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Depression, antidepressants, and sexual function

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Editorial

Sexologists are well aware that the major sex organ is the brain. The sex act serves to perpetuate the species, with sexual pleasure functioning as a remarkable motivational force. Sexuality has left its imprint on art, culture, and religion. It is thus only natural that it should play a major role in the life of any individual.

The two most vulnerable aspects of behavior in mental illness, and the first to bear its brunt, are sleep and sexuality; libido and sexual activity are both impaired. In depression, sexuality is often decreased to a greater or lesser degree. This is because the core feature of depression is anhedonia, meaning the difficulty or, in some cases, impossibility of experiencing pleasure — the archetypal pleasure being that of the sex act.

In general practice one of the most frequent complaints by depressed men is impotence; in women it is frigidity. In such cases, practitioners can be sorely tempted to look for a putative organic cause using a battery of investigations. However urologists know that the vast majority of such complaints are psychological in origin. There is also a great temptation to prescribe symptomatic medication for erectile dysfunction, as if the sex organ was disconnected from the source of that dysfunction, namely the unwell brain. Obviously it is important not to overlook an organic cause, but the pursuit of strenuous efforts in this direction (tests for diabetes or other endocrine mechanisms) should be based only on valid clinical evidence.

Clinicians should need no reminding that approximately one third of patients in general practice have no organic problem, and that an anxiety or depressive disorder underlies their unexplained complaints, whether these be sexual or not. Approximately one sixth of general practice patients are depressed; it therefore makes sense to include depression in the differential diagnosis of any sexual complaint, in the hope — which practice often confirms — that antidepressive treatment will relieve not only the depression but also the associated sexual symptom.

One complication is that antidepressants themselves, in particular tricyclics and specific serotonin reuptake inhibitors, can have varying degrees of sexual side effects. If the depressive episode fails to fully resolve, and residual depressive symptoms persist, it can be difficult to know how much this is still driven by depression, and how much it is a side effect of therapy. Changing the antidepressant medication may provide a clue.

Having long been neglected by psychiatrists, sexuality has become a major focus in the follow-up of patients with depression, since it is just as important to improve their quality of life as to rid them of their symptoms. What could be more important in this regard, including in menopausal women and the elderly, than the benefits of a harmonious sex life? This is true for patients, but even more so for their partners. One reason for the noxious effect of depression on relationships is the disappointing sex life it can cause.

The excellent contributions by Gabrielle Marzani-Nissen and Anita Clayton, Angel L. Montejo and Susana Majadas, and Cyril Höschl and Jan Prasko throw valuable light on these and many other aspects. Advances in the psychobiology of depression and the biology of sexual life must not make us forget that in this area we are dealing with the most intimate layer of any human being, one where difficulties are all the harder to cope with in that they are often not voiced readily to a doctor, especially by women from a traditional background. This is a field which more than any other in medicine requires an attentive and sympathetic listener. When differentiating between the organic and psychological approaches to sexual life, or considering the relationship between sexual life and depression, I cannot resist the temptation to quote from Shakespeare, in A Midsummer Night's Dream: "Love looks not with the eyes, but with the mind". This is true in health, and even more so in depression.

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Sexual disturbances in depression

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The presence of sexual function impairment in patients with psychiatric disorders is very common. This review will serve to describe the sexual response cycle, outline the prevalence of sexual dysfunction in the general population, identify contributors or mimickers of sexual dysfunction in the general and depressed populations, and aid in the identification and assessment of sexual dysfunction in depressed patients.

The sexual response cycle and neuromodulators

The sexual response cycle is divided into four phases: desire, arousal, orgasm, and resolution, and involves a complex interplay between physical and psychological components.

Neuromodulators, including sex hormones, are involved in sexual behavior (*Table I*). Testosterone is prominent in desire and sexual activity in both men and women. In women, the metabolism of testosterone to estrogen is implicated in aspects of desire and arousal. Both dopamine and norepinephrine are involved in arousal; dopamine enhances sexual motivation and behavior.

Complex positive and negative feedback loops affect these substances. For example, testosterone may be modulated by dopamine and serotonin. Elevated levels of prolactin diminish sexual arousal and other phases of sexual functioning. Progesterone may mediate receptivity to partner approach, but inhibit sexual desire and activity. Oxytocin may enhance sexual receptivity and promote orgasm.

The role of testosterone in sexual dysfunction and mood

The incidence of sexual dysfunction in certain populations is related to testosterone in both men and women. In a study with women aged 35 to 47 years old, vaginal dryness and fluctuation in total testosterone were independently identified as risk factors for decreased libido. Other studies also refer to the association of libido with low androgen levels in women. For men, there is an association between low testosterone levels and depression; the term "andropause" is now recognized, with the advent of hormone manipulation and ablative therapies for prostate cancer. Described as a constellation of symptoms, andropause can include depressed mood, diminished libido, and a general loss of well being. The diagnosis of depression may be erroneous in this population if a bioavailable testosterone level is not checked.

Shores et al noted the increased incidence of diagnosed depressive illness in hypogonadal older men. Two hundred and seventy-eight men aged 45 and above without a history of depression or hypogonadism were followed for 2 years. The incidence of depression in men with low testosterone levels was 21.7% compared with 7.1% in men with normal testosterone levels. Although the conclusion of the researchers was that "hypogonadal men showed an increased incidence of depressive illness and a shorter time to diagnosis", it can be argued that these men could only be given a diagnosis of a mood disorder due to a general medical condition (hypogonadism).

The interplay between the individual and the environment

For both depressed and nondepressed individuals, investigators acknowledge the complex interplay between the individual, the partner, and the environment. Beyond medications and illness, the causes of sexual dysfunction may be related to issues of self-esteem, conflict

	Desire	Arousal	Behavior	Pleasure	Receptivity	Orgasm
Estrogen	+	+				
Testosterone	+	+ (men)	+	+		
Dopamine	+	+				
Progesterone	(-)	+			+ (-)	
Oxytocin					+	+
Norepinephrine		+				
Serotonin (5-HT_2)	+ (-)					+ (-)
Prolactin		(-) when increased				+ (men)
Nitric oxide	+					
Vasoactive intestinal peptide		+				

Table I. Neuromodulators involved in the phases of sexual functioning.

within a relationship, partner performance and technique, issues related to prior abuse, fatigue, and the presence of children under the age of 18 in the home.

