

Sexual dysfunction and depression in patients with multiple sclerosis in Croatia

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UNIVERSITY OF ZAGREB

SCHOOL OF MEDICINE

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**SEXUAL DYSFUNCTION AND DEPRESSION IN PATIENTS WITH
MULTIPLE SCLEROSIS IN CROATIA**

GRADUATE THESIS



Zagreb, 2021

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ABBREVIATIONS

CNS *Central nervous system*

EDSS *Expanded Disability Status Scale*

HCP *Healthcare professionals*

MS *Multiple sclerosis*

MSISQ *Multiple sclerosis intimacy and sexuality questionnaire*

PPMS *Primary progressive multiple sclerosis*

PRMS *Progressive-relapsing multiple sclerosis*

pwMS *Persons with multiple sclerosis*

RRMS *Relapse-remitting multiple sclerosis*

SD *Sexual dysfunction*

SPMS *Secondary progressive multiple sclerosis*

SSS *Sexual satisfaction scale*

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SUMMARY

Title: SEXUAL DYSFUNCTION AND DEPRESSION IN PATIENTS WITH MULTIPLE SCLEROSIS IN CROATIA

Author: Hanna Pašić

Keywords: multiple sclerosis (MS) - sexual dysfunction (SD) - depression - Croatia - Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ)

Background: Both depression and sexual dysfunction (SD) may be present in patients with multiple sclerosis (MS).

Objective: The aim of this study was to evaluate a possible association between SD and depression in patients with MS in Croatia.

Subjects and methods: This was a prospective cross-sectional study carried out in tertiary healthcare centre over 10 months, which included 101 consecutive pwMS (mean age 42.09 (range 19-77) years, 75 female, 26 male, EDSS score 3.1 (range 0.0-7.0)). SD was assessed using Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ), which was for this purpose successfully translated and validated into Croatian. Information on treatment for depression was obtained during the medical interview. Data were analysed and interpreted using parametric statistics (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

Results: 89 patients completed MSISQ. 25 patients were in treatment for depression, while 75 did not have depressive symptoms. On MSISQ 57 (43women, 14 men) patients had responded with ‘almost always/ always’ suggestive of SD. Majority of patients reported primary SD, followed by secondary and tertiary SD. Most difficulties were found regarding difficulty in getting or keeping a satisfactory erection (34.6% (N=9) men), followed by 32.9% (N=27) reporting that it takes too

long to orgasm or climax, followed with bladder or urinary symptoms in 32.6% (N=29). There were no significant differences between female and male patients regarding treatment for depression ($\chi^2=0.018$, $df=1$, $p>0.05$). Results in all subcategories on t-test found that depressive patients had higher impact on SD when compared to non-depressive: overall ($t=-2.691$, $df=87$, $p<0.01$) and in regards to primary ($t=-2.086$, $df=87$, $p<0.05$), secondary ($t=-2.608$, $df=87$, $p<0.05$) and tertiary ($t=-2.460$, $df=86$, $p<0.05$) SD. Depressive patients on 7 questions showed significantly ($p<0.05$) higher SD symptoms: Muscle tightness or spasms in my arms, legs, or body; Tremors or shaking in hands or body; Pain, burning, or discomfort in their body; Feeling less attractive; Fear of being rejected sexually because of MS; Lack of sexual interest or desire; Less intense or pleasurable orgasms or climaxes.

Conclusions: This study gives insight into the presence of depression and SD in Croatian patients with MS for which purpose valid questionnaire for the assessment of SD in MS patients MSISQ was with permission successfully translated and validated into Croatian. The connection between depression and SD must be considered when managing patients with MS.

SAŽETAK

Naslov: SEKSUALNA DISFUNKCIJA I DEPRESIJA U PACIJENATA S MULTIPLOM SKLEROZOMU HRVATSKOJ

Autor: Hanna Pašić

Ključne riječi: multipla skleroza (MS) - seksualna disfunkcija (SD) - depresija - Hrvatska - Upitnik za intimnost i seksualnost multiple skleroze (MSISQ)

Cilj: Cilj ovog istraživanja bio je procijeniti moguću povezanost SD-a i depresije u bolesnika s MS-om u Hrvatskoj.

