



Sexual dysfunction in Huntington's Disease — a systematic review

Klaudia Szymuś¹, Artur Bystrzyński¹, Magdalena Kwaśniak–Butowska², Agnieszka Konkel²,
Agata Leśnicka³, Magdalena Nowacka⁴, Jarosław Sławek²

¹Faculty of Medicine, Medical University of Gdansk, Gdansk, Poland

²Department of Neurological–Psychiatric Nursing, Medical University of Gdansk, Gdansk, Poland; Neurology Department, St. Adalbert Hospital, Copernicus, Gdansk, Poland; European Huntington's Disease Network

³Department of Developmental Psychiatry, Psychotic and Geriatric Disorders, Medical University of Gdansk, Gdansk, Poland

⁴Doctoral School in the Social Sciences, University of Gdansk, Gdansk, Poland

ABSTRACT

Introduction. Huntington's Disease (HD) is a neurodegenerative disorder of which the main symptoms are motor, cognitive and behavioural problems sometimes including sexual dysfunction.

Aim. To review the current knowledge on sexual dysfunction in HD.

Methods. Databases of Pubmed and Scopus were searched. Only original studies performed after 1994 were included (from 1994 a genetic test = proven diagnosis).

Results. 162 publications were found, but only nine met our established criteria. The majority of patients with HD suffer from sexual disorders. The most common are: hypoactive sexual disorder (53–83% of patients), hyperactive sexual disorder (6–30%), erectile (48–74%) and ejaculatory dysfunctions (30–65%), lubrication problems (53–83%), and orgasmic dysfunction (35–78%).

Discussion. Results may be biased for several reasons e.g.: social taboos regarding sex lives, medications that affect sexual function, impaired self-awareness of patients, small study samples, a lack of standardised questionnaires, and a focus only on the presence of sexual problems without describing them.

Conclusions. Sexual disorders in HD are common. This is a problem that is probably underestimated, both by patients/caregivers and physicians, who should focus more on these symptoms in order to improve patient quality of life.

Key words: Huntington's Disease, sexual disorder, sexual dysfunction, sexuality, depression

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Introduction

Huntington's Disease (HD) is an autosomal dominant inherited disorder. The main symptoms consist of cognitive, behavioural and motor dysfunctions. The cause is a mutation in the *HTT* gene located on chromosome 4, which results in CAG codon expansion [1, 2]. The product of the *HTT* gene is a huntingtin protein toxic for cells [3].

According to Wexler et al., when George Huntington described the disease for the first time he mentioned “two married men, whose wives are living, and who are constantly making love to some young lady, not seeming to be aware that

there is any impropriety in it” and who “never let an opportunity to flirt with a girl go past unimproved” [4].

Current classifications define sexual dysfunction as a heterogeneous group of disorders that are typically characterised by a clinically significant disturbance in a person's ability to respond sexually or to experience sexual pleasure. An individual may have several sexual dysfunctions at the same time. They affect 41% of women and 34% of men in the general population and include: delayed ejaculation, erectile disorder, female orgasmic disorder, female sexual interest/arousal disorder, genito-pelvic pain/penetration disorder, male hypoactive sexual desire, premature (early) ejaculation,

Corresponding author: Klaudia Szymuś, Medical University of Gdansk, Gdansk, Poland, e-mail: szymus.klaudia@gmail.com

substance/medication-induced sexual dysfunction, as well as other unspecified sexual dysfunctions [5, 6].

HD can affect patient behaviour very early, even at the pre-motor stage, and at the same time may significantly influence the sex lives of HD patients and their partners [7].

Many factors can interfere with sexual health: the sexual partner (i.e. her/his general health), medications taken (Selective Serotonin Reuptake Inhibitors: SSRIs, H2 and D2 blockers, dopamine depleting agents, beta-adrenolytics), chronicity of the disease, other chronic comorbidities, religiousness, cultural factors, and individual predispositions to face stressful situations [8, 9].

As the problem of sexual dysfunction in HD seems to be important in terms of quality of life (QoL), we searched databases to see how HD affects the sex lives of patients and partners.

Methods

We performed a literature search. We searched through the databases of Scopus and PubMed. The search terms we used were: 'Huntington's disease' and 'sexual disorder', 'sexual dysfunction', and 'sexuality' in different combinations. Titles and abstracts were checked if they matched our criteria; the studies we included in the research were read in full versions.