Disorders of sexual function

The sexual dysfunction disorders delineated in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition - Text Revised (DSM-IV-TR)* acknowledge the overlap between physical and psychological aspects of sexual functioning. These include disorders of desire, which encompass fantasy and avoidance, such as hypoactive sexual desire disorder and sexual aversion disorder, disorders of arousal, such as female sexual arousal disorder and male erectile disorder, and male and female orgasmic disorders. Additionally, dyspareunia and vaginismus, both pain disorders, are included. These disorders of sex may be life-long or acquired, and be situational, generalized, or mixed.

Sexual dysfunction in the general population

The incidence of sexual dysfunction in the general population provides a context for understanding sexual dysfunction in depression. A landmark study published in 1999 in the *Journal of the American Medical Association* assessed the prevalence of sexual complaints in the USA. Individuals between the ages of 18 to 59 were included: 1754 women and 1410 men. Seventy-nine percent of respondents completed the average 90-minute interview. Analysis only included those who had had sex in the past year. The authors recognized that this omitted those who had already avoided sex due to sexual dysfunction. The items included: lacking desire for sex, arousal difficulties, inability to reach orgasm, anxiety about sexual performance, premature orgasm, pain during sex, and lack of pleasure during sex. In this context, sex was described as intercourse. Forty-three percent of women and 31% of men were identified as having had sexual dysfunction. The authors cited other studies of sexual dysfunction in men and women ranging from 10% to 52% in men and 25% to 63% of women, and found that their results were similar. It is important to note that, in population studies, about 10% of women have never had an orgasm.

For some women, sexual functioning has been found to vary across the menstrual cycle. Clayton et al evaluated women during the menstrual cycle who were being assessed for premenstrual symptoms and who did not have a major psychiatric illness. These women were assessed during the midfollicular and late luteal phases with the Changes in Sexual Functioning Questionnaire (CSFQ). Scores on orgasm (more frequent orgasms, better timed orgasms, and more pleasurable) were marginally higher in the midfollicular phase compared to the late luteal phase, suggesting differences in sexual functioning across the menstrual cycle.

It is reported that women tend to complain of the subjective quality of their sexual experience (eg, lack of interest or enjoyment), whereas men often describe the failure of a specific response such as an erection. It is not uncommon to have more than one component of sexual functioning affected.

Sexual dysfunction in depression

Casper et al cited a decrease in libido, desire, and potency in 72% of 160 hospitalized individuals with major depressive disorder. They found a similar rate (77%) in depressed individuals with bipolar affective disorder.

In a review article in 1999, Bartlik cited seven studies from 1957-1997. Decreased libido was recognized in patients with manic depressive psychosis (83% men, 53% women), decreased libido was found in 61% of men and women with major depression, and a 52% decrease was found in libido in anxiety neurosis compared to 14% of controls. A correlation has also been found between primary sexual dysfunction in men with anxiety (but not for women).

Segraves notes the association between sexual dysfunction and other psychiatric disorders such as anxiety disorders, specifically hypoactive sexual desire disorder with anorexia nervosa and schizophrenia.

In 1982, Mathew and Weinman differentiated the types of sexual dysfunction in unmedicated individuals with depression. Looking at 16 men and 35 women, they found 31% of men and women with diminished libido, compared to 6% of controls. Of note, 22% experienced an increase in libido, compared to 0% of controls. Other findings of lack of orgasm, delayed ejaculation, erectile dysfunction, and premature ejaculation were not statistically significant. In general, the loss of sexual desire tends to predominate over disorders of arousal in depressed individuals.

Kennedy et al assessed the rate of sexual dysfunction in men and women with major depression before the initiation of medication. They found that, of the 134 individuals studied, 40% had not had sexual activity in the past month. Fifty percent of women and 42% of men reported a decrease in sexual desire before starting treatment. For both men and women with depression, reduced arousal was more affected (40% to 50%) compared to other phases; 15% of women had difficulty attaining orgasm. They found no difference in libido between individuals with atypical depression versus melancholic depression.

In a prospective Swiss study of individuals interviewed aged 28% to 35, 45% of depressed individuals had sexual problems, compared with 26% in the general population and 63% of treated depressed patients. A correlation of libido and emotional problems and sexual dysfunction was noted.

Cyranowksi et al assessed 68 women recruited from a larger study of women with unipolar depression. The incidence of sexual dysfunction was assessed using the Derogatis Interview for Sexual Functioning (DISF-SR). After controlling for

medication use and sexual partner availability, the authors reported that depressive symptoms were associated with decreased levels of sexual desire, sexual thoughts and fantasies, sexual arousal, and orgasmic function. Depressive symptoms were also associated with negative reports of sexual function. With the resolution of depressive symptoms, sexual function initially described as inadequate improved by over 20% (from 78% to 50%). However, remission of sexual complaints, such as a complete absence of sexual desire, lubrication difficulties with sex, and inability to reach orgasm remained essentially unchanged during the 12-month study.

Confounding variables for depressed patients with sexual dysfunction

Illnesses and medications can affect sexual functioning in depressed individuals, and certain illnesses can mimic depression (*Table II*). It is prudent to screen the patient with a history and targeted physical exam, and basic laboratory tests, such as a complete blood count, a metabolic panel and thyroid function tests. Free testosterone levels in men and women should be considered. A primary care provider should be involved in the initial assessment of a depressed individual, and more specific laboratory studies may be warranted. These include a hemoglobin A1c, lipid levels, sex-hormone-binding globulin, free and total testosterone, estradiol, prolactin, follicle-stimulating hormone, lutenizing hormone, electrocardiogram, and MRI of the pituitary (if prolactin levels are elevated).

Barriers

There are barriers to assessment of sexual function, as both the patient and physician may be reluctant to initiate a conversation about the patients' sexual function. Personal and cultural factors, such as shame, ignorance, or embarrassment, play a role. Patients may be reluctant to discuss painful or embarrassing aspects of their marriage or homosexual partnership, or may not have an ongoing relationship. The constraints of time impede physicians from asking these questions, and physicians may feel that they are perceived as intrusive or seductive. However, studies have shown that patients are not likely to volunteer this information spontaneously. Two main approaches can be utilized; a clinical interview or a validated sexual function instrument, alone or in combination.