Pacijenti i metode: Ovo je prospektivno presječno istraživanje provedeno u tercijarnom zdravstvenom centru tijekom 10 mjeseci, koja je uključivala 101 uzastopni pwMS (prosječna dob 42,09 (raspon 19-77) godina, 75 žena, 26 muškaraca, EDSS ocjena 3,1 (raspon 0,0-7,0)). SD je procijenjen pomoću upitnika za intimnost i seksualnost multiple skleroze (MSISQ), koji je u tu svrhu uspješno preveden i validiran na hrvatski jezik. Podaci o liječenju depresije dobiveni su tijekom medicinskog razgovora. Podaci su analizirani i interpretirani pomoću parametarske statistike (IBM Corp. Objavljeno 2015. IBM SPSS Statistics za Windows, Verzija 23.0. Armonk, NY: IBM Corp.).

Rezultati: 89 pacijenata završilo je MSISQ. 25 pacijenata liječilo se od depresije, dok 75 nije imalo simptome depresije. Na MSISQ 57 (43 žene, 14 muškaraca) pacijenti su odgovorili "gotovo uvijek / uvijek" nagovještavajući SD. Većina pacijenata prijavila je primarni SD, a zatim sekundarni i tercijarni SD. Najviše poteškoća pronađeno je u vezi s poteškoćama u postizanju ili održavanju zadovoljavajuće erekcije (34,6% (N = 9) muškaraca), nakon čega slijedi 32,9% (N = 27) koji izvješćuju da predugo traje orgazam ili vrhunac, praćeno simptomima mokraćnog mjehura ili mokraće u 32,6% (N = 29). Nije bilo značajnih razlika između bolesnika i pacijenata u pogledu liječenja

depresije ($2 = 0,018$, $df = 1$, $p > 0,05$). Rezultati u svim potkategorijama t-testa otkrili su da su depresivni bolesnici imali veći utjecaj na SD u usporedbi s nedeprisivnim: ukupno ($t = -2,691$, $df = 87$, $p < 0,01$) i u odnosu na primarni ($t = -2,086$, $df = 87$, $p < 0,05$), sekundarni ($t = -2,608$, $df = 87$, $p < 0,05$) i tercijarni ($t = -2,460$, $df = 86$, $p < 0,05$) SD. Pacijenti depresivni na 7 pitanja pokazali su značajno ($p < 0,05$) veće simptome SD-a: Mišićna napetost ili grčevi u rukama, nogama ili tijelu; Drhtanje ili drhtanje ruku ili tijela; Bol, peckanje ili nelagoda u tijelu; Osjećaj manje privlačnosti; Strah od seksualnog odbijanja zbog MS-a; Nedostatak seksualnog interesa ili želje; Manje intenzivni ili ugodni orgazmi ili vrhunci.

Zaključci: Ova studija daje uvid u prisutnost depresije i SD u hrvatskih bolesnika s MS-om za koju je valjani upitnik za procjenu SD-a u bolesnika s MS-om MSISQ uz dopuštenje uspješno preveden i validiran na hrvatski jezik. Pri liječenju bolesnika s MS-om mora se uzeti u obzir povezanost depresije i SD-a.

1. INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS) (Peterson & Fujinami 2007). Published literature on MS in Croatia shows that the overall MS prevalence rate is 143.8 per 100 000 population (6160 patients identified, majority - 72% women) (Benjak et al. 2018). Both depression and sexual dysfunction (SD) may be present in people with MS (Zavoreo et al. 2016, Odabas et al. 2018, Rommer et al. 2018, Tudor et al. 2018, Konstantinidis et al. 2019). Recent joint study in the region found depression in 54.7% of patients with MS (Drulovic et al. 2015), what is also consistent with earlier results of studies in Croatia where symptoms of depression in MS patients in Croatia were identified in about 57% of patients (Zavoreo et al. 2016). Sexual function is an important part of human behavior (Reamy 1984, Nusbaum et al. 2000, El-Kak et al. 2004). It has been estimated that 50-90% of patients with MS have SD (Tudor & Panicker 2017). In published literature we found only one study evaluating symptoms of SD in MS patients in Croatia (using Sexual Satisfaction Scale (SSS)), where SD was found in 71% of patients with no significant gender differences (Zavoreo et al. 2016). This study found positive correlation between SD and depression what is consistent with earlier international published data (Zavoreo et al. 2016, Hosl et al. 2018, Tudor et al. 2018, Alehashemi et al. 2019). It is known that SD in patients with MS is multidimensional with multiple contributing factors. Foley et al. proposed a conceptual model for sexual problems in MS in terms of primary, secondary and tertiary SD to characterise three levels of influence (Foley et al. 2013). Also, different medication may potentially also affect sexual function (Fletcher et al. 2009). Although commonly experienced in MS patients, still it is known that SD in MS is underreported and undertreated (Janardhan & Bakshi 2000, Zorzon et al. 2001b,

Hemmett et al. 2004, Rubin 2005, Redelman 2009, Bronner et al. 2010, Guo et al. 2012, Tudor & Panicker 2017). Different barriers, faced both by patients with MS and HCPs, may be responsible for difficulties in communication about SD in MS and different mechanisms have been proposed to address these barriers and to raise awareness on this matter (Tudor et al. 2018). The objective of this study was to give further insight on presence of depression and SD in patients with MS in Croatia, as well as to translate and validate into Croatian a questionnaire that is a known reliable and valid international measure of SD in men and women with MS - the Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ) (Foley et al. 2013)

2. AIM OF THE STUDY

The aim of this study was to evaluate possible association and to give further insight on presence of depression and SD in patients with MS in Croatia, as well as to translate and validate into Croatian a questionnaire that is a known reliable and valid international measure of SD in men and women with MS - the Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ) (Foley et al. 2013)

3. SUBJECTS AND METHODS

This was a prospective cross-sectional study carried out in a tertiary healthcare centre (University Hospital Centre Zagreb, Croatia) over 10 months. Research was approved by the local Ethics Committee. SD was assessed using MSISQ (Foley et al. 2013). MSISQ was with permission translated into Croatian and validated. Questionnaire consists of 15 questions and evaluates symptoms of SD in patients with MS assessing primary, secondary, and tertiary factors that contribute to SD. It enquires about 15 different symptoms/domains that interfered with sexual activity or satisfaction over the last 6 months. For validation purposes questionnaire MSISQ was initially translated into Croatian then back translated to English. Back translated version was then evaluated to identify wording in either the instructions or questions that are significantly distorted/different from the original English version (no further clarifications of the wording were necessary). The Croatian version was piloted on ten patients (there were no questions or instructions that were found confusing). Information regarding treatment for depression was obtained during the medical interview. Data were analysed and interpreted using parametric statistics (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) and a p-value<0.05 was considered to be significant.

4. RESULTS

Hundred and one consecutive patient with MS (75 female, 26 male, mean age 42.09 (range 19-77) years, mean Expanded Disability Status Scale (EDSS) score 3.1 (range 0.0-7.0), 95 patients with relapse-remitting MS (RRMS), 5 secondary progressive MS (SPMS), and one patient with primary progressive MS (PPMS)) participated in this study (Table 1).

Table 1. Patients with MS that participated in this study

Patients with MS	N=101
Female	75 (84.26%)
Male	26 (29.21%)
Age	42.09 (range 19-77)
EDSS (0-10)	3.1 (range 0.0-7.0)
Type of MS	
RRMS	95 (94.05%)
SPMS	5 (4.95%)
PPMS	1 (0.99%)
PRMS	0
Depression	25 (24.7%)
Female	19 (18.8%)
Male	6 (5.9%)