Eligibility criteria

We included only studies published from 1994 (i.e. after the discovery of the HD gene) up to 2019, in order to include patients with genetically proven diagnosis. Studies needed to examine at least 20 patients with HD (only human subjects) and refer to their sexual life. Case studies, systematic reviews, opinions, and animal studies were excluded.

Results

We found 404 research papers, but 242 were duplicated in the two databases. Of the remaining 162, only nine fulfilled our eligibility criteria.

Almost all of the included studies identified several sexual dysfunctions related to HD, with the most prevalent being sexual desire disorder [7, 10, 11, 12, 13] and hyposexuality rather than hypersexuality.

All sexual dysfunctions were more common in HD patients than in the general population, with the exception of premature ejaculation [7]. The majority of HD patients (85% of males, 75% of females) were affected by at least one sexual disorder [7]. All included studies are presented in concise form in Table 1.

Erectile dysfunction

According to the DSM-V definition, erectile dysfunction is an inability to obtain an erection and/or maintain it sufficiently

for sexual performance, or a marked decrease of erectile rigidity. This is the dysfunction with the highest difference between HD patients and control groups in several studies: 48% vs 30% [7], 69% vs 22% [11], and 67% vs 22% [14].

Ejaculatory dysfunction

Premature or delayed ejaculation has been found significantly more frequently in HD patients in several studies: inhibited orgasm – 56% vs 0% [7], premature ejaculation – 30% vs 50% [7], any ejaculation problem – 59% vs 19% [14]. Another study found the difference to be insignificant: 65% vs 63% [11]. The incidence of inhibited male orgasm remained high even after the elimination of the influence of medications. There is also a correlation between age at onset of the disease and age at onset of inhibited male orgasm – the sexual dysfunction occurred a few years after the onset of the disease. Premature ejaculation is the only dysfunction which has been observed less frequently in HD patients than in control groups [7]. Both ejaculatory and erectile dysfunctions were more frequent in patients with HD than in pre-manifest mutation carriers.

Orgasmic dysfunctions

The term 'female orgasmic disorder' refers to a marked delay, infrequency or absence of orgasm or orgasmic sensations that are markedly reduced in intensity [6]. Women with HD have reported more or the same level of problems regarding orgasm than control groups: 42% vs 9% [7], 53% vs 51% [14], and 78% vs 49% [12]. Unlike the male HD population, this problem does not correlate with age at disease onset [7].

Sexual aversion and satisfaction

Sexual aversion is defined as occurring when "the prospect of sexual interaction produces sufficient fear or anxiety that sexual activity is avoided, or, if it occurs, is associated with strong negative feelings and an inability to experience any pleasure" [15]. In females, no difference was found between HD patients and a non-HD group. In males, it was not observed in controls but 15% of HD patients reported sexual aversion [7].

Diminished or lack of sexual enjoyment (intercourse satisfaction) was studied in only one research regarding males, where it was reported by 74% of HD patients vs 37% controls [11].

Arousal problems

Problems with arousal in women (failure of genital response to sexual activity where the principal problem is vaginal dryness or failure of lubrication) [15] have been observed to be more prevalent in HD: 33% vs 14% [7] and 91% vs 62% [12]. Two research papers distinguished a vaginal lubrication problem separately, but the results are inconsistent between the two, with virtually no difference and a significant difference: 53% vs 49% [14] and 83% vs 44% [12].

Vaginismus and dyspareunia

Vaginismus is a spasm of the pelvic floor muscles that surround the vagina, causing occlusion of the vaginal opening [15]. It has not been observed in any study.

Dyspareunia describes a pain during intercourse and was investigated in two studies, showing it to be more common in HD: 33% vs 9% [7] and 61% vs 43% [12]. Dyspareunia in men was measured only in one study, where it was observed neither in control nor patient groups [7].

These two nosological units are distinguished by ICD-10. However, they were merged into 'genito-pelvic pain/penetration disorder' in DSM-5 and classified under 'sexual pain disorders' in ICD-11.

Paraphilia

Paraphilia is defined as "recurrent intense sexual urges and fantasies involving unusual objects or activities" (e.g. paedophilia, exhibitionism, transvestic fetishism) [15]. Only one study has reported paraphilias in HD. The findings show they are more prevalent in the presence of the disease: 19% vs 10% males, 8% vs 0% female [7]. Both non-HD subjects and HD patients who suffered inhibited orgasm and increased sexual interest reported significantly more paraphilias [7].