Methods of inquiry

Balon and Segraves propose a series of clinical questions that are applicable for both men and women in assessing for sexual dysfunction. They screen for all of the disorders of sexual function: "Has your sexual drive or desire changed since I last saw you or since you have started medication?". They include level of distress and self–reflection; "What are your thoughts regarding the cause of your difficulties?" They address both masturbation and partnered sexual activity, and include an inquiry into whether the patient is in a sexual relationship, sexual fantasy, frequency, a change in initiation of sexual activity, difficulties in achieving climax/orgasm, or partner complaints. They also include situational questions such as "Are the changes in your sexual function/enjoy-

Comorbid illnesses
Other Axis I diagnosis: tobacco abuse, alcohol abuse, and other substance abuse, anorexia nervosa, panic disorder, obsessive compulsive disorder, posttraumatic stress disorder, social phobia, schizophrenia
Cardiovascular disease: hypertension, vascular disease, dyslipidemia
Neurologic: neuropathy, spinal cord disease, multiple sclerosis, pelvic trauma
Low estrogen states: menopause, surgical or pharmacologic menopause, lactation
Low testosterone states: hypogonadism, hypoandrogenism
Fibromyalgia
Irritable bowel syndrome
Premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD)
Medications
Antidepressants
Dopamine antagonists (eg, antipsychotics)
Hormonal contraceptives (eg, oral contraceptives, depo provera, estrogen patch)
Antihypertensives (eg, α_2 agonists, β-blockers)
Herbal medications/nutritional supplements
H_2 blockers

Table II. Comorbid illnesses and medications that can affect sexual functioning in depressed individuals.

ment happening during sexual encounters with your partner only? During masturbation? Possibly with another partner?" Men are also asked about difficulty achieving an erection during intercourse or masturbation, morning erections, and pain during ejaculation or penetration.
The important aspects of any interview are to ask generally about sexual activity, then follow up with more specific questions using simple, but medically correct language. Education about the prevalence of sexual dysfunction can help normalize the experience.

Assessment tools

In the assessment of sexual dysfunction, the valid and reliable instruments include:

1. The Changes in Sexual Functioning Questionnaire (CSFQ/CSFQ-CI) – male and female versions
2. The Derogatis Interview for Sexual Functioning (DISF/DISF-SR) – male and female versions
3. The Female Sexual Function Index (FSFI) – heterosexual and homosexual use – women only
4. The Golombok-Rust Inventory of Sexual Satisfaction (GRISS) – heterosexual sex therapy clients, both men and women
5. The International Index of Erectile Function (IIEF) – men only
6. The Sexual Function Questionnaire (SFQ-V1 and Abbreviated SFQ) – for women

Additionally, there is the Female Sexual Distress Scale (FSDS) used to assess and measure the level of distress related to a woman's sexual dysfunction.
Each instrument emphasizes different domains (such as desire, arousal, orgasm, and satisfaction). The time required to complete each tool varies between 5 and 15 min. The questions vary for both men and women, and some are gender- and sexual orientation-neutral. All are available in English. Other language availability varies. Only the CSFQ and DISF were designed to assess for changes in sexual function due to illness and medication effects.

Conclusions

The assessment of sexual dysfunction in depressed individuals includes the recognition of possible premorbid sexual disorders, as well as the complex relationship between the neurochemistry of the individual, comorbid conditions, and the dynamics of the patient's life. It is important to establish whether the sexual disturbance was present prior to the onset of depressive symptomatology or rather a sequel of the depressive disorder or its treatment. Sexual functioning should ideally be assessed before the onset of depression, and prior to the initiation of pharmacotherapy. In unmedicated depressed individuals, disorders of desire are most prevalent. A screening evaluation including a targeted physical exam and laboratory tests may be warranted, as well as recognition of contributing agents. There are validated instruments available for use by practitioners that may aid in recognition of sexual dysfunction and response to intervention.

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Sexual disturbances associated with antidepressant treatments

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In patients with depression, many factors such as the disease itself, deterioration in social and interpersonal relationships, and effect of the medication are involved in the occurrence of sexual dysfunction (SD).

The difficulties that the patient has in communicating the adverse effect, and the assessment of these changes by the physician make a real estimate of SD difficult. This adverse event is frequently underestimated by the physician, although fortunately in recent years more attention has been paid to the appearance of SD. SD is the most frequent adverse effect of certain antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs], venlafaxine, and clomipramine). This problem, which has a high incidence, affects the patient's quality of life and can lead to therapeutic noncompliance in long-term treatments, and has been cited among the most common (50.8%) side effects leading to dropout.

Approximately 40% of males and 50% of females with major depression have a decrease in libido and problems associated with sexual arousal, as shown by specific questionnaires used to investigate sexual activity during the month prior to diagnosis. However, orgasmic problems occur in a lower percentage, 15% to 20%, prior to taking the antidepressant drug.

The incidence of SD seems to differ according to the antidepressant used. A greater frequency is found with monoamine oxidase inhibitor (MAOIs), SSRIs, venlafaxine, and tricyclic agents (particularly those with a high serotonin reuptake blocker profile such as clomipramine). Bupropion, mirtazapine, moclobemide, and tianeptine are implicated to a much lesser degree, due to their lack of serotonergic activity.

Antidepressant drugs can cause deterioration in previous sexual activity levels with regard to desire, arousal, orgasm, and ejaculation. Less frequent alterations may also be found such as penile anesthesia or clitoral anesthesia, painful orgasm, orgasm associated with yawning, priapism associated with paroxetine and trazodone, increased libido, spontaneous orgasm, and decreased ejaculation volume.

The real incidence is often not determined if the interview is not directed toward examining this adverse effect. Spontaneous reports are uncommon, even though this side effect can considerably affect drug compliance. In a specific study, only 14% of the patients reported SD spontaneously, but this increased to 58% when sexual questionnaires were used. A recent survey has shown that patients are reluctant to speak about sexual problems with the physician, because they are afraid of finding themselves in an embarrassing situation and they expect little help from their doctors in this regard. Reports on secondary SD have significantly increased since the 1980s, and studies performed in comparison with placebo-treated and healthy volunteers have demonstrated a close relationship between the use of antidepressants and the appearance of SD. Thus, the clinician should be on the alert for the appearance of these undesirable effects in order to adopt the best strategy for managing SD.

