A comprehensive review of the use of antipressants drugs in Major Depressive Disorder and Sexuality.

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The object of this comprehensive review is to provide the clinician with an overview of the factors involved in everyday clinical practice when sexuality is an element of a major depressive episode in monopolar patients. In our opinion, functional recovery in patients with monopolar depressive disorder includes achieving healthy sexuality. This requires the clinician to bear this issue in mind, consider it in his/her assessment, be familiar with these bidirectional relations and involve these variables in his choice of pharmacological treatment. We also consider it important to include sexuality in the profiling process in order to select the most effective antidepressant treatment. We analyse the most frequent antidepressant strategies and the pharmacological groups most used in this area, consistent with what is known today about this diad and how it relates with antidepressant action mechanisms.

Key words: *major depressive disorder, sexuality, sexual dysfunctions, antidepressants, adverse sexual effects*

INTRODUCTION

We all know that functional recovery and restoring the patient's previous capabilities completely are the goals of our treatments of Major Depressive Disorder (MDD).[1] Patients today seek to recover their lives as they were before the episode; to recover their positive affect, hedonic tone and cognitive functioning.[2]

For this reason, sexuality assumes a basic role in achieving functional recovery, and in our opinion is part of it. As clinicians we tend to concentrate on relieving the depressive symptoms, while the patients focus on restoring positive affect and functional recovery.[3]

It is said, moreover, that the most important sexual organ is the brain; and we know that many patients passing through a monopolar disturbance of the mind (episodic, dysthymic or recurrent) have high rates of sexual dysfunction (SD), reaching levels twice as high as in the general population (50% vs. 24%).[4]

On the other hand, classic antidepressant treatment presents high rates of SD of various orders, which have a huge impact on adherence

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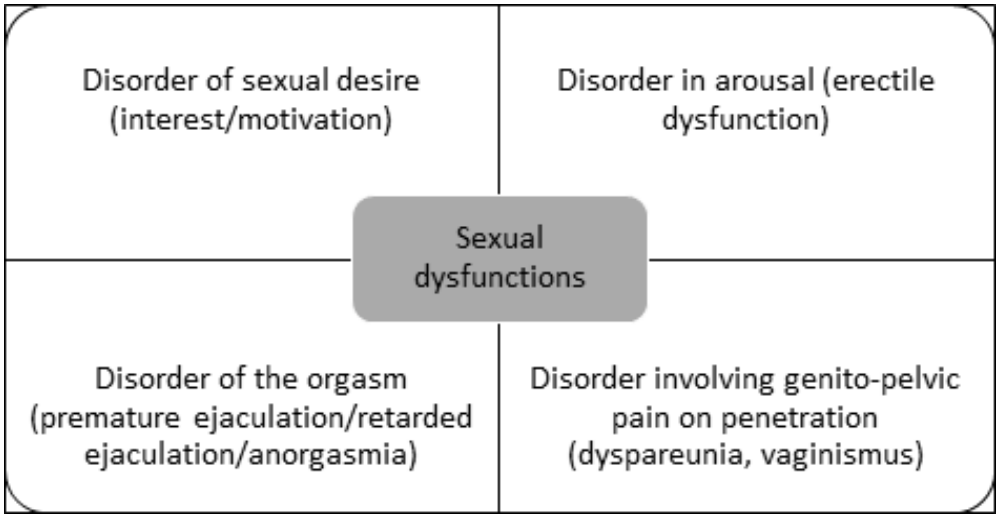
to treatment. Psychoactive drugs are very frequently discontinued for this reason, in up to 42% of cases.[5]

As clinicians, therefore, we must ask where we should place our emphasis when selecting an antidepressant to treat a major depressive episode and its sexual dysfunctions, either comorbid or emergent due to the treatment (adverse sexual effects – ASE). Is a powerful antidepressant treatment able to reverse the basic sexual dysfunctions present in these patients? Or is it our treatment which generates these pictures, and for that reason the patients discontinue the drug? These questions are fundamental given the prevalence of these associations in our patients.

A powerful antidepressant treatment can reverse sexual dysfunction

We know that achieving good remission and functional recovery is fundamental for avoiding the risk of relapse and recurrence. The presence of residual symptoms is an almost certain predictor of recurrence, since a follow-up study at 15 months showed that 76% of these patients relapsed, compared to 25% who achieved remission.[6] This imposes on us as clinicians the duty to install an effective antidepressant treatment early on.

SD are a heterogeneous group of disorders characterised by a clinically significant alteration in sexual response or in the ability to experience pleasure from sex.[7] The frequency of SD in the general population is high. In epidemiological studies, not comparable with one another due to the diversity of their methods, variable figures are found for these pictures in different populations. The most frequent are hypoactive sexual desire in women and premature ejaculation in men,[8] with rates of the order of 40% in women (lower sexual desire accounting for 22%) and 30% in men (premature ejaculation being 21%) in USA.[9] In Europe, the reported figures are 34% for women and 19% for men.[10] In general, these pictures correspond to:[7]



Although these concepts are permanently under discussion, both conceptually and in terms of classification, a degree of consensus exists that these are disorders related to alterations associated with dysfunctionality.[11] In general, approaches which involve ordering towards happiness – the acceptance of one's own sexuality and that of others, knowledge of the diversity and multiplicity of one's own sexuality and that of others and way of experiencing the erotic not solely as performance or in coitus – are today increasingly accepted concepts, beyond the over-pathologisation which occurred in the past due to archaic viewpoints. To classify an SD appropriately, current classification principles require discarding of organic pathology, or other substances present in the majority of sexual relations (70-80%), as the cause; and the condition must have persisted for more than six months.[7]

