Sexual dysfunction during long-term treatment with antidepressants in unipolar disorder: clinical and management aspects

Disfunzione sessuale nel corso di terapia a lungo termine nel disturbo unipolare: aspetti clinici e di management

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Summary

Objective

Major depression is a chronic condition. Treatment with antidepressants is often stopped due to long-term side effects. Antidepressants are frequently associated with sexual dysfunction (SD), which can have a negative impact on adherence to treatment and quality of life, although it is often underestimated by clinicians and underreported by patients. The purpose of the present study is to determine the presence of SD using specific self-rating scales in a sample of euthymic unipolar patients undergoing long-term treatment with antidepressants.

Method

The sample was recruited from the Neuroscience Department of San Raffaele-Turro Hospital in Milan. A total of 66 female and 31 males, with a mean age of 55.2 ± 12.5 years and a mean number of episodes of 3.7 ± 3.3, were included. Patients answered specific questionnaires for quality of life (WHOQoL) and sexual dysfunction (SD): IIEF for males and FSFI females. The possible role of sexual dysfunction on long-term adherence to treatment was also evaluated using the MARS self-rating scale. The euthymic condition was assessed with the Hamilton depressive rating scale (mean score < 8).

Results

73.2% of the patient population reported SD, affecting all sexuality domains. Self-rating scales showed high levels of SD in both males and females: in males, the total mean IIEF score was 34.25 ± 20.35; in females, the total mean FSFI score was 15.22 ± 11.26. A majority of patients (55.6%) reported the presence of SD associated with antidepressant therapy, 37.11% referred SD only during a depressive episode and 7.12% reported pre-existent SD. The quality of life was affected by SD in the Environment (p = 0.000), Physical Health (p = 0.000) and Social Relationship (p = 0.000) domains. In males, the quality of life was not affected by SD. However, in females all domains were compromised (Physical, p = 0.001; Psychological, p = 0.022; Environment, p = 0.001; Social Relationship, p = 0.018). All patients with SD showed poorer adherence to therapy (p = 0.001). Male subjects with SD were characterized by greater scores in the subscale that evaluates intentional non-adherence (p = 0.041), while female subjects with SD had lower global adherence to therapy (p = 0.018) and to common stereotypes about antidepressants (p = 0.003). With regard to clinical variables, male subjects with SD were characterized by a shorter duration of both euthymia (p = 0.005) and antidepressant therapy (p = 0.007).

Conclusion

Long-treatment antidepressant treatment is associated with SD regardless of gender. In this study, unipolar patients with SD undergoing long-term antidepressant therapy showed a poorer quality of life and lower adherence to treatment, compared to those without SD, thus increasing the risk of recurrence. Adequate assessment of sexual side effects during antidepressant therapy can help in better defining symptomatic remission. Thus, evaluation of sexual side effects and their management are key points in choosing the optimal therapy for depression and improving physician-patient relationships.

Key words

Depression • Sexual dysfunction • Antidepressants • Quality of life • Adherence to therapy

Introduction

Recurrent major depression is a chronic condition that requires prolonged treatment with antidepressants, which are often interrupted due to drug-related adverse effects, and in particular sexual dysfunction (SD) [1 2]. The frequency of SD varies among antidepressants: fluoxetine 57.7%, sertraline 62.9%, fluvoxamine 62.3%, paroxetine 70.7%, citalopram 72.7%, venlafaxine 67.3%, mirtazapine 24.4%, nefazodone 8.0%, amineptine 6.9% and moclobemide 3.9% [3]. The association between antidepressants and SD, even if less important during an acute depressive episode, becomes problematic in the euthymic phase. In this period, maintenance therapy has a key role in prevention of recurrences, and thus even a euthymic patient should continue correct and constant pharmacological therapy in spite of the presence of adverse effects.