Mechanisms involved in antidepressant-related SD

The normal sexual response includes a combination of neurogenic, psychogenic, vascular, and hormonal factors that are coordinated by hypothalamic, limbic system, and cerebral cortex centers. Nowadays, it is accepted that human sexual function is influenced by the intervention of many neurotransmitters: dopamine, serotonin, noradrenaline, acetylcholine, gamma-aminobutyric acid (GABA), oxytocin, arginine-vasopressin, angiotensin II, growth hormone releasing hormone (GRH), substance P, neuropeptide Y, and cholecystokinin 8, among others.

Dopamine enhances sexual function, while serotonin (5-hydroxytryptamine [5-HT]) inhibits sexual desire, ejaculation, and orgasm. This inhibitory action is mediated by the postsynaptic 5-HT2 receptors. SSRIs have been found to cause a high incidence of SD in sexually active patients.

Although the role of *noradrenergic* activity in sexual intercourse is unclear, it seems that it has a close relationship with the onset and maintenance of copulatory behavior in male rats. Blocking of the peripheral α-adrenergic and cholinergic receptors in the genitourinary tract also impairs sexual function. Drugs with potent anticholinergic and/or α_1 receptor blocking action (such as antidepressants and some antipsychotic agents) have a great capacity to impair the sexual arousal process.

Nitric oxide (NO) activity has been related to SD secondary to antidepressant agents. Sildenafil, which stimulates NO action, has demonstrated great usefulness in erection problems of different etiologies.

SD has also been related to other pharmacological groups such as cardiovascular agents, antihypertensive drugs, anti-histamine H2 agents, digoxin, hor-

mones, antineoplastic agents and lipid lowering agents, although these are rarely reported to the pharmacovigilance systems and, when they are reported, it is almost always done so by the manufacturers. Antihypertensive agents (methyldopa, reserpine, clonidine, and propranolol) have demonstrated some relationship with erectile dysfunction or ejaculatory problems, possibly due to adrenergic inhibition.

Use of specific questionnaires to measure sexual problems

In the last years, a few validated questionnaires have been developed to measure SD. PRSexDQ (Psychotropic-Related Sexual Dysfunction Questionnaire), CSFQ (Changes in Sexual Functioning Questionnaire), and the ASEX (Arizona Sexual Experiences Scale) have been used worldwide.

The PRSexDQ has been used in different samples of depressed and schizophrenic patients on medication. It was used in a direct clinical interview for the Spanish Group to Study Psychotropic Related Sexual Dysfunction. It has shown adequate feasibility and good psychometric properties. It consists of 7 items on SD. The first item is a screening one, to assess whether the patient has any sort of SD. The second item assesses whether the patient has reported any SD to his or her physician. The next items (items 3-7) assess 5 dimensions of SD according to severity or frequency: loss of libido, delayed orgasm or ejaculation, absence of orgasm or ejaculation, erectile dysfunction (in men)/vaginal lubrication dysfunction (in women), and patient's tolerance of SD. The first two items are answered on a scale with 2 response options. The next items are answered on a scale with 4 response options. In addition to scores for each item, an overall score may be obtained as a summated rating scale with items 3 to 7 ranging from 0 to 15 (severe SD).

Frequency of antidepressant-related SD

In agreement with previous studies, which have shown frequencies of SD between 30% and 70%, a very significant increase in SD incidence (59.1%) was found when the patients were examined using the PRSexDQ Scale. Only 24% of the patients reported SD spontaneously, and the remaining 76% would have gone unnoticed if a questionnaire aimed at measuring sexual response had not been used.

Figure 1 shows the overall frequency of SD for each of the antidepressants analyzed. Citalopram, venlafaxine, and paroxetine have the highest incidences. In keeping with these results, it has been published that the number of reports on masculine SD received by the British Committee on Safety of Medicines (CSM) during the first 2 years after SSRIs went on the market in Great Britain was 10 times greater for paroxetine than for the remaining SSRIs (fluvoxamine, fluoxetine, sertraline, and citalopram). Similarly, a greater frequency of SD and sedation has been reported with paroxetine than with other SSRIs when a meta-analysis is used. Citalopram and paroxetine are the most potent serotonin reuptake inhibitors compared with other SSRIs. In our group of patients, fluoxetine had a slightly lower incidence of SD compared with the other SSRIs. This fact could be related to the recent discovery that fluoxetine has certain postsynaptic $5HT_{2A}$ receptor blocking activity related to the appearance of SD. The increase in serotonin activity is clearly related to the low levels of libido and problems with ejaculation (delay and anorgasmia). Nevertheless, erectile dysfunction is more likely related to other factors such as an anticholinergic effect. The stimulating action on the adrenergic system could be responsible for the stimulation of peripheral postsynaptic α_1 receptors that are related to the emptying of the corpora cavernosa, provoking erectile dysfunction. There might be an effect of nitric oxide (NO) in the genitourinary tract, as occurs with paroxetine.

Moclobemide, a reversible monoamine oxidase A inhibitor has very little effect on sexual function, probably due to stimulation of dopaminergic activity and the absence of a serotonergic effect.

Bupropion has shown a low SD frequency due to its dopaminergic mechanism of action. Clayton et al in a large sample of 6300 patients comparing SSRIs, buproprion, and placebo, showed SD on buproprion to be no different from placebo. Coleman et al found that orgasmic dysfunction on buproprion is less than with SSRIs. Because bupropion is a selective norepinephrine and dopamine reuptake inhibitor with no serotonergic activity, common antidepressant-associated side effects, such as SD, weight gain, and sedation, are not associated with bupropion therapy.

Tianeptine does not seems to be associated with SD as reported by Bonierbale and Lançon.