Validation of the MSISQ showed favourable results. Internal consistency (reliability) was found to be very high ($\alpha=0.930$) (Table 2). Stability (test-retest reliability) was found to be very high ($r=0.978$, $p<0.001$) (Table 3). Content/face validity was found to be good (Table 4). On MSISQ 57 (56.4% of the whole group (valid percent 64.0% of 89 patients with MS that filled the questionnaire), 43 women, 14 men) patients chose almost always/ always suggestive of SD. Majority of patients reported primary SD, followed by secondary and tertiary SD, which was found also true in women, while men most often reported primary, followed by tertiary and the secondary SD (Table 5). Most difficulties were found regarding difficulty in getting or keeping a satisfactory erection (34.6% (N=9) men, while 50% (N=13) men reported difficulties when asked about ejaculation out of which 4 did not report any symptoms of SD on

MSISQ), followed by 32.9% (N=27) reporting that it takes too long to orgasm or climax (with less intense or pleasurable orgasms or climaxes found in 31.6% (N=25)), followed with bladder or urinary symptoms in 32.6% (N=29) as a cause of SD. 25 patients were in treatment for depression (19 (18.8%) women, 6 (5.9%) men). There were no significant differences between female and male patients regarding treatment for depression ($\chi^2=0.018$, $df=1$, $p>0.05$) (Tables 6). Results in all subcategories on t-test found that depressive patients had higher impact on SD when compared to non-depressive: overall ($t=-2.691$, $df=87$, $p<0.01$) and in regards to primary ($t=-2.086$, $df=87$, $p<0.05$), secondary ($t=-2.608$, $df=87$, $p<0.05$) and tertiary ($t=-2.460$, $df=86$, $p<0.05$) SD (Table 7). Depressive patients on 7 questions showed significantly ($p<0.05$) higher SD symptoms: Muscle tightness or spasms in my arms, legs, or body; Tremors or shaking in my hands or body; Pain, burning, or discomfort in their body; Feeling less attractive; Fear of being rejected sexually because of MS; Lack of sexual interest or desire; Less intense or pleasurable orgasms or climaxes (Table 8). Neurological deficit on EDSS scale was not found to be significantly connected to SD nor to depression.

Table 2. Validation of the questionnaire MSISQ: Internal consistency (reliability) was found to be very high ($\alpha=0.930$)

		Item-Total Statistics			
Over the last six months, the following symptoms have interfered with my sexual activity or satisfaction (using a 5-point Likert scale 1(never) - 5 (always))		Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	Cronbach's Alpha if Item Deleted
1	Muscle tightness or spasms in my arms, legs or body	32.0000	177.200	0.517	0.929
2	Bladder or urinary symptoms	32.1538	175.015	0.551	0.929
3	Bowel symptoms	32.5000	180.980	0.357	0.933
4	Tremors or shaking in my hands or body	32.5000	171.860	0.634	0.927
5	Pain, burning, or discomfort in my body	32.1923	167.282	0.789	0.923
6	Feeling that my body is less attractive	32.6538	175.515	0.548	0.929
7	Feeling less masculine or feminine due to MS	32.4615	163.778	0.870	0.920
8	Less feeling or numbness in my genitals	32.3077	167.022	0.724	0.924
9	Fear of being rejected sexually because of MS	32.6154	168.646	0.770	0.923
10	Worries about sexually satisfying my partner	32.2692	166.285	0.762	0.923
11	Feeling less confident about my sexuality due to MS	32.4231	169.214	0.830	0.922
12	Lack of sexual interest or desire	32.1538	163.655	0.782	0.922
13	Less intense or pleasurable orgasms or climaxes	32.0000	168.560	0.748	0.924
14	Takes too long to orgasm or climax	32.0000	168.400	0.754	0.923
15	If you are a woman, is there inadequate vaginal wetness or lubrication/ If you are a man, any difficulty in getting or keeping a satisfactory erection	32.6154	167.366	0.646	0.927
Added	When you had sexual stimulation or intercourse, how often did you ejaculate?	34.3846	191.206	0.069	0.938
MSISQ - Multiple Sclerosis Intimacy and Sexuality Questionnaire; α - Cronbach's alpha					

Table 3. Validation of the MSISQ questionnaire: Stability (test-retest reliability) was found to be very high ($r=0.978$, $p<0.001$) (Correlations)