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TABLE I.
Clinical and demographic variables in the global sample (n = 97). *Variabili cliniche e socio-demografiche nel campione totale (n = 97).*

Continuous variables	Mean	SD
Age	55.19	12.52
Scholastic education (years)	11.14	4.60
Age at onset of depression (years)	41.50	14.71
# depressive episodes	3.71	3.31
Duration of euthymia (months)	34.76	46.98
Duration sexual dysfunction (months)	76.15	137.59
Duration antidepressant therapy (months)	55.27	58.70

Categorical variables	%
Marital status	61.85% → married 11.43% → divorced/separated 15.46 % → single 6.18% → live with partner 5.15% → widowed
Partner	78.35% → stable 15.46 % → no partner 6.18% → occasional
Profession	42.26% → factory/office worker 8.24% → freelance 31.95% → retired 10.3% → housewife 6.10 % → unemployed
Night-time shifts	13.40 % → yes 86.59% → no
Week-end	89.69 % → free 10.3% → work
Menopause	56.06 %
Hormonal replacement therapy	7.57%
Smoking	57.73% → yes 41.23% → no
Antidepressant therapy	71.10% → SSRI 24.78% → SNRI 4.12% → tricyclics

However, the presence of SD places adherence to pharmacological therapy at risk [4] as the patient may not find adequate motivation in the absence of symptoms. Therapy may thus be interrupted or doses may be skipped, increasing the risk of recurrence [5]. SD has a negative impact on the quality of life: sexuality is considered an integral part of overall well-being [6] and is important in maintaining good relationships [7].
Despite its clinical relevance, according to the literature, SD is difficult to evaluate and has received little attention [1 3], and the presence of sub-clinical depressive symptoms relative to the sexual area can persist in patients treated with antidepressants [8 9]. Moreover, accurate evaluation of the association between SD and antidepressants is subject to several methodological limits such as the lack of use of valid assessment scales for SD and problems related to the use of a control group and randomization, which can lead to underestimation of the actual prevalence of SD [10 11].
The primary objective of the present study was to evaluate the frequency of SD, in terms of incidence and dimension of the problem in a cohort of euthymic unipolar outpatients undergoing long-term antidepressant therapy at the Centre for Mood Disturbances, Department of Clinical Neurosciences, San Raffaele-Turro Hospital in Milan. The secondary objective was to assess the impact of SD on adherence to antidepressant therapy and the quality of life.

Materials and methods

The study population was recruited among outpatients attending the ambulatory clinic of the Department of Clinical Neurosciences, San Raffaele-Turro Hospital in Milan from April 2009 to June 2010. Inclusion criteria included: diagnosis of unipolar depression using DSM-IV criteria, in clinical euthymia (Hamilton score ≤ 8 and recovery of functioning), undergoing long-term treatment with an antidepressant and informed consent for participation. Exclusion criteria were alcohol/substance abuse, presence of an Axis II diagnosis or presence of an Axis III diagnosis that severely invalidated SD. Clinical and demographic information were collected from clinical charts and from interviews with patients with the attending psychiatrist.
Patients were assessed using the following evaluation scales: Hamilton 21-item for depressive symptoms [12]; IIEF (International Index of Erectile Function) in male patients [13]; FSFI (Female Sexual Function Index) in female patients [14]; WHOQoL-Bref (World Health Organization Quality of Life) for self-assessment of quality of life [15]; MARS (Medical Adherence Rating Scale)[16].

Assessment tools

The IIEF is a self-administered questionnaire containing 15 questions that evaluate 5 aspects or domains of sexual functioning in males: erectile function, intercourse satisfaction, orgasmic function, sexual desire and overall satisfaction. The total score varies from a minimum of 5 (corresponding to poorest sexual functioning) to a maximum of 75 (corresponding to best sexual functioning). The FSFI is a brief self-administered questionnaire composed of 19 multiple choice items that evaluate sexual

TABLE II.
Mean scores in sexual function evaluation scales (IIEF/FSFI) (n = 97). *Punteggi medi alla scala della valutazione della funzione sessuale (IIEF/FSFI) (n = 97).*

	Mean in subjects without dysfunction	Mean in subjects with dysfunction	t-value	p
Males	**(n = 10)**	**(n = 21)**		
Erectile function	25.00 ± 3.39	8.28 ± 8.18	6.168	0.000
Orgasm	9.00 ± 1.49	2.61 ± 2.87	6.576	0.000
Desire	7.20 ± 1.13	5.14 ± 2.57	2.401	0.022
Intercourse satisfaction	9.90 ± 1.59	2.85 ± 3.00	6.920	0.000
Overall satisfaction	7.90 ± 1.28	4.19 ± 2.76	4.009	0.000
Females	**(n = 16)**	**(n = 50)**		
Arousal	1.34 ± 1.38	4.61 ± 0.81	-8.964	0.000
Orgasm	1.48 ± 1.84	4.90 ± 1.21	-6.921	0.000
Desire	1.84 ± 0.82	4.08 ± 1.06	-8.569	0.000
Sexual satisfaction	2.34 ± 1.47	5.20 ± 0.70	-7.473	0.000
Lubrication	1.43 ± 1.65	5.62 ± 0.43	-9.955	0.000
Pain	1.90 ± 2.41	5.92 ± 0.21	-6.609	0.000