Correlations and comparative studies

In females, a positive correlation between Total Functioning Capacity (TFC) score and arousal, lubrication and orgasms, as well as total FSFI (Female Sexual Function Index; a standardised questionnaire used to assess sexual dysfunction in women) score was observed. There was a borderline correlation between TFC and pain and sexual satisfaction, but no correlation between TFC and desire. In one study, patients' FSFI score increased with the loss of functional capacity: FSFI = 9.4 with TFC = 3-6; FSFI = 24.6 at TFC = 10-7 [11, 12].

A concomitant decrease of average FSFI and TFC scores was noticed after 2-4 years follow-up [12]. In men, there was a correlation between almost all International Index of Erectile Function domains (IIEF, a standardised questionnaire used to assess sexual dysfunction in men), TFC and motor indices of Unified Huntington's Disease Rating Scale (UHDRS) [11]. Another study associated sexual dysfunctions with all UHDRS indices, depressive disorders and the use of antidepressants [14].

Only two studies have focused on the association between CAG triplets and sexual dysfunction. In men, no significant correlation between the IIEF score and the number of repeats was found [11, 12]. A positive correlation between the number of triplets and sexual desire has been shown in women [11, 12].

The research observed that sexual function worsens as the disease progresses, although it has no correlation with disease duration, but only with decreased functional capacity measured using TFC and TMS [11, 12, 16].

Medications used for the treatment of depression or chorea may have also a negative impact on sexual function. A positive correlation was found for antidepressants, neuroleptics and benzodiazepines [13, 14]. Sexual dysfunctions have been found to be increased with higher Body Mass Index (BMI) and depressive symptoms (in both cases only in men) [11, 14].

One study compared the sex lives of patients with HD to those of patients with multiple sclerosis (MS). HD patients experienced a higher level of arousal at intercourse, more frequently experienced orgasms and satisfaction, and generally had fewer sexual problems than MS patients [17].

Discussion

Sexual dysfunctions are largely ignored symptoms in many diseases, by physicians, patients, caregivers and partners alike. Patients focus on cardinal problems such as depressive, behavioural or motor problems in HD, and are unaware that sexual problems may be disease-related. Nevertheless, they can influence the daily lives of patients and families, and may well have a negative impact on their QoL.

One of the major problems affecting all the studies was the social taboo regarding sex. Many studies reported that patients left blank questionnaires concerning sexual functions or marked them as "not applicable" [12, 14, 16, 17]. This may explain why so few studies performed over the last 25 years have fulfilled the criteria of eligibility, and why it is so difficult to study sexual dysfunction in patients with chronic and multifactorial diseases.

Sexual desire disorders are the most common dysfunctions found in the majority of studies. That might be why the focus has been on hypo- and hypersexuality rather than the wider spectrum of sexual dysfunctions. Erectile and ejaculatory problems, as well as orgasmic disorders and lubrication, are the second most studied group of dysfunctions. The most comprehensive study, by Fedoroff et al., included also dyspareunia, sexual aversion, vaginismus and paraphilia, whereas other studies have treated sexual dysfunction as a generally reported problem or focused on pre-specified problems [16, 18].

The variability of methods used for the assessment and the lack of controls (only 3/9 studies included a control group) make comparisons between studies difficult.

HD patients are also a multi-faceted population in terms of age at disease onset, the wide spectrum of symptoms and co-morbidities, number of CAG triplets, number of medications used for symptomatic treatment, and social and educational level. Therefore, to obtain statistically significant data, larger study groups are required. The number of patients included in the nine studies which we analysed varied from 56 up to 2,591 (Tab. 1). But in the two largest (1,238 and 2,591) there were no control groups and the data was obtained from very simple questionnaires [16, 18]. Some studies have indicated

Table 1. Concise review of studies included into analysis, showing both patient and control groups results