	MSISQ_1_mean	MSISQ_2_mean
MSISQ_1_mean		
Pearson Correlation	1	<i>0.978*</i>
Sig. (2-tailed)		0.000
N	16	16
MSISQ_2_mean		
Pearson Correlation	<i>0.978*</i>	1
Sig. (2-tailed)	0.000	
N	16	16

* Correlation is significant at the 0.01 level (2-tailed); MSISQ - Multiple Sclerosis Intimacy and Sexuality Questionnaire; r - Pearson Correlation

Table 4. Validation of the MSISQ questionnaire: Content/face validity was found to be good (Statistics)

MSISQ	Valid	N	Missing
1	99		2
2	91		10
3	87		14
4	89		12
5	89		12
6	89		12
7	87		14
8	89		12
9	90		11
10	88		13
11	87		14
12	90		11
13	88		13
14	91		10
15	61		40
Added	55		46

MSISQ - Multiple Sclerosis Intimacy and Sexuality Questionnaire (each number in the table on the MSISQ corresponds to the questions in the Table 2 along with the added question about the ejaculation)

Table 5. On MSISQ majority of patients reported primary SD, followed by secondary and tertiary SD

Type of SD (MSISQ)	Total (N=101)	Women (N=75)	Men (N=26)
Primary			
Lack of sexual interest or desire	28.39% (N=23)	25.3% (N=19)	15.3% (N=4)
Takes too long to orgasm or climax	32.9% (N=27)	25.3% (N=19)	30.7% (N=8)
Less feeling or numbness in my genitals	19.8% (N=17)	17.3% (N=13)	15.3% (N=4)
Less intense or pleasurable orgasms or climaxes	31.6% (N=25)	22.6% (N=17)	30.7% (N=8)
Men reported difficulty in getting or keeping a satisfactory erection	34.6% (N=9)	NA	34.6% (N=9)
Women reported inadequate lubrication or wetness	21.3% (N=16)	21.3% (N=16)	NA
Total	N=118	N=84	N=33
Secondary			
Bladder or urinary symptoms	32.6% (N=29)	28.0% (N=21)	30.7% (N=8)
Muscle tightness or spasms in arms, legs or body	28.1% (N=25)	28.0% (N=21)	15.3% (N=4)
Pain, burning or discomfort in body	16.3% (N=14)	13.3% (N=10)	15.3% (N=4)
Bowel symptoms	14.11% (N=12)	10.6% (N=8)	15.3% (N=4)
Tremors or shaking in hands or body	20.9% (N=18)	14.6% (N=11)	26.9% (N=7)
Total	N=101	N=71	N=27
Tertiary			
Feeling less confident about my sexuality due to MS	18.9% (N=15)	12% (N=9)	23.0% (N=6)
Worries about sexually satisfying my partner	21.2% (N=17)	14.6% (N=11)	23.0% (N=6)
Feeling less masculine or feminine due to MS	20.2% (N=17)	14.6% (N=11)	23.0% (N=6)
Feeling their body is less attractive	16.4% (N=14)	10.6% (N=8)	23.0% (N=6)
Fear of being rejected sexually because of MS	12.3% (N=10)	8% (N=6)	15.3% (N=4)
Total	N=73	N=45	N=28

MSISQ - Multiple Sclerosis Intimacy and Sexuality Questionnaire; SD - sexual dysfunction; NA - non-applicable

Table 6. There were no significant differences between female and male patients regarding treatment for depression ($\chi^2=0.018$, $df=1$, $p>0.05$) (Chi-Square Tests)

	Value	df	Asymptotic Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	0.018*	1	0.894		
Continuity Correction**	0.000	1	1.000		
Likelihood Ratio	0.018	1	0.894		
Fisher's Exact Test				1.000	0.562
Linear-by-Linear Association	0.018	1	0.894		
N of Valid Cases	100				

* 0 cells (0,0%) have expected count less than 5. The minimum expected count is 6.25; ** Computed only for a 2x2 table
 χ^2 - Pearson Chi-Square