TABLE III.
Comparison of patients with and without sexual dysfunction (n = 97). *Confronto tra i pazienti con e senza disfunzione sessuale (n = 97).*

	Mean in subjects without dysfunction (n = 26)	Mean in subjects with dysfunction (n = 71)	t-value	p
Age	53.07 ± 10.99	55.97 ± 13.02	-1.008	0.315
Age at onset of depression	36.56 ± 12.72	43.22 ± 15.04	-1.977	0.050
Depressive episodes	3.56 ± 2.21	3.77 ± 3.64	-0.272	0.786
Duration of euthymia (months)	43.50 ± 43.08	31.56 ± 48.22	1.109	0.269
Mean dose of antidepressant	76.00 ± 74.86	106.59 ± 104.41	-1.343	0.182
Duration of antidepressive therapy (months)	67.50 ± 70.66	50.80 ± 53.54	1.244	0.216
WQ Physical Area	15.17 ± 1.92	12.91 ± 2.70	3.894	0.000
WQ Psychological Area	12.75 ± 2.65	12.00 ± 2.09	1.451	0.150
WQ Environmental Area	14.35 ± 1.82	12.60 ± 2.14	3.692	0.000
WQ Social Relations Area	15.28 ± 3.41	12.35 ± 2.99	4.096	0.000
MARS	7.73 ± 1.61	6.94 ± 1.92	1.856	0.066
Unintentional non-adherence	4.38 ± 1.20	4.59 ± 1.90	-0.517	0.606
Intentional non-adherence	8.80 ± 1.95	9.22 ± 1.75	-1.004	0.317
Assessment of antidepressive therapy	3.07 ± 2.34	4.87 ± 2.43	-3.251	0.001
Assessment of physician-patient relationship	22.23 ± 4.19	20.54 ± 3.51	1.979	0.050

functioning in women over 6 domains: desire, arousal, orgasm, pain, sexual satisfaction and lubrication. FSFI can be administered to women with a wide age range, including those in menopause. The score ranges from a minimum of 0 (corresponding to no sexual activity) to a maximum of 6 (full sexual functioning) for each domain. Considering the total score from 0 to 36, 26.55 was used a significant cut-off for the presence of SD in women [17]. The WHOQoL-Bref instrument for evaluation of the quality of life is a self-administered 26-item scale covering

TABLE IV.
Comparison of males with and without sexual dysfunction (n = 31). *Confronto tra i pazienti con e senza disfunzione sessuale nel sottocampione maschile (n = 31).*

	Mean in subjects without dysfunction (n = 10)	Mean in subjects with dysfunction (n = 21)	t-value	p
Age	55.20 ± 7.00	56.57 ± 15.34	-0.267	0.790
Age at onset of depression	34.44 ± 11.43	47.28 ± 18.30	-1.938	0.062
Depressive episodes	3.55 ± 1.42	3.35 ± 2.62	0.219	0.827
Duration of euthymia (months)	65.40 ± 56.31	22.71 ± 23.77	2.997	0.005
Mean dose of antidepressant	57.77 ± 42.58	106.50 ± 102.94	-1.357	0.185
Duration of antidepressive therapy (months)	97.20 ± 67.27	37.90 ± 46.13	2.879	0.007
WQ Physical Area	15.31 ± 2.53	13.54 ± 2.40	1.874	0.070
WQ Psychological Area	12.09 ± 3.76	12.63 ± 1.52	-0.570	0.572
WQ Environmental Area	13.95 ± 1.69	12.90 ± 1.6030	1.669	0.105
WQ Social Relations Area	14.26 ± 3.82	12.55 ± 2.83	1.401	0.171
MARS	7.20 ± 2.04	7.28 ± 1.84	-0.116	0.907
Unintentional non-adherence	4.60 ± 1.34	4.23 ± 1.54	0.633	0.531
Intentional non-adherence	8.00 ± 2.62	9.61 ± 1.59	-2.135	0.041
Assessment of antidepressive therapy	3.40 ± 2.01	4.76 ± 2.86	-1.349	0.187
Assessment of physician-patient relationship	22.30 ± 4.347	20.00 ± 3.79	1.506	0.142