For the new antidepressants, the first case was recently described of a patient having successful reversal of SSRI-

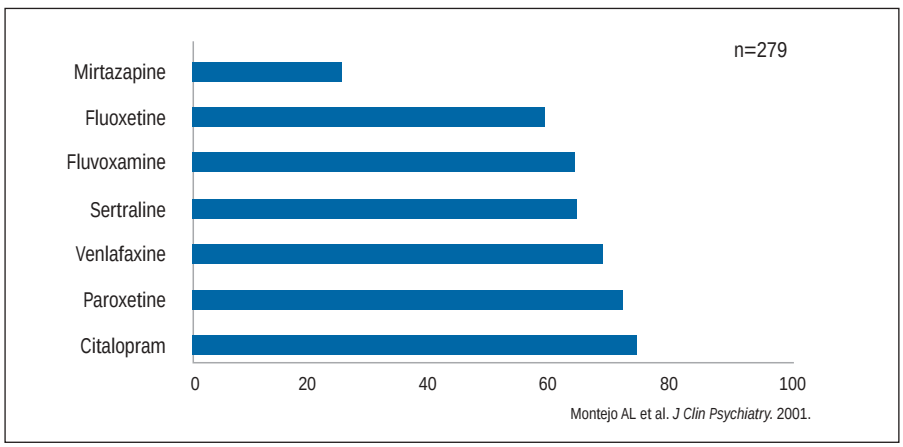

Figure 1. Frequency of antidepressant-related sexual dysfunction

induced SD by switching from an SSRI to escitalopram. Duloxetine (with a dual serotonergic and adrenergic activity) seems to have few sexual adverse events compared with paroxetine. Agomelatine (a melatonin agonist and 5-HT_{2C} antagonist) did not cause SD in clinical trials.

Table I shows the incidence of each of the adverse effects observed (decreased libido, orgasm delay/ejaculation, anorgasmia, or erectile dysfunction) in a prospective multicenter study in 1022 patients. The decreased libido and delayed orgasm make up the most frequent sexual effect in SSRIs and venlafaxine. The frequency of erectile dysfunction is significantly less than that of orgasmic problems, suggesting a different mechanism of action for this adverse effect, that is not related to serotonin but rather to the peripheral adrenergic and cholinergic pathways in combination with other factors. The differences between paroxetine, citalopram, and venlafaxine are significant, since erectile dysfunction values approach 30% to 40%. Paroxetine is associated with a significantly greater incidence of erectile dysfunction in men or adequate vaginal lubrication in women.

The decreased sexual activity produced by paroxetine and other SSRIs has been taken advantage of in clinical use, since it seems to be useful in patients with excessive sexual libido, premature ejaculation, or paraphilias. It could also be used in sex offenders and sex addiction as a coadjuvant treatment to psychotherapy.

The intensity of the SD caused by each drug was measured for each group of symptoms. A severity scale divided into four levels was used: 0=absence of adverse effect, 1= mild, 2=moderate; 3=severe. No differences were found between the SSRIs and venlafaxine with regard to intensity of decreased libido, but there were differences in the remaining sexual function items. Paroxetine showed significantly greater erectile dysfunction intensity (1.13) compared with fluoxetine (0.63), fluvoxamine (0.65), and sertraline (0.83) (chi-squared $P<0.05$). This result can be explained by the greater capacity of paroxetine to bind to the cholinergic receptors, as it is 5 to 160 times more potent in its cholinergic blocker capacity than the remaining SSRIs. On the other hand, it has been recently found that paroxetine is a potent inhibitor of NO (as it inhibits NO synthetase) both in vitro as well as in vivo, which could explain the data found by our group with regard to its greater capacity to cause erectile dysfunction compared with the other SSRIs.

N=1010	Fluoxetine n=279	Paroxetine n=208	Fluvoxetine n=77	Sertraline n=159	Citalopram n=66	Venlafaxine n=55	Mirtazapine n=49
Decrease in libido	50.2%	63.9%	48.1%	54.7%	62.1%	60.0%	20.4%
Orgasm delayed	49.5%	63.9 %	54.5%	56.6%	63.6%	61.9%	18.4%
Anorgasmia	39.1%	52.8 %	37.6%	47.1%	51.5%	41.8%	8.2%
Erectile/ lubrication dysfunction	21.8%	41.4%*	20.8%	28.9%	34.8%	40.0%	14.2%

*$P<0.05$ paroxetine versus other antidepressants

Montejo et al. *J Clin Psychiatry.* 2001.

Table I. Observed frequency by items

Mirtazapine causes SD much less frequently (24.4%) than SSRIs and venlafaxine, and when it does cause it, its intensity is significantly lower (delayed orgasm and milder anorgasmia). However, erectile dysfunction occurs at the same intensity as with the other drugs, due to the different mechanisms involved in orgasmic and erectile function. In several studies, patients who were switched to mirtazapine because of SD related to other antidepressants showed a clear improvement in all sexual items after switching. There are some reports that mirtazapine reverses sexual side effects when added to SSRI treatment. Mirtazapine also seems to improve sexual difficulties in depressed men and women. Nevertheless, the presence of other adverse effects that can appear (weight increase or somnolence) must be considered. The global improvement found (64.7%) suggests that mirtazapine is a good therapeutic alternative in patients with severe SD secondary to other drugs, especially with orgasmic problems.

Gender and age differences

Differences in frequency and intensity between sexes have been found. Males suffered a greater incidence of SD (62.4%) compared with females (56.9%); however, women had a greater severity in decreased libido, delayed orgasm, and anorgasmia. The dose used was less in women and age was also significantly lower (37.4) than that of the men (45.4). Since women are generally more reluctant to report adverse sexual effects than men, it is especially important to examine their sexual function after initiating antidepressant drug treatment.

Surprisingly, a positive correlation between the patient's age and a lower tolerance of SD has been shown, suggesting that age makes the patient more critical about the onset of sexual problems. There is also a positive correlation between the severity of difficulty in maintaining sexual arousal and the number of months elapsed since treatment has begun. This result suggests that treatment length may be an important variable in the occurrence of this dysfunction, and that the presence of impotence could be secondary to disorders of libido, orgasm, and ejaculation that have lasted for months.

Acceptance of the SD by the patient and/or his or her partner

A total of 27.2% of the patients showed good tolerance of the dysfunction, 34.5% accepted it with some complaints, and 38.3% considered it unacceptable with a serious risk of noncompliance with the treatment. The worst drug tolerance observed in patients with SD was with paroxetine when compared with fluoxetine. As mentioned previously, from data from surveys performed in large series of patients which, when analyzed, demonstrated that between 41.7% and 50.8% of the total

of the withdrawals were due to adverse effects, poor tolerance has a close relationship with treatment withdrawal. Thus, the use of alternative treatments that can decrease the frequency or intensity of SD of these patients with poor tolerance and in whom the probability of discontinuing treatment is significantly increased must be considered.