Table 7. Results in all subcategories on MSISQ on t-test found that depressive patients had higher impact on SD when compared to non-depressive: overall ($t=-2.691$, $df=87$, $p<0.01$) and in regards to primary ($t=-2.086$, $df=87$, $p<0.05$), secondary ($t=-2.608$, $df=87$, $p<0.05$) and tertiary ($t=-2.460$, $df=86$, $p<0.05$) SD (Independent Samples Test)

		Levene's Test for Equality of Variances		t-test for Equality of Means					95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Primary	Equal variances assumed	0.438	0.510	-2.086	87	0.040	-0.58536	0.28065	-1.14319	-0.02754
	Equal variances not assumed			-2.151	40.684	0.037	-0.58536	0.27214	-1.13508	-0.03565
Secondary	Equal variances assumed	0.816	0.369	-2.608	87	0.011	-0.61713	0.23664	-1.08747	-0.14678
	Equal variances not assumed			-2.679	40.373	0.011	-0.61713	0.23038	-1.08262	-0.15164
Tertiary	Equal variances assumed	0.292	0.591	-2.460	86	0.016	-0.69744	0.28348	-1.26098	-0.13389
	Equal variances not assumed			-2.461	38.690	0.018	-0.69744	0.28336	-1.27073	-0.12414
Total	Equal variances assumed	0.424	0.517	-2.691	87	0.009	-0.63568	0.23621	-1.10517	-0.16618
	Equal variances not assumed			-2.724	39.284	0.010	-0.63568	0.23335	-1.10757	-0.16378

*MSISQ - Multiple Sclerosis Intimacy and Sexuality Questionnaire; SD - sexual dysfunction

Table 8. Depressive patients on 7 questions on MSISQ showed significantly ($p < 0.05$) higher SD symptoms: Muscle tightness or spasms in my arms, legs, or body; Tremors or shaking in hands or body; Pain, burning, or discomfort in their body; Feeling less attractive; Fear of being rejected sexually because of MS; Lack of sexual interest or desire; Less intense or pleasurable orgasms or climaxes (Independent Samples Test)

		Levene's Test for Equality of Variances		t-test for Equality of Means					95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
1	Equal variances assumed	0.687	0.409	-3.328	87	0.001	-0.946	0.284	-1.511	-0.381
	Equal variances not assumed			-3.425	40.507	0.001	-0.946	0.276	-1.504	-0.388
2	Equal variances assumed	0.779	0.380	-1.174	87	0.244	-0.375	0.319	-1.010	0.260
	Equal variances not assumed			-1.199	39.962	0.238	-0.375	0.313	-1.007	0.257
3	Equal variances assumed	0.194	0.661	-0.546	83	0.586	-0.177	0.324	-0.821	0.467
	Equal variances not assumed			-0.514	28.927	0.611	-0.177	0.344	-0.881	0.527
4	Equal variances assumed	0.426	0.516	-2.296	84	0.024	-0.756	0.329	-1.410	-0.101
	Equal variances not assumed			-2.295	36.472	0.028	-0.756	0.329	-1.423	-0.088
5	Equal variances assumed	0.609	0.437	-2.174	84	0.033	-0.663	0.305	-1.270	-0.056
	Equal variances not assumed			-2.224	38.014	0.032	-0.663	0.298	-1.267	-0.059
6	Equal variances assumed	0.291	0.591	-2.560	83	0.012	-0.810	0.316	-1.440	-0.181
	Equal variances not assumed			-2.536	33.580	0.016	-0.810	0.319	-1.460	-0.161
7	Equal variances assumed	0.380	0.539	-1.846	82	0.069	-0.635	0.344	-1.319	0.049
	Equal variances not assumed			-1.746	31.406	0.091	-0.635	0.364	-1.376	0.106
8	Equal variances assumed	0.167	0.684	-1.354	84	0.179	-0.446	0.329	-1.101	0.209
	Equal variances not assumed			-1.297	33.958	0.203	-0.446	0.344	-1.145	0.253
9	Equal variances assumed	0.141	0.708	-2.137	79	0.036	-0.683	0.320	-1.320	-0.047
	Equal variances not assumed			-2.001	31.344	0.054	-0.683	0.342	-1.380	0.013
10	Equal variances assumed	0.389	0.535	-1.785	78	0.078	-0.603	0.338	-1.275	0.069
	Equal variances not assumed			-1.651	30.880	0.109	-0.603	0.365	-1.348	0.142
11	Equal variances assumed	3.970	0.050	-0.638	77	0.525	-0.210	0.329	-0.866	0.446
	Equal variances not assumed			-0.701	39.390	0.487	-0.210	0.300	-0.816	0.396
12	Equal variances assumed	0.671	0.415	-2.020	79	0.047	-0.668	0.331	-1.326	-0.010
	Equal variances not assumed			-2.036	38.277	0.049	-0.668	0.328	-1.332	-0.004
13	Equal variances assumed	5.513	0.021	-2.605	77	0.011	-0.846	0.325	-1.494	-0.199
	Equal variances not assumed			-2.893	44.130	0.006	-0.846	0.293	-1.436	-0.257
14	Equal variances assumed	0.840	0.362	-1.719	80	0.089	-0.589	0.343	-1.272	0.093
	Equal variances not assumed			-1.768	39.513	0.085	-0.589	0.333	-1.264	0.085
15a	Equal variances assumed	0.032	0.859	-1.284	58	0.204	-0.544	0.424	-1.393	0.305
	Equal variances not assumed			-1.290	29.721	0.207	-0.544	0.422	-1.407	0.318
15b	Equal variances assumed	0.181	0.675	-1.050	22	0.305	-0.863	0.822	-2.569	0.842
	Equal variances not assumed			-1.032	6.155	0.341	-0.863	0.836	-2.897	10.171
Added	Equal variances assumed	0.465	0.501	-1.075	30	0.291	-0.646	0.601	-1.872	0.581
	Equal variances not assumed			-1.165	10.881	0.269	-0.646	0.554	-1.868	0.576