TABLE V.
Comparison between females with and without sexual dysfunction (n = 66). *Confronto tra i pazienti con e senza disfunzione sessuale nel sottocampione femminile (n = 66).*

	Mean in subjects without dysfunction (n = 26)	Mean in subjects with dysfunction (n = 71)	t-value	p
Age	51.75 ± 12.92	55.72 ± 12.09	-1.124	0.265
Age at onset of depression	37.75 ± 13.60	41.52 ± 13.29	-0.918	0.329
Depressive episodes	3.56 ± 2.60	3.94 ± 3.99	-0.353	0.724
Duration of euthymia (months)	29.81 ± 25.90	35.28 ± 55.17	-0.381	0.704
Mean dose of antidepressant	86.25 ± 87.68	106.63 ± 106.06	-0.694	0.490
Duration of antidepressive therapy (months)	48.93 ± 68.19	56.22 ± 55.90	-0.429	0.668
WQ Physical Area	15.08 ± 1.51	12.64 ± 2.80	3.314	0.001
WQ Psychological Area	13.16 ± 1.66	11.73 ± 2.25	2.340	0.022
WQ Environmental Area	14.60 ± 1.92	12.47 ± 2.33	3.293	0.001
WQ Social Relations Area	15.92 ± 3.08	12.26 ± 3.09	4.107	0.000
MARS	8.06 ± 1.24	6.80 ± 1.95	2.421	0.018
Unintentional non-adherence	4.25 ± 1.12	4.74 ± 2.02	-0.918	0.361
Intentional non-adherence	9.31 ± 1.25	9.06 ± 1.81	0.518	0.606
Assessment of antidepressive therapy	2.87 ± 2.58	4.92 ± 2.25	-3.047	0.003
Assessment of physician-patient relationship	22.18 ± 4.25	20.78 ± 3.40	1.355	0.180

4 areas: physical (PA), psychological (PsyA), social relations (SR) and environment (ENV). Patients rate their condition with a score that varies from 1 to 5 for each item: low scores correspond to a poor life condition.
Four scales were used to assess adherence to pharmacotherapy. MARS [16] is a self-administered questionnaire composed of 10 items that evaluate behaviour in adherence to therapy, taking medicines and collateral effects (minimum score= 0; maximum score= 10). The non-adherence to antidepressant therapy scale [18] is a self-administered questionnaire composed of 5 items that assess both non-intentional non-adherence (minimum score = 3; maximum score = 18) and intentional non-adherence (minimum score = 2; maximum score = 10). The evaluation of antidepressive treatment scale [19] is a self-administered questionnaire that assesses collateral effects, stereotypes about psychoactive drugs and social stigma (minimum score = 0; maximum score = 12). Physician-patient relationships were evaluated using a self-administered questionnaire [19] that queries satisfaction in physician-patient relationships (minimum score = 0; maximum score = 26).
StatSoft STATISTICA 7.0 software was used for statistical analyses.