Study	Diagnostic tool	Sexual dysfunction in HD patients	Sexual dysfunction in a control group
Fedoroff et al., 1994 [7] N = 71 M = 37 F = 34 Mean age: 45.8 ± 11.9 years	For sexual dysfunctions diagnosis: DSM-III-R	N = 39, M = 27, F = 12 Hyposexual: 63% M, 75% F Hypersexual: 30% M, 25% F Inhibited orgasm: 56% M, 42% F Erectile dysfunction: 48% Dyspareunia: 0% M, 33% F Female sexual arousal disorder: 33% Premature ejaculation: 30% Sexual aversion disorder: 15% M, 25% F Paraphilias: 19% M, 8% F Vaginismus: 0% Any sexual disorder: 85% M, 75% F	HD-patients' partners, N = 32, M = 10, F = 22 Hyposexual: 50% M, 50% F Hypersexual: 20% M, 0% F Inhibited orgasm: 0% M, 9% F Erectile dysfunction: 30% Dyspareunia: 0% M, 9% F Female sexual arousal disorder: 14% Premature ejaculation: 50% Sexual aversion disorder: 0% M, 18% F Paraphilia: 10% M, 0% F Vaginismus: 0% Any sexual disorder: 60% M, 68% F
Craufurd et al., 2001 [10] N = 134 M = 63 F = 71 Mean age = 50 ± 12 years	For assessing behavioural changes: PBA-HD	Hyposexual: 62% (65% M, 58% F) Hypersexual: sexual disinhibition (6%; 6% M, 6% F), sexually demanding behaviour (5%; 7% M, 3% F)	No control group
Kirkwood et al., 2001 [16] N = 1,238 M = 607 F = 631	For first-degree relatives: AQ	HD-patients with minimum 6-years history of symptomatic disease Any sexual dysfunction: 9.4% after one year, 12.7% after 2-5 years, 9.8% after 6-10 years, 5.1% after more than 10 years	No control group
Aziz et al., 2010 [14] N = 169 M = 75 F = 94	For autonomic symptoms: SCOPA-AUT For motor, cognitive, behavioural functions: UHDRS For depression: BDI	Patients with symptomatic HD, N = 63, M = 29, F = 34, mean age = 48.5 ± 10.7 years Erectile dysfunction: 67% Ejaculatory problems: 59% Vaginal lubrication: 53% Problems with orgasm: 53% F Pre-manifest patients, N = 21, M = 9, F = 12, mean age = 44.4 ± 8.7 years Erectile dysfunction: 22% Ejaculatory problems: 0% Vaginal lubrication: 42% Problem with orgasm: 67% F	Randomly selected non-mutation-carrying family members, partners or acquaintances of participating patients, employees at our department or their acquaintances, N = 64, M = 27, F = 37, mean age = 47.4 ± 10.4 years Erectile dysfunction: 22% Ejaculatory problems: 19% Vaginal lubrication: 49% Problems with orgasm: 51% F
Reininghaus et al., 2012 [17] N = 56 M = 28 F = 28	For progression of HD: UHDRS For progression of MS: EDSS For body image: FBeK For quality of relationship: PFB For partnership satisfaction: ZIP For sexual behaviour: TSST	Patients with genetically proven HD, N = 29, M = 19, F = 10, mean age = 43 years <i>Percentage assessment was not provided. Instead, mean TSST score was presented.</i> N = 14 Sexual dysfunction = 1.56 ± 0.69	Patients who met criteria for clinically definite MS, N = 27, M = 9, F = 18, mean age = 42.8 years <i>Percentage assessment was not provided. Instead, mean TSST score was presented</i> N = 21 Sexual dysfunction = 2.29 ± 1.03
Kolenc et al., 2015 [11] N = M = 64	For sexual dysfunction: IIEF For neurological assessment: UHDRS and TFC For depression: BDI	Patients with genetically proven HD (pre-symptomatic carriers not included in final analysis), N = M = 23, mean age = 46 years Hyposexual: 74% M Erectile dysfunction: 69% Diminished intercourse satisfaction: 74% M Ejaculatory problems: 65% Orgasmic dysfunction: 35% M	Staff members, general practitioners' patients, HD-negative family members, N = M = 41, mean age = 42 years Hyposexual: 56% M Erectile dysfunction: 24% Diminished intercourse satisfaction: 37% M Ejaculatory problems: 63% Orgasmic dysfunction: 29% M



Table 1. cont. Concise review of studies included into analysis, showing both patient and control groups results