*MSISQ - Multiple Sclerosis Intimacy and Sexuality Questionnaire; SD - sexual dysfunction

5. DISCUSSION

This study was carried out with the intention of assessment of SD and depression in patients with MS in Croatia. Also, our intention with this study was to translate and validate into Croatian the questionnaire MSISQ, a known reliable and valid measure of SD in men and women with MS (Foley et al. 2013). We wanted to do this study to raise awareness and to provide a valid tool to help with the assessment of SD in MS patients in Croatia in the future. Since the topic of SD in patients with MS in Croatia was until now not thoroughly investigated and we are aware there could be barriers in communication about sexual problems we found that internationally acclaimed and validated questionnaire for the assessment of SD in MS patients could help address this issue. For this purpose we, with permission translated and validated questionnaire MSISQ into Croatian. The results of analysis show that this questionnaire is reliable also in this setting. This is consistent with translation and validation of this questionnaire into other language (Noordhoff et al. 2018). In our opinion both patients with MS and HCPs may find this questionnaire useful in initial assessment of SD which could help with further directed discussion and if needed referral to uro-neurologist or other specialties that cover the issue of sexuality (e.g. urologist, gynecologist, endocrinologist, psychologist, psychiatrist). Earlier literature suggests that 50-90% of patients with MS have SD (Tudor & Panicker 2017). In public- shed literature we found only one study evaluating symptoms of SD in MS patients in Croatia by Zavoreo et al. performed in another institution using SSS with SD found in 71% of patients (Zavoreo et al. 2016). Our results suggest a somewhat lower incidence of SD in our group of MS patients. We need to mention that some of the patients that did not report SD on MSISQ had ejaculatory difficulties and we find that male patients should be asked about this issue as well when given the questionnaire.