Spontaneous remission of SD

Some patients can experience partial or total improvement in their dysfunction, either immediately or after some weeks or months of treatment. However, up to now, specific data on the mean time required for this adverse effect to disappear or on the probability of whether the patients can expect a spontaneous remission have not been obtained. Only 9.7% of the patients showed a total improvement or spontaneous remission at the end of 6 months of treatment, 11.2% showed partial improvement, and unfortunately 79.1% showed no improvement. Although some patients benefit from this "spontaneous remission" mechanism, it does not seem to be practical to adopt a "wait and see" attitude, hoping for this to occur as a first therapeutic alternative in patients who are very affected by their dysfunction. Although it could be expected that a greater number of patients would have shown improvement at 12 months from the onset, many of them only remained in treatment for a shorter period, so it is difficult to obtain consistent data on this point. The data from our study suggest that at least 15% would have experienced spontaneous improvement some time after the onset of treatment.

The pathophysiogical mechanisms of this adaptation are still unknown, although the improvement of several interrelated factors could be hypothesized: individual susceptibility, enzyme autoinduction mechanisms with a consequent decrease in plasma levels, the presence of mildly intense SD from the onset, decrease in compliance over time, or even improvement in mood after treatment that would include an improvement in the couple's relationship.

Considering that the correct duration of treatment for a depressive episode is at least 6 months, and that this time needs to be extended for years and even for a lifetime in some cases, therapeutic alternatives must be found to treat the SD when this is poorly tolerated by the patient.

Conclusions

The incidence of antidepressant-related SD is presently underestimated, and occurs mainly with SSRIs and venlafaxine. Physicians should focus more attention on this problem due to the combination of several factors, such as the impairment in the quality of life and the risk of dropouts. Taking a psychosexual clinical history prior to initiating treatment with antidepressants is always needed to handle SD secondary to the treatment. Treatments with antidepressants, which must often be used for a long period of time or even indefinitely, must not jeopardize compliance, and should help the patient and family to obtain the best possible quality of life. Direct and detailed examination of previous sexual function with specific scales is a decisive factor in the detection of dysfunction. Sexual side effects should be an important factor when selecting antidepressants to be used for a long period.

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Management of depressed patients with sexual dysfunction

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The management of sexual dysfunction related to depression or to psychopharmacological treatment with antidepressants has become an important and complex problem in recent years.

Both depression and its treatment can lead to sexual dysfunction. In some patients, additional comorbid somatic disorders can occur, which also have to be treated. Again, both the disorder (eg, hypertension and/or diabetes mellitus) and the treatment can cause sexual dysfunction. To sum up, we can state that sexual dysfunction can:

a) precede (or even contribute to) the development of a depressive disorder
b) be one among other depressive symptoms
c) be a side effect of antidepressants
d) be part of a clinical picture of a comorbid somatic condition, eg, hypertension or diabetes
e) be a side effect of the treatment of somatic comorbid state, eg with antihypertensive agents
f) be a consequence of drug and particularly alcohol abuse, which is often a sort of "self-treatment" in depressed patients;
g) be a result of a combination of above-mentioned factors
h) persist as residual symptoms even after the depression has resolved.

Sexual dysfunction related to depression or to its treatment further worsens the patient's quality of life, impairs self-confidence, which was already decreased by the depression, and can threaten sexual partnership and family life. Sexual dysfunction related to antidepressant treatment often leads to noncompliance, thus increasing the risk of treatment interruption or withdrawal and the consequent relapse of the depression.

Assessment of sexual function

The relationship between depressive disorders and sexual dysfunction is complicated by the fact that treatment with antidepressants can also worsen the pre-existing sexual dysfunction or induce a sexual disorder in previously well-functioning patients. Sexual dysfunction is one of the most common reasons for noncompliance and treatment withdrawal. Therefore, the structured and repeated evaluation of sexual function in the depressed patient is very important from the very beginning of the therapeutic relationship. Although loss of libido can be merely a part of a general loss of interest, most patients can clearly distinguish specific sexual disorders from depressive symptoms.

Patients and doctors, however, are reluctant to talk openly about sexual problems. Patients usually do not like to disclose such intimate matters; they are sometimes ashamed or do not regard the topic as important. Doctors as well are hesitant to speak about sex with patients of the opposite sex, or with elderly or important people, etc.

The physician often omits sexual issues due to the influence of various misleading myths about sex and depression, eg:

- Depressed patients do not care about sex;
- If sex (and dysfunction thereof) is important for the patient, he/she will refer to it spontaneously;
- Whatever the dysfunction, the patient will continue to use the medication;
- All drugs are similar in terms of sexual adverse effects.

The basic evaluation must therefore include more than the usual question "How is your sex life?" It is important to ask specifically about libido, arousal, lubrication, erection, orgasm, interpersonal relationships, and medications. The answers must be carefully noted down. The same applies for follow-up visits during treatment with antidepressants. Only if based on careful evaluation can the doctor differentiate depressive symptoms from more specific sexual disorders. Physicians almost always have to determine whether the sexual dysfunction preceded the depressive disorder, and whether it is related to the disorder or to the treatment. The doctor cannot do this without a careful and detailed examination.

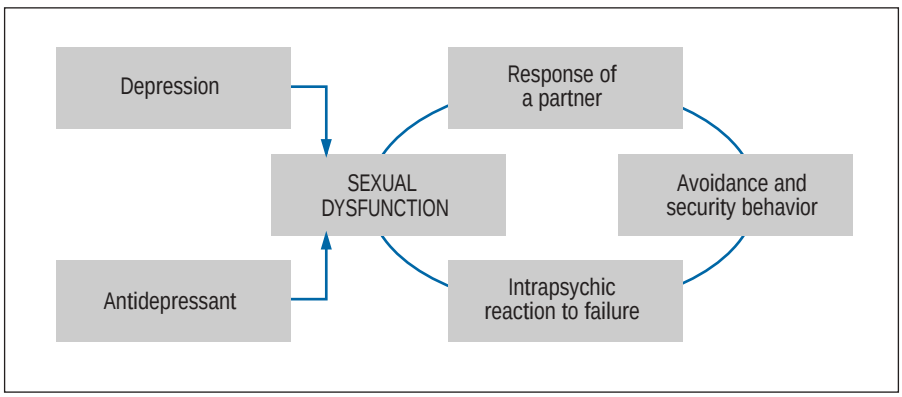

Figure 1. Factors contributing to the development and maintenance of sexual dysfunction in depressed patients.