Study	Diagnostic tool	Sexual dysfunction in HD patients	Sexual dysfunction in a control group
Simpson et al., 2016 [18] N = 2,591	For symptoms assessment: FDA-approved, self-created surveys	Patients with HD = 536, patients with JHD = 20, mean age = 47.1 years Loss of ability to perform sexual activity: 14.6% Sexual problems: 35.7%	No control group, but caregivers participated in study assessing which patient symptoms most impactful for them Past or current caregivers of HD patients = 1,904, past or current caregivers of JHD patients = 109, mean age = 52.5 years Loss of ability to perform sexual activity: 62.3% Sexual problems: 34.4%
Kolenc et al., 2017 [12] N = F = 70	For sexual dysfunction: FSFI For neurological assessment: UHDRS and TFC For depression: BDI	Women with genetically proven HD (also pre-symptomatic carriers), N = F = 23, mean age = 53 years Hyposexual: 83% F Sexual arousal disorder: 91% F Problem with lubrication: 83% Problem with orgasm: 78% F Dyspareunia: 61% F Pre-symptomatic carriers separately, N = F = 8, mean age = 35 years Hyposexual: 25% F Sexual arousal disorder: 0% F Problem with lubrication: 13% Problem with orgasm: 13% F Dyspareunia: 25% F	General practitioners' patients, hospital staff members, HD-negative family members, N = F = 47, mean age = 47 years Hyposexual: 66% F Sexual arousal disorder: 62% F Problem with lubrication: 44% Problem with orgasm: 49% F Dyspareunia: 43% F
Aldaz et al., 2019 [13] N = 123	For motor symptoms: UHDRS-TMS For classification of stage of disease: TFC For non-motor symptoms: PD NMS-Quest	HD patients were participants of ENROLL-HD study, N = 53, M = 24, F = 29, mean age = 52.3 years Sexual desire disorder: 32% Sex difficulty: 30%	HD-negative family members, partners, caregivers, acquaintances, N = 25, M = 11, F = 14, mean age = 55.4 years Sexual desire disorder: 8% Sex difficulty: 12%

AQ – Affected Individual Questionnaire; BDI – Beck Depression Inventory; DSM-III-R – Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised; EDSS – Expanded Disability Status Scale; F – female; FBeK – Fragebogen zur Beurteilung des eigenen Körpers; FDA – Food and Drug Administration; HD – Huntington's Disease; IIEF – International Index of Erectile Function; JHD – Juvenile Huntington's Disease; M – male; MS – multiple sclerosis; PBA-HD – Problem Behaviours Assessment for Huntington Disease; PD NMS-Quest – Parkinson's Disease PD non-motor symptoms questionnaire; PFB – Partnership Questionnaire; SCOPA-AUT – Scales for Outcomes in Parkinson's Disease-Autonomic Dysfunction; TFC – Total Functional Capacity; TSST – Tübingen Scales for Sexual Therapy; UHDRS – Unified Huntington's Disease Rating Scale; UHDRS-TMS – Unified Huntington's Disease Rating Scale Total Motor Score; ZIP – a German version of the Relationship Assessment Scale

dysexecutive symptoms to be the most troublesome, which include daily life activities and possibly also sexual performance [18]. Since HD is a rare condition, the problem of sample size was common across the studies. Studies including more than 1,000 participants asked about sexual dysfunction very briefly, and their capacity to provide valuable data is limited. Those studies which were much more detailed featured fewer than 100 participants with the exception of Aziz et al. [14], who collected 169 responses, although the number of HD patients remained below 100 (Tab. 1). Such small samples make all conclusions less credible. Studies with a larger representation concerning detailed records of sexual functioning should be performed.

Neuropsychiatric symptoms like depression and cognitive decline may influence sexual dysfunction, although few correlations have been found so far. In only a few studies, patients' behavioural changes such as apathy or irritability as well as psychiatric problems like depression, anxiety or hallucinations were investigated and correlated with sexual dysfunction [10, 16, 18]. The only neuropsychiatric symptom to be associated

with sexual problems in HD was depression [11, 13, 14, 17]. In one study correlation was not possible due to the low response rate to the Beck's questionnaire [12]. Depressive symptoms require further research because their treatment can positively or negatively influence sexual dysfunction.

Other culprits for sexual dysfunctions have been found to be antidepressants, neuroleptics and benzodiazepines, which have generally been associated with hyposexuality [11, 13, 14], maintaining patients' well-being and safety (e.g. antidepressants) and should not be withdrawn in order to improve sex lives. They should be used with caution and not over-prescribed if symptoms such as mild choreatic movements do not imply everyday dysfunction. Not addressing sexual dysfunction in a treatment process might result in the withdrawal of drugs if the patient associates a deterioration of their sex life with them. Although one study suggested that these symptoms are not the result of antidepressant use, but rather the depression itself, the influence remains unclear [14].