Results

The study population was composed of 97 subjects, 31 men (32%) and 66 women (68%) with a mean age of 55.19 ± 12.52 years and a mean schooling of 11.14 ± 4.6 years, undergoing maintenance therapy with antidepressants (Table I). Following clinical interviews after administration of the battery of tests, 73.2% of patients referred SD (67.74% of males and 75.7% of females). In particular, the total score in men using the IIEF scale (34.25 ± 20.35; maximum score = 75) indicated the presence of significant impact on sexual functioning in all areas of the test as shown in Table II. In women, likewise, the total score in the FSFI scale (15.22 ± 11.26; maximum score = 36) indicated the presence of significant impact on sexual functioning in all areas (Table II). A total of 55.67% of the overall cohort reported onset of SD following initiation of antidepressive therapy, 37.11% referred SD only during a depressive episode and 7.12% reported SD prior to onset of depression. There were no significant differences in clinical characteristics relative to the Axis I pathology in patients with and without SD.
Considering the quality of life evaluated using the WHO-QoL, patients with SD (n = 70) reported significant differences in the Physical (p = 0,000), Environmental (p = 0.000) and Social areas (p = 0.000) as shown in Table III. Global adherence to therapy, assessed with the MARS, was not altered by the presence of SD, even if the scores were at the limits of statistical relevance (p = 0.066). Subjects with SD showed significantly greater adherence to negative stereotypes about pharmacological therapy (p = 0.001).
Dividing the cohort by gender, it was observed that males with SD had a significantly lower duration of normothymia (p = 0.005) and a lesser duration of antidepressive therapy (p = 0.005) compared to males without SD (Table IV). There was no negative impact of SD on the quality of life as men reported less intentional adherence to therapy as shown in Table. In women, there were no clinical differences considering the presence of SD. However, women with SD reported significant negative impact on all areas of quality of life (PA p = 0.001; PsyA p = 0.022; Env p = 0.001; SR p = 0.018), with a significant effect on global adherence to therapy (p = 0.003). This was also associated with a greater perception of the stigma and stereotypes of psychotherapy (4.92 ± 2.25) as shown in Table V.

Discussion

Literature data report that the antidepressants are associated with SD in both men and women [2,20,] and that the presence of SD places the patient at risk for long-term adherence [4] as adequate motivation in the absence of symptoms, thus interrupting therapy or skipping doses [5]. Moreover, SD can have a negative impact on the quality of life [21 22]. Considering this, it is important for the psychiatrist to frequently monitor complications related to the use of antidepressants and to pay attention to the mechanisms that lead to interruption of therapy [23]. In the present study, there were no difficulties in addressing this problem. Even if not quantified in the questionnaires used, our results confirm previous reports: if patients are appropriately queried, they will discuss sexual problems [1 24 25].
In the present cohort of patients, 73.2% of those in maintenance therapy with antidepressants referred adverse sexual effects. These dysfunctions involved all areas of sexuality in both women (desire, orgasm, lubrication, pain, satisfaction), and men (erectile function/excitation, ejaculation/orgasm, desire, satisfaction in intercourse, overall satisfaction). In our population, both quality of life [26 27] and adherence to therapy were compromised by SD, as previously reported [28 29]. Specifically, a significant reduction in the quality of life in the Physical (perception of health status), Environmental (evaluation of perceived environmental safety) and Social Relation areas (perception of support received from others and in interpersonal relations) were seen in addition to a significant sensitivity to social stigma and stereotypes about psychopharmacological therapies, which are responsible for nervousness, chronic pathologies, hepatotoxicity, personality changes, risk of suicide and dependence. Thus, all areas of quality of life were compromised, although only females showed

global impairment. This should not be surprising as sexuality in women is multifactorial and depends on both biological and psychosexual factors that are correlated with the context as well as sociocultural aspects, in addition to the couple's relationship [30-35].

The global evaluation of scales on adherence to therapy appeared to be affected only in females who may be more sensitive to social stigma and stereotypes. In contrast, in men, we observed an association between intentional non-adherence and the presence of SD. Investigation of SD in patients with mood disturbances may represent a clinical instrument for evaluation of the achievement of euthymia during the period in which the subject maintains a state in which fluctuations are within physiological limits. In fact, in our study, males showed a significant difference in clinical variables: subjects with SD had a shorter of clinical euthymia and took antidepressants for less time. If confirmed, this data could provide a useful instrument for clinical intervention.

SD may be reduced by the duration of treatment, and thus investigation of the sexual area could define euthymia in a more complete manner. Indeed, the definition of euthymia using tools such as the Hamilton scale may not be sufficient in defining actual remission of symptoms. This is because some residual depressive symptoms can involve other areas, including sexual, that are not normally investigated in detail.

Conclusions

Long-term treatment with antidepressants is associated with the presence of SD that affects the quality of life and adherence to therapy. On the basis of the present results, adequate evaluation of sexual collateral effects related to psychopharmacological therapy could aid in better defining remission of symptoms. Moreover, evaluation of sexual functioning and its impact on the quality of life can provide information that may be useful for psychoeducational prevention of recurrences. In our study, which should be verified in a larger patient cohort, and in particular women, SD was associated with poorer quality of life and lower adherence to therapy, thereby increasing the risk of recurrence.

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