If the sexual dysfunction is merely a side effect of the antidepressant, there are several strategies to manage the problem (see below). The dysfunction is, however, often a result of both the depressive episode and of the treatment, reinforced, in addition, by interpersonal problems and increasing worries about failure (*Figure 1*).

At the interview with the patient, it is important not only to sort out the relationship between depression, its treatment, and the sexual dysfunction, but also to monitor the dysfunction in the course of treatment and to explore lifelong sexual functioning and compare it with the current condition. Sexual functioning in depression is also influenced, besides biological factors and medication, by negative thoughts, loss of interest, anhedonia, isolation, and avoidance behaviors (*Table I*).

• Age (over 50)	• Comorbid disease
• Married	• A history of sexual dysfunction after antidepressants
• Low educational level	• A history of low or no sexual pleasure
• Less than full-time job	• Sexual functioning is not, or on the contrary is, too important
• Smoking (6-20 cigarettes daily)	
• Higher doses of antidepressants	
• Concomitant medication	

Table I. Risk factors for the development of sexual dysfunction in depressed patients. (According to Clayton et al, 2002)

• Wait for spontaneous remission of sexual dysfunction
• Lower the drug dose or stop the treatment
• Plan sexual activities according to the treatment regimen
• Switch to an antidepressant with a different pharmacological profile
• Drug holidays
• Add an adjuvant remedy
• Cognitive-behavioral therapy

Table II. Management of sexual dysfunctions induced by antidepressants.

Clinical management of sexual dysfunction in depressed patients

If the sexual dysfunction preceded the onset of depression (further worsening it) or if has developed during the depressive episode, novel antidepressants with minimum sexual adverse effects or even with a positive effect on the dysfunction are recommended, eg, bupropion, mirtazapine, moclobemide, nefazodone, reboxetine, or tianeptine. It should be kept in mind, however, that even these antidepressants can exceptionally elicit sexual dysfunctions.

If antidepressants are commenced in patients who have never suffered from sexual dysfunction, it is essential to provide them with comprehensive information about that risk. The drug choice should also take into account the risk/benefit ratio concerning sex life, the patient's values, age, compliance, etc. Sexual adverse effects induced by antidepressants can be managed using several treatment strategies (*Table II*).

- **Waiting for spontaneous remission:** This strategy is not too successful. In the course of a 6-month treatment, only 10% to 19% of patients with drug-induced sexual dysfunction recovered spontaneously. This approach requires good doctor-patient collaboration and is acceptable in patients with low sexual activity, as otherwise the dysfunction can easily lead to noncompliance and treatment omission. This strategy applies mostly to patients with only mild and noncomplicated sexual impairment, or where the main problem is simply delayed orgasm. Nevertheless, anorgasmia after tricyclics usually persists.
- **Lowering the dose of antidepressant or treatment withdrawal:** As sexual adverse effects of antidepressants are dose-dependent, dose reduction is often sufficient to reduce them, particularly if the patient has been in remission for more than 1 month; in this case dose reduction is a suitable strategy. Nevertheless, if it does not lead to relief from dysfunction or if depressive symptoms reoccur, treatment withdrawal and switch to an antidepressant from a different group should be considered. In general, this strategy is mostly used in the event of erectile dysfunction.
- **Planning of sexual activity according to the treatment regimen (dosage):** This strategy, in principle, implies taking the main dose of antidepressant after sexual intercourse, ie, before sleep. This strategy may be successful in the case of treatments with antidepressants with a short elimination half-time, like paroxetine.
- **Switch to an antidepressant with a different pharmacological profile:** The switch to a compound from the same class of antidepressants (for example from paroxetine to citalopram) usually fails to achieve improvement, because these drugs have the same mode of action. Therefore, a new antidepressant from a different group is preferable. The study by Montejo et al (2001) showed that switches to mirtazapine, nefazodone or moclobemide were highly effective, with a 66% to 80% rate of improvement in sexual functioning. Reboxetine and tianeptine or agomelatine also appear to be promising. This strategy is often described as one of the most effective.
- **Drug holidays:** Some patients can profit from a brief (1-2 days) washout period without any treatment, for

example during the weekend, and enjoy unimpaired sex. Approximately half of patients following this strategy report marked improvement in their sexual functioning during one half of weekends, when they do not take the medication, eg, SSRIs with a short half-life (paroxetine or sertraline). Sexual activity improves with the time passed after the last dose of the drug. Sometimes even a small dose reduction results in significant improvement. Withdrawal symptoms after 1 to 2 days of the washout period are a potential drawback of this strategy. However, an even more serious aspect is the negative psychological example of the "successful noncompliance," which can lead to spontaneous treatment cessation. We do not know exactly what the long-term impact of this strategy is ("kindling"?).

- **Addition of adjuvant remedy or antidote:** This strategy is recommended whenever an antidepressant works well and to change it would be too risky. Adjuvant treatment is the most frequently applied strategy in clinical practice. The drugs most frequently used as an "antidote" to antidepressant sexual side effects are listed in *Table III.*

As in other fields of medicine, where many treatment approaches exist, none is efficient in all cases. Furthermore, the real effectiveness of various "antidotes" is questionable, because many of them have been tested only in open trials.

Bupropion at a dose of 75 to 150 mg/day added to an SSRI was shown to be quite effective in improving libido. In one case study, yohimbine (18 to 42 mg/day) improved sexual dysfunction occurring after fluoxetine in 8 out of 9 males and females.

These drugs are administered in parallel with antidepressants. In arousal or erectile disorder, yohimbine or neostigmine are often used; in orgasmic dysfunction, cyproheptadine or amantadine are recommended (Pollack and Rosenbaum, 1987). Their administration should be interrupted every 3 months to avoid spontaneous adaptation. If the efficacy persists, they can be reintroduced.

Sildenafil is a very different compound. It is effective in many types of sexual dysfunction, mostly in males. Sildenafil should be taken in case of need 30 to 90 minutes before sexual intercourse at a dose of 25 to 100 mg. Clinical studies of sildenafil in depressed patients bear evidence of its good efficacy. Sildenafil is contraindicated in males using nitrates. Reports on the use of other inhibitors of type 5 phosphodiesterase isoenzyme, PDE5, in depressed patients have not yet been published.

- Cognitive-behavioral therapy (CBT): many cases with residual sexual dysfunction persisting after depression has been relieved and even after cessation of antidepressant treatment can be successfully treated with CBT. Change of attitudes towards sex, better communication with the partner, and training in sexual skills can provide significantly help to cope with sexual dysfunction, even if the sexual dysfunction was originally induced by antidepressants, because negative attitudes and avoidance behavior reinforce them.
- Mechanical tools such as vacuum pumps, penile rings etc, as well as intracorporeal injections can be theoretically of use even in sexual dysfunction related to depression and its treatment,

ANTIDOTE	DOSE	REVERSES
Stimulants		
Methylphenidat	5-20 mg/d	Lack of sexual desire,
Dextroamphetamine	5-40 mg/d	lack of arousal and
Pemoline	18.75-75 mg/d	orgasm
Cholinergic synergism		
Bethanechol	10-50 mg prn	
Neostigmine	1 hour before sex or 50-200 mg tid	Insufficient arousal
Antidepressants		
Bupropion	75-150 mg/d gd or bid max. 450 mg/d	Insufficient desire, arousal or orgasm
Mirtazapine	15-45 mg/d	Insufficient orgasm
Nefazodone	Start with 50 mg/d, titrate max. up to 150 mg/d	Insufficient orgasm
Anxiolytics		
Buspirone	30-60 mg/d bid	Decreased libido, impaired orgasm
Miscellaneous	Prn 5.4-10.8 mg	Lack of desire,
Yohimbine	1-2 hours before coitus, or 5.4 mg/d	arousal and orgasm
Amantadine	100-600 mg in divided doses or prn	Anorgasmia; can help also in loss of desire or arousal
Cyproheptadine	Prn 4-12 mg before coitus or 4-16 mg/d	Anorgasmia
Granisetron	1 mg prn	Anorgasmia
Estrogen creams or lubricants	Ad hoc	Lack of arousal
Sildenafil	50 – 100 mg/d	Lack of libido, arousal and orgasm

Table III. Pharmacological "antidotes" to sexual dysfunction induced by antidepressants. (Modified from Zajecka, 2001; Segraves and Balon, 2003)

but clinical data are scarce or missing. No controlled studies in depressed patients have been carried out.

Therapeutic approaches to sexual dysfunction in depressed patents are summarized in Table IV.

Conclusions

When sexual dysfunction is part of a depressive syndrome, it should disappear together with other symptoms, providing the depression is properly treated. Current antidepressants, however, exert side effects, some of which negatively affect sexual functioning and interfere with almost all phases of the sexual cycle. The first step in the therapeutic process should be a comprehensive medical and psychiatric examination, looking for the origin of the sexual dysfunction, and seeking to develop of a good doctor-patient relationship. This also includes the careful evaluation of all important circumstances such as somatic (age), psychological (attitudes), religious, and cultural factors, which can significantly influence the doctor's decision-making process, and the outcome of the treatment. When the sexual dysfunction is caused (or worsened) by antidepressants, there are several possible approaches. These include dose reduction or even drug cessation, switch to another antidepressant or adding an adjuvant treatment to correct the dysfunction. Some novel antidepressants induce minimum or no sexual dysfunctions, or even exert prosexual effects.

TYPE OF DYSFUNCTION	POSSIBLE STRATEGIES
Loss of libido	• Try to reduce the dose • Drug holidays (not recommended) • Low dose of neostigmine (7.5 – 15 mg) 30 minutes before coitus • Add dopaminergic compound (eg, bupropion 150 mg or more; dextroamphetamine, methylphenidate, pemoline (start with low dose, eg, 5 mg of methylphenidate and titrate up) • Switch to another antidepressant (bupropion, nefazodone, trazodone—caution: in males priapism after trazodone can rarely occur
Erectile dysfunction	• Try to reduce the dose • Drug holidays (?) • Add "antidotes" (eg, bethanechol 30 mg 1-2 hours before coitus) • Switch to another antidepressant (buspirone, mirtazapine, nefazodone, trazodone – caution: in males priapism after trazodone can exceptionally occur)
Dysfunction of ejaculation/orgasm (rare)	• Wait for spontaneous remission/recovery • Reduce the dose or try drug holidays (?) • Add "antidotes": - Amantadine 100-600 mg/day or prn (SSRI) - Bethanechol 10-20 mg 1-2 hours before coitus (to heterocyclic antidepressants) - Bupropion 75 mg/day or more (to SSRI) - Buspirone 30 mg/ day or more (to SSRI) - Cyproheptadine* 4-12 mg 1-2 hours before coitus (to heterocyclic antidepressants) - Yohimbine† 5.4 mg TID or 5.4 mg or more prn 2-4 hours before coitus (to SSRI) • Switch to another antidepressant (bupropion, mirtazapine, nefazodone, tianeptine°)

Table IV. Therapeutic approaches to sexual dysfunction occurring during depression and its treatment. (Adapted from Segraves and Balon, 2003).
*Cyproheptadine can induce marked sedation and also depression
†Yohimbine can induce anxiety, especially in patients with panic disorder.
°Suggestion based on a recent large survey (Bonierbale and Lançon, in press)

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Indications: Major depressive episodes (mild, moderate, or severe). **Properties:** In man, tianeptine is characterized by an action on anxious symptomatology associated with depression. **Dosage and administration:** The recommended dosage is 3 tablets daily, 1 in the morning, 1 at midday, and 1 in the evening before the main meals of the day. In chronic alcoholics, whether cirrhotic or not, no alteration of dosage is necessary. In subjects over 70 years of age, and in subjects with renal insufficiency, the dosage should be restricted to 2 tablets per day. **Contraindications:** Children under 15 years of age; combination with MAOIs; pregnancy; lactation. **Precautions:** Given the inherent suicide risk in depressed patients, patients should be carefully monitored, especially at the beginning of treatment; precautions in case of anesthesia; the attention of drivers and machine-operators should be drawn to the risk of drowsiness; as with all psychotropic agents, if the treatment is to be interrupted, the dosage should be gradually reduced. **Drug interactions:** With nonselective MAOIs. **Side effects:** Rare and generally not severe: epigastric pain, abdominal pain, dry mouth, anorexia, nausea, vomiting, constipation, flatulence; insomnia, drowsiness, nightmares, asthenia; tachycardia, extrasystoles, precordial pain; vertigo, headache, lipothymia, tremor, hot flushes; respiratory discomfort, lump in the throat; myalgia, back pain. **How supplied:** Coated tablets of 12.5 mg tianeptine sodium salt per tablet.

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