The incidence of SD in patients with mind disorders is almost twice that in the general population. Unfortunately, this symptomatological group is not recorded by clinicians, nor is it represented correctly in the scales most widely used to detect the evolution of these symptoms. A clear example of this is the absence of items to record these aspects in the Montgomery Asberg Depression Rating Scale,[12] and the existence of only one item in the HAM-D Scale, which moreover includes other somatomorphic gynaecological-pelvic symptoms.[13]

It is clear that sexual symptoms exist in all MDD, regardless of its severity, including diminution of the frequency of the sexual encounters, appearance of erectile dysfunction, alterations in the arousal phase, dyspareunia and/or retarded or absent orgasm in both sexes; and it is reasonable to suppose that the patient may recover from these with good antidepressant treatment.

At the same time, depression increases high-risk sexual behaviours, since it is closely related with sexual assertiveness, i.e. the capacity to negotiate and begin desired sexual activity, and to reject undesired. Motivation, desire and psychic indemnity are fundamental for integral sexuality.[14]

In a study of 5010 patients in Asturias, the rate of SD (SDM-IV-TR criteria) was observed at the baseline and three months after diagnosis in patients with MDD (CIE10 criteria). SD was monitored with scales which included HAM-D, CGI, Motivation and Energy Inventory (MEI) and the Visual Analogue Scale for Sexual Functioning Satisfaction (VAS-SFS). At the baseline, the rates of sexual dysfunction were of the order of 52% in women and 63% in men. The most frequent for both sexes were disorders related with the orgasm. The patients presented mean scores of 24.3 in HAM-D; 46.4 in MEI; and 4.2 in CGI. After three months, with varying treatments, the rates of SD were 35% in women and 37% in men, with mean scores of 11.3 in HAM-D; 76.5 in MEI; and 3 in CGI.[15] This shows us that the impact of depression on sexuality is enormous; that powerful, appropriate treatment is mandatory in this group of patients; and that correct use of antidepressants improves the symptoms.

Unfortunately, this has not been clearly recorded in studies, since these dysfunctions are under-reported by patients and not asked about by clinicians. A useful scale for obtaining data on sexual functioning is the Arizona Sexual Experience Scale (ASEX), which has been used most frequently in studies. It is a scale consisting of five questions to be answered by the patient on a six-point Likert-type scale. The questions are: 1) How strong is your sex drive? 2) How easily are you sexually aroused (turned on)? 3) Women: How easily does your vagina become moist or wet during sex? Men: Can you easily get and keep an erection? 4) How easily can you reach an orgasm? and 5) Are your orgasms satisfying?[16] Questions such as those listed below should be included in the evaluation of all patients with MDD: What was your baseline sexual functionality and how has it been affected by your MDD? What are your expectations or fears of treatment and its side effects in this respect? and How important is this subject for you, and for your partner (if you talk about it)?

This is clear from controlled studies like that of Hudson et al., a follow-up study of 34 weeks in patients with MDD and Generalised Anxiety Disorder (GAD), treated with duloxetine in doses of 40 to 120 mg/day vs. placebo. Sexual alterations were reported spontaneously of the order of 4% (duloxetine) vs. 1% (placebo) for diminished libido; 3% vs. <1% for abnormal orgasm; 5% vs. 1% for erectile dysfunction; 3% vs. <1% for retarded ejaculation. The figures change when scales like ASEX are applied. In general, sexual dysfunction occurred more often in the patients treated with duloxetine than in those treated with the placebo; the difference was greater when the ASEX scale was used for evaluation.[17]

The initial approach is the key

According to philosophers, a small mistake at the beginning becomes a big one at the end. For this reason the concepts discussed above must be taken into account from the start in addressing these issues.

As mentioned previously, a healthy sexuality is one in which the individual accepts himself, and knows, expresses and experiences his eroticism satisfactorily. Sexual health is the

little sister of health and the bigger sister of happiness.[18]

We all know that sexuality is the result of various bio-psychosocial processes that involve the body from the angles of reproduction, eroticism and pleasure, love and bonding, identity and gender. All these areas, analysed as a whole, involve multiple factors and are not limited to a science or a single theory.

WHO defines sexual health as "a state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity. Sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence. For sexual health to be attained and maintained, the sexual rights of all persons must be respected, protected and fulfilled."[19]

The physiological model proposed long ago by Masters and Johnson is widely known, with its 4 phases: excitement, plateau, orgasm and resolution (EPOR),[20] to which Kaplan added desire (DEO).[21]

Cerebral response includes various hormone systems and neurotransmitters like nitric oxide, testosterone, dehydroepiandrosterone, oestrogens, dopamine, oxytocin, melatonin, norepinephrine, phenylethylamine, prolactin, and of course serotonin.[22]

Evaluating sexual problems is complex; their origin is often multicausal, so evaluating adverse sexual effects (ASE) is not easy. Proper sexual functioning requires physical and psychological health. If either of these is affected, the individual may suffer some kind of SD: problems with the current partner, traumatic events, difficulties in maintaining a loving relