorbidity mainly related to conduct disorder, mood disorders and cocaine addiction [32]. ADHD appears to be a risk factor for the severity of the sexual delinquency in convicted men with comorbidity. Little is still known about the treatment of this group.

In a treatment study among 26 men with ADHD, mood disorders, paraphilia and associated disorders who responded insufficiently to treatment with either a stimulant drug or an SSRI, an SSRI or stimulant drug was added to the treatment, respectively. Outcome measures were the severity of the ADHD, the mood disorder and

the paraphilia. Addition of the SSRI was significantly effective for the decrease of behaviour associated with paraphilia. Addition of the stimulant drug was associated with an increased effect on the paraphilia, the mood and the ADHD symptoms [33].

In sum, relationships and sexuality are not unaffected in people with ADHD. The clinician may pay attention to psychiatric and somatic comorbidities as well as the quality of relationships and sexuality during diagnostic assessment, in order to develop a treatment plan that suits the needs of the patient.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5). Washington, D.C.: American Psychiatric Association; 2013.
2. Michielsen M, Semeijn E, Comijs HC, van de Ven P, Beekman AT, Deeg DJ, Kooij JJ. Prevalence of attention-deficit hyperactivity disorder in older adults in The Netherlands. Br J Psychiatry. 2012;201(4):298–305.
3. Rubia K, Alegría AA, Brinson H. Brain abnormalities in attention-deficit hyperactivity disorder: a review. Rev Neurol. 2014;58(Suppl 1):S3–16.
4. Rubia K, Alegria A, Brinson H. Imaging the ADHD brain: disorder-specificity, medication effects and clinical translation. Expert Rev Neurother. 2014;14(5):519–38.
5. Simon V, Czobor P, Bálint S, Mészáros A, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. Br J Psychiatry. 2009;194(3):204–11.
6. Biederman J, Faraone SV, Spencer T, Wilens T, Norman D, Lapey KA, Mick E, Lehman BK, Doyle A. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. Am J Psychiatry. 1993;150(12):1792–8.
7. Bijlenga D, van der Heijden KB, Breuk M, van Someren EJ, Lie ME, Boonstra AM, Swaab HJ, Kooij JJ. Associations between sleep characteristics, seasonal depressive symptoms, lifestyle, and ADHD symptoms in adults. J Atten Disord. 2013;17(3):261–75.
8. Kooij JJS. Adult ADHD: diagnostic assessment and treatment. 3rd ed. London: Springer; 2012.
9. Robin LA. The impact of ADHD on marriage. ADHD Rep. 2002;10(3):9–14.
10. Greenfield B, Hechtman L, Stehli A, Wigal T. Sexual maturation among youth with ADHD and the impact of stimulant medication. Eur Child Adolesc Psychiatry. 2014;23(9):835–9.
11. Barkley RA, Fischer M, Smallish L, Fletcher K. Young adult outcome of hyperactive children: adaptive functioning in major life activities. J Am Acad Child Adolesc Psychiatry. 2006;45(2):192–202.
12. Flory K, Molina BS, Pelham WE Jr, Gnagy E, Smith B. Childhood ADHD predicts risky sexual behavior in young adulthood. J Clin Child Adolesc Psychol. 2006;35(4):571–7.
13. Van Veen MM, Kooij JJ, Boonstra AM, Gordijn MC, Van Someren EJ. Delayed circadian rhythm in adults with attention-deficit/hyperactivity disorder and chronic sleep-onset insomnia. Biol Psychiatry. 2010;67(11):1091–6.
14. Canu WH, Carlson CL. Differences in heterosocial behavior and outcomes of ADHD-symptomatic subtypes in a college sample. J Atten Disord. 2003;6(3):123–33.
15. Bijlenga D, Vroege JA, Stammen AJM, Breuk M, Boonstra AM, van der Rhee K, et al. Prevalence of sexual disorders in adults with attention-deficit/hyperactivity disorder. 2018;10:87–96. https://doi.org/10.1007/s12402-017-0237-6.
16. Strang JF, Kenworthy L, Dominska A, Sokoloff J, Kenealy LE, Berl M, et al. Increased gender variance in autism spectrum disorders and attention deficit hyperactivity disorder. Arch Sex Behav. 2014;43(8):1525–33.
17. McLeer SV, Callaghan M, Henry D, Wallen J. Psychiatric disorders in sexually abused children. J Am Acad Child Adolesc Psychiatry. 1994;33(3):313–9.
18. Merry SN, Andrews LK. Psychiatric status of sexually abused children 12 months after disclosure of abuse. J Am Acad Child Adolesc Psychiatry. 1994;33(7):939–44.

19. Ouyang L, Fang X, Mercy J, Perou R, Grosse SD. Attention-deficit/hyperactivity disorder symptoms and child maltreatment: a population-based study. J Pediatr. 2008;153(6):851–6.
20. Briscoe-Smith AM, Hinshaw SP. Linkages between child abuse and attention-deficit/hyperactivity disorder in girls: behavioral and social correlates. Child Abuse Negl. 2006;30(11):1239–55.
21. Rucklidge JJ, Brown DL, Crawford S, Kaplan BJ. Retrospective reports of childhood trauma in adults with ADHD. J Atten Disord. 2006;9(4):631–41.
22. Bryer JB, Nelson BA, Miller JB, Krol PA. Childhood sexual and physical abuse as factors in adult psychiatric illness. Am J Psychiatry. 1987;144(11):1426–30.
23. JJS K. ADHD in adults. In: Clinical studies on assessment and treatment. Thesis. Amsterdam: Harcourt Assessment BV; 2006.
24. Zanarini MC, Williams AA, Lewis RE, Reich RB, Vera SC, Marino MF, et al. Reported pathological childhood experiences associated with the development of borderline personality disorder. Am J Psychiatry. 1997;154(8):1101–6.
25. Zanarini MC, Frankenburg FR, Reich DB, Hennen J, Silk KR. Adult experiences of abuse reported by borderline patients and Axis II comparison subjects over six years of prospective follow-up. J Nerv Ment Dis. 2005;193(6):412–6.
26. Guendelman MD, Ahmad S, Meza JI, Owens EB, Hinshaw SP. Childhood attention-deficit/hyperactivity disorder predicts intimate partner victimization in young women. J Abnorm Child Psychol. 2015;44(1):155–66. https://doi.org/10.1007/s10802-015-9984-z.
27. Snyder JA. The link between ADHD and the risk of sexual victimization among college women: expanding the lifestyles/routine activities framework. Violence Against Women. 2015;21(11):1364–84. https://doi.org/10.1177/1077801215593647.
28. Wymbs B, Molina B, Pelham W, Cheong J, Gnagy E, Belendiuk K, et al. Risk of intimate partner violence among young adult males with childhood ADHD. J Atten Disord. 2012;16(5):373–83.
29. Fang X, Massetti GM, Ouyang L, Grosse SD, Mercy JA. Attention-deficit/hyperactivity disorder, conduct disorder, and young adult intimate partner violence. Arch Gen Psychiatry. 2010;67(11):1179–86.
30. Blocher D, Henkel K, Retz W, Retz-Junginger P, Thome J, Rosler M. Symptoms from the spectrum of attention-deficit/hyperactivity disorder (ADHD) in sexual delinquents. [German]. Fortschr Neurol Psychiatr. 2001;69(10):453–9.
31. Kafka MP, Prentky RA. Attention-deficit/hyperactivity disorder in males with paraphilias and paraphilia-related disorders: a comorbidity study. J Clin Psychiatry. 1998;59(7):388–96.
32. Kafka MP, Hennen J. A DSM-IV Axis I comorbidity study of males (n = 120) with paraphilias and paraphilia-related disorders. Sex Abus. 2002;14(4):349–66.
33. Kafka MP, Hennen J. Psychostimulant augmentation during treatment with selective serotonin reuptake inhibitors in men with paraphilias and paraphilia-related disorders: a case series. J Clin Psychiatry. 2000;61(9):664–70.

Psychosis, Antipsychotic Medication, and Sexual Dysfunctions

8

Marc De Hert and Johan Detraux

8.1 Introduction

Research among patients with psychosis has found rates of sexual dysfunctions (SDs) far beyond the levels observed in the general population [1]. SDs in patients with psychoses are estimated to affect 30–80% of women and 45–80% of men [2–4], having a severe impact on their quality of life and medication adherence [5, 6]. These side effects may be related to the disease itself, psychosocial and genetic factors, comorbid diseases, as well as the pharmacological actions of antipsychotic drugs and co-medication with known effects on sexual performance [6–9].

8.2 Sexual Dysfunctions and Antipsychotic Medication

SDs are among the most frequently reported or observed side effects of antipsychotics [10, 11]. According to several recent reviews [4, 11], the prevalence rate of SDs in patients treated with antipsychotics seems to be higher in men (between 49 and 59%) than women (between 25 and 49%). Antipsychotic polytherapy can be associated with even higher prevalence rates of SDs [11]. Although there are significant differences in the SD rates of second-generation antipsychotics (SGA), there is strong evidence that actually all of these compounds can affect sexual function [6, 12].

M. De Hert (✉) · J. Detraux
Universitair Psychiatrisch Centrum – Z.org KU Leuven, Department of Neurosciences, Campus Kortenberg, Kortenberg, Belgium
e-mail: marc.dehert@upckuleuven.be; johan.detraux@upckuleuven.be

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*, Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_8

8.2.1 Amisulpride

Although only few reports about the effect of amisulpride on sexual functioning are available, the galactorrhea- and amenorrhea-inducing properties of amisulpride are well known [13–16]. Results from the EUFEST (*European First Episode Schizophrenia Trial*) Study Group, for example, showed a significantly larger increase of amenorrhea and galactorrhea with amisulpride in first-episode schizophrenic patients over the course of the study, compared with the other SGA (olanzapine, quetiapine, ziprasidone) or haloperidol [16].

8.2.2 Aripiprazole

Aripiprazole seems to be associated with the lowest SD rates for each phase of sexual function (desire, arousal, and orgasm). Moreover, available naturalistic data consistently show that aripiprazole reduces SDs in patients previously treated with other SGA (including risperidone, olanzapine, and quetiapine) [17–22]. However, a meta-analysis showed that percentages of aripiprazole-treated patients with desire, arousal, and orgasm dysfunction still are substantial: 26%, 15%, and 11%, respectively [17].

8.2.3 Clozapine

Clozapine treatment, although significantly lower as compared with the first-generation antipsychotics (FGA) (with the exception of thioridazine and haloperidol), seems to be associated with high rates of SDs [12, 17, 18, 23]. Pertaining to phase-specific SDs, the percentage of patients with desire dysfunction is even higher when they are treated with clozapine, as compared with risperidone and olanzapine. Orgasm dysfunction seems to be less often in patients treated with clozapine in comparison with these latter compounds [17].

8.2.4 Olanzapine

In comparison with aripiprazole and quetiapine, olanzapine is associated with higher SD rates (about 40%) [17]. Pertaining to phase-specific SDs, olanzapine mostly seems to affect orgasm and desire functioning, whereas arousal phase of the normal sexual response seems to be less affected with this compound [2, 17].

8.2.5 Paliperidone

Only a few reports about the effect of paliperidone on sexual functioning are available. A Cochrane review of five short-term (≤12 weeks), randomized

placebo-controlled trials (N = 2215) found no evidence of SDs with paliperidone palmitate. No statistical significant increase in the incidence of amenorrhea or dysmenorrhea, abnormal sexual function, decreased libido, male gynecomastia, erectile dysfunction, or female galactorrhea was identified. However, all of these outcomes had large confidence intervals, which suggests uncertainty in the mean occurrence of these outcomes. Moreover, because of the short duration of the included studies, there is also uncertainty of the long-term clinical implications of this finding [24]. A meta-analysis of randomized, controlled trials on the tolerability of paliperidone (N = 3779) equally found only limited evidence for an increased risk of SDs, with nonpregnancy-related lactation being a possible problem [25]. However, once again, owing to the short duration of the trials included in this analysis, the results of this study cannot be generalized to patients treated with paliperidone for a long period of time. Therefore, taken together, as until now, no specifically designed long-term studies in this research field has been conducted with paliperidone, currently no conclusive statement can be made regarding this compound [6].

8.2.6 Quetiapine

A meta-analysis has found that, of all SGA, quetiapine is the drug that has the lowest impact on total sexual function (16%) [17]. However, according to a review of Baggaley [18], taken together, results suggest that SD prevalence rates with quetiapine can vary between 10 and 60%: similar to or lower than those with risperidone and similar to those with olanzapine. Chiesa et al., reviewing current evidence about SDs related to antipsychotics, mentioned that total SD percentages among patients treated with quetiapine vary between 1 and 53% [2]. The severity of SDs, however, seems to be lower among patients receiving quetiapine than among patients receiving risperidone or olanzapine [18]. Pertaining to phase-specific SDs, the percentage of patients with desire, arousal, and orgasm dysfunction seems to be, with the exception of aripiprazole, equally lowest with quetiapine [17].

8.2.7 Risperidone

Although some studies have found other results [26–28], most studies showed that treatment with risperidone is associated with (somewhat) higher levels of total SDs compared with olanzapine and quetiapine [17, 29–33] but lower [17] or similar [12] rates as compared with clozapine. Of all SGA, it seems to have the most profound impact on orgasm functioning [17].

8.2.8 Newly Approved Antipsychotics

Evidence-based data regarding SDs with the newly approved antipsychotics asenapine, iloperidone, and lurasidone are at the moment scarce.

Asenapine probably has a good profile of tolerability in the area of sexual effects as SDs seem to be rare with this agent [34, 35].

According to a pooled analysis of clinical studies, including longer-term trials, in 3210 adults treated with iloperidone, gynecomastia was seen in 0.1% ($n = 2$) of the iloperidone-treated patients, compared to 0% in placebo-treated patients; galactorrhea was reported in 0.2% ($n = 8$) of the iloperidone-treated patients, compared with 0.5% in placebo-treated patients [36–38]. Amenorrhea occurred in 0.01–0.001% of the iloperidone-treated patients. Erectile dysfunction was seen in at least 0.01% of patients and ejaculation failure in 2% of the patients in any of the iloperidone dose groups (10–16 mg/day, $N = 483$; 10–24 mg/day, $N = 391$) [36]. Results from a 25-week, open-label extension trial reported retrograde ejaculation in 7.3% of iloperidone-treated patients (12 mg BID) [39].

For lurasidone, amenorrhea has been reported to be infrequent (0.01–0.001%), galactorrhea and erectile dysfunction to be rare (<0.001%) [40]. For example, in the 6-week placebo-controlled study of Ogasa et al., no prolactin (PRL)-related clinical symptoms (e.g., galactorrhea) were observed [41]. However, long-term clinical trials reporting on the frequency of SDs with lurasidone are still lacking.

8.2.9 Results from Comparative Studies

Several studies [13, 16, 26, 32, 42–50] have directly compared the sexual functioning associated with different SGA. As definition and measurement of SDs are inconsistent across studies, these variations for assessing sexual functioning limit direct comparisons of these studies. In fact, rates of SDs can vary depending on the method of assessment used (spontaneous report, structured interview, questionnaire), as well as from scale to scale. As SDs are rarely reported spontaneously, studies on SDs that use spontaneous reports probably lead to an underestimation of its prevalence. Other limitations of these studies on SDs in patients with psychosis concern the mostly small sample sizes and the lack of baseline assessment of sexual functioning. Moreover, differences in treatment duration, age (age-related decreases in libido and some sex hormones such as testosterone), and gender (men have lower PRL levels than women) across studies make it even more difficult to interpret the data. Despite all this, these studies indicate that the relative impact of antipsychotics on SDs can be summarized as risperidone (=paliperidone?) ≥ clozapine > olanzapine > quetiapine > aripiprazole. SDs with FGA are less frequently than with risperidone but more than with the other SGA [6, 18, 47, 51, 52]. A meta-analysis [17] largely confirmed that significant differences seem to exist across different SGA in terms of total SDs, such that quetiapine and aripiprazole were associated with relatively lower rates of total SDs (16–27%), whereas olanzapine, risperidone, and clozapine were associated with higher total SD rates (40–60%). Of the SGA, quetiapine was the drug that had the lowest impact on sexual function (16%), clozapine the one with the highest (52%). However, sensitivity analyses showed a significant impact of several other variables (e.g., method of inquiry, concomitant medication) on SD rates.

8.3 Pharmacological Mechanisms in Antipsychotic-Induced Sexual Dysfunction

Although the pathogenetic mechanisms of antipsychotic-induced SDs are still not fully understood [10], it is well known that antipsychotics can affect sexual function in several ways. SDs during antipsychotic treatment can be attributed to central non-specific effects, central specific effects, peripheral effects, and hormonal effects [9]. Non-specific effects on the central nervous system, such as sedation, will lead to a general reduce in sexual function and interest, and extrapyramidal symptoms may reduce mobility and sexual functioning [4, 53, 54]. Because the dopamine system is involved in sexual arousal and the ability to experience pleasure, sustained blockade of this system might be one of the reasons for decreased libido and orgasm. However, in addition to dopaminergic D2 receptor blockade, antipsychotics vary in the extent to which they block other transmitter pathways (including noradrenaline, acetylcholine, and serotonin, as well as nitric oxide function), which are involved in sexual responsiveness, ejaculation, and orgasm [8, 9, 23]. Serotonin inhibits dopaminergic activity, thus reducing sexual activity. Antagonism of the histaminergic receptors may impair desire and arousal indirectly by increasing sedation. Abnormal ejaculation is correlated with α-adrenergic receptor antagonism [2].

For years there exists considerable debate about the impact of antipsychotic-induced hyperprolactinemia (HPRL) in patients with psychosis. Frequently HPRL has been linked to osteoporosis [55] and breast cancer [56], but it is also suggested that increased PRL levels, due to the blockade of dopamine receptors, are responsible for sexual impairment in antipsychotic-treated patients with psychosis [6]. As risperidone (with the exception of amisulpride) causes more marked elevations in PRL than any other antipsychotic, it is often used as a representative "PRL-raising" antipsychotic drug in research on the association between PRL and sexual side effects. However, although it is clear that risperidone raises serum PRL concentrations, and, according to available comparative studies on SGA, in many studies is associated with more SDs, it has not been shown clearly that PRL increases are correlated with increases in sexual side effects. One is struck by the fact that the evidence concerning this topic is contradictory [16, 57, 58]. Although some studies noticed a relationship between PRL values and SDs, with higher PRL levels correlating with a higher risk of PRL-related side effects [16, 59–65], most studies failed to find an association between sexual side effects and PRL elevation in patients treated with risperidone [20, 26, 28, 32, 33, 44, 57, 66–69] or other antipsychotics [20, 22, 26, 28, 32, 46, 69–72]. In fact, nearby 70% of the studies do not find a significant correlation between PRL levels and sexual side effects that are attributed to high PRL values. Conversely, SDs are also found in patients with normal serum PRL values and have equally been observed with the so-called "PRL-sparing" antipsychotics [26, 29, 69, 73, 74]. For example, up to 50% of women with galactorrhea have normal PRL levels, making galactorrhea an unreliable marker of HPRL [70]. The fact that clozapine, having no sustained influence on PRL levels, nevertheless is associated with sexual problems indirectly supports the notion that PRL levels are not the only or major driving force behind antipsychotic-induced sexual problems

[60]. Moreover, many patients with elevated PRL levels (even with PRL levels >100 ng/mL) may be without the symptoms of HPRL [65, 75, 76]. Thus, PRL elevation can be significant even when the patient is asymptomatic [76]. It is therefore important to distinguish between symptomatic and asymptomatic HPRL, although this distinction is seldom made in the literature [77].

Knegtering et al. [57] tried to assess the degree to which sexual side effects are associated with "PRL-raising" antipsychotics and to what degree such side effects are reducible to serum PRL levels. They found that around 40% of emerging sexual side effects in psychosis are attributable to the "PRL-raising" antipsychotics. Of this attributable fraction, around one-third to two-thirds was directly reducible to the effects of serum PRL. Thus, although results of this study, as well as these of the abovementioned reports, do suggest that antipsychotics may impair sexual functioning through mechanisms involving blockade of dopamine, including the elevation of serum PRL, many other factors and mechanisms are involved with SDs in patients with psychosis [32]. The CUtLASS (*Cost Utility of the Latest Antipsychotics in Schizophrenia Study*) data equally underscore the argument that sexual side effects are likely to occur secondary to multifactorial causes rather than simply PRL levels alone [78].

8.4 Sexual Dysfunctions and Non-antipsychotic Medication-Related Factors

Identifying the specific role of antipsychotic medications in the sexual dysfunction of persons with psychosis is difficult because there are many other potential confounding factors, including the disease itself, genetic factors, and the use of co-medications.

8.4.1 Disease-Related Factors

It has been shown that SDs can already be present in individuals with prodromal signs of psychosis (and thus in the absence of antipsychotic medication), suggesting that SDs may also be a consequence of the disease itself. In a study of Reis Marques et al. [79], sexual functioning was assessed in a ultrahigh-risk group (n = 31), a group with first-episode psychosis (n = 37) and a matched control group of healthy volunteers (n = 56), using the Sexual Function Questionnaire. SDs were evident in 50% of the ultrahigh-risk group, 65% of first-episode patients, and 21% of controls. These high rates of dysfunction were not specific to particular domains of sexual function, affecting sexual interest (libido) and arousal as well as erectile functioning and orgasm. Within the ultrahigh-risk group, SDs were more marked in those who subsequently developed psychosis than in those who did not. The severity of SDs was correlated with the severity of psychotic symptoms ($p < 0.001$).

In patients with psychosis, particularly negative symptoms, such as anhedonia, avolition, and blunted affect, can cause severe harm in the ability to enjoy sexual life

and negatively interfere with interpersonal and sexual relationships [7, 52]. Comorbid depression can reduce interest, including sexual libido [52]. Finally, as a result of (antipsychotic-induced) obesity, low self-esteem, deficits in social functioning, and recurrent psychotic episodes, patients with psychosis can face difficulties in establishing social relationships [80].

8.4.2 Genetic Factors

Genetic factors can also be relevant. Evidence indicated an influence of polymorphisms in the dopamine D2 receptor genes on sexual function in male patients with schizophrenia. Zhang et al. [81] found that the -141C Ins/Del polymorphism of the D2 dopamine receptor gene was significantly associated with SDs, with the Del allele being less frequent in SD subjects.

8.4.3 Co-medication

Depressive symptoms are common in people with psychosis [82]. Antidepressant therapy frequently induces or exacerbates SDs. Although SDs has been reported with all classes, antidepressants with strong serotonergic properties are associated with higher rates [51, 83–85]. Selective serotonin reuptake inhibitors (SSRIs) may particularly delay ejaculation and female orgasm but also can cause decreased libido and erectile difficulties [52]. One meta-analysis [86], including studies with differing methodologies, showed that the incidence of SDs ranged in descending order from percentages between 70 and 80% for sertraline (SSRI) and venlafaxine (serotonin and norepinephrine reuptake inhibitors), citalopram (SSRI), paroxetine (SSRI), and fluoxetine (SSRI) to 26% for fluvoxamine (SSRI). SD was no more common with mirtazapine (other antidepressants), bupropion (other antidepressants), nefazodone (other antidepressants), amineptine (tricyclic antidepressants), moclobemide (reversible inhibitors of monoamine oxidase A), and agomelatine (other antidepressants) than placebo (mean total SD = 14%). Nevertheless, due to inconsistencies and shortcomings of many individual trials, the current degree of evidence does not allow a precise estimate of comparative risk of SDs associated with a specific antidepressant [87].

8.5 Management of Sexual Dysfunctions

There is limited information for the management of SDs and/or HPRL resulting from antipsychotics in patients with psychosis, and no universal guidelines exist [7, 53]. A Cochrane review, trying to determine the effects of different strategies (e.g., dose reduction, drug holidays, adjunctive medication, switching to another drug) for the treatment of SDs due to antipsychotic therapy, concluded that well-designed, blinded, randomized control trials are urgently needed. According to this review,

only two well-designed randomized controlled trials could be relied on for determining the effects for treatment of SDs due to antipsychotic therapy [88].

8.5.1 Diagnostic Considerations

Clinicians should actively and routinely question the patient in a sensitive manner about potentially antipsychotic-induced SDs. Patients can appear asymptomatic but may have difficulties in providing information on SDs [52, 89]. Not only feelings of embarrassment but also the clinical picture of psychosis itself, the accuracy with which patients are capable of answering questions about sexuality, age, and the dose of the prescribed medication play a role in the reporting of SDs [90].

If the patient shows symptoms of sexual dysfunction, repeated PRL measurements, including a baseline measure of PRL level, are essential for making a differential diagnosis [91–93]. An accurate anamnesis can disclose whether the observed symptoms or indications of HPRL coincide in time with the initiation of the antipsychotic treatment. This should include screening for symptoms and signs suggestive of other causes of raised PRL, for example, headache and visual deficits suggestive of a pituitary tumor [94]. If the onset of HPRL does not coincide with initiation of therapy, pituitary magnetic resonance imaging should be performed to exclude or diagnose a pituitary or hypothalamic lesion [95], and the patient eventually should be referred to an endocrinologist. Finally, clinicians should also inquire about and, if necessary, test for pregnancy in all female patients of reproductive age [94].

8.5.2 Therapeutic Considerations

When SDs are identified, potential management strategies include gradually decreasing the antipsychotic dose, switching to an antipsychotic with a better sexual profile, or specifically targeting sexual function by prescribing drugs such as dopamine agonists [3, 18, 96].

8.5.2.1 Dose Reduction

The simplest and most logical clinical approach is to consider lowering the dose in order to see whether the observed SDs react to that [9, 10, 53, 90]. However, although the simplest strategy, this may increase the risk of exacerbating symptoms or a relapse [53, 97]. Therefore this must be done carefully together with a psychiatric follow-up and evaluation so as to avoid a sudden worsening of the underlying psychiatric disorder [91].

8.5.2.2 Switching

Switching to an antipsychotic with less detrimental effects on sexual functioning is another way to solve the problem [9, 10, 90, 91]. In the event of raised PRL values, whether or not associated with SDs, one should ask in particular whether, in this

specific patient, there are sufficient grounds for switching to another, so-called "PRL-sparing" antipsychotic. It is well known that switching, like dose lowering, can increase the risk of a relapse or decompensation [53, 98, 99] and/or provoke other side effects [91], such as diabetes, which may be more serious than the SDs.

8.5.2.3 Addition of a Dopamine Agonist or Drug with Specific Effects on Sexual Functioning

If dose lowering or switching is not justified or helpful, the addition of a dopamine agonist (bromocriptine or cabergoline) can be considered as an alternative [9, 84, 90, 91, 100]. This, however, is a difficult treatment adjustment. There is a small risk that bromocriptine will exacerbate the underlying psychosis [95, 101]. The package insert mentions hallucinations as a side effect and lists severe psychoses as a contraindication [102]. Consequently, at first sight, cabergoline seems to be a better alternative, because the shorter duration of D2 agonism with this compound may make psychotic symptoms less likely [3, 103, 104]. However, cabergoline, like bromocriptine, should nevertheless be used with caution in psychotic patients, as patients treated with this dopamine agonist may also develop a subsequent psychotic exacerbation [105]. Moreover, cardiopulmonary complications have been reported with ergot-derived dopamine agonists, including cabergoline [53, 106–108].

Herbal therapy (saikokaryukotsuboreito, peony-glycyrrhiza decoction, shakuyaku-kanzo-to) has been explored as an alternative to treat antipsychotic-induced SDs [101, 109–111]. Open-label studies including other medications, such as vardenafil [112], amantadine [113, 114], and imipramine [115], also exist [5]. All these trials showed improvement in sexual functioning and/or hormonal profile. However, these studies had a small sample ($\leq$30 patients), and they were conducted for a short period of time (<3 months) [7]. Finally, adding aripiprazole to "PRL-raising" antipsychotics is another therapeutic option that can be effective at decreasing PRL levels and improving related side effects [53, 95, 116]. However, the add-on effects of aripiprazole in reversing antipsychotic-induced HPRL depend on the pharmacological properties of the preexisting antipsychotic: adjunctive aripiprazole treatment reverses effectively HPRL induced by risperidone and olanzapine but seems to be less effective for that induced by benzamide antipsychotics (amisulpride and sulpiride) [116].

Conclusion

Too few well-designed, randomized, double-blind, and particularly longer-term studies are available to estimate SD rates associated with the different antipsychotic medications accurately. Especially regarding amisulpride, paliperidone, aripiprazole, and the newly approved antipsychotics, more solid, evidence-based data are needed, as these are at the moment scarce. Not only the lack of data but also methodological problems of the existing studies make it difficult to determine the exact prevalence rate of SDs in schizophrenic patients. One of the reasons for the wide variation in SD prevalence rates reported in the literature may be due to the measures used for the assessment of SDs. Different methods of

inquiry (a recent review revealed the existence of 52 different rating scales to measure side effects of antipsychotic medication) [117] probably lead to different rates of SDs.

Research indicates that there are multiple causes of SDs in schizophrenia and that the dopaminergic antagonistic (including the PRL-elevating) property of antipsychotic medication should be seen as one potential mechanism. From all evidence taken together, it is clear that it is highly unlikely that PRL elevation is the sole cause of SDs. Specific non-dopaminergic pharmacological profiles, the impact of the illness itself (e.g., negative symptoms) together with the presence of comorbid depressive symptoms, and co-medications known to have an influence on sexual functioning need to be considered as well.

References

1. Ostman M. Low satisfaction with sex life among people with severe mental illness living in a community. Psychiatry Res. 2014;216:340–5.
2. Chiesa A, Leucci V, Serretti A, et al. Antipsychotics and sexual dysfunction: epidemiology, mechanisms and management. Clin Neuropsychia. 2013;10(1):31–6.
3. Kalkavoura CS, Michopoulos I, Arvanitakis P, et al. Effects of cabergoline on hyperprolactinemia, psychopathology, and sexual functioning in schizophrenic patients. Exp Clin Psychopharmacol. 2013;21(4):332–41.
4. Just MJ. The influence of atypical antipsychotic drugs on sexual function. Neuropsychiatr Dis Treat. 2015;11:1655–61.
5. de Boer MK, Castelein S, Wiersma D, Schoevers RA, Knegtering H. A systematic review of instruments to measure sexual functioning in patients using antipsychotics. J Sex Res. 2014;51(4):383–9.
6. De Hert M, Detraux J, Peuskens J. Second-generation and newly approved antipsychotics, serum prolactin levels and sexual dysfunctions: a critical literature review. Expert Opin Drug Saf. 2014;13(5):605–24.
7. Nunes LV, Moreira HC, Razzouk D, et al. Strategies for the treatment of antipsychotic-induced sexual dysfunction and/or hyperprolactinemia among patients of the schizophrenia spectrum: a review. J Sex Marital Ther. 2012;38(3):281–301.
8. Yasui-Furukori N. Update on the development of lurasidone as a treatment for patients with acute schizophrenia. Drug Des Devel Ther. 2012;6:107–15.
9. Cookson J, Hodgson R, Wildgust HJ. Prolactin, hyperprolactinaemia and antipsychotic treatment: a review and lessons for treatment of early psychosis. J Psychopharmacol. 2012;26(5 Suppl):42–51.
10. de Boer MK, Castelein S, Wiersma D, Schoevers RA, Knegtering H. The facts about sexual (Dys)function in schizophrenia: an overview of clinically relevant findings. Schizophr Bull. 2015;41(3):674–86.
11. Young SL, Taylor M, Lawrie SM. "First do no harm." A systematic review of the prevalence and management of antipsychotic adverse effects. J Psychopharmacol. 2015;29(4):353–62.
12. Serretti A, Chiesa A. Sexual side effects of pharmacological treatment of psychiatric diseases. Clin Pharmacol Ther. 2011;89(1):142–7.
13. Novick D, Haro JM, Perrin E, et al. Tolerability of outpatient antipsychotic treatment: 36-month results from the European Schizophrenia Outpatient Health Outcomes (SOHO) study. Eur Neuropsychopharmacol. 2009;19(8):542–50.
14. Kropp S, Ziegenbein M, Grohmann R, et al. Galactorrhea due to psychotropic drugs. Pharmacopsychiatry. 2004;37(Suppl 1):S84–8.

15. Mortimer A, Martin S, Lôo H, et al. A double-blind, randomized comparative trial of amisulpride versus olanzapine for 6 months in the treatment of schizophrenia. Int Clin Psychopharmacol. 2004;19(2):63–9.
16. Malik P, Kemmler G, Hummer M, et al. Sexual dysfunction in first-episode schizophrenia patients: results from European First Episode Schizophrenia Trial. J Clin Psychopharmacol. 2011;31(3):274–80.
17. Serretti A, Chiesa A. A meta-analysis of sexual dysfunction in psychiatric patients taking antipsychotics. Int Clin Psychopharmacol. 2011;26(3):130–40.
18. Baggaley M. Sexual dysfunction in schizophrenia: focus on recent evidence. Hum Psychopharmacol. 2008;23(3):201–9.
19. Montejo AL, Riesgo Y, Luque J, et al. Observational, open-label, prospective multicenter study of sexual function in patients starting treatment with aripiprazole. Actas Esp Psiquiatr. 2010;38(1):13–21.
20. Hanssens L, L'Italien G, Loze JY, et al. The effect of antipsychotic medication on sexual function and serum prolactin levels in community-treated schizophrenic patients: results from the Schizophrenia Trial of Aripiprazole (STAR) study (NCT00237913). BMC Psychiatry. 2008;8:95.
21. Ziadi Trives M, Bonete Llácer JM, García Escudero MA, Martínez Pastor CJ. Effect of the addition of aripiprazole on hyperprolactinemia associated with risperidone long-acting injection. J Clin Psychopharmacol. 2013;33(4):538–41.
22. Mir A, Shivakumar K, Williamson RJ, et al. Change in sexual dysfunction with aripiprazole: a switching or add-on study. J Psychopharmacol. 2008;22(3):244–53.
23. Park YW, Kim Y, Lee JH. Antipsychotic-induced sexual dysfunction and its management. World J Mens Health. 2012;30(3):153–9.
24. Nussbaum AM, Stroup TS. Paliperidone palmitate for schizophrenia. Cochrane Database Syst Rev. 2012;6:CD008296.
25. Harrington CA, English C. Tolerability of paliperidone: a meta-analysis of randomized, controlled trials. Int Clin Psychopharmacol. 2010;25(6):334–41.
26. van Bruggen M, van Amelsvoort T, Wouters L, et al. Sexual dysfunction and hormonal changes in first episode psychosis patients on olanzapine or risperidone. Psychoneuroendocrinology. 2009;34(7):989–95.
27. Byerly MJ, Nakonezny PA, Rush AJ. Sexual functioning associated with quetiapine switch vs. risperidone continuation in outpatients with schizophrenia or schizoaffective disorder: a randomized double-blind pilot trial. Psychiatry Res. 2008;159(1–2):115–20.
28. Kelly DL, Conley RR. A randomized double-blind 12-week study of quetiapine, risperidone or fluphenazine on sexual functioning in people with schizophrenia. Psychoneuroendocrinology. 2006;31(3):340–6.
29. Bobes J, Garc A-Portilla MP, et al. Frequency of sexual dysfunction and other reproductive side-effects in patients with schizophrenia treated with risperidone, olanzapine, quetiapine, or haloperidol: the results of the EIRE study. J Sex Marital Ther. 2003;29(2):125–47.
30. Knegtering R, Castelein S, Bous H, et al. A randomized open-label study of the impact of quetiapine versus risperidone on sexual functioning. J Clin Psychopharmacol. 2004;24(1):56–61.
31. Byerly MJ, Nakonezny PA, Bettcher BM, et al. Sexual dysfunction associated with second-generation antipsychotics in outpatients with schizophrenia or schizoaffective disorder: an empirical evaluation of olanzapine, risperidone, and quetiapine. Schizophr Res. 2006;86(1–3):244–50.
32. Konarzewska B, Wołczyński S, Szulc A, et al. Effect of risperidone and olanzapine on reproductive hormones, psychopathology and sexual functioning in male patients with schizophrenia. Psychoneuroendocrinology. 2009;34(1):129–39.
33. Conley RR, Mahmoud R. A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. Am J Psychiatry. 2001;158(5):765–74.
34. Grande I, Hidalgo-Mazzei D, Nieto E, Mur M, Sàez C, Forcada I, Vieta E. Asenapine prescribing patterns in the treatment of manic in- and outpatients: results from the MANACOR study. Eur Psychiatry. 2015;30(4):528–34.

35. SAPHRIS® (asenapine). Highlights of prescribing information. Silver Spring: U.S. Food and Drug Administration; 2015. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022117s017s018s019lbl.pdf. Last Accessed 17 Sept 2015.
36. FANAPT® (iloperidone). Highlights of prescribing information. Silver Spring: U.S. Food and Drug Administration; 2014. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022192s013lbl.pdf. Last Accessed 17 Sept 2015.
37. Citrome L. Iloperidone: a clinical overview. J Clin Psychiatry. 2011;72(Suppl 1):19–23.
38. Arif SA, Mitchell MM. Iloperidone: a new drug for the treatment of schizophrenia. Am J Health Syst Pharm. 2011;68(4):301–8.
39. Cutler AJ, Kalali AH, Mattingly GW, et al. Long-term safety and tolerability of iloperidone: results from a 25-week, open-label extension trial. CNS Spectr. 2013;18(1):43–54.
40. LATUDA® (lurasidone). Highlights of prescribing information. Silver Spring: U.S. Food and Drug Administration; 2013. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/200603s015lbl.pdf. Last Accessed 17 Sept–Nov 2013.
41. Ogasa M, Kimura T, Nakamura M, et al. Lurasidone in the treatment of schizophrenia: a 6-week, placebo-controlled study. Psychopharmacology. 2013;225(3):519–30.
42. Shah SK. A comparative study of sexual dysfunction in schizophrenia patients taking aripiprazole versus risperidone. Kathmandu Univ Med J (KUMJ). 2013;11:121–5.
43. Chaves KM, Serrano-Blanco A, Ribeiro SB, et al. Quality of life and adverse effects of olanzapine versus risperidone therapy in patients with schizophrenia. Psychiatr Q. 2013;84:125–35.
44. Yasui-Furukori N, Fujii A, Sugawara N, et al. No association between hormonal abnormality and sexual dysfunction in Japanese schizophrenia patients treated with antipsychotics. Hum Psychopharmacol. 2012;27:82–9.
45. Nebhinani N, Grover S, Avasthi A. Sexual dysfunction in male subjects receiving trifluoperazine, risperidone, or olanzapine: rates vary with assessment questionnaire. Prim Care Companion CNS Disord. 2012;14:PCC.11m01199.
46. Kikuchi T, Iwamoto K, Sasada K, et al. Sexual dysfunction and hyperprolactinemia in Japanese schizophrenic patients taking antipsychotics. Prog Neuro-Psychopharmacol Biol Psychiatry. 2012;37:26–32.
47. de Boer MK, Wiersma D, Bous J, et al. A randomized open-label comparison of the impact of aripiprazole versus risperidone on sexual functioning (RAS study). J Clin Psychopharmacol. 2011;31:523–5.
48. Fujii A, Yasui-Furukori N, Sugawara N, et al. Sexual dysfunction in Japanese patients with schizophrenia treated with antipsychotics. Prog Neuro-Psychopharmacol Biol Psychiatry. 2010;34:288–93.
49. Montejo AL, Majadas S, Rico-Villademoros F, et al. Frequency of sexual dysfunction in patients with a psychotic disorder receiving antipsychotics. J Sex Med. 2010;7:3404–13.
50. Nagaraj AK, Pai NB, Rao S. A comparative study of sexual dysfunction involving risperidone, quetiapine, and olanzapine. Indian J Psychiatry. 2009;51:265–71.
51. Montejo AL, Montejo L, Navarro-Cremades F. Sexual side-effects of antidepressant and antipsychotic drugs. Curr Opin Psychiatry. 2015;28(6):418–23.
52. Waldinger MD. Psychiatric disorders and sexual dysfunction. Handb Clin Neurol. 2015;130:469–89.
53. Kelly DL, Wehring HJ, Earl AK, et al. Treating symptomatic hyperprolactinemia in women with schizophrenia: presentation of the ongoing DAAMSEL clinical trial (Dopamine partial Agonist, Aripiprazole, for the Management of Symptomatic Elevated prolactin). BMC Psychiatry. 2013;13:214.
54. Peuskens J, Sienaert P, De Hert M. Sexual dysfunction: the unspoken side effect of antipsychotics. Eur Psychiatry. 1998;13(1 Suppl 1):23s–30s.
55. De Hert M, Detraux J, Stubbs B. Antipsychotic medication, serum prolactin levels and osteoporosis/osteoporotic fractures: a critical literature review. Expert Opin Drug Saf. 2015;15(6):809–23.

56. De Hert M, Peuskens J, Sabbe T, Mitchell AJ, Stubbs B, Neven P, Wildiers H, Detraux J. Relationship between prolactin, breast cancer risk, and antipsychotics in patients with schizophrenia: a critical review. Acta Psychiatr Scand. 2015;133(1):5–22. https://doi.org/10.1111/acps.12459.
57. Knegtering H, van den Bosch R, Castelein S, et al. Are sexual side effects of prolactin-raising antipsychotics reducible to serum prolactin? Psychoneuroendocrinology. 2008;33(6):711–7.
58. McEvoy JP, Citrome L, Hernandez D, et al. Effectiveness of lurasidone in patients with schizophrenia or schizoaffective disorder switched from other antipsychotics: a randomized, 6-week, open-label study. J Clin Psychiatry. 2013;74(2):170–9.
59. Melkersson K. Differences in prolactin elevation and related symptoms of atypical antipsychotics in schizophrenic patients. J Clin Psychiatry. 2005;66(6):761–7.
60. Rettenbacher MA, Hofer A, Ebenbichler C, et al. Prolactin levels and sexual adverse effects in patients with schizophrenia during antipsychotic treatment. J Clin Psychopharmacol. 2010;30(6):711–5.
61. Dickson RA, Dalby JT, Williams R, et al. Risperidone-induced prolactin elevations in premenopausal women with schizophrenia. Am J Psychiatry. 1995;152(7):1102–3.
62. Liu-Seifert H, Kinon BJ, Tennant CJ, et al. Sexual dysfunction in patients with schizophrenia treated with conventional antipsychotics or risperidone. Neuropsychiatr Dis Treat. 2009;5:47–54.
63. Kinon BJ, Gilmore JA, Liu H, et al. Prevalence of hyperprolactinemia in schizophrenic patients treated with conventional antipsychotic medications or risperidone. Psychoneuroendocrinology. 2003;28(Suppl 2):55–68.
64. Nakonezny PA, Byerly MJ, Rush AJ. The relationship between serum prolactin level and sexual functioning among male outpatients with schizophrenia or schizoaffective disorder: a randomized double-blind trial of risperidone vs. quetiapine. J Sex Marital Ther. 2007;33(3):203–16.
65. Ali S, Miller KK, Freudenreich O. Management of psychosis associated with a prolactinoma: case report and review of the literature. Psychosomatics. 2010;51(5):370–6.
66. Westheide J, Cvetanovska G, Albrecht C, et al. Prolactin, subjective well-being and sexual dysfunction: an open label observational study comparing quetiapine with risperidone. J Sex Med. 2008;5(12):2816–26.
67. Kleinberg DL, Davis JM, de Coster R, et al. Prolactin levels and adverse events in patients treated with risperidone. J Clin Psychopharmacol. 1999;19(1):57–61.
68. Chue P, Eerdekens M, Augustyns I, et al. Comparative efficacy and safety of long-acting risperidone and risperidone oral tablets. Eur Neuropsychopharmacol. 2005;15(1):111–7.
69. Berry S, Martinez A, Myers J, et al. Serum prolactin in schizophrenia. Poster presented at the 7th world congress of biological psychiatry, July 1–6, 2001, Berlin, Germany.
70. Eberhard J, Lindström E, Holstad M, et al. Prolactin level during 5 years of risperidone treatment in patients with psychotic disorders. Acta Psychiatr Scand. 2007;115(4):268–76.
71. Howes OD, Wheeler MJ, Pilowsky LS, et al. Sexual function and gonadal hormones in patients taking antipsychotic treatment for schizophrenia or schizoaffective disorder. J Clin Psychiatry. 2007;68(3):361–7.
72. Atmaca M, Kuloglu M, Tezcan E. A new atypical antipsychotic: quetiapine-induced sexual dysfunctions. Int J Impot Res. 2005;17(2):201–3.
73. Lundberg PO, Hulter B. Sexual dysfunction in patients with hypothalamo-pituitary disorders. Exp Clin Endocrinol. 1991;98(2):81–8.
74. Canuso CM, Goldstein JM, Wojcik J, et al. Antipsychotic medication, prolactin elevation, and ovarian function in women with schizophrenia and schizoaffective disorder. Psychiatry Res. 2002;111(1):11–20.
75. Smith SM. The impact of hyperprolactinaemia on sexual function in patients with psychosis. J Psychopharmacol. 2008;22(2 Suppl):63–9.
76. Peveler RC, Branford D, Citrome L, et al. Antipsychotics and hyperprolactinaemia: clinical recommendations. J Psychopharmacol. 2008;22(2 Suppl):98–103.

77. Citrome L. Current guidelines and their recommendations for prolactin monitoring in psychosis. J Psychopharmacol. 2008;22(2 Suppl):90–7.
78. Peluso MJ, Lewis SW, Barnes TR, et al. Non-neurological and metabolic side effects in the cost utility of the latest antipsychotics in schizophrenia randomised controlled trial (CUtLASS-1). Schizophr Res. 2013;144(1–3):80–6.
79. Reis Marques T, Smith S, Bonaccorso S, et al. Sexual dysfunction in people with prodromal or first-episode psychosis. Br J Psychiatry. 2012;201:131–6.
80. Zemishlany Z, Weizman A. The impact of mental illness on sexual dysfunction. Adv Psychosom Med. 2008;29:89–106.
81. Zhang XR, Zhang ZJ, Zhu RX, et al. Sexual dysfunction in male schizophrenia: influence of antipsychotic drugs, prolactin and polymorphisms of the dopamine D2 receptor genes. Pharmacogenomics. 2011;12(8):1127–36.
82. Bosanac P, Castle DJ. Schizophrenia and depression. Med J Aust. 2013;199(6 Suppl):S36–9.
83. Pereira VM, Arias-Carrión O, Machado S, Nardi AE, Silva AC. Bupropion in the depression-related sexual dysfunction: a systematic review. CNS Neurol Disord Drug Targets. 2014;13:1079–88.
84. La Torre A, Giupponi G, Duffy D, Conca A. Sexual dysfunction related to psychotropic drugs: a critical review – part I: antidepressants. Pharmacopsychiatry. 2013;46:191–9.
85. Clayton AH, Croft HA, Handiwala L. Antidepressants and sexual dysfunction: mechanisms and clinical implications. Postgrad Med. 2014;126:91–9.
86. Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. J Clin Psychopharmacol. 2009;29:259–66.
87. Reichenpfader U, Gartlehner G, Morgan LC, et al. Sexual dysfunction associated with second-generation antidepressants in patients with major depressive disorder: results from a systematic review with network meta-analysis. Drug Saf. 2014;37:19–31.
88. Schmidt HM, Hagen M, Kriston L, et al. Management of sexual dysfunction due to antipsychotic drug therapy. Cochrane Database Syst Rev. 2012;11:CD003546.
89. Byerly M, Suppes T, Tran QV, et al. Clinical implications of antipsychotic-induced hyperprolactinemia in patients with schizophrenia spectrum or bipolar spectrum disorders: recent developments and current perspectives. J Clin Psychopharmacol. 2007;27(6):639–61.
90. Knegtering R, Castelein S, Bruggeman R. Vaak seksuele functiestoornissen door antipsychotica, vooral bij prolactineverhoging. Resultaten van een aantal vergelijkende onderzoeken. Tijdschrift Voor Seksuologie. 2004;28:140–6.
91. Molitch ME. Medication-induced hyperprolactinemia. Mayo Clin Proc. 2005;80(8):1050–7.
92. Serri O, Chik CL, Ur E, et al. Diagnosis and management of hyperprolactinemia. CMAJ. 2003;169(6):575–81.
93. De Hert M, Cohen D, Bobes J, et al. Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. World Psychiatry. 2011;10(2):138–51.
94. Walters J, Jones I. Clinical questions and uncertainty – prolactin measurement in patients with schizophrenia and bipolar disorder. J Psychopharmacol. 2008;22(2 Suppl):82–9.
95. Ajmal A, Joffe H, Nachtigall LB. Psychotropic-induced hyperprolactinemia: a clinical review. Psychosomatics. 2014;55(1):29–36.
96. Costa AM, Lima MS, Mari JD. A systematic review on clinical management of antipsychotic-induced sexual dysfunction in schizophrenia. Sao Paulo Med J. 2006;124(5):291–7.
97. Montejo AL. Prolactin awareness: an essential consideration for physical health in schizophrenia. Eur Neuropsychopharmacol. 2008;18(Suppl 2):S108–14.
98. Howes O, Smith S. Hyperprolactinaemia caused by antipsychotic drugs. Endocrine antipsychotic side effects must be systemically assessed. BMJ. 2002;324(7348):1278.
99. Henderson DC, Doraiswamy PM. Prolactin-related and metabolic adverse effects of atypical antipsychotic agents. J Clin Psychiatry. 2008;69(Suppl 1):32–44.

100. Goffin V, Touraine P, Culler MD, et al. Drug insight: prolactin-receptor antagonists, a novel approach to treatment of unresolved systemic and local hyperprolactinemia? Nat Clin Pract Endocrinol Metab. 2006;2(10):571–81.
101. Yuan HN, Wang CY, Sze CW, et al. A randomized, crossover comparison of herbal medicine and bromocriptine against risperidone-induced hyperprolactinemia in patients with schizophrenia. J Clin Psychopharmacol. 2008;28(3):264–370.
102. CYCLOSET® (bromocriptine mesylate). Highlights of prescribing information. Revised 7/2015. https://shared.salix.com/shared/pi/cycloset-pi.pdf?id=811731. Last Accessed 20 Oct 2015.
103. Cavallaro R, Cocchi F, Angelone SM, et al. Cabergoline treatment of risperidone-induced hyperprolactinemia: a pilot study. J Clin Psychiatry. 2004;65(2):187–90.
104. Baeza Pertegaz I, Goikolea Alberdi JM, Parellada Rodón E. Is cabergoline a better drug to inhibit lactation in patients with psychotic symptoms? J Psychiatry Neurosci. 2002;27(1):54.
105. Chang SC, Chen CH, Lu ML. Cabergoline-induced psychotic exacerbation in schizophrenic patients. Gen Hosp Psychiatry. 2008;30(4):378–80.
106. De Vecchis R, Esposito C, Ariano C. Cabergoline use and risk of fibrosis and insufficiency of cardiac valves: meta-analysis of observational studies. Herz. 2013;38(8):868–80.
107. Bogazzi F, Manetti L, Raffaelli V, et al. Cabergoline therapy and the risk of cardiac valve regurgitation in patients with hyperprolactinemia: a meta-analysis from clinical studies. J Endocrinol Invest. 2008;31(12):1119–23.
108. Andersohn F, Garbe E. Cardiac and noncardiac fibrotic reactions caused by ergot-and nonergot-derived dopamine agonists. Mov Disord. 2009;24(1):129–33.
109. Takashi T, Uchida H, Suzuki T, Mimura M. Effectiveness of saikokaryukotsuboreito (herbal medicine) for antipsychotic-induced sexual dysfunction in male patients with schizophrenia: a description of two cases. Case Rep Psychiatry. 2014;2014:784671.
110. Wang D, Wong HK, Zhang L, et al. Not only dopamine D2 receptors involved in Peony-Glycyrrhiza Decoction, an herbal preparation against antipsychotic-associated hyperprolactinemia. Prog Neuro-Psychopharmacol Biol Psychiatry. 2012;39(2):332–8.
111. Yamada K, Kanba S, Yagi G, Asai M. Effectiveness of herbal medicine (shakuyaku-kanzo-to) for neuroleptic-induced hyperprolactinemia. J Clin Psychopharmacol. 1997;17(3):234–5.
112. Mitsonis CI, Mitropoulos PA, Dimopoulos NP, et al. Vardenafil in the treatment of erectile dysfunction in outpatients with chronic schizophrenia: a flexible-dose, open-label study. J Clin Psychiatry. 2008;69(2):206–12.
113. Correa N, Opler LA, Kay SR, Birmaher B. Amantadine in the treatment of neuroendocrine side effects of neuroleptics. J Clin Psychopharmacol. 1987;7(2):91–5.
114. Valevski A, Modai I, Zbarski E, Zemishlany Z, Weizman A. Effect of amantadine on sexual dysfunction in neuroleptic-treated male schizophrenic patients. Clin Neuropharmacol. 1998;21(6):355–7.
115. Aizenberg D, Shiloh R, Zemishlany Z, Weizman A. Low-dose imipramine for thioridazine-induced male orgasmic disorder. J Sex Marital Ther. 1996;22(3):225–9.
116. Peuskens J, Pani L, Detraux J, De Hert M. The effects of novel and newly approved antipsychotics on serum prolactin levels: a comprehensive review. CNS Drugs. 2014;28(5):421–53.
117. van Strien AM, Keijsers CJ, Derijks HJ, van Marum RJ. Rating scales to measure side effects of antipsychotic medication: a systematic review. J Psychopharmacol. 2015;29(8):857–66.

Sexual Dysfunctions and Mood and Anxiety Disorders

9

Cinzia Niolu, Giulia Lisi, and Alberto Siracusano

9.1 Introduction

Sexual dysfunctions are commonly associated with psychiatric disorders and sometimes need to be considered a very early sign of depression and anxiety disorders. However, it is commonly known that the pharmacological treatments used routinely may cause alterations in desire, excitement, and orgasm. Although various studies have been published on these topics, the results are questionable and difficult to be compared. Evaluation of depression and anxiety should be carried out routinely in individuals presenting with sexual complaints in order to define the best possible treatment for the patient.

9.2 Depression and Sexual Dysfunctions

Major Depression is one of the most common mental disorders worldwide. According to the World Health Organization, Major Depression also carries the heaviest burden of disability among mental and behavioral disorders. Depressive disorders are, in fact, globally ranked as the single largest contributor to non-fatal health loss (7.5% of all YLD—*years lived with disability*) (World Health Organization, 2017).

Depressive disorders are characterized by pervasive and persistent depressed mood that is accompanied by low self-esteem, loss of interest or pleasure, and a

C. Niolu (✉) · A. Siracusano
Psychiatry and Clinical Psychology Unit, Fondazione Policlinico Tor Vergata, Rome, Italy

Psychiatry, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
e-mail: niolu@med.uniroma2.it; siracusano@med.uniroma2.it

G. Lisi
Psychiatry and Clinical Psychology Unit, Fondazione Policlinico Tor Vergata, Rome, Italy

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*, Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_9

number of other symptoms that reflect a change in subjective functioning such as sleep problems, loss of energy, and loss of concentration [1]. These symptoms are often associated with a reduction in sexual desire.

With the expression *sexual dysfunction* is intended any difficulty experienced by an individual or a couple during any stage of a normal sexual activity, including physical pleasure, desire, preference, arousal, or orgasm. According to DSM -5, sexual dysfunction requires a person to feel extreme distress and interpersonal strain for a minimum of 6 months [1].

Sexual dysfunctions are reported to be two to three times more likely in a depressed population than in a non-depressed population [2, 3]. Playing depressed mood a central role in the etiology of sexual dysfunctions, their prevalence ranges from 40% to 65% prior to antidepressant treatment initiation [4–8].

Interestingly, according to literature, different depressive subtypes show no difference in sexual functioning, while different degrees of depressive severity show instead a clear association to lower or higher levels of sexual functioning. An expert clinician should look carefully at the occurrence of the association between depression and sexual dysfunction: having a serious impact on the patient's subjective well-being and quality of life, this combination can, in fact, often result in a dramatic increase of suicide risk [9]. According to Adinkrah, patients with sexual dysfunction may themselves be at an elevated risk of suicide, especially in traditional societies where "*the ability to 'perform sexually' and to have children is the ultimate test of masculinity*" [9, 10].

Studies in literature show contradictory results concerning the stage of normal sexual activity that more frequently happens to be compromised during depression. A number of authors highlight a gender difference on this topic: in women samples the effect of depression severity is weaker for sexual desire than for orgasm, with only the most extreme levels of depression showing statistical significance. The effect on orgasm is, in fact, more evident in the majority of the studies with each level of depression (mild, moderate, severe) being statistically different from the others. In male adult samples, Major Depression is more frequently associated with a reduction of sexual desire, though 25% of male patients with depression may also experience erectile dysfunction [9]. Interestingly the relationship between depression and erectile dysfunction is thought to be bidirectional: a depressed mood can impair sexual arousal and cause erectile dysfunction, and on the other hand, a decreased sexual activity and the lack of sexual satisfaction can represent a trigger for depressive symptoms. According to literature, depressive symptoms are commonly associated with erectile dysfunction even in the absence of syndromic depression. Moreover affective disorders have also been strongly associated with premature ejaculation [2]. Even though the underlying cause-effect mechanism has not been fully elucidated, some authors suggested an impact of premature ejaculation on sexual confidence and interpersonal relationships. Interestingly other studies highlighted the existence of a possible common etiological factor involving polymorphisms in the promoter region of the serotonin transporter (5-HTTLPR) gene. The short allele of this gene is associated with both an increased risk of premature ejaculation [11, 12] and higher levels of trait anxiety and depression [13, 14]. Genetically influenced abnormalities in serotoninergic transmission may, then, play a substantial role in these conditions.

9.3 Bipolar Disorder and Sexual Dysfunctions

Bipolar Disorder is a severe and disabling mental illness, considered to be the sixth leading cause of disability in the developed world countries for patients aged between 19 and 45 [15].

Lifetime prevalence of Bipolar Disorder in the USA is estimated to be between 0.5% and 1.0% [16]. While Bipolar Disorder type 1 affects men and women equally, Bipolar Disorder type II in the USA involves women more frequently than men [15]. The core symptoms of this disorder consist of recurrent episodic pathological mood oscillations toward either euphoria, irritability, or depression [15]. A disruption in sexual functioning can often be associated with both depressive and manic episodes, and severe fluctuations in sexual life may be difficult to manage for both the patients and their partners. In particular every clinician will have to manage hypersexuality during manic and hypomanic episodes, disruption of couple relationships due to mood cycling, and the frequent assumption, during manic or hypomanic episodes, of risky sexual behaviors.

DSM -5 incorporates increased or disordered sexuality as a criterion for manic and hypomanic episodes under the criterion "*excessive involvement in pleasurable activities that have a high potential for painful consequences*," examples of which include "sexual indiscretions" [1].

Geller and colleagues have proposed in 2002 "hypersexuality" in children and adolescents as a core feature of juvenile Bipolar Disorder, helping in distinguishing it from attention deficit hyperactivity disorder (ADHD), a condition that shares many features with Bipolar Disorder in youth [17]. In spite of sexual health being crucial to improve treatment compliance, and quality of life [18, 19], very little literature exists on the topic.

9.3.1 Hypersexuality

Even though hypersexuality is notably linked to bipolar disorder both from a research and a clinical point of view [17, 20, 21], a lack of consensus exists on the exact definition of this term. Sexual norms are, in fact, strongly dependent on culture and historical context, and comparing different studies has been proved to be difficult. For example, Carta and colleagues in 2014 compared an Italian and a Korean sample that completed the mood disorder questionnaire and reported that while, for the Italian participants, the item "much more sex" on the questionnaire was related to self-confidence and energy, the same item was connected to risky/unusual behaviors and excessive money spending for Asian participants [22].

We could refer to hypersexuality as to a fluid concept that can be mainly conceptualized as a dysfunctional preoccupation with sexual fantasy, often in combination with the obsessive pursuit of casual or non-intimate sex, pornography, and compulsive masturbation [23].

The link between mania and hypersexuality was first documented in the 1960s, when different authors reported how both men and women could exhibit, during

manic episodes, a substantial increase in libido and sexual activity, with women more likely than men to be involved in sexual activity and provocative sexual behaviors such as flirtation, mentions of sex, and seductive behavior [20, 24]. Moreover, Carlson and Goodwin in 1973 hypothesized the existence of three stages in a manic episode for what concerns sexual behavior: (1) heightened sexual thoughts and activity, (2) sexual preoccupation and "provocativeness," and (3) sexual delusions [20, 25].

9.3.2 Risky Sexual Behaviors

The expression "risky sexual behavior" entangles a wide spectrum of behaviors that goes from less risky to very risky behaviors.

Fletcher and colleagues, in a cross-sectional study, recruited a sample of bipolar II outpatients and asked them to report "the most dangerous thing ever done" while hypomanic. The authors stated that about 24.6% of the total sample reported engaging in some form of sexual activity. However, the answers varied tremendously in terms of potential risk, with some patients giving answers such as flirting and going home with strangers, while others reported engagement in unprotected sex, potential exposure to sexually transmitted disorders and sexual assault [20, 26]. Studies in literature report that there is a substantial increase in hypersexual activity and risky sexual behaviors in bipolar patients during or immediately after a manic or hypomanic episode; this risk is however considerably attenuated during the intervals between the episodes [20].

The first study to look at risky sexual behavior in patients with bipolar disorder was conducted in 1975, and even if it did not report significant results, it showed that during a manic phase, patients with bipolar disorder more frequently show extramarital sexual activity and that they are more likely to be involved in prostitution when compared to patients with other affective disorders [27]. A more recent cross-sectional study of 205 individuals admitted for acute psychiatric care to an inpatient unit found that other than substance dependence, bipolar disorder was the only disorder associated with HIV risk factors [28].

What is more, bipolar patients have a higher rate of unplanned pregnancies compared to other groups of patients [20].

9.3.3 Disruption of Couple Relationships

Research on bipolar disorder indicated that divorce and separation are two to three times more likely than in the general population [29, 30]. Moreover, some author has shown that bipolar disorder significantly affects the caregiver's quality of life [31]. In a recent study, Granek and colleagues separately interviewed 11 patients with bipolar disorder and 10 partners about the impact of bipolar disorder on their marital relationship.

The partners referred during the interview to an emotional impact that included helplessness, loneliness, embarrassment, fear, and anxiety [31]. According to them,

bipolar disorder determines an important rise of self-sacrifice and a significant tendency in giving up on numerous important areas of life, such as participating in their own life pleasures or more frequently giving up on having more children because of the difficulty experienced by the patient in participating fully in child raising [31]. Moreover they mentioned an increase in their charge of responsibility including the perception of being employed in a "full-time job" of caring the patient. In some of the cases, the partner is moreover the sole financial provider of the family in a context where medical care usually adds expenses and is the one that takes full responsibility for the care of the house and the children [31].

When asked about the impact of bipolar disorder on their relationship, both patients and partners reported that the volatility of the patient's mood and condition had an impact on their relationship and on their family planning [31].

9.4 Anxiety and Sexual Dysfunctions

Anxiety is defined as "a state of intense apprehension, uncertainty, and fear resulting from the anticipation of a threatening event or situation, often to a degree that normal physical and psychological functioning is disrupted" [15]. According to the American Psychiatric Association, anxiety disorders share features of fear and anxiety [1]. While fear can be considered the emotional response to a real or perceived threat, anxiety is experienced when anticipating a future threat [15].

Various anxiety disorders have been associated with sexual dysfunction. A number of studies have shown an association between social phobia and sexual interaction in both genders; in particular social phobia has been associated with premature ejaculation in men and to desire disorders and dyspareunia in women [2]. Other authors reported the existence of a link between panic disorder, generalized anxiety disorder, and erectile dysfunction in men and between these conditions and low sexual desire and orgasmic disorder in women [2]. In susceptible patients the intensity of sexual anxiety can reach panic proportions. According to Kaplan, patients with sexual aversion disorder and phobic avoidance of sex have a high incidence of panic disorders [32]. Kaplan argued that some of the patients experienced panic about their loss of control during arousal and orgasm [32]. According to Jonusiene and Griffioen, it is the increased heart rate of sexual arousal that could produce this fear and panic [33].

There is a bidirectional relationship between anxiety and sexual dysfunctions. Patients with generalized premature ejaculation more frequently develop lower sexual satisfaction and control, higher distress, and higher social anxiety [2]. Patients with only situational premature ejaculation are characterized by higher levels of satisfaction, greater feelings of control, less distress, but higher trait anxiety scores [2].

On the other hand, anxiety is considered a major factor in the etiology of sexual dysfunction, and anxiety concerning sexual performance or relationship issues, such as intimacy and partner rejection, is also a crucial factor in the development of sexual avoidance behaviors [32]. A significant association between pre-existing

anxiety disorders and sexual performance anxiety has, in fact, been well documented in literature. It is possible that pre-existing anxiety triggers sexual dysfunction, with the establishment of a vicious cycle that goes from anxiety to sexual dysfunction to performance anxiety increasing the severity of distress [9]. Interestingly research has demonstrated that anxiety is not always disruptive to sexual functioning; it seems that moderate anxiety levels can, in fact, enhance sexual arousal and desire [2].

9.5 Psychopharmacological Treatments and Sexual Dysfunctions

9.5.1 Tricyclic Antidepressants

Clomipramine induces sexual side effects in a variable rate that goes from 17 to 40% of the cases [34]. In some studies it is reported that depressed patients treated with clomipramine have anorgasmia in 96% of the cases [35]. Sexual disturbances were more common in patients taking high doses of tricyclic drugs [36]. Several studies highlight an association between erectile dysfunction, delayed ejaculation, libido reduction, and assumption of tricyclic drugs [37].

9.5.2 MAOIs

Delayed ejaculation is frequent during treatment with monoamine oxidase inhibitors; these kinds of drugs have in fact been even used in early ejaculation treatment as well as antidepressants [38].

9.5.3 SSRIs

Selective serotonin reuptake inhibitors (SSRIs) are frequently associated with sexual side effects in both genders [36]. The primarily involved mechanism seems to be the inhibition of the transporter of 5-hydroxytryptamine (5-HT, serotonin); this is, in fact, thought to be at the basis of delayed ejaculation and erectile dysfunction [38]. However, even altered dopaminergic and noradrenergic systems appear to play an important role in the pathophysiology of sexual dysfunctions induced by SSRIs [38]. According to literature, paroxetine is, among SSRIs, associated with a higher prevalence of sexual dysfunctions: this may be caused by its greater affinity for the 5-HT transporter, which results in a greater inhibition of serotonin reuptake [39]. In addition, in vivo and in vitro, paroxetine appears to inhibit the nitric oxide synthase enzyme, as evidenced by the reduction of concentrations of nitrite and nitrate in plasma levels [40]. The nitric oxide synthase enzyme plays, in fact, various roles, and in particular it mediates the vasodilatation of the cervical caverns of the penis [41].

Interestingly, a recent meta-analysis has pointed out that citalopram, which is one of the most specific SSRIs on 5-HT reuptake, causes sexual dysfunctions in higher percentages if compared to paroxetine while its enantiomer, escitalopram, only in very few cases [42].

The different receptor affinity of the various SSRIs can be translated into a real difference between drug and drug in the incidence of side effects on sexual function. Therapeutic strategies to address these issues currently involve decreasing doses of antidepressants or discontinuing short-term therapy, such as at weekends, or switching to a different type of antidepressant with reduced effects on the sexual sphere, such as trazodone or mirtazapine or bupropion. Agomelatine, a recently introduced antidepressant in clinical practice, acting as a melatoninergic receptor agonist, in particular toward MT1 and MT2 receptors, and having antagonistic properties on serotoninergic receptors 5-HT2C, does not interfere with sexual functioning [43]. Bupropion has not been associated with sexual dysfunctions: its mechanism of action, which consists in dopamine and noradrenaline reuptake, does not have an impact on sexual life, and many studies report instead an increase in sexual desire during treatment with bupropion [44]. It should be, however, highlighted that both tricyclic antidepressants and SSRIs, due to their characteristics, have been particularly useful in the treatment of patients with premature ejaculation [45].

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC; 2013.
2. Brotto L, Atallah S, Johnson-Agbakwu C, Rosenbaum T, Abdo C, Byers ES, et al. Psychological and interpersonal dimensions of sexual function and dysfunction. J Sex Med. 2016;13(4):538–71. https://doi.org/10.1016/j.jsxm.2016.01.019.
3. Waldinger MD. Psychiatric disorders and sexual dysfunction. Handb Clin Neurol. 2015;130:469–89. https://doi.org/10.1016/B978-0-444-63247-0.00027-4.
4. Mathew RJ, Weinman ML. Sexual dysfunctions in depression. Arch Sex Behav. 1982;11(4):323–8.
5. Casper RC, Redmond DE Jr, Katz MM, Schaffer CB, Davis JM, Koslow SH. Somatic symptoms in primary affective disorder. Presence and relationship to the classification of depression. Arch Gen Psychiatry. 1985;42(11):1098–104.
6. Angst J. Sexual problems in healthy and depressed persons. Int Clin Psychopharmacol. 1998;13(Suppl 6):S1–4.
7. Derogatis LR, Burnett AL. The epidemiology of sexual dysfunctions. J Sex Med. 2008;5(2):289–300. https://doi.org/10.1111/j.1743-6109.2007.00668.x.
8. Lee KC, Fahmy N, Brock GB. Sexual dysfunction in 2013: advances in epidemiology, diagnosis and treatment. Arab J Urol. 2013;11(3):194–202. https://doi.org/10.1016/j.aju.2013.06.002.
9. Rajkumar RP, Kumaran AK. Depression and anxiety in men with sexual dysfunction: a retrospective study. Compr Psychiatry. 2015;60:114–8. https://doi.org/10.1016/j.comppsych.2015.03.001.
10. Adinkrah M. Better dead than dishonored: masculinity and male suicidal behavior in contemporary Ghana. Soc Sci Med. 2012;74(4):474–81. https://doi.org/10.1016/j.socscimed.2010.10.011.
11. Ozbek E, Tasci AI, Tugcu V, Ilbey YO, Simsek A, Ozcan L, et al. Possible association of the 5-HTTLPR serotonin transporter promoter gene polymorphism with premature ejaculation in a Turkish population. Asian J Androl. 2009;11(3):351–5. https://doi.org/10.1038/aja.2008.3.

12. Zhu L, Mi Y, You X, Wu S, Shao H, Dai F, et al. A meta-analysis of the effects of the 5-hydroxytryptamine transporter gene-linked promoter region polymorphism on susceptibility to lifelong premature ejaculation. PLoS One. 2013;8(1):e54994. https://doi.org/10.1371/journal.pone.0054994.
13. Osher Y, Hamer D, Benjamin J. Association and linkage of anxiety-related traits with a functional polymorphism of the serotonin transporter gene regulatory region in Israeli sibling pairs. Mol Psychiatry. 2000;5(2):216–9.
14. Wray NR, James MR, Gordon SD, Dumenil T, Ryan L, Coventry WL, et al. Accurate, large-scale genotyping of 5HTTLPR and flanking single nucleotide polymorphisms in an association study of depression, anxiety, and personality measures. Biol Psychiatry. 2009;66(5):468–76. https://doi.org/10.1016/j.biopsych.2009.04.030.
15. Siracusano A. Manuale di psichiatria. Roma: II Pensiero Scientifico; 2014.
16. Blanco C, Compton WM, Saha TD, Goldstein BI, Ruan WJ, Huang B, et al. Epidemiology of DSM-5 bipolar I disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions – III. J Psychiatr Res. 2017;84:310–7. https://doi.org/10.1016/j.jpsychires.2016.10.003.
17. Geller B, Zimerman B, Williams M, Delbello MP, Frazier J, Beringer L. Phenomenology of prepubertal and early adolescent bipolar disorder: examples of elated mood, grandiose behaviors, decreased need for sleep, racing thoughts and hypersexuality. J Child Adolesc Psychopharmacol. 2002;12(1):3–9. https://doi.org/10.1089/10445460252943524.
18. Byers ES. Relationship satisfaction and sexual satisfaction: a longitudinal study of individuals in long-term relationships. J Sex Res. 2005;42(2):113–8. https://doi.org/10.1080/00224490509552264.
19. Zemishlany Z, Weizman A. The impact of mental illness on sexual dysfunction. Adv Psychosom Med. 2008;29:89–106. https://doi.org/10.1159/000126626.
20. Kopeykina I, Kim HJ, Khatun T, Boland J, Haeri S, Cohen LJ, et al. Hypersexuality and couple relationships in bipolar disorder: a review. J Affect Disord. 2016;195:1–14. https://doi.org/10.1016/j.jad.2016.01.035.
21. Basco MR, Celis-de Hoyos CE. Biopsychosocial model of hypersexuality in adolescent girls with bipolar disorder: strategies for intervention. J Child Adolesc Psychiatr Nurs. 2012;25(1):42–50. https://doi.org/10.1111/j.1744-6171.2011.00312.x.
22. Carta MG, Massidda D, Moro MF, Aguglia E, Balestrieri M, Caraci F, et al. Comparing factor structure of the Mood Disorder Questionnaire (MDQ): in Italy sexual behavior is euphoric but in Asia mysterious and forbidden. J Affect Disord. 2014;155:96–103. https://doi.org/10.1016/j.jad.2013.10.030.
23. Walton MT, Cantor JM, Bhullar N, Lykins AD. Hypersexuality: a critical review and introduction to the "sexhavior cycle". Arch Sex Behav. 2017;46(8):2231–51. https://doi.org/10.1007/s10508-017-0991-8.
24. Allison JB, Wilson WP. Sexual behavior of manic patients: a preliminary report. South Med J. 1960;53:870–4.
25. Carlson GA, Goodwin FK. The stages of mania. A longitudinal analysis of the manic episode. Arch Gen Psychiatry. 1973;28(2):221–8.
26. Fletcher K, Parker G, Paterson A, Synnott H. High-risk behaviour in hypomanic states. J Affect Disord. 2013;150(1):50–6. https://doi.org/10.1016/j.jad.2013.02.018.
27. Spalt L. Sexual behavior and affective disorders. Dis Nerv Syst. 1975;36(12):644–7.
28. Sacks MH, Silberstein C, Weiler P, Perry S. HIV-related risk factors in acute psychiatric inpatients. Hosp Community Psychiatry. 1990;41(4):449–51.
29. Kogan JN, Otto MW, Bauer MS, Dennehy EB, Miklowitz DJ, Zhang HW, et al. Demographic and diagnostic characteristics of the first 1000 patients enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Bipolar Disord. 2004;6(6):460–9. https://doi.org/10.1111/j.1399-5618.2004.00158.x.
30. Suppes T, Leverich GS, Keck PE, Nolen WA, Denicoff KD, Altshuler LL, et al. The Stanley Foundation Bipolar Treatment Outcome Network. II. Demographics and illness characteristics of the first 261 patients. J Affect Disord. 2001;67(1–3):45–59.

31. Granek L, Danan D, Bersudsky Y, Osher Y. Living with bipolar disorder: the impact on patients, spouses, and their marital relationship. Bipolar Disord. 2016;18(2):192–9. https://doi.org/10.1111/bdi.12370.
32. Kaplan HS. Anxiety and sexual dysfunction. J Clin Psychiatry. 1988;49(Suppl):21–5.
33. Jonusiene G, Zilaitiene B, Adomaitiene V, Aniuliene R, Bancroft J. Sexual function, mood and menopause symptoms in Lithuanian postmenopausal women. Climacteric. 2013;16(1):185–93. https://doi.org/10.3109/13697137.2012.682746.
34. Segraves RT, Balon R. Antidepressant-induced sexual dysfunction in men. Pharmacol Biochem Behav. 2014;121:132–7. https://doi.org/10.1016/j.pbb.2013.11.003.
35. Montejo AL, Llorca G, Izquierdo JA, Rico-Villademoros F. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. J Clin Psychiatry. 2001;62(Suppl 3):10–21.
36. Dell'Osso L. Sessualità, depressione e ansia. In: Sessuologia medica. Milano: Elsevier; 2007.
37. Hsu JH, Shen WW. Male sexual side effects associated with antidepressants: a descriptive clinical study of 32 patients. Int J Psychiatry Med. 1995;25(2):191–201. https://doi.org/10.2190/1DHU-Y7L7-9GKG-V7WV.
38. 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.
39. Clayton AH, Owens JE, McGarvey EL. Assessment of paroxetine-induced sexual dysfunction using the Changes in Sexual Functioning Questionnaire. Psychopharmacol Bull. 1995;31(2):397–413.
40. Segraves RT. Effects of psychotropic drugs on human erection and ejaculation. Arch Gen Psychiatry. 1989;46(3):275–84.
41. Finkel MS, Laghrissi-Thode F, Pollock BG, Rong J. Paroxetine is a novel nitric oxide synthase inhibitor. Psychopharmacol Bull. 1996;32(4):653–8.
42. Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. J Clin Psychopharmacol. 2009;29(3):259–66. https://doi.org/10.1097/JCP.0b013e3181a5233f.
43. Green B. Focus on agomelatine. Curr Med Res Opin. 2011;27(4):745–9. https://doi.org/10.1185/03007995.2011.554534.
44. Pereira VM, Arias-Carrion O, Machado S, Nardi AE, Silva AC. Bupropion in the depression-related sexual dysfunction: a systematic review. CNS Neurol Disord Drug Targets. 2014;13(6):1079–88.
45. Hisasue S. The drug treatment of premature ejaculation. Transl Androl Urol. 2016;5(4):482–6. https://doi.org/10.21037/tau.2016.06.10.

Sexual Dysfunctions in Obesity

10

Emanuela Bianciardi

10.1 The Burden of Sexual Dysfunctions in Obesity

The worldwide prevalence of obesity has dramatically increased from 6.4% in 1980 to 12.0% in 2008. Half of this rise occurred in the last 15 years [1]. It was estimated that almost 1.5 billion individuals were overweight in 2015 [2]. Data from the European Health Interview Survey (EHIS), which was conducted between 2013 and 2015, had shown that among European Union, above 50% of the adult population was calculated as overweight or obese [3].

Therefore, obesity is an increasing global epidemic leading to short- and long-term complications impacting subjective well-being, physical health, mental health, and quality of life. The majority of patients with obesity show an impaired quality of life in respect to the general population, irrespective of their psychological suffering. The construct of quality of life is multidimensional and can be considered as an "umbrella term" that includes either medical or psychological issues. In particular, sexual dysfunctions are critically related to the quality of life and represent a topic of growing interest in the obesity field. In individuals with severe obesity (body mass index > 35 kg/m^2), sexual dysfunctions have been reported with a prevalence rate of 7–22% in women and 5–21% in men [4]. The real diffusion of sexual disorders could even be higher given that clinicians often do not ask and underestimate their prevalence as much as the repercussions on the patient's quality of life. Sexuality is often a disregarded issue by mental health practitioners; some psychiatrists may be not sufficiently trained about this topic, and they can feel embarrassed and uncomfortable with the theme [5]. In contrast, most patients, when asked, are encouraged to discuss sexual problems finding that discussion helpful.

Recent data from a multicenter large cohort study reported that during the month prior the clinical assessment, one third of women and a quarter of men with extreme

E. Bianciardi
Psychiatry, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
e-mail: emanuelabianciardi@libero.it

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*,
Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_10

obesity were not sexually active, alone, or with a partner. Moreover 49% of women and 54% of men were found with moderate to high level of sexual dissatisfaction [6].

The relationship between obesity and sexual dysfunction is complex and multidimensional with many aspects playing a role, such as biological and hormonal factors, gender differences, medical comorbidities, and psychosocial issues.

10.1.1 Neurobiological Factors

Existing research highlighted that eating and sex shared common underlying brain representations. In fact, the same hypothalamic areas of the limbic system were found to influence feeding and sexuality.

As for libido and coitus components of sexuality, eating is made of a motivational factor that is hunger and a consummatory part with rhythmicity that is the alimentation [7].

The orbitofrontal cortex is implicated in the encoding of sex and food representations with associations of positive or negative judgment. The insula, the anterior cingulate cortex, and the amygdala ventral striatum are engaged in the phases of anticipation, consummation, and satiety in both sexuality and alimentation [8]. Moreover, eating and sexual functioning are similar in terms of neurotransmission as the case of dopamine system. Numerous neurotransmitters are implicated in sexual desire and behaviors, with dopamine playing a crucial role in the neural reward pathways and emotionally regulated limbic system neural circuits [9]. Behind the homeostatic hunger, palatable food is consumed for its hedonic properties. Such hedonic hunger may lead to an exceeding caloric intake and weight gain. According to a promising research line about the etiology of obesity, reward mechanisms after food intake are related to dopamine transmission in the mesolimbic pathway and to the expression of dopamine D2 receptors (D2Rs) in the nucleus striatum, as demonstrated in the rodent experimental model. In particular, overconsumption of palatable food may weaken the mesolimbic dopamine neurotransmission by reducing the expression of striatal D2Rs which in turns lead to a lower responsiveness of brain reward systems. In obese rats, a significant impairment of dopaminergic transmission in brain circuits has been observed [10].

These findings have been confirmed in a clinical study on human subjects, showing that the dopaminergic alterations and the consequent drop of the reward hedonic mechanism could determine a vicious circle producing hyperphagia [11].

Taken together, these researches support the hypothesis for a dopaminergic signaling that regulates consummatory aspects of sexual and feeding behavior.

10.1.2 Reproductive Hormones

The levels of testosterone and its carrier protein, sex hormone-binding globulin (SHBG), decrease as BMI increases, particularly in men with abdominal obesity (waist circumference >102 cm, waists-to-hip ratio >0.9, or BMI >30) [12]. In men with obesity, the decreased testosterone levels range from 20% to 64% of the

patients, depending on the characteristics of the population, the age, and on whether total or free circulating testosterone was measured [13].

Testosterone is the leading sex hormone in men, and it plays a crucial role either in libido or in sexual functioning. Lower testosterone levels can contribute to impaired sexual desire. Androgen deficiency can directly affect erectile dysfunction. Despite the clear association between obesity and low testosterone levels, the causal directionality of this observed link is still uncertain.

Low testosterone levels in obese men have been associated with increased estrogen production by the adipose tissue, insulin resistance, and low-grade systemic inflammatory process (C-reactive protein values). Leptin levels are higher individuals with obesity and negatively correlate with testosterone values; thus, the excess of circulating leptin may play an important role in the development of decreased androgens in male obesity [14]. Sleep apnea, which is a common comorbidity of obesity, has been associated with decreased testosterone levels [15]. It is noteworthy that although the decrease of testosterone level, in men with obesity, the exogenous testosterone replacement is not found to be an effective treatment for erectile dysfunctions [16]. In fact, among men with obesity, lifestyle interventions aimed at removing the multiple metabolic risk factors of erectile dysfunctions seem to be the most favorable approach. In obese women the excess body weight is associated with an elevation of androgens and estradiol leading to amenorrhea, irregular menstrual cycles, polycystic ovarian syndrome, infertility, preterm labor, miscarriage, and failed fertility treatments [17]. Moreover, weight loss improves female reproductive and sexual health [18]. But, as discussed above, in obese women sexual dysfunctions are more affected by psychological aspects respect to men.

10.1.3 Gender Differences

Gender is a leading determinant of physical and mental health and prejudices individuals' access to health service. Accordingly, it has been demonstrated that females were more likely to consult a mental health specialist when it was needed [19]. In particular, some researchers brought out that men were less inclined than women to receive medical counseling for sexual dysfunctions [20, 21]. Accordingly, in clinical studies, female sexual disorders are more prevalent compared to population studies.

Moreover, fat storage and metabolism differed considerably between men and women [22], and gender plays a role in the efficacy of weight-loss treatments either nonsurgical or surgical [23, 24]. Thus, it is reasonable that the relationship between obesity and sexual functioning may be sex specific. Although many researchers investigated sexual dysfunctions in individuals with eating disorders [25], the literature about gender differences in sexual dysfunctions in those with obesity is still lacking.

Factors that are involved in the relationship between sexual dysfunctions and obesity such as hormones, psychiatric and somatic comorbidities, and the use of medications are all issues that are influenced by gender differences. It is widely recognized that men and women show different response to pharmacotherapies in terms of efficacy and side effects [26]. In women with obesity, sexual disorders seem to be more related to the motivational interface of sexuality, that is, the libido,

and studies reported higher rate of psychiatric concerns compared to men as body image dissatisfaction, trauma-related disorders, depression, and eating disorders. On the other hand, in men, sexual dysfunctions are more likely to be attributed to somatic comorbidities of obesity [27].

Up to one third of patients with morbid obesity had a lifetime history of any substance use disorder, including alcohol abuse, and men seemed to be more vulnerable to alcohol-related disorders [28].

It was argued that obese women were less sexually active than those with normal weight [29]. In fact, sexual functioning was documented as poorer in obese women, with a more serious impairment in the case of a comorbid binge eating disorder [30, 31].

However, a higher body mass index was not associated with a lower frequency of heterosexual intercourse, and overweight and obese women were more likely than non-obese women to address ever having any sexual relationship with men [32]. An European survey reported high number of unintended pregnancies in obese women [33]. As for the women, normal-weight men indicated ten more lifetime partners than obese men [34].

Another relevant issue is that gender may influence the doctor-patient relationship, peculiarly in the field of weight-loss counseling. Patients may experience different emotions according to the gender of clinician, which in turn may compromise the adherence to treatment [35]. At similar body mass index, physicians seem to be more prone to promote weight loss in women pointing out possible weight concerns [36].

Finally, there are substantial concerns about the assessment of sexual functioning. Given that not all psychometric instruments are gender-specific, they might not capture topics that are differently relevant to each gender, leading to erroneous diagnoses. It is strongly recommended to use validated and gender-specific instruments such as Female Sexual Function Index (FSFI) [37], Sexual Quality of Life-Female questionnaire (SQOL-F) [38], Brief Sexual Function Inventory (BSFI) [39], and International Index of Erectile Function [40] (Table 10.1).

Table 10.1 Self-report instruments assessing sexual dysfunctions

FSFI [37]	The Female Sexual Function Index (FSFI) is a 19-item self-report questionnaire that assesses sexual functioning in the past 6 months across six domains: sexual desire, sexual arousal, lubrication, orgasm, satisfaction, and pain during sexual intercourse
SQoL-F [38]	The Sexual Quality of Life-Female questionnaire (SQoL-F) is an 18-item self-report questionnaire assessing the impact of sexual dysfunction on a woman's sexual quality of life. Each question is scored on a six-point scale ranging from completely agree to completely disagree. A higher total score reflects a better sexual quality of life
BSFI [39]	The Brief Sexual Function Inventory (BSFI) is 11-item self-report questionnaire that measures sexual function in males covering five aspects: sexual drive, erection, ejaculation, perception of problems with sexual function in each of these areas, and overall satisfaction
IIEF [40]	The International Index of Erectile Function (IIEF) is a 15-item self-report questionnaire assessing erectile dysfunctions exploring five domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction

10.1.4 Medical Comorbidities

Indirectly, obesity may cause sexual dysfunction through the effect of medical comorbidities, namely, high blood pressure, diabetes, and high cholesterol levels. In erectile dysfunctions, lipid disorders and hypertension may cause atherosclerotic damage of penile arteries leading to reduced blood flow in and out of the penis and compromised beginning and maintenance of erection [41]. A reduced blood flow of the vagina may similarly affect sexual arousal in women. Furthermore, symptoms of headache, fatigue, low energy, tiredness, and general weakness that may occur with hypertension affect sexual functioning.

A large body of evidences demonstrated a chronic pro-inflammatory state in obesity, influencing endothelial functioning and contributing to the increased risk of thrombotic accidents [42]. In particular, high levels of pro-inflammatory interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor-α, and C-reactive protein were found [43]. Whereas it is widely accepted that erectile dysfunction and atherosclerosis share common vascular mechanisms, a diagnosis of erectile dysfunction may represent an alarm of the risk to develop coronary heart disease.

Moreover, although up to 50% of erectile dysfunctions may be ascribed to hypertension and cardiovascular diseases, the activitiy of many antihypertensive drugs may itself undermine erection [44].

Almost half of men with diabetes experienced sexual dysfunctions with an earlier onset of 10–15 years than nondiabetic population [45]. The limited number of findings about sexual disorders in women with diabetes has documented problems in vaginal lubrication and sexual desire [46].

Insulin resistance is highly prevalent in obese individuals. The insulin-resistant, hyperinsulinemic state has been associated with a heightened endothelial vasoconstriction, which may possibly contribute to the impaired erection [47]. The usage of diabetic agents, such as metformin and the thiazolidinedione, is not without risks and potential sexual side effects [48].

10.1.5 Psychosocial Factors

Obesity may be associated with an open range of psychological issues that may affect sexual functioning. Major depression is highly prevalent in persons with morbid obesity representing the leading cause of mental health suffering [49]. Up to up to 78% of individuals with depression treated with antidepressants suffer from a sexual dysfunction [50]. The low self-esteem, fatigue, and the diminished libido characterizing atypical depression may be some of the mediating factors contributing to the link between obesity and sexual function in both men and women. However, despite obesity and depression are often in comoridity, it is virtually impossible to establish if depression or obesity may be the first trigger for sexual dysfunctions. Moreover, many antidepressant drugs are frequently correlated with the onset of sexual dysfunctions [51].

Body image dissatisfaction is prevalent in patients with obesity, with almost 74% of individuals reporting some distress and concerns about one's own body. Moreover,

body image was estimated as poorer in morbid obese individuals seeking surgical treatment comparing to participants in weight-loss programs and nonobese controls with various gender differences [52, 53]. Since adolescent women developed a cognitive vulnerability to body image disturbances, it may reinforce in adulthood with weight gain and obesity [54]. In a survey of obese men and women, body dissatisfaction was found to be increased in women, with men easily describing themselves as stronger rather than fat [55].

Body dissatisfaction can inhibit intimate relationship particularly the sexual intercourses. Women satisfied with their body image reported more numerous and pleasant sexual experiences, a broader range of sexual activities with no preoccupations of being sexually undesirable and naked [56].

The widespread cultural belief that obese individuals are lacking of the willingness to lose weight makes such patients poorly accepted from society leading to problematic and exiguous relationships. In addition, it has been documented that obese individuals often reported a lifetime history of discrimination, stigma, and self-stigma due to their physical appearance [57]. During childhood people with obesity were frequently victim of bullying [58] that represents a traumatic experience with negative lifelong consequence in peer, romantic, and sexual adult relationships.

Another psychiatric aspect that may play a role in the interface between obesity and sexuality is the field of eating disorder. Among people with obesity, eating patterns may be different from those developing in normal-weight individuals. As discussed above, traumatic events and stigma are two factors influencing relationships that are highly prevalent in obesity. Furthermore, while one who suffers from eating disorder might hide the problem from society, people with obesity are suspected from others as suffering from a problematic eating behavior with a potential stigma effect. Emotional eating is a maladaptive eating behavior that was described as "the tendency to eat in response to emotional distress (i.e. a range of negative, and for some authors positive, emotions) and during stressful life situations." Eating emotionally is related to binge eating and other problematic eating behaviors like grazing, nibbling, and "uncontrolled" eating which are prevalent in obese individuals [59]. Moreover, the endogenous opioid system was found to regulate emotional eating and sexuality [60], and it has been associated with impaired sexual desire, arousal, lubrication, orgasm, and satisfaction in women [61].

Finally, alcohol use disorder that may seriously affect sexual functioning [62] is prevailing in obese individual with binge eating disorder [63, 64].

Conclusion

In conclusion, sexual dysfunctions are common and critical disorders affecting individuals with severe obesity, leading to considerable psychological distress and impaired quality of life.

Although surgical and diet-induced weight loss seemed to ameliorate sexual functioning, such improvement may be not only attributable to the amount of weight loss [65]. The connections between obesity and sexual functioning are multifactorial (Fig. 10.1). Sexuality in obese people may depend on reproductive hormones, gender, weight-related somatic and psychiatric comorbidities, and social and environmental factors. According to the multidisciplinary approach to obesity, it is mandatory that general practitioners, endocrinologists, nutritionists,

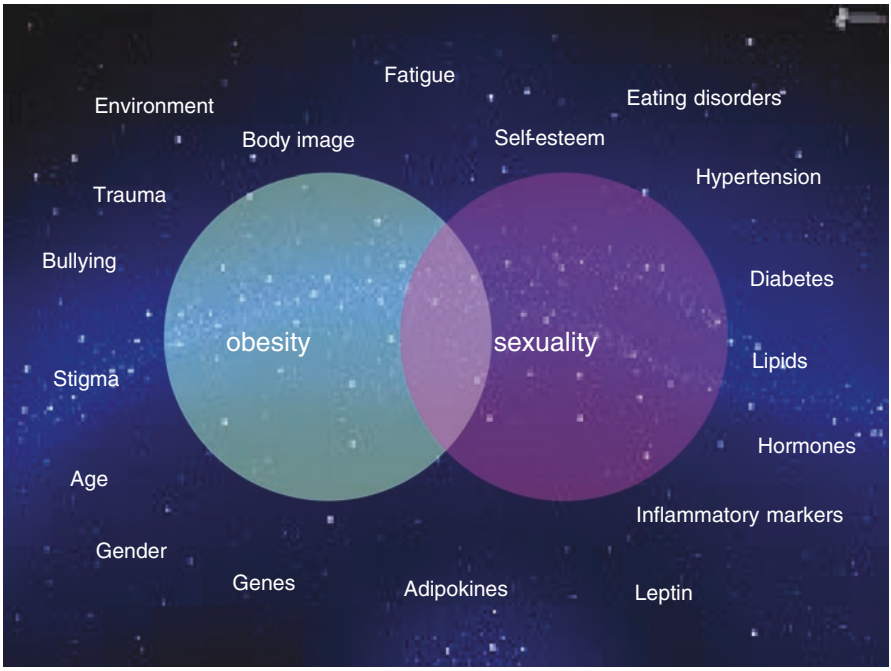

Fig. 10.1 Constellation of factors influencing obesity and sexuality

surgeons, and psychiatrists are capable to establish a diagnosis and treat sexual disorders with their targeted competences and contributions.

Sexuality is warranted to be clearly addressed by clinicians with open and specific questions in the initial screening and during counseling performed with the weight-loss programs. Particular attention is a big demand for gender differences.

Deepening the comprehension and consideration of the suffering of obese individuals with sexual disorders may lead to advances in the obesity treatments and improvement of well-being and quality of life.

Moreover, calling the attention on the advantages of weight loss, some individuals may be more confident with the policy of treatments.

References

1. Scully T. Public health: society at large. Nature. 2014;508(7496):S50–1.
2. World Health Organization. Global health risks: mortality and burden of disease attributable to selected major risks. 2009. http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf.
3. European Health Interview Survey (EHIS). Health status statistics. 2015. http://ec.europa.eu/eurostat/statisticsexplained/index.php/Glossary:European_health_interview_survey_(EHIS).
4. Niolu C, Bianciardi E, Siracusano A. Gender differences in sexual dysfunctions among individuals with obesity. Ital J Gend Specif Med. 2016;2(2):69–74.
5. Pinderhughes CA, Grace EB, Reyna LJ. Psychiatric disorders and sexual functioning. Am J Psychiatry. 1972;128:1276–83.

6. Steffen KJ, King WC, White GE, Subak LL, Mitchell JE, Courcoulas AP, Flum DR, Strain G, Sarwer DB, Kolotkin RL, Pories W, Huang AJ. Sexual functioning of men and women with severe obesity before bariatric surgery. Surg Obes Relat Dis. 2017;13(2):334–43.
7. Kim SW, Schenck CH, Grant JE, Yoon G, Dosa PI, Odlaug BL, et al. Neurobiology of sexual desire. NeuroQuantology. 2013;11(2):332–59.
8. Limoncin E, Ciocca G, Mollaioli D, Jannini EA. Sexual distress in obesity. In: Lenzi A, Migliaccio S, Donini L, editors. Multidisciplinary approach to obesity. Cham: Springer; 2015.
9. Micevych PE, Meisel RL. Integrating neural circuits controlling female sexual behavior. Front Syst Neurosci. 2017;11:42.
10. Moraes JC, Coope A, Morari J, Cintra DE, Roman EA, Pauli JR, et al. High-fat diet induces apoptosis of hypothalamic neurons. PLoS One. 2009;4(4):e5045.
11. Kenny PJ. Reward mechanisms in obesity: new insights and future directions. Neuron. 2011;69(4):664–79. https://doi.org/10.1016/j.neuron.2011.02.016.
12. Brand JS, Rovers MM, Yeap BB, et al. Testosterone, sex hormone-binding globulin and the metabolic syndrome in men: an individual participant data meta-analysis of observational studies. PLoS One. 2014;9(7):e100409.
13. Kalyani RR, Dobs AS. Androgen deficiency, diabetes, and the metabolic syndrome in men. Curr Opin Endocrinol Diabetes Obes. 2007;14:226–34.
14. Isidori AM, Caprio M, Strollo F, Moretti C, Frajese G, Isidori A, Fabbri A. Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. J Clin Endocrinol Metab. 1999;84(10):3673–80.
15. Rao SR, Kini S, Tamler R. Sex hormones and bariatric surgery in men. Gend Med. 2011; 8(5):300–11.
16. Rajfer J. Relationship between testosterone and erectile dysfunction. Rev Urol. 2000;2(2):122–8.
17. Butterworth J, Deguara J, Borg CM. Bariatric surgery, polycystic ovary syndrome, and infertility. J Obes. 2016;2016:1871594.
18. Shekelle PG, Newberry S, Maglione M, Li Z, Yermilov I, Hilton L, Suttorp M, Maggard M, Carter J, Tringale C, Chen S. Bariatric surgery in women of reproductive age: special concerns for pregnancy. Evid Rep Technol Assess (Full Rep). 2008;169:1–51.
19. Magaard JL, Seeralan T, Schulz H, Brütt AL. Factors associated with help-seeking behaviour among individuals with major depression: a systematic review. PLoS One. 2017;12(5):e0176730.
20. Kolotkin RL, Crosby RD, Williams GR. Health-related quality of life varies among obese subgroups. Obes Res. 2012;10(8):748–56. https://doi.org/10.1038/oby.2002.102.
21. Kedde H, Donker G, Leusink P, Kruijer H. The incidence of sexual dysfunction in patients attending dutch general practitioners. Int J Sex Health. 2011;23(4):269–77. https://doi.org/10.1080/19317611.2011.620686.
22. Löfgren P, Hoffstedt J, Rydén M, et al. Major gender differences in the lipolytic capacity of abdominal subcutaneous fat cells in obesity observed before and after long-term weight reduction. J Clin Endocrinol Metab. 2002;87(2):764–71.
23. Perrone F, Bianciardi E, Benavoli D, Tognoni V, Niolu C, Siracusano A, Gaspari AL, Gentileschi P. Gender influence on long-term weight loss and comorbidities after laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass: a prospective study with a 5-year follow-up. Obes Surg. 2016;26(2):276–81.
24. Bhogal MS, Langford R. Gender differences in weight loss; evidence from a NHS weight management service. Public Health. 2014;128(9):811–3.
25. Pinheiro AP, Raney TJ, Thornton LM, Fichter MM, Berrettini WH, Goldman D, et al. Sexual functioning in women with eating disorders. Int J Eat Disord. 2010;43(2):123–9. https://doi.org/10.1002/eat.20671.
26. Sramek JJ, Murphy MF, Cutler NR. Sex differences in the psychopharmacological treatment of depression. Dialogues Clin Neurosci. 2016;18(4):447–57.
27. Carrilho PJ, Vivacqua CA, Godoy EP, Bruno SS, Brígido AR, Barros FC, et al. Sexual dysfunction in obese women is more affected by psychological domains than that of non-obese. Rev Bras Ginecol Obstet. 2015;37(12):552–8. https://doi.org/10.1590/SO100-720320155443.
28. Kalarchian MA, Marcus MD, Levine MD, Courcoulas AP, Pilkonis PA, Ringham RM, et al. Psychiatric disorders among bariatric surgery candidates: relationship to obesity and functional health status. Am J Psychiatry. 2007;164:328–34. https://doi.org/10.1176/ajp.2007.164.2.328.

29. Nagelkerke NJ, Bernsen RM, Sgaier SK, Jha P. Body mass index, sexual behaviour, and sexually transmitted infections: an analysis using the NHANES 1999-2000 data. BMC Public Health. 2006;6:199. https://doi.org/10.1186/1471-2458-6-199.
30. Wilfley DE, Wilson GT, Agras WS. The clinical significance of binge eating disorder. Int J Eat Disord. 2003;34(Suppl):S96–106. https://doi.org/10.1002/eat.10209.
31. Lewer M, Nasrawi N, Schroeder D, Vocks S. Body image disturbance in binge eating disorder: a comparison of obese patients with and without binge eating disorder regarding the cognitive, behavioral and perceptual component of body image. Eat Weight Disord. 2016;21(1):115–25. https://doi.org/10.1007/s40519-015-0200-5.
32. Kaneshiro B, Jensen JT, Carlson NE, Harvey SM, Nichols MD, Edelman AB. Body mass index and sexual behavior. Obstet Gynecol. 2008;112:586–92. https://doi.org/10.1097/AOG.0b013e31818425ec.
33. Bajos N, Wellings K, Laborde C, Moreau C, CSF Group. Sexuality and obesity, a gender perspective: results from French national random probability survey of sexual behaviours. BMJ. 2010;340:c2573. https://doi.org/10.1136/bmj.c2573.
34. Wee CC, Huang A, Huskey KW, McCarthy EP. Obesity and the likelihood of sexual behavioral risk factors for HPV and cervical cancer. Obesity (Silver Spring). 2008;16(11):2552–5. https://doi.org/10.1038/oby.2008.394.
35. Dutton GR, Herman KG, Tan F, Goble M, Dancer-Brown M, Van Vessem N, et al. Patient and physician characteristics associated with the provision of weight loss counseling in primary care. Obes Res Clin Pract. 2014;8(2):e123–30. https://doi.org/10.1016/j.orcp.2012.12.004.
36. Anderson C, Peterson CB, Fletcher L, Mitchell JE, Thuras P, Crow SJ. Weight loss and gender: an examination of physician attitudes. Obes Res. 2001;9(4):257–63. https://doi.org/10.1038/oby.2001.30.
37. Rosen R, Brown C, Heiman J, Leib S. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000;26(2):191–208.
38. Symonds T, Boolell M, Quirk F. Development of a questionnaire on sexual quality of life in women. J Sex Marital Ther. 2005;31(5):385–97.
39. O'Leary MP, Fowler FJ, Lenderking WR, Barber B, Sagnier PP, Guess HA, Barry MJ. A brief male sexual function inventory for urology. Urology. 1995;46(5):697–706.
40. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology. 1997;49(6):822–30.
41. Walczak MK, Lokhandwala N, Hodge MB, Guay AT. Prevalence of cardiovascular risk factors in erectile dysfunction. J Gend Specif Med. 2002;5(6):19–24.
42. Sell H, Poitou C, Habich C, Bouillot JL, Eckel J, Clément K. Heat shock protein 60 in obesity: effect of bariatric surgery and its relation to inflammation and cardiovascular risk. Obesity (Silver Spring). 2017;25(12):2108–14. https://doi.org/10.1002/oby.22014.
43. Illán-Gómez F, Gonzálvez-Ortega M, Orea-Soler I, Alcaraz-Tafalla MS, Aragón-Alonso A, Pascual-Díaz M, et al. Obesity and inflammation: change in adiponectin, C-reactive protein, tumour necrosis factor-alpha and interleukin-6 after bariatric surgery. Obes Surg. 2012;22(6):950–5. https://doi.org/10.1007/s11695-012-0643-y.
44. Stehouwer CD, Henry RM, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. Diabetologia. 2008;51:527–39. https://doi.org/10.1007/s00125-007-0918-3.
45. Al Khaja KA, Sequeira RP, Alkhaja AK, Damanhori AH. Antihypertensive drugs and male sexual dysfunction: a review of adult hypertension guideline recommendations. J Cardiovasc Pharmacol Ther. 2016;21(3):233–44. https://doi.org/10.1177/1074248415598321.
46. Johannes CB, Araujo AB, Feldman HA, Derby CA, Kleinman KP, McKinlay JB. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study. J Urol. 2000;163(2):460–3.
47. Rochester-Eyeguokan C, Meade L. A practical approach to managing hypoactive sexual desire disorder in women with diabetes. Diabetes Ther. 2017;8(5):991–8. https://doi.org/10.1007/s13300-017-0313-0.

48. Borges R, Temido P, Sousa L, Azinhais P, Conceição P, Pereira B, et al. Metabolic syndrome and sexual (dys)function. J Sex Med. 2009;6:2958–75. https://doi.org/10.1111/j.1743-6109.2009.01412.x.
49. Olvera RL, Williamson DE, Fisher-Hoch SP, Vatcheva KP, McCormick JB. Depression, obesity, and metabolic syndrome: prevalence and risks of comorbidity in a population-based representative sample of Mexican Americans. J Clin Psychiatry. 2015;76(10):e1300–5. https://doi.org/10.4088/JCP.14m09118.
50. Dawes AJ, Maggard-Gibbons M, Maher AR, Booth MJ, Miake-Lye I, Beroes JM, et al. Mental health conditions among patients seeking and undergoing bariatric surgery: a meta-analysis. JAMA. 2016;315(2):150–63. https://doi.org/10.1001/jama.2015.18118.
51. McCabe MP, Sharlip ID, Lewis R, Atalla E, Balon R, Fisher AD, et al. Incidence and prevalence of sexual dysfunction in women and men: a consensus statement from the Fourth International Consultation on Sexual Medicine 2015. J Sex Med. 2016;13(2):144–52. https://doi.org/10.1016/j.jsxm.2015.12.034.
52. Baldwin DS, Manson C, Nowak M. Impact of antidepressant drugs on sexual function and satisfaction. CNS Drugs. 2015;29(11):905–13. https://doi.org/10.1007/s40263-015-0294-3.
53. Polce-Lynch M, Myers B, Kliewer W, Kilmartin C. Adolescent self-esteem and gender: exploring relations to sexual harassment, body image, media influence, and emotional expression. J Youth Adolesc. 2001;30:225–44. https://doi.org/10.1023/A:1010397809136.
54. Wimmelmann CL, Dela F, Mortensen EL. Psychological predictors of weight loss after bariatric surgery: a review of the recent research. Obes Res Clin Pract. 2014;8(4):e299–313. https://doi.org/10.1016/j.orcp.2013.09.003.
55. Wardle J, Johnson F. Weight and dieting: examining levels of weight concern in British adults. Int J Obes Relat Metab Disord. 2002;26(8):1144–9. https://doi.org/10.1038/sj.ijo.0802046.
56. Hyde JS, Mezulis AH, Abramson LY. The ABCs of depression: integrating affective, biological, and cognitive models to explain the emergence of the gender difference in depression. Psychol Rev. 2008;115(2):291–313. https://doi.org/10.1037/0033-295X.115.2.291.
57. Kolotkin RL, Crosby RD, Gress RE, Hunt SC, Engel SG, Adams TD. Health and health-related quality of life: differences between men and women who seek gastric bypass surgery. Surg Obes Relat Dis. 2008;4(5):651–8. https://doi.org/10.1016/j.soard.2008.04.012.
58. Flint SW, Snook J. Disability discrimination and obesity: the big questions? Curr Obes Rep. 2015;4(4):504–9. https://doi.org/10.1007/s13679-015-0182-7.
59. Baldwin JR, Arseneault L, Odgers C, Belsky DW, Matthews T, et al. Childhood bullying victimization and overweight in young adulthood: a cohort study. Psychosom Med. 2016;78(9):1094–103. https://doi.org/10.1097/PSY.0000000000000388.
60. Leehr EJ, Krohmer K, Schag K, Dresler T, Zipfel S, Giel KE. Emotion regulation model in binge eating disorder and obesity – a systematic review. Neurosci Biobehav Rev. 2015;49:125–34. https://doi.org/10.1016/j.neubiorev.2014.12.008.
61. Bodnar RJ. Endogenous opiates and behavior: 2014. Peptides. 2016;75:18–70. https://doi.org/10.1016/j.peptides.2015.10.009.
62. Castellini G, Mannucci E, Mazzei C, Lo Sauro C, Faravelli C, Rotella CM, et al. Sexual function in obese women with and without binge eating disorder. J Sex Med. 2010;7(12):3969–78. https://doi.org/10.1111/j.1743-6109.2010.01990.x.
63. Christensen BS, Grønbaek M, Pedersen BV, Graugaard C, Frisch M. Associations of unhealthy lifestyle factors with sexual inactivity and sexual dysfunctions in Denmark. J Sex Med. 2011;8(7):1903–16. https://doi.org/10.1111/j.1743-6109.2011.02291.x.
64. Wiedemann AA, Saules KK, Ivezaj V. Emergence of new onset substance use disorders among post-weight loss surgery patients. Clin Obes. 2013;3(6):194–201.
65. Bond DS, Wing RR, Vithiananthan S, Sax HC, Roye GD, Ryder BA, et al. Significant resolution of female sexual dysfunction after bariatric surgery. Surg Obes Relat Dis. 2011;7(1):1–7. https://doi.org/10.1016/j.soard.2010.05.015.

Sexual Dysfunction in Eating Disorders

11

Giovanni Castellini, Mario Maggi, and Valdo Ricca

11.1 Introduction

Eating disorders (EDs) are serious and chronic syndromes involving in most of the cases young women and affecting their personality development as well as their body health [1, 2]. The new edition of the DSM created a new category named *feeding and eating disorders*, encompassing different psychopathological conditions such as anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), pica (defined as persistent craving and compulsive eating of non-food substances), rumination disorder, and avoidant/restrictive food intake disorder [3]. For all this conditions, nutrition is no longer anchored to its physiological meaning, and the food loses its main value of nourishment or pleasure; rather it is considered as negative and potentially dangerous. Consequently, the power supply is no longer determined by a gut feeling of hunger or satiety, but it is both quantitatively and qualitatively based on arbitrary parameters (such as rigid rules, concept of control). All these diagnoses are defined by pathological behaviors combined in different patterns—dieting, avoiding specific foods, using food to manage emotions, body checking, binge eating, and vomiting—and result in specific medical complications due to unbalanced assumption or absorption of food or purging behaviors, such as weight loss, obesity, heart or kidneys failures, and hematic alterations. Moreover, EDs are frequently associated with several psychiatric comorbidities, such as

G. Castellini · V. Ricca (✉)
Psychiatric Unit, Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy
e-mail: valdo.ricca@unifi.it

M. Maggi
Department of Experimental, Clinical and Biomedical Sciences, University of Florence, Florence, Italy

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*,
Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_11

anxiety and mood disorders, or personality disorders, which in many cases challenged the long-term outcome [4, 5].

EDs and sexual dysfunctions share risk and maintaining factors, including biological alterations (e.g., hormonal pattern), life event association (e.g., sexual abuse), and relationship with psychopathological underpinning (e.g., body image perception, body dissatisfaction, impulsivity). Despite this clear overlap between these conditions, only recently, the scientific community appeared to be interested in sexuality of these patients. In a recent review, Castellini et al. [6] found that few studies considered sexual dysfunctions in ED patients. Indeed, recent changes in the psychiatric classification reduced the importance of amenorrhea for the diagnosis of AN, and sexual functioning is seldom considered an important component of treatment or outcome predictor.

11.2 Dysfunction vs Hypersexuality

The issue of sexual functioning in patients with EDs is controversial, as for the majority of clinicians hardly assess it, and few empirical data are available. However, it has been noticed that patients with AN and BN described their first sexual experiences such as kiss, petting, and first sexual intercourse with a profound uneasiness as compared to the general population [6]. As for other psychiatric conditions, patients with EDs often report a significant reduction of frequency of their sexual activity [6]. However, it has been suggested that sexual dysfunction in this particular condition cannot be measured by a mere reduction of frequency of sexual activity [6]. Indeed, some patients with AN and BN report a frequency of sexual intercourse comparable to healthy controls [7] or sometimes compulsive sexual activity [6]. Therefore, what should be primarily assessed by clinicians is the subjective reduction of pleasure and satisfaction associated with sexual activity, the reduction of sexual fantasies, which are frequently reported by patients with EDs [7, 8]. Indeed, a general consideration regarding ED psychopathology is that a fine-tuned characterization should be based on qualitative and subjective (body image satisfaction and perception, self-worth, weight subjective estimation) rather than merely quantitative measures (weight loss, frequency of pathological behaviors).

According to different reports [9, 10], sexual dysfunction is not limited to AN but can be found also in BN patients [11, 12] and BED patients [13, 14], who usually do not suffer from hypogonadism, due to emaciation. Nevertheless, most of the pathological behaviors (such as binge eating) reported in these diagnoses can be derived by a common vicious cycle, based on overestimation and overevaluation of body shape, association between self-worth and weight control, and utilization of eating assumption to manage dysfunctional emotions [15].

Few studies compared ED diagnoses between them, in terms of sexual functioning. Indeed, it is possible that different pathological behaviors underlie specific personality traits, which account for peculiar sexual deficits. For example, comparing AN subtypes, Castellini et al. [7] demonstrated that purging anorectics had greater sexual drive than non-purging patients and that AN restricting/type patients showed

lower female sexual function index arousal, lubrication, orgasm, satisfaction, and pain scores compared with AN binge/purging type and BN patients. Furthermore, Rothschild et al. [16] reported that sexual fantasy distinguished AN subgroups, with a paucity of fantasy among restrictive anorectics at normal weight compared with binge/purging anorectics. It has been hypothesized that individuals with EDs who are emotionally constricted and over-controlled (as AN restricting patients) report limited sexual functioning, whereas those with emotional dysregulation and low self-control report more impulsive and chaotic sexual profiles [17]. However, being in a stable relationship can be considered a protective factor for psychopathology and especially for EDs, for different reasons correlated with the ability to establish emotional bonding, as well as with self-esteem and quality of life. Indeed, several studies showed that married women have lower ED symptomatology as compared with single women [18]. For example, Keel et al. [18] found that being married predicted significant decreases in drive for thinness and bulimic symptoms.

On a different perspective, sexual functioning in EDs has been considered as either hypersexuality or decreased sexuality [6]. In particular, in the period between 1995 and 2005, a large number of studies supported a model which was based on impulsivity as a mediator of the relationships between trauma, pathological eating behaviors, and the tendency to impulsively engage in sexual activities with strangers or in risky situations and without using protections [19]. The so-called multi-impulsive BN—a subpopulation of patients with EDs—often reports compulsive sexual activity, promiscuity, and other risky sexual behaviors, which have been found to be correlated with the severity of binge eating and vomiting [20]. Indeed, BN patients and AN binge/purging type patients reported higher rate of multiple partners compared with AN restricting type patients [7]. Promiscuity and sexual intercourses have been associated with multi-impulsivity, and the heterogeneity of disordered eating behaviors was found to be correlated with higher numbers of sex partners [21]. Different research demonstrated an association between bulimic and purging behaviors and a number of dyscontrol behaviors, namely bullying, truancy, excessive drinking, and sexual disinhibition in BN patients [22].

11.3 Maintaining Factors of Sexual Dysfunction in Patients with Eating Disorders

Sexual dysfunction in patients with EDs should be always considered in the light of the multifactorial etiopathology if these conditions. First of all, medical comorbidities due to pathological eating behaviors are generally associated with sexual functioning, both in the sense of weight loss and obesity. Indeed, hypogonadism and emaciation are responsible for a part of the decrease sexual interest in patients with AN [23]. Some studies demonstrated a significant association between the degree of weight loss and the sexual impairment [12], even though other observations did not confirm these findings Castellini et al. [7]. Furthermore, recovery of a normal weight has been reported to restore sexual drive in a considerable rate of patients [8, 24]. However, central hypogonadism is not merely related with weight loss; rather it has been associated also with

the quality of diet [6] or to severe stress reactions [11]. Accordingly, hormonal alterations can be detected also in patients without emaciation such as BN or even BED patients. The comparisons of sexuality between AN and BN subjects showed conflicting results, with a similar pattern found in Castellini et al.'s study [7], while a Mangweth-Matzek et al. [25] demonstrated a worse condition in AN.

BED and a subpopulation of BN patients report different degree of obesity, which has been demonstrated to affect several aspects of sexual functioning [26, 27]. The weight loss following bariatric surgery was found to be associated with an improvement of hormonal profiles, as well as sexual functioning in both men [28] and women [29]. The impaired sexuality in obese subjects can be due to the organic consequences of chaotic food assumption, such as diabetes, hypertension, or hormonal alterations due to metabolic syndrome [30].

However, recent data demonstrated that sexual functioning of obese patients with EDs were more impaired as compared with obese subjects without EDs [13, 31]. Accordingly, it has been suggested that for BED as well as for the other ED diagnoses, it might exist a specific effect of psychopathology, regardless of the medical consequences of pathological eating behaviors [6].

Body image distortion and body dissatisfaction represent the core psychopathological features of all ED diagnoses [15]. Stable impairment in body image representation often precedes the onset of almost all patients with EDs [32] and is one of the most relevant predictors of treatment response and long-term outcome of both AN and BN [4, 33]. Body dissatisfaction is a key factor also for sexual functioning. A healthy attitude toward one's own body is correlated with more frequent sexual experiences and with a wider range of sexual activities [34]. Persons satisfied of their physical appearance generally feel more sexually desirable and self-confident [35]. On the contrary, loss of sexual attractiveness, body worry during sexual activity, or preoccupations about body weight correlated with sexual dysfunctions, especially in young women [36].

In line with these observations, the lived corporeality and the representation of one's own body has been considered as a possible mediator of the sexual dysfunction in EDs [6]. Accordingly, recent findings demonstrated that pathological concerns about body shape were inversely correlated with subjectively perceived satisfaction in sexual activity in both patients with AN and BN [7] as well as in patients with BED [13]. A further confirmation of the role of body dissatisfaction in the maintenance of sexual dysfunction in AN and BN [8] is provided by a recent follow-up analysis of EDs outcome. In this study, Castellini et al. [8] evaluated the effect on sexual functioning of a cognitive behavioral intervention, an intervention targeted to the common core psychopathological features of EDs. The effects of this psychological intervention included a relevant improvement in sexual functioning in both AN and BN groups. This effect was mediated by the specific intrapsychic processes occurring during the intervention, including amelioration of body dissatisfaction and weight control.

Emotion dysregulation has considered a psychopathological feature, accounting for both sexual dysfunction [37] and binge eating or vomiting. Dysfunctional mood modulatory mechanisms are responsible for alterations of women's sexual desire or

the phenomenon of *spectatoring* [38]. Furthermore, sexual dysfunction has been associated with different adverse emotional states such as sadness, guilt, and anger associated with negative automatic thoughts during sexual activity. Dysfunctional mood regulation is also considered a latent mechanism underlying the relationship between low sexual desire and frequency of binge eating behaviors in AN binge/purging type and BN [7] and BED [13] patients. In both these studies, sexual dysfunction was correlated with emotional eating, a psychological dimension defined as "eating in response to a range of negative emotions" [39].

Finally, sexual abuse is the life event that mostly impacts the pathogenesis of both sexual dysfunction and EDs [6]. Consequences of sexual abuse and in particular abuse intervening during childhood include binge eating and purging behaviors [11, 40, 41], sexual dysfunction [42], dissociative experiences [43, 44], mood disorders [45], and suicidal thoughts [45].

Given that a person's sexuality, mood regulation, and eating behaviors are multifaceted and interconnected phenomena, several models of interaction related with sexual abuse have been proposed involving biologic, cognitive, and affective processes [46]. Therefore, common underlying maintaining factors of these symptoms which are typical consequences of traumatic sexual experience have been proposed, such as severe body image disturbances [21] and emotion dysregulation [47]. Sexual abuse may interfere with sexual maturation [48], leading a woman to feel revulsion about her body in a way that may manifest with concerns about body weight, shape, and size [49]. Furthermore, sexual trauma might act specifically by inducing feelings of poor self-esteem, triggering self-starvation, as a reflection of the individual's effort at regaining control on her life [50]. Finally, dissociation, which consists in "a disruption in the usually integrated functions of consciousness, memory, identity, and perception of the environment" [43], has been considered as a shared maintaining factor of both sexual dysfunction and pathological eating behaviors in sexual abuse survivors [7].

References

1. Fairburn CG, Harrison PJ. Eating disorders. Lancet. 2003;361:407–16.
2. Fichter MM, Quadflieg N, Hedlund S. Twelve-year course and outcome predictors of anorexia nervosa. Int J Eat Disord. 2006;39:87–1003.
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Association; 2013.
4. Castellini G, Lo Sauro C, Mannucci E, Ravaldi C, Rotella CM, Faravelli C, Ricca V. Diagnostic crossover and outcome predictors in eating disorders according to DSM-IV and DSM-V proposed criteria: a 6-year follow-up study. Psychosom Med. 2011;73:270–9.
5. Nagata T, Kawarada Y, Kiriike N, Iketani T. Multi-impulsivity of Japanese patients with eating disorders: primary and secondary impulsivity. Psychiatry Res. 2000;94:239–50.
6. Castellini G, Lelli L, Ricca V, Maggi M. Sexuality in eating disorders patients: etiological factors, sexual dysfunction and identity issues. A systematic review. Horm Mol Biol Clin Investig. 2016;25(2):71–90.
7. Castellini G, Lelli L, Lo Sauro C, Fioravanti G, Vignozzi L, Maggi M, Faravelli C, Ricca V. Anorectic and bulimic patients suffer from relevant sexual dysfunctions. J Sex Med. 2012;9:2590–9.

8. Castellini G, Lo Sauro C, Lelli L, Godini L, Vignozzi L, Rellini AH, Faravelli C, Maggi M, Ricca V. Childhood sexual abuse moderates the relationship between sexual functioning and eating disorder psychopathology in anorexia nervosa and bulimia nervosa: a 1-year follow-up study. J Sex Med. 2013;10:2190–200.
9. McNicholas F, Dooley B, McNamara N, Lennon R. The impact of self-reported pubertal status and pubertal timing on disordered eating in Irish adolescents. Eur Eat Disord Rev. 2012;20:355–62.
10. Meyer C, Blissett J, Oldfield C. Sexual orientation and eating psychopathology: the role of masculinity and femininity. Int J Eat Disord. 2001;29:314–8.
11. Castellini G, Lelli L, Lo Sauro C, Vignozzi L, Maggi M, Faravelli C, Ricca V. Childhood abuse, sexual function and cortisol levels in eating disorders. Psychother Psychosom. 2012;81:380–2.b.
12. Pinheiro AP, Raney TJ, Thornton LM, Fichter MM, Berrettini WH, Goldman D, Halmi KA, Kaplan AS, Strober M, Treasure J, Woodside DB, Kaye WH, Bulik CM. Sexual functioning in women with eating disorders. Int J Eat Disord. 2010;43:123–9.
13. Castellini G, Mannucci E, Mazzei C, Lo Sauro C, Faravelli C, Rotella CM, Maggi M, Ricca V. Sexual function in obese women with and without binge eating disorder. J Sex Med. 2010;7:3969–78.
14. Grilo CM, Masheb RM. Childhood psychological, physical, and sexual maltreatment in outpatients with binge eating disorder: frequency and associations with gender, obesity, and eating related psychopathology. Obes Res. 2001;9:320–5.
15. Fairburn CG. Eating disorders: the transdiagnostic view and the cognitive behavioral theory. In: Fairburn CG, editor. Cognitive behavior therapy and eating disorders. New York: Guilford; 2008. p. 7–22.
16. Rothschild BS, Fagan P, Woodall C, Andersen AE. Sexual functioning of female eating disordered patients. Int J Eat Disord. 1991;10:389–94.
17. Westen D, Harnden-Fischer J. Personality profiles in eating disorders: rethinking the distinction between axis I and axis II. Am J Psychiatry. 2001;158:547–62.
18. Keel PK, Baxter MG, Heatherton TF, Joiner TE Jr. A 20-year longitudinal study of body weight, dieting, and eating disorder symptoms. J Abnorm Psychol. 2007;116:422–32.
19. Culbert KM, Klump KL. Impulsivity as an underlying factor in the relationship between disordered eating and sexual behaviour. Int J Eat Disord. 2005;38:361–6.
20. Paul T, Schroeter K, Dahme B, Nutzinger DO. Self-injurious behavior in women with eating disorders. Am J Psychiatry. 2002;159:408–11.
21. Ackard DM, Peterson CB. Association between puberty and disordered eating, body image, and other psychological variables. Int J Eat Disord. 2001;29:187–94.
22. Kaltiala-Heino R, Rissanen A, Rimpelä M, Rantanen P. Bulimia and impulsive behaviour in middle adolescence. Psychother Psychosom. 2003;72:26–33.
23. Tuiten A, Panhuysen G, Everaerd W, Koppeschaar H, Krabbe P, Zelissen P. The paradoxical nature of sexuality in anorexia nervosa. J Sex Marital Ther. 1993;19:259–75.
24. Meguerditchian C, Samuelian-Massat C, Valéro R, Begu-Le Corroller A, Fromont I, Mancini J, Sparrow JD, Poinso F, Vialettes B. The impact of weight normalization on quality of recovery in anorexia nervosa. J Am Coll Nutr. 2009;28:397–404.
25. Mangweth-Matzek B, Rupp CI, Hausmann A, Kemmler G, Biebl W. Menarche, puberty, and first sexual activities in eating disordered patients as compared with a psychiatric and a non-psychiatric control group. Int J Eat Disord. 2007;40:705–10.
26. Kolotkin RL, Binks M, Crosby RD, Østbye T, Gress RE, Adams TD. Obesity and sexual quality of life. Obesity. 2006;14:472–9.
27. Esposito K, Ciotola M, Giugliano F, Bisogni C, Schisano B, Autorino R, Cobellis L, De Sio M, Colacurci N, Giugliano D. Association of body weight with sexual function in women. Int J Impot Res. 2007;19:353–7.
28. Reis LO. Sexual functioning in men who underwent bariatric surgery: far beyond sex hormones. Surg Obes Relat Dis. 2015;11:651–2.
29. Sarwer DB, Spitzer JC, Wadden TA, Mitchell JE, Lancaster K, Courcoulas A, Gourash W, Rosen RC, Christian NJ. Changes in sexual functioning and sex hormone levels in women following bariatric surgery. JAMA Surg. 2014;149:26–33.

30. Borges R, Temido P, Sousa L, Azinhais P, Conceição P, Pereira B, Leão R, Retroz E, Brandão A, Cristo L, Sobral F. Metabolic syndrome and sexual (dys)function. J Sex Med. 2009;6: 2958–75.
31. Folope V, Chapelle C, Grigioni S, Coëffier M, Déchelotte P. Impact of eating disorders and psychological distress on the quality of life of obese people. Nutrition. 2012;28:7–13.
32. Rosen JC. Assessment and treatment of body image disturbance. In: Brownell KD, Fairburn CG, editors. Eating disorders and obesity. A comprehensive handbook. New York: Guilford; 1995. p. 369–73.
33. Ricca V, Castellini G, Lo Sauro C, Mannucci E, Ravaldi C, Rotella F, Faravelli C. Cognitive-behavioral therapy for threshold and subthreshold anorexia nervosa: a three-year follow-up study. Psychother Psychosom. 2010;79:238–48.
34. Kinzl JF, Trefalt E, Fiala M, Hotter A, Biebl W, Aigner F. Partnership, sexuality, and sexual disorders in morbidly obese women: consequences of weight loss after gastric banding. Obes Surg. 2001;11:455–8.
35. Holmes T, Chamberlin P, Young M. Relations of exercise to body image and sexual desirability among a sample of university students. Psychol Rep. 1994;74:920–2.
36. Pujols Y, Cindy MM, Seal Brooke N. The association between sexual satisfaction and body image in women. J Sex Med. 2010;7:905–16.
37. Carvalho J, Nobre P. Predictors of women's sexual desire: the role of psychopathology, cognitive-emotional determinants, relationship dimensions, and medical factors. J Sex Med. 2010;7:928–37.
38. Nobre PJ, Pinto-Gouveia J. Emotions during sexual activity: differences between sexually functional and dysfunctional men and women. Arch Sex Behav. 2006;35:8–15.
39. Arnow B, Kenardy J, Agras WS. The emotional eating scale: the development of a measure to assess coping with negative affect by eating. Int J Eat Disord. 1995;18:79–90.
40. Faravelli C, Gorini Amedei S, Rotella F, Faravelli L, Palla A, Consoli G, Ricca V, Batini S, Lo Sauro C, Spiti A, Catena Dell'osso M. Childhood traumata, dexamethasone suppression test and psychiatric symptoms: a trans-diagnostic approach. Psychol Med. 2010;40: 2037–48.
41. Castellini G, Maggi M, Ricca V. Childhood sexual abuse and psychopathology. In: Corona G, Jannini EA, Maggi M, editors. Emotional, physical and sexual abuse. Impact in children and social minorities. Cham: Springer International; 2014.
42. Rellini AH, Hamilton LD, Delville Y, Meston CM. The cortisol response during physiological sexual arousal in adult women with a history of childhood sexual abuse. J Trauma Stress. 2009;22:557–65.
43. Vanderlinden J, Van Dyck R, Vandereycken W, Vertommen H. Dissociation and traumatic experiences in the general population of the Netherlands. Hosp Community Psychiatry. 1993;44(8):786.
44. La Mela C, Maglietta M, Castellini G, Amoroso L, Lucarelli S. Dissociation in eating disorders: relationship between dissociative experiences and binge-eating episodes. Compr Psychiatry. 2010;51:393–400.
45. Cutajar MC, Mullen PE, Ogloff JR, Thomas SD, Wells DL, Spataro J. Psychopathology in a large cohort of sexually abused children followed up to 43 years. Child Abuse Negl. 2010;34:813–22.
46. Ackard DM, Neumark-Sztainer D. Multiple sexual victimizations among adolescent boys and girls: prevalence and associations with eating behaviors and psychological health. J Child Sex Abus. 2003;12:17–37.
47. Wonderlich SA, Brewerton TD, Jocic Z, Danskey BS, Abbott DW. Relationship of childhood sexual abuse and eating disorders. J Am Acad Child Adolesc Psychiatry. 1997;36:1107–15.
48. Walsh J, Burns F. Sexual maturation and control issues among sexually abused and non-abused anorexia patients. Br J Clin Psychol. 2000;39:307–10.
49. Kearney-Cooke A, Ackard DM. The effects of sexual abuse on body image, self-image, and sexual activity of women. J Gend Specif Med. 2000;3:54–60.
50. Smolak L, Murnen SK. Meta-analytic examination of the relationship between child sexual abuse and eating disorders. Int J Eat Disord. 2002;31:136–50.

Psychiatric Aspects of Gender Dysphoria

12

Jiska Ristori, Alessandra Daphne Fisher, Giovanni Castellini, and Mario Maggi

12.1 Introduction

Gender dysphoria (GD) refers to the distress resulting from the discrepancy between a person's gender identity and that person's assigned gender at birth [1]. The core of the diagnosis is the distress that must be caused by such discrepancy.

GD involves psychiatric aspects at different levels. First of all, GD is classified as a formal psychiatric diagnosis in both the current fifth version of the *Diagnostic and Statistical Manual of Mental Disorders* [1] and with the term of *Transsexualism* in the *International Classification of Diseases* [2]. GD manifests itself differently in different age groups, and therefore separate diagnostic criteria sets in childhood and in adolescence/adulthood are defined.

The presence of GD within the main classification manuals of mental health disorders is highly controversial and increasingly a matter of debates between dedicated professionals, LGBTQI (lesbian, gay, bisexual, trans, queer, intersex) activists, and trans people that range widely in their opinions [3]. Some challenge the existence of a GD diagnosis within mental illnesses as having a pathologizing effect on gender nonconforming people and, therefore, reinforcing stigma. Accordingly, the complete removal of the diagnosis from both the DSM and the ICD is proposed.

J. Ristori · A. D. Fisher · M. Maggi (✉)
Department of Experimental, Clinical and Biomedical Sciences, University of Florence, Florence, Italy
e-mail: jiskaristori@libero.it; m.maggi@dfc.unifi.it

G. Castellini
Psychiatric Unit, Department of Neuroscience, Careggi University Hospital, Florence, Italy

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*,
Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_12

On the contrary, it has been suggested to include GD within the classification of physical conditions in order to guarantee medical care when people with GD desire a gender-affirming medical intervention to alleviate their GD [4–6].

Mental health professionals (MHPs) may serve trans people in different ways depending on each person's needs: assess GD, offer family counseling and supportive psychotherapy, assess and address coexisting mental health problems (if present), refer for medical interventions, provide information, and advocate in the community [7]. Trans people (especially transwomen) attending transgender healthcare services are described as being socially and psychologically more vulnerable than the general population and often present with a high prevalence of psychiatric disorders and psychopathology, in particular in terms of depression and anxiety, suicidality, and body image disorders [7–14]. Therefore, coexisting psychological problems, when present, should be properly assessed and addressed. Recent reviews underline how levels of psychopathology and psychiatric disorders in trans people tend to improve after medical gender-affirming interventions [8, 15], stressing the importance of a multidisciplinary approach within gender teams. Co-occurring psychological problems seem to derive from both the condition of GD itself and being a consequence of living in a not accepting environment of gender variant roles and behaviors.

The present contribution is aimed to underline the main psychiatric aspects related to the care, during both diagnosis and treatment, of people struggling with GD and to describe the role of MHPs during the steps of care and in the different age groups.

12.2 Diagnosis

GD is a complex and dimensional condition that can occur with different degrees of intensity. Therefore, it requires an extensive assessment in order to properly serve the specific needs of each person with gender issues [7]. In fact, treatment options offered to people with GD should always be individualized: what can be of help for one person to alleviate GD can be very different from what helps another person. Usually, only the most extreme form of GD is accompanied by the desire for a complete medical gender-confirming trajectory (cross-sex hormones and surgery). Therefore, a psychiatric assessment of GD should not be aimed at characterizing GD as a mental illness, rather at carefully understanding the subjective meaning of cross-gender behaviors and feelings presented by the person [7]. In line, the World Professional Association for Transgender Health (WPATH) in its Standards of Care (SOC) states that gender nonconformity "is a common and culturally-diverse human phenomenon [that] should not be judged as inherently pathological or negative." The DSM and ICD classify clusters of symptoms that a person might be struggling with and are not a description of the person or of the person's identity.

12.2.1 GD Diagnosis in Children

According to the DSM-5, a diagnosis of GD of childhood can be made if a child shows a marked incongruence between the experienced/expressed gender and the assigned gender at birth, of at least 6 months' duration. In particular, six out of the

following eight criteria have to be assessed with the experience of a strong desire to be of another gender or the insistence to be another gender as a sine qua non criterion (e.g., an assigned girl at birth affirming *I am a boy*). In addition, the child has to manifest anatomic dysphoria that can be expressed by the dislike of the child's sexual anatomy and the desire for primary/secondary sex characteristics of the experienced gender (e.g., a natal boy insisting *When I grow older, my penis will fall off and I will grow breasts*). Furthermore, there are five behavioral criteria: (1) a preference for cross-dressing; (2) adopting cross-gender roles in fantasy play; (3) a strong preference for toys, games, and activities of the other gender; (4) a preference for playmates of the other gender; and (5) a strong aversion or rejection of typically gender-congruent roles, interests, preferences, and behaviors. The condition must cause clinically significant distress or impairment in social, school, or other important areas of functioning [1].

In the ICD-10, gender dysphoria is classified as *gender identity disorder of childhood*. The diagnosis can be made if the following criteria are satisfied:

1. A persistent and intense distress about being of the other gender and a stated desire to be of the other gender (not merely a desire for any perceived cultural advantages to being the other gender) or insistence of being the other gender.
2. A persistent marked aversion to normative clothing of the other gender and insistence on wearing stereotypical clothing of the other gender or a persistent repudiation of anatomical structures of own sex (as evidenced, e.g., in girls by assertion that she has, or will grow, a penis or by the rejection of urinating in a sitting position and in boys that his penis or testes are disgusting or will disappear).
3. The child has not yet reached puberty.
4. The disorder must have been present for at least 6 months.

In the current revision of the ICD, the terminology of gender identity disorder of childhood will most probably be changed into *gender incongruence in childhood* [16].

The diagnosis of GD in children is highly controversial [3] in particular because of the outcomes of GD in adolescence and adulthood. To date, follow-up studies describe that childhood GD is strongly associated with a later lesbian, gay, or bisexual sexual orientation and that for the majority of the children (85.2%), the gender-dysphoric feelings will remit around or after puberty [17–19]. For this reason, some critic the diagnosis of GD in childhood as a way to pathologize a condition related to a later homosexual outcome in adolescence or adulthood. Furthermore, considering that no medical intervention is provided in childhood, the presence of the diagnosis seems to be not necessary.

12.2.2 GD Diagnosis in Adolescents and Adults

In the DSM-5, GD can be diagnosed in adults and adolescents when a marked incongruence between one's experienced/expressed gender and the assigned one

occurs; furthermore, the condition must be present for at least 6 months and must be associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning [1]. In particular, two of the following criteria must be shown: (1) a marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics, (2) a strong desire to be rid of one's primary and/or secondary sex characteristics, (3) a strong desire for the primary and/or secondary sex characteristics of the other gender, (4) a strong desire to be of the other gender, (5) a strong desire to be treated as the other gender, and (6) a strong conviction that one has the typical feelings and reactions of the other gender.

In the ICD-10, gender dysphoria in adulthood is defined as transsexualism by three criteria: (1) the desire to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone treatment; (2) the transsexual identity has been present persistently for at least 2 years; and (3) the disorder is not a symptom of another mental disorder or a chromosomal abnormality. The 11th version of the ICD is currently under revision, and it has been proposed also for adults to replace the term transsexualism with *gender incongruence* and to move the diagnosis into the section "Condition related to sexual heath" [20].

12.3 Differential Diagnosis

Within a psychiatric assessment, MPHs should make sure that gender-dysphoric feelings and behaviors are not secondary to other conditions and therefore perform an accurate differential diagnosis.

First of all, GD should be distinguished from nonconformity to stereotypical gender roles within the broad transgender spectrum, a condition that is not necessarily associated with distress. In fact, gender-atypical behaviors and feelings do not necessarily underlie a GD condition but rather refer to somatic features or behaviors that are not typical (in a statistical sense) of individuals with the same assigned gender in a given society and historical era [21]. There is nothing pathological with a boy not wanting to play football and preferring to play with dolls or with a girl refusing to wear shirts and dresses. This is the same for gender-variant expressions in adolescence or adult age. Only when gender incongruence is experienced as problematic and when it impairs social and/or psychological functioning that it may need clinical attention [3].

Special attention should be paid in excluding GD from cases of internalized homophobia, especially in adolescence. Some adolescents with a homosexual orientation may in fact struggle in accepting their sexual orientation and therefore present to clinical attention with a request for a gender-affirming medical intervention. Others may confuse sexual orientation and gender identity due to a history of cross-gender behaviors and interests in childhood (e.g., as in the case of a natal girl saying *When I was a child I was always playing with boys, wanted short hair and hated to wear dresses, therefore I thought I was boy*) [22, 23].

The main differential diagnoses of GD are eating disorders and body dysmorphic disorders, transvestic disorder, and disorders within the psychotic spectrum [1, 24, 25].

Body dissatisfaction is a psychopathological feature for GD as well as for other psychiatric disorders such as eating disorders and body dysmorphic disorders [11, 26]. However, in eating disorders the "core psychopathology" is an overconcern about one's body shape and body weight, and self-worth is judged largely or exclusively in terms of satisfaction-unsatisfaction with them [11, 26, 27]. This is the psychopathological correlate of the main pathological behaviors such as food avoidance and consequent weight loss. However, in eating disorders, the body shape disturbance is generally not related with body shaping toward a masculine or feminine direction, as it happens in GD (as in the case of a natal girl with GD remembering *I lost weight to control my body so that it would not develop in a masculine direction but not because I wished to be thin*). Body dysmorphic disorder focuses on the removal of a body part that is perceived as abnormally formed but not because it is related to the unwanted assigned gender at birth as in GD (*I want to get rid of my breasts because they are ugly and have a funny shape, but not because they remind me of my female body*).

GD could be mistaken with transvestic disorder, which occurs mainly in heterosexual males that show cross-dressing behaviors associated to sexual arousal and that causes distress and/or impairment. However, the primary gender is not drawn into question [1].

In the specific case of psychotic spectrum conditions, delusions of belonging to the other gender may be present; this is a rare clinical presentation, and differential diagnosis can be performed by assessing other psychotic symptoms.

12.4 Co-occurring Psychiatric Conditions

Studies investigating the prevalence of psychiatric disorders among trans individuals have identified elevated rates of psychopathology [8]. Persons with GD are described as a psychologically and socially vulnerable population [14] and may present with co-occurring psychopathology. These may derive from GD itself and/or from minority stress [7–10] that results from the conflict between being a member of a minority group and the dominant values in a given society.

The psychological functioning of referred children with GD is described considerably differently across studies [28–30]. Such variability seems to depend on the level of social acceptance of gender nonconformity and gender variance within the culture or environment the child lives in [17, 18]. However, psychological functioning may be impaired also by some risk factors such as parental psychopathology and social class background [28–30]. Furthermore, in children with GD, a relationship between autism spectrum disorders (ASD) and GD has been found with a higher prevalence of ASD (6.4%) in gender-referred children [31, 32] than in the general population (0.6–1%) [33]. The nature of the association between these two conditions is not yet clear, and further studies are needed.

Adolescents with GD are described across studies as characterized by social and psychological impairment. Emotional and behavioral problems, self-harm,

substance use and abuse, suicide risk, and body dissatisfaction are often reported [14, 34]. In particular, adolescents referred to gender identity clinics tend to show higher rates of internalizing psychopathologies, as compared with peers of the general population [35, 36]. Furthermore, they often experience discrimination and social stigma [37, 38] that also negatively affect psychological functioning. The distress related to GD in adolescence seems to increase with the onset of puberty with adolescents with GD struggling with a body developing in an unwanted direction (*When I realized my body started changing with puberty, my whole world collapsed. I hated my body and wanted to stop time*). In fact, this is the moment where psychological problems often tend to either arise or intensify [39]. Furthermore, the physical changes that come within puberty can further increase social marginalization, isolation from family, and early dropping out from school [40].

Adults with GD present higher psychiatric comorbidity than cis persons. In particular, mainly affective and anxiety disorders are reported in studies [8]. Self-harm, substance abuse, and personality disorders (primarily paranoid and avoidant) are also described [4–6, 8, 38]. Furthermore, transwomen show higher rates of affective problems closer to cis women than to cis men in their psychological characteristics [41]. However, overall, in the majority of studies, no differences are found between transwomen and transmen in the levels of psychopathology shown. The occurrence of schizophrenia or bipolar disorder is rare and does not seem to differ from the rates in the general population.

All these psychiatric aspects should be carefully assessed and addressed in order to properly plan further steps in medical and psychological treatment. Co-occurring mental health concerns may in fact be sources of distress and, if untreated, interfere with the process of care of GD [7, 42], as well as with quality of life and psychosocial well-being [43]. A recent study reported that behavioral and emotional problems as well as depressive symptoms decreased and general functioning significantly improved with access to a specialized GD service, especially in adolescence [44]. In line, there is a general agreement that an early evaluation of GD seems necessary to ward off an eventual delay or arrest in emotional, social, or intellectual development [14]. In cases of major psychopathological conditions, the opportunity for a medical transition must be carefully evaluated and postponed in order to allow first the treatment of the psychiatric disorder and assess the levels of the psychosocial functioning over time [37]. Only if these are taken care of, the person with GD can be eligible for medical intervention. Youth with coexisting psychiatric problems who will receive hormone treatment need good and regular contacts with mental health clinicians [29, 43–47].

12.5 Treatment

People with GD may struggle with many issues that make the range of psychological treatment goals broad: dealing with the gender identity issue itself, doubts about the type of medical interventions that may solve GD, or the consequences of one's gender variance such as the shame of being different, the guilt toward parents (*I feel*

bad I am a cause of worry for my parents), or low self-esteem [48]. People with GD may also struggle due to social ostracism and because of being victims at different levels of homo- and transphobic bullying [49–51]. A young trans girl remembers: *School was horrible. I got bullied all the time. Because I had long hair, because I did not like playing football, because I was feminine and never liked boys things. It was a nightmare. Then I dropped out of school to find some rest.*

Psychotherapy offered to gender-dysphoric people is mainly focused on making the person aware that any outcome of the therapy (whether this is acceptance of living in the social role congruent with the natal sex or partial medical treatment or complete medical transition) is acceptable as long as it leads to the relief of the person's GD and to a better quality of life. Therefore, psychological and medical interventions have to be individualized and differ throughout age groups.

The psychological intervention of children who present with gender issues is continuously evolving with a progressive increase of new specialized gender clinics for youth spread worldwide [52–54]. Currently, there is still not a general consensus among dedicated professionals about the best psychological model of care for children with GD. This is also a consequence of empirical treatment models not being available [55]. However, MHPs agree that psychological interventions with children with GD should focus on reducing the child's distress related to the GD, helping with co-occurring psychopathologies (if present), and optimizing psychological adjustment and well-being [7, 55]. Furthermore, it is important to underline that any psychological intervention aimed to lessen cross-gender behaviors and feelings to decrease the persistence of GD into adolescence and/or to prevent adult transsexualism are currently considered not ethic [7, 56]. Two main treatment models for the care of gender-variant children are described in the scientific literature [20, 55]. The first one is usually referred to as *watchful waiting* and is aimed to allow the natural development of the child's gender identity and GD [20]. MPHs interventions within this approach are focused on the co-occurring psychological problems when present, on helping the parents and the child to bear the uncertainty of the child's psychosexual outcomes, and on psycho-education to assist the child and the parents in making balanced decisions on topics such as the child's coming out, early social transitioning, and/or how to handle peer rejection or social ostracism [17]. In particular, parents are helped to find a balance between allowing the child to explore the gender-dysphoric feelings and at the same time keeping all possible outcomes open [37, 45, 47]. The other approach is referred to as *affirming* and is focused on totally supporting the child in completely socially transitioning to the desired/experienced gender role in line with the child's gender identity. Such position is supported in order to relieve the child and allow a positive self-identity and gender resilience [16, 55, 57]. Some critic that supporting social gender transition in childhood may have an effect on later gender identity development: will an early social transition increase the likelihood of persistence with the child no longer confronting with gender issues? Will the child be worried about the complexity and distress of a second social transition [17, 18]? Changing back to the original gender role can indeed be distressing if GD does not persist especially for the fear of being teased or judged by peers as described in a recent study [58]. In this regard, the SOC

guidelines sustain a balanced position, not against and not pro an early social transition [7]: MHPs are encouraged to evaluate every single case individually and to help parents in making decisions where the potential benefits and challenges of any choice are always carefully weighted.

Adolescents with GD may be referred to psychotherapy for various reasons. Some homosexual adolescents may mistake their gender identity with their sexual orientation and need to solve confusion about their sexual identity. In other cases, severe internalized homophobia may be present, and therefore the lack of acceptance of one's homosexuality may induce to consider medical gender reassignment as solution to their condition. Psychotherapy may be of help also in those cases of adolescents that do not present with a clear GD but who adopt an androgynous, bigendered, or "gender queer" form of expression [59, 60] usually without the desire for a complete medical gender-affirming intervention (cross-sex hormones and surgery). MHPs may therefore help in finding out how these adolescents can integrate their masculine and feminine aspects and find psychological balance [48].

MHPs have the role to assess eligibility criteria during the different phases of a medical gender-affirming path. In some selected adolescents with GD, the first step regards eligibility for puberty suppression with gonadotropin-releasing hormone analogs (GnRHa), a medical option that can be considered as an extended diagnostic phase rather than an actual treatment. In fact, the use of GnRHa allows to *buy time* and explore cross-gender feelings. According to the SOC, the current eligibility criteria for puberty suppression are defined as follows: (1) an early history of GD that has intensified during the early pubertal phases, (2) no serious psychosocial problems interfering with the diagnostic assessment or treatment, (3) a good comprehension of the impact of medical gender-affirming assignment on one's life, and (4) presence of support from the family or other caregivers which is very important. Awareness that this treatment will temporarily stop the physical changes associated with puberty results in an important reduction of the psychological distress that the physical feminization or masculinization was producing. Furthermore, co-occurring psychopathologies in terms of depression, anxiety, social withdrawal, and body satisfaction significantly decrease, improving adolescents' quality of life [14, 37, 44]. On the contrary, if medical treatment is denied, adolescents may lose trust in professional help and engage in irresponsible behaviors such as seeking medication illegally. Puberty suppression does not automatically imply that cross-sex hormone treatment (CHT) will take place later on. On the contrary, during this phase all possible outcomes are explored and kept open without the MHP addressing in any direction. During GnRHa treatment, cross-gender feelings are in fact constantly evaluated. This helps the adolescent to be more conscious of his/her situation and therefore to take a balanced and aware decision.

In case GD persists and the adolescent later on will decide to start a medical gender-affirming assignment, the use of GnRHa is associated to positive consequences. For example, the adolescent is spared from the irreversible signs of secondary sex characteristics such as breast development in trans boys and a male voice and male facial and bodily features in trans girls. Furthermore, early treatment will likely make certain surgeries not necessary or less invasive, for example, breast

reduction in trans boys. So far, the use of GnRHa has proven to have a positive effect on decreasing associated psychopathologies and improving social and psychological functioning [37, 44]. However, research on the long-term effects of medical gender-affirming interventions starting with a GnRHa treatment is still preliminary, and follow-up studies are needed. For adolescents who start medical gender-affirming treatment, psychotherapy becomes a space where various topics (e.g., fertility, relationships, and sexuality) have to be brought up repeatedly, as views can rapidly change during this period of time. In particular, youth benefit the most from acquiring a balanced view of the short- and long-term costs and benefits in order to make aware choices without unrealistic expectations.

Historically, the main clinical approach to assist adult GD clients was focused on providing assistance to alleviate GD through CHT and surgery, along with a change in gender role once the appropriate candidates for a gender-affirming intervention completed psychological assessment with a MHP. This approach has been proved as highly effective with clients being satisfied in the majority of cases (rates across studies range from 87% of transwomen to 97% of transmen) [61] and with rare regrets (1–1.5% of transwomen clients and <1% of transmen) [62]. CHT is aimed to feminizing or masculinizing the body to align it to the experienced gender identity. A transman reported just before starting CHT: *I feel I need immediately hormones and surgery. I feel I am like an ugly monster and I am embarrassed if people look at me or if I look at myself in the mirror. I feel I have to hide myself all the time. I feel I have to hide my body. Only with hormones and surgery I can find a way to start living again.*

However, in the last years, it became clear that a complete medical gender-confirming assignment does not represent a standard solution for every person with GD. Therefore, an individualized treatment should always be considered throughout the whole assessment process in order to cover the wide GD spectrum: while some persons need both CHT and surgery, others may benefit only of one of these or neither [1, 4–6] in order to alleviate their GD. Recent studies have underlined the positive effects on psychological well-being from CHT alone by improving quality of life, reducing significantly co-occurring psychopathologies, and lowering body dissatisfaction [13, 15, 63, 64]. In other cases, the trans- or cross-gender feelings may be integrated into the gender role people were assigned at birth finding a balance that does not require to feminize or masculinize the body through any medical intervention.

A regular contact with a MHP during the gender-affirming process is necessary for adequate preparation for next treatment steps. When surgery is discussed, unrealistic expectations have to be put into perspective, and MHP has to make sure that the person is psychologically ready as well as fully able to make informed decisions about the timing and implications in the context of the overall coming out or transition process [7]. According to the SOC, once a person with GD has been referred for medical gender-affirming intervention, psychotherapy is not a requirement.

However, different forms of psychotherapy may be offered with the overall goal to maximize a person's psychological well-being, quality of life, and self-fulfillment [7]. Psychotherapy includes individual, couple, family, or group

interventions. They are aimed at exploring gender identity and gender role, addressing the negative impact of GD and stigma on mental health, alleviating internalized transphobia, enhancing social and peer support, improving body image, and promoting resilience. While meeting with other trans people has formally a social goal, it often has also a therapeutic effect due to sharing personal experiences, concerns, and information with people who may be struggling with similar issues. Family therapy can help resolving conflicts between family members. For example, parents may have different views about the transition process of their child. Furthermore, transphobic attitudes and prejudices may be present toward the member of the family with gender issues. Also, parents and/or adolescents can have trouble distinguishing between what is related to the GD and what is not. For example, they may wonder if their child is being oppositive due to being an adolescent or as an effect of the distress related to GD. In counseling families, parents are supported in finding realistic requests and to work on the development of healthy boundaries and limits [48]. MHPs may work at different stages of their life on various issues throughout the life cycle.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5). DSM-5. Washington: American Psychiatric Association; 2013.
2. World Health Organization. International statistical classification of diseases and related health problems. 10th ed. Geneva: World Health Organization; 1992.
3. Meyer-Bahlburg H. From mental disorder to iatrogenic hypogonadism – dilemmas in conceptualizing gender identity variants as psychiatric conditions. Arch Sex Behav. 2010;39(2):461–76.
4. Bockting WO. Psychotherapy and the real-life experience. From gender dichotomy to gender diversity. Sexologies. 2008;17(4):211–24.
5. Bockting WO, Goldberg JM. Guidelines for transgender care. Int J Transgend. 2006;9(3–4):35.
6. Bockting WO, Miner MH, Swinburne Romine RE, Hamilton A, Coleman E. Stigma, mental health, and resilience in an online sample of the US transgender population. Am J Public Health. 2013;5:943–95.
7. Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Wylie KR, Zucker K. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. Int J Transgenderism. 2011;13:165–232.
8. Dhejne C, Van Vlerken R, Heylens G, Arcelus J. Mental health and gender dysphoria: a review of the literature. Int Rev Psychiatry. 2016;28(1):44–57.
9. Mazaheri Meybodi A, Hajebi A, GhanbariJolfaei A. Psychiatric axis I comorbidities among patients with gender Dysphoria. Psychiatry J. 2014;2014:1–5.
10. Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, Erwin PJ, Montori VM. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. Clin Endocrinol. 2010;72:214–31.
11. Bandini E, Fisher AD, Castellini G, Lo Sauro C, Lelli L, Meriggiola MC, Casale H, Benni L, Ferruccio N, Faravelli C. Gender identity disorder and eating disorders: similarities and differences in terms of body uneasiness. J Sex Med. 2013;10:1012–23.
12. Fisher AD, Castellini G, Bandini E, Casale H, Fanni E, Benni L, Ferruccio N, Meriggiola MC, Manieri C, Gualerzi A, Jannini E, Oppo A, Ricca V, Maggi M, Rellini AH. Cross-sex

hormonal treatment and body uneasiness in individuals with gender dysphoria. J Sex Med. 2014;11(3):709–19.
13. Fisher AD, Ristori J, Bandini E, Giordano S, Mosconi M, Jannini EA, Greggio NA, Godano A, Manieri C, Meriggiola C, Ricca V, Italian GnRH Analogs Study Onig Group, Dèttore D, Maggi M. Medical treatment in gender dysphoric adolescents endorsed by SIAMS–SIE–SIEDP–ONIG. J Endocrinol Invest. 2014;37:675–87.
14. Fisher AD, Ristori J, Castellini G, Sensi C, Cassioli E, Prunas A, Mosconi M, Vitelli R, Dèttore D, Ricca V, Maggi M. Psychological characteristics of Italian gender dysphoric adolescents: a case-control study. J Endocrinol Invest. 2017;40(9):953–65. https://doi.org/10.1007/s40618-017-0647-5.
15. Fisher AD, Castellini G, Ristori J, Casale H, Cassioli E, Sensi C, Fanni E, Amato AM, Bettini E, Mosconi M, Dèttore D, Ricca V, Maggi M. Cross-sex hormone treatment and psychobiological changes in transsexual persons: two-year follow-up data. J Endocrinol Metab. 2016;101(11):4160–9.
16. Drescher J, Cohen-Kettenis P, Winter S. Minding the body: situating gender identity diagnoses in the ICD-11. Int Rev Psychiatry. 2012;24:568–77.
17. Ristori J, Steensma T. Gender dysphoria in childhood. Int Rev Psychiatry. 2016;28:13–20.
18. Steensma TD, Biemond R, de Boer F, Cohen-Kettenis PT. Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study. Clin Child Psychol Psychiatry. 2011;16(4):499–516.
19. Steensma TD, McGuire JK, Kreukels BP, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. J Am Acad Child Adolesc Psychiatry. 2013;52:582–90.
20. Drescher J. Controversies in gender diagnoses. LGBT Health. 2013;1:10–4.
21. Castellini G. Gender dysphoria. In: Stanghellini G, Aragona M, editors. An experiential approach to psychopathology. Heidelberg: Springer; 2016.
22. Lippa RA. The relation between childhood gender nonconformity and adult masculinity–femininity and anxiety in heterosexual and homosexual men and women. Sex Roles. 2008;59(9/10):684–93.
23. Rottnek M. Sissies & tomboys: gender nonconformity & homosexual childhood. New York: New York University Press; 1999.
24. Korte A, Goecker D, Krude H, Lehmkuhl U, Grüters-Kieslich A, Beier KM. Gender identity disorders in childhood and adolescence. Dtsch Ärtzenbl. 2008;105(48):834–41.
25. à Campo J, Nijman H, Merckelbach H, Evers C. Psychiatric comorbidity of gender identity disorders: a survey among Dutch psychiatrists. Am J Psychiatr. 2003;160:1332–6.
26. Fairnburn CG. Cognitive behavioral therapy and eating disorders. New York: Guilford; 2008.
27. Senol T, Cana AP, Alaattin D. Prolonged anorexia nervosa associated with female –to-male gender dysphoria: a case report. Eat Behav. 2015;18:54–6.
28. Zucker KJ. Associated psychopathology in children and adolescents with gender identity disorder. In: Meyer-Bahlburg HFL, editor (Chair). From mental disorder to iatrogenic hypogonadism: dilemmas in conceptualizing gender identity disorder (GID) as a psychiatric condition. Symposium presented at the meeting of the American Academy of Child and Adolescent Psychiatry, Chicago; 2008.
29. Zucker KJ, Bradley SJ, Owen-Anderson A, Kibblewhite SJ, Wood H, Singh D, Choi K. Demographics, behavior problems, and psychosexual characteristics of adolescents with gender identity disorder or transvestic fetishism. J Sex Marital Ther. 2012;38:151–89.
30. Zucker KJ, Wood H, VanderLaan DP. Models of psychopathology in children and adolescents with gender dysphoria. In: Kreukels BPC, Steensma TD, de Vries ALC, editors. Gender dysphoria and disorders of sex development, progress in care and knowledge (chapter 9). New York: Springer; 2013.
31. de Vries AL, Noens IL, Cohen-Kettenis PT, van Berckelaer-Onnes IA, Doreleijers TA. Autism spectrum disorders in gender dysphoric children and adolescents. J Autism Dev Disord. 2010;40(8):930–6.

32. VanderLaan DP, Postema L, Wood H, Singh D, Fantus S, Hyun J, Leef J, et al. Do children with gender dysphoria have intense/obsessional interests? J Sex Res. 2014;52:213–9.
33. Fombonne E. Epidemiology of autistic disorder and other pervasive developmental disorders. J Clin Psychiatry. 2005;66:3–8.
34. Grossman AH, D'Augelli A. Transgender youth and life-threatening behaviors. Suicide Life Threat Behav. 2007;37(5):527–37.
35. D'Augelli AD, Grossman AH, Starks MT. Childhood gender, atypicality, victimization, and PTSD among lesbian, gay, and bisexual youth. J Interpers Violence. 2006;21:1462–76.
36. Wallien MSC, Swaab H, Cohen-Kettenis PT. Psychiatric comorbidity among children with gender identity disorder. J Am Acad Child Adolesc Psychiatry. 2007;46:1307–14.
37. de Vries A, Cohen-Kettenis PT, Delemarre-Van de Waal H. Clinical management of gender dysphoria in adolescents. Int J Transgenderism. 2006;9:83–94.
38. Nuttbrock L, Hwahng S, Bockting W, Rosenblum A, Mason M, Macri M, Becker J. Psychiatric impact of gender-related abuse across the life course of male-to-female transgender persons. J Sex Res. 2009;47(1):12–23.
39. Delamarre-van de Waal HA, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and pediatric endocrinology aspects. Eur J Endocrinol. 2006;155:131–7.
40. Spack NP. Management of transgenderism. JAMA. 2013;309(5):478–84.
41. Auer MK, Hohne N, Bazzara-Castro MA, Pfister H, Fuss J, Stalla GK, Sievers C, Ising M. Psychopathological profiles in transsexuals and the challenge of their special status among the sexes. PLoS One. 2013;8(10):78469.
42. Lev AI. Transgender emergence. New York: The Haworth Clinical Practice; 2004.
43. de Vries AL, Cohen-Kettenis PT. Clinical management of gender dysphoria in children and adolescents: the Dutch approach. J Homosex. 2012;59:301–20.
44. de Vries A, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. J Sex Med. 2011;8(8):2276–83.
45. Di Ceglie D. Management and therapeutic aims with children and adolescents with gender identity disorders and their families. In: Di Ceglie D, Freedman D, editors. A stranger in my own body: atypical gender identity development and mental health. London: Karnac; 1998. p. 185–97.
46. Cohen-Kettenis, P. Early interventions with GD adolescents. In: Dettore, D., Ristori, J., Antonelli P. (2015). La Disforia di Genere in Età Evolutiva. Roma: Alpes Italia S.r.l.
47. Skagerberg E, Parkinson R, Carmichael P. Self-harming thoughts and behaviors in a group of children and adolescents with gender dysphoria. Int J Transgenderism. 2013;14:86–92.
48. Burgess C. Internal and external stress factors associated with the identity development of transgendered youth. In: Mallon GP, editor. Social services with transgendered youth. Binghamton: Harrington Park; 1999. p. 35–47.
49. Russell ST, Ryan C, Toomey RB, Diaz RM, Sanchez J. Lesbian, gay, bisexual, and transgender adolescent school victimization: implications for young adult health and adjustment. J Sch Health. 2011;81:223–30.
50. Duncan DT, Hatzenbuehler ML. Lesbian, gay, bisexual, and transgender hate crimes and suicidality among a population-based sample of sexual-minority adolescents in Boston. Am J Public Health. 2014;104(2):272–8.
51. Hsieh S, Leininger J. Resource list: clinical care programs for gender-nonconforming children and adolescents. Pediatr Ann. 2014;43:238–44.
52. Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender dysphoria in Vancouver. J Pediatr. 2014;164:906–11.
53. Riittakerttu K, Sumia M, Työläjärvi M, Lindberg N. Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent in development. Child Adolesc Psychiatry Ment Health. 2015;9:1–9.

54. Byne W, Bradley SJ, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HFL, Pleak RR, Tompkins DA. Report of the American Psychiatric Association task force on treatment of gender identity disorder. Arch Sex Behav. 2012;41:759–96.
55. Adelson SL. Practice parameter on gay, lesbian, or bisexual sexual orientation, gender nonconformity, and gender discordance in children and adolescents. J Am Acad Child Adolesc Psychiatry. 2012;51:957–74.
56. Hill DB, Menvielle E, Sica KM, Johnson A. An affirmative intervention for families with gender variant children: parental ratings of child mental health and gender. J Sex Marital Ther. 2010;36:6–23.
57. Steensma TD, Zucker KJ, Kreukels BPC, VanderLaan DP, Wood H, Fuentes A, Cohen-Kettenis PT. Behavioral and emotional problems on the teacher's report form: a cross-national, cross-clinic comparative analysis of gender dysphoric children and adolescents. J Abnorm Child Psychol. 2014;42(4):635–47.
58. Janssen A, Erickson-Schroth L. A new generation of gender: learning patience from our gender nonconforming patients. J Am Acad Child Adolesc Psychiatry. 2013;52(10):995–7.
59. Saltzburg S, Davis TS. Co-authoring gender queer identities: discursive tellings and re-tellings. J Ethn Cult Divers Soc Work. 2010;19:87–108.
60. Green R, Fleming D. Transsexual surgery follow-up: status in the 1990s. Annu Rev Sex Res. 1990;1(1):163–74.
61. Pfafflin F, Junge A. Sex reassignment. Thirty years of international follow-up studies after sex reassignment surgery: a comprehensive review, 1961–1991. Düsseldorf: Symposion; 1998. International journal of transgenderism
62. Bartolucci C, Gómez-Gil E, Salamero M, Esteva I, Guillamón A, Zubiaurre L, Molero F, Montejo AL. Sexual quality of life in gender-dysphoric adults before genital sex reassignment surgery. J Sex Med. 2015;12:180–8.
63. Colizzi M, Costa R, Todarello O. Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: results from a longitudinal study. Psychoneuroendocrinology. 2014;39:65–73.
64. Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Penochet JC, Pringuey D, Albarel F, Morange I, Bonierbale M, Lancon C, Auquier P. Hormonal therapy is associated with better self-esteem, mood, and quality of life in transsexuals. J Nerv Ment Dis. 2013;201:996–1000.

Trauma-Related Disorders: Sexual Abuse and Psychiatric Comorbidities

13

Cinzia Niolu, Giulia Lisi, and Alberto Siracusano

13.1 What Is Trauma?

The term trauma comes from the Greek word τραῦμα (-ατος) that stands for "stroke or wound" and is a concept of difficult definition. In psychopathology, trauma can be defined as a lesion, an injury, or a wound of the psychic organism due to a single event or to a series of events that suddenly break out in a subject's life abruptly in a destructive way [1]. In addition, trauma can be defined as a real process throughout which the victim is concretely reduced *from subject to object*, where with subject we intend the person or the thing doing something and with object we intend the person or the thing that is having something done to [2]. The subject who happens to face a trauma is then victimized by human anger or by the fury of nature. Bowlby, already in 1969, argued that trauma is a process that takes place within the attachment relationships. Loss of family bounds, separations, and mournings are therefore considered obvious traumatic situations in this frame [1, 3].

According to DSM-5, trauma occurs when a subject happens to be exposed to death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence. This exposure can be direct or indirect: the subject might have witnessed in person or indirectly the scene of trauma, or he could have learned that a close relative or close friend was exposed to that trauma. Moreover, the definition of trauma can include a repeated extremely indirect exposure to aversive details of a traumatic event; this is the case of first responders, obliged

C. Niolu (✉) · A. Siracusano
Psychiatry, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

Psychiatry and Clinical Psychology Unit, Fondazione Policlinico Tor Vergata, Rome, Italy
e-mail: niolu@med.uniroma2.it; siracusano@med.uniroma2.it

G. Lisi
Psychiatry, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*,
Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_13

to collect body parts after disasters, or even the case of health professionals, repeatedly exposed to details of child sexual abuse.

13.2 Sexual Trauma

Child sexual abuse and *adult sexual violence* have been defined by the American Medical Association and by the US Centers for Disease Control and Prevention. The expression *child sexual abuse* is intended as an abusive behavior that can include fondling, rape, and noncontact abuse, such as forced involvement in child pornography or exhibitionism. The expression *adult sexual violence* is referred to as nonconsensual contact and noncontact acts that involve subjects that are more than 18 years of age. According to the US Centers for Disease Control and Prevention, *sexual violence* is precisely defined as completed or attempted penetration of the genitalia or the anus; contact between the mouth and the penis, vulva, or anus; or penetration of the anus or genital opening or intentional touching of the genitalia, anus, groin, breast, inner thigh, or buttocks. Noncontact acts include voyeurism and verbal or behavioral sexual harassment [4].

Sexual violence involves one woman out of five; in national surveys approximately 18.3% of women and 7.4% of men have reported experiencing rape at some time in their lives [5].

What is more, the National Intimate Partner and Sexual Violence Survey that was conducted by Black and colleagues in 2010 and 2011 highlighted that 5.6% of women and 5.3% of men experienced during the previous year sexual violence other than rape, such as being made to penetrate someone else, sexual coercion, unwanted sexual contact, or noncontact unwanted sexual experiences [6].

For what concerns the age of occurrence of trauma, the same survey reported that while the 42.2% of victims were first raped before age 18, the 29.9% were first raped between the ages of 11 and 17 and the 12.3% were first raped when they were aged 10 or younger [6].

13.3 From Trauma to Trauma-Related Disorders: Clinical Pathways

In a strictly neurobiological point of view, confrontation with trauma results in the release of important neurochemical factors, capable of compromising subjective integrative capacity and the ordinary process of neurodevelopment [7, 8].

Experiencing threat can alter the way in which the events are perceived as well as the emotional experience connected to them, triggering the biological chain of stress response and resulting in a substantial alteration of different important processes such as neurogenesis, migration, synaptogenesis, and neurochemical differentiation. Some of the consequences of the exposure to unpredictable or chronic stress include functional deficiencies and dramatic vulnerabilities to future stressors [9]. In humans, as in other animal species, two different reaction mechanisms are possible when

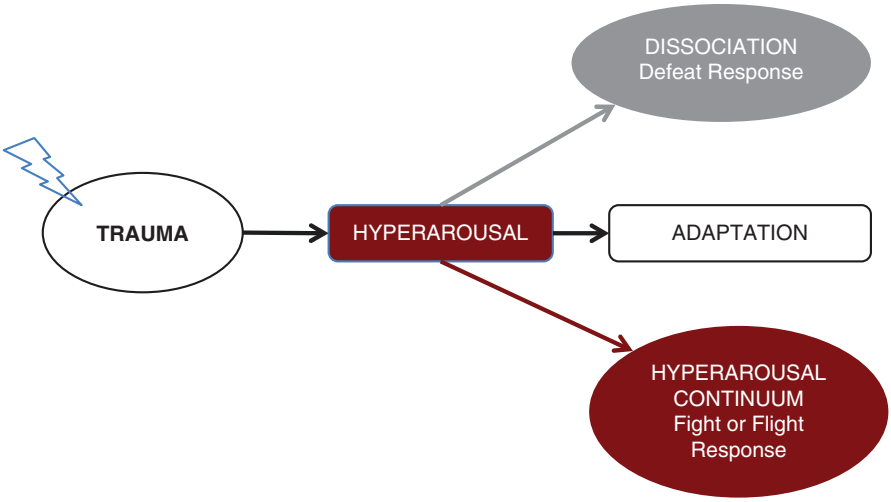

Fig. 13.1 Pathways of trauma

facing danger: the hyperarousal pathway (fight-or-flight response) and the dissociation pathway (defeat response) (Fig. 13.1); recent studies reported that these two different kinds of responses only share a part of their specific neurobiological mechanism [1]. The choice toward the first or the second option is related to different factors that not only include type, frequency, and intensity of trauma but also take into account the availability of a valid protection network for the subject. Several studies based on animal models have demonstrated, however, that excessive dangers, sexual trauma, or inadequate coping skills lead in most cases to defeat responses [10, 11]. In experimental animal studies that recreated inescapable shock patterns such as electric shocks or cold water swimming, the traumatic response is always characterized by helplessness, freezing phenomena, tonic immobility, analgesia, and dissociative states [8]. According to literature, peritraumatic stress reactions are substantial predictors of the development of a trauma-related disorder: in particular, the first hours following trauma are considered a critical window for interventions that aim at prevention of trauma-related disorders and have been characterized as the "golden hours" [12, 13]. Animal and human studies highlighted that memory consolidation occurs, in fact, during the first night's sleep following the exposure, supporting the rationale for immediate intervention [14]. Several neurotransmitter systems have been implicated in the etiopathogenetic mechanisms of trauma-related disorders; recent studies on children samples reported that a persistent traumatic stimulus can cause a permanent neurobiological modification of the subject's stress response [15]: these subjects show in fact increased urinary epinephrine, norepinephrine, and dopamine, alterations of alpha-2-adrenergic receptors, increase or decrease in baseline heart rate, altered EEG pattern suggesting limbic and cortical abnormalities, and altered development of some cortical areas [8]. Moreover, for what concerns the psychic response to trauma, an adequate resilience capacity is decisive: the ability to

"positively adapt" to different circumstances and the ability of being "flexible" in response to an adverse situation represents, in fact, a crucial protective factor for the occurrence of a trauma-related disorder after the event [16].

13.4 Trauma-Related Disorders

DSM-5 classifies *trauma- and stressor-related disorders* in a specific chapter, separated from *anxiety disorders* and *obsessive-compulsive disorder*. The symptoms that characterize the disorders included in this chapter typically develop after the occurrence of one or more traumatic or stressful events in which the subject is involved. While some of the disorders included originate in childhood, such as the *reactive attachment disorder* and the *disinhibited social engagement disorder*, others specifically address the adult population: the *acute stress disorder*, the *adjustment disorders*, and *post-traumatic stress disorder (PTSD)* [1, 17]. Unlike previous editions, specific PTSD criteria for patients under 6 years of age are also provided in DSM-5.

Reactive attachment disorder can be considered an internalizing disorder and consists of a persistent inability in social interaction that hesitates in inhibited responses, defensive hypervigilance, or highly contradictory behaviors.

The *disinhibited social engagement disorder* is characterized by a total lack of selectivity in the choice of attachment figures and by an indiscriminate sociability toward others. This disorder usually develops in response to an exceptional physical or mental stress in individuals that do not exhibit any other comorbid mental disorder; it typically regresses after a few hours or days. The *adjustment disorder* has been described in DSM-5 as a stress-response syndrome; it begins within 3 months from the occurrence of the stressful event, and it usually recovers within 6 months from the end of the stressful period. The most complex trauma-related disorder is PTSD.

This disorder is mainly characterized by intrusive re-experiencing symptoms and avoidant, numbing, and hyperarousal symptoms that start after the occurrence of an event that has threatened the subject's physical integrity or that has caused serious injury to the subject or to people related with him/her [8, 17]. In defining PTSD, DSM-5 specifically mentions sexual trauma, underlining the dramatic nature of this experience. The severity of the episodes is always assessed taking into account the ability of the subject to cope with the threat occurred, the symptoms "must cause clinically significant discomfort or interfere with important areas of functioning" [2, 16].

As mentioned before, unlike previous editions, DSM-5 lists specific criteria for patients under 6 years of age. PTSD symptoms may not be particularly manifest in children, these symptoms, in fact, are not often verbally expressed and therefore clearly communicated by children: a careful observation of the child's behavior can clarify the effects of trauma in these cases [18]. The clinical frame may include difficulties in interpersonal relationships, the development of an insecure disorganized attachment style, or the development of a contradictory behavior often characterized by episodes of aggression toward peers and difficulty in affective regulation [1,

18]. Several important factors, such as age, level of development at the time of trauma, child temperament, personal vulnerability, environmental and relational characteristics, trauma exposure, duration of trauma exposure, and level of intimacy with the possible aggressor, need to be considered in trying to determine the outcome of trauma exposure: these variables interact with each other producing different evolutionary frameworks.

PTSD diagnosis is over three times more frequent among women who were raped during childhood, and recent studies report that women who were victims of childhood sexual abuse are five times more likely to be diagnosed with PTSD in adulthood [19]: survivors of childhood sexual trauma are at high risk of developing PTSD. PTSD has an important incidence even after adulthood sexual violence: the reported rates of PTSD among rape survivors vary, in fact, from approximately 30% to 65% depending on how and when the PTSD symptoms are assessed [20].

Sexual violence is often associated with a particular type of PTSD, first described in 1992 by Judith Herman in the textbook *Trauma and Recovery*: the complex posttraumatic stress disorder (C-PTSD) [21]. C-PTSD is associated with forms of trauma that include prolonged subjection, totalitarian control, physical or emotional abuse, and every traumatic condition in which the victim concretely experiences an impossible escape. C-PTSD is a severe condition that may result in a progressive disintegration of the sense of self and of the sense of reality; even though several journals have published numerous articles about this disorder, it is not formally recognized in nosographic systems yet [22].

13.5 Dissociative Disorders

Numerous studies have demonstrated the existence of a substantial association between childhood trauma and dissociation [23–26]. Many authors suggested that dissociative symptoms have, in these cases, a specific role of defense: they represent, in fact, a psychic defense mechanism against intolerable traumatic memories, thoughts, and feelings [27].

DSM-5 defines dissociation as a disruption of and/or a discontinuity in the normal integration of consciousness, memory, emotion, perception, body representation, motor control, and behavior. Dissociative symptoms can potentially disrupt every area of psychological functioning [17].

When dissociation occurs during or soon after trauma, the so-called peritraumatic dissociation, this needs to be considered an important risk factor for a subsequent development of PTSD: Ozer and colleagues reported, in a recent metanalysis, that peritraumatic dissociation yielded the largest effect size as a predictor for PTSD in adulthood [14]. What is more, these subjects may develop a pattern of persistent dissociation in response to every potential reminder of the traumatic situation.

The main dissociative symptoms are *depersonalization*, *derealization*, *amnesia*, *identity confusion*, and *identity alteration* (Table 13.1).

Table 13.1 Dissociative symptoms

Depersonalization	The subjective feeling of detachment from one's own body and the feeling of being strange or unreal
Derealization	The feeling of lack of familiarity or the unreality of one's physical and/or interpersonal environment
Amnesia	The inability to remember both personal information and significant periods of time in one's life, which cannot be explained by ordinary forgetfulness or by other medical conditions
Identity confusion	Experience of confusion and conflict over the subject's own personal identity
Identity alteration	The assumption of other identities

DSM-5 distinguishes the following conditions: *dissociative identity disorder*, *dissociative amnesia*, *depersonalization/derealization disorder*, the *otherwise specified dissociative disorder*, and the *unspecified dissociative disorder* [17].

Primary and secondary forms of dissociative disorders can be distinguished; the latter are commonly diagnosed as secondary to other pathologies, such as epilepsy and cranial traumas, or may result from the use of drugs or other substances [1].

13.6 Borderline Personality Disorder

According to literature, *borderline personality disorder* is a particularly common diagnosis among victims of childhood sexual trauma [28]. *Borderline personality disorder* is mainly characterized by a recurring pattern of instability in relationships, continuous efforts to avoid abandonment, identity disturbance, an important level of impulsivity, emotional instability, and chronic feelings of emptiness. Researchers suggested that the etiopathology of borderline personality disorder is based on the combination of a vulnerable genetic background with the occurrence of adverse environmental factors during childhood [1].

Studies reported that prolonged severe trauma, and in particular early trauma, can result in a chronic inability to modulate emotions. In these cases, patients frequently show dysfunctional behaviors often described as self-soothing attempts. Some of these behaviors include clinging and entangling indiscriminate relationships with others in which old traumas can be re-enacted over time, as well as more self-directed behaviors such as self-mutilation, eating disorders, and substance abuse. Suicidal attempts and chronic self-destructive behaviors are relatively common in patients with complicated trauma histories [29–31].

A growing body of literature reports that the occurrence of traumatic and stressful events results in important alterations in the hypothalamic-pituitary-adrenal (HPA) axis, in neurotransmission mechanisms, in the endogenous opioid system regulation, and in neuroplasticity [32, 33].

Interestingly, these are the main biological systems involved also in borderline personality disorder's pathogenesis. Neuroimaging studies widely confirm these data showing volume reductions and μ-opioid receptor increase mainly located in brain regions notably involved in stress responses, cognition, memory, and emotion regulation, such as the hippocampus and the amygdala. Not so many studies are

available on epigenetic changes in patients with borderline personality disorder, although these mechanisms are widely investigated in relation to stress-related disorders [34].

Traumatic childhood experiences are, therefore, capable of determining a damage effect on the developing brain, leading this to permanent alterations.

13.7 Sexual Abuse: General Psychological and Behavioral Consequences

Historical studies raised much interest on the persistent role of past traumatic experiences on people's current lives. Charcot, Janet, and Freud all noted that fragmented memories of traumatic events dominated their patient's mental life; many traumatized people unconsciously expose themselves to situations reminiscent of the original trauma [35]. Freud firstly theorized that the aim of repetition was to gain power and mastery, but clinical experience has shown that this rarely happens; instead, repetition causes further suffering both for the victim and for their relatives [35]. Focusing on behavioral and psychological consequences of trauma, recent studies reported that these outcomes importantly depend on the age of traumatization: child sexual abuse and adulthood sexual violence will therefore have different psychopathological and behavioral effects on the victim.

13.7.1 Childhood Sexual Abuse

Several studies highlighted an important association between child sexual abuse and relational problems: while some survivors report low sexual interest and few close relationships, others display high-risk sexual behaviors such as promiscuity, later engagement in unprotected sexual relationships, multiple sexual partners, and sex trading [36]. These behaviors have been considered, in part, as an unconscious attempt to model some of the behaviors shaped earlier in life by the perpetrator. Moreover, survivors are at greater risk for experiencing depression in adulthood: in one study, the rate of lifetime depression among childhood rape survivors was, in fact, 52% compared to 27% among non-victims [37]. Authors showed an association with an increased risk of suicide even after accounting for the effects of previous psychological problems and after accounting for a twin's history of suicidal behaviors [38]. In a review by Jumper and colleagues published in 1995, later confirmed by Paolucci and colleagues in 2001 and by Klonsky and Moyer in 2008, child sexual abuse results to be significantly related to depression, self-esteem impairment, and other severe psychological problems such as suicidal ideation or behavior, anxiety, and psychotic and dissociative disorders [39–41]. Survivors of childhood sexual trauma have also been shown to be at greater risk of alcohol abuse [42] and eating disorders [43, 44] later in life.

In their review of student samples, Rind and colleagues moreover reported an association between the occurrence of childhood sexual trauma and a substantial interpersonal sensitivity pattern characterized by feelings of inadequacy, inferiority,

or discomfort when interacting with others [45]. What is more, authors highlighted the establishment of a personality pattern importantly characterized by hostility and anger in adults victims of childhood sexual trauma.

Whitaker and colleagues in 2008 reported that sexual offenders against children were highly likely to have a history of childhood sexual abuse in comparison with both individuals who had committed an offense of a nonsexual nature and individuals who had not committed any offense [46]. These data have been widely confirmed: re-enactment of victimization is a major cause of violence and needs to be considered an important risk factor for the perpetration of childhood sexual abuse.

According to literature, criminals have often been physically or sexually abused as children. Lewis and colleagues, in the 1980s, showed that of 14 juveniles condemned to death for murder in the United States in 1987, 12 had been brutally physically abused, and 5 had been sodomized by one of their relatives [47].

13.7.2 Adulthood Sexual Violence

A widely confirmed concept states that women who are victimized in adulthood develop an important vulnerability toward both short- and long-term psychological consequences. Immediate distress may include shock, acute anxiety, confusion, and social withdrawal [48]. Shortly after a violent act has occurred, survivors usually experience *post-traumatic stress disorder* symptoms such as emotional detachment, flashbacks, and insomnia [8]. The majority of survivors experience a reduction in psychological symptoms within the first few months, but in a consistent group of survivors, symptoms can persist for years [49]. Psychological symptoms typically include depression, somatic disorders, body dysmorphic disorders, disordered eating behaviors, sexual dysfunctions, and compulsory body mutilation. Risks of developing mental health disorders as a consequence of sexual trauma are strictly related to assault severity, the occurrence of other negative life events, maladaptive beliefs, and having experienced perceptions of lack of control during trauma.

13.8 Sexual Abuse and Impact on Health

Latthe and colleagues reported an association between child sexual abuse and chronic pelvic pain [50]. In their narrative synthesis of the evidences for sexual transmission of genital herpes in children, Reading and Rannan-Eliya showed in 2007 that while among children assessed for possible, probable, or known sexual abuse, genital herpes was rarely reported, in children presenting to hospitals with genital herpes, sexual transmission occurred in over half the cases. In particular, sexual transmission was reported more commonly in older children, in children presenting with genital lesions alone, and in children who were positive for herper simplex virus type 2 [51].

According to literature, a strong association exists between child sexual abuse and the occurrence of non-epileptic seizures: in a review by Sharpe and Faye, the odds of having a history of child sexual abuse were, in fact, almost three times higher in patients with a diagnosis of non-epileptic seizures [52]. Non-epileptic seizures are an important problem in clinical neurology: their identification is critical to avoid potentially severe consequences that attend errors of either failing to recognize non-epileptic seizures or mistaking true epileptic seizures for non-epileptic ones. According to several authors, the similarity between the typical movements observed in non-epileptic seizures and sexual movements can be explained though Freud's theories: this similarity could exemplify, in fact, the symbolic relationship of the conversion symptom to an underlying conflict. According to Freud, incestuous sexual abuse inevitably associates normal sexual drives to a pattern of negative affectivity pattern including fear, guilt, and shame, and resulting in an unconscious painful conflict between the innate sexual drives and those aversive feelings with which they have become associated [52].

References

1. Siracusano A. Manuale di Psichiatria. Rome: Il pensiero scientifico; 2014.
2. Maj MMC, Siracusano A. Lessico di Psicopatologia. Rome: Il Pensiero Scientifico Editore; 2010.
3. Bowlby J. Attachment and loss. New York: Basic; 1969.
4. Basile KC. Prevalence of wife rape and other intimate partner sexual coercion in a nationally representative sample of women. Violence Vict. 2002;17(5):511–24.
5. Abrahams N, Devries K, Watts C, Pallitto C, Petzold M, Shamu S, et al. Worldwide prevalence of non-partner sexual violence: a systematic review. Lancet. 2014;383(9929):1648–54. https://doi.org/10.1016/S0140-6736(13)62243-6.
6. Black DS, Sussman S, Unger JB. A further look at the intergenerational transmission of violence: witnessing interparental violence in emerging adulthood. J Interpers Violence. 2010;25(6):1022–42. https://doi.org/10.1177/0886260509340539.
7. Gonzalez A, Del Rio-Casanova L, Justo-Alonso A. Integrating neurobiology of emotion regulation and trauma therapy: reflections on EMDR therapy. Rev Neurosci. 2017;28(4):431–40. https://doi.org/10.1515/revneuro-2016-0070.
8. Yehuda R, Hoge CW, McFarlane AC, Vermetten E, Lanius RA, Nievergelt CM, et al. Post-traumatic stress disorder. Nat Rev Dis Primers. 2015;1:15057. https://doi.org/10.1038/nrdp.2015.57.
9. Brand BL. What we know and what we need to learn about the treatment of dissociative disorders. J Trauma Dissociation. 2012;13(4):387–96. https://doi.org/10.1080/15299732.2012.672550.
10. Meng L, Chen Y, Xu X, Chen T, Lui S, Huang X, et al. The neurobiology of brain recovery from traumatic stress: a longitudinal DTI study. J Affect Disord. 2017;225:577–84. https://doi.org/10.1016/j.jad.2017.08.075.
11. Kalaf J, Coutinho ESF, Vilete LMP, Luz MP, Berger W, Mendlowicz M, et al. Sexual trauma is more strongly associated with tonic immobility than other types of trauma – a population based study. J Affect Disord. 2017;215:71–6. https://doi.org/10.1016/j.jad.2017.03.009.
12. Moller A, Sondergaard HP, Helstrom L. Tonic immobility during sexual assault – a common reaction predicting post-traumatic stress disorder and severe depression. Acta Obstet Gynecol Scand. 2017;96(8):932–8. https://doi.org/10.1111/aogs.13174.

13. Gandubert C, Scali J, Ancelin ML, Carriere I, Dupuy AM, Bagnolini G, et al. Biological and psychological predictors of posttraumatic stress disorder onset and chronicity. A one-year prospective study. Neurobiol Stress. 2016;3:61–7. https://doi.org/10.1016/j.ynstr.2016.02.002.
14. Birmes P, Brunet A, Carreras D, Ducasse JL, Charlet JP, Lauque D, et al. The predictive power of peritraumatic dissociation and acute stress symptoms for posttraumatic stress symptoms: a three-month prospective study. Am J Psychiatry. 2003;160(7):1337–9. https://doi.org/10.1176/appi.ajp.160.7.1337.
15. Jeter WK, Brannon LA. Moving beyond "sticks and stones": chronic psychological trauma predicts posttraumatic stress symptoms. J Trauma Dissociation. 2014;15(5):548–56. https://doi.org/10.1080/15299732.2014.907596.
16. Bonanno GA. Loss, trauma, and human resilience: have we underestimated the human capacity to thrive after extremely aversive events? Am Psychol. 2004;59(1):20–8. https://doi.org/10.1037/0003-066X.59.1.20.
17. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington: American Psychiatric Association; 2013.
18. Perrin S. Children exposed to trauma should be screened for symptoms of PTSD. Evid Based Ment Health. 2014;17(4):107. https://doi.org/10.1136/eb-2014-101888.
19. Robinaugh DJ, McNally RJ. Trauma centrality and PTSD symptom severity in adult survivors of childhood sexual abuse. J Trauma Stress. 2011;24(4):483–6. https://doi.org/10.1002/jts.20656.
20. Lang AJ, Rodgers CS, Laffaye C, Satz LE, Dresselhaus TR, Stein MB. Sexual trauma, posttraumatic stress disorder, and health behavior. Behav Med. 2003;28(4):150–8. https://doi.org/10.1080/08964280309596053.
21. Herman J. Trauma and recovery. New York: Basic; 1962.
22. Sack M. Diagnostic and clinical aspects of complex post-traumatic stress disorder. Nervenarzt. 2004;75(5):451–9.
23. Terock J, Van der Auwera S, Janowitz D, Spitzer C, Barnow S, Miertsch M, et al. From childhood trauma to adult dissociation: the role of PTSD and alexithymia. Psychopathology. 2016;49(5):374–82. https://doi.org/10.1159/000449004.
24. Kong SS, Kang DR, Oh MJ, Kim NH. Attachment insecurity as a mediator of the relationship between childhood trauma and adult dissociation. J Trauma Dissociation. 2017;19:1–18. https://doi.org/10.1080/15299732.2017.1329772.
25. Ozcetin A, Belli H, Ertem U, Bahcebasi T, Ataoglu A, Canan F. Childhood trauma and dissociation in women with pseudoseizure-type conversion disorder. Nord J Psychiatry. 2009;63(6):462–8. https://doi.org/10.3109/08039480903029728.
26. Johnston C, Dorahy MJ, Courtney D, Bayles T, O'Kane M. Dysfunctional schema modes, childhood trauma and dissociation in borderline personality disorder. J Behav Ther Exp Psychiatry. 2009;40(2):248–55. https://doi.org/10.1016/j.jbtep.2008.12.002.
27. van der Kolk BA, van der Hart O. Pierre Janet and the breakdown of adaptation in psychological trauma. Am J Psychiatry. 1989;146(12):1530–40. https://doi.org/10.1176/ajp.146.12.1530.
28. Sam Warner TW. Between subjugation and survival: women, borderline personality disorder and high security mental hospitals. J Contemp Psychother. 2004;34(3):265–78.
29. Cattane N, Rossi R, Lanfredi M, Cattaneo A. Borderline personality disorder and childhood trauma: exploring the affected biological systems and mechanisms. BMC Psychiatry. 2017;17(1):221. https://doi.org/10.1186/s12888-017-1383-2.
30. Flasbeck V, Enzi B, Brune M. Childhood trauma affects processing of social interactions in borderline personality disorder: an event-related potential study investigating empathy for pain. World J Biol Psychiatry. 2017:1–11. https://doi.org/10.1080/15622975.2017.1333147.
31. Westphal M, Olfson M, Bravova M, Gameroff MJ, Gross R, Wickramaratne P, et al. Borderline personality disorder, exposure to interpersonal trauma, and psychiatric comorbidity in urban primary care patients. Psychiatry. 2013;76(4):365–80. https://doi.org/10.1521/psyc.2013.76.4.365.
32. Goodman M, New A, Siever L. Trauma, genes, and the neurobiology of personality disorders. Ann N Y Acad Sci. 2004;1032:104–16. https://doi.org/10.1196/annals.1314.008.

33. van der Kolk BA. The neurobiology of childhood trauma and abuse. Child Adolesc Psychiatr Clin N Am. 2003;12(2):293–317, ix.
34. Guendelman S, Garay L, Mino V. Neurobiology of borderline personality disorder. Rev Med Chil. 2014;142(2):204–10. https://doi.org/10.4067/S0034-98872014000200009.
35. van der Kolk B. Posttraumatic stress disorder and the nature of trauma. Dialogues Clin Neurosci. 2000;2(1):7–22.
36. Roller C, Martsolf DS, Draucker CB, Ross R. The sexuality of childhood sexual abuse survivors. Int J Sex Health. 2009;21(1):46–60. https://doi.org/10.1080/19317610802661870.
37. Canton-Cortes D, Cortes MR, Canton J. Child sexual abuse, attachment style, and depression: the role of the characteristics of abuse. J Interpers Violence. 2015;30(3):420–36. https://doi.org/10.1177/0886260514535101.
38. Statham DJ, Heath AC, Madden PA, Bucholz KK, Bierut L, Dinwiddie SH, et al. Suicidal behaviour: an epidemiological and genetic study. Psychol Med. 1998;28(4):839–55.
39. Jumper SA. A meta-analysis of the relationship of child sexual abuse to adult psychological adjustment. Child Abuse Negl. 1995;19(6):715–28.
40. Paolucci EO, Genuis ML, Violato C. A meta-analysis of the published research on the effects of child sexual abuse. J Psychol. 2001;135(1):17–36. https://doi.org/10.1080/00223980109603677.
41. Klonsky ED, Moyer A. Childhood sexual abuse and non-suicidal self-injury: meta-analysis. Br J Psychiatry. 2008;192(3):166–70. https://doi.org/10.1192/bjp.bp.106.030650.
42. Galaif ER, Stein JA, Newcomb MD, Bernstein DP. Gender differences in the prediction of problem alcohol use in adulthood: exploring the influence of family factors and childhood maltreatment. J Stud Alcohol. 2001;62(4):486–93.
43. Smolak L, Murnen SK. A meta-analytic examination of the relationship between child sexual abuse and eating disorders. Int J Eat Disord. 2002;31(2):136–50.
44. Wonderlich SA, Crosby RD, Mitchell JE, Thompson K, Smyth JM, Redlin J, et al. Sexual trauma and personality: developmental vulnerability and additive effects. J Personal Disord. 2001;15(6):496–504.
45. Rind B, Tromovitch P, Bauserman R. A meta-analytic examination of assumed properties of child sexual abuse using college samples. Psychol Bull. 1998;124(1):22–53.
46. Whitaker DJ, Le B, Karl Hanson R, Baker CK, McMahon PM, Ryan G, et al. Risk factors for the perpetration of child sexual abuse: a review and meta-analysis. Child Abuse Negl. 2008;32(5):529–48. https://doi.org/10.1016/j.chiabu.2007.08.005.
47. Lewis DO, Pincus JH, Bard B, Richardson E, Prichep LS, Feldman M, et al. Neuropsychiatric, psychoeducational, and family characteristics of 14 juveniles condemned to death in the United States. Am J Psychiatry. 1988;145(5):584–9. https://doi.org/10.1176/ajp.145.5.584.
48. Yuan NP, Koss MP, Stone M. The psychological consequences of sexual trauma. National online resource center on violence against women VAWnetorg. 2006.
49. Turchik JA, Hebenstreit CL, Judson SS. An examination of the gender inclusiveness of current theories of sexual violence in adulthood: recognizing male victims, female perpetrators, and same-sex violence. Trauma Violence Abuse. 2016;17(2):133–48. https://doi.org/10.1177/1524838014566721.
50. Maniglio R. The impact of child sexual abuse on health: a systematic review of reviews. Clin Psychol Rev. 2009;29(7):647–57. https://doi.org/10.1016/j.cpr.2009.08.003.
51. Reading R, Rannan-Eliya Y. Evidence for sexual transmission of genital herpes in children. Arch Dis Child. 2007;92(7):608–13. https://doi.org/10.1136/adc.2005.086835.
52. Sharpe D, Faye C. Non-epileptic seizures and child sexual abuse: a critical review of the literature. Clin Psychol Rev. 2006;26(8):1020–40. https://doi.org/10.1016/j.cpr.2005.11.011.

14 Sexual Dysfunctions and Substance-Related and Addictive Disorders

Giovanni Martinotti, Emanuela Belfiglio, Rita Santacroce, and Massimo di Giannantonio

14.1 Introduction

The relationship between sex and substance use/misuse is as long as mankind, if one considers the number of ancient reports of plants and other natural psychoactives employed to treat sexual dysfunctions or to enhance performances [1, 2]. On the other hand, men had also to manage the possible negative effects on sex life of recreational substances misuse, which may affect libido and erectile function [3]. Therefore, the "sex and drugs" issue may be examined from two different perspectives: (a) psychoactive effects of drugs/natural preparations used as sexual enhancers and (b) sexual effects of recreational use of alcohol and other drugs. It has to be considered that both sex and drugs of abuse have a common neurochemical pathway in the reward circuit of the brain. The dopaminergic mesolimbic system may be activated by a variety of substances and activities, among which of course psychoactive substances and sex [4]. Addictive drugs have been shown to preferentially increase the release of dopamine (DA) at the nucleus accumbens (NAc) [5]. Brain DA systems, which link the hypothalamus and limbic system, appear to form the core of the sexual excitatory system, while brain opioid, endocannabinoid, and serotonin systems are activated during periods of sexual inhibition [6]. It is noteworthy that sexual experience, like repeated drug use, may determine long-term modifications, including sensitization in the NAc and dorsal striatum [7]. These neurobiological considerations reinforce the relevance of dopaminergic pathways in the modulation of all kinds of hedonic behaviors.

A further theme of interest for mental health service workers is the intentional practice of sex under the influence of psychoactive drugs, known as "chemsex,"

G. Martinotti (✉) · E. Belfiglio · R. Santacroce · M. di Giannantonio
"G.d'Annunzio" University, Department of Neuroscience, Imaging and Clinical Sciences, Chieti, Italy
e-mail: giovanni.martinotti@gmail.com

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*, Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_14

and acted mainly among homosexual males [8]. This issue will be discussed in more details later in this chapter.

14.2 Psychoactive Effects of Drugs/Natural Preparations Used as Sexual Enhancers

The use of herbal supplements and synthetic drugs to enhance erectile function as well as sexual arousal and desire has become increasingly popular in the past few years [9, 10]. Erectile dysfunction and other sexual debilities are among the most explored areas in traditional medicine, and a number of natural products, mostly plant based, have been claimed to have therapeutic properties. Natural products are often perceived as safer alternatives to pharmaceutical products, but their active component may frequently interact/interfere with medical conditions or other medications. Moreover, plant products sold on the Internet may be adulterated and contain undeclared natural/synthetic contaminants or different active ingredients [2, 11].

Maca (*Lepidium meyenii*) is a plant typically grown in the Andean area, constituted of a flat overground portion and underground hypocotyl and roots. Dried hypocotyls have been used for centuries by local populations for their aphrodisiac, energizing, and fertility-enhancing properties [12]. Studies on animal models have demonstrated an increased sexual behavior in rats treated with maca extracts [13, 14]. The efficacy and safety of maca on humans are however still debated [15, 16]. (1*R*,3*S*)-1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (MTCA) has been demonstrated to be present in the extracts of maca. This compound is an inhibitor of the monoamine oxidase (MAO) enzyme and a co-mutagenic or a precursor to mutagenic compounds [17]. MTCA-like compounds have also been suggested to be associated with craving behavior, which is common in addictions [17]. Moreover, subjective reports of moodiness and insomnia are referred by maca users in online fora.

Similarly, products containing yohimbine, a natural tryptamine alkaloid advertised for treating erectile dysfunction and enhancing sexual performance, should not be consumed by subjects with a history of schizophrenia, anxiety, depression, or post-traumatic stress disorder, as cases of dissociative experiences, severe agitation, and hypertension have been reported [18, 19]. Yohimbine is also believed to reinforce drug-seeking behaviors in animal models [20, 21], acting as an experimental stressor. Yohimbine also elicits objective and subjective opioid withdrawal and elevates craving for opioid drugs in methadone- or buprenorphine-treated patients [22, 23].

Ginkgo biloba, a plant used in Chinese traditional medicine for memory enhancement and blood flow improvement, may interact with a number of psychiatric medications, such as bupropion, alprazolam, valproic acid, and MAO-inhibitor antidepressants [24].

Turnera diffusa, also known as "damiana," is a shrub common in Central and South America. Aphrodisiac and psychoactive properties have been traditionally

ascribed to damiana leaves [25], which may be boiled to make infusions or smoked. In the latter case, damiana leaves may produce effects similar to those of cannabis [26]. Dried leaves may constitute the substrate on which synthetic cannabinoids are sprayed in order to produce the so-called spice drugs, advertised online as herbal incenses not for human consumption but endowed with intense psychoactive properties when smoked [27, 28].

Nymphaea caerulea, also known as "blue water lily" or "Egyptian lotus," is sold as a powder named "blue lotus." The flower has been used by ancient Egyptians to enhance sex drive and to improve sexual performance but also to stimulate blood flow and as an antiaging treatment. It has also recreational potential when added to wine or smoked, due to its psychoactive proprieties. The flower may indeed induce both narcotic and euphoric effects, and, if taken in large amounts, it may cause slightly hallucinogenic symptoms [29].

Not only natural substances but also synthetic drugs of abuse may be consumed specifically to enhance libido and sexual performance in general. Methamphetamine is a strong central nervous system stimulant belonging to the substituted phenethylamine class. Methamphetamine is often used recreationally for its effects as a potent euphoriant and stimulant as well as for its aphrodisiac qualities. It has in fact gained the reputation of being able to increase sexual desire and to intensify orgasm, which was also evidenced in murine models [30]. The effects of methamphetamine on sexual behavior and performances appear to be dose dependent: low doses of the drug can increase enjoyment, reduce inhibitions, and delay orgasm, while at higher doses subjects lose their interest for sex and experience difficulties in achieving orgasms [31, 32]. When consumed with sex-enhancing purposes, methamphetamine is commonly re-dosed, which increases the risks of severe health-threatening events such as panic attacks and acute psychosis [33]. The association between sex and meth use becomes quickly unbreakable [34], driving to a chronic use of methamphetamine. This is strongly linked to the development of longer-lasting psychotic symptoms, defined as methamphetamine-associated psychosis (MAP) [35]. MAP has been most consistently described in Asian populations (mainly Japanese), and it is typically associated with long-standing methamphetamine use and characterized as resembling paranoid schizophrenia [36]. Prolonged use of meth has also been associated with erectile dysfunction and delayed ejaculation in men, as well as delayed orgasm in women [37].

3,4-methylenedioxymethamphetamine (MDMA, ecstasy) is also chemically related to amphetamines. Despite being patented in the 1930s, its recreational use emerged only since the 1970s [38]. MDMA acts primarily as a presynaptic releasing agent of serotonin, norepinephrine, and dopamine [39]; MDMA also has a weak agonist activity at postsynaptic serotonin receptors 5-HT1 and 5-HT2 [40]. MDMA is often associated to rave subculture, as well as electronic dance clubs, festivals, and parties. This is mainly due to its sensation-enhancing properties, together with euphorigenic, entactogenic, and mildly hallucinogenic effects [41]. Due to the increased feelings of empathy and bonding, ecstasy is also described as a "love drug," rapidly leading to affectionate physical contact and decreasing inhibition. Research has found that MDMA has an enhancing effect on sexual desire,

satisfaction, female arousal, and orgasmic intensity but an inhibitory effect on orgasm latency (delay). The inhibitory effect on orgasm is similar to that induced by widely prescribed antidepressants, including selective serotonin reuptake inhibitors (SSRIs) [41], and may be related to stimulation of the serotonergic system. Lowered inhibition increases the risk of engaging in risky sexual behavior. People who have sex while on ecstasy are more likely to have unprotected sex. This can increase the risk of unwanted pregnancies and/or contracting a sexually transmitted infection (STI) [42]. MDMA consumption has also been associated with a decrease in erectile ability [43]. To overcome this issue, ecstasy users often combine the drug with sildenafil, a phosphodiesterase 5 (PDE5) inhibitor, in order to mix up their positive effect on sexual desire and performance [44]. The combination, known as "sextasy," greatly increases the risk of acute cardiac failure and priapism [45].

Poppers, which is a slang term for alkyl, amyl, or butyl nitrites, represent a recreational drug widely associated with sexual encounters, due to their vasodilating and myorelaxing properties [46]. Typically, these products are sold in small ampoules containing 10–30 ml of the drug; inhaling the vapor of the volatilized organic liquid is the only possible route of administration. Users describe a sensation of "rush," followed by euphoria, with intensification of positive emotions. Poppers are mainly diffuse among homosexual or bisexual men and appear to be strongly associated with having greater numbers of casual partners and with having anal intercourse with casual partners, which may greatly increase the risks of STIs and HIV infection [47]. Poppers may also be responsible for permanent eye lesions (so-called poppers maculopathy): the exact mechanism through which poppers cause damage to central photoreceptors is unknown, but there is a clear cause–effect relationship [48]. Moreover, alkyl nitrites interact with other vasodilators, such as PDE5 inhibitor, possibly causing severe hypotension [49]. Methemoglobinemia is a potentially fatal consequence of popper use [50], as well as swallowing or aspirating the liquid [51].

14.3 Sexual Effects of Recreational Use of Alcohol and Other Drugs

Drug abusers frequently experience sexual dysfunctions, sometimes previously to their addiction and sometimes as a result of their habit. In fact, people may use alcohol and/or other substances to counter sexual performance anxiety or to overcome sexual dysfunctions [52]. Alcohol consumption often precedes sexual activity, as it is commonly perceived as a sexual facilitator due to its disinhibiting properties [32]. A World Health Organization cross-cultural study for alcohol and high-risk sexual behaviors across eight countries reported that 12% of the male respondents in general population consumed alcohol before first sexual intercourse due to perceived positive effect in improving sexual pleasure [53]. Actually, the belief that alcohol can intensify sexual response is mainly a myth: at low doses, the first effects that are observed are euphoria and disinhibition, but as blood alcohol level rises, cognitive, perceptual, and motor functions become impaired. Moreover, ethanol can

affect erectile function increasing the inhibitory activity of GABA-A receptor and decreasing the excitatory activity of glutamate receptor in CNS [3]. Subjects with chronic alcohol abuse may experiment a wide range of sexual dysfunctions, including decreased sexual desire, difficulty in erection, difficulty in achieving orgasm, and premature ejaculation [54].

The findings on cocaine effects on sexuality are mixed. Its action on dopamine reuptake may justify the reported acute positive impact on sexual behavior (e.g., induced spontaneous erection and ejaculation, facilitation of multiple orgasms). Conversely, other research has shown that chronic cocaine use may diminish sexual desire and ability for both sexes and contributes to greater difficulty in achieving orgasm [54].

Δ9-tetrahydrocannabinol (THC) is the main active metabolite of cannabis; its action is mediated by endocannabinoid receptors CB1 and CB2, which are located, respectively, in the central nervous system and in peripheral tissues. Data from animal models support the inhibitory role of the endocannabinoid system on male sexual function. Moreover, it is also well established that a group of neurons containing CB1 receptors in the paraventricular nucleus (PVN) of the hypothalamus regulate erectile function and copulatory behavior of men [55]. Many studies definitely concluded that cannabis negatively affects male fertility [56]. However, the role of cannabinoid receptors in the regulation of sexual function has not yet been precisely identified. Subjects who consume cannabis on a daily basis showed rates of erectile dysfunction more than double in comparison to nonconsumers. According to recent findings, erectile dysfunction may be caused by cannabis due to a damage of the endothelial function [57].

Opioid abuse may have dual effects on sexual functions: many patients experience an early improvement in their sexuality, with delayed ejaculation in men and improvement of vaginismus in women, while later on both men and women report decreased libido and orgasmic functions [55]. Low libido and impotence have been described in heroin-addicted subjects, as well as in subjects enrolled in methadone maintenance programs. The mechanisms though which opioids act on sexual functions are still unclear, but animal studies confirm that opioids may lower testosterone levels and suppress penile erectile reflexes [58].

14.4 Chemsex

Chemsex (a contraction of "chemical sex") is a term used to describe the practice of intentional sex under the influence of non-prescription psychoactive drugs, mainly among males who have sex with males (MSM) [8]. Intentionality is the distinctive trait of chemsex, which distinguishes it from coincidental sex on drugs, as may happen when drugs are used recreationally in social contexts such as clubs and other nightlife venues [59]. Such sexual sessions can last for several days, involve multiple partners, and include high-risk behavior. In the USA and Australia, the practice is known as "party and play" (PNP) and is more common in urban areas with a large gay population [60]. Chemsex presents a wide number of physical and mental health

risks, considering both the direct and indirect adverse consequences of drug abuse/misuse and the possible risks associated with having sex in altered psychic conditions (e.g., unprotected sex may cause STIs or HIV or may result in rectal trauma or penile abrasions) [61]. Chemsex is not a new phenomenon, but healthcare professionals are worried that increased availability and accessibility of drugs and sex through websites and mobile applications have increased the acceptability, fashionableness, and incidence of chemsex. The psychoactives mostly involved in chemsex practice are mephedrone, γ-hydroxybutyrate (GHB), γ-butyrolactone (GBL), and crystallized methamphetamine. The latter has already been examined in a previous paragraph ("Psychoactive Effects of Drugs/Natural Preparations Used as Sexual Enhancers"); therefore this section will focus on the other molecules.

Mephedrone is the most popular among cathinone derivatives, which are beta-ketophenethylamines structurally similar to amphetamines/catecholamines [62]. Synthetic cathinones show stimulant and empathogenic effects, similar to those of amphetamines, methamphetamine, and cocaine [63]. Mephedrone gained its biggest popularity in the UK at the end of the past decade, concurrently with a shortage and a decrease in purity of cocaine and MDMA [64]. It is most commonly sold as a white or yellowish powder or fine crystals and is mainly inhaled or ingested orally; being water soluble, it may also be used by rectal administration (dissolved in an enema) or injected intravenously [65].

Mephedrone half-life is about 1 h, which increases the risks of re-dosing. Its desired effects may include euphoria, empathy and increased sociability, intensification of sexual experiences and increased sexual arousal, and perceptual distortions; unwanted effects are many and may involve different body systems, such as the gastrointestinal system (nausea, vomiting), central nervous system (tremors, numbness, paranoid delusions, depressive/manic symptoms, aggressiveness, memory impairment), and cardiovascular system (tachycardia, hypertension, chest pain) [66]. Fatal intoxications have been reported in scientific literature: in the UK, between September 2009 and October 2011, 128 alleged cases of mephedrone-related deaths have been included in the UK National Programme on Substance Abuse Deaths database. Typical mephedrone victims were young (mean age, 28.8 years), male, and with a previous history of drug misuse [67]. Repeated mephedrone use may induce tolerance symptoms, with a consequent increase of the doses and/or more frequent consumption [68]. Although withdrawal symptoms are not typically reported, users often describe strong cravings for the drug, with self-report of "addiction or dependence" [69].

γ-hydroxybutyrate (GHB) and its precursor γ-butyrolactone (GBL) are primarily central nervous system depressants [70]. GHB, known with the slang names "liquid ecstasy," "liquid G," and "liquid X," was patented in the 1960s as an anesthetic [71], acting as a modulator in the GABA system. Its possible clinical uses also include the treatment of cataplexy, narcolepsy, and alcoholism; body builders and athletes may improperly use GHB as a doping agent, due to its property of increasing the release of human growth hormone. At low doses, around 0.5–1 g, the drug has desirable effects, including euphoria, increased sex drive, and disinhibition, and is therefore becoming increasingly popular recreationally as a "party drug," often taken

alongside stimulants such as cocaine and amphetamines [72]. GHB may be implicated in sexual assaults as a "date rape" drug: it is available as an odorless and colorless salt that may be used to "spike" beverages given to unsuspecting victims. The subjects become incapacitated due to the sedative effects of GHB, which are amplified when the drug is mixed with alcohol [73]. Anterograde amnesia is also often reported [74]. Common intoxication symptoms include confusion, hallucinations, delusions, agitation, bizarre behavior, and seizures but also bradycardia and hypotension [70]. Doses over 50 mg/kg may cause coma [70]. GHB/GBL can be responsible of a dangerous physiological dependence: some users may need drug treatment to support detoxification [75]. GHB-associated deaths have been reported worldwide [76], but an increase in their prevalence has been recently reported in the UK, possibly associating the phenomenon to the rise of GHB popularity in chemsex contexts [77].

One of the major problems to establish health policy priority interventions for chemsex is the lack of available epidemiological data. Moreover, social actions should be taken in order to break down the barriers that currently exist among chemsex drug users in accessing services, including the shame and stigma often associated with drug use.

References

1. Nair R, Sellaturay S, Sriprasad S. The history of ginseng in the management of erectile dysfunction in ancient China (3500-2600 BCE). Indian J Urol. 2012;28:15–20.
2. Evans-Brown M, McVeigh J, Perkins C, Bellis M. Human enhancement drugs. The emerging challenges to public health. Liverpool: John Moore; 2012.
3. Jiann B. Erectile dysfunction associated with psychoactive substances. Chonnam Med J. 2008;44(3):117–24.
4. Blum K, Werner T, Carnes S, Carnes P, Bowirrat A, Giordano J, et al. Sex, drugs, and rock "N" roll: hypothesizing common mesolimbic activation as a function of reward gene polymorphisms. J Psychoactive Drugs [Internet]. 2012;44(1):38–55. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4040958/.
5. Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A. 1988;85(14):5274–8.
6. Pfaus JG. Pathways of sexual desire. J Sex Med. 2009;6(6):1506–33.
7. Bradley KC, Boulware MB, Jiang H, Doerge RW, Meisel RL, Mermelstein PG. Changes in gene expression within the nucleus accumbens and striatum following sexual experience. Genes Brain Behav. 2005;4(1):31–44.
8. McCall H, Adams N, Mason D, Willis J. What is chemsex and why does it matter? BMJ [Internet]. 2015;351:h5790. http://www.bmj.com/lookup/doi/10.1136/bmj.h5790.
9. Corazza O, Martinotti G, Santacroce R, Chillemi E, Di Giannantonio M, Schifano F, et al. Sexual enhancement products for sale online: raising awareness of the psychoactive effects of yohimbine, maca, horny goat weed, and ginkgo biloba. Biomed Res Int. 2014;2014:13.
10. Pratap SA, Rajender S. Potent natural aphrodisiacs for the management of erectile dysfunction and male sexual debilities. Front Biosci (Schol Ed). 2012;4:167–80.
11. Kenyon SL, Button J, Perella P, McKeown DA, Holt DW. An herbal remedy for impotence: more than was bargained for. J Clin Pharmacol. 2006;46:1379–81.
12. Gonzales GF. Ethnobiology and ethnopharmacology of lepidium meyenii (Maca), a plant from the Peruvian Highlands. Evid Based Complement Alternat Med. 2012;2012:10.

13. Zheng BL, He K, Kim CH, Rogers L, Shao Y, Huang ZY, et al. Effect of a lipidic extract from lepidium meyenii on sexual behavior in mice and rats. Urology. 2000;55(4): 598–602.
14. Cicero AFG, Piacente S, Plaza A, Sala E, Arletti R, Pizza C. Hexanic Maca extract improves rat sexual performance more effectively than methanolic and chloroformic Maca extracts. Andrologia. 2002;34(3):177–9.
15. Lee MS, Shin B-C, Yang EJ, Lim H-J, Ernst E. Maca (Lepidium meyenii) for treatment of menopausal symptoms: a systematic review. Maturitas. 2011;70(3):227–33.
16. Shin B-C, Lee MS, Yang EJ, Lim H-S, Ernst E. Maca (L. meyenii) for improving sexual function: a systematic review. BMC Complement Altern Med. 2010;10:44.
17. Piacente S, Carbone V, Plaza A, Zampelli A, Pizza C. Investigation of the tuber constituents of maca (Lepidium meyenii Walp.). J Agric Food Chem. 2002;50(20):5621–5.
18. Linden CH, Vellman WP, Rumack B. Yohimbine: a new street drug. Ann Emerg Med. 1985;14(10):1002–4.
19. Kearney T, Tu N, Haller C. Adverse drug events associated with yohimbine-containing products: a retrospective review of the California poison control system reported cases. Ann Pharmacother. 2010;44(6):1022–9.
20. Gass JT, Olive MF. Reinstatement of ethanol-seeking behavior following intravenous self-administration in Wistar rats. Alcohol Clin Exp Res. 2007;31(9):1441–5.
21. Feltenstein MW, See RE. Potentiation of cue-induced reinstatement of cocaine-seeking in rats by the anxiogenic drug yohimbine. Behav Brain Res. 2006;174(1):1–8.
22. Stine SM, Southwick SM, Petrakis IL, Kosten TR, Charney DS, Krystal JH. Yohimbine-induced withdrawal and anxiety symptoms in opioid-dependent patients. Biol Psychiatry. 2002;51(8):642–51.
23. Greenwald MK, Lundahl LH, Steinmiller CL. Yohimbine increases opioid-seeking behavior in heroin-dependent, buprenorphine-maintained individuals. Psychopharmacology. 2013;225:811–24.
24. Abad MJ, Bedoya LM, Bermejo P. An update on drug interactions with the herbal medicine Ginkgo biloba. Curr Drug Metab. 2010;11(2):171–81.
25. Kumar S, Madaan R, Sharma A. Pharmacological evaluation of bioactive principle of Turnera aphrodisiaca. Indian J Pharm Sci. 2008;70(6):740–4.
26. Arletti R, Benelli A, Cavazzuti E, Scarpetta G, Bertolini A. Stimulating property of Turnera diffusa and Pfaffia paniculata extracts on the sexual-behavior of male rats. Psychopharmacology. 1999;143(1):15–9.
27. Santacroce R, Corazza O, Martinotti G, Bersani FS, Valeriani G, Di Giannantonio M. Psyclones: a roller coaster of life? Hidden synthetic cannabinoids and stimulants in apparently harmless products. Hum Psychopharmacol Clin Exp [Internet]. 2015;30(4):265–71. https://doi.org/10.1002/hup.2410.
28. Martinotti G, Lupi M, Carlucci L, Cinosi E, Santacroce R, Acciavatti T, et al. Novel psychoactive substances: use and knowledge among adolescents and young adults in urban and rural areas. Hum Psychopharmacol. 2015;30(4):295–301.
29. Emboden WA. Transcultural use of narcotic water lilies in ancient Egyptian and Maya drug ritual. J Ethnopharmacol. 1981;3(1):39–83.
30. Fiorino DF, Phillips a G. Facilitation of sexual behavior in male rats following d-amphetamine-induced behavioral sensitization. Psychopharmacology. 1999;142(2):200–8.
31. Semple SJ, Patterson TL, Grant I. The context of sexual risk behavior among heterosexual methamphetamine users. Addict Behav. 2004;29(4):807–10.
32. Palha AP, Esteves M. Drugs of abuse and sexual functioning. Adv Psychosom Med. 2008;29:131–49.
33. Degenhardt L, Topp L. "Crystal meth" use among polydrug users in Sydney's dance party subculture: characteristics, use patterns and associated harms. Int J Drug Policy. 2003;14:17–24.
34. Rawson RA, Washton A, Domier CP, Reiber C. Drugs and sexual effects: role of drug type and gender. J Subst Abus Treat. 2002;22(2):103–8.

35. Grant KM, LeVan TD, Wells SM, Li M, Stoltenberg SF, Gendelman HE, et al. Methamphetamine-associated psychosis. J Neuroimmune Pharmacol. 2012;7:113–39.
36. Kobayashi H, Ujike H, Iwata N, Inada T, Yamada M, Sekine Y, et al. Association analysis of the tryptophan hydroxylase 2 gene polymorphisms in patients with methamphetamine dependence/psychosis. Curr Neuropharmacol. 2011;9:176–82.
37. Peugh J, Belenko S. Alcohol, drugs and sexual function: a review. J Psychoactive Drugs. 2001;33(3):223–32.
38. Gourley M. A subcultural study of recreational ecstasy use. J Sociol. 2004;40(1):59–73.
39. NIH. HSDB: 3,4-Methylenedioxymethamphetamine [Internet]. US National Library of Medicine. 2008 [cited 2017 Jan 20]. https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@rn+@rel+42542-10-9.
40. Lyon RA, Glennon RA, Titeler M. 3,4-Methylenedioxymethamphetamine (MDMA): Stereoselective interactions at brain 5-HT1 and 5-HT2 receptors. Psychopharmacology (Berl) [Internet]. 1986;88(4):525–6. https://doi.org/10.1007/BF00178519.
41. Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. J Clin Psychopharmacol. 1999;19(1):67–85.
42. McElrath K. MDMA and sexual behavior: ecstasy users' perceptions about sexuality and sexual risk. Subst Use Misuse. 2005;6084:1461–77.
43. Zemishlany Z, Aizenberg D, Weizman A. Subjective effects of MDMA ("ecstasy") on human sexual function. Eur Psychiatry. 2001;16(2):127–30.
44. Breslau K. The "sextasy" craze. Clubland's dangerous party mix: Viagra and ecstasy. Newsweek. 2002;139:30.
45. Tran QT, Wallace RA, Sim EHA. Priapism, ecstasy, and marijuana: is there a connection? Adv Urol. 2008;2008:193694.
46. Romanelli F, Smith KM, Thornton AC, Pomeroy C. Poppers: epidemiology and clinical management of inhaled nitrite abuse. Pharmacotherapy. 2004;24(1):69–78.
47. Lampinen TM, Mattheis K, Chan K, Hogg RS. Nitrite inhalant use among young gay and bisexual men in Vancouver during a period of increasing HIV incidence. BMC Public Health. 2007;7:35.
48. Gruener AM, Jeffries MAR, El Housseini Z, Whitefield L. Poppers maculopathy. Lancet. 2014;384(9954):1606.
49. Romanelli F, Smith KM. Recreational use of sildenafil by HIV-positive and -negative homosexual/bisexual males. Ann Pharmacother [Internet]. 2004;38(6):1024–30. https://doi.org/10.1345/aph.1D571.
50. Stalnikowicz R, Amitai Y, Bentur Y. Aphrodisiac drug-induced Hemolysis. J Toxicol Clin Toxicol [Internet]. 2004;42(3):313–6. https://doi.org/10.1081/CLT-120037435.
51. Hagan IG, Burney K. Radiology of recreational drug abuse. RadioGraphics [Internet]. 2007;27(4):919–40. https://doi.org/10.1148/rg.274065103.
52. Grover S, Mattoo SK, Pendharkar S, Kandappan V. Sexual dysfunction in patients with alcohol and opioid dependence. Indian J Psychol Med. 2014;36:355–65.
53. Alcohol use and sexual risk behaviour: a cross-cultural study in eight countries. Geneva: World Health Organization; 2005. p. 148.
54. Arackal BS, Benegal V. Prevalence of sexual dysfunction in male subjects with alcohol dependence. Indian J Psychiatry [Internet]. 2007;49(2):109–12. http://www.ncbi.nlm.nih.gov/pubmed/20711392.
55. Zaazaa A, Bella AJ, Shamloul R. Drug addiction and sexual dysfunction. Endocrinol Metab Clin N Am. 2013;42(3):585–92.
56. Amoako AA, Marczylo TH, Marczylo EL, Elson J, Willets JM, Taylor AH, et al. Anandamide modulates human sperm motility: implications for men with asthenozoospermia and oligoasthenoteratozoospermia. Hum Reprod. 2013;28(8):2058–66.
57. Aversa A, Rossi F, Francomano D, Bruzziches R, Bertone C, Santiemma V, et al. Early endothelial dysfunction as a marker of vasculogenic erectile dysfunction in young habitual cannabis users. Int J Impot Res. 2008;20(6):566–73.

58. Pake JA, Penn RD, Ryan WG. Altered sexual function and decreased testosterone in patients receiving intraspinal opioids. J Pain Symptom Manag. 1994;9(2):126–31.
59. Bourne A, Reid D, Hickson F, Torres-Rueda S, Weatherburn P. Illicit drug use in sexual settings ('chemsex') and HIV/STI transmission risk behaviour among gay men in South London: findings from a qualitative study. Sex Transm Infect [Internet]. 2015;91(8):564–8. http://apps.webofknowledge.com/full_record.do?product=WOS&search_mode=CitingArticles&qid=1&SID=W1HnFq71TOmNoSHorBF&page=1&doc=1&cacheurlFromRightClick=no.
60. Race K. "Party 'n' play": online hook-up devices and the emergence of PNP practices among gay men. Sexualities. 2015:1–40.
61. Giorgetti R, Tagliabracci A, Schifano F, Zaami S, Marinelli E, Busardo FP. When "chems" meet sex: a rising phenomenon called "ChemSex". Curr Neuropharmacol. 2016;15(5):762–70.
62. Schifano F, Orsolini L, Duccio Papanti G, Corkery JM. Novel psychoactive substances of interest for psychiatry. World Psychiatry. 2015;14(1):15–26.
63. Winstock AR, Marsden J, Mitcheson L. What should be done about mephedrone? BMJ. 2010;340:c1605.
64. Nelson ME, Bryant SM, Aks SE. Emerging drugs of abuse. Emerg Med Clin North Am. 2014;32(1):1–28.
65. Schifano F, Albanese A, Fergus S, Stair JL, Deluca P, Corazza O, et al. Mephedrone (4-methylmethcathinone; "meow meow"): chemical, pharmacological and clinical issues. Psychopharmacology. 2011;214(3):593–602.
66. Wood DM, Greene SL, Dargan PI. Clinical pattern of toxicity associated with the novel synthetic cathinone mephedrone. Emerg Med J. 2011;28(4):280–2.
67. Schifano F, Corkery J, Ghodse AH. Suspected and confirmed fatalities associated with mephedrone (4-methylmethcathinone, "meow meow") in the United Kingdom. J Clin Psychopharmacol. 2012;32(5):710–4.
68. Emcdda. Risk assessment report of a new psychoactive substance: 4-methylmethcathinone (mephedrone) In accordance with Article 6 of Council Decision 2005/387/JHA on information exchange, risk assessment and control of new psychoactive substances. EMCDDA Risk Assessments. 2011.
69. Newcombe R. Mephedrone: the use of mephedrone (M-cat, Meow) in Middlesbrough. Manchester: Lifeline Publications and Research; 2009. p. 1–16.
70. Schep LJ, Knudsen K, Slaughter RJ, Vale JA, Mégarbane B. The clinical toxicology of gamma-hydroxybutyrate, gamma-butyrolactone and 1,4-butanediol. Clin Toxicol [Internet]. 2012;50(6):458–70. https://doi.org/10.3109/15563650.2012.702218.
71. Vickers MD. Gamma hydroxybutyric acid. Clinical pharmacology and current status. Proc R Soc Med [Internet]. 1968;61(8):821–4. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1902450&tool=pmcentrez&rendertype=abstract.
72. Sumnall HR, Beynon CM, Conchie SM, Riley SCE, Cole JC. An investigation of the subjective experiences of sex after alcohol or drug intoxication. J Psychopharmacol [Internet]. 2007;21(5):525–37. https://doi.org/10.1177/0269881106075590.
73. Brewster VL, Edwards HGM, Hargreaves MD, Munshi T. Identification of the date-rape drug GHB and its precursor GBL by Raman spectroscopy. Drug Test Anal. 2009;1(1):25–31.
74. Barker JC, Harris SL, Dyer JE. Experiences of gamma hydroxybutyrate (GHB) ingestion: a focus group study. J Psychoactive Drugs. 2007;39:115–29.
75. Abdulrahim D, Bowden-Jones O. Guidance on the clinical management of acute and chronic harms of club drugs and novel psychoactive substances. 2015. 335 p. http://www.drugsandalcohol.ie/24292/.
76. Corkery JM, Loi B, Claridge H, Goodair C, Corazza O, Elliott S, et al. Gamma hydroxybutyrate (GHB), gamma butyrolactone (GBL) and 1,4-butanediol (1,4-BD, BDO): a literature review with a focus on UK fatalities related to non-medical use. Neurosci Biobehav Rev. 2015;53:52–78.
77. Hockenhull J, Murphy KG, Paterson S. An observed rise in γ-hydroxybutyrate-associated deaths in London: evidence to suggest a possible link with concomitant rise in chemsex. Forensic Sci Int [Internet]. 2017;270:93–7. https://doi.org/10.1016/j.forsciint.2016.11.039.

Sexual Dysfunctions in the Internet Era

15

Daniele Mollaioli, Andrea Sansone, Francesco Romanelli, and Emmanuele A. Jannini

15.1 Introduction

Low sexual desire, reduced satisfaction in sexual intercourse, and erectile dysfunction (ED) are increasingly common in young population. In an Italian study from 2013, up to 25% of subjects suffering from ED were under the age of 40 [1], and in a similar study published in 2014, more than half of Canadian sexually experienced men between the age of 16 and 21 suffered from some kind of sexual disorder [2]. At the same time, prevalence of unhealthy lifestyles associated with organic ED has not changed significantly or has decreased in the last decades, suggesting that psychogenic ED is on the rise [3]. The DSM-IV-TR defines some behaviors with hedonic qualities, such as gambling, shopping, sexual behaviors, Internet use, and video game use, as "impulse control disorders not elsewhere classified"—although these are often described as behavioral addictions [4]. Recent investigation has suggested the role of behavioral addiction in sexual dysfunctions: alterations in neurobiological pathways involved in sexual response might be a consequence of repeated, supernormal stimuli of various origins.

15.2 Online Pornography and Sexual Dysfunctions

Among behavioral addictions, problematic Internet use and online pornography consumption are often cited as possible risk factors for sexual dysfunction, often without definite boundary between the two phenomena [5, 6]. Since 2007, mounting

D. Mollaioli (✉) · E. A. Jannini
Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
e-mail: daniele.mollaioli@gmail.com; eajannini@gmail.com

A. Sansone · F. Romanelli
Department of Experimental Medicine, University of Rome Sapienza, Rome, Italy

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*,
Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_15

evidence has suggested that Internet pornography might be a risk factor for sexual dysfunctions, including low libido and impaired erectile and orgasmic functions [7]. Case series have provided the first hints in these regards; however, more solid evidence has emerged from longitudinal studies in married couples. Pornography consumption has been considered one of the strongest predictors of poor marital quality [8]—and, therefore, of poor sexual health. Studies aimed to directly assess the role of Internet pornography use and male sexual dysfunction have described an association between the two phenomena [9, 10]. Sexual dysfunctions typically manifest in physical relationships with women and more rarely in relation to sexually explicit material; unsurprisingly, abstinence from "cybersex" and from masturbation has been proposed as a treatment, although evidence in support is still lacking.

Sexually explicit material is widely available on the Internet, often at no cost and virtually without any controls for age, therefore providing a plausible reason for the rapid increase in a condition most frequently associated with aging. It should come as no surprise that pornography is the most common among the chief reasons for compulsive Internet use [11] and that cybersex is the third largest economic sector on the Internet. Besides being freely available, Internet pornography features a seemingly endless supply of contents, providing novelty and freedom of choice: in these regards, it is significantly different from printed material, as any user is able to quickly access new videos and scenes, or even genres. In short, users are attracted to Internet pornography because of its anonymity, affordability, and accessibility—the "Triple A Engine" [12].

The extreme ease in finding the adult material is also accompanied by a strict categorical organization of porn videos: alongside the giants of porn online such as Pornhub, YouPorn, and RedTube, there are a whole series of smaller sites that aggregate videos, categorizing them by type of sexual act, the age of the actors, the video quality (amateur or professional), the sexual orientation, and the body and sexual preferences. This categorization has generated a sort of a constantly evolving encyclopedia of porn, directing the user toward increasingly specific and refined tastes (Table 15.1).

Table 15.1 Most researched porn categories

Amateur	Amputee	Anal	Animal
Asian	Babe	Bareback	BBW
BDSM	Big Ass	Bisexual	Bizarre
Black/ebony	Blowjob	Bondage	Bukkake
Casting	Cheating	Cheerleaders	Creampie
Cuckold	Deepthroat	Dildo	Doggy style
Double penetration	Exhibitionist	Extreme	Facial
Feet	FemDom	Fetish	Fisting
Gangbang	Gay	Gloryhole	Granny
Group	Hairy	Handjob	Hardcore
Hentai	Homemade	Interracial	Ladyboy
Latin	Lesbian	Lingerie	Lolita
Massage	Mature	Masturbating/solo	Masturbation
Mature	Menstrual	Midget	Milf/mom
Oral Sex	Orgy	Pantyhose/Stockings	Pissing
POV (Point of View)	Pregnant	Public	Reality
Schoolgirl	Shaving	Shemale	Skinny
Slave	Small tits	Smoking	Solo
Squirt	Squirting	Straight	Submale
Sucking	Teens	Threesome	Torture
Transsexual	Upskirt	Vampire	Vintage
Vintage	Voyeur	Wet	Young

Internet pornography use shares many similarities with substance addiction [13], such as the activation of the same reward circuitry in the basolateral amygdala, the anterior cingulate area, and the nucleus accumbens [14]. Upregulation of the truncated splice variants (ΔFosB) of the Finkel-Biskis-Jinkins (FBJ) murine osteosarcoma viral oncogene homolog B (FosB) in the nucleus accumbens has been observed following both sexual stimuli and substance abuse; overexpression of the ΔFosB is necessary and sufficient for many of the neural adaptations commonly observed in addiction. This process allows hypersensitization to stimuli while possibly facilitating compulsive behaviors. Internet pornography use triggers dopamine bursts in the reward circuitry of the brain, which increase the sense of well-being associated with masturbation while at the same providing the neurobiological grounds for addiction; not all subjects respond to external stimuli in the same way, but those who are predisposed to harmful or obsessive behaviors are more likely to become addicted to pornography. Users are more likely to forget the "evolutionary" role of sex, finding more excitement in self-selected sexually explicit material than in intercourse: sexual conditioning might be the missing link between the impaired sexual function during partnered sexual interactions and the increased arousal coming from Internet adult movies [15]. Failure to meet sexual expectations, together with the inability to obtain more stimulation by a simple "click", may lead to a decline in dopamine in the mesolimbic pathway, ultimately resulting in loss of interest for intercourse and sexual dysfunction.

The increase in the vision of online pornographic content has developed a still unsolved debate among scientists about the negative and positive effects of viewing pornography on the users.

15.3 Negative Aspects of Pornography on Sexual Quality of Life

From a negativistic perspective, the increased access to online pornography has been accompanied by growing concerns that may negatively affect personal, sexual, and relational health and well-being [16, 17]. The cybersex addiction represents the most frequent form between all the Internet addictions [16, 18].

The main feature of porn addiction is the compulsive pursuit of sexual pleasure that the user tries to achieve when masturbating through the viewing of adult content. Individuals suffering from porn addiction are completely absorbed by their stereotyped sexual practices: the interest is directed exclusively to find the most self-suitable porn content, dedicating up to several hours in researching, viewing, and classifying the erotic material; the sexual behavior is characterized by compulsive masturbation, with the intention of reaching ejaculation (one or more times) to relieve sexual tension [10].

Sutton et al. found that men affected by hypersexual behavior and compulsive masturbation in association with frequent pornography use, presented also sexual dysfunctions, reporting mostly difficulties reaching orgasm during sexual intercourse [19]. Anxiety about sexual performance may impel further reliance on pornography as a sexual outlet [20].

In these people the addictive consumption of pornographic material worsens sexual health with a progressive interruption of sexual intimacy with the partner [21, 22].

Several studies have reported that porn addiction can negatively impact on attitudes and sexual life, diminishing satisfaction and increasing cases of infidelity and occasional relationships with different partners [16–20]. It could also contribute to an early debut of sexual activity in adolescence, exposing teens to an experience of sexual "failure" that over time could evolve to a sexual dysfunction, like loss of libido, erectile dysfunction (ED) and premature ejaculation (PE) for men, and problems in sexual desire and orgasm in women [21, 22].

Moreover, porn movies rarely contemplate the condom use, giving a negative message especially among young viewers about the right ways to approach to sexuality, with a potential increased risk of sexually transmitted diseases (STD) [17].

The severity of the effects seems to be correlated with the years of use: males who started using cybersex at a younger age are less likely to prefer partnered sex. The effects of sexual conditioning have similarly been described regarding risky sexual behaviors: subjects accustomed to more extreme videos are more frequently involved in similar acts, such as unprotected anal intercourse. It is likely, although yet unproven, that precocious exposure to pornography might have deleterious effects on sexual development during puberty: this is alarming, considering that Internet pornography use is increasingly accepted as an ordinary behavior [23].

Although this aspect is poorly studied, several studies report that pornography, especially the violent one, reproduces negative feminine and masculine models in which woman is represented only as a "puppet" under the man control, emphasizing psychological, physical, and sexual violence toward women [17, 22].

15.4 Positive Aspects of Pornography on Sexual Quality of Life

Although it is a common opinion that cybersex addiction can generate negative outcomes from both psychological and sexual, more and more researchers point out that pornography could also be an important therapeutic instrumental in sexological treatments [24–26]. According to some studies, the vision of pornographic material would act by improving the sexual fantasies through normalization and facilitating the willingness to explore them [24, 27]. Pornography in some respects could even improve the sexual life of men and women by reducing the feeling of unease about sex and encouraging sexual expression [28].

For example, it could be used in an early phase of psychoeducation for male and female sexuality, at a later stage of treatment (e.g., in the case of female hypoactive sexual desire), or in couple therapy [24–27]. In favor of this perspective, it has been highlighted that the viewing porn by women improves their sexual satisfaction in real life as well as being a useful way to better investigate the field of female sexuality [24–27].

Pornography could be a valuable aid in the sexual field for people with disabilities and those who have some dysfunction with a strong anxious component since it has been seen that pornography acts on the dysfunction through a reduction of anxiety associated with sexual activity [11].

Finally, online pornography lends itself very efficiently to frequency studies [28, 29]. Although there is no certainty about gender and psychopathological conditions at the base of network access, online porn allows to evaluate a very large population, classifying subjects according to specific and well-defined sexual interests, from the most trivial to the rarest (Table 15.1), so as to build tables of frequency otherwise not compiled.

15.5 Sexual Dysfunctions and Other Behavioral Addiction

Gaming is closely associated with cybersex as both are potentially addicting media. Given the widespread availability of gaming devices, including tablets, smartphones, and laptops, video games reach all ages, genders, and demographics [30]; for many people, playing is a means for connecting with other players or for escaping from the boredom of everyday life. However, excessive use of video games might have serious consequences for everyday life: players might be more concerned with the game than with routine activities, including personal hygiene, work, and social interaction. On this basis, despite the small prevalence of health issues related to gaming, the American Psychiatric Association has suggested that video game addiction might be worth investigating and has thus filed Internet gaming disorder as a "condition requiring further study" in the DSM 5.

Video game addiction, being a relatively novel issue, is still mostly unknown in regards to both its pathogenesis and its evolution. Although overexpression of ΔFosB has not been documented in gamers, several mechanisms might provide an explanation for the addictive nature of gaming [31]. Compulsion loops, i.e., designed chains of activities that will be repeated to gain a neurochemical reward (such as dopamine release), are among often used by designers in order to keep players attached to the game ("grinding"); a similar phenomenon ("chasing losses") has been described in gambling, as the player will keep playing in the often unlikely event of winning. Brain functional changes have been discovered via PET imaging in Internet gaming addiction [32], suggesting that loss of control and similar compulsive behaviors observed in gamers might be associated with dysregulation in D2 receptors and glucose metabolism. Downregulation and reduced expression of D2 receptors have both been associated with erectile dysfunction and reduced libido, therefore suggesting that excessive use of gaming might have negative effects on sexual health. However, at the present time, there is little evidence suggesting a causative association between gaming and sexual dysfunction; some authors have in fact suggested that video game addiction might be a consequence of other mental issues, rather than a risk factor per se [33].

To the present date, no studies have adequately addressed whether Internet and video game use should be considered risk factors for sexual dysfunction or if there are "threshold" values for their consumption; likewise, little is known regarding individual response to these stressors. The only study assessing the impact of videogames on male sexual health has found a significantly reduced prevalence of premature ejaculation among gamers, together with reduced sexual desire [34]. These findings, however, are far from conclusive and deserve further validation. Genetic bases for addiction have been recently described [35] and might be involved in the pathogenesis of sexual dysfunctions.

15.6 Internet-Based Therapy for Sexual Dysfunctions

The use of the Internet as a clinical intervention space for male and female sexual dysfunction has a relatively short history. Above all in recent years, the use of the Internet in clinical practice has proved effective in resolving certain psychopathologies, such as anxiety and depressive disorders [36–38]. To a lesser extent, these interventions have also become available in the treatment of sexual dysfunction.

The network tool has advantages over face-to-face contact [39]:

- It can guarantee anonymity in the initial phases of the intervention, allowing many individuals to face the problem without fear of being judged or discovered.
- No need for a coexistence of the patient and the doctor in the same space or time. The asynchronous nature of the contact between client and therapist can in some cases be a valuable service for those who have difficulty attending face-to-face meetings due to physical or geographical constraints or for reasons related to work.
- Clinical treatment is followed daily directly in the real-life environment, skipping the stage where improvements are only present during the therapy session.
- The patient may feel more active and responsible in therapy, attributing to himself and not to the doctor any improvements in sexual functioning, resulting in increased self-esteem.

Although the use of Internet therapy as a potential treatment for sexual dysfunction has often been encouraged [40–42], only few scientific contributions are surprisingly present in the literature. Most of the studies describing the results of online sexual therapy are without a control sample [43–45].

Among these, one of the most famous online programs in the field of sexology is "Sexpert." Although initial research has shown promising positive effects of the use of "Sexpert" in the modification of sexual behavior, the results have never been published [46].

Internet-based therapy is founded on the theoretical models of psychopathology and sexual dysfunction [38, 39]. Usually, online interventions are organized in a website, containing informative material and individual and couple exercises, structured in a temporal way. In addition, one or more contacts with a sexual health professional are also provided.

Studies on the Internet-based sexual therapy (IBST) for male erectile dysfunction suggest substantial equality in treatment efficacy compared to face-to-face therapies [26, 44, 47, 48].

In the study, men with ED treated with IBST reported improvements (similar to waiting list group) on erectile function, sexual desire, sexual satisfaction, and self-confidence between pretreatment and posttreatment and were to be largely maintained until 3 and 6 months after treatment termination [26] (Fig. 15.1a).

Similarly, men with PE and treated with IBST reported improvements in ejaculatory control, sexual desire, and satisfaction between pretreatment and posttreatment and were maintained until 6 months follow-up [26] (Fig. 15.1b).

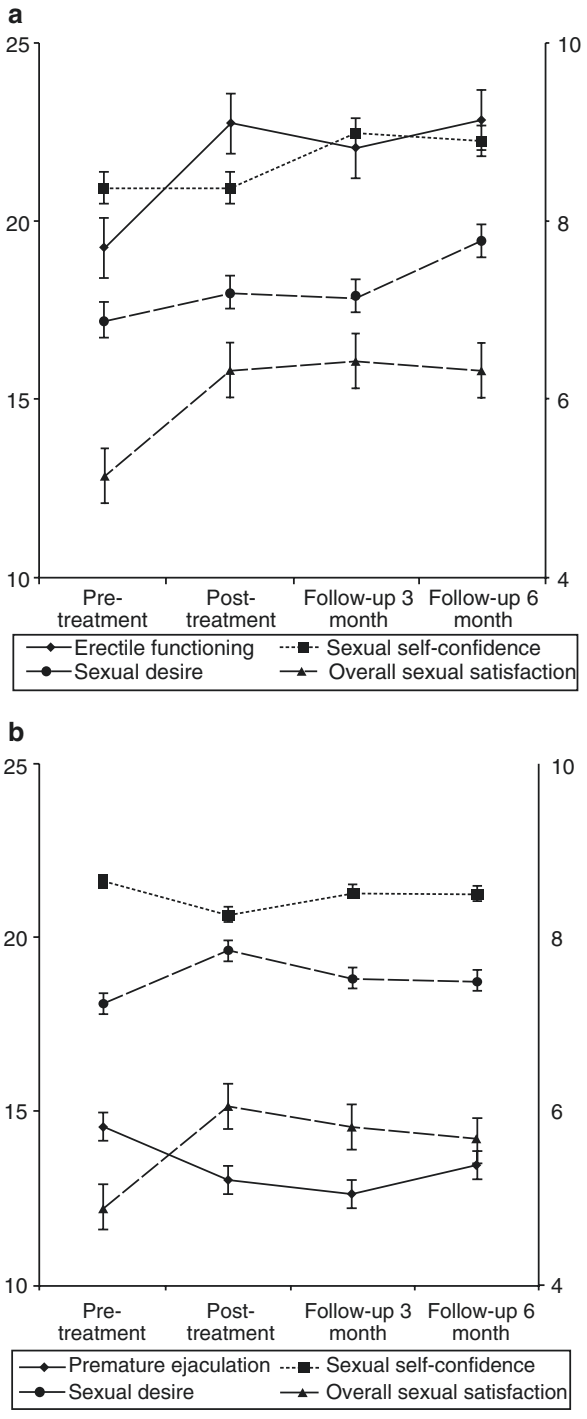

Fig. 15.1 (**a**) Sexual functioning at pretreatment, posttreatment, and follow-up assessment at 3 and 6 months posttreatment in participants with ED (means ± SEM) [26]. (**b**) Sexual functioning at pretreatment, posttreatment, and follow-up assessment at 3 and 6 months posttreatment in participants with PE (means ± SEM) [26]

In the studies investigating IBST for female sexual dysfunctions, we found similar results of male studies.

In these studies [49–51], improvements were reported after posttreatment in sexual functioning, intimacy, and relational quality of life (with better communication and emotional intimacy). Posttreatment gains regarding sexual and relational functioning were generally maintained until follow-up assessment [49, 51].

Curiously, no significant improvements were reported in anxiety or mood [50]: this is because these interventions are extremely focused on targeted problem areas, such as sexual and relational.

References

1. Capogrosso P, Colicchia M, Ventimiglia E, Castagna G, Clementi MC, Suardi N, et al. One patient out of four with newly diagnosed erectile dysfunction is a young man – worrisome picture from the everyday clinical practice. J Sex Med. 2013;10:1833–41.
2. O'Sullivan LF, Brotto LA, Byers ES, Majerovich JA, Wuest JA. Prevalence and characteristics of sexual functioning among sexually experienced middle to late adolescents. J Sex Med. 2014;11:630–41.
3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. Washington, DC: American Psychiatric Association, 2000.
4. McCabe MP, Sharlip ID, Lewis R, Atalla E, Balon R, Fisher AD, et al. Incidence and prevalence of sexual dysfunction in women and men: a consensus statement from the Fourth International Consultation on Sexual Medicine 2015. J Sex Med. 2016;13:144–52.
5. Grubbs JB, Stauner N, Exline JJ, Pargament KI, Lindberg MJ. Perceived addiction to Internet pornography and psychological distress: examining relationships concurrently and over time. Psychol Addict Behav. 2015;29(4):1056–67.
6. Ross MW, Mansson SA, Daneback K. Prevalence, severity, and correlates of problematic sexual Internet use in Swedish men and women. Arch Sex Behav. 2012;41:459–66.
7. Landripet I, Stulhofer A. Is pornography use associated with sexual difficulties and dysfunctions among younger heterosexual men? J Sex Med. 2015;12:1136–9.
8. Perry SL. Does viewing pornography reduce marital quality over time? Evidence from longitudinal data. Arch Sex Behav. 2017;46(2):549–59.
9. Garcia-Cruz E, Romero-Otero J, Fode M, Alcaraz A. The digital environment in men's sexual disorders: a systematic review. Actas Urol Esp. 2017; pii: S0210–4806(17)30177–8.
10. Blais-Lecours S, Vaillancourt-Morel MP, Sabourin S, Godbout N. Cyberpornography: time use, perceived addiction, sexual functioning, and sexual satisfaction. Cyberpsychol Behav Soc Netw. 2016;19(11):649–55.
11. Southern S. Treatment of compulsive cybersex behavior. Psychiatr Clin North Am. 2008;31(4):697–712.
12. Cooper A. Sexuality and the internet: surfing into the new millennium. Cyberpsychol Behav. 1998;1:181–7.
13. Zou Z, Wang H, d'Oleire Uquillas F, Wang X, Ding J, Chen H. Definition of substance and non-substance addiction. Adv Exp Med Biol. 2017;1010:21–41.
14. Ruffle JK. Molecular neurobiology of addiction: what's all the (Delta)FosB about? Am J Drug Alcohol Abuse. 2014;40:428–37.
15. Brom M, Both S, Laan E, Everaerd W, Spinhoven P. The role of conditioning, learning and dopamine in sexual behavior: a narrative review of animal and human studies. Neurosci Biobehav Rev. 2014;38:38–59.
16. Doring MN. The Internet's impact on sexuality. A critical review of 15 years of research. Comput Hum Behav. 2009;25:1089–101.

17. Lim MS, Carrotte ER, Hellard ME. The impact of pornography on gender-based violence, sexual health and well-being. What do we know? J Epidemiol Community Health. 2016;70:3–5.
18. Laier C, Pawlikowski M, Pekal J, Schulte FP, Brand M. Cybersex addiction. Experienced sexual arousal when watching pornography and not real-life sexual contacts makes the difference. J Behav Addict. 2013;2:100–7.
19. Sutton KS, Stratton N, Pytyck J, Kolla NJ, Cantor JM. Patient characteristics by type of hypersexuality referral: a quantitative chart review of 115 consecutive male cases. J Sex Marital Ther. 2015;41:563–80.
20. Castellini G, Fanni E, Corona G, Maseroli E, Ricca V, Maggi M. Psychological, relational, and biological correlates of ego-dystonic masturbation in a clinical setting. Sex Med. 2016;4:e156–65.
21. Braithwaite SR, Coulson G, Keddington K, Fincham FD. The influence of pornography on sexual scripts among emerging adults in college. Arch Sex Behav. 2015;44:111–23.
22. Fisher WA, Kohut T, Di Gioacchino LA, Fedoroff P. Pornography, sex crime, and paraphilia. Curr Psychiatry Rep. 2013;15:362.
23. Park BY, Wilson G, Berger J, Christman M, Reina B, Bishop F, et al. Is Internet pornography causing sexual dysfunctions? A review with clinical reports. Behav Sci (Basel). 2016;6(3):17.
24. Jannini EA, Limoncin E, Ciocca G, Buehler S, Krychman M. Ethical aspects of sexual medicine. Internet, vibrators, and other sex aids: toys or therapeutic instruments? J Sex Med. 2012;9:2994–3001.
25. van Lankveld JJ. Internet-based interventions for women's sexual dysfunction. Curr Sex Health Rep. 2016;8:136–43.
26. van Lankveld JJ, Leusink P, van Diest S, Gijs L, Slob AK. Internet-based brief sex therapy for heterosexual men with sexual dysfunctions: a randomized controlled pilot trial. J Sex Med. 2009;6:2224–36.
27. Daneback K, Sevcikova A, Månsson SA, Ross MW. Outcomes of using the Internet for sexual purposes: fulfilment of sexual desires. Sex Health. 2013;10:26–31.
28. Weinberg MS, Williams CJ, Kleiner S, Irizarry Y. Pornography, normalization and empowerment. Arch Sex Behav. 2010;39:1389–401.
29. Scorolli C, Ghirlanda S, Enquist M, Zattoni S, Jannini EA. Relative prevalence of different fetishes. Int J Impot Res. 2007;19:432–7.
30. Naskar S, Victor R, Nath K, Sengupta C. "One level more:" a narrative review on internet gaming disorder. Ind Psychiatry J. 2016;25:145–54.
31. Palaus M, Marron EM, Viejo-Sobera R, Redolar-Ripoll D. Neural basis of video gaming: a systematic review. Front Hum Neurosci. 2017;11:248.
32. Tian M, Chen Q, Zhang Y, Du F, Hou H, Chao F, et al. PET imaging reveals brain functional changes in internet gaming disorder. Eur J Nucl Med Mol Imaging. 2014;41:1388–97.
33. Dong G, Li H, Wang L, Potenza MN. Cognitive control and reward/loss processing in Internet gaming disorder: results from a comparison with recreational Internet game-users. Eur Psychiatry. 2017;44:30–8.
34. Sansone A, Sansone M, Proietti M, Ciocca G, Lenzi A, Jannini EA, et al. Relationship between use of videogames and sexual health in adult males. J Sex Med. 2017;14:898–903.
35. Ducci F, Goldman D. The genetic basis of addictive disorders. Psychiatr Clin North Am. 2012;35:495–519.
36. Emmelkamp PM, David D, Beckers T, Muris P, Cuijpers P, Lutz W, et al. Advancing psychotherapy and evidence-based psychological interventions. Int J Methods Psychiatr Res. 2014;23:58–91.
37. Månsson KNT, Skagius Ruiz E, Gervind E, Dahlin M, Andersson G. Development and initial evaluation of an internet-based support system for face-to-face cognitive behavior therapy: a proof of concept study. J Med Internet Res. 2013;15:220–33.
38. Palmqvist B, Carlbring P, Andersson G. Internet-delivered treatments with or without therapist input: does the therapist factor have implications for efficacy and cost? Exp Rev Pharmacoecon Outcomes Res. 2007;7:291–7.

39. Andersson G, Titov N. Advantages and limitations of internet-based interventions for common mental disorders. World Psychiatry. 2014;13:4–11.
40. Cooper A, Scherer C, Mathy RM. Overcoming methodological concerns in the investigation of online sexual activities. Cyberpsychol Behav. 2001;4:437–47.
41. Griffin-Shelley E. The Internet and sexuality: a literature review 1983–2002. Sex Relation Ther. 2003;18:355–70.
42. Leiblum SR. Women, sex and the Internet. Sex Relation Ther. 2001;16:389–405.
43. Hall P. Online psychosexual therapy: a summary of pilot study findings. Sex Relation Ther. 2004;19:167–78.
44. Van Diest SL, Van Lankveld JJDM, Leusink PM, Slob AK, Gijs L. Sex therapy through the Internet for men with sexual dysfunctions: a pilot study. J Sex Marital Ther. 2007;33:115–33.
45. Abdo CH, Afif-Abdo J, Otani F, Machado AC. Sexual satisfaction among patients with erectile dysfunction treated with counseling, sildenafil, or both. J Sex Med. 2008;5:1720–6.
46. Strecher V. Internet methods for delivering behavioral and health-related interventions (eHealth). Annu Rev Clin Psychol. 2007;3:53–76.
47. McCabe MP, Price E, Piterman L, Lording D. Evaluation of an Internet-based psychological intervention for the treatment of erectile dysfunction. Int J Impot Res. 2008;20:324–30.
48. McCabe M, Price E. Internet-based psychological and oral medical treatment compared to psychological treatment alone for ED. J Sex Med. 2008;5:2338–46.
49. Hucker A, McCabe MP. An online, mindfulness-based, cognitive-behavioral therapy for female sexual difficulties: impact on relationship functioning. J Sex Marital Ther. 2014;40:561–76.
50. Hummel SB, van Lankveld JJ, Oldenburg HS, Hahn DE, Broomans E, Aaronson NK. Internet-based cognitive behavioral therapy for sexual dysfunctions in women treated for breast cancer: design of a multicenter, randomized controlled trial. BMC Cancer. 2015;15:321.
51. Jones LM, McCabe MP. The effectiveness of an Internet-based psychological treatment program for female sexual dysfunction. J Sex Med. 2011;8:2781–92.

Sexual Dysfunctions in Personality Disorders: Is the Personality Connected to the Sexual Dysfunctions?

16

Alberto Collazzoni, Giacomo Ciocca, Carmela Marucci, and Alessandro Rossi

16.1 Introduction

Personality disorders (PD) can be defined as a pattern of behavior, thoughts, and emotions that negatively affects the individual and interpersonal life, because PD patients tend to deviate markedly from the expectations of their own culture [1]. This pattern is pervasive and stable, and it begins during the late adolescence and the first adult age. The *Diagnostic and Statistical Manual of Mental Disorders* defines three specific personality disorder clusters [1]; the first (A), defined as "bizarre-eccentric" (paranoid, schizoid, and schizotypal disorders); the second (B), defined as "dramatic-unpredictable" (antisocial, borderline, histrionic, and narcissistic disorders); and the third (C), defined as "anxious-fearful" (avoidant, dependent, and obsessive-compulsive disorders). The disorder remains stable during the time and increases social, work, and interpersonal malfunctioning. These subdivisions were also, mostly, maintained and confirmed in the latest version of the DSM [2].

PD patients find difficulties in conducting and developing a normal and satisfactory interpersonal life, because they do not create and maintain adequate relationships. The importance of interpersonal functioning in personality disorders has also been underlined in the DSM-5 [2], because a healthy personality is also defined by two interpersonal skills, empathy for others and intimacy, that seem to

A. Collazzoni · C. Marucci · A. Rossi (✉)
Department of Biotechnological and Applied Clinical Sciences (DISCAB), University of L'Aquila, L'Aquila, Italy
e-mail: alessandro.rossi@univaq.it

G. Ciocca
Endocrinology and Sexual Medicine (ENDOSEX), Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*, Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_16

be less prevalent in PD patients than in healthy people [3]. An empathic person understands the experiences of others, the feelings, and motivation, and he/she could understand the consequences of their own actions on the lives of others. Instead the intimacy allows the person to create and maintain reciprocal and caring relationships [3]. These disturbed interpersonal characteristics may also influence the sexual functioning in PD patients negatively [4]. In fact the PD patients could experience various sexual difficulties, depending on the PD characteristics. However the role of personality characteristics in the etiology and maintenance of sexual dysfunctions has not been systematically studied [4]. In particular the study about which sexual dysfunctions are related to a specific PD has not been expanded in literature [4].

The authors' aim is to highlight the state of the art of the connection between PD and sexual dysfunctions, to better understand which PD have been studied in connection with sexual dysfunctions, trying to clarify the underlying mechanisms between PD characteristics and sexual dysfunctions. Moreover another aim is to better understand how the PD may influence the sexuality and also how the sexual dysfunctions may influence the personality characteristics, representing as maintaining factors for PD.

16.2 Method

A computerized search was performed to identify all relevant studies in PubMed with no precise starting date until March 2017. The following search terms were used in PubMed: "sexual dysfunction" AND "personality disorders." The search was limited to English-language publications and human samples, specifically regarding personality disorders. Inclusion criterion of studies for our analysis was as follows: (1) the link between sexual dysfunctions and personality disorders, both for DSM-IV and DSM-5. The previous criterion has been searched for in both females and males. The exclusion criteria were as follows: (1) review articles, (2) studies concerning characteristics of personality not connectable to personality disorders of DSM-IV and DSM-5, (3) studies concerning psychopathological symptoms of Axis I, DSM-IV, and (4) chemical, biological, and other field studies different from psychology and sexology. A total of 456 articles were retrieved from PubMed, by typing in the abovementioned keywords. Comparison of the retrieved titles identified 34 articles. Subsequently 22 articles were selected on the basis of the abstracts. Finally nine articles fully satisfied the criteria for the review (Fig. 16.1).

16.3 Results

The research produced a scarce number of papers about the relationship between personality disorders and sexual dysfunctions. The authors tried to report and comment on these results, starting from the personality disorder with more studies, following a descending order (Fig. 16.2). The summary of the main results is reported in Table 16.1.

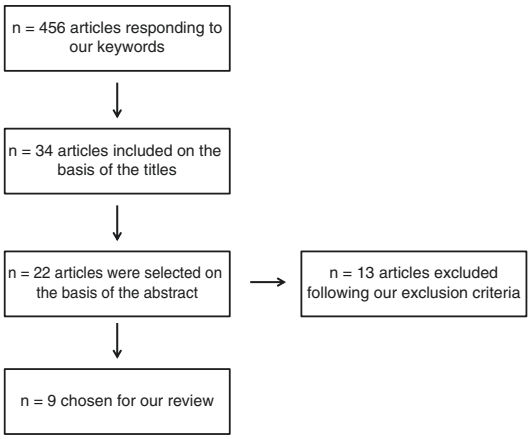

Fig. 16.1 The selection process for the articles in this review is shown. The first step ($n = 456$) is the result by keywords from "PubMed." The last step is the final choice of included and discussed articles

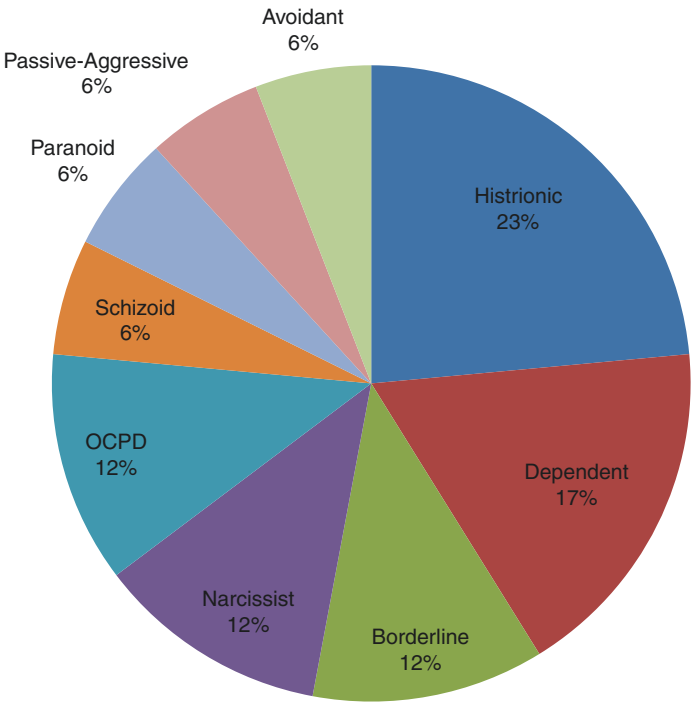

Fig. 16.2 Percentage of the frequencies of the studies about personality disorders and sexual dysfunctions respect to the total of the found studies

One study reported data about the morbidity between erectile deficit and psychiatric diagnosis [5]. This cross-sectional study, considering 103 patients between 20 and 76 years, with erectile dysfunction (ED), showed that 5.6% of the sample had a diagnosis of personality disorder. Unfortunately a consideration between the different personality disorders, connected to ED, was lacking in this study, preventing any consideration about this concern [5].

Table 16.1 Sexual dysfunctions in personality disorders: selection of experimental investigations until March 2017

Personality disorders	Main considerations	Sexual dysfunctions	
		Nature of study	Authors
No specification	The 5,6% of a sample, with erectile deficit, showed personality disorder diagnosis	Cross-sectional	Mallis et al. [5]
Histrionic	Histrionic women showed sexual abnormalities compared to a control group	Cross-sectional	Merskey and Trimble [8]
	Histrionic females showed inhibited sexual desire	Cross-sectional	Fagan et al. [7]
	As compared to the control group, women with histrionic personality were found to have significantly lower sexual assertiveness, greater sexual preoccupation, lower sexual desire, and greater orgasmic dysfunction	Cross-sectional	Apt and Hurlbert [6]
	Men, with higher histrionic/hysteric traits, showed higher androgenization and better sexual functioning	Retrospective	Bandini et al. [9]
Borderline	Borderline females showed inhibited orgasm, while males showed inhibited desire	Cross-sectional	Fagan et al. [7]
	Borderline females have more sexual impairments than healthy subjects. Moreover, BPD subjects, showing sexual traumatizations have more sexual inactivity than the others	Cross-sectional	Schulte-Herbrüggen et al. [10]
Narcissist	A group of women, with hypoactive sexual desire, showed higher narcissist characteristics than a control group	Cross-sectional	Hartmann et al. [11]
	Four narcissist male subjects showed inhibited sexual excitement disorder	Cross-sectional	Fagan et al. [7]
Dependent	In a group of women, with diagnosis of fibromyalgia, the association between dependent traits and sexual aversion and avoidance has been found	Cross-sectional	Kayhan et al. [14]
	Three men with dependent traits showed inhibited sexual excitement in a group of subjects with sexual dysfunctions	Cross-sectional	Fagan et al. [7]
	A woman, with dependent characteristics, also had inhibited sexual desire diagnosis	Cross-sectional	Fagan et al. [7]
Obsessive-compulsive	OCPD male showed inhibited sexual excitement and premature ejaculation, while both (males and females) showed inhibited orgasm	Cross-sectional	Fagan et al. [7]
	OCPD traits were the most diffused in a male sample with sexual dysfunctions	Cross-sectional	Krause et al. [13]
Avoidant	Avoidant traits are connected to sexual aversion and avoidant in a female group with fibromyalgia diagnosis	Cross-sectional	Kayhan et al. [14]

(continued)

Table 16.1 (continued)

Personality disorders	Main considerations	Sexual dysfunctions	
		Nature of study	Authors
Passive-aggressive	Women and men, with these personality traits, showed several sexual dysfunctions, as well as premature ejaculation and inhibited sexual desire	Cross-sectional	Fagan et al. [7]
Paranoid	Paranoid men showed inhibited sexual excitement, among a group of subjects with sexual dysfunctions	Cross-sectional	Fagan et al. [7]
Schizoid	A schizoid man reported dyspareunia typical among other personality disorder subjects with sexual dysfunctions	Cross-sectional	Fagan et al. [7]

The most studied personality disorder in connection with sexual dysfunction resulted to be the histrionic. It is characterized by a pattern of attention seeking, ego gratification research, manipulative behavior, and rapidly shifting emotions [2]. In an interesting cross-sectional study, a group of women with histrionic personality has been compared with a control group for several sexual domains [6]. The histrionic women have been found to have significantly lower sexual assertiveness, greater erotophobic attitudes toward sex, and greater marital dissatisfaction than the control subjects. Moreover, they showed greater sexual preoccupation, lower sexual desire, more sexual boredom, and greater orgasmic dysfunction. At the end they were more likely to enter into an extramarital affair than their counterparts [6]. These data confirmed two previous studies that underlined the inhibited sexual desire [7] and sexual abnormalities compared to a control group in histrionic women [8]. On the contrary, other scholars, in a large sample of men, attending an outpatient clinic for sexual dysfunction, found that subjects with higher levels of histrionic traits have higher androgenization and better sexual functioning [9]. This contraposition may be explained following an "evaluative" point of view. The histrionic traits could "directly" work for histrionic men, because they could improve the opportunities to have sex and then to procreate. On the contrary, the histrionic women may be in a psychological conflict, between the need to be protected and cared by a singular partner (a careful condition for the offspring, following an evaluative view) and the need to have ego gratification and more attention from more partners. This conflict may be crucial for the sexual and marital dissatisfaction of histrionic [6].

The borderline personality disorder (BPD) has also been deeply studied in connection with sexual dysfunctions. This result probably depends on the borderline characteristics in relationships, as well as instability, impulsivity, manipulation of others, fear of abandonment by loved ones, and the continuing alternation between extremes of idealization and devaluation of others [2].These characteristics may influence sexual functioning in BPD. With regard to this, a cross-sectional study expands on this topic, considering a comparison between BPD and healthy female subjects [10]. The results showed that BPD has significant lower points than healthy subjects in several sexual response phases (arousal, lubrication, orgasm, satisfaction,

and pain). These last data confirmed previous results about the inhibited orgasm in borderline women [7]. Schulte-Herbrüggen et al. [10] did not find, however, differences with healthy subjects in the "desire" domain. On the contrary a male borderline has been found with an inhibited sexual desire [7], in a cross-sectional study. It may be interesting to improve the knowledge about this sex difference in borderline personality disorders, with a large sample and different scales on personality characteristics. Nevertheless, this last data may confirm that BPD females are interested in sex, but they are not "actively" searching for sex, creating more personal dissatisfaction. This lack of sex activation in BPD is more present in sexually traumatized subjects than non-traumatized, suggesting that this sexual traumatization could "block" the personal sexual activity [10]. This inactivity is also related to major depressive symptoms and SSRI medication that could increase the inactivity.

The female hypoactive sexual desire is also problematic for another kind of cluster B disorder, e.g., the narcissist. In fact a cross-sectional study showed that a group of females with hypoactive sexual desire showed higher points of narcissism, as well as helpless self, derealization/depersonalization, basic potential of hope, smallness of self, negative body self, and social isolation (measured by the Narcissism Inventory, [11]). These data confirmed that some personality characteristics, concerning the body, the self-esteem, the hope, and the social life, could negatively influence the sexual life of a woman, lowering the sex desire [11]. Instead, four male narcissistic patients, among a sample of subjects with sexual dysfunctions, showed inhibited sexual excitement disorder [7]. Despite the low number of subjects, the connection between male narcissistic and inhibited sexual excitement may suggest that these subjects could suffer because they could connect their values and their self-esteem (e.g., the core of the narcissist psychopathology [2]) to the sexual performances. Consequently, the male narcissists, with inhibited sexual excitement, may avoid sexual occasions.

The obsessive-compulsive personality disorder (OCPD) is characterized by an enduring and pervasive maladaptive pattern of excessive perfectionism, order, and rigid control. This pattern may manifest through the cognitive, behavioral, and emotional ways [2], influencing, obviously, the interpersonal life. But how is sexuality influenced by OCPD traits? An interdisciplinary study focused the attention on the male sexual dysfunction, examining the Axis II of DSM-III [12] in connection with sexual dysfunction (desire, arousal, and orgasm or ejaculation disorders), in a sample of 25 subjects suffering from sexual dysfunction [13]. The study did not exactly report the connection between specific sexual dysfunctions and personality disorder traits, but the most diffused personality disorder was the OCD in the whole sample. This study, unfortunately, did not let to do hypothesis about the causal relationships between OCD personality and sexual dysfunctions [13]. Another study added information about this concern. In fact, among a sample of subjects with sexual dysfunctions, OCPD men showed inhibited sexual excitement and premature ejaculation, while both OCPD men and women showed inhibited orgasm [7]. All of the previous sexual dysfunctions may, hypothetical, be connected to the OCPD rigid control, but this study does not directly investigate this hypothesis.

The dependent disorder is characterized by a pattern of submissive behavior related to a need to be taken care of [2]. It is easily understandable that dependent women and men may have non-assertive behavior. This non-assertiveness may also be connected to the loss of their own sexual willingness, as may be connected to the inhibited sexual desire found in a woman with dependent diagnosis and to the inhibited sexual excitement in three men with the same diagnosis [7]. To confirm this thesis, the results of a study, concerning the personality disorder characteristics and sexual dysfunction in a sample of women with fibromyalgia, reported that dependent traits were connected to sexual aversion and avoidance [14].

The avoidant personality disorder shares the same characteristics with the dependent disorder of the previous study [14]. In fact, the avoidant may prefer to be submissive to the partner because she/he wants to avoid finding a new partner in a new social environment. For this reason the avoidant subject prefers to be non-assertive with their partner. This situation could be lived negatively because the avoidant could lose his sexual freedom and react with sexual aversion and avoidance [14].

Finally there are few results about the passive-aggressive, the paranoid, and the schizoid. All of them are present in Fagan's study [7].

The passive-aggressive, not considered in DSM-5 [2], is characterized by passive resistance to fulfilling routine social and occupational tasks, complains of being misunderstood and unappreciated by others, unreasonably criticizes and scorns authority, expresses envy and resentment toward those apparently more fortunate [1], and has been studied in connection with sexual dysfunctions [7]. This type of personality disorder is the most connected to sexual dysfunctions in men. In fact two men, with passive-aggressive diagnosis, showed inhibited sexual desire, and the same number showed inhibited sexual excitement and premature ejaculation. In the same way, the women showed inhibited sexual desire. These results may be explained on the basis of the passive-aggressive characteristics, because the continual alternating between hostile defiance and contrition may influence the sexual life, contributing to a lack of clarity about own intentions.

The last two considered personality disorders, in connection with sexual dysfunction, are paranoid and schizoid. In particular one paranoid man showed inhibited sexual excitement and one schizoid dyspareunia atypical. These two personality disorders, which appertain to the odd and eccentric behaviors [1], showed difficulty to have normal relationships, so that schizoid is completely not interested in creating intimate relationships, in some cases even real asexuality [15], and the paranoid is completely involved in their own jealous vicious circle [2]. These characteristics may influence the sexual approach of these two personality disorders.

Conclusion

The first result that has to be discussed is the paucity of the results. Following the selected criteria, only nine studies were able to be considered (see Fig. 16.1). Similar results have been found in a previous and "in press" review about the mating strategies and the sexual dysfunctions in personality disorders [16]. This lack of the results may also be connected to the nature of the considered phenomena and to the complexity to study them. In fact it is difficult to study and to

approach personality disorder patients, and it is more difficult to study a delicate and private problem such as sexual dysfunction.

The second result is that the nature of all studies is cross-sectional (only one is retrospective; see Table 16.1). This last data prevents any considerations about the hypothetical predictive relationship between sexual dysfunctions and personality disorder traits. What comes first? It is impossible to precisely determine. Moreover sexuality (and then also the dysfunctions) and personality traits evolve in all life and cross-sectional studies do not help to improve knowledge concerning it. Instead it is possible to hypothesize that personality disorder patients may suffer dramatically from sexual dysfunctions, more than the normal population, because most of them (e.g., narcissist, borderline, histrionic, dependent, etc.) focus their life on their relationship with others. On the other hand, sexual dysfunctions may increase some negative cognitive and behavior maintaining factors connected to the personality disorders, as well as the avoidance of sexual opportunities, the rumination about sexual performances, and the aggressiveness against humiliating partners for sexual "failures." The first implication for future studies is that more longitudinal (prospective and retrospective) studies have to be implemented from, at least, adolescence age to fully understand this relationship.

The third result that the study mostly considered [7] did not show a great number of subjects and did not suggest any connection between personality disorders and sexual dysfunctions. The second implication may be that the future study may associate sexual dysfunction assessments, with other personal and interpersonal factor assessment to better understand the "psychological" roots of sexual dysfunctions. In particular the use of validated and largely diffused assessments is requested.

In any case, the results show that the histrionic, borderline, and dependent disorders are the most studied in connection with sexual dysfunctions. This result, in the authors' opinion, depends on the "tragic-dramatic" characteristics of the histrionic and borderline subjects, organizing their lives and their personal values on the basis of the relationship. In fact both histrionic and borderline subjects "use" sex as a "strategy" for their interpersonal life (e.g., the sexual seduction in histrionic and the sexual impulsiveness and ambiguity of the borderline). In the same way, dependent disorder subjects may "use" sex to avoid being abandoned by their partner and then may become sexually non-assertive, contributing to the condition for live sexual dysfunctions.

Another interesting concern may be the depth of the relationship between OCPD and sexuality and, in particular, how the rigidity and the need for the respect of the precision of OCPD may influence the sexual life.

One limitation of this review is, surely, the consideration of the only psychological process connected to sexual dysfunction. In fact the biological process has not been considered, because the authors were mostly interested in the psychological profile connected to sexual dysfunctions in personality disorder subjects.

References

1. APA. In: Press AP, editor. Diagnostic and statistical manual of mental disorders, DSM-IV-TR. Washington, DC: American Psychiatric Association; 2000.
2. APA. In: Incorporated APP, editor. Diagnostic and statistical manual of mental disorders: DSM-5. Washington, DC: American Psychiatric Association; 2013.
3. Bell CC. Dynamic descriptions of personality disorder in the DSM-5. Virtual Mentor. 2013;15(10):857–9. https://doi.org/10.1001/virtualmentor.2013.15.10.stas1-1310.
4. Waldinger MD. Psychiatric disorders and sexual dysfunction. Handb Clin Neurol. 2015;130:469–89. https://doi.org/10.1016/B978-0-444-63247-0.00027-4.
5. Mallis D, Moysidis K, Nakopoulou E, Papaharitou S, Hatzimouratidis K, Hatzichristou D. Psychiatric morbidity is frequently undetected in patients with erectile dysfunction. J Urol. 2005;174(5):1913–6. https://doi.org/10.1097/01.ju.0000176746.73667.3c.
6. Apt C, Hurlbert DF. The sexual attitudes, behavior, and relationships of women with histrionic personality disorder. J Sex Marital Ther. 1994;20(2):125–33. https://doi.org/10.1080/00926239408403423.
7. Fagan PJ, Schmidt CW Jr, Wise TN, Derogatis LR. Sexual dysfunction and dual psychiatric diagnoses. Compr Psychiatry. 1988;29(3):278–84.
8. Merskey H, Trimble M. Personality, sexual adjustment, and brain lesions in patients with conversion symptoms. Am J Psychiatry. 1979;136(2):179–82. https://doi.org/10.1176/ajp.136.2.179.
9. Bandini E, Corona G, Ricca V, Fisher AD, Lotti F, Sforza A, Faravelli C, Forti G, Mannucci E, Maggi M. Hysterical traits are not from the uterus but from the testis: a study in men with sexual dysfunction. J Sex Med. 2009;6(8):2321–31. https://doi.org/10.1111/j.1743-6109.2009.01322.x.
10. Schulte-Herbrüggen O, Ahlers CJ, Kronsbein JM, Ruter A, Bahri S, Vater A, Roepke S. Impaired sexual function in patients with borderline personality disorder is determined by history of sexual abuse. J Sex Med. 2009;6(12):3356–63. https://doi.org/10.1111/j.1743-6109.2009.01422.x.
11. Hartmann U, Heiser K, Ruffer-Hesse C, Kloth G. Female sexual desire disorders: subtypes, classification, personality factors and new directions for treatment. World J Urol. 2002;20(2):79–88. https://doi.org/10.1007/s00345-002-0280-5.
12. APA. In: Washinton A, editor. Diagnostic and statistical manual of mental disorders. 3rd revised ed. Washington, DC: American Psychiatric Association; 1987.
13. Krause J, Herth T, Maier W, Steiger A, Schoneich S, Benkert O. An interdisciplinary study towards a multiaxial classification of male sexual dysfunction. Acta Psychiatr Scand. 1991;84(2):130–6.
14. Kayhan F, Kucuk A, Satan Y, Ilgun E, Arslan S, Ilik F. Sexual dysfunction, mood, anxiety, and personality disorders in female patients with fibromyalgia. Neuropsychiatr Dis Treat. 2016;12:349–55. https://doi.org/10.2147/NDT.S99160.
15. Brotto LA, Knudson G, Inskip J, Rhodes K, Erskine Y. Asexuality: a mixed-methods approach. Arch Sex Behav. 2010;39(3):599–618. https://doi.org/10.1007/s10508-008-9434-x.
16. Collazzoni A, Ciocca G, Limoncin E, Marucci C, Mollaioli D, Di Sante D, Di Lorenzo G, Niolu C, Siracusano A, Maggi M, Castellini G, Rossi A, Jannini EA. Mating strategies and sexual functioning in personality disorders: a comprehensive review of literature. Sex Med Rev. 2017;5:414–28. https://doi.org/10.1016/j.sxmr.2017.03.009.

Sexual Assistance for People Affected by Intellectual Disabilities

17

Erika Limoncin and Emmanuele A. Jannini

17.1 Introduction

Physical or mental disability may alter the way individuals express their sexuality and may profoundly change feelings about sex. However, disabilities do not necessarily destroy interest in sexual activity, and people with disabilities can frequently both experience and provide sexual pleasure. If people affected by disabilities are, at different levels, interested to express their sexuality and emotions, on the other hand, they can also be the object of desire of some people sexually aroused by the disability itself.

Social attitudes toward the sexuality of people affected by disabilities are changing, shifting the general opinion from a concept of handicapped people as asexual individuals or as potential sex offenders to a concept of disabled people having natural sexual needs and rights [1]. However, the contemporary social model of disability still pays attention to sexually related civil rights, such as the right to marriage, procreation, and protection against unconditional sterilization, rather than to the way in which people affected by disabilities can satisfy their sexual drives [2]. Despite the shift in opinion, the acceptance of a physical sexuality associated with individuals affected by an intellectual disability remains difficult. In fact, the topic of masturbation (which is often the only way for disabled individuals to satisfy their own sexual needs) is generally associated with the stereotypical idea of pathological masturbation performed in public places [3].

Based on this background, it is easy to understand how people affected by disabilities live their sexuality, which is often also compromised by limited opportunities to meet other people and by the difficulty in negotiating possible relationships

E. Limoncin (✉) · E. A. Jannini
Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
e-mail: erika.limoncin@gmail.com; eajannini@gmail.com

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*,
Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_17

and shared emotions. In this social context, sexual assistants may represent an option to satisfy sexual needs and to give these subjects, who otherwise may have little chance of being sexually active, the opportunity to improve their sexual health.

17.2 The Figure of the Sexual Assistant

The sexual assistant is in most cases a professional figure (www.proinfirmis.ch/it/home.html). In fact, many sexual assistants are trained in specific educational courses to approach in a professional way people with particular needs, such are people affected by physical and/or intellectual disabilities (www.swissinfo.ch/ita/oltre-l-handicap--il-diritto-alla-sessualità). This professional figure regularly works in some European countries and in few extra-European nations. In some countries, the National Health Service provides payment for the assistance.

Since the sexual assistance is socially often confounded with prostitution, the associations organizing educational courses distance themselves from aspects of prostitution by highlighting that the service is only for the kind of assistance given to people affected by disabilities. Specifically, the sexual assistance includes:

- Physical and emotional nearness: people affected by disabilities frequently complain about the absence of physical and emotional contact rather than the simple absence of sexual intercourse.
- Helping people affected by disabilities to discover, with caresses and massages, their own body.
- Teaching masturbation to people affected by disabilities.
- Since people affected by disabilities are often distressed by the dissatisfaction of their sexual needs, the sexual assistant has the duty to help the person with disability to express her/his negative emotions related to sexuality.
- Attention toward the disabled person's emotions expressed by nonverbal communication, especially in the case of people suffering from a stroke.
- Discussion about contraception and secure sexuality.
- Promotion of self-esteem.
- Teaching social interaction modalities (how to court someone, how to refuse an invite).

Sexual assistance is a service offered to people who are born with physical and/or intellectual disabilities or have developed a disability later in their lives (www.lovegiver.it). In the field of sexual assistance, professionals choose which kind of disability they will work with. Some sexual assistants work exclusively with physical or intellectual disability, while others choose to work with both physical and intellectual disabilities. In addition, the sexual assistants may specialize to work with heterosexual or with homosexual people affected by disabilities.

17.3 The Legal Status of Sexual Assistants

The professionally trained sexual assistant only has legitimate legal status in some countries, such as Australia, Denmark, Germany, Nederland, New Zeeland, Spain, and Tanzania. In Switzerland, a specific statute exists to protect this figure (www.swissinfo.ch/ita/oltre-l-handicap--il-diritto-alla-sessualità).

In Switzerland only individuals training as sexual assistants may work in this field. The sexual assistants have to also be engaged in another job (the primary occupation), and their parents have to be informed of the sexual assistance conducted in their "free time" (www.swissinfo.ch/ita/oltre-l-handicap--il-diritto-alla-sessualità).

In Australia, Denmark, and Tanzania, another regulation is in force: any person affected by disability who would benefit from sexual assistance may receive economic sustenance by the system. On the other hand, some European countries, such as Germany, make brothels available to people affected by disabilities, in which prostitutes dedicated to disabled individuals work.

One of the first European projects having the objective the sexual education of people affected by disabilities was developed in 2002 by the Swiss association "Pro Infirmis" [4]. However, since this project was considered by sponsors as a promotion of prostitution, many grants were removed. Afterward, another Swiss association, "Fachstelle Behinderung & Sexualität" (FABS) of Basilea, directed by a psychotherapist, organized two courses for sexual assistants in 2004 and 2007 (www.swissinfo.ch/ita/oltre-l-handicap--il-diritto-alla-sessualità). The first course trained ten sexual assistants, six women and four men. These sexual assistants were prepared to address the sexuality of people affected by disabilities, thanks to the contribution of a sexologist. After this course, the number of individuals participating in trainings for sexual assistants increased considerably.

17.4 The Training for Sexual Assistance

Generally, individuals training as sexual assistants are young women and men between 35 and 55 years old. Many of these people mostly work in the field of physiotherapy, reflexology, medical corps, and alternative medical science. The fundamental prerequisite required for future sexual assistants is the motivation to discover herself/himself, in order to individuate and control their own psychological limits.

The training for sexual assistants is structured in a series of weekly gatherings for the duration of 6 months. At the beginning, the person learns about disability, the difficulties of disabled people, the relationship with parents of disabled people, and the legal aspects of sexual assistance. After this general introduction, the training aims to go deeper into the matter of sexual assistance. In particular, the participants have to reflect and learn about the following issues:

- Their own motivation to work as a sexual assistant: any person interested in working as sexual assistant has to reflect on her/his motivations to do this type of

job. In addition, the participants have to consider the significance of sexual work with people affected by disabilities and their attitude toward disability.

- The relationship with their body and mind: the future sexual assistants have to reflect on the relationship with their body image. In addition, the participants are driven to get in contact with their negative emotions in order to learn to verbally express them.
- The sexual assistant's role: the participant has to define the objective of sexual assistance. In particular, the person has to learn how to approach disabled people's sexual needs.
- Self-esteem level: the future sexual assistant needs to have good self-esteem in order to sustain disabled people's frustration and anger.
- Any future sexual assistant has to reflect on her/his sexual history (i.e., received sexual education, first sexual experiences, and current relationship with sexuality in general).
- The nurturing of meditation: any person willing to work as a sexual assistant has to learn to meditate and to relax her/his body and mind in order to approach in an equivalent manner the person affected by disability.
- The nurturing of intuition: the sexual assistant has to develop her/his intuition in order to understand in advance the difficulties of such situation and to engage the problems.
- The study of massage technique.

After this preparation course, the participant is considered sufficiently educated and authorized to work with disabled people's sexual needs. Any sexual assistant specifies which kind of disability and sexual orientation they will work with and what are the limits of her/his intervention. The first contact occurs by telephone with the person affected by physical disability or with the parents of the person affected by disability, in case of intellectual disability. The encounters take place in the disabled person's home or in hotels. The duration of any encounter is 1 h, in which the client is requested to pay a fee. Generally, the sexual assistant adopts the limit to not have a full sexual intercourse with the client. This limit is established because the clients affected by disabilities often develop a different sensibility of her/his body and a different way to live sexually. Many people affected by paraplegia become particularly sensitive in other body areas, which may assume an erotic value.

17.5 The Italian Point of View on Sexual Assistance

Although the figure of sexual assistant established itself in some European countries, in Italy this professional figure still meets contrasting opinions. On the one hand, people affected by disabilities highlight the utility of this service for the satisfaction of their sexual and emotional needs. On the other hand, other people consider this service a form of legalized prostitution and, for this reason, believe that this service should be not approved.

However, the difficulties regarding the legalization of sexual assistance in Italy are also due to many other ethical and cultural aspects, still attributable to a common belief that a person affected by disability is an asexual person.

In the wake of other European countries, in 2013 Bologna, a city of central Italy, organized the first professional course for sexual assistants (www.lovegiver.it). Despite the bureaucratic difficulties, this service has been initiated, and many requests for participation have been received. A future objective will be to make a normative change in order to permit the recognition of this professional figure.

17.6 Literature Evidence

People affected by disabilities have limited opportunities to meet other people and to negotiate possible relationships. Hence, also their sexuality is often compromised. A possibility to satisfy sexual needs and to improve sexual health is given by sexual assistance. However, since this professional figure is legalized only in some world's countries, people affected by disabilities wishing sexual intercourse would require often the help of local prostitutes, who are for the most part untrained with respect to the special needs of men and women with disabilities. The legalization of sexual assistance by the side of some countries is maybe difficult due to a presence of a social paradigm, which presupposes that people affected by disabilities are asexual individuals not needing sexual satisfaction. If it is true, it is also possible that among people sexually attracted by disabilities, there are some persons who will have a stable relationship, or a simply sexual intercourse, together with other persons, who will take advantage of people affected by disabilities. The sexual attraction toward disabilities is known as *devotism* [4] as the sexual attraction to people affected by disabilities that identify themselves as *devotees* (Box 17.1). Surely, people referring to be sexually attracted to disability per sé, rather than by the person as a whole, might adopt some potentially dangerous behaviors for people affected by disabilities (Fig. 17.1). For this reason, devotees showing characteristics

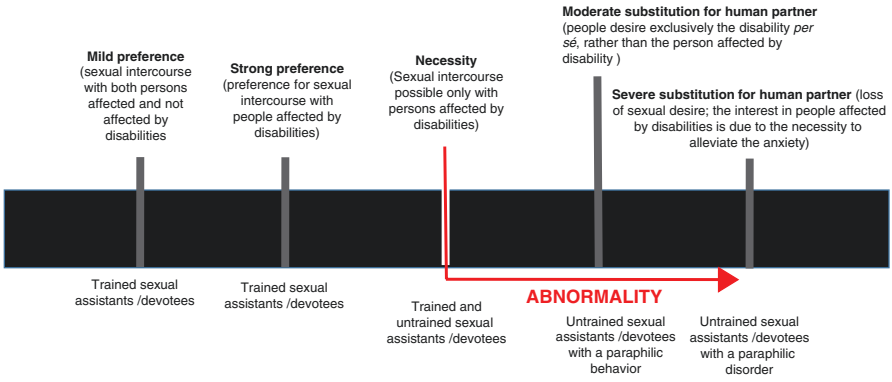

Fig. 17.1 Levels of sexual preference for disability

suggestive of a paraphilic behavior might represent a kind of sexual predators. It is also possible that among sexual assistants, there are some people that behind the professional role choose to work in this field prevalently to satisfy an own sexual interest.

Although the sexuality of people affected by disabilities is a cumbersome social dilemma, which deserves a particular attention, due to the possible risk factors to which these persons may be exposed, there is only one study in literature investigating the characteristics of untrained and trained sexual assistants [5]. The aim of this study was to evaluate whether trained and untrained sexual assistants had characteristics suggestive of a paraphilic behavior, interpreted as a dangerous behavior, and whether sexual assistance may configure as a prostitution rather than as a social service (Fig. 17.1). A first interesting finding of this study was the identification, within the sexual assistant groups, of subjects with an atypical sexual interest in disability [4]. These behavioral aspects were found especially in the group of untrained sexual assistants, who also report experiencing distress over their sexual interest more often than trained subjects do. This information may suggest that untrained sexual assistants experience more sexual attraction to disability and that they perceive this attraction as a non-conventional or atypical sexual interest.

The existence of subjects with an atypical sexual interest (paraphilic behavior) among sexual assistants may have significant consequences. It is well known that people affected by physical and/or by intellectual disabilities may be subject to physical and/or sexual violence [6, 7]. In this case, personnel involved in sexual assistance might commit violence against disabled people. This aspect was investigated asking sexual assistants what they found most attractive about people affected by disabilities. Some attractions may look like as expressions of sadistic behavior, such as the attraction to disabled people's impotence and obedience or the possibility of satisfying the assistants' own sexual fantasies.

Data of this study also highlight how trained sexual assistants have, in a greater measure than untrained sexual assistants, "noble" motivations to make this kind of job. In particular, trained sexual assistants referred more frequently to help individuals affected by disabilities to live their sexual needs. On the other hand, untrained sexual assistants prevalently work as prostitutes, hence without any trained skill to approach disabled people. As hypothesized, the vast majority of trained sexual assistants exhibit behaviors resembling prostitution less frequently than untrained sexual assistants do.

The professional figures involved in this activity must have a strong sense of altruism and a great open-mindedness. Sexual assistance may be understood as prostitution when the remunerative or commercial character is coupled with specific sexual activities, such as sexual intercourse, oral sex, masturbatory activities, or any activity which involves physical contact and the use of one person by another for her/his sexual satisfaction: in other words, when the exchange becomes "the provision of sexual services for money or its equivalent" [8, 9]. It has been found that both trained and untrained sexual assistants provide their services under remunerative or commercial conditions. However, the main difference between these two

groups lies in the activities carried out. The trained group mainly provides massage therapy, including erotic massage, and discussion about sexuality, contraception, and the appropriate use of sex toys. These activities cannot be strictly considered prostitution. A minority of trained assistants refer to being engaged in masturbatory activities or sexual intercourse that, on the contrary, may be considered activities more typical of prostitution. However, these activities are mainly provided outside of their job as sexual assistants. In contrast, untrained sexual assistants provide sexual services such as oral sex, masturbation, or sexual intercourse much more frequently. These findings seem to confirm that when sexual assistants are trained and carefully selected by specialized organizations, they provide services and activities that do not resemble prostitution.

Conclusion

Evidences suggest that trained sexual assistants present rarely the characteristics suggestive of a paraphilic behavior, nor that of the average sex worker. Hence, the sexual assistance provides a way for people affected by disabilities to take back the right to explore their sexuality in a safeguarded setting. This goal is more easily reached if sexual assistants are trained and carefully selected by specialized educational agencies.

Box 17.1 Devotism

Devotism is a term used by people that are sexually attracted to physical and/or intellectual disabilities to define themselves. *Devotism* comprises also two additional subgroups, including people who want to become amputees and refer to themselves as wannabes and able-bodied people who act as if they have a disability by using assistive devices (pretenders) [10–12]. These subgroups do not always have clear boundaries; therefore, a devotee can interchange her/his condition with that of a wannabe or a pretender.

The term *devotism* may be understood as a "jargon" term. In fact, this term was created expressly by individuals attracted to disabilities, who would identify on websites, utilizing the abbreviation "DEV." However, albeit in a limited manner, the term is also referenced in scientific literature. Other scientifically sounding terms, such as *acrotomophilia* [11, 12], refer to subjects attracted to amputation alone and do not include all kinds of disabilities. In addition to other sub-categories, Money created the term *abasiophilia* [13] to individuate people expressly attracted to individuals utilizing surgical devices (e.g., wheelchairs, crutches, and orthopedic corsets).

To date, many etiological hypotheses on *devotism* have been developed. However, none of the explanations seem to be really convincing.

At first, it could be assumed that a person affected by disability is an, due to her/his condition, "easy prey" for able-bodied individuals having social difficulties. In this manner the able-bodied person, probably having an

avoidant-insecure attachment style, could think that a disabled individual might represent the unique individual able to love them. But this interpretation does not consider that people affected by disabilities could be interesting beyond their disabled body or mind.

A second interpretation, based on an etiological theory, might interpret vice versa that people sexually attracted to disabilities are individuals with a secure attachment style, since people affected by disabilities might represent a "difficult prey" due to the presence of good genes. In fact, the "theory of handicap" [14, 15] explains how exaggerated traits, which jeopardize animals' lives, are interpreted as a guarantee of good genes. In the light of this theory, the person also affected by disability, having an "exaggerated trait," may be seen as a bearer of good genes.

Other theories have been developed to comprehend the motivations of people to choose as a sexual object an individual affected by disabilities.

In the field of psychiatry, it was supposed that devotees develop this kind of sexual attraction to satisfy a paraphilic need. In particular, it was assumed that these individuals might have a sadistic or a masochistic need. In the first case, the sexual satisfaction might be due to a need to subjugate the disabled person, while in the second case, the devotee might interpret herself/himself as a person not worthy to be loved by an able-bodied person. In addition, it was also hypothesized that devotees, publicly accompanying a person with disability, would satisfy their exhibitionistic need. Finally, it was that devotees simply adopt a fetishistic behavior, because in this paraphilic behavior or disorder, the person is sexually aroused by parts of a body/object rather than by an individual.

Other explanation theories were developed in the field of sexology.

The influence of imprinting is also proposed since devotees state that their sexual attraction toward disability begun after an influential meeting in childhood with a person affected by disability [16], on the basis of which individuals behaved in peculiar ways if they were exposed to abnormal environments during a specific moment in childhood.

Another theory refers to the concept of a lovemap developed by Money [11, 12]. Based on the lovemap, a devotee may have this sexual attraction because encountering someone with a disability during childhood has attended to parental approval. Therefore, the child has learned that people with disabilities should be respected and admired, triggering in the child the sexual attraction.

Similarities may be also seen with Munchausen syndrome [17]. In this case, since illness and disability may lead up to compassion and benefits, a devotee might project her/his desire to be disabled onto others, activating the sexual attraction toward disability.

The sexuality of people affected by physical and/or intellectual disabilities is still far of being universally accepted. In fact, it is common to consider

people affected by disabilities as asexual individuals. However, both disabled people and their parents know that sexual needs naturally emerge, as in able-bodied persons, during prepuberty and puberty. The central problem concerns how and with whom people affected by disabilities can satisfy their sexual needs. Often the sexualized behaviors become the object of educational programs aiming to limit the execution of these behaviors in a social context. Conversely, few educational programs aim to teach people affected by disabilities how to address their sexual needs in a private context, alone or with a partner.

Nowadays we can observe a shift from a medical model to a social model for the physical and psychological care of disabled people. This change entails the shift of attention from the deficit aspects to the social (and sexual) needs of people affected by disabilities. It remains, however, a tendency to consider the sexuality of disabled people as an argument engaged by way of contraception or protection against unconditional sterilization [2].

Basing on these premises, the first consideration about the sexual interest on the side of devotees toward people affected by disabilities is that devotees may represent a fundamental resource for disabled people to realize their sexuality. However, some considerations should be made about this claim. Firstly, it is not correct to think that people affected by disabilities can be loved exclusively for their disability. Secondly, it is not obvious that devotees are interested in creating and maintaining healthy long-lasting relationships with people affected by disabilities. In fact, some studies [4, 18] provide evidence that devotees are more inclined to have exclusively sexual intercourse rather than long-lasting relationships with people affected by disabilities. In addition, studies have shown [4] how a subpopulation of devotees and untrained sexual assistants show a sexual interest toward a part of the disabled body rather than toward a disabled person as an individual. For this reason, a paraphilic behavior might turn, in some cases, elicit risks for people affected by disabilities.

References

1. Bigby C. Known well by no-one: trends in the informal social networks of middle-aged and older people with intellectual disability five years after moving to the community. J Intellect Develop Disabil. 2008;33:148–57.
2. Rembis MA. Beyond the binary: rethinking the social model of disabled sexuality. Sex Disabil. 2010;28:51–60.
3. Lockhart K, Guerin S, Shanahan S, Coyle K. Defining “sexualized challenging behavior” in adults with intellectual disabilities. J Policy Pract Intel. 2009;6:293–301.
4. Limoncin E, Carta R, Gravina GL, Carosa E, Ciocca G, Di Sante S, Isidori AM, Lenzi A, Jannini EA. The sexual attraction toward disabilities: a preliminary internet-based study. Int J Impot Res. 2014;26(2):51–4.

5. Limoncin E, Galli D, Ciocca G, Gravina GL, Carosa E, Mollaioli D, Lenzi A, Jannini EA. The psychosexual profile of sexual assistants: an internet-based explorative study. PLoS One. 2014;9(2):e98413.
6. Kuosmanen J, Starke M. Women and men with intellectual disabilities who sell or trade sex: voices from the professionals. J Soc Work Disabil Rehabil. 2011;10:129–49.
7. Cellerino A, Jannini EA. Male reproductive physiology as a sexually selected handicap? Erectile dysfunction is correlated with general health and health prognosis and may have evolved as a marker of poor phenotypic quality. Med Hypotheses. 2005;65:179–84.
8. Harcourt C, Donovan B. The many faces of sex work. Sex Transm Infect. 2005;81:201–6.
9. Patton M. In: Park N, editor. Qualitative evaluation and research methods. California: Sage; 1990.
10. Bruno RL. Devotees, pretenders and wannabes: two cases of factitious disability disorder. Sex Disabil. 1997;15:243–60.
11. Money J, Simcoe KW. Acrotomophilia, sex and disability: new concepts and case report. Sex Disabil. 1986;7:43–50.
12. Money J. Lovemaps: clinical concepts of sexual/erotic health and pathology, paraphilia, and gender transposition in childhood, adolescence, and maturity. Irvington, NY: Ardent Media; 1986.
13. Money J. Paraphilia in females fixation on amputation and lameness; two personal accounts. J Psychol Hum Sex. 1990;3:165–72.
14. Zahavi A. Mate selection-a selection for a handicap. J Theor Biol. 1975;53:205–14.
15. Zahavi A. Sexual selection: badges and signals. Trends Ecol Evol. 1992;7(1):30.
16. Hess EJ. Imprinting: early experience and the developmental psychobiology of attachment. New York: D Van Nostrand; 1973.
17. Money J. The Adam principle. Buffalo: Prometheus; 1993.
18. Aguilera RJ. Disability and delight: staring back at the devotee community. Sex Disabil. 2000;18:255–61.

Paraphilia and Paraphilic Disorders

18

Giorgio Di Lorenzo, Fiorela Gorea, Lucia Longo, and Michele Ribolsi

18.1 Introduction

Throughout human history, the term perversion has been used to indicate an aberration or a deviation from norm, based on moral, theological, and juridical principles. During the nineteenth century, much attention was centered on the study of perversions and the causes that originate them, finding a connection between sexual desire and sexual instinct, thought of as a reproductive instinct. Perversions were so considered as functional diseases of this same instinct and, in particular, as though characterized by a deviation of this compulsion from its natural purpose.

In the very famous *Psychopathia Sexualis*, Krafft-Ebing (a German neurologist and psychiatrist) proposed once again the idea of perversion as a functional deviation of sexual instinct, sustaining that these perversions should be considered part of an individual's personality in a psychological level [1]. So, if the term perverse was once utilized to describe individuals that turned themselves toward "evil," Krafft-Ebing changed this preconceived idea when defining perversions as different ways of being a person, paying particular attention to the differences between simple immorality and criminal sexual offenses. After that, Freud [2] characterized children's sexuality as

G. Di Lorenzo (✉) · L. Longo
Psychiatry and Clinical Psychology Unit, Department of Neurosciences, Fondazione Policlinico Tor Vergata, Rome, Italy

Psychiatry, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
e-mail: di.lorenzo@med.uniroma2.it

F. Gorea
Psychiatry, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

University of "Our Lady of Good Counsel", Tirana, Albania

M. Ribolsi
Psychiatry, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*, Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_18

being perverse, saying it's composed of a series of partial sexual instincts, every one of which originates in one of the very erogenous zones of a child's body, pursuing its finalities. He explained the pathological mechanism that conducts toward said perversions as a combination of fixation in one of the psychosexual phases of development during the first 5 or 6 years of life and a regression of said fixation in the beginning of puberty. Freud then continued by considering fixation a direct result of the denial of a traumatic sexual experience, in particular of the castration anxiety that accompanies a child's oedipal desire. He, in fact, sustained that every perversion should be interpreted as an attempt of reassurance and defense against castration anxiety. Freud even coined the term by combining the Greek words for "along the side" (para) and "love" (philia). Then it was Kinsey [3] who demonstrated, in his statistical reports on human sexual behavior, that most of these so-called perversions weren't necessarily pathological. In particular, he revealed that many deviant sexual practices were in fact quite common in the American population, and since many perversions could be also found among animals, Kinsey affirmed that there was no sense in considering said perversions a violation of natural norms. According to Aggrawal, who published in 2008 one of the most complete lists of paraphilias with hundreds of descriptions [4], because sexual arousal may arise from any type of human experience, unusual sexual attractions that are sometimes so harmless don't arrive to the clinicians' attention and consequently may remain unknown. Table 18.1 lists the most common paraphilias [4, 5].

In current times, it is quite obvious that paraphilias are conditions characterized by atypical sexual interests that can affect individuals of all kinds of orientations and even different gender identities. There are no more prejudices against homosexuality or transsexuality, which were once thought as the bases of various deviant sexual behaviors. In this same way of thinking and differently from the fourth edition [6], the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) doesn't consider paraphilia per se a mental disorder [7]. Only the actual experiencing of distress referred to by the patient and/or a possible damage to other people completes the diagnosis of a paraphilic disorder. A paraphilic disorder is in fact a paraphilia that causes distress or compromises the sexual functioning of the individual or a paraphilia whose fulfillment implicates personal damage or risk of damage to others [8]. Also the 11th revision of the *International Classification of Diseases for Mortality and Morbidity Statistics* (ICD-11), which will be officially published by the World Health Organization (WHO) during 2018 [9], is in line with the changes on paraphilia that appeared in DSM-5. In fact, whereas in Chapter V "Mental and Behavioral Disorders" of the 10th revision of *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) [10] paraphilias are classified as "Disorders of sexual preference" in the group of "Disorders of adult personality and behavior" [11], in Sect. 18.6 "Mental, Behavioural or Neurodevelopmental Disorders" of ICD-11, paraphilias are classified as "paraphilic disorders" and are emphasized for the diagnosis to have the presence of the marked subjective distress generated by atypical sexual thinking, desires, and conducts [12].

Paraphilia, one of the most misunderstood categories of diagnosis in psychiatry, is frequently associated with sexual offense; the two concepts do not necessarily go hand in hand. Sometimes the sexual offense may be directed toward people affected by disabilities [13, 14].

Table 18.1 Description of most common paraphilias [4, 5]

Paraphilia classification		Description
Paraphilias of act		
Visual	Exhibitionism	Arousal from exposing genitals in public; rare in females
	Voyeurism	Sexual arousal achieved by watching sexual acts (e.g., coitus or naked person)
	Icolagnia	Arousal from contemplation of, or contact with, sculptures or pictures; a form of voyeurism
	Candaulism	Sexual practice or fantasy in which a man (usually) exposes his female partner, or images of her, to other people for their voyeuristic pleasure
	Sadism	Sexual arousal resulting from causing mental or physical suffering to another person
	Capnolagnia	Arousal from watching others smoke
Acoustic	Mixacusi	Sexual arousal resulting from listening in on couples engaged in sexual intercourse
	Pornolalia	Sexual arousal results from the use of naughty/vulgar words during coitus
	Sadism	Sexual arousal resulting from causing mental or physical suffering to another person
Olfactory	Coprolagnia	The thought, sight, or smell of excrement causing pleasurable sexual sensation
	Urophilia	Sexual arousal achieved from smelling urine (usually urinating on one's partner)
	Osphresiolagnia	Erotic excitement produced by odors; an inordinate love of smells
	Mysophilia	Sexual pleasure resulting from interaction with dirt or garbage or in general getting sexually aroused by a dirty/filthy person or object
	Sadism	Sexual arousal resulting from causing mental or physical suffering to another person
Gustatory	Coprourofagia	Sexual arousal results from eating/drinking feces and urine
	Picacism	Sexual pleasure resulting from eating body parts (e.g., nails, hair, sperm, etc.)
	Dermatofagia	Sexual pleasure deriving from eating parts of the skin
	Vampirism	Seeing, feeling, or ingesting blood while having the illusion of being a vampire
	Cannibalism	Sexual pleasure achieved by eating human flesh
	Sadism	Sexual arousal resulting from causing mental or physical suffering to another person
	Lactofilia	Sexual arousal derives from observing a woman while nursing a child or more specifically from being nursed by the woman (ingesting a woman's milk during the lactation period)

(continued)

Table 18.1 (continued)

Paraphilia classification		Description
Tactile	Frotteurism	Rubbing genitalia against strangers to achieve sexual arousal/pleasure
	Copro-/urolagnia	Arousal from feces/urine or being defecated/urinated on
	Mysophilia	Sexual pleasure resulting from interaction with dirt or garbage or generally getting sexually aroused by dirty/filthy people or objects
	Automasochism	Inflicting intense pain on one's own body; different from masochism in which a partner inflicts pain. Also sometimes referred to as autosadism
	Masochism	Sexual pleasure derived from being abused mentally or physically or from being humiliated by another person
	Sadomasochism	Giving or receiving sexual pleasure from acts involving the receipt or infliction of pain or humiliation
	Sadism	Sexual arousal resulting from causing mental or physical suffering to another person
Of incorporation	Catheterophilia	Arousal from use of catheters
	Klismaphilia	Sexual arousal is achieved in receiving or administering enemas (or both)
	Impalement	Sexual arousal is achieved by being impaled or impaling others
	Injection-mania	Sexual arousal derives from injections (being injected or injecting others)
Paraphilias of object		
Age	Pedophilia	Sexual activity with prepubescent children; most common paraphilia
	Gerontophilia	Arousal from a partner from an older generation
Parentage	Incest	Sexual activity between family members or close relatives
	Narcissism	Sexual arousal results from watching oneself or images of one's self
Species	Zoophilia/bestiality	Sexual intercourse with animals
	Zoorape	Sexual pleasure achieved through the rape of animals
	Necrozoophilia/necrobestiality	Arousal from having sex with dead animals
	Dendrophilia	Sexually attracted to/sexually aroused by trees
Vitality	Iconolagny	Arousal from pictures or statues of nude people
	Necrophilia	Sexual pleasure deriving from intercourse with corpses
	Necrosadism	Arousal from mutilating a corpse
	Sexual homicide	Arousal is achieved by killing the victim with the only purpose of sexual pleasure/intercourse
Imagination	Spectrophilia	Sexual attraction to ghosts or sexual arousal from images in mirrors, as well as the phenomenon of sexual encounters between ghosts and humans
	Demonphilia	Sexual attraction for demons
	Religious possession	Sexual fantasies of religious nature (e.g., sexual intercourse with angels, saints, etc.)
Fetishism	All of the above	Sexual arousal with inanimate objects or part(s) of a person's body

Actually, many people that commit a sexual offense do not meet the criteria for a sexual paraphilia, and likewise, people diagnosed with a paraphilia may never have committed a sexual crime.

Paraphilias are deviant sexual behaviors characterized by experiencing, over a period of at least 6 months, "recurrent, intense sexually arousing fantasies, sexual urges, or behaviors" that mostly involve inhuman objects or non-consenting partners. To be able to make a paraphilia diagnosis, a necessary criterion is that the person must have actually acted on these urges or is at least remarkably distressed by them. Some people may have only had the urges or the fantasies of a paraphilia but have never acted upon them.

18.2 The Specific Paraphilias

18.2.1 Criminal Sex Offending Behaviors

18.2.1.1 Exhibitionism

Exhibitionism generally involves men displaying their genitalia to unsuspecting strangers so that they will be shocked or (in the paraphilic's fantasy) sexually interested. There may or may not be masturbation involved during or immediately following the act. In later years, the exhibition of your own body and genitalia has seen a significant increase thanks to the new technologies and social networks, giving life to the much-discussed phenomenon of cybersex and sexting. In this context exhibitionism as a deviant behavior is classified as a paraphilia when it involves non-consenting spectators. The diagnosis is not usually made when a man is arrested for "public indecency" and his penile exposures are motivated to arrange homosexual contact in a public place generally unseen by heterosexuals (penile display in parks is one way to make anonymous contact). In the latest version of the DSM, a distinction is made between exhibitionism and exhibitionist disorder; exhibitionism is about fantasies, impulses, and/or behaviors that have as a principal purpose the exposure of genitalia to an unsuspecting stranger. This generally doesn't provoke a significant discomfort to the subject and is expression of a non-pathological sexual preference. In case of the exhibitionistic disorder, these same fantasies, impulses, and/or behaviors provoke, for a period of at least 6 months, a clinically significant discomfort in one or more functional areas (familiar, social, occupational, etc.). Even in the absence of discomfort, the clinician is obliged to make a diagnosis of exhibitionistic disorder in case the subject has acted on his impulses with three different non-consenting persons in different occasions. This phenomenon is characterized by an early onset (generally before 18), by a process of selection of the victim (usually of the opposite sex) and from the acting on sexual autoerotic behavior and in situations that there is always the risk of being found out. The intent of this behavior is to generate reactions of surprise, fear, and embarrassment. Being seen and the victim's reaction are what are deemed as exciting by the paraphilic. The unsuspecting stranger represents the spectator/witness necessary for the exhibitionist to enact his fantasy. This is generally associated with masturbation, and usually there is no intention of making any physical contact with the victim.

18.2.1.2 Pedophilia

The etymology of the term pedophilia originates from Greek, παις pais (child/boy) and φιλι′α philia (love), and signifies love for children/boys. This love doesn't have a sexual prerogative, differently from the word pederastia, a combination of the words pais ed. érastes (lover), whose etymological root derives from the word Eros and stands for a sexualized love. In the general public's eye and in the clinical language, the word pedophile stands for an adult that shows erotic/sexual attraction toward prepubescent children, even though it doesn't exactly correspond to the etymological definition.

Pedophilia is the most socially repudiated of the paraphilias. Pedophiles are usually men who sexually prefer children or prepubescent adolescents. They are grouped into categories depending upon their erotic preferences for boys or girls and for infant, young, or pubertal children. Society thinks of a pedophile as a person who sexually targets a minor and therefore prosecutes under this term adults who target adolescents. Some pedophiles have highly age- and sex-specific tastes; others are less discriminating.

Even though there have been some changes in the definition from an edition to another, the DSM and the ICD have always classified pedophilia in the lists of mental and sexual disorders. Psychiatry has in this way always confirmed the pathological nature of this behavior, because an individual that has surpassed puberty can't desire a sexual relationship with a prepubescent child since their sensualities result as being incompatible. For this reason, no society, no culture, or even period can ever declassify it from being a pathological condition. It's also fundamental that pedophilia should not be confused with or be considered synonymous with child abuse. The diagnosis of any paraphilia including pedophilia requires recurrent, intense sexually arousing fantasies, sexual urges, or behaviors involving sexual activity with a prepubescent child or children over a period of at least 6 months, so the disorder should not be expected to be present in every person who is guilty of child molestation. Some cases of child abuse can occur over a shorter time interval and result from the combination of several factors like deteriorated marriages, sexual deprivation, sociopathy, and substance abuse. Child molestation, whether paraphilic or not, is a crime, however.

18.2.1.3 Voyeurism

Although the act of being sexually aroused by watching erotic scenes is becoming more diffused and accepted, voyeurism is recognized as a paraphilia when it involves unsuspecting people. In the latest version of the DSM, this paraphilia is classified, together with exhibitionism and frotteurism, in the courtship disorders, since it's usual in love advances to touch or look at a lover's body to experience pleasure or even show your own nudity for your lover's pleasure, even though this happens in a consensual relationship between adults. The fifth edition of the DSM distinguishes voyeurism as an expression of a sexual preference that is not necessarily pathological. It is described as a condition of recurrent and intense sexual arousal manifested through fantasies, desires, and/or behaviors that derive from observing unsuspecting people naked, during the act of getting naked, or engaged in sexual activities. This situation doesn't involve discomfort for the subject who experiences it and so is not necessarily in need of a clinical intervention. In the voyeuristic disorder, these fantasies and behaviors cause a significant clinical discomfort or a

dysfunction of social and occupational areas for a period of at least 6 months. Another element that directs the clinician toward the diagnosis of a voyeuristic disorder is a behavior that is damaging to other unsuspecting people while they're naked, engaged in sexual intercourse, etc.

Voyeurism circles around the concept of "power unbalancing": the paraphilic exercises an indirect control over the stranger; the unsuspecting victim goes through his/her intimate activities while spied by the peeping tom, who gets on a higher power level through "watching without being seen." Men whose sexual life consists of watching homosexual or heterosexual videos in sexual bookstores occasionally come to psychiatric attention after being charged with a crime following a police raid. The voyeurs who are more problematic for society are those who watch women through windows or break into their dwellings for this purpose. Some of these crimes result in rape or nonsexual violence, but many are motivated by pure voyeuristic intent (which is subtly aggressive).

18.2.1.4 Sexual Sadism

According to the latest version of the DSM, to make a diagnosis of sexual sadism disorder, the presence of intense and recurrent sexual arousal that manifests itself through fantasies, desires, or behaviors closely connected to the physical or psychological sufferance of another person is necessary. The individual has to also take act of these fantasies on another non-consenting person, or in alternative, these sexual desires or fantasies need to cause a significant clinical discomfort or a functional impairment in a social or occupational sphere.

While rape may occur in extreme cases of sadism, paraphilic sadism is correlated with only a minority of rape cases. It usually happens in cases where the rapist uses prior erotic scripts that involve a partner's fear, pain, humiliation, and suffering. Rapists, whether paraphilic or not, are dangerous men who show antisocial behaviors that make them generally unresponsive to psychiatric treatments. Most commonly sexual sadism is found among individuals who enjoy sadomasochistic sexual practices, unrelated to them enjoying either the dominant or the submissive role or even exclusively like to be controlling and pain or fear inducing. Many murderers (have long been recognized) have a need to torture their victims prior to killing them, showing thus a sadistic nature.

18.2.1.5 Frotteurism

Frotteurism is a sexual paraphilic behavior that an individual, usually male, experiences through a strong and intense compulsion where they feel the need to touch and rub against non-consenting persons. From the clinical description that Krafft-Ebing made in 1862 [1] until today, frotteurism has been classified in at least three categories: frottage, toucherism, and grabbage. Individuals that prefer to rub their genitals (covered) on the body of an unsuspecting victim are classified in frottage, others that prefer to rub parts of their own body on the body of an unknown unsuspecting victim are classified in toucherism, and those that act "attacking" a person from behind and grabbing parts of their body usually associated with intimacy (breasts-hips-genitals) enter in the grabbage category.

The location where it occurs is usually public. The frotteur chooses carefully the places where he can act on his erotic/sexual desires in full freedom. Manifestations,

public events, concerts, buses, and metropolitans are the usual surroundings where the frotteur can easily fool the victim, getting lost inside the crowd. This permits him to act undisturbed and to especially experience physical contact with the victim without causing any particular physical harm. The frotteur is rarely aggressive and usually doesn't act like a typical sex offender.

18.2.1.6 Stalking

Although stalking is not classified as a paraphilia in the DSM, it is surely one of the most worrying of the latest criminalized erotic preoccupations. Forensic psychiatry has defined various motivations for arrested stalkers, like a gradual transition that changes a romantic preoccupation with the victim to a violent one. It is a particularly serious condition since not rarely murder occurs. Considered to be a behavior that is produced by the deterioration of an already compromised mind but not necessarily a paraphilic one, stalking is not rarely correlated with sexual sadism.

18.2.2 Non-criminal Forms of Paraphilia

18.2.2.1 Fetishism

Fetishism is described as a form of recurrent and intense sexual arousal from either the use of nonliving objects or a highly specific focus on non-genital body parts. Fetishism has a range of manifestations that vary from *infantilism*, where the individual dresses up in diapers and pretends to be a baby, to the far more common use of a female undergarment for arousal purposes.

It came to attention that fetishism is often combined with masochistic fantasies and acts: a man that gets excited only when a woman wears a certain type of shoe (generally high heels), usually wants that said woman walk all over him with these same shoes, etc. Often the fetish involves unpleasant or degrading sensations (e.g., female socks need to be filthy and stinky). It may occur that fetishism is associated with a transvestic disorder, meaning men that like to dress up as women.

Lately there has been some criticism regarding what is to be considered a fetish and what not. Some psychiatrists sustain that not everything considered different by our rigid norms needs to be called a fetish. In our culture some body parts (like breasts, butts, lips, etc.) and garments (like panties, miniskirts, bras, etc.) are considered normal and so they are legitimized, while other body parts and garments are not and so get cataloged as pathological only because our dominant erotic culture doesn't consider them erogenous. It needs to be clarified though that in most fetishism disorders the garment that is considered the main attraction is so even when isolated from the female body. The use of objects to play out erotic fantasies, such as vibrators or dildos, is not to be considered a fetish.

18.2.2.2 Sexual Masochism

Sexual masochism disorder is characterized by an intense recurrent sexual arousal that manifests itself through fantasies, desires, or behaviors consisting in the need of being humiliated, bound, beaten, tied, or made to suffer in a way or another. To be

considered clinically relevant, said fantasies or sexual behaviors need to persist for a period of at least 6 months and cause a significant discomfort in one of the important spheres of a person's life (social, occupational, etc.). Frequent practices are bonding, genital tying, cigarette burning, biting on various body parts, autoflagellation, and anal stimulation with dildos, etc.

It is diagnosed over a range of behaviors from the need to nearly asphyxiate oneself to the request to be spanked by the partner in order to be excited. It may be the most commonly acknowledged form of female paraphilia, although it is still more common among men. Sadists and masochists sometimes find one another and work out an arrangement to act out their fantasies and occasionally reverse roles.

18.2.2.3 Transvestic Disorder

The concept of cross-dressing, which is the basis of the transvestic disorder, has always rendered the description of this paraphilia very complex and contradictory. In literature transvestic disorder and transvestic fetishism were considered synonymous or just simply variations of one another, but the fifth edition of the DSM classified it as a specific paraphilia saying it is characterized by a discomfort the individual experiences that is relieved only by his acting out his fantasies usually consisting in cross-dressing.

It's fundamental understanding the various shades of cross-dressing that are individualized and interpreted on the basis of three elements of sexual identity (gender identity, gender expression, and sexual orientation); these are observed inside a continuum that goes from the androgynous, to the gender mimic (drag queen or drag king), on the transvestic homosexual, to transgender, until what is the maximum expression of the difficult integration of the physical and psychical identity that is gender dysphoria.

The transvestic disorder is a paraphilic disorder where an individual, despite his gender identity, gender expression, and sexual orientation, has sexual fantasies and arousal patterns only when cross-dressing. Usually this disorder is referred to exclusively by the male gender. These men can get aroused even by simply wearing an article of female clothing or lingerie or by putting an act of a real gender transformation that implies not only clothing in general but also jewelry, bags, various accessories, makeup, and wigs.

Recent researches have shown that 88% of the men suffering from transvestic disorder have a heterosexual orientation and that they're mostly engaged in stable intimate relationships.

18.2.2.4 Paraphilia Not Otherwise Specified

There are numerous other sexually deviant fantasies or behaviors that do not fit any of the paraphilic categories described here or variations that do not meet the full criteria. The diagnosis of paraphilia not otherwise specified can be given in these situations, including such examples as telephone scatologia (obscene phone calls), necrophilia (if not part of a sexually sadistic diagnosis), partialism (exclusive focus on part of the body), zoophilia (animals), coprophilia (feces), klismaphilia (enemas), and urophilia (urine). Sometimes the act of rape would fit in this category if another paraphilia such as sadism did not fit the particular case.

18.3 Epidemiology

Paraphilias rarely cause personal distress, and individuals with these disorders usually come for treatment pressured by their partners or the authorities. Thus, there are few data on the prevalence or course of many of these disorders.

Pedophilia affects about 1% of the male population [15]. As pedophilia is the paraphilia most shown from media [16], it is not surprising that most research on the prevalence of pedophilia involves samples of individuals in forensic contexts. Consequently, there is nothing known about the ways to live with that sexual interest without causing damage [16].

Notwithstanding the potential for reporting bias, paraphilic disorder is mainly a male disorder at 90–99% of cases, except for masochism where female prevalence may be higher [17].

Scientifically sound information about unusual paraphilia is very scarce [15]. Acts of frotteurism and exhibitionism are frequent, but the number of perpetrators seems to be much smaller [18]. In fact, through the victim self-reports, the lifetime victimization rates have been estimated ranging from 33 to 52% for women [18].

18.4 Etiopathophysiology

The etiology of paraphilias is still unknown. Several hypotheses, including psychological and biological elements, have been postulated to give an explanation for the generation of complex emotional, cognitive, and behavioral phenomena present in paraphilias.

Since Krafft-Ebing and Freud's initial theories [1, 2] a number of psychological explanations about the development of paraphilias have been presented. Table 18.2

Table 18.2 Psychological theories of paraphilia and child molestation

	Theory	Description
Paraphilia	Castration anxiety [2]	A severe castration anxiety during the child's development makes for a substitution of the mother with a symbolic object
	Anxiety over arousal to the mother	The anxiety leads to the development of "safe" sexual practices/behaviors with inappropriate sexual partners (pedophilia, zoophilia) or through the absence of a real sexual contact (exhibitionism and voyeurism)
	Cognitive distortions [19]	Distortions in thinking, or thinking errors, provide a way for an individual to give himself or herself permission to engage in inappropriate or deviant sexual behaviors (it is all right to have sex with a child as long as the child agrees; watching a woman through a window as she undresses does not cause her any harm)
	Childhood abuse/ humiliation [20]	The paraphilia develops as an attempt to master or recreate early childhood abuse
	Acceptance of unrepressed infantile sexual fantasies [21]	The deviant sexual behavior is an alternative to neurotic development

Table 18.2 (continued)

	Theory	Description
Child molestation	Four preconditions model [22]	According to this theory, there are four underlying factors involved in child molestation. Specifically, emotional congruence (they find sex with children to be emotionally satisfying), inappropriate sexual arousal (they find their deviant behavior sexually arousing), inability to meet their sexual needs in a socially appropriate way (blockage), and disinhibition (they are able to behave in ways contrary to social norms)
	Quadripartite model [23]	This model identified physiological sexual arousal, cognitive distortions that justify sex with children, personality problems, and affective dyscontrol as the main components of child abuse
	The integrated theory [24]	It proposed that individuals who engage in sexual activity with children during their own childhood go through development adverse events. During puberty, their sexual fantasies may involve scripts that include aggression and sex. These youths may have a lack of self-regulation skills and social skills and may experience negative states that increase the probability of their engagement in inappropriate sexual behavior
	The pathways model [25]	There are multiple pathways that lead to behavior involving the sexual abuse of a child. Each one of the pathways involves a set of dysfunctional psychological mechanisms that constitute vulnerability factors that are influenced by distal and proximal factors including environmental, cultural, and biological events
	The integrated theory of sexual offending (ITSO) and integrated theory of sexual reoffending (ITSR) [26, 27]	Two integrated models explain the onset, development, and maintenance of sexual offending behavior and reoffending. It examines factors that affect the developing brain and its neuropsychological functioning like genetic variations, neurobiology, evolution, and ecological factors (personal circumstances and physical environment)
	Cognitive distortions [28]	Child sex offenders' cognitive distortions, including impairment of social cognition abilities, are complex neuropsychological and behavioral phenomena, composed of several and distinct cognitive components
	The social disorganization theory [29]	This theory considers elements of social disorganization (economic and social disadvantage, community cohesion, and population ((in)stability) as potential predictors of child sexual abuse

lists and briefly describes the most common psychological theories that have been postulated for the development of paraphilias [2, 19–29].

Some studies show how paraphilias and paraphilic disorders, as complex multifactorial phenomena, are correlated with genetics [30], life stress events [31], neurotransmitters, and endocrinological factors. Focusing on forensic samples, there is also evidence of a correlation between paraphilia and aggression [15]. Table 18.3 lists some biological factors associated with paraphilias.

Table 18.3 Biological factors implicated in etiopathophysiology of paraphilias

	Research findings
Genetics	– *Altered dopamine receptor genes* – *Altered COMT gene* – *Altered DAT gene* – *Altered serotonin transporter gene* – *Altered serotonin receptor type 2A gene* – *Altered MAO gene* – *Altered tryptophan hydroxylase 2 gene* – *Altered BDNF gene* – Altered androgen receptor gene
Endocrinological modifications	– Prenatal androgen exposure – Testosterone – Hypothalamic-pituitary function – Prolactin levels
Neurotransmitter disbalance	– *Low serotonergic inhibition* – *High dopaminergic excitation*
Neuropsychological alterations	
General neuropsychological dysfunctions	– Lower total IQ – Lower levels of academic achievement – Lower job capacity
Specific neuropsychological dysfunctions	– Verbal word fluency – Verbal and spatial working memory – Attention – Executive functioning
Structural brain alterations	– *Volume reduction of amygdala and hypothalamus* – *Limbic system (including temporal lobe)* – *Frontal abnormalities* – Lower gray matter volume of the dorsomedial prefrontal and anterior cingulated cortex

In italic are incoherent results

Among the most replicated findings in subjects with paraphilic behaviors and paraphilic disorders, we find the presence of life events (particularly those stressful events that occurred during childhood, including sexual abuse), a number of head injuries (before of 13 years), lower intelligence quotient (IQ), shorter stature, higher rates of left-handedness (sinistrality), and altered D2:D4 ratio.

As showed in Table 18.3, several genes have been associated with paraphilias. However, no specific gene seems to be linked to paraphilias supporting the theories that paraphilic behavior is at least an expression of polygenic combination or the results of gene(s) × environmental factor(s) interaction(s). A recent study of paraphilic sexual offenders (pedophilic child molesters and rapists) and controls showed no association between a history of sexual offense and the distribution of genotypes or alleles of dopamine receptor genes (DRD1, DRD2, DRD4), catechol-*O*-methyltransferase gene (COMT), dopamine transporter gene (DAT), serotonin transporter gene (SLC6A4), serotonin type 2A receptor gene (5HTR2A), tryptophan hydroxylase 2 gene (TPH2), monoamine oxidase A gene (MAOA), and brain-derived neurotrophic factor gene (BDNF) [32].

Androgen receptors and their numerous mechanisms can be implicated in sexuality and paraphilia in every aspect of sexual behavior—not only autonomic

functions but also emotional, motivational, and cognitive aspects. Inappropriate sexual arousal has been also hypothesized to be generated by abnormal circulating levels of androgens. Furthermore, testosterone participates in excitatory and inhibitory processes of sexual functions by modulating the activity of mainly dopaminergic neurotransmitter systems [33]. Not only testosterone but also some other endocrinological and neurochemical parameters could be disturbed in pedophilic patients and child molesters; these include changes in hypothalamic-pituitary function, prolactin levels, and dopaminergic or serotonergic functions [34].

A relation was also found between prenatal androgen exposure and sinistrality in pedophilic men with a history of sex offences against children [31]. Furthermore, the prenatal testosterone exposure influences the D2:D4 ratio, but the data are equivocal, and no firm conclusions have been drawn regarding the absolute relation between hand preference and D2:D4 [31].

General and specific neuropsychological functions result altered in paraphilias, particularly in those individuals affected by pedophilia. In their meta-analysis, Cantor et al. showed the association between sexual offending and lower IQ (ranging between 90 and 95), particularly in the adult sexual offender sample; moreover, they demonstrated a significant correlation between IQ level and victims' age (lower IQs, lower (child/adolescent) victims' age) [35]. Joyal et al. found a significant impairment of executive functions among people with sexual deviance: they showed impaired verbal skills, with deficit in verbal fluency and in verbal processing and memory [36]. Moreover, a different cognitive profile was also observed in the sex offenders [37]. Performances in higher-order executive function tasks were lower in sex offenders against children than those of sex offenders against adults; except for lower scores in verbal fluency and inhibition, sex offenders against adults showed cognitive performances similar to those of non-sex offenders [37].

Among pedophilic men, Sucky et al. found that those with sex offences against children are characterized by a low processing speed, that appears not as a slow/deliberate response style but as a fundamental neurocognitive weakness. This constitutive impairment of perception processing and information integration supports a general neuronal processing deficit in pedophilic sex offenders against children, providing, moreover, an additional contribution to the neurodevelopmental etiological hypothesis of pedophilia [38].

From a German multi-side research project on the neural mechanisms underlying pedophilia and sex offences against children (called NeMUP; http://www.nemup.de/), Massau et al. [39] evaluated the executive functioning in pedophiles with and without a history of sex offences against children, child molesters without pedophilia and non-offending controls. Pedophiles with or without a history of sex offences against children show a worsened response inhibition ability. However, only non-pedophilic offenders showed additionally disabled strategy use ability. Moreover, they found that those performances were affected by age: only in pedophiles, response inhibition worsened with age, while age-related deficits in set-shifting abilities were restricted to non-pedophilic subjects.

Literature shows brain abnormalities in individuals with pedophilia [40]. A recent study from the German research network NeMUP [41] suggests that child sex offenses in pedophilia rather than pedophilia alone are associated with gray

matter anomalies and thus shed new light on the results of previous studies on this topic. In fact, although no difference in the relative gray matter volume of the brain was specifically associated with pedophilia, the statistical parametric maps show a significant child sex offending-related pattern of above *vs*. below the "normal" gray matter volume in the right temporal pole, whereas non-offending pedophiles exhibit larger volumes than offending pedophiles. Furthermore, the results of this study show that the lower gray matter volume of the dorsomedial prefrontal or anterior cingulate cortex was associated with a higher risk of reoffending in pedophilic child molesters [41].

Sartorius et al. [42] reported that, during a functional magnetic resonance imaging (fMRI) paradigm of sexually non-explicit images, in respect to control, male subjects with pedophilia showed an abnormally increased amygdala activation profile for children pictures rather than adult ones. These findings support the hypothesis that an increased emotional arousal for children relative to adults is present in pedophilia. A review of brain alterations in pedophilia [43] shows that case studies of men who have committed sex offences against children implicate frontal and temporal abnormalities that may be associated with impaired impulse inhibition. Moreover, structural neuroimaging investigations show volume reductions in pedophilic men. Although the findings have been heterogeneous, smaller amygdala volume has been replicated repeatedly [43].

Sexual sadists, relative to non-sadists, showed greater amygdala activation when viewing pain pictures. Sexual sadists, but not non-sadists, showed a positive correlation between pain severity ratings and activity in the anterior insula [44].

Nevertheless, functional neuroimaging has not been able to support the association of pedophilic behavior with frontal lobe disorder [45]. However, structural brain modifications observed in pedophilia have been suggested to affect brain networks for sexual stimulus processing through impaired functional connectivity, which may account for atypical sexual arousal patterns as well as prevalent affective symptoms and neuropsychological deficits of subjects affected by pedophilia [46].

Massau et al. [47], in a study on fMRI of pedophilic men and healthy controls, showed the presence of neural correlates of moral judgment in pedophilia. In particular, they showed that scenarios depicting sex offences against children compared to those depicting adults were associated with higher patterns of activation in the left temporoparietal junction (TPJ) and left posterior insular cortex, the posterior cingulate gyrus, as well as the precuneus in controls relative to pedophiles and vice versa. Moreover, the lack of association between brain activation and behavioral responses in pedophiles seems to suggest a biased response pattern or dissected implicit valuation processes. Kargel et al. [48], in an fMRI study of pedophiles with and without history of hands-on sex offences against children as well as healthy non-offending controls, found the presence of neuronal correlates. Compared to offending pedophiles, non-offending pedophiles exhibited superior inhibitory control as reflected by the significantly lower rate of commission error, inhibition-related activation in the left posterior cingulate and the left superior frontal cortex that distinguished between offending and non-offending pedophiles, while no significant differences were found between pedophiles and healthy controls. The

authors concluded that heightened inhibition-related recruitment of these areas as well as decreased amount of commission errors is related to better inhibitory control in pedophiles who successfully avoid committing hands-on sex offences against children [48].

For medical personnel's differential diagnosis process, it is important to be aware of the fact that paraphilias sometimes also emerge during neurodegenerative disorders such as Parkinson's disease, in some cases as a side effect of treatment [15]. Also, some neurological diseases based on dysfunctions of limbic structures (including amygdalae, hippocampi, and temporal lobes) may determinate hypersexuality (such as the case of Klüver-Bucy syndrome) or paraphilic behaviors (such as the case of temporal lobe seizures or tumors). Moreover, paraphilias have been associated with the presence of other psychiatric disorders; however, it is not yet clear if this comorbidity has etiopathophysiological implications.

18.5 Methods for Diagnosing Paraphilia and Paraphilic Disorders

The most important method for ascertaining the phenotype of sexual preference is the clinical exploration [31]. In this process, it is possible to assess the sexual preference structure in detail including the differentiation between specific paraphilia and paraphilic disorders. The Tanner stages have proven useful for the exploration of sexual preference [31] and are an essential component of the diagnostic procedure of treatment and research programs [49]. These five stages describe the process of physiological maturing by focusing on the development of the secondary sex characteristics from stage 1 (prepubescent) to stage 5 (adult) [50]. The Tanner stage 1 concerns the prepubescent developmental phase, displaying a complete lack of secondary sex characteristics showing no facial or pubic hair, no penile or scrotal enlargement in males, and no breast development or pubic hair growth in females. Tanner stage 2 corresponds to the onset of breast budding in females and testicular enlargement in males. Tanner stage 3 depicts the breast and areola development in females, continued testicular growth, and initial penile lengthening in males. Tanner stage 4 corresponds to increased breast and areola growth and initial separation from surrounding breast tissue in females, while in males, testicular volume increases, scrotum darkens, and penile elongation continues. Tanner stage 5 represents full maturity, complete breast development, and separation from surrounding breast tissue in females, full penile growth and scrotum darkness and testicular volume in males, and full pubic hair coverage in both [50].

Phallometry has long been the "gold standard" in assessing sexual preferences, but other methods have been developed as the viewing time paradigm (measuring the length of time a participant spends looking at specific images as an indicator for sexual preference) [51] and the eye tracking and pupil dilation [52]. These methods have not yet been used in the sexual age preference measurement of pedophiles though [31], but seem to be promising nevertheless.

18.6 Treatment

Sadly, the therapy for paraphilia has scarcely been expound upon, since it's very rare that those suffering from it decide to seek help from a therapist, unless they are caught in the act or someone has forced them to do so. Even in these cases the patient is very rarely motivated or cooperative, very similar in some ways to a drug addict. Also, there is quite a difference between paraphilic disorders that imply a crime and those who don't.

Four general approaches are employed to treat paraphilias and they are typically multimodal in application.

18.6.1 Evaluation Only

Evaluation only is applied when it is concluded that the paraphilia is benign (does not imply a risk for society) and the patient could be resistant to other therapeutic approaches and does not suffer greatly in terms of social functioning. These patients are often men with private paraphilic sexual pleasures, like telephone sex with a masochistic scenario, etc.

18.6.2 Psychotherapy

Psychotherapy for paraphilia can consist in changing, at least temporarily, the erotic script of a patient, even though there is great controversy about the ability of criminal paraphilic minds to be changed. Over the years, all treatments have tended to strongly resemble cognitive behavioral interventions, showing to be very useful in diminishing paraphilic intensifications and gradually teaching these patients better management techniques of the situations that have triggered their acting out. Treatments often consist in attempts of interrupting the paraphilic arousal through pairing masturbatory excitement with aversive imagery or aversive stimuli, social skills training, assertiveness training, and confrontation with the rationalizations that are used to minimize awareness of the victims of sexual crimes and marital therapy.

The self-help movement has created 12-step programs for sexual addictions, and these interventions are usually conducted in group therapy during a period of at least 6 months (generally two encounters every week); the intervention comprehends five modules, each one of which has a variable number of sessions.

Recent evaluation of psychological treatment for adolescent sexual offenders found cognitive behavioral therapy (CBT) and multisystemic therapy (MST) were favorable though randomized studies were sparse, CBT augmented with family therapy was promising, and results for psychosocial education were unconvincing [17].

Although the counseling and psychotherapy for patients with pedophilia are often a core part of prevention strategies, motivation among healthcare professionals to work with this group is low [53].

18.6.3 Medications

The main purpose of the medical treatment of paraphilias consists in reducing the relapse of sex offences and the eventual distress that accompanies said behavior. As reported by various authors, only incarceration is not sufficient to reduce the risk of reiteration, and so the treatment of sexual felons diagnosed with paraphilia needs to aim at preventing sexual violence and reducing the risk to potential victims. The heterogeneity of paraphilia makes it necessary for the medical treatment to be global, where several options of treatment need to be integrated and the therapy needs to be individualized and adaptable to the diverse necessities of the paraphilic subject.

The treatment modalities of the medical therapy in use for paraphilic disorders are divided in essentially two categories:

- Chemical castration
- Pharmacotherapy

The pharmacological intervention aims to significantly reduce or entirely eliminate desire or sexual function with the purpose of controlling fantasies and paraphilic behavior.

In the 1980s, depomedroxyprogesterone was first used to treat men who were constantly masturbating, seeking out dangerous sexual outlets, or committing sex crimes. The drug injection and oral formulation often though enabled these men to work, study, or participate in activities that were previously beyond them because of concentration or attention difficulties. Currently, gonadotrophin-releasing blockers such as leuprolide acetate are sometimes used for this purpose, with possible side effects that are similar to oral depomedroxyprogesterone.

Occasionally, through the years, many drugs were used to reduce the level of sexual arousal: lithium, antidepressants, antipsychotics, and anticonvulsants. No randomized studies have been able to document the real efficiency in case of paraphilic sexual offenders, and the level of scientific evidence is quite mediocre.

These days, the use of SSRIs for the treatment of paraphilic disorders has become the standard of care [54]: in fact, SSRIs can impair libido, orgasm, and ejaculation via their activation of the 5HT2 receptors [55]. Current available data on the use of SSRIs in the treatment of paraphilic disorders are limited. The most studied SSRIs for paraphilic disorders are fluoxetine and sertraline, which have demonstrated efficacy in reducing fantasies and paraphilic behaviors in pedophilia, exhibitionism, voyeurism, and fetishism [56].

Current meta-analyses are, however, still skeptical about the actual effectiveness of these pharmacological agents [57–59].

The mainstay of treatment of paraphilic disorders, especially in sexual offending populations, has been antiandrogen agents. Reductions in testosterone result in reductions of libido, erection, sperm count, and masturbation frequency, which explain why testosterone has become a primary target in the treatment of paraphilic disorders [60].

Antiandrogen treatment is currently offered to sex offenders in many countries as an additional strategy alongside psychotherapy [15]. After cessation of chemical castration, the kinetics of serum testosterone recovery vary with treatment duration [61]. Although chemical castration is not to be considered the preferred paraphilia treatment for obvious ethical reasons, in some cases, such as mental retardation, the administration of antiandrogen medication may be used as an alternative therapeutic method [62]. Because of the coincidence of Parkinson's disease and compulsive sexual behavior, the potential case of an individual with Parkinson's disease and pedophilia is an example of an ethical treatment dilemma. In this case, administering an effective treatment to an individual may have an unwanted side effect of impulse control impairment, with the consequence of potential harm to others [15].

18.6.4 External Controls

Sexual advantage-taking may be stopped by making these deviant behaviors known to most people in the paraphilic's life. The doctor's staff should be told, and the family and the neighbors can be notified of these behaviors. This concept of "external control" is taken over by the judicial system when sex crimes are highly repugnant or heinous. The offender is removed from society for the protection of the public.

Psychiatrists, though, need to acknowledge the limitations of the various therapeutic approaches, since these sexual acting outs can still continue during therapy without the therapist being aware of it. The more violent and destructive the paraphilic behavior is to others, the less the therapist should risk by seeking an ambulatory treatment. Unfortunately, besides a few forensic mental hospitals and occasion prisons, there are limited treatment programs for sex offenders, be they paraphilic or not. Since paraphilias occur in patients with other psychiatric comorbidities, the psychiatrist needs to remain vigilant by choosing a comprehensive treatment program and should not lose sight of the paraphilia just because depressive or obsessive-compulsive symptoms are improved.

References

1. Von Krafft-Ebing R. Psychopathia sexualis. Stuttgart: Verlag Von Ferdinand Enke; 1886.
2. Freud S. Three essays on the theory of sexuality. In: Strachey J, editor. The standard edition of the complete psychological works of Sigmund Freud. London: Hogarth; 1960.
3. Kinsey A, Pomeroy W, Martin C, Gebhard P. Sexual behavior in the human female. Philadelphia: Saunders; 1953.
4. Aggrawal A. Forensic and medico-legal aspects of sexual crimes and unusual sexual practices. Boca Raton: CRC; 2008.
5. Limoncin E, Solano C. Parafilie e disturbi parafilici – Introduzione alle parafilie. In: Jannini EA, Lenzi A, Maggi M, editors. Sessuologia medica. Trattato di psicosessuologia, medicina della sessualità e salute della coppia. Milan: Edra; 2017.
6. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 2000.

7. American Psychiatric Association. Paraphilic disorders. In: Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013. p. 685–705.
8. Beech AR, Miner MH, Thornton D. Paraphilias in the DSM-5. Annu Rev Clin Psychol. 2016;12(1):383–406. https://doi.org/10.1146/annurev-clinpsy-021815-093330.
9. World Health Organization. International statistical classification of diseases – for mortality and morbidity statistics (ICD-11-MMS). Geneva: World Health Organization (WHO); 2018. http://www.who.int/classifications/icd/revision/en/. Accessed 10 Jan 2018.
10. World Health Organization. The ICD-10 chapter V: classification of mental and behavioural disorders. International statistical classification of diseases and related health problems, 10th revision (ICD-10). Geneva: World Health Organization (WHO); 1992.
11. World Health Organization. F65 Disorders of sexual preference. In: ICD-10 Version 2016. http://apps.who.int/classifications/icd10/browse/2016/en-/F65. Accessed 10 Jan 2018.
12. World Health Organization. Paraphilic disorders. In: ICD-11 Beta draft (mortality and morbidity statistics). https://icd.who.int/dev11/l-m/en-/http%3a%2f%2fid.who.int%2ficd%2fentity%2f2110604642. Accessed 10 Jan 2018.
13. Limoncin E, Carta R, Gravina GL, Carosa E, Ciocca G, Di Sante S, et al. The sexual attraction toward disabilities: a preliminary internet-based study. Int J Impot Res. 2014;26(2):51–4. https://doi.org/10.1038/ijir.2013.34.
14. Limoncin E, Galli D, Ciocca G, Gravina GL, Carosa E, Mollaioli D, et al. The psychosexual profile of sexual assistants: an internet-based explorative study. PLoS One. 2014;9(2):e98413. https://doi.org/10.1371/journal.pone.0098413.
15. Konrad N, Welke J, Opitz-Welke A. Paraphilias. Curr Opin Psychiatry. 2015;28(6):440–4. https://doi.org/10.1097/yco.0000000000000202.
16. Gross M. Paraphilia or perversion? Curr Biol. 2014;24(17):R777–80.
17. Thibaut F, Bradford JMW, Briken P, De La Barra F, Häßler F, Cosyns P, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the treatment of adolescent sexual offenders with paraphilic disorders. World J Biol Psychiatry. 2016;17(1):2–38. https://doi.org/10.3109/15622975.2015.1085598.
18. Clark SK, Jeglic EL, Calkins C, Tatar JR. More than a nuisance: the prevalence and consequences of frotteurism and exhibitionism. Sex Abus. 2016;28(1):3–19. https://doi.org/10.1177/1079063214525643.
19. Abel GG, Becker JV, Cunningham-Rathner J. Complications, consent, and cognitions in sex between children and adults. Int J Law Psychiatry. 1984;7(1):89–103.
20. Stoller RJ. Perversion: the erotic form of hatred. New York: Pantheon; 1975.
21. Abel GG, Osborn CA, Twigg DA. Sexual assault through the life span: adult offenders with juvenile histories. In: Barbaree HE, Marshall WL, Hudson SM, editors. The juvenile sex offender. New York: Guilford; 1993. p. 104–17.
22. Finkelhor D. Child abuse: new theory and research. New York: Free Press; 1984.
23. Hall GCN, Hirschman R. Sexual aggression against children: a conceptual perspective of etiology. Crim Justice Behav. 1992;19(1):8–23. https://doi.org/10.1177/0093854892019001003.
24. Marshall WL, Barbaree HE. An integrated theory of the etiology of sexual offending. In: Marshall WL, Laws DR, Barbaree HE, editors. Handbook of sexual assault: issues, theories and treatment of the offender. New York: Plenum; 1990. p. 257–75.
25. Ward T, Siegert RJ. Toward a comprehensive theory of child sexual abuse: a theory knitting perspective. Psychol Crime Law. 2002;8(4):319–51. https://doi.org/10.1080/10683160208401823.
26. Ward T, Beech A. An integrated theory of sexual offending. Aggress Violent Behav. 2006;11(1):44–63. https://doi.org/10.1016/j.avb.2005.05.002.
27. Thakker J, Ward T. An integrated theory of sexual reoffending. Psychiatry Psychol Law. 2012;19(2):236–48. https://doi.org/10.1080/13218719.2011.561765.
28. Navathe S, Ward T, Gannon T. Cognitive distortions in child sex offenders: an overview of theory, research & practice. J Forensic Nurs. 2008;4(3):111–22. https://doi.org/10.1111/j.1939-3938.2008.00019.x.

29. Mustaine EE, Tewksbury R, Corzine J, Huff-Corzine L. Differentiating single and multiple victim child sexual abuse cases: a research note considering social disorganization theory. J Child Sex Abus. 2014;23(1):38–54. https://doi.org/10.1080/10538712.2014.863260.
30. Blanchard R, Kolla NJ, Cantor JM, Klassen PE, Dickey R, Kuban ME, et al. IQ, handedness, and pedophilia in adult male patients stratified by referral source. Sex Abus. 2007;19(3):285–309. https://doi.org/10.1177/107906320701900307.
31. Tenbergen G, Wittfoth M, Frieling H, Ponseti J, Walter M, Walter H, et al. The neurobiology and psychology of pedophilia: recent advances and challenges. Front Hum Neurosci. 2015;9:344. https://doi.org/10.3389/fnhum.2015.00344.
32. Jakubczyk A, Krasowska A, Bugaj M, Kopera M, Klimkiewicz A, Łoczewska A, et al. Paraphilic sexual offenders do not differ from control subjects with respect to dopamine- and serotonin-related genetic polymorphisms. J Sex Med. 2017;14(1):125–33. https://doi.org/10.1016/j.jsxm.2016.11.309
33. Jordan K, Fromberger P, Stolpmann G, Muller JL. The role of testosterone in sexuality and paraphilia – a neurobiological approach. Part I: testosterone and sexuality. J Sex Med. 2011;8(11):2993–3007. https://doi.org/10.1111/j.1743-6109.2011.02394.x.
34. Jordan K, Fromberger P, Stolpmann G, Muller JL. The role of testosterone in sexuality and paraphilia – a neurobiological approach. Part II: testosterone and paraphilia. J Sex Med. 2011;8(11):3008–29. https://doi.org/10.1111/j.1743-6109.2011.02393.x.
35. Cantor JM, Blanchard R, Robichaud LK, Christensen BK. Quantitative reanalysis of aggregate data on IQ in sexual offenders. Psychol Bull. 2005;131(4):555–68. https://doi.org/10.1037/0033-2909.131.4.555.
36. Joyal CC, Black DN, Dassylva B. The neuropsychology and neurology of sexual deviance: a review and pilot study. Sex Abus. 2007;19(2):155–73. https://doi.org/10.1177/107906320701900206.
37. Joyal CC, Beaulieu-Plante J, de Chanterac A. The neuropsychology of sex offenders: a meta-analysis. Sex Abus. 2014;26(2):149–77. https://doi.org/10.1177/1079063213482842.
38. Suchy Y, Eastvold AD, Strassberg DS, Franchow EI. Understanding processing speed weaknesses among pedophilic child molesters: response style vs. neuropathology. J Abnorm Psychol. 2014;123(1):273–85. https://doi.org/10.1037/a0035812.
39. Massau C, Tenbergen G, Kargel C, Weiss S, Gerwinn H, Pohl A, et al. Executive functioning in pedophilia and child sexual offending. J Int Neuropsychol Soc. 2017;23(6):460–70. https://doi.org/10.1017/s1355617717000315.
40. Polisois-Keating A, Joyal CC. Functional neuroimaging of sexual arousal: a preliminary meta-analysis comparing pedophilic to non-pedophilic men. Arch Sex Behav. 2013;42(7):1111–3. https://doi.org/10.1007/s10508-013-0198-6.
41. Schiffer B, Amelung T, Pohl A, Kaergel C, Tenbergen G, Gerwinn H, et al. Gray matter anomalies in pedophiles with and without a history of child sexual offending. Transl Psychiatry. 2017;7(5):e1129. https://doi.org/10.1038/tp.2017.96.
42. Sartorius A, Ruf M, Kief C, Demirakca T, Bailer J, Ende G, et al. Abnormal amygdala activation profile in pedophilia. Eur Arch Psychiatry Clin Neurosci. 2008;258(5):271–7. https://doi.org/10.1007/s00406-008-0782-2.
43. Mohnke S, Muller S, Amelung T, Kruger TH, Ponseti J, Schiffer B, et al. Brain alterations in paedophilia: a critical review. Prog Neurobiol. 2014;122:1–23. https://doi.org/10.1016/j.pneurobio.2014.07.005.
44. Harenski CL, Thornton DM, Harenski KA, Decety J, Kiehl KA. Increased frontotemporal activation during pain observation in sexual sadism: preliminary findings. Arch Gen Psychiatry. 2012;69(3):283–92. https://doi.org/10.1001/archgenpsychiatry.2011.1566.
45. Habermeyer B, Esposito F, Handel N, Lemoine P, Kuhl HC, Klarhofer M, et al. Response inhibition in pedophilia: an FMRI pilot study. Neuropsychobiology. 2013;68(4):228–37. https://doi.org/10.1159/000355295.
46. Poeppl TB, Eickhoff SB, Fox PT, Laird AR, Rupprecht R, Langguth B, et al. Connectivity and functional profiling of abnormal brain structures in pedophilia. Hum Brain Mapp. 2015;36(6):2374–86. https://doi.org/10.1002/hbm.22777.

47. Massau C, Kargel C, Weiss S, Walter M, Ponseti J, Hc Krueger T, et al. Neural correlates of moral judgment in pedophilia. Soc Cogn Affect Neurosci. 2017;12(9):1490–9. https://doi.org/10.1093/scan/nsx077.
48. Kärgel C, Massau C, Weiß S, Walter M, Borchardt V, Krueger TH, et al. Evidence for superior neurobiological and behavioral inhibitory control abilities in non-offending as compared to offending pedophiles. Hum Brain Mapp. 2017;38(2):1092–104. https://doi.org/10.1002/hbm.23443.
49. Seto MC. Pedophilia and sexual offending against children: theory, assessment, and intervention. Washington, DC: American Psychological Association; 2008.
50. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969;44(235):291–303.
51. Mokros A, Gebhard M, Heinz V, Marschall RW, Nitschke J, Glasgow DV, et al. Computerized assessment of pedophilic sexual interest through self-report and viewing time: reliability, validity, and classification accuracy of the affinity program. Sex Abus. 2013;25(3):230–58. https://doi.org/10.1177/1079063212454550.
52. Fromberger P, Jordan K, Steinkrauss H, von Herder J, Witzel J, Stolpmann G, et al. Diagnostic accuracy of eye movements in assessing pedophilia. J Sex Med. 2012;9(7):1868–82. https://doi.org/10.1111/j.1743-6109.2012.02754.x.
53. Jahnke S, Philipp K, Hoyer J. Stigmatizing attitudes towards people with pedophilia and their malleability among psychotherapists in training. Child Abuse Negl. 2015;40:93–102. https://doi.org/10.1016/j.chiabu.2014.07.008.
54. Thibaut F. Pharmacological treatment of paraphilias. Isr J Psychiatry Relat Sci. 2012;49(4):297–305.
55. Bijlsma EY, Chan JS, Olivier B, Veening JG, Millan MJ, Waldinger MD, et al. Sexual side effects of serotonergic antidepressants: mediated by inhibition of serotonin on central dopamine release? Pharmacol Biochem Behav. 2014;121:88–101. https://doi.org/10.1016/j.pbb.2013.10.004.
56. Garcia FD, Thibaut F. Current concepts in the pharmacotherapy of paraphilias. Drugs. 2011;71(6):771–90. https://doi.org/10.2165/11585490-000000000-00000.
57. Khan O, Ferriter M, Huband N, Powney MJ, Dennis JA, Duggan C. Pharmacological interventions for those who have sexually offended or are at risk of offending. Cochrane Database Syst Rev. 2015;2:Cd007989. https://doi.org/10.1002/14651858.CD007989.pub2.
58. Långström N, Enebrink P, Laurén EM, Lindblom J, Werkö S, Hanson RK. Preventing sexual abusers of children from reoffending: systematic review of medical and psychological interventions. BMJ. 2013;347:f4630. https://doi.org/10.1136/bmj.f4630.
59. Schmucker M, Lösel F. The effects of sexual offender treatment on recidivism: an international meta-analysis of sound quality evaluations. J Exp Criminol. 2015;11(4):597–630. https://doi.org/10.1007/s11292-015-9241-z.
60. Craissati J. Managing high risk sex offenders in the community: a psychological approach. New York: Routledge; 2004.
61. Koo KC, Shim GS, Park HH, Rha KH, Choi YD, Chung BH, et al. Treatment outcomes of chemical castration on Korean sex offenders. J Forensic Legal Med. 2013;20(6):563–6. https://doi.org/10.1016/j.jflm.2013.06.003.
62. Park WS, Kim KM, Jung YW, Lim MH. A case of mental retardation with paraphilia treated with depot leuprorelin. J Korean Med Sci. 2014;29(9):1320–4. https://doi.org/10.3346/jkms.2014.29.9.1320.

Pharmachosexology: Use of Sex Hormones in Psychiatric Conditions

19

Alessandra Daphne Fisher, Jiska Ristori, and Mario Maggi

19.1 Introduction

Increasing evidence supports the role of sex hormones on the central nervous system's (CNS) plasticity and mental state [1]. Indeed, two different mechanisms of action of sex steroids on the brain and behavior have been historically described: organizational and activational [2]. Organizational effects occur prenatally and neonatally and are permanent [2]. In contrast, activational effects occur later in life and are associated with concomitant changes in circulating gonadal hormone levels [2]. Research has highlighted a complex interaction between organizational and activational influences, and the distinction between the two effects is not always clear. For example, recently, a role of gonadal hormones in maintaining or increasing basic neuroanatomical differences between sexes in puberty and, maybe, later on has been reported [3].

The organizational/activational role of gonadal steroids on the brain development may partially explain the reported sex differences in the vulnerability and clinical expression of different psychiatric and neurological diseases.

A. D. Fisher · J. Ristori · M. Maggi (✉)
Department of Experimental, Clinical and Biomedical Sciences,
University of Florence, Florence, Italy
e-mail: afisher@unifi.it; m.maggi@dfc.unifi.it

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*,
Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_19

The present contribution is aimed at summarizing the possible interplay between gonadal hormones and mental health. Indeed, sex hormones may be relevant in mentally ill patients for three reasons:

1. They can play a role in the pathophysiology of psychiatric disorders.
2. They may be used to treat mental illness.
3. Treatment with sex hormones may have psychiatric side effects [4].

19.2 Sex Hormones' Role in the Pathophysiology of Psychiatric Disorders

Many psychiatric and neurological diseases are characterized by sexual differences in incidence between men and women [5]. In particular, depression [6], anxiety, trauma- and stress-related disorders [7], as well as Alzheimer's [8, 9] are more frequent in women than in men. In contrast, an opposite trend is described for autism [10, 11], attention deficit hyperactivity disorder [12, 13], and Parkinson's disease, to which men are more prone compared to women [14].

In addition, biological aspects can affect the clinical presentation of some mental diseases, such as schizophrenia. In fact, although there is no sex difference in terms of its incidence, an earlier onset of schizophrenia is usually described in men compared to women. Furthermore, men with schizophrenia have more cognitive disturbances than affected women [5].

Although genetic, socioeconomic, or reporting biases may contribute to these gender discrepancies, significant evidence suggests that organic factors play a crucial role, including prenatal and postnatal sex hormones [7].

Indeed, animal models show that cyclical fluctuations during estrous cycle have a neural and behavioral impact. In particular, in mice and rats, densities of hippocampal dendritic spines are higher during proestrus and estrus (i.e., the phases with high estradiol levels) and lower during diestrus (i.e., the phase with low estradiol levels) [15]. Moreover, estrogens can inhibit the action of dopamine and increase the expression of serotonin, mimicking actions of atypical antipsychotics [1]. In addition, estrogens are able to induce neuronal regeneration and to suppress oxidative stress and can contribute to preventing or repairing cortical neurodegeneration [1].

In line, in humans, changes in hormonal levels across the life span may also affect mental illness expression. For example, pubertal hormonal changes are associated with an increased risk for anxiety and impulse-control disorders [16]. In postpubertal women, hormonal fluctuations during the menstrual cycle are related to mood changes (i.e., premenstrual dysphoric disorders) [17]; conversely, more stable hormonal levels resulting from oral contraceptive use are associated with a lower incidence of mood disorders [18]. In addition, clinical manifestations of some psychiatric diseases, such as schizophrenia, are influenced by menstrual phases in women. Indeed, schizophrenic symptoms are more intense during the low-estradiol phase, suggesting that estradiol may have a protective role in schizophrenia expression (estrogen protection hypothesis) [19].

Also hormonal changes during pregnancy and postpartum are associated with a great vulnerability to psychiatric manifestations [5]. The high concentration of

steroids secreted from the placenta during pregnancy is followed by low levels during the postpartum and lactation period. These changes may explain why approximately 80% of women experience mood changes (so-called baby blues) after childbirth, 12% prenatal depressions, and 10–15% postpartum depression [5].

While hormonal changes in females seem to increase the vulnerability of experiencing mood disorders, both preclinical and clinical studies in males suggest that testosterone has a protective role against anxiety and depression [20, 21]. Indeed, testosterone does clearly play a role in anxiety-related behaviors in animal models [22, 23]. In fact, gonadectomy results in increased anxiety and fear-related behaviors in male rodents, and testosterone supplementation enhances antianxiety behaviors and cognitive performance [23, 24]. In humans, clear evidence of testosterone's role in mood disturbance is represented by male hypogonadism. In fact, hypogonadal men have a significantly increased prevalence of anxiety disorder and major depression, compared to men with normal testosterone levels [25]. In addition, an association between depressive symptomatology, phobic and somatic anxiety, and lower levels of testosterone has been reported [26]. Accordingly, androgen deprivation therapy was found to be associated with a diagnosis of anxiety disorders de novo in more than 8% of treated persons [27]. Moreover, the majority of available studies show that testosterone replacement therapy significantly improves depressive symptoms and alleviates anxiety [25, 28].

Different studies have also investigated the role of testosterone in regulating social behavior, such as mating and aggression in primates [29–31]. Indeed, it has been reported that testosterone potentiates circuits involved in aggression in different species [26, 32–36]. In humans, prenatal exposure to exogenous androgen steroids results in slight increases of aggressive behavior in both boys and girls [37, 38].

Finally, the reproductive experience seems able to moderate psychiatric illness risk [5]. Indeed, parenthood increases the risk for Alzheimer's in women but not in men [39]. Animal studies showed that in female rats without a reproductive experience, hippocampal cell proliferation is not affected by acute estradiol administration; in contrast, exposure to estradiol increases hippocampal cell proliferation in multiparous female rats [40]. These results suggest that the hormonal changes experienced during motherhood may affect the sensitivity of the CNS to estrogens in the long term.

19.3 Therapeutic Effects of Exogenous Hormones in Mental Illness

Evidence supporting the psychotherapeutic effect of exogenous hormones has started emerging in the recent decades.

Indeed, in animal models, estrogens are reported to have anxiolytic and antidepressive properties, which are estrogen receptor-beta mediated [41, 42]. In addition, estrogen replacement in ovariectomized rats has been demonstrated as effective in enhancing cognitive performance [42].

Accordingly, in women with anorexia nervosa (AN), an improvement in cognitive measures has been observed only in those who spontaneously resumed menses or were treated with estrogen-progesterone combination pills, whereas this improvement was not observed in those who recovered weight alone, without resuming menses [43]. These data suggest that hormonal milieu, rather than weight recovery

alone, is important in improving cognitive status in AN [43]. In addition, a recent randomized placebo-controlled study showed a reduction in the tendency to experience anxiety in adolescents with AN treated with estrogens, independently of weight modifications [44]. Furthermore, a correlation between increases in estradiol and decreases in trait anxiety (the proneness to respond with or to feel a certain anxiety) over 18 months was also observed [44]. However, estrogen treatment was not effective in modifying eating behavior, body image, or state anxiety (which reflects the feelings at any given moment) [44]. These results may highlight the importance of transdermal estradiol therapy (with oral progestin) in women with functional hypothalamic amenorrhea whose menses have not returned after a reasonable trial of nutritional, psychological, and/or modified exercise intervention, as suggested by the Endocrine Society Clinical Practice Guidelines [45].

Concerning psychosis treatment, previous studies have reported that patients receiving adjunctive transdermal estradiol showed a greater improvement from acute symptoms, compared to patients receiving adjunctive placebo [46, 47]. In addition, raloxifene, a selective estrogen receptor modulator (SERM), has been demonstrated as effective in reducing the risk of cognitive impairment in both healthy and schizophrenic postmenopausal women [1, 48–50].

Conversely, estrogens have shown a detrimental effect in women with mania, in which, in fact, antiestrogen agents were successful in some reported cases [51]. In line with this, the use of adjunctive tamoxifen, a SERM with an estrogen receptor antagonist effect in the CNS, has been associated with an improvement in mania symptoms compared to placebo [1, 47].

Clinical evidence suggests that testosterone has an anxiolytic and antidepressant effect in both women and men [20]. For example, Miller and coll. showed that the administration of a low dose of testosterone in women with treatment-resistant major depressive disorder resulted in a significant improvement in depression levels, compared to placebo-treated subjects [52]. Moreover, mood disturbances and depression resulting from ovariectomy were reversed by testosterone treatment [53]. In addition, transdermal testosterone was effective in improving mood and psychological well-being in women experiencing age-related declines in androgens, compared to placebo-treated individuals [54].

Additional studies are needed to better understand the neurobiological mechanism underlying the protective effects of testosterone in males and females [20]. In particular, it is not clear if these effects are the result of the action of androgens on the androgen receptors or, indirectly, of aromatized estrogens.

Another condition where hormonal treatment has been demonstrated as being effective in reducing psychopathology is represented by gender dysphoria (GD) [55]. According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), GD refers to the distress resulting from the discrepancy between gender identity and sex assigned at birth [56]. This distress represents a dimensional phenomenon that can occur with different degrees of intensity. The most extreme form (i.e., *transsexualism*) is usually accompanied by a desire for social or somatic transition, aimed at aligning the body with the gender identity, according to individual needs and wishes [56–58].

Even if the presence of GD within the classification of the manual of mental disorders is highly controversial and a matter of debate, its inclusion in the DSM-5 is justified by the importance of medical and psychological support in some affected persons. In accordance with this view, its inclusion in the present paragraph is only aimed to emphasize the important role and efficacy of medical intervention in some transsexual persons and not to pathologize GD. Indeed, the significant distress experienced by a transsexual person may lead to the need for cross-sex hormonal treatment (CHT) in order to reduce the perceived incongruence [55, 57]. Different cross-sectional studies have reported that CHT in transsexuals is associated with a better quality of life [59, 60], reduction of psychiatric comorbidity [61, 62], lower social distress [62], and less body dissatisfaction [57]. Recently, a prospective study has corroborated these results, demonstrating the positive effect of CHT in decreasing psychopathology levels and depressive symptoms in transsexual individuals [55]. In addition, hormonal treatment was effective in alleviating body-related uneasiness and GD levels in this population. These results underline the importance, in GD individuals, of modifying sexually dimorphic characteristics of the body through hormonal treatment. Minimizing the incongruence between body and gender identity is in fact able to decrease GD-related sufferance [58]. In addition, the CHT-induced concurrent improvement in both GD and body uneasiness levels highlights the centrality of body image concerns in GD development [63, 64]. Previous studies have in fact reported that the more advanced the phase of the gender confirming path is (and consequently more actual body characteristics mirror the anticipated body), the more satisfactory the body image [65]. Indeed, sex-specific body features represent a painful reminder of the individual's unwanted assigned sex [63]. Moreover, besides the positive effect of CHT related to the induced body modifications, activational and psycho-protective role of sex steroids may also contribute to improving the psychological distress perceived by GD persons.

19.4 Psychiatric Side Effects of Treatment with Sex Hormones

Considering the reported effect of sex steroids on the brain and behavior, possible psychiatric side effects need to be taken into consideration when hormonal treatment should be prescribed in mentally ill or vulnerable patients.

This may be the case of Klinefelter patients, who often present with physical characteristics including tall stature, hypogonadism, and fertility problems. The majority of affected men carry a 47,XXY karyotype, while the other cases have supernumerary X chromosomes or mosaic forms [66]. The presence of the extra X chromosome can lead to characteristic cognitive and language deficits of varying severity [67]. In particular, individuals with Klinefelter syndrome (KS) seem to be at a higher risk of intellectual disability [67], as well as for difficulties in communication and social skills [68, 69]. In addition, a vulnerability in emotional and behavioral dysregulation, anxiety, depression, attention deficit hyperactivity disorder, and social difficulties, including autism, has been observed [68]. Even if androgen

deficiency is a characteristic feature of KS, only few studies have directly examined the effects of testosterone therapy on psychological features in KS. Indeed, a recent cross-sectional study in 50 KS patients did not find differences in the neuropsychological profile between androgen-treated and androgen-untreated patients [70, 71]. An improvement in energy levels and attention with testosterone treatment was also observed in treated patients by different authors [70, 72]. However, prospective, controlled studies in the KS population aimed at determining whether psychological functioning may change with androgen therapy are missing.

Also transsexual persons have been reported to be a more vulnerable population for co-occurring psychiatric conditions. Indeed, studies investigating the prevalence of psychopathology among transindividuals have shown elevated rates of psychiatric disorders in this population [73]. This may be the result from both GD itself and the minority distress experienced [73, 74]. In particular, mainly affective and anxiety disorders have been reported [73], as well as self-harm, substance abuse, and personality disorders [73, 75, 76]. Moreover, male-to-female transsexuals have higher rates of depressive symptoms compared to female-to-male ones, showing a more similar psychopathological profile to biological females than to biological males [58, 77, 78]. Thus, considering the vulnerability to psychiatric illness, assessing and monitoring psychopathological well-being is mandatory during hormonal confirming treatment in GD persons. In fact, the possible exacerbation of underlying co-occurring psychiatric conditions may be detrimental during gender transition.

Conclusion

The available literature exploring the relationship between sex hormones and psychiatric conditions highlights the importance of a multidisciplinary assessment in mentally ill patients.

Prospective randomized studies investigating the impact of hormone replacement therapy on psychological profiles may provide crucial information in better understanding sex hormones' influences on mental state, as well as optimizing treatments in mentally vulnerable patients.

References

1. Kulkarni J, Gurvich C, Gilbert H, Mehmedbegovic F, Mu L, Marston N, Gavrilidis E, de Castella A, Aust NZ. Hormone modulation: a novel therapeutic approach for women with severe mental illness. J Psychiatry. 2008;42(1):83–8.
2. Cohen-Bendahan CC, van de Beeka C, Berenbaum SA. Prenatal sex hormone effects on child and adult sex-typed behavior: methods and findings. Neurosci Biobehav Rev. 2005;29:353–84.
3. Raznahan A, Lee Y, Stidd R, Long R, Greenstein D, Clasen L, Addington A, Gogtay N, Rapoport JL, Giedd JN. Longitudinally mapping the influence of sex and androgen signaling on the dynamics of human cortical maturation in adolescence. Proc Natl Acad Sci U S A. 2010;107:16988–93.
4. Golightly L, Young A. Sex hormones and mental health. Adv Psychiatr Treat. 1995;5:126–34.
5. Gobinath AR, Choleris E, Galea LA. Sex, hormones, and genotype interact to influence psychiatric disease, treatment, and behavioral research. J Neurosci Res. 2017;95:50–64.

6. Angst J, Gamma A, Gastpar M, Lepine JP, Mendlewicz J, Tylee A, Depression Research in European Society Study. Gender differences in depression. Epidemiological findings from the European DEPRES I and II studies. Eur Arch Psychiatry Clin Neurosci. 2002;252:201–9.
7. Li SH, Graham BM. Why are women so vulnerable to anxiety, trauma-related and stress related disorders? The potential role of sex hormones. Lancet. 2016;4:73–82.
8. Ruitenberg A, Ott A, Van Swieten JC, Hofman A, Breteler MM. Incidence of dementia: does gender make a difference? Neurobiol Aging. 2001;22:575–80.
9. Zhou DF, Wu CS, Qi H, Fan JH, Sun XD, Como P, Qiao YL, Zhang L, Kieburtz K. Prevalence of dementia in rural China: impact of age, gender and education. Acta Neurol Scand. 2006;114:273–80.
10. Fombonne E. Epidemiology of pervasive developmental disorders. Pediatr Res. 2009;65:91–598.
11. Werlin DM, Geschwindm DH. Understanding sex bias in autism spectrum disorder. Proc Natl Acad Sci. 2013;110:4868–9.
12. Ramtekkar UP, Reiersen AM, Todorov AA, Todd RD. Sex and age differences in attention-deficit/hyperactivity disorder symptoms and diagnoses: implications for DSM-V and ICD-11. J Am Acad Child Adolesc Psychiatry. 2010;49:217–228, e211–e213.
13. Rucklidge JJ. Gender differences in attention–deficit/hyperactivity disorder. Psychiatr Clin North Am. 2010;33:357–73.
14. Van Den Eeden SK, Tanner CM, Bernstein AL, Fross RD, Leimpeter A, Bloch DA, Nelson LM. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. Am J Epidemiol. 2003;157:1015–22.
15. Woolley CS, Gould E, Frankfurt M, Mcewen BS. Naturally occurring fluctuation in dendritic spine density on adult hippocampal pyramidal neurons. J Neurosci. 1990;10:4035–9.
16. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:593–602.
17. Steiner M, Dunn E, Born L. Hormones and mood: from menarche to menopause and beyond. J Affect Disord. 2003;74:67–83.
18. Keyes KM, Cheslack-Postava K, Westhoff C, Heim CM, Haloossim M, Walsh K, Koenen K. Association of hormonal contraceptive use with reduced levels of depressive symptoms: a national study of sexually active women in the United States. Am J Epidemiol. 2013;178:1378–88.
19. Bergemann N, Parzer P, Nagl I, Salbach B, Runnebaum B, Mundt C, Resch F. Acute psychiatric admission and menstrual cycle phase in women with schizophrenia. Arch Womens Ment Health. 2002;5:119–26.
20. McHenry J, Carrier N, Hull E, Kabbaj M. Sex differences in anxiety and depression: role of testosterone. Front Neuroendocrinol. 2014;1:42–57.
21. Ciocca G, Limoncin E, Carosa E, Di Sante S, Gravina GL, Mollaioli D, Gianfrilli D, Lenzi A, Jannini EA. Is testosterone a food for the brain? Sex Med Rev. 2016;4:15–25.
22. Zuloaga DG, Puts DA, Jordan CL, Breedlove SM. The role of androgen receptors in the masculinization of brain and behavior: what we've learned from the testicular feminization mutation. Horm Behav. 2008;53:613–26.
23. Frye CA, Edinger K, Sumida K. Androgen administration to aged male mice increases anti-anxiety behavior and enhances cognitive performance. Neuropsychopharmacology. 2008;33:1049–61.
24. Frye CA, Edinger KL. Testosterone's metabolism in the hippocampus may mediate its anti-anxiety effects in male rats. Pharmacol Biochem Behav. 2004;78:473–81.
25. Zarrouf FA, Artz S, Griffith J, Sirbu C, Kommor M. Testosterone and depression: systematic review and meta-analysis. J Psychiatr Pract. 2009;4:289–305.
26. Bandini E, Corona G, Ricca V, Fisher AD, Lotti F, Sforza A, Faravelli C, Forti G, Mannucci E, Maggi M. Hysterical traits are not from the uterus but from the testis: a study in men with sexual dysfunction. J Sex Med. 2009;6:2321–31.
27. DiBlasio CJ, Hammett J, Malcolm JB, Judge BA, Womack JH, Kincade MC, Ogles ML, Mancini JG, Patterson AL, Wake RW, Derweesh IH. Prevalence and predictive factors for the development of de novo psychiatric illness in patients receiving androgen deprivation therapy for prostate cancer. Can J Urol. 2008;15:4249–56.

28. Kanayama G, Amiaz R, Seidman S, Pope HG Jr. Testosterone supplementation for depressed men: current research and suggested treatment guidelines. Exp Clin Psychopharmacol. 2007;15(6):529–38.
29. Anestis SF. Testosterone in juvenile and adolescent male chimpanzees (pan troglodytes): effects of dominance rank, aggression, and behavioral style. Am J Phys Anthropol. 2006;130:536–45.
30. Muehlenbein MP, Watts DP, Whitten PL. Dominance rank and fecal testosterone levels in adult male chimpanzees (Pan troglodytes schweinfurthii) at Ngogo, Kibale National Park, Uganda. Am J Primatol. 2004;64:71–82.
31. Rose RM, Holaday JW, Bernstein IS. Plasma testosterone, dominance rank and aggressive behavior in male rhesus monkeys. Nature. 1971;231:366–8.
32. Klinkova E, Heistermann M, Hodges JK. Social parameters and urinary testosterone level in male chimpanzees (Pan troglodytes). Horm Behav. 2004;46:474–81.
33. Fisher AD, Bandini E, Rastrelli G, Corona G, Monami M, Mannucci E, Maggi M. Sexual and cardiovascular correlates of male unfaithfulness. J Sex Med. 2012;6:1508–18.
34. Fisher AD, Bandini E, Corona G, Monami M, Cameron Smith M, Melani C, Balzi D, Forti G, Mannucci E, Maggi M. Stable extramarital affairs are breaking the heart. Int J Androl. 2012;1:11–7.
35. Fisher AD, Rastrelli G, Bandini E, Corona G, Balzi D, Melani C, Monami M, Matta V, Mannucci E, Maggi M. Metabolic and cardiovascular outcomes of fatherhood: results from a cohort of study in subjects with sexual dysfunction. J Sex Med. 2012;9:2785–94.
36. Fisher AD, Corona G, Bandini E, Mannucci E, Lotti F, Boddi V, Forti G, Maggi M. Psychobiological correlates of extramarital affairs and differences between stable and occasional infidelity among men with sexual dysfunctions. J Sex Med. 2009;6:866–75.
37. Pasterski V, Hindmarsh P, Geffner M, Brook C, Brain C, Hines M. Increased aggression and activity level in 3- to 11-year-old girls with congenital adrenal hyperplasia (CAH). Horm Behav. 2007;52:368–74.
38. Cohen-Bendahan CC, Buitelaar JK, van Goozen SH, Orlebeke JF, Cohen-Kettenis PT. Is there an effect of prenatal testosterone on aggression and other behavioral traits? A study comparing same-sex and opposite-sex twin girls. Horm Behav. 2005;47:230–7.
39. Ptok U, Barkow K, Heun R. Fertility and number of children in patients with Alzheimer's disease. Arch Womens Ment Health. 2002;5:83–6.
40. Barha CK, Galea LA. Motherhood alters the cellular response to estrogens in the hippocampus later in life. Neurobiol Aging. 2011;32:2091–5.
41. Lund TD, Rovis T, Chung WC, Handa R. Novel actions of estrogen receptor-beta on anxiety-related behaviors. Endocrinology. 2005;2:797–807.
42. Walf AA, Frye CA. Estradiol reduces anxiety- and depression-like behavior of aged female mice. Physiol Behav. 2010;99:169–74.
43. Chui HT, Christensen BK, Zipursky RB, Richards BA, Hanratty MK, Kabani NJ, Mikulis DJ, Katzman DK. Cognitive function and brain structure in females with a history of adolescent-onset anorexia nervosa. Pediatrics. 2008;122:426–37.
44. Misra M, Katzman DK, Estella NM, Eddy KT, Weigel T, Goldstein MA, Miller KK, Klibanski A. Impact of physiologic estrogen replacement on anxiety symptoms, body shape perception, and eating attitudes in adolescent girls with anorexia nervosa: data from a randomized controlled trial. J Clin Psychiatry. 2013;8:e765–71.
45. Gordon CM, Ackerman KE, Berga SL, Kaplan JR, Mastorakos G, Misra M, Murad MH, Santoro NF, Warren MP. Functional hypothalamic amenorrhea: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2017;102:1413–39.
46. Kulkarni J, de Castella A, Smith D, Taffe J, Keks N, Copolov D. A clinical trial of the effect of estrogens in acutely psychotic women. Schizophr Res. 1996;20:247–52.
47. Kulkarni J, Riedel A, de Castella AR, et al. A clinical trial of adjunctive oestrogen treatment in women with schizophrenia. Arch Womens Ment Health. 2002;5:99–104.
48. Manji HK, Lenox RH. Ziskind-Somerfeld Research Award. Protein kinase C signaling in the brain: molecular transduction of mood stabilization in the treatment of manic depressive illness. Biol Psychiatry. 1999;46:1328–51.

49. Haskell SG, Richardson ED. The effect of raloxifene on cognitive function in postmenopausal women: a randomized clinical trial. Conn Med. 2004;68:355–8.
50. Vercammen A, Skilletere AJ, Lenroot R, Catts SV, Weickert CS, Weickert TW. Testosterone is inversely related to brain activity during emotional inhibition in schizophrenia. PLoS One. 2013;8:e77496.
51. Goldstein JA. Danazol and the rapid-cycling patient. J Clin Psychiatry. 1986;3:153–4.
52. Miller KK, Perlis RH, Papakostas GI, Mischoulon D, Losifescu DV, Brick DJ, Fava M. Low-dose transdermal testosterone augmentation therapy improves depression severity in women. CNS Spectr. 2009;12:688–94.
53. Shifren JL, Braunstein GD, Simon JA, Casson PR, Buster JE, Redmond GP, Burki RE, Ginsburg ES, Rosen RC, Leiblum SR, Caramelli KE, Mazer NA. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. N Engl J Med. 2000;343:682–8.
54. Goldstat R, Briganti E, Tran J, Wolfe R, Davis SR. Transdermal testosterone therapy improves wellbeing, mood, and sexual function in premenopausal women. Menopause. 2003;10: 390–8.
55. Fisher AD, Castellini G, Ristori J, Casale H, Cassioli E, Sensi C, Fanni E, Amato AM, Bettini E, Mosconi M, Dèttore D, Ricca V, Maggi M. Cross-sex hormone treatment and psychobiological changes in transsexual persons: two-year follow-up data. J Endocrinol Metab. 2016;11:4160–9.
56. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5). 2DSM-5. Washington DC: American Psychiatric Association; 2013.
57. Fisher AD, Ristori J, Bandini E, Giordano S, Mosconi M, Jannini EA, Greggio NA, Godano A, Manieri C, Meriggiola C, Ricca V, Italian GnRH analogs study ONIG group, Dettore D, Maggi M. Medical treatment in gender dysphoric adolescents endorsed by SIAMS-SIE-SIEDP-ONIG. J Endocrinol Invest. 2014;37:675–87.
58. Fisher AD, Castellini G, Bandini E, Casale H, Fanni E, Benni L, Ferruccio N, Meriggiola MC, Manieri C, Gualerzi A, Jannini E, Oppo A, Ricca V, Maggi M, Rellini AH. Cross-sex hormonal treatment and body uneasiness in individuals with gender dysphoria. J Sex Med. 2014;3:709–19.
59. Fisher AD, Bandini E, Casale H, Ferruccio N, Meriggiola MC, Gualerzi A, Manieri C, Jannini E, Mannucci E, Monami M, Stomaci N, Delle Rose A, Susini T, Ricca V, Maggi M. Sociodemographic and clinical features of gender identity disorder: an Italian multicentric evaluation. J Sex Med. 2013;10:408–19.
60. Gorin-Lazard A, Baumstarck K, Boyer L, et al. Hormonal therapy is associated with better self-esteem, mood, and quality of life in transsexuals. J Nerv Ment Dis. 2013;201:996–1000.
61. Gorin-Lazard A, Baumstarck K, Boyer L, et al. Is hormonal therapy associated with better quality of life in transsexuals? A cross-sectional study. J Sex Med. 2012;9:531–41.
62. Colizzi M, Costa R, Todarello O. Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: results from a longitudinal study. Psychoneuroendocrinology. 2014;39:65–73.
63. Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godas T, Cruz Almaraz M, Halperin I, Salamero M. Hormone-treated transsexuals report less social distress, anxiety and depression. Psychoneuroendocrinology. 2012;37:662–70.
64. Jones BA, Haycraft E, Murjan S, Arcelus J. Body dissatisfaction and disordered eating in trans people: a systematic review of the literature. Int Rev Psychiatry. 2016;28:81–94.
65. van de Grift TC, Cohen-Kettenis PT, Steensma TD, De Cuypere G, Richter-Appelt H, Haraldsen IR, Dikmans RE, Cerwenka SC, Kreukels BP. Body satisfaction and physical appearance in gender dysphoria. Arch Sex Behav. 2016;3:575–85.
66. Fleming MZ, MacGowan BR, Robinson L, Spitz J, Salt P. The body image of the postoperative female-to-male transsexual. J Consult Clin Psychol. 1982;50:461–2.
67. Achermann JC, Hughes IA. Disorders of sex development. In: Kronenberg HM, Melmed S, Polonsky JS, Larsen PRXI, editors. Williams textbook of endocrinology, vol. 22. Philadelphia: Elsevier; 2008. p. 783–848.

68. Boada R, Janusz J, Hutaff-Lee C, Tartaglia N. The cognitive phenotype in Klinefelter syndrome: a review of the literature including genetic and hormonal factors. Dev Disabil Res Rev. 2009;15:284–94.
69. Bruining H, Swaab H, Kas M, Van Engeland H. Psychiatric characteristics in a self-selected sample of boys with Klinefelter syndrome. Pediatrics. 2009;123:e865–70.
70. Fisher AD, Castellini G, Casale H, Fanni E, Bandini E, Campone B, Ferruccio N, Maseroli E, Boddi V, Dèttore D, Pizzocaro A, Balercia G, Oppo A, Ricca V, Maggi M. Hypersexuality, paraphilic behaviors, and gender dysphoria in individuals with Klinefelter's syndrome. J Sex Med. 2015;12:2413–24.
71. Ross JL, Roeltgen D, Stefanatos G, et al. Cognitive and motor development during childhood in boys with Klinefelter syndrome. Am J Med Genet A. 2008;146:708–19.
72. Geschwind DH, Boone KB, Miller BL, et al. Neurobehavioral phenotype of Klinefelter syndrome. Ment Retard Dev Disabil Res Rev. 2000;6:107–16.
73. Simpson JL, Swerdloff RS, Samango-Sprouse CA, et al. Klinefelter syndrome. In: Cassidy SB, Allanson JE, editors. Management of genetic syndromes. 2nd ed. Hoboken: Wiley-Liss; 2004. p. 323–34.
74. Dhejne C, Van Vlerken R, Heylens G, Arcelus J. Mental health and gender dysphoria: a review of the literature. Int Rev Psychiatry. 2016;28:44–57.
75. Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, Erwin PJ, Montori VM. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. Clin Endocrinol. 2010;72:214–31.
76. Bockting WO, Goldberg JM. Guidelines for transgender care. Int J Transgenderism. 2006;9:3–4.
77. Nuttbrock L, Hwahng S, Bockting W, Rosenblum A, Mason M, Macri M, Becker J. Psychiatric impact of gender-related abuse across the life course of male-to-female transgender persons. J Sex Res. 2009;1:12–23.
78. Auer MK, Hohne N, Bazzara-Castro MA, Pfister H, Fuss J, Stalla GK, et al. Psychopathologic profiles in transsexuals and the challenge of their special status among the sexes. PLoS One. 2013;10:78469.

Pharmacosexology: Psychiatric Side Effects of Drugs for the Treatment of Sexual Dysfunction

20

Carmita Helena Najjar Abdo

20.1 Introduction

In the last two decades, in particular, research and clinical practice related to pharmacosexology have developed in an excellent way.

Medication used nowadays to improve male and female sexual function can be classified as follows:

1. Medication which, by treating the illnesses that are detrimental to sexual performance, corrects any blocks against sexual activity resulting from such illnesses. For example, testosterone for men with secondary hypogonadism [1, 2].
2. Medication that acts peripherally, recovering erection capability (in men) and lubrication (in women). The most typical among this medication are the phosphodiesterase type 5 (PDE-5) inhibitors, used to treat erectile dysfunction (ED) [3].
3. Central action medication, so named because it acts in the central nervous system (CNS), producing changes in neurotransmission and/or in the intracellular and extracellular concentration of substances that control both the male and female sexual response cycles. As examples, there are sex hormones [4, 5], postsynaptic 5-HT_{1A} agonist and 5-HT_{2A} antagonist drugs [6], and norepinephrine-dopamine reuptake inhibitors [7].

For illustrative purposes, it is appropriate to mention the case of testosterone, administered to women with a loss in desire/sexual interest. The task force appointed by the Endocrine Society, the American Congress of Obstetricians and Gynecologists (ACOG), the American Society for Reproductive Medicine (ASRM), the European

C. H. N. Abdo
Department and Institute of Psychiatry, Program of Studies in Sexuality (ProSex), Medical School, University of Sao Paulo (FMUSP), Sao Paulo, Brazil
e-mail: carmita.abdo@uol.com.br

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*, Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_20

Society of Endocrinology (ESE), and the International Menopause Society (IMS) recommend against the general use of testosterone for the following indications: infertility; sexual dysfunction other than hypoactive sexual desire disorder (HSDD); cognitive, cardiovascular, metabolic, or bone health; or general well-being [4].

20.2 Negative (or Positive) Side Effects of Some Psychotropics on Sexual Function

It is not appropriate to discuss at this point the adverse effects of medication used to treat systemic conditions (which may have an effect on the sexual function) because this is not within the scope of this chapter. Even though there is quite a number of medicines falling in this case, their administration serves an essential purpose (overcoming the systemic disease), and specialists in sexual medicine should conduct an integrated line of work with clinicians to find a more satisfactory alternative that contemplates the remission of the clinical condition, at the same time preventing the sexual function from undergoing a major loss.

Considering hypertension as an example, let us imagine that a patient is being treated with β-blockers, which significantly interfere with his sexual desire and/or erectile capability [8]. If there is no loss to the hypertension treatment, the clinician may replace this medication by angiotensin receptor blockers, thus preserving the sexual activity of the relevant patient [9].

Still for illustrative purposes, the histamine-2 antagonists, ranitidine and cimetidine, may also cause loss of libido and ED [10].

Sexual dysfunction is frequently associated with depression and its treatment. Some antidepressants such as selective serotonergic reuptake inhibitors (SSRIs) are well known to induce sexual side effects, affecting patients' quality of life [11, 12]. The incidence of treatment-emergent sexual dysfunction can be high, especially when the mechanism of action is related to the high profile of 5-HT reuptake blockade [13, 14].

However, patients suffering from significant depressive symptoms could cover up sexual adverse events, making it quite difficult to distinguish between real antidepressant-related sexual dysfunction and depression-related sexual disturbances [15].

Further comparative and well-controlled studies are strongly needed in order to alleviate patients from this quite frequently, under-recognized, and adverse event. New compounds should be investigated with adequate methodology to describe their capacity to affect sexual life [16].

20.2.1 Antidepressants

A retrospective study suggests an improvement in sexual dysfunction after switch from fluoxetine, paroxetine, citalopram, and sertraline to escitalopram [17]. There have been isolated case reports of increased sexual desire, spontaneous orgasms, and orgasms during exercise with fluoxetine, priapism with citalopram, and increased desire as well as anorgasmia with sertraline [18].

Among the tricyclic antidepressants (TCAs), a recent review found that research has pointed to clomipramine, amitriptyline, and imipramine as the worst offenders, with sexual dysfunction manifesting as decreased desire, lubrication difficulties, and inhibition of ejaculation and orgasm [18]. Another review found spontaneous orgasms and painful ejaculation with clomipramine [19]. Desipramine and nortriptyline (secondary amines) seem to have lower rates of sexual adverse effects than tertiary amines. Amoxapine (tetracyclic antidepressant or secondary amine TCA) is associated with painful and retrograde ejaculation [18].

Based on the available evidence, it seems that among the antidepressants, bupropion [7, 20–30] and mirtazapine [13, 31–34] have the lowest reported rates of sexual dysfunction. Newer agents with differences in mechanism of action, such as vilazodone [35–41] and vortioxetine [42–45], show promise, with some evidence of low rate of side effects on sexual function.

20.2.2 Antipsychotics

Sexual dysfunction is common in treatment with antipsychotics [46]. It has been related to several factors such as hyperprolactinemia, with a decrease in dopamine activity and α1-receptor blockade [47] (with secondary hypogonadism) [48]. Risperidone, haloperidol, amisulpride, and paliperidone are more likely associated with libido decrease and/or arousal difficulties, affecting more than 60% of patients. Nevertheless, olanzapine, clozapine, aripiprazole, ziprasidone, and quetiapine are less or not related to sexual dysfunction and could be the first election in many patients [15].

Aripiprazole is the only antipsychotic that has strong evidence to support its favorable profile in terms of sexual adverse effects [49].

Because of great variety of designs, further studies are needed to determine better evidence related to antipsychotic-induced sexual dysfunction [15].

20.2.3 Mood Stabilizers

Lithium is primarily used for the treatment of psychiatric disorders. A higher prevalence of hypothyroidism before the onset of lithium treatment has been described in women versus men (14.5% vs. 4.5%), pointing to the need of control of thyroid function parameters, especially in women [50]. This evidence suggests that female sex is an independent risk factor for lithium-associated thyroid impairment [51].

Valproic acid and carbamazepine are used as mood stabilizers in the treatment of bipolar and unipolar depression. Bodyweight gain is observed in valproic acid treatment compared with carbamazepine [52].

Among the mood stabilizers, anticonvulsants, especially those that lower bioavailable testosterone, seem to have a stronger association to sexual dysfunction [53].

It is worth noting that the effects of the medications (abovementioned) may impair some domains of sexual function (e.g., desire). On the other hand, they may

favor others (e.g., lack of ejaculatory control). These aspects will be detailed in the next subitems of this chapter.

20.2.4 Psychiatric Illness Versus Medication-Induced Sexual Dysfunction

Norms regarding sexual function can differ in different cultures, resulting in variances in willingness of patients to report and of physicians to ask about expectations of what is natural sexual functioning [54]. Studies published after the year 2000 report a significantly higher percentage of drug-induced sexual dysfunction compared with studies before that year [55]. Clinicians may not accurately estimate how much of the level of sexual dysfunction is due to the psychiatric illness versus the medications. It is important to keep these factors in mind when reviewing the current evidence (Fig. 20.1) [53].

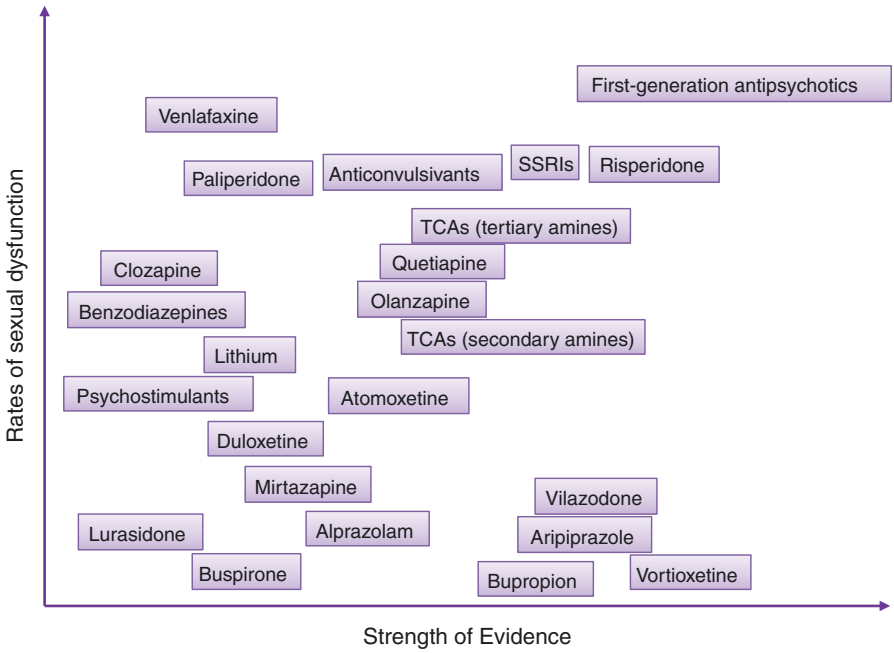

Fig. 20.1 An approximation of rates of sexual dysfunction with various psychotropics and associated strength of evidence. It would be most appropriate to compare drugs within each class because supporting studies do not compare interclass (i.e., TCAs are shown above quetiapine, but it may not actually cause higher rates because study populations and comparators are different) (adapted from Clayton et al. 2016) [53]

20.2.5 Comparison of Incidence of Sexual Adverse Effects Among Antidepressants

Antidepressants associated with a lower incidence of sexual adverse effects include bupropion, mirtazapine, vilazodone, vortioxetine, nefazodone, agomelatine, and moclobemide [18, 20, 37, 56–59]. A recent meta-analysis was able to quantify the risk of sexual dysfunction with certain medications, with the stratification being as follows: moclobemide (4%), agomelatine (4%), amineptine (7%), nefazodone (8%), bupropion (10%), mirtazapine (24%), fluvoxamine (26%), escitalopram (37%), duloxetine (42%), phenelzine (42%), imipramine (44%), fluoxetine (70%), paroxetine (71%), citalopram (79%), and venlafaxine (80%) [20]. Table 20.1 shows the

Table 20.1 Drugs with favorable and unfavorable sexual dysfunction profiles and sexual dysfunction antidotes (adapted from La Torre et al. [18]; Serretti and Chiesa [20]; Schmidt et al. [49]; Clayton et al. [53])

More favorable SD profiles	Class	Antidote
Treatment of antidepressant-induced SD		
Agomelatine	Agonist at melatonin MT_1 and MT_2 receptors and a 5-HT_{2C} antagonist	–
Bupropion	Unicyclic, aminoketone antidepressant, classified as NDRI	Bupropion[a]
Desvenlafaxine	Cyclohexanol and phenol derivative and metabolite of venlafaxine that functions as a SNRI	–
Mirtazapine	Antagonist of central presynaptic a-2-adrenergic, 5-HT_2, 5-HT_3, $histamine_1$, and muscarinic receptors. It is a noradrenergic and specific serotonergic antidepressant	Mirtazapine
Moclobemide	Reversible monoamine oxidase-A inhibitor	
Nefazodone	Serotonin reuptake inhibitor and a 5-HT_2 receptor antagonist	
Vilazodone	SSRI and 5-HT_{1A} partial agonist	
Vortioxetine	Newer antidepressant that is a serotonin reuptake inhibitor and a 5-HT receptor modulator (agonist at 5-HT_{1A}, partial agonist at 5-HT_{1B}, and antagonist of 5-HT_3, 5-HT_{1D}, and 5-HT_7 receptors)	PDE-5 inhibitor[a]
Treatment of antipsychotic-induced SD		
Aripiprazole	Partial agonist of serotonin receptor, 5-$HT_{1A,}$ and dopamine D_2 receptors, where it also functions as a postsynaptic antagonist and an antagonist of serotonin receptor 5-HT_{2A}	Aripiprazole[a]
Clozapine	Tricyclic dibenzodiazepine, classified as an atypical antipsychotic agent; is a serotonin antagonist, with strong binding to 5-$HT_{2A/2C}$ receptor subtype	–
Olanzapine	Synthetic derivative of thienobenzodiazepine; as a selective monoaminergic antagonist, binds with high-affinity binding to the following receptors: serotoninergic, dopaminergic, muscarinic $M_{1–5}$, $histamine_1$, and alpha-1-adrenergic receptors; it binds weakly to gamma-aminobutyric acid type A, benzodiazepine, and beta-adrenergic receptors	–

(continued)

Table 20.1 (continued)

More favorable SD profiles	Class	Antidote
Quetiapine	Dibenzothiazepine that targets the serotonin 5-HT_2 receptor, $histamine_1$ receptor, adrenergic alpha-1 and alpha-2 receptors, as well as the dopamine D_1 receptor and dopamine D_2 receptor	PDE-5 inhibitor[a] (men only)
Ziprasidone	Benzothiazolylpiperazine derivative; as an antagonist at the dopamine D_2 and serotonin 5-HT_{2A} and 5-HT_{1D} receptors and as an agonist at the 5-HT_{1A} receptor; also inhibits the synaptic reuptake of serotonin and norepinephrine	–
More unfavorable SD profiles	*Class*	*Antidote*
Antidepressants		
Citalopram	SSRI	Bupropion
Duloxetine	Thiophene derivative and SNRI	–
Escitalopram	SSRI, is a pure S-enantiomer of the racemic bicyclic phthalane derivative citalopram	Bupropion
Fluoxetine	SSRI	Bupropion
Imipramine	TCA	–
Paroxetine	SSRI	Bupropion
Antipsychotics		
Amisulpride	Selective dopamine antagonist; not approved for use in the United States, but is approved in Europe and Australia	–
Haloperidol	Phenylbutylpiperadine derivative; competitively blocks postsynaptic dopamine D_2 receptors in the mesolimbic system of the brain, thereby eliminating dopamine neurotransmission	–
Paliperidone	Benzisoxazole derivative and active metabolite of risperidone that functions as a dopamine D_2 receptor antagonist and serotonin 5-HT_2 receptor antagonist	–
Perphenazine	Phenothiazine derivative and a dopamine antagonist	
Risperidone	Atypical antipsychotic; it is a selective blocker of dopamine D_2 receptors and serotonin 5-HT_2 receptors	–
Thioridazine	Piperidine phenothiazine derivative and dopamine antagonist	–

5-HT 5-hydroxytryptamine, *NDRI* norepinephrine-dopamine reuptake inhibitor, *PDE-5* phosphodiesterase type 5, *SNRI* serotonin and noradrenaline reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant
[a]Drugs with level 1A (highest level) evidence

drugs with favorable and unfavorable sexual dysfunction profiles and sexual dysfunction antidotes.

20.2.6 Relevance of Sex Differences in Psychotropic Drug Side Effects

The available published literature on sex-specific reports on adverse psychotropic drug reactions revealed differences in frequency and/or severity of adverse effects of antipsychotics, antidepressants, and mood stabilizers. In some cases, sex is

interrelated with other factors influencing side effects such as age, disease, and body weight [51].

Despite criticism of the quality and amount of data available, there is evidence for sex-related differences that might have a clinical relevance. A higher risk of drug-induced weight gain was observed for women in several studies on antipsychotic drugs, as well as on mood stabilizers, which means clinicians should pay more attention to this side effect when treating women [60]. The clinical consequences of drug-induced metabolic changes might be worse in men than in women since the cardiovascular risk was consistently higher in men than in women [51].

Interestingly, no relevant sex differences in occurrence of side effects such as sexual dysfunction, tardive dyskinesia, and acute extrapyramidal are evident [51].

While the individualization of pharmacogenetics therapy requires molecular generic tests, sex differences can be easily recognized and translated into clinical practice [61].

It is essential to tailor treatment to the individual with attention to efficacy and tolerability and to manage any treatment-emergent side effects adequately in order to facilitate compliance and achieve the best possible outcomes [15].

There is good evidence for drug-associated sexual dysfunction in prolactogenic medications, such as first-generation antipsychotics, risperidone, and paliperidone [62]. Lower rates of sexual dysfunction are seen with aripiprazole [49] and lurasidone [63].

Further studies are needed, especially prospective trials on sex-related differences in specific drug side effects, to confirm the exploratory findings from retrospective data and meta-analyses [51].

20.3 Mental Health Benefits of Drugs for the Treatment of Sexual Dysfunctions

20.3.1 Phosphodiesterase Type 5 Inhibitors

The relationship between depression and ED appears to be bidirectional: the presence of or alteration in one of these conditions may be the cause, consequence, or modifier of the other [64–67]. In depressed men, ED may be a symptom or a treatment-emergent side effect of antidepressant medication [68]. Alternatively, men with ED may develop a "secondary" depression as a reaction to the biopsychosocial stress commonly associated with loss of sexual functioning [69].

The mechanisms underlying the link between depression and ED are complex and not fully understood [70, 71]. Accumulating data support a strong link between ED and depression [65, 67, 72, 73]. While ED can lead to depression, loss of self-esteem, and relationship as marital difficulties [74, 75], the successful treatment of ED can improve a man's mental health, well-being, and self-esteem [70, 76–80].

When the PDE-5 inhibitors improve erections, thus promotes improved cognition and general health, because enhances self-confidence and performance anxiety [71, 81].

Daily dosing with a PDE-5 inhibitor seems to improve cognitive function, depression, and somatization, as well as erectile function, without adverse side

effects. In particular, improvement in ED correlated with improvements in general cognitive function, frontal lobe function, and depression [71].

Depressive men with ED treated with sildenafil but no treated depressive symptoms respond to the ED treatment and showed a clinically significant improvement in depressive symptoms and quality-of-life measures compared with subjects whose ED did not respond to treatment. These results suggest that sildenafil may be as, or more, effective for the treatment of ED in mildly depressed men: 90.9% of subjects receiving sildenafil answered "yes" to global efficacy question, compared to 11.4% of subjects receiving placebo, a difference of 79.5% [64]. This study suggests that men with ED and comorbid depression may be among those most likely to respond positively to treatment with sildenafil. The authors speculated that sildenafil offered a unique opportunity to study "secondary" depression, i.e., depression associated with a specific medical disorder. In conclusion, this study shows that successful treatment of ED in depressed men is associated with depressive remission: substantially more treatment-responsive subjects demonstrated a ≥50% reduction in Hamilton Depression Rating Scale (HAM-D) score (76%) or CGI improvement score of 1 or 2 (82.8%) than did nonresponsive subjects (14.1% and 9.0%, respectively) [64].

Numerous clinical trials have showed that ED can be successfully treated in men with comorbid depression, whether or not they are taking concomitant antidepressant medications, resulting in a subsequent improvement in quality of life [82–90].

ED was also strongly correlated with Beck Depression Inventory (BDI) score. Patients whose mood and overall sexual functioning are improved following ED treatment are likely to experience greater satisfaction in their partner relationship and family life, in general, and these changes will be associated with positive changes in overall life satisfaction [83].

20.3.1.1 Improving Erectile Function and Psychological Health

As we know, the emotional consequences of ED include depression, anxiety, and loss of self-esteem [80, 91–93]. The synergistic interaction between ED, depression, and physical illness means that a correct differential diagnosis is essential to target treatment to the primary disease [94].

All PDE-5 inhibitors have been shown to be effective in men with ED and comorbid depression [88, 95–98], including men with milder depressive symptoms who were not receiving concomitant antidepressant therapy [64].

Improvement of ED was associated with marked improvement of depressive symptoms, suggesting the efficacy of treatment of ED to reduce psychological distress in men affected by a diagnosed psychiatric disorder who also complained for ED [70].

Successful treatment of ED with PDE-5 inhibitors may enhance men's compliance with their antidepressant treatment, and the beneficial effects of the medication in improving erection hardness in men with ED associated with depression and antidepressant therapy appear to be maintained in the long term (i.e., over 26 weeks) [96]. Such results should not be interpreted to suggest that PDE-5 inhibitors have a primary effect on depression, since these intermittently administered, peripherally

acting drugs have no known effects on the central nervous system. It is more likely that, by increasing erection hardness and successful intercourse attempts, effective treatment of ED has positive effects on a man's mood, self-esteem, self-confidence, psychosocial well-being, quality of sex life [80, 99–102], as well as in cognition and frontal executive function [71], resulting in an increased desire for sexual intimacy that improves a man's relationship with his partner and overall life satisfaction [83].

Treatment of ED with PDE-5 inhibitor was also associated with a significantly reduced level of obsessive-compulsive, anxiety, and interpersonal sensitivity that includes feelings of inadequacy and of inferiority [103].

Population-based cross-sectional surveys on middle-aged and elderly individuals have largely confirmed the predictive role of depressive symptoms or of a diagnosed depression on ED [66, 104–106]. Furthermore, ED treatment might be viewed as aimed to reduce psychological risk factors for future cardiovascular events in men with vascular risk factors [103, 107].

20.3.2 Dapoxetine

Several years ago, the observation that one of the adverse effects of SSRIs when used to treat depression and other psychological disorders, i.e., anorgasmia or delayed ejaculation, suggested SSRIs as a possible pharmacotherapy for premature ejaculation (PE) [108–110].

Dapoxetine was developed specifically for treatment of PE and is the only SSRI approved for treatment of this condition due to its pharmacological profile. The mechanism of action of dapoxetine is unclear; however, it is believed to be associated with the inhibition of the neuronal reuptake of serotonin and the ensuing potentiation of the neurotransmitter's action at pre- and postsynaptic receptors [111, 112]. Prolongation of the ejaculatory interval within few days of treatment suggests that this acute effect is due to direct blocking of central serotonergic reuptake by dapoxetine [113].

Dapoxetine is a potent and short-acting SSRI, a class of drugs that are used frequently to treat depression [110]. Maximum plasma concentrations are reached within approximately 1 h of oral administration and fall to less than 5% of this peak within 24 h. These features make dapoxetine suitable for on-demand dosing, which may have several advantages, including convenient dosing before anticipated sexual intercourse, cost savings compared with daily-dosing regimens, and reduced drug exposure without accumulation of drug and/or active metabolites [114].

Unlike other SSRIs used to treat depression, which have been associated with high incidences of sexual dysfunctions [31, 115], dapoxetine was associated with low rates of sexual dysfunction. The most adverse effect in this category was ED (dapoxetine 30 and 60 mg, 2.3% and 2.6%, respectively) [116].

Studies of SSRIs in patients with major psychiatric disorders, for example, depression or obsessive-compulsive disorder, suggest that SSRIs are potentially associated with certain safety risks, including neurocognitive adverse effects such

as anxiety, hypomania, akathisia, and changes in mood [117–120]. Unlike dapoxetine, most off-label SSRI drugs have not been specifically evaluated for known class-related safety effects, including potential for withdrawal effects, treatment-emergent suicidality, and effects on mood and affect in men with PE [116]. In turn, results from the Beck Depression Inventory II (BDI-II) and Montgomery-Åsberg Depression Rating Scale (MADRS) questionnaires showed a lack of clinically relevant changes in mood with dapoxetine treatment, whereas Hamilton Anxiety Rating Scale (HAM-A) and Barnes Akathisia Rating Scale (BARS) results indicated no evidence of anxiety or akathisia, respectively, with dapoxetine treatment. Evaluations of possibly suicide-related adverse events (PSRAEs) and results from the BDI-II and MADRS showed no evidence of treatment-emergent suicidality [121].

An analysis of pooled phase III data confirms that dapoxetine 30 and 60 mg increased intravaginal ejaculation latency time (IELT) and improved patient-reported outcomes (PROs) of control, ejaculation-related distress, interpersonal distress, and sexual satisfaction compared with placebo [121].

In summary, dapoxetine is a SSRI, with antidepressant action, effective in the treatment of PE, but was not associated with significant changes in erectile or orgasmic function, changes in sexual desire, or effects on anxiety or depression, compared with placebo. Additionally, dapoxetine was associated with low incidence of mood-related adverse effects and improvement of personal distress [122, 123].

20.3.3 Testosterone

The beneficial effect of testosterone on sexual motivation and the presence of sexual thoughts have been reported by several studies [124–126]. In turn, sexual function is related to a man's androgen status, with hypogonadal men having an increased incidence of ED [127–129] and low sexual desire [5, 126, 129].

Studies have provided good evidence that low free testosterone levels can be associated with depression in men [130–132].

Testosterone also maintains psychological aspects such as libido, sexual interest, mood, and energy, which contribute to an overall sense of well-being and health-related quality of life (HRQoL). Consequently, in men with late-onset hypogonadism (LOH), there is an increase in symptoms such as decreased energy, motivation, initiative, poor concentration and memory, diminished libido and orgasm, decreased cognitive function, irritability, and increased risk of depression [132–136].

Current evidence indicates that sexual dysfunction and depression frequently coexist [65, 67, 72, 137, 138], and this relationship relates to the severity of depressive symptoms. Sexual dysfunction and depression in men are correlated, and the presence of depressive symptoms is related to both the psychological and the physical aspects of sexual function, and the severity of depressive symptoms is related to the degree of sexual dysfunction [139]. It was also demonstrated, in patients with prostate cancer, the relationship between androgen deprivation therapy (ADT) and the risk of subsequently depressive disorder during a 3-year follow-up period. These

patients treated with ADT have double depressive disorder incidence than those not treated with ADT (13.9 vs. 6.7 per 1000 person-years) [140].

Depressed mood is a frequently observed phenomenon in patients with hypogonadism, and this can be managed by testosterone supplementation. Indeed, the most striking evidence that reduced testosterone can lead to increased depression comes from treatment studies in which mood is greatly enhanced by the use of testosterone supplementation [141]. In this sense, a meta-analysis concluded that testosterone therapy can be used as monotherapy in dysthymia and minor depression or as augmentation therapy in major depressive disorder [142].

Increases in positive mood and decreases in negative mood with testosterone replacement therapy (TRT) were confirmed by several studies [143–145]. Furthermore, it has been reported that testosterone can restore erections in men who had originally showed no response to PDE-5 inhibitors [146, 147] and that it is especially beneficial only in hypogonadal men with a baseline total testosterone level of <3 ng/ml [148].

The Olmsted County Study, with its large number of subjects, showed an association between a higher testosterone level and an increase in sexual desire [149]. When reduced sexual desire is primarily due to hypogonadism, two meta-analyses of RCTs demonstrated a significant improvement in sexual desire after TRT [150, 151].

A randomized, placebo-controlled phase III trial in which men with hypogonadism and metabolic syndrome were treated with testosterone for 30 weeks showed at the end of the trial period significantly improved depressive symptoms as measured by the Beck Depression Inventory (BDI-IA) [152]. Other studies showed that hypogonadal men undergoing TRT had improved parameters of well-being, bone density, muscle mass, physical strength, sexual function and libido [153], metabolic syndrome, and mood [154].

A parallel-group, double-blind, placebo-controlled randomized trial of testosterone gel augmentation was conducted with men with major depressive disorder who were incompletely responsive to serotonergic antidepressants and who displayed morning total testosterone levels of ≤350 ng/dl. Exogenous testosterone was associated with significant improvement in all of the five domains of sexual function: erectile function, intercourse satisfaction, orgasmic function, sexual desire, and overall sexual satisfaction. This finding suggests that the positive influence of testosterone replacement on sexual function occurs despite concomitant antidepressant use and comorbid major depressive disorder [155].

20.3.4 Bupropion

There are three main reasons for investigating the sexual function before, during, and after treatment of depression. First, there is a well-established relationship between sexual functioning and quality of life [19, 31, 156, 157], and sexual functioning is important to people regardless of mood state [158, 159]. Second, in depressed patients, sexual dysfunction can be an added source of distress, thereby prolonging or worsening their illness [157, 160]. Finally, antidepressant-induced

sexual dysfunction can lead to noncompliance with treatment including medication discontinuation, thereby interfering with recovery [31, 159, 161, 162].

Bupropion, a norepinephrine-dopamine reuptake inhibitor, is approved as an antidepressant and a treatment for smoking cessation, but it is used as an off-label treatment for HSDD, at the dose of 150–400 mg daily [163–165].

Dopaminergic agents may enhance quality of life by acting directly on some of the symptoms of major depression that may be postulated to diminish quality of life, such as fatigue, drowsiness, cognitive dysfunction, anhedonia, and difficulty concentrating. They are associated with a decreased likelihood of sexual side effects and problems with weight gain, two common medication-related effects that may decrease quality of life [166].

Many antidepressants may worsen sexual function by decreasing libido, delaying orgasm and ejaculation, and decreasing erectile function. Dopaminergic agents, such as bupropion, have few to no adverse sexual side effects [167].

Weight gain, which may negatively affect quality of life by worsening patients' self-image and potentially affecting interpersonal relationships, is another side effect common to many antidepressants [167]. Dopaminergic agents are no more likely to cause weight gain than placebo [168].

Bupropion is beneficial not only for symptom reduction in major depression but also for improving quality of life [169–172]. It is suggested that dopaminergic agents exert this effect by improving sexual and cognitive functioning, promoting weight loss, decreasing fatigue and hypersomnia, and improving interest, pleasure, and energy [166].

The role of individualized treatment in the management of sexual dysfunction cannot be overemphasized. For a sexually active patient with a first episode of depression, for example, antidepressant-induced sexual dysfunction may result in treatment nonadherence and potentially a worsening of depression by stopping antidepressant therapy. Conversely, for a patient who has failed multiple antidepressants, and an effective antidepressant results in sexual dysfunction, the focus should be on quality of life via management options such as use of antidotes or augmentation strategies to minimize side effects without sacrificing efficacy [173]. Bupropion is thought to be good choices for avoiding antidepressant-associated sexual dysfunction or for switching patients in whom antidepressant-associated sexual dysfunction emerged [174].

There have been numerous studies comparing the side effect profile of bupropion, with serotonergic agents, especially the SSRIs [175]. In general, these studies have demonstrated a statistically significant difference between bupropion and the serotoninergic drugs [18]. In all of these studies, the SSRI comparator antidepressant had a higher incidence of sexual dysfunction than bupropion.

In a placebo-controlled study involving patients of both sexes, 30% of patients on fluoxetine as compared to 10% of placebo or bupropion patients had orgasmic or ejaculatory problems on fluoxetine [27]. A double-blind controlled comparison of the sexual side effect profile of bupropion and sertraline in the treatment of patients of both sexes with major depressive disorder found that orgasmic or ejaculatory delay was more common on sertraline as compared to bupropion, 52% vs. 8% [176].

Other studies comparing the sexual side effect profile of escitalopram [26], venlafaxine [7], and paroxetine [22] to bupropion found similar results with bupropion having a lower incidence of treatment-emergent sexual dysfunction.

A recent Cochrane review and meta-analysis concluded that for women with antidepressant-induced sexual dysfunction, the addition of bupropion at higher doses appears to be the most promising approach studied so far, but further data from randomized trials are likely to be required before it can be recommended confidently [21]. Other meta-analyses support the use of bupropion as a sole or coprescribed antidepressant, particularly if weight gain or sexual dysfunction are, or are likely to be, significant problems [177].

Although safety data for bupropion is not specifically available in women diagnosed as having HSDD, the most common adverse effects compared to placebo in clinical trials for depression were tremor (13.5%), dry mouth (9.2%), constipation (8.7%), excessive sweating (7.7%), dizziness (6.1%), and nausea/vomiting (4%) [178]. In a pooled analysis of patients receiving bupropion SR 300 or 400 mg/day or placebo, the incidences of agitation were 3%, 9%, and 2%; of anxiety were 5%, 6%, and 3%; of insomnia were 11%, 16%, and 6%; of nervousness were 5%, 3%, and 3%; and of irritability were 3%, 2%, and 2%, respectively [178]. These specific side effects can negatively affect sexual function [179], although there is no data on this regard related to bupropion.

20.3.5 Flibanserin

Flibanserin is a nonhormonal, central-acting agent, which affects serotonin, dopamine, and norepinephrine activity with affinity for 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, $5HT_{2C,}$ and dopamine D_4 receptors in the brain [180–182]. Initial studies were based on an understanding of these neurotransmitters and their role in depression but failed to prove effective in treating depression [183]. However, clinical trials demonstrating increased sexual desire, decreased sexually related distress, and increased satisfying sexual events in pre- and postmenopausal women [184–187]. This improvement in sexual desire was felt to be related to flibanserin's effect on neurotransmitters in the limbic system, and this led to a rerouting of the development of the drug as a potential nonhormonal treatment for HSDD in women [180]. In 2015, the FDA approved flibanserin for treatment of HSDD in premenopausal woman [188].

The most common adverse events (AEs) in terms of placebo-corrected rates of occurrence in premenopausal women were dizziness (9.2%), somnolence (8.3%), nausea (6.5%), and fatigue (3.7%). Most AEs were transient or episodic, were mild to moderate in severity, and were mitigated by bedtime dosing. The discontinuation rate due to AEs was 13% in patients treated with flibanserin 100 mg and 6% in patients treated with placebo [186–189]. Severe AEs including, among others, syncope, hypotension, and sedation can occur with flibanserin use alone but are amplified with concurrent alcohol use [188, 190]. Therefore, simultaneous use of alcohol and this medication is contraindicated.

However, the real benefits of flibanserin in the treatment of HSDD are controversial. Three meta-analyses reviewing the available literature on flibanserin produced conflicting findings [191]. The first reviewed four published clinical trials based on 3414 women and found statistically greater increases in sexually satisfying events, sexual desire, overall sexual function, and significant reductions in sex-related distress compared with placebo [6]. A second meta-analysis based on five studies, including unpublished randomized controlled trials, showed that flibanserin led to a mean increase of only 0.5 sexually satisfying events per month as well as clinically significant risk of dizziness, somnolence, nausea, and fatigue [192]. A third meta-analysis involved six published and four unpublished studies on a total of 8345 women and concluded that although flibanserin was associated with significant increases in sexual desire, the magnitude of this increase did not differ from the effect of placebo [193]. The conflicting findings in these three meta-analyses further fueled the debate associated with the nature of and optimal treatment for low desire in women [191]. In addition, future clinical trials with flibanserin should include women from diverse populations, particularly women with a history of somatic and psychological comorbidities, medication use, and surgical menopause [192].

Conclusion

The knowledge of the psychiatric side effects of drugs for the treatment of sexual dysfunction led to the treatment of some sexual dysfunctions, through the use of off-label drugs of the same ones. From there, studies were developed, taking advantage of characteristics of the centrally acting drugs, in benefit of the sexual function of men and women. Thus, a new era was inaugurated in the treatment of sexual dysfunction, valuing these findings and researching new drugs capable of promoting sexual activity, through action on the CNS.

References

1. Aversa A, Morgentaler A. The practical management of testosterone deficiency in men. Nat Rev Urol. 2015;12(11):641–50.
2. Surampudi P, Swerdloff RS, Wang C. An update on male hypogonadism therapy. Expert Opin Pharmacother. 2014;15(9):1247–64.
3. Hatzimouratidis K, Salonia A, Adaikan G, Buvat J, Carrier S, El-Meliegy A, McCullough A, Torres LO, Khera M. Pharmacotherapy for erectile dysfunction: recommendations from the Fourth International Consultation for Sexual Medicine (ICSM 2015). J Sex Med. 2016;13(4):465–88.
4. Wierman ME, Arlt W, Basson R, Davis SR, Miller KK, Murad MH, Rosner W, Santoro N. Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(10):3489–510.
5. Yassin AA, Saad F. Improvement of sexual function in men with late-onset hypogonadism treated with testosterone only. J Sex Med. 2007;4(2):497–501.
6. Gao Z, Yang D, Yu L, Cui Y. Efficacy and safety of flibanserin in women with hypoactive sexual desire disorder: a systematic review and meta-analysis. J Sex Med. 2015;12(11):2095–104.

7. Thase ME, Clayton AH, Haight BR, Thompson AH, Modell JG, Johnston JA. A double-blind comparison between bupropion XL and venlafaxine XR: sexual functioning, antidepressant efficacy, and tolerability. J Clin Psychopharmacol. 2006;26(5):482–8.
8. Rosen RC, Kostis JB, Jekelis AW. Beta-blocker effects on sexual function in normal males. Arch Sex Behav. 1988;17(3):241–85.
9. Manolis A, Doumas M. Antihypertensive treatment and sexual dysfunction. Curr Hypertens Rep. 2012;14(4):285–92.
10. White JM, Rumbold GR. Behavioural effects of histamine and its antagonists: a review. Psychopharmacology (Berl). 1988;95(1):1–14.
11. Clayton AH, Croft HA, Handiwala L. Antidepressants and sexual dysfunction: mechanisms and clinical implications. Postgrad Med. 2014;126(2):91–9.
12. Baldwin DS, Foong T. Antidepressant drugs and sexual dysfunction. Br J Psychiatry. 2013;202:396–7.
13. Clayton AH, Montejo AL. Major depressive disorder, antidepressants, and sexual dysfunction. J Clin Psychiatry. 2006;67(Suppl 6):33–7.
14. Bijlsma EY, Chan JS, Olivier B, Veening JG, Millan MJ, Waldinger MD, Oosting RS. Sexual side effects of serotonergic antidepressants: mediated by inhibition of serotonin on central dopamine release? Pharmacol Biochem Behav. 2014;121:88–101.
15. Montejo AL, Montejo L, Navarro-Cremades F. Sexual side-effects of antidepressant and antipsychotic drugs. Curr Opin Psychiatry. 2015;28(6):418–23.
16. Baldwin DS, Palazzo MC, Masdrakis VG. Reduced treatment-emergent sexual dysfunction as a potential target in the development of new antidepressants. Depress Res Treat. 2013;2013:256841.
17. Ashton AK, Mahmood A, Iqbal F. Improvements in SSRI/SNRI-induced sexual dysfunction by switching to escitalopram. J Sex Marital Ther. 2005;31(3):257–62.
18. La Torre A, Giupponi G, Duffy D, Conca A. Sexual dysfunction related to psychotropic drugs: a critical review—part I: antidepressants. Pharmacopsychiatry. 2013;46(5):191–9.
19. Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. J Clin Psychopharmacol. 1999;19(1):67–85.
20. Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. J Clin Psychopharmacol. 2009;29(3):259–66.
21. Taylor MJ, Rudkin L, Bullemor-Day P, Lubin J, Chukwujekwu C, Hawton K. Strategies for managing sexual dysfunction induced by antidepressant medication. Cochrane Database Syst Rev. 2013;5:CD003382.
22. Kennedy SH, Fulton KA, Bagby RM, Greene AL, Cohen NL, Rafi-Tari S. Sexual function during bupropion or paroxetine treatment of major depressive disorder. Can J Psychiatr. 2006;51(4):234–42.
23. Kennedy SH, Rizvi S, Fulton K, Rasmussen J. A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR. J Clin Psychopharmacol. 2008;28(3):329–33.
24. Modell JG, Katholi CR, Modell JD, DePalma RL. Comparative sexual side effects of bupropion, fluoxetine, paroxetine, and sertraline. Clin Pharmacol Ther. 1997;61(4):476–87.
25. Dhillon S, Yang LP, Curran MP. Bupropion: a review of its use in the management of major depressive disorder. Drugs. 2008;68(5):653–89.
26. Clayton AH, Croft HA, Horrigan JP, Wightman DS, Krishen A, Richard NE, Modell JG. Bupropion extended release compared with escitalopram: effects on sexual functioning and antidepressant efficacy in 2 randomized, double-blind, placebo-controlled studies. J Clin Psychiatry. 2006;67(5):736–46.
27. Coleman CC, King BR, Bolden-Watson C, Book MJ, Segraves RT, Richard N, Ascher J, Batey S, Jamerson B, Metz A. A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. Clin Ther. 2001;23(7):1040–58.
28. Walker PW, Cole JO, Gardner EA, Hughes AR, Johnston JA, Batey SR, Lineberry CG. Improvement in fluoxetine-associated sexual dysfunction in patients switched to bupropion. J Clin Psychiatry. 1993;54(12):459–65.

29. Croft H, Settle E Jr, Houser T, Batey SR, Donahue RM, Ascher JA. A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. Clin Ther. 1999;21(4):643–58.
30. Gartlehner G, Hansen RA, Morgan LC, Thaler K, Lux L, Van Noord M, Mager U, Thieda P, Gaynes BN, Wilkins T, Strobelberger M, Lloyd S, Reichenpfader U, Lohr KN. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. Ann Intern Med. 2011;155(11):772–85.
31. Montejo AL, Llorca G, Izquierdo JA, Rico-Villademoros F. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. J Clin Psychiatry. 2001;62(Suppl 3):10–21.
32. Gelenberg AJ, McGahuey C, Laukes C, Okayli G, Moreno F, Zentner L, Delgado P. Mirtazapine substitution in SSRI-induced sexual dysfunction. J Clin Psychiatry. 2000;61(5):356–60.
33. Wade A, Crawford GM, Angus M, Wilson R, Hamilton L. A randomized, double-blind, 24-week study comparing the efficacy and tolerability of mirtazapine and paroxetine in depressed patients in primary care. Int Clin Psychopharmacol. 2003;18(3):133–41.
34. Versiani M, Moreno R, Ramakers-van Moorsel CJ, Schutte AJ, Comparative Efficacy Antidepressants Study Group. Comparison of the effects of mirtazapine and fluoxetine in severely depressed patients. CNS Drugs. 2005;19(2):137–46.
35. Clayton AH, Gommoll C, Chen D, Nunez R, Mathews M. Sexual dysfunction during treatment of major depressive disorder with vilazodone, citalopram, or placebo: results from a phase IV clinical trial. Int Clin Psychopharmacol. 2015;30(4):216–23.
36. Clayton AH, Kennedy SH, Edwards JB, Gallipoli S, Reed CR. The effect of vilazodone on sexual function during the treatment of major depressive disorder. J Sex Med. 2013;10(10):2465–76.
37. Khan A, Cutler AJ, Kajdasz DK, Gallipoli S, Athanasiou M, Robinson DS, Whalen H, Reed CR. A randomized, double-blind, placebo-controlled, 8-week study of vilazodone, a serotonergic agent for the treatment of major depressive disorder. J Clin Psychiatry. 2011;72(4):441–7.
38. Citrome L. Vilazodone for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant – what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Int J Clin Pract. 2012;66(4):356–68.
39. Robinson DS, Kajdasz DK, Gallipoli S, Whalen H, Wamil A, Reed CR. A 1-year, open-label study assessing the safety and tolerability of vilazodone in patients with major depressive disorder. J Clin Psychopharmacol. 2011;31(5):643–6.
40. Rickels K, Athanasiou M, Robinson DS, Gibertini M, Whalen H, Reed CR. Evidence for efficacy and tolerability of vilazodone in the treatment of major depressive disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2009;70(3):326–33.
41. Clayton AH, Durgam S, Tang X, Chen C, Ruth A, Gommoll C. Characterizing sexual function in patients with generalized anxiety disorder: a pooled analysis of three vilazodone studies. Neuropsychiatr Dis Treat. 2016;12:1467–76.
42. Jacobsen PL, Clayton AH, Mahableshwarkar AR, Chen Y, Chrones L, Clayton AH. The effect of vortioxetine on sexual dysfunction in adults with major depressive disorder or generalized anxiety disorder. ASCP Meeting. Hollywood. 2014.
43. Jacobsen PL, Mahableshwarkar AR, Chen Y, Chrones L, Clayton AH. Effect of vortioxetine vs. escitalopram on sexual functioning in adults with well-treated major depressive disorder experiencing SSRI-induced sexual dysfunction. J Sex Med. 2015;12(10):2036–48.
44. Sanchez C, Asin KE, Artigas F. Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. Pharmacol Ther. 2015;145:43–57.
45. Jacobsen PL, Mahableshwarkar AR, Palo WA, Chen Y, Dragheim M, Clayton AH. Treatment-emergent sexual dysfunction in randomized trials of vortioxetine for major depressive disorder or generalized anxiety disorder: a pooled analysis. CNS Spectr. 2016;21(5):367–78.

46. La Torre A, Conca A, Duffy D, Giupponi G, Pompili M, Grözinger M. Sexual dysfunction related to psychotropic drugs: a critical review part II: antipsychotics. Pharmacopsychiatry. 2013;46(6):201–8.
47. de Boer MK, Castelein S, Wiersma D, Schoevers RA, Knegtering H. The facts about sexual (Dys)function in schizophrenia: an overview of clinically relevant findings. Schizophr Bull. 2015;41(3):674–86.
48. Besnard I, Auclair V, Callery G, Gabriel-Bordenave C, Roberge C. Antipsychotic-drug-induced hyperprolactinemia: physiopathology, clinical features and guidance. Encéphale. 2014;40(1):86–94.
49. Schmidt HM, Hagen M, Kriston L, Soares-Weiser K, Maayan N, Berner MM. Management of sexual dysfunction due to antipsychotic drug therapy. Cochrane Database Syst Rev. 2012;11:CD003546.
50. Johnston AM, Eagles JM. Lithium-associated clinical hypothyroidism. Prevalence and risk factors. Br J Psychiatry. 1999;175:336–9.
51. Haack S, Seeringer A, Thürmann PA, Becker T, Kirchheiner J. Sex-specific differences in side effects of psychotropic drugs: genes or gender? Pharmacogenomics. 2009;10(9):1511–26.
52. Jallon P, Picard F. Bodyweight gain and anticonvulsants: a comparative review. Drug Saf. 2001;24(13):969–78.
53. Clayton AH, Alkis AR, Parikh NB, Votta JG. Sexual dysfunction due to psychotropic medications. Psychiatr Clin N Am. 2016;39(3):427–63.
54. Knegtering H, van der Moolen AE, Castelein S, Kluiter H, van den Bosch RJ. What are the effects of antipsychotics on sexual dysfunctions and endocrine functioning? Psychoneuroendocrinology. 2003;28(Suppl 2):109–23.
55. Haberfellner EM. A review of the assessment of antidepressant-induced sexual dysfunction used in randomized, controlled clinical trials. Pharmacopsychiatry. 2007;40(5):173–82.
56. Clayton AH, Pradko JF, Croft HA, Montano CB, Leadbetter RA, Bolden-Watson C, Bass KI, Donahue RM, Jamerson BD, Metz A. Prevalence of sexual dysfunction among newer antidepressants. J Clin Psychiatry. 2002;63(4):357–66.
57. Labbate LA, Croft HA, Oleshansky MA. Antidepressant-related erectile dysfunction: management via avoidance, switching antidepressants, antidotes, and adaptation. J Clin Psychiatry. 2003;64(Suppl 10):11–9.
58. Montejo AL, Deakin JF, Gaillard R, Harmer C, Meyniel F, Jabourian A, Gabriel C, Gruget C, Klinge C, MacFayden C, Milligan H, Mullings E, Goodwin G. Better sexual acceptability of agomelatine (25 and 50 mg) compared to escitalopram (20 mg) in healthy volunteers. A 9-week, placebo-controlled study using the PRSexDQ scale. J Psychopharmacol. 2015;29(10):1119–28.
59. Baldwin DS, Loft H, Dragheim M. A randomised, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in acute treatment of major depressive disorder (MDD). Eur Neuropsychopharmacol. 2012;22(7):482–91.
60. Barbui C, Nosè M, Bindman J, Schene A, Becker T, Mazzi MA, Kikkert M, Camara J, Born A, Tansella M. Sex differences in the subjective tolerability of antipsychotic drugs. J Clin Psychopharmacol. 2005;25(6):521–6.
61. Yonkers KA, Brawman-Mintzer O. The pharmacologic treatment of depression: is gender a critical factor? J Clin Psychiatry. 2002;63(7):610–5.
62. Shiloh R, Weizman A, Weizer N, Dorfman-Etrog P, Munitz H. Risperidone-induced retrograde ejaculation. Am J Psychiatry. 2001;158(4):650.
63. Clayton AH, Baker RA, Sheehan JJ, Cain ZJ, Forbes RA, Marler SV, Marcus R, Berman RM, Thase ME. Comparison of adjunctive use of aripiprazole with bupropion or selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors: analysis of patients beginning adjunctive treatment in a 52-week, open-label study. BMC Res Notes. 2014;7:459.
64. Seidman SN, Roose SP, Menza MA, Shabsigh R, Rosen RC. Treatment of erectile dysfunction in men with depressive symptoms: results of a placebo-controlled trial with sildenafil citrate. Am J Psychiatry. 2001;158(10):1623–30.

65. Araujo AB, Durante R, Feldman HA, Goldstein I, McKinley J. The relationship between depressive symptoms and male erectile dysfunction: cross-sectional results from the Massachusetts Male Aging Study. Psychosom Med. 1998;60(4):458–65.
66. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol. 1994;151(1):54–61.
67. Seidman SN, Roose SP. The relationship between depression and erectile dysfunction. Curr Psychiatry Rep. 2000;2(3):201–5.
68. Seidman SN, Shabsigh R, Roose S. Pharmacologic treatments of sexual dysfunction. In: Dunner DL, editor. Psychiatric clinics of North America annual of drug therapy. Philadelphia: WB Saunders; 1999. p. 21–33.
69. Zurowski K, Kayne H, Goldstein I. The social and behavioral costs of organic impotence (Abstract). J Urol. 1994;319A:151.
70. Rosen R, Shabsigh R, Berber M, Assalian P, Menza M, Rodriguez-Vela L, Porto R, Bangerter K, Seger M, Montorsi F, Vardenafil Study Site Investigators. Efficacy and tolerability of vardenafil in men with mild depression and erectile dysfunction: the depression-related improvement with vardenafil for erectile response study. Am J Psychiatry. 2006;163(1):79–87.
71. Shim YS, Pae CU, Cho KJ, Kim SW, Kim JC, Koh JS. Effects of daily low-dose treatment with phosphodiesterase type 5 inhibitor on cognition, depression, somatization and erectile function in patients with erectile dysfunction: a double-blind, placebo-controlled study. Int J Impot Res. 2014;26(2):76–80.
72. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA. 1999;281(6):537–44.
73. Shabsigh R, Klein LT, Seidman S, Kaplan SA, Lehrhoff BJ, Ritter JS. Increased incidence of depressive symptoms in men with erectile dysfunction. Urology. 1998;52(5):848–52.
74. Althof SE. Quality of life and erectile dysfunction. Urology. 2002;59(6):803–10.
75. Cappelleri JC, Althof SE, Siegel RL, Stecher VJ, Tseng LJ, Duttagupta S. Association between the erectile dysfunction inventory of treatment satisfaction and the self-esteem and relationship questionnaire following treatment with sildenafil citrate for men with erectile dysfunction. Value Health. 2005;8(1 suppl):S54–60.
76. Althof SE, O'Leary MP, Cappelleri JC, Glina S, King R, Tseng LJ, Bowler JL. Self-esteem, confidence and relationships in men treated with sildenafil citrate for erectile dysfunction: results of two double-blind, placebo-controlled trials. J Gen Intern Med. 2006;21(10):1069–74.
77. Althof SE, O'Leary MP, Cappelleri JC, Hvidsten K, Stecher VJ, Glina S, King R, Siegel RL. Sildenafil citrate improves self-esteem, confidence, and relationships in men with erectile dysfunction: results from an international, multi-center, double-blind, placebo-controlled trial. J Sex Med. 2006;3(3):521–9.
78. Cappelleri JC, Duttagupta S, Shpilsky A, Diuguid C, Stecher V, Sweeney M, Althof S. Correlating scores on the erectile dysfunction inventory of treatment satisfaction (EDITS) with the self-esteem and relationship (SEAR) questionnaire following treatment with Viagra (sildenafil citrate) for men with erectile dysfunction: results from a multi-center open-label study. Qual Life Res. 2002;11:668.
79. O'Leary MP, Althof SE, Cappelleri JC, Crowley A, Sherman N, Duttagupta S. Self-esteem, confidence and relationship satisfaction of men with erectile dysfunction treated with sildenafil citrate: a multicenter, randomized, parallel group, double-blind, placebo-controlled study in the United States. J Urol. 2006;175(3 Pt 1):1058–62.
80. Steidle CP, Stecher VJ, Pace C, Tseng LJ. Correlation of improved erectile function and rate of successful intercourse with improved emotional wellbeing assessed with the self-esteem and relationship questionnaire in men treated with sildenafil for erectile dysfunction and stratified by age. Curr Med Res Opin. 2006;22(5):939–48.
81. Shim YS, Pae CU, Kim SW, Kim HW, Kim JC, Koh JS. Effects of repeated dosing with Udenafil (Zydena) on cognition, somatization and erection in patients with erectile dysfunction: a pilot study. Int J Impot Res. 2011;23(3):109–14.

82. Willke RJ, Glick HA, McCarron TJ, Erder MH, Althof SE, Linet OI. Quality of life effects of alprostadil therapy for erectile dysfunction. J Urol. 1997;157(6):2124–8.
83. Rosen RC, Seidman SN, Menza MA, Shabsigh R, Roose SP, Tseng LJ, Orazem J, Siegel RL. Quality of life, mood, and sexual function: a path analytic model of treatment effects in men with erectile dysfunction and depressive symptoms. Int J Impot Res. 2004;16(4):334–40.
84. Williams G, Abbou CC, Amar ET, Desvaux P, Flam TA, Ljcklama GA, Nileholt A, Lynch SF, Morgan RJ, Müller SC, Porst H, Pryor JP, Ryan P, Witzsch UK, Hall MM, Place VA, Spivack AP, Todd LK, Gesundheit N. The effect of transurethral alprostadil on the quality of life of men with erectile dysfunction, and their partners. MUSE Study Group. Br J Urol. 1998;82(6):847–54.
85. Muller MJ, Benkert O. Lower self-reported depression in patients with erectile dysfunction after treatment with sildenafil. J Affect Disord. 2001;66(2–3):255–61.
86. Paige NM, Hays RD, Litwin MS, Rajfer J, Shapiro MF. Improvement in emotional well-being and relationships of users of sildenafil. J Urol. 2001;166(5):1774–8.
87. Seidman SN, Roose RP. Sexual dysfunction and depression. Curr Psychiatry Rep. 2001;3(3):202–8.
88. Morgentaler A, Barada J, Niederberger C, Donatucci C, Garcia CS, Natanegara F, Ahuja S, Wong DG. Efficacy and safety of tadalafil across ethnic groups and various risk factors in men with erectile dysfunction: use of a novel noninferiority study design. J Sex Med. 2006;3(3):492–503.
89. Nurnberg HG, Gelenberg A, Hargreave TB, Harrison W, Siegel R, Smith M. Efficacy of sildenafil citrate for the treatment of erectile dysfunction in men taking serotonin reuptake inhibitors. Am J Psychiatry. 2001;158(11):1926–8.
90. Tignol J, Furlan PM, Gomez-Beneyto M, Opsomer R, Schreiber W, Sweeney M, Wohlhuter C. Efficacy of sildenafil citrate (Viagra) for the treatment of erectile dysfunction in men in remission from depression. Int Clin Psychopharmacol. 2004;19(4):191–9.
91. Derogatis LR, Meyer JK, King KM. Psychopathology in individuals with sexual dysfunction. Am J Psychiatry. 1981;138(6):757–63.
92. Mallis D, Moysidis K, Nakopoulou E, Papaharitou S, Hatzimouratidis K, Hatzichristou D. Psychiatric morbidity is frequently undetected in patients with erectile dysfunction. J Urol. 2005;174(5):1913–6.
93. Mihalca R, Bocchio M, Pelliccione F, Ciociola F, Necozione S, Rossi A, Francavilla F, Francavilla S. Psychological features in men with erectile dysfunction with or without preclinical atherosclerosis. Int J Impot Res. 2007;19(6):597–601.
94. Dean J, de Boer B-J, Graziottin A, Hatzichristou D, Heaton J, Tailor A. Psychological, social, and behavioural benefits for men following effective erectile dysfunction (ED) treatment: men who enjoy better sex experience improved psychological well-being. Eur Urol. 2006;5:773–8.
95. Montorsi F, Salonia A, Briganti A, Barbieri L, Zanni G, Suardi N, Cestari A, Montorsi P, Rigatti P. Vardenafil for the treatment of erectile dysfunction: a critical review of the literature based on personal clinical experience. Eur Urol. 2005;47(5):612–21.
96. Nurnberg HG, Siegel R. Phosphodiesterase type 5 inhibitor treatment of erectile dysfunction may impart long-term benefits for patients with depression. Presented at 30th Annual Meeting of the American Society for Andrology, Seattle. 2005.
97. Lewis RW, Sadovsky R, Eardley I, O'Leary M, Seftel A, Wang WC, Shen W, Walker DJ, Wong DG, Ahuja S. The efficacy of tadalafil in clinical populations. J Sex Med. 2005;2(4):517–31.
98. Hatzichristou D, Moysidis K, Apostolidis A, Bekos A, Tzortzis V, Hatzimouratidis K, Ioannidis E. Sildenafil failures may be due to inadequate patient instructions and follow-up: a study on 100 non-responders. Eur Urol. 2005;47(4):518–23.
99. Stecher VJ, Tseng L-J. Increased rate of successful intercourse correlates with improved self-esteem in men with erectile dysfunction treated with Viagra (sildenafil citrate). J Sex Med. 2005;2(Suppl 1):83. (abstract no. P–157).
100. King R, Juenemann KP, Levinson IP, Stecher VJ, Creanga DL. Correlations between increased erection hardness and improvements in emotional well-being and satisfaction

outcomes in men treated with sildenafil citrate for erectile dysfunction. Int J Impot Res. 2007;19(4):398–406.
101. Glina S, Damião R, Abdo C, Afif-Abdo J, Tseng LJ, Stecher V. Self-esteem, confidence, and relationships in Brazilian men with erectile dysfunction receiving sildenafil citrate: a randomized, parallel-group, double-blind, placebo-controlled study in Brazil. J Sex Med. 2009;6(1):268–75.
102. Montorsi F, Padma-Nathan H, Glina S. Erectile function and assessments of erection hardness correlate positively with measures of emotional well-being, sexual satisfaction, and treatment satisfaction in men with erectile dysfunction treated with sildenafil citrate (Viagra). Urology. 2006;68(3 Suppl):26–37.
103. Bocchio M, Pelliccione F, Mihalca R, Ciociola F, Necozione S, Rossi A, Francavilla F, Francavilla S. Treatment of erectile dysfunction reduces psychological distress. Int J Androl. 2009;32(1):74–80.
104. Nicolosi A, Moreira ED Jr, Shirai M, Bin Mohd Tambi MI, Glasser DB. Epidemiology of erectile dysfunction in four countries: cross-national study of the prevalence and correlates of erectile dysfunction. Urology. 2003;61(1):201–6.
105. Nicolosi A, Moreira ED Jr, Villa M, Glasser DB. A population study of the association between sexual function, sexual satisfaction and depressive symptoms in men. J Affect Disord. 2004;82(2):235–43.
106. Cameron A, Sun P, Lage M. Comorbid conditions in men with ED before and after ED diagnosis: a retrospective database study. Int J Impot Res. 2006;18(4):375–81.
107. Moncada I, Martínez-Jabaloyas JM, Rodriguez-Vela L, Gutiérrez PR, Giuliano F, Koskimaki J, Farmer IS, Renedo VP, Schnetzler G. Emotional changes in men treated with sildenafil citrate for erectile dysfunction: a double-blind, placebo-controlled clinical trial. J Sex Med. 2009;6(12):3469–77.
108. McMahon CG, Althof SE, Waldinger MD, Porst H, Dean J, Sharlip ID, Adaikan PG, Becher E, Broderick GA, Buvat J, Dabees K, Giraldi A, Giuliano F, Hellstrom WJ, Incrocci L, Laan E, Meuleman E, Perelman MA, Rosen RC, Rowland DL, Segraves R. An evidence-based definition of lifelong premature ejaculation: report of the International Society for Sexual Medicine (ISSM) ad hoc committee for the definition of premature ejaculation. J Sex Med. 2008;5(7):1590–606.
109. Giuliano F, Hellstrom WJ. The pharmacological treatment of premature ejaculation. BJU Int. 2008;102(6):668–75.
110. McCarty E, Dinsmore W. Dapoxetine: an evidence-based review of its effectiveness in treatment of premature ejaculation. Core Evid. 2012;7:1–14.
111. Janssen-Cilag (New Zealand) Ltd. Priligy_data sheet [online]. http://www.medsafe.govt.nz/Profs/Datasheet/p/Priligytab.pdf. Accessed 20 Apr 2017.
112. Hoy SM, Scott LJ. Dapoxetine: in premature ejaculation. Drugs. 2010;70(11):1433–43.
113. Safarinejad MR. Safety and efficacy of dapoxetine in the treatment of premature ejaculation: a double-blind, placebo-controlled, fixed-dose, randomized study. Neuropsychopharmacology. 2008;33(6):1259–65.
114. Modi NB, Dresser MJ, Simon M, Lin D, Desai D, Gupta S. Single- and multiple-dose pharmacokinetics of dapoxetine hydrochloride, a novel agent for the treatment of premature ejaculation. J Clin Pharmacol. 2006;46(3):301–9.
115. Lane RM. A critical review of selective serotonin reuptake inhibitor-related sexual dysfunction; incidence, possible aetiology and implications for management. J Psychopharmacol. 1997;11(1):72–82.
116. McMahon CG. Dapoxetine: a new option in the medical management of premature ejaculation. Ther Adv Urol. 2012;4(5):233–51.
117. Coupland NJ, Bell CJ, Potokar JP. Serotonin reuptake inhibitor withdrawal. J Clin Psychopharmacol. 1996;16(5):356–62.
118. Khan A, Khan S, Kolts R, Brown WA. Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo: analysis of FDA reports. Am J Psychiatry. 2003;160(4):790–2.
119. Tamam L, Ozpoyraz N. Selective serotonin reuptake inhibitor discontinuation syndrome: a review. Adv Ther. 2002;19(1):17–26.

120. Zajecka J, Tracy KA, Mitchell S. Discontinuation symptoms after treatment with serotonin reuptake inhibitors: a literature review. J Clin Psychiatry. 1997;58(7):291–7.
121. McMahon CG, Althof SE, Kaufman JM, Buvat J, Levine SB, Aquilina JW, Tesfaye F, Rothman M, Rivas DA, Porst H. Efficacy and safety of dapoxetine for the treatment of premature ejaculation: integrated analysis of results from five phase 3 trials. J Sex Med. 2011;8(2):524–39.
122. Casey R, Tesfaye F, Mudumbi R, Rothman M, Rivas D. Effects of dapoxetine for the treatment of premature ejaculation on erectile function and scales of mood and affect. Eur Urol. 2008;7(3):186.
123. Kaufman JM, Rosen RC, Mudumbi RV, Tesfaye F, Hashmonay R, Rivas D. Treatment benefit of dapoxetine for premature ejaculation: results from a placebo-controlled phase III trial. BJU Int. 2009;103(5):651–8.
124. Isidori AM, Giannetta E, Gianfrilli D, Greco EA, Bonifacio V, Aversa A, Isidori A, Fabbri A, Lenzi A. Effects of testosterone on sexual function in men: results of a meta-analysis. Clin Endocrinol. 2005;63(4):381–94.
125. Wang C, Swerdloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, Matsumoto AM, Weber T, Berman N, The Testosterone Gel Study Group. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. J Clin Endocrinol Metab. 2000;85(8):839–53.
126. Allan CA, Forbes EA, Strauss BJ, McLachlan RI. Testosterone therapy increases sexual desire in ageing men with low-normal testosterone levels and symptoms of androgen deficiency. Int J Impot Res. 2008;20(4):396–401.
127. Liu PY, Swerdloff RS, Veldhuis JD. Clinical review 171: the rationale, efficacy and safety of androgen therapy in older men: future research and current practice recommendations. J Clin Endocrinol Metab. 2004;89(10):4789–96.
128. Shelton JB, Rajfer J. Androgen deficiency in aging and metabolically challenged men. Urol Clin North Am. 2012;39(1):63–75.
129. Travison TG, Morley JE, Araujo AB, O'Donnell AB, McKinlay JB. The relationship between libido and testosterone levels in aging men. J Clin Endocrinol Metab. 2006;91(7):2509–13.
130. Wang C, Alexander G, Berman N, Salehian B, Davidson T, McDonald V, Steiner B, Hull L, Callegari C, Swerdloff RS. Testosterone replacement therapy improves mood in hypogonadal men – a clinical research center study. J Clin Endocrinol Metab. 1996;81(10):3578–83.
131. Burris AS, Banks SM, Carter CS, Davidson JM, Sherins RJ. A long-term, prospective study of the physiologic and behavioral effects of hormone replacement in untreated hypogonadal men. J Androl. 1992;13(4):297–304.
132. Barrett-Connor E, Von Muhlen DG, Kritz-Silverstein D. Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo Study. J Clin Endocrinol Metab. 1999;84(2):573–7.
133. Rizvi SJ, Kennedy SH, Ravindran LN, Giacobbe P, Eisfeld BS, Mancini D, McIntyre RS. The relationship between testosterone and sexual function in depressed and healthy men. J Sex Med. 2010;7(2 Pt 1):816–25.
134. Shores MM, Moceri VM, Sloan KL, Matsumoto AM, Kivlahan DR. Low testosterone levels predict incident depressive illness in older men: effects of age and medical morbidity. J Clin Psychiatry. 2005;66(1):7–14.
135. Almeida OP, Yeap BB, Hankey GJ, Jamrozik K, Flicker L. Low free testosterone concentration as a potentially treatable cause of depressive symptoms in older men. Arch Gen Psychiatry. 2008;65(3):283–9.
136. Almehmadi Y, Yassin AA, Nettleship JE, Saad F. Testosterone replacement therapy improves the health-related quality of life of men diagnosed with late-onset hypogonadism. Arab J Urol. 2016;14(1):31–6.
137. El-Sakka AI. Erectile dysfunction, depression, and ischemic heart disease: does the existence of one component of this triad necessitate inquiring the other two? J Sex Med. 2011;8(4):937–40. quiz 941.

138. Tan HM, Tong SF, Ho CC. Men's health: sexual dysfunction, physical, and psychological health – is there a link? J Sex Med. 2012;9(3):663–71.
139. Pastuszak AW, Badhiwala N, Lipshultz LI, Khera M. Depression is correlated with the psychological and physical aspects of sexual dysfunction in men. Int J Impot Res. 2013;25(5):194–9.
140. Chung SD, Kao LT, Lin HC, Xirasagar S, Huang CC, Lee HC. Patients receiving androgen deprivation therapy for prostate cancer have an increased risk of depressive disorder. PLoS One. 2017;12(3):e0173266.
141. Zitzmann M. Testosterone and the brain. Aging Male. 2006;9(4):195–9.
142. Amanatkar HR, Chibnall JT, Seo BW, Manepalli JN, Grossberg GT. Impact of exogenous testosterone on mood: a systematic review and meta-analysis of randomized placebo-controlled trials. Ann Clin Psychiatry. 2014;26(1):19–32.
143. Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, Weber T, Berman N, Hull L, Swerdloff RS. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. J Clin Endocrinol Metab. 2004;89(5):2085–98.
144. Loizides E, Swierzewski MJ, O'neill C, Griesser J, Smith T. Early response time in sexual activity and mood following testosterone gel replacement in hypogonadal males from the Testim(R) START study. Rev Urol. 2004;6(Suppl 6):S16–21.
145. McNicholas TA, Dean JD, Mulder H, Carnegie C, Jones NA. A novel testosterone gel formulation normalizes androgen levels in hypogonadal men, with improvements in body composition and sexual function. BJU Int. 2003;91(1):69–74.
146. Hwang TI, Chen HE, Tsai TF, Lin YC. Combined use of androgen and sildenafil for hypogonadal patients unresponsive to sildenafil alone. Int J Impot Res. 2006;18(4):400–4.
147. Morley JE, Tariq SH. Sexuality and disease. Clin Geriatr Med. 2003;19(3):563–73.
148. Buvat J, Montorsi F, Maggi M, Porst H, Kaipia A, Colson MH, Cuzin B, Moncada I, Martin-Morales A, Yassin A, Meuleman E, Eardley I, Dean JD, Shabsigh R. Hypogonadal men nonresponders to the PDE5 inhibitor tadalafil benefit from normalization of testosterone levels with a 1% hydroalcoholic testosterone gel in the treatment of erectile dysfunction (TADTEST study). J Sex Med. 2011;8(1):284–93.
149. Gades NM, Jacobson DJ, McGree ME, St Sauver JL, Lieber MM, Nehra A, Girman CJ, Klee GG, Jacobsen SJ. The associations between serum sex hormones, erectile function, and sex drive: the Olmsted County Study of urinary symptoms and health status among men. J Sex Med. 2008;5(9):2209–20.
150. Buvat J, Maggi M, Gooren L, Guay AT, Kaufman J, Morgentaler A, Schulman C, Tan HM, Torres LO, Yassin A, Zitzmann M. Endocrine aspects of male sexual dysfunctions. J Sex Med. 2010;7(4 Pt 2):1627–56.
151. Corona G, Mannucci E, Petrone L, Giommi R, Mansani R, Fei L, Forti G, Maggi M. Psychobiological correlates of hypoactive sexual desire in patients with erectile dysfunction. Int J Impot Res. 2004;16(3):275–81.
152. Giltay EJ, Tishova YA, Mskhalaya GJ, Gooren LJ, Saad F, Kalinchenko SY. Effects of testosterone supplementation on depressive symptoms and sexual dysfunction in hypogonadal men with the metabolic syndrome. J Sex Med. 2010;7(7):2572–82.
153. Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Holmes JH, Dlewati A, Staley J, Santanna J, Kapoor SC, Attie MF, Haddad JG Jr, Strom BL. Effect of testosterone treatment on bone mineral density in men over 65 years of age. J Clin Endocrinol Metab. 1999;84(6):1966–72.
154. Permpongkosol S, Tantirangsee N, Ratana-olarn K. Treatment of 161 men with symptomatic late onset hypogonadism with long-acting parenteral testosterone undecanoate: effects on body composition, lipids, and psychosexual complaints. J Sex Med. 2010;7(11):3765–74.
155. Amiaz R, Pope HG Jr, Mahne T, Kelly JF, Brennan BP, Kanayama G, Weiser M, Hudson JI, Seidman SN. Testosterone gel replacement improves sexual function in depressed men taking serotonergic antidepressants: a randomized, placebo-controlled clinical trial. J Sex Marital Ther. 2011;37(4):243–54.

156. Dueñas H, Brnabic AJ, Lee A, Montejo AL, Prakash S, Casimiro-Querubin ML, Khaled M, Dossenbach M, Raskin J. Treatment-emergent sexual dysfunction with SSRIs and duloxetine: effectiveness and functional outcomes over a 6-month observational period. Int J Psychiatry Clin Pract. 2011;15(4):242–54.
157. Derogatis LR. Sexual function and quality of life: endpoints and outcomes. J Gend Specif Med. 2001;4(4):35–42.
158. Rothschild AJ. New directions in the treatment of antidepressant-induced sexual dysfunction. Clin Ther. 2000;22:A42–57. discussion A8–61.
159. Clayton A. The impact of antidepressant associated sexual dysfunction on treatment adherence in patients with major depressive disorder. Curr Psychiatr Rev. 2013;9(4):293–301.
160. Kennedy SH, Rizvi S. Sexual dysfunction, depression, and the impact of antidepressants. J Clin Psychopharmacol. 2009;29(2):157–64.
161. Zajecka JM. Clinical issues in long-term treatment with antidepressants. J Clin Psychiatry. 2000;61(Suppl 2):20–5.
162. Montejo-Gonzalez AL, Llorca G, Izquierdo JA, Ledesma A, Bousoño M, Calcedo A, Carrasco JL, Ciudad J, Daniel E, De la Gandara J, Derecho J, Franco M, Gomez MJ, Macias JA, Martin T, Perez V, Sanchez JM, Sanchez S, Vicens E. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. J Sex Marital Ther. 1997;23(3):176–94.
163. Stahl SM, Pradko JF, Haight BR, Modell JG, Rockett CB, Learned-Coughlin S. A review of the neuropharmacology of bupropion, a dual norepinephrine and dopamine reuptake inhibitor. Prim Care Companion J Clin Psychiatry. 2004;6(4):159–66.
164. Segraves RT, Croft H, Kavoussi R, Ascher JA, Batey SR, Foster VJ, Bolden-Watson C, Metz A. Bupropion sustained release (SR) for the treatment of hypoactive sexual desire disorder (HSDD) in non-depressed women. J Sex Marital Ther. 2001;27(3):303–16.
165. Segraves RT, Clayton A, Croft H, Wolf A, Warnock J. Bupropion sustained release for the treatment of hypoactive sexual desire disorder in premenopausal women. J Clin Psychopharmacol. 2004;24(3):339–42.
166. IsHak WW, Davis M, Jeffrey J, Balayan K, Pechnick RN, Bagot K, Rapaport MH. The role of dopaminergic agents in improving quality of life in major depressive disorder. Curr Psychiatry Rep. 2009;11(6):503–8.
167. Demyttenaere K, Jaspers L. Review: bupropion and SSRI-induced side effects. J Psychopharmacol. 2008;22(7):792–804.
168. Fava M, Rush AJ, Thase ME, Clayton A, Stahl SM, Pradko JF, Johnston JA. 15 years of clinical experience to bupropion XL. Prim Care Companion J Clin Psychiatry. 2005;7(3):106–13.
169. Fortner MR, Brown K, Varia IM, Gersing KR, O'Connor C, Doraiswamy PM. Effect of bupropion SR on the quality of life of elderly depressed patients with comorbid medical disorders. Prim Care Companion J Clin Psychiatry. 1999;1(6):174–9.
170. Dunner DL, Kwong WJ, Houser TL, Richard NE, Donahue RM, Khan ZM. Improved health-related quality of life and reduced productivity loss after treatment with bupropion sustained release: a study in patients with major depression. Prim Care Companion J Clin Psychiatry. 2001;3(1):10–6.
171. Herrera-Guzman I, Gudayol-Ferre E, Lira-Mandujano J, Herrera-Abarca J, Herrera-Guzmán D, Montoya-Pérez K, Guardia-Olmos J. Cognitive predictors of treatment response to bupropion and cognitive effects of bupropion in patients with major depressive disorder. Psychiatry Res. 2008;160(1):72–82.
172. Jefferson JW, Rush AJ, Nelson JC, VanMeter SA, Krishen A, Hampton KD, Wightman DS, Modell JG. Extended-release bupropion for patients with major depressive disorder presenting with symptoms of reduced energy, pleasure, and interest: findings from a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2006;67(6):865–73.
173. Clayton AH, El Haddad S, Iluonakhamhe JP, Ponce Martinez C, Schuck AE. Sexual dysfunction associated with major depressive disorder and antidepressant treatment. Expert Opin Drug Saf. 2014;13(10):1361–74.

174. Clayton AH, Warnock JK, Kornstein SG, Pinkerton R, Sheldon-Keller A, McGarvey EL. A placebo-controlled trial of bupropion SR as an antidote for selective serotonin reuptake inhibitor-induced sexual dysfunction. J Clin Psychiatry. 2004;65(1):62–7.
175. Segraves RT, Balon R. Antidepressant-induced sexual dysfunction in men. Pharmacol Biochem Behav. 2014;121:132–7.
176. Segraves RT, Kavoussi R, Hughes AR, Batey SR, Johnson JA, Donahue R, Ascher JA. Evaluation of sexual functioning in depressed outpatients: a double-blind comparison of sustained-release bupropion and sertraline treatment. J Clin Psychopharmacol. 2000;20(2):122–8.
177. Patel K, Allen S, Haque MN, Angelescu I, Baumeister D, Tracy DK. Bupropion: a systematic review and meta-analysis of effectiveness as an antidepressant. Ther Adv Psychopharmacol. 2016;6(2):99–144.
178. Bupropion [prescribing information]. Research Triangle Park: GlaxoSmithKline. https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Wellbutrin_Tablets/pdf/wellbutrin-tablets-pi-mg.pdf. Revised April 2016. Accessed 21 Apr 2017.
179. Yang BK, Donatucci CF. Drugs that affect male sexual function. In: Mulcahy J, editor. Male sexual function: a guide to clinical management. 2nd ed. Totowa: Humana; 2006. p. 155–94.
180. Stahl SM, Sommer B, Allers KA. Multifunctional pharmacology of flibanserin: possible mechanism of therapeutic action in hypoactive sexual desire disorder. J Sex Med. 2011;8(1):15–27.
181. Presentation at meeting of the FDA advisory committee for reproductive health drugs. 2010. http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/reproductivehealthdrugsadvisorycommittee/ucm248751.pdf. Published June 18, 2010. Accessed 8 May 2017.
182. Popova NK, Amstislavskaya TG. Involvement of the 5-HT (1A) and 5-HT (1B) serotonergic receptor subtypes in sexual arousal in male mice. Psychoneuroendocrinology. 2002;27(5):609–18.
183. Sang JH, Kim TH, Kim SA. Flibanserin for treating hypoactive sexual desire disorder. J Menopausal Med. 2016;22(1):9–13.
184. Kennedy S. Flibanserin: initial evidence of efficacy on sexual dysfunction, in patients with major depressive disorder. J Sex Med. 2010;7(10):3449–59.
185. Flibanserin [prescribing information]. Bridgewater: Valeant Pharmaceuticals. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022526lbl.pdf. Accessed 2 May 2017.
186. Katz M, Derogatis LR, Ackerman R, Hedges P, Lesko L, Garcia M Jr, Sand M, BEGONIA trial investigators. Efficacy of flibanserin in women with hypoactive sexual desire disorder: results from the BEGONIA trial. J Sex Med. 2013;10(7):1807–15.
187. Simon JA, Kingsberg SA, Shumel B, Hanes V, Garcia M Jr, Sand M. Efficacy and safety of flibanserin in postmenopausal women with hypoactive sexual desire disorder: results of the SNOWDROP trial. Menopause. 2014;21(6):633–40.
188. Flibanserin for the treatment of hypoactive sexual desire disorder in premenopausal women: Flibanserin Advisory Committee briefing document. http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/drugsafetyandriskmanagementadvisorycommittee/ucm449090.pdf. Published June 4, 2015. Accessed 15 Apr 2017.
189. US Food and Drug. FDA briefing document. US food and drug. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm458734.htm. Published August 18, 2015. Accessed 15 Apr 2017.
190. Goldstein I, Kim NN, Clayton AH, DeRogatis LR, Giraldi A, Parish SJ, Pfaus J, Simon JA, Kingsberg SA, Meston C, Stahl SM, Wallen K, Worsley R. Hypoactive sexual desire disorder: International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review. Mayo Clin Proc. 2017;92(1):114–28.
191. Brotto LA. Evidence-based treatments for low sexual desire in women. Front Neuroendocrinol. 2017;45:11–7.

192. Jaspers L, Feys F, Bramer WM, Franco OH, Leusink P, Laan ET. Efficacy and safety of flibanserin for the treatment of hypoactive sexual desire disorder in women: a systematic review and meta-analysis. JAMA Intern Med. 2016;176(4):453–62.
193. Sahebkar A, Saadat SH, Panahi Y, Kabir A, Rahmani K, Hosseinialhashemi M. Systematic review and meta-analysis of flibanserin's effects and adverse events in women with hypoactive sexual desire disorder. Curr Drug Metab. 2016. Online publication. http://benthamscience.com/journals/currentdrug-metabolism/. Accessed 26 May 2017.

Medication-Associated Sexual Dysfunction in Patients with Mental Illness

21

Alessandro Cuomo, Arianna Goracci, and Andrea Fagiolini

21.1 Introduction

Sexual dysfunction (SD) is a common symptom in patients with mental illness and is a frequent side effect of antipsychotics and antidepressant medications, which are frequently used to treat such conditions. Worldwide, it is estimated that approximately 20–30% of adult men and 40–45% of adult women experience SD [1]. In the US general population, up to 31% of men and 43% of women complain of SD [2].

The prevalence of SD in patients with mental illness is even higher than the prevalence in the general population. For instance, in patients with depression, SD has been described with a prevalence of 40–69% even before antidepressant treatment is started [3]. Indeed, depression presents with several symptoms that may directly or indirectly decrease interest and satisfaction in sex, independent on medications. For instance, symptoms like reduced interest, loss of energy, reduced self-esteem, and anhedonia may adversely impact sexual function. Also, symptoms such as social isolation, dysphoria, and irritability are capable to impair the ability to initiate or sustain intimate bonds.

A prospective cohort study [4] evaluated a group of young patients of age 28–35 years, with major depression, dysthymia, or recurrent brief depression. The overall prevalence of SD was twice as much the prevalence observed in a control group (50% vs. 24%). The study also investigated the differences in the prevalence of SD between patients who were untreated and patients who were receiving medications (either benzodiazepines or antidepressants) or psychotherapy. SD was more frequent in the 78 individuals who were treated (62%) than in the 122 subjects who did not receive any treatment (45%). Of interest, no statistically significant

A. Cuomo · A. Goracci · A. Fagiolini (✉)
Department of Molecular and Developmental Medicine, Division of Psychiatry, Ospedale le Scotte, Clinica Psichiatrica, University of Siena, Siena, Italy
e-mail: andreafagiolini@unisi.it

E. A. Jannini, A. Siracusano (eds.), *Sexual Dysfunctions in Mentally Ill Patients*, Trends in Andrology and Sexual Medicine, https://doi.org/10.1007/978-3-319-68306-5_21

difference was found in the prevalence of any form of sexual dysfunction between patients treated with medication or psychotherapy alone. However, this may be attributable to the young age of the study groups, and the results may be not applicable to older age groups [5].

Only few studies have investigated sexual function in patients with schizophrenia. Delusions and hallucinations involving sexual issues may represent core symptoms of schizophrenia, and, in those cases, treating psychosis is likely to be associated with an improvement in sexual functions. Not surprisingly, the onset of psychosis was often associated with reduced sexual activity [6].

Interestingly, a study comparing individuals treated with depot antipsychotics to a group of untreated patients found that the active treatment improved sexual desire and thoughts but was also followed by increased complains of sexual dysfunction [7]. A study involving inpatients reported that 25% of women and 62% of men with schizophrenia complained sexual or relationship problems, compared with 50–100% of women and 63–75% of men with affective disorders [8]. In another trial, SD resulted significantly more common in individuals with schizophrenia who were treated with medications than in subjects with anxiety disorders who were not receiving medications [9].

Olfson et al. [10] studied the prevalence and clinical correlates of sexual dysfunction in males with schizophrenia treated with olanzapine, risperidone, quetiapine, or haloperidol and evaluated the associations between sexual dysfunction and quality of life. Sexual dysfunction resulted to be common and occurred in 45.3% of patients, who also reported significantly lower ratings on quality of life and enjoyment in their life and were significantly less likely to report having a romantic partner. Among patients with romantic partners, those with SD were found to have a significantly poorer quality of their relationships.

SD has been reported as a side effect of several psychotropic medications, and the classes that are more frequently been involved are antidepressants and antipsychotics. The reported prevalence of sexual dysfunction induced by psychotropic medications (PMSD) varied depending on the methodology of assessment. Indeed, spontaneous reporting or similar nonspecific assessment strategies were very unlikely to produce the same results of direct questioning. For instance, Montejo-Gonzalez et al. [11] reported a prevalence of antidepressant-associated SD of 14.2% with spontaneous reporting versus a prevalence of 58.1% obtained with direct questioning. These results were similar to those of other reports, such as the ELIXIR study, where spontaneous SD reporting was 35% versus a percentage of 69% that was recorded with direct patient questioning [12].

21.2 Pathophysiology of Medication-Induced Sexual Dysfunction

Usually, SDs involve one or more phases of sexual functioning: libido (desire, interest in sex), arousal (erection or vaginal lubrication), and/or orgasm and ejaculation. Different hormones and neurotransmitters may be involved in each of the three

phases, including acetylcholine, angiotensin II, cholecystokinin, dopamine, gonadotrophin-releasing hormone, oxytocin, nitric oxide, neuropeptide Y, noradrenaline, serotonin (5-hydroxytryptamine; 5-HT), substance P, vasopressin, and γ-aminobutyric acid.

The neurotransmitters and hormones that are most involved in sexual *desire* include dopamine (DA), melanocortin, testosterone and estrogen, which enhance desire, and prolactin and serotonin (5HT) which exerts a negative influence. In general, the serotonin system exerts an inhibitory role on sexual desire, orgasm, and ejaculation, via the stimulation of 5HT type 2 and 5-HT3 receptors. However, stimulation of 5-HT1A receptors facilitates these functions [13].

The neurotransmitters and hormones that have a positive influence on sexual *arousal* include acetylcholine (Ach), dopamine (DA), estrogen, melanocortin, nitric oxide (NO), norepinephrine (NE), and testosterone, whereas serotonin inhibits arousal, similarly to what happens for sexual desire. Sexual *orgasm* is inhibited by serotonin as well and facilitated by norepinephrine and, to a lesser degree, by dopamine and nitric oxide.

Serotonin, dopamine, and nitric oxide are thought to be among the neurotransmitters that contribute the most to antidepressant and antipsychotic medication-induced SD [14]. For instance, increased serotonergic neurotransmission may inhibit sexual behavior. In animal models, sexual behavior is reduced by stimulation of 5-HT2 receptors and antagonists at this receptor, such as cyproheptadine, or agonists at the 5-HT1a receptor, such as buspirone, are able to contrast sexual dysfunction caused by selective serotonin reuptake inhibitors (SSRIs). While an increase of serotonergic stimulation is widely considered the most important cause of SSRI-induced SD, secondary effects like dopamine release reduction, increased prolactin, and reduced nitric oxide synthesis may play a significant role as well [15].

Dopamine is another important neurotransmitter involved in sexual function. For instance, it is known that increased levels of central dopamine are associated with an increase in sexual arousal and with an enhancement of penile erection. In animal models, dopaminergic medications have shown the ability to enhance sexual behavior. In men with hyperprolactinemia, bromocriptine (a dopamine agonist) is known to be able to improve SD [15, 16]. Conversely, antipsychotic medications, most of which work as antagonist at the dopamine 2 receptor, may reduce sexual function, either directly or indirectly, via hyperprolactinemia and its effects on testosterone [17]. In fact, testosterone release is inhibited by prolactin, and drugs that are able to increase prolactin levels (e.g., antipsychotics and tricyclic antidepressants) indirectly reduce the levels of testosterone [18]. Moreover, a rise in prolactin level is associated with an increase of GABAergic transmission and of endogenous opioid levels, which both adversely affect libido and erection [19].

The parasympathetic system is involved in sexual function as well. In fact, acetylcholine leads to vasodilation and erection of the penis and clitoris, as well as to vaginal swelling, whereas norepinephrine inhibits erection by binding to peripheral alpha-1 receptors, which explains the cases of priapism that may be observed in patients taking antipsychotics with significant blockade of alpha-1 adrenergic receptors. Nitric oxide is also involved in the erection process. In fact, penile and clitoris

erection are due to the vasodilatation that follows relaxation of smooth muscle in the corpus cavernosum and are primarily mediated by nitric oxide, which increases the levels of cGMP (nucleotide guanosine monophosphate, cyclic). Similarly, an increase in cGMP may be obtained via the inhibition of the enzymes which are involved in its breakdown, i.e., phosphodiesterases. For instance, sildenafil is able to increase nitric oxide-mediated vasodilatation in the corpus cavernosum by inhibiting phosphodiesterase-5 enzyme, thus inhibiting the breakdown of cGMP.

Genetic factors may be involved in drug-induced SD. For instance, genetic polymorphisms of the serotonin 5HT2a, dopamine D4 receptor, cytochrome P450, serotonin transporter and SLC6A4, glutamate, GNB3, BDNF, and ABCB1 genes may play a role [20–25].

21.3 Antidepressants

Most antidepressants have been associated with SD, with differences likely determined by the specific mechanisms of action and pharmacodynamics profiles. The highest SD prevalence has been observed with SSRIs, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) [15].

SD is frequent with all SSRIs, but some studies have described higher prevalence with paroxetine [15], and some authors postulated that paroxetine's greater anticholinergic effects and/or its ability to decrease nitric oxide synthesis may be one of the reasons [26]. Clayton et al. evaluated more than 6000 patients receiving antidepressant monotherapy and measured the prevalence of sexual dysfunction using the Changes in Sexual Functioning Questionnaire. SD was observed at a rate between 35% and 45% in patients on citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine [27].

TCAs' SD prevalence and features correlate to the extent to which they inhibit serotonin reuptake. For instance, clomipramine strongly inhibits the serotonin reuptake and carries a high rate of SD in general and of anorgasmia in particular. However, SD was also reported for TCAs with a lower effect on serotonergic reuptake. In these cases, cholinergic and/or alpha-adrenergic blockade might be the culprit of SD such as erectile dysfunction.

Sexual side effects appear to be more prevalent with MAOIs than with TCAs, perhaps similar to the rate seen with SSRIs. MAOIs directly increase serotonergic neurotransmission, and their substantial alpha-adrenergic antagonist effects may also produce sexual side effects.

A lower SD prevalence has been observed with patients taking nefazodone, a 5-HT2 antagonist, and bupropion, a norepinephrine dopamine reuptake inhibitor. Of interest, mirtazapine showed a rate of sexual dysfunction of approximately 40%, which is similar to the rate that was observed for SSRI medications. However, this could be due to the older age of mirtazapine-treated subjects. In a head-to-head trial between duloxetine and escitalopram, SD was significantly higher for escitalopram compared with placebo and duloxetine, at the 4-week assessment, and higher than placebo at the 8-week assessment [28]. Montejo et al. [26] evaluated the

relationship between SD and the different medication classes. The overall prevalence of SD was assessed via the Psychotropic-Related Sexual Dysfunction Questionnaire (PrSexDQ) and resulted 60%. Subjects treated with SSRIs (57.7–72.7%) or venlafaxine (67.3%) showed the highest rates overall.

Lower prevalence was found with amineptine (6.9%), mirtazapine (24.4%), moclobemide (3.9%), and nefazodone (8.0%).

Serretti and Chiesa [29] conducted a meta-analysis reporting an incidence of SD ranging from 4% (moclobemide and agomelatine) to 80% (venlafaxine and sertraline). The incidence for amineptine was 7%, for nefazodone 8%, for bupropion 10%, for mirtazapine 24%, for fluvoxamine 26%, for escitalopram 37%, for duloxetine and phenelzine 42%, for imipramine 44%, for fluoxetine 70%, for paroxetine 71%, and for citalopram 79%. Some of these results, however, could be influenced by the use of assessment instruments that are more or less sensitive than others in assessing the presence of SD [29, 30].

21.4 Antipsychotics

Several studies have pointed to antipsychotic-induced SD. For instance, a study on patient satisfaction with antipsychotics found that 43% of the 202 individuals who were studied reported SD [31].

Sexual side effects of antipsychotic drugs may arise both from their direct pharmacological effects, such as antagonism at the dopamine receptor, and from secondary hyperprolactinemia. However, a study involving individuals treated with conventional antipsychotics found that hyperprolactinemia was the main determinant of SD, despite the fact that SD occurred both in patients with increased prolactin levels and in patients whose levels were normal [32]. Indeed, hyperprolactinemia was often associated with a significant reduction in sexual desire, erectile dysfunction, and lowered spermatogenesis in men and with reduced sexual desire, abnormalities in the ovarian cyclic function, amenorrhea, and hirsutism in women [33]. However, side effects such as sedation, extrapyramidal symptoms, and weight gain might contribute to the other mechanisms involved in antipsychotic-induced SD.

Although it is more common that patients experience difficulties achieving and maintaining erection than priapism, cases of antipsychotic-induced priapism have been reported.

Antipsychotic-induced priapism may be due to a combined α-adrenergic and cholinergic antagonism. Hence, antipsychotics with anti- α-adrenergic and anticholinergic profile such as chlorpromazine or thioridazine may prevent detumescence but, at the same time, carry a higher risk of priapism. Not surprisingly, up to 20% of reports of drug-induced priapism were due to antipsychotic drugs [34, 35].

Ejaculatory problems, such as complete inhibition of ejaculation, reduced ejaculatory volume, retrograde ejaculation, or painful ejaculation, have been described in patients treated with antipsychotics [34, 36, 37].

Second-generation atypical antipsychotics may be correlated to a lower degree of SD, owing to their relatively high affinity for 5-HT2 receptors, upon which they

act as antagonists. Antagonism at 5-HT2 receptors has been associated with enhanced sexual behavior. Of interest, a study comparing men receiving first-generation antipsychotics or clozapine demonstrated that clozapine was associated with significantly better frequency of orgasm and sexual pleasure [38]. Among other things, clozapine is one of the antipsychotics that is less likely to induce hyperprolactinemia. Quetiapine is another medication that has not been associated with hyperprolactinemia, and a retrospective cross-sectional study showed that SD was less prevalent with quetiapine (18% at a mean dose of 360.5 mg/day) than with haloperidol (38% at 10.6 mg/day), risperidone (43%, at 5.3 mg/day), or olanzapine (35% at 13.5 mg/day) [39].

Not surprisingly, a study comparing olanzapine and risperidone found that sexual dysfunction was significantly more common with risperidone, a medication that is more frequently associated with hyperprolactinemia [40]. Cases of retrograde ejaculation and priapism were reported with clozapine, risperidone, and olanzapine [41–45]. As mentioned above, those cases may have been due to α-adrenergic and (particularly for clozapine and olanzapine) cholinergic antagonism.

21.5 Mood Stabilizers

Valproate may increase estrogen and testosterone levels, which in turn may lead to reduced testicular volume in men and hirsutism and polycystic ovarian syndrome in women. Valproate has been associated to decreased libido and anorgasmia, which may be secondary to a raise of serotonergic transmission induced by the medication. Valproate may also decrease the levels of sex hormone-binding globulin (SHBG), which increases free testosterone levels and causes hyperandrogenism [22]. Conversely, carbamazepine may increase the levels of SHBG, which decreases free testosterone and causes hypogonadism [22]. Cases of SD have been reported with lithium, but the mechanisms are not yet well understood [22].

21.6 Treatment Strategies

21.6.1 Giving Time

Sexual side effects may subside spontaneously in about 20% of cases [26]. However, a number of months may be necessary before SD diminish, which makes this strategy unviable for patients with significant SD [15].

21.6.2 Reducing Medication Dosage or Changing the Time of Administration

Medication-induced SD may be dose related [11, 15], and a dose reduction might improve this side effect without jeopardizing antidepressant efficacy. However, the risk of a relapse into an acute episode should be adequately considered.

Other strategies to decrease SD might include splitting the dosage or waiting to administration until after sexual activity, which may reduce the concentration at the time of a sexual intercourse. A 2–3-day "medication holiday" may be considered as well [46].

Drug holidays are unlikely to help patients taking medications with a long half-life, such as fluoxetine, as plasma level would not drop sufficiently fast. Also, medication holidays may not be a valid option for patients who are still experiencing acute symptoms or have a history of withdrawal symptoms or symptom recurrence when discontinuing medications [15].

21.6.3 Switching Antidepressant Medication

There clearly are differences among different medications for the risk of inducing SD. For instance, among antidepressants the risks of developing SD were four times greater for fluoxetine, five times greater for sertraline and paroxetine, and six times greater for venlafaxine XR and citalopram, compared to bupropion [27].

Bupropion has shown a relatively favorable SD profile compared to escitalopram [47] and venlafaxine XR [48].

Vortioxetine may be another useful medication to switch to. In fact, a number of randomized, placebo-controlled trials in patients with major depressive disorder (MDD) have shown that vortioxetine is similar to placebo in terms of rates of sexual dysfunction. Also, a recent trial [49] demonstrated its superiority versus escitalopram to improve SD in patients with MDD and treatment-emergent SD. In fact, vortioxetine showed significantly greater improvements in the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14); score and significant benefits vs. escitalopram were observed on 4 out of 5 dimensions and all three phases of sexual functioning that were assessed by the CSFQ-14. Vortioxetine is a multimodal antidepressant combining the inhibition of the serotonin transporter (SERT) with a direct modulation of several receptors. Specifically, vortioxetine is an agonist at 5-HT1A receptor; an antagonist at 5-HT1D, 5-HT3, and 5-HT7 receptors; and a partial agonist at 5-HT1B receptors [50].

Agomelatine is another antidepressant with relatively low incidence of SD. In clinical trials, agomelatine showed a rate of only 7.3% compared with 15.7% for venlafaxine XR [51].

21.6.4 Augmentation Therapy

Adding a new drug to the ongoing treatment may help continued efficacy while reducing SD. For instance, bupropion reversed the SD in 66% of a group of patients participating in a study evaluating the combination of bupropion SR with fluoxetine, paroxetine, or venlafaxine [52].

In another trial that compared bupropion SR and placebo as augmenting strategy for patients on SSRIs, bupropion SR 150 mg twice daily for 4 weeks resulted in a significant improvement in the frequency and desire of sexual activity (as reported on the CSFQ), compared to placebo, both used as adjunctive treatments of a SSRI [53].

Of interest, bupropion may also reduce residual depressive symptoms, if present, and may offer an additional benefit in individuals with residual symptoms of depression [54].

Phosphodiesterase type 5 (PDE5) inhibitors, such as sildenafil, tadalafil, and vardenafil, have benefited millions of patients and their partners who took advantage from this simple and highly efficacious treatment for SD in general and erectile dysfunction in particular. For instance, three placebo-controlled randomized, clinical trials evaluated the efficacy of sildenafil to improve SD in patients receiving SSRI/SNRIs. The first trial studied men who received sildenafil 50–100 mg dose compared with placebo and reported a significant improvement for the sildenafil group in SD as assessed via the Clinical Global Impression–Sexual Function [CGI-SF], ASEX, and Massachusetts General Hospital–Sexual Function Questionnaire [MGH-SFQ]. All individual parameters of male sexual function were shown to be significantly improved with sildenafil [55]. In a second trial, 142 men with a history of major depressive disorder and SSRI-associated erectile dysfunction (ED) were enrolled in a placebo-controlled, 6-week, randomized, flexible-dose, double-blind trial. Sildenafil resulted well tolerated and was significantly better than placebo in improving ED and sexual satisfaction [56]. In a third trial, women experiencing antidepressant-induced SD were prescribed sildenafil 50–100 mg dose, and adverse sexual effects, such as delayed orgasm and inadequate lubrication, were significantly reduced [57].

Evliyaoğlu et al. [58] conducted a double-blind, randomized, placebo-controlled trial to test the safety and efficacy of tadalafil in men with SD due to serotonin reuptake inhibitors and found that treatment with tadalafil 20 mg significantly improved SD with mild-to-moderate and well-tolerable adverse events.

PDE5 medications are contraindicated in subjects treated with nitrates owing to the severe risk of excessive hypotensive effects. Nitrates are mainly prescribed for their vasodilatory properties, for instance, in the treatment of angina and heart failure. However, nitrates may be prescribed for other indications and sometimes used intermittently for recreational/abuse purposes, often in a nonclinical form such as amyl nitrate or "poppers." Caution is also necessary for patients with a history of myocardial infarction, stroke, arrhythmia, low or high blood pressure, heart failure, angina, or retinitis pigmentosa [15, 54]. In addition to erection, PDE5 may be helpful in premature ejaculation. In clinical trials [59] PDE5 has proven significantly better than placebo, and PDE5 combined with an SSRI was significantly better than SSRIs alone at improving premature ejaculation and other effectiveness outcomes.

Of interest, bupropion seems more effective than sildenafil for increasing sexual desire and thus may be the medication of choice for patients in whom a decrease in sexual desire is the prominent SD symptoms. However, sildenafil seems to be more effective than bupropion for increasing overall sexual satisfaction in men with erectile dysfunction and thus may be may be the medication of choice for those patients [15].

Additional augmentation strategies include the possibility to use cholinergic agonists such as bethanechol, administered at doses of 10–50 mg/day, to treat SD caused by anticholinergic effects [60].TCA-related SD may be also reversed by cyproheptadine, a serotonin receptor antagonist, at doses between 4 and 12 mg/day [61].

Conclusion

Although there is extensive evidence that medications such as antidepressants, mood stabilizers, and antipsychotics cause SD, it is difficult to estimate the exact prevalence. There is a large variation in methodological approaches. Moreover, SD is often underestimated since patients are reluctant to discuss SD with their clinicians. In addition, clinicians may not care about SD during the acute phase, finding it difficult to distinguish between SD induced by medication, those caused by the mental illness itself, by other diseases, and psychosocial factors.

However, it is clear that SD is a frequent and impairing side effect of many psychotropic medications with negative impact on patient's and partner's quality of life. Hence, obtaining a sexual history before starting medications and monitoring sexual functions thereafter is paramount.

The risk of medication associated SD should be one of the informants when choosing treatment for patients with mental illness, especially when it is predicted that the patient will likely to take the drug for long periods. This may help to minimize the impact on quality of life and help with treatment adherence. Once SD arises, it should be promptly recognized and treated with one of the many options that are available. This may improve patient's quality of life, functioning, treatment satisfaction, and adherence to the medication regimen.

References

1. Lewis RW, Fugl-Meyer KS, Bosch R, Fugl-Meyer AR, Laumann EO, Lizza E, et al. Epidemiology/risk factors of sexual dysfunction. J Sex Med. 2004;1(1):35–9.
2. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA. 1999;281(6):537–44. Erratum in: JAMA 1999; 281: 1174.
3. Johannes CB, Clayton AH, Odom DM, Rosen RC, Russo PA, Shifren JL, et al. Distressing sexual problems in United States women revisited: prevalence after accounting for depression. J Clin Psychiatry. 2009;70:1698–706.
4. Ernst C, Foldenyi M, Angst J. The Zurich Study: XXI. Sexual dysfunctions and disturbances in young adults. Eur Arch Psychiatry Clin Neurosci. 1993;243:179–88.
5. Angst J. Sexual problems in healthy and depressed patients. Int Clin Psychopharmacol. 1998;13(suppl 6):S1–3.
6. Rozan GH, Tuchin T, Kurland ML. Some implications of sexual activity for mental illness. Ment Hyg. 1971;55:318–23.
7. Aizenberg D, Aizenberg D, Zemishlany Z, Dorfman-Etrog P, Weizman A. Sexual dysfunction in male schizophrenic patients. J Clin Psychiatry. 1995;56:137–41.
8. Bhui K, Puffet A, Herriot P. A survey of sexual problems amongst psychiatric inpatients. Soc Psychiatry Psychiatr Epidemiol. 1995;30:73–7.
9. Teusch L, Scherbaum N, Böhme H, Bender S, Eschmann-Mehl G, Gastpar M. Different patterns of sexual dysfunctions associated with psychiatric disorders and psychopharmacological treatment. Results of an investigation by semistructured interview of schizophrenic and neurotic patients and methadone substituted opiate addicts. Pharmacopsychiatry. 1995;28:84–92.
10. Olfson M, Uttaro T, Carson WH, Tafesse E. Male sexual dysfunction and quality of life in schizophrenia. J Clin Psychiatry. 2005;66:331–8.
11. Montejo-González AL, Llorca G, Izquierdo JA, Ledesma A, Bousoño M, Calcedo A, et al. SSRI induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a

prospective, multicenter, and descriptive clinical study of 344 patients. J Sex Marital Ther. 1997;23:176–94.
12. Bonierbale M, Lançon C, Tignol J. The ELIXIR study: evaluation of sexual dysfunction in 4557 depressed patients in France. Curr Med Res Opin. 2003;19:114–24.
13. Just MJ. The influence of atypical antipsychotic drugs on sexual function. Neuropsychiatr Dis Treat. 2015;11:1655–61.
14. Baldwin D, Mayers A. Sexual side-effects of antidepressant and antipsychotic drugs. Adv Psychiatr Treat. 2013;9:202–10.
15. Nelson E. Sex and antidepressants: when to switch drugs or try an antidote. Curr Psychiatry. 2004;3:53–66.
16. Ramirez G, Butcher DE, Newton JL, Brueggemeyer CD, Moon J, Gomez-Sanchez C. Bromocriptine and the hypothalamic hypophyseal function in patients with chronic renal failure on chronic haemodialysis. Am J Kidney Dis. 1985;6:111–8.
17. Segraves RT. Effects of psychotropic drugs on human erection and ejaculation. Arch Gen Psychiatry. 1989;46:275–84.
18. Waldinger MD. Psychiatric disorders and sexual dysfunction. Handb Clin Neurol. 2015;130:469–89.
19. Freeman ME, Kanyicska B, Lerant A, Nagy G. Prolactin: structure, function, and regulation of secretion. Physiol Rev. 2000;80:1523–63.
20. Ben Zion IZ, Tessler R, Cohen L, Lerer E, Raz Y, Bachner-Melman R, et al. Polymorphisms in the dopamine D4 receptor gene (DRD4) contribute to individual differences in human sexual behavior: desire, arousal and sexual function. Mol Psychiatry. 2006;11:782–6.
21. Bishop JR, Ellingrod VL, Akroush M, Moline J. The association of serotonin transporter genotypes and selective serotonin reuptake inhibitor (SSRI)-associated sexual side effects: possible relationship to oral contraceptives. Hum Psychopharmacol. 2009;24:207–15.
22. Clayton AH, Alkis AR, Parikh NB, Votta JG. Sexual dysfunction due to psychotropic medications. Psychiatr Clin North Am. 2016;39:427–63.
23. Bishop JR, Moline J, Ellingrod VL, Schultz SK, Clayton AH. Serotonin 2A-1438 G/A and G-protein Beta 3 subunit C825T polymorphisms in patients with depression and SSRI associated sexual side effects. Neuropsychopharmacology. 2006;31:2281–8.
24. Zourková A, Hadasová E. Relationship between CYP 2D6 metabolic status and sexual dysfunction in paroxetine treatment. J Sex Marital Ther. 2002;28:451–61.
25. Zourková A, Cesková E, Hadasová E, Ravcuková B. Links among paroxetine induced sexual dysfunctions, gender, and CYP2D6 activity. J Sex Marital Ther. 2007;33:343–55.
26. Montejo AL, Llorca G, Izquierdo JA, Rico-Villademoros F. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. J Clin Psychiatry. 2001;62(suppl 3):10–21.
27. Clayton AH, Pradko JF, Croft HA, Montano CB, Leadbetter RA, Bolden-Watson C, et al. Prevalence of sexual dysfunction among newer antidepressants. J Clin Psychiatry. 2002;63:357–66.
28. Clayton A, Kornstein S, Prakash A, Mallinckrodt C, Wohlreich M. Changes in sexual functioning associated with duloxetine, escitalopram, and placebo in the treatment of patients with major depressive disorder. J Sex Med. 2007;4:917–29.
29. Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. J Clin Psychoparmacol. 2009;29:259–66.
30. La Torre A, Giupponi G, Duffy D, Conca A. Sexual dysfunction related to psychotropic drugs: a critical review–part I: antidepressants. Pharmacopsychiatry. 2013;46:191–9.
31. Wallace M. Real progress – the patient's perspective. Int Clin Psychopharmacol. 2001;16(suppl 1):S21–4.
32. Smith S, O'Keane V, Murray R. Sexual dysfunction in patients taking conventional antipsychotic medication. Br J Psychiatry. 2002;181:49–55.
33. Petty RG. Prolactin and antipsychotic medications: mechanism of action. Schizophr Res. 1999;35(suppl):S67–73.

34. Baldwin D, Birtwistle J. Schizophrenia, antipsychotic drugs and sexual function. Prim Care Psychiatry. 1997;3:115–23.
35. Patel AG, Mukherji K, Lee A. Priapism associated with psychotropic drugs. Br J Hosp Med. 1996;55:315–9.
36. Mitchell J, Popkin M. The pathophysiology of sexual dysfunction associated with antipsychotic drug therapy in males: a review. Arch Sex Behav. 1983;12:173–83.
37. Ghadirian AM, Chouinard G, Annable L. Sexual dysfunction and plasma prolactin levels in neuroleptic treated schizophrenic outpatients. J Nerv Ment Dis. 1982;170:463–7.
38. Aizenberg D, Modai I, Landa A, Gil-Ad I, Weizman A. Comparison of sexual dysfunction in male schizophrenic patients maintained on treatment with classical antipsychotics versus clozapine. J Clin Psychiatry. 2001;62:541–4.
39. Bobes J, Garc A-Portilla MP, Rejas J, Hern Ndez G, Garcia-Garcia M, Rico-Villademoros F, et al. Frequency of sexual dysfunction and other reproductive side-effects in patients with schizophrenia treated with risperidone, olanzapine, quetiapine, or haloperidol: the results of the EIRE study. J Sex Marital Ther. 2003;29:125–47.
40. Tran PV, Hamilton SH, Kuntz AJ, Potvin JH, Andersen SW, Beasley C Jr, et al. Double blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol. 1997;17:407–18.
41. Rosen SI, Hanno PM. Clozapine-induced priapism. J Urol. 1992;148:876–7.
42. Emes CE, Milson RC. Risperidone-induced priapism. Can J Psychiatry. 1994;39:315–6.
43. Deirmenjian JH, Erhart SM, Wirshing DA, Spellberg BJ, Wirshing WC. Olanzapine-induced reversible priapism: a case report. J Clin Psychopharmacol. 1998;18:351–3.
44. Compton MT, Saldivia A, Berry SA. Recurrent priapism during treatment with clozapine and olanzapine. Am J Psychiatry. 2000;157:659.
45. Songer DA, Barclay JC. Olanzapine-induced priapism. Am J Psychiatry. 2001;158:2087–8.
46. Rothschild AJ. Selective serotonin reuptake inhibitor-induced sexual dysfunction: efficacy of a drug holiday. Am J Psychiatry. 1995;152:1514–6.
47. Clayton AH, Croft HA, Horrigan JP, Wightman DS, Krishen A, Richard NE, et al. Bupropion extended release compared with escitalopram: effects on sexual functioning and antidepressant efficacy in 2 randomized, double-blind, placebo-controlled studies. J Clin Psychiatry. 2006;67:736–46.
48. Thase ME, Clayton AH, Haight BR, Thompson AH, Modell JG, Johnston JA. A double-blind comparison between bupropion XL and venlafaxine XR: sexual functioning, antidepressant efficacy, and tolerability. J Clin Psychopharmacol. 2006;26:482–8.
49. Jacobsen PL, Mahableshwarkar AR, Chen Y, Chrones L, Clayton AH. Effect of vortioxetine vs. escitalopram on sexual functioning in adults with well-treated major depressive disorder experiencing SSRI-induced sexual dysfunction. J Sex Med. 2015;12:2036–48.
50. Bang-Andersen B, Ruhland T, Jorgensen M, Smith G, Frederiksen K, Jensen KG, et al. Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. J Med Chem. 2011;54:3206–21.
51. Ereshefsky L, Saragoussi D, Despiégel N, Hansen K, François C, Maman K. The 6-month persistence on SSRIs and associated economic burden. J Med Econ. 2010;13:527–36.
52. Kennedy SH, McCann SM, Masellis M, McIntyre RS, Raskin J, McKay G, et al. Combining bupropion SR with venlafaxine, paroxetine, or fluoxetine: a preliminary report on pharmacokinetic, therapeutic, and sexual dysfunction effects. J Clin Psychiatry. 2002;63:181–6.
53. Clayton AH, Warnock JK, Kornstein SG, Pinkerton R, Sheldon-Keller A, McGarvey EL. 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.
54. Nurnberg HG, Gelenberg A, Hargreave TB, Harrison WM, Siegel RL, Smith MD. Efficacy of sildenafil citrate for the treatment of erectile dysfunction in men taking serotonin reuptake inhibitors. Am J Psychiatry. 2001;158:1926–8.

55. Nurnberg HG, Hensley PL, Gelenberg AJ, Fava M, Lauriello J, Paine S. Treatment of antidepressant-associated sexual dysfunction with sildenafil: a randomized controlled trial. JAMA. 2003;289:56–64.
56. Fava M, Nurnberg HG, Seidman SN, Holloway W, Nicholas S, Tseng LJ, et al. Efficacy and safety of sildenafil in men with serotonergic antidepressant-associated erectile dysfunction: results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2006;67:240–6.
57. Nurnberg HG, Hensley PL, Heiman JR, Croft HA, Debattista C, Paine S. Sildenafil treatment of women with antidepressant associated sexual dysfunction: a randomized controlled trial. JAMA. 2008;300:395–404.
58. Evliyaoğlu Y, Yelsel K, Kobaner M, Alma E, Saygılı M. Efficacy and tolerability of tadalafil for treatment of erectile dysfunction in men taking serotonin reuptake inhibitors. Urology. 2011;77:1137–41.
59. Martyn-St James M, Cooper K, Ren S, Kaltenthaler E, Dickinson K, Cantrell A, et al. Phosphodiesterase type 5 inhibitors for premature ejaculation: a systematic review and meta-analysis. Eur Urol Focus. 2017;3:119–29.
60. Gross MD. Reversal by bethanechol of sexual dysfunction caused by anticholinergic antidepressants. Am J Psychiatry. 1982;139:1193–4.
61. Sovner R. Treatment of tricyclic antidepressant-induced orgasmic inhibition with cyproheptadine. J Clin Psychopharmacol. 1984;4:169.