We found one of the strongest determinants of sexual dysfunction to be TFC score, which reflects global patient

functioning [11]. This indicates that sexual dysfunction could be caused by dysfunctions in the hypothalamus [19, 20] or in the brainstem and spinal cord [14]. Considering sexual dysfunction as an autonomic symptom makes it unlikely to be secondary to functional impairment. This is proven by the finding that autonomic symptoms' severity in HD with depression was independent of any other accompanying variable, e.g. functional disability. On the other hand, depression might be partially a result of autonomic symptoms [11, 13, 14]. One study stated that males with HD have lower testosterone levels and the percentage mirrors the frequency of hyposexual desire disorder; however, the correlation was not given, hence this remains unconfirmed [21]. Nevertheless, it shows that sexual dysfunction, especially hyposexuality, might be also caused by hormonal imbalance.

In one study that investigated paraphilia it was noted that the usual age of onset for paraphilic symptoms is adolescence, and that for the patients in the study the average age of onset was 32 years. It was therefore suggested that paraphilic behaviour could be an early symptom of HD. However, the study also indicated that it might be a result of increased sexual needs combined with a difficulty in reaching orgasm through conventional means, since significantly more participants with paraphilia had also hypersexual desire disorder and inhibited orgasm [7].

Only two studies analysed sexual dysfunction in pre-symptomatic carriers [11, 12], but, as mentioned before, the number of patients was not representative. The quantity of CAG repeats was taken into consideration in two studies [11, 12], but conclusions were inconsistent.

Another obstacle was that patients with HD may have impaired self-awareness of their symptoms, so they tend to overestimate their performance [22, 23, 24, 25], which might also affect the credibility of their sex problem reporting. That was proven in one study included in the review, where agreement between patient and partner answers was measured. This showed that they were more likely to agree on the absence of dysfunction rather than its presence [7]. That makes all sexual problems more likely to be underreported rather than overreported.

Like patients with HD, partners have reported a higher frequency of sexual dysfunction than the general population [7]. The mental burden of the disease might be one explanation of this phenomenon. Sexual dysfunction in a partner causes a higher risk of its occurrence in an individual, which may explain also the healthy partner's problems [26]. In all papers, the general population comparison was impeded because either control groups were composed of patients' partners and/or only heterosexual and monogamic couples were examined, which might have potentially biased the results.

The major limitation of all studies was the lack of use of standardised questionnaires and different definitions and durations for sexual dysfunctions, not consistent with DSM criteria (Tab. 1.). No studies used the same questionnaires.

Only Fedoroff et al. in 1994 used the DSM criteria, and those changed in subsequent years.

Although we did not consider reviews in our paper (as stated in the methodology), one, the most recent performed by Schmidt and Bonelli (2008), should be mentioned. This paper included only five original studies and only one of these selected patients based on genetic testing [27]. The limitations enumerated in the review were similar to ours: different strategies of patient recruitment, the self-assessment of dysfunction instead of standardised methods making studies difficult to compare, and the fact that a reliable diagnosis only emerged with genetic testing after 1993. This shows that during the last decade there has been no substantial progress in this field.

Treatment recommendations released this year contain a section for sexual disorders. They state that in a case of decreased libido, we should consider lowering the dose or substituting the treatment because the cause could be iatrogenic, but they do not explain the procedure if possibly-affecting medications are not taken (i.e. if sexual dysfunction occurs in a not-previously treated patient). For erectile dysfunction – a consultation with an endocrinologist and a specialist in psychosexual disorders is suggested as well as considering symptomatic treatment such as phosphodiesterase 5 inhibitors. For hypersexual behaviour – a psychological approach is recommended, but when associated with violence or social discomfort – neuroleptics and/or SSRI are proposed. If this is not working, then adding/replacing with an anti-androgen under the guidance of a specialist in sexology or endocrinology, or in severe cases a visit to a psychiatrist, is recommended [28].

The guidelines show that sexual dysfunction is no longer a neglected area and is now taken into consideration. However, the focus is still on the most common (hyposexuality, problems with erection) or the most impactful for the patient and his or her family, such as hypersexuality. They are based mostly on good clinical practice instead of randomised studies. Therefore we still need studies on sexual problems and the ways to resolve them in the HD population.

Conflicts of interest: *There is no conflict of interest*

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