In our study the domain that scored the highest was ‘getting or keeping a satisfactory erection’. This result is consistent with the above mentioned study by Zavoreo et al. where the most prominent symptom was erectile dysfunction reported with similar incidence (Zavoreo et al. 2016). Results of analysis regarding other domains are consistent regarding orgasm issues in men and women and lack of sexual interest or desire in women. It should be mentioned that in this study both men and women reported bladder problems with high incidence. On MSISQ overall majority of patients reported primary SD, followed by secondary and tertiary SD, which was found also true in analysis of results in women. This is consistent with results of study by Tudor et al. (2018), where primary SD was most common, but with tertiary SD found overall to be more often reported than secondary SD. That finding, also present when analyzing both women and men separately, is consistent with results of this study regarding men who most often reported primary, followed by tertiary and the secondary SD. In this study depressive patients on 7 questions on MSISQ showed significantly higher SD symptoms: Muscle tightness or spasms in my arms, legs, or body; Tremors or shaking in hands or body; Pain, burning, or discomfort in their body; Feeling less attractive; Fear of being rejected sexually because of MS; Lack of sexual interest or desire; Less intense or pleasurable orgasms or climaxes. It is worthy to mention that all the above cover different domains (primary, secondary and tertiary) of SD. Results of study by Tudor et al. and this study overlap regarding three MSISQ domains (Muscle tightness or spasms in my arms; Fear of being rejected sexually because of MS; Lack of sexual interest or desire) where patients with higher scores on these domains more often reported depressive symptoms (Tudor et al. 2018). This highlights the need for a comprehensive approach in management and care of patients with MS making sure that all these aspects are taken care of. Previous

studies investigating prevalence of depression and anxiety in MS show significant discrepancy, ranging from 14 to 54%, and 1.24 to 36% (Zorzon et al. 2001a, Hellmann-Regen et al. 2013, Marrie et al. 2015, Liu & Tang 2018). In this study 25% of patients are receiving treatment for depression. Recent joint study in the region found higher numbers regarding depression that was found in 54.7% of patients with MS (Drulovic et al. 2015). This is also consistent with earlier results of studies in Croatia where symptoms of depression in MS patients in Croatia were identified in about 57% of patients (Zavoreo et al. 2016). Limitations of this study include a small sample of patients. Also there is a possibility that if further evaluation tools (e.g. questionnaires) were used to investigate further presence of depressive symptoms in patients not treated for depression that the numbers would be higher. In the future we intend to follow-up on our patients and hope to bring data on the bigger sample. This study was performed with the idea of raising awareness, providing a valid tool and further evaluation of SD and depression in MS patients in Croatia. Management should include appropriate assessment of both and therapy tailored accordingly.

6. CONCLUSION

This study evaluated the presence of SD and depression in patients with MS. The results show that depressive patients have more pronounced SD symptoms on several domains. For the purpose of SD assessment, internationally acclaimed questionnaire MSISQ was successfully translated and validated into Croatian. Management should include appropriate assessment of both, SD and depression, and therapy tailored accordingly.

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9. BIOGRAPHY

Hanna Pašić was born in 1996 in Zagreb, Croatia. She finished elementary school in Zagreb in 2011, and II. General Gymnasium in 2015. She began her university education in 2015 at the Faculty of Medicine, University of Zagreb, studying in English. Academic years 2018/2019 she was awarded the Dean's Award for Best Fourth-Year Medical Student in English. She is fluent in English and Italian, which she taught as part of her primary and secondary education, and attended extracurricular French and Spanish classes. In 2021 she attempted IELTS academic exam where she scored 8, as well as got certified in French language by French alliance. In addition to the listed languages, she studied Latin during the first two grades of high school. For four consecutive years, she attended workshops as part of the Novigrad Spring event, and two years of workshops for researching vitamin C and 'Truth or False: CSI' at the MedILS research institute. She has participated in numerous congresses and papers related to neurology (eg AAN and EAN), some of which have been published in eminent journals ("Clinical trials in developing countries - ethical considerations" in the journal "Psychiatria Danubina"), as well as presented. In the academic year of 2019/2020 she became Vice President of the Student Section for Dermatovenerology, where she currently holds the position of President of the Student Section for Dermatovenerology. She has also participated in research about the genotype of Parkinson's disease, comparison study about cardiac surgery outcomes, Diabetes mellitus terminology, and so on. And she had participated on conferences as CROSS15 and CROSS16 as a individual presenter and as part of the Student section of Dermatovenerology, BFH2020, ZIMS2020. CONy2020. In 2020 on the Innovation Days – University of Zagreb, together with her group Powerpuff girls, she won second place with their innovation. During the Covid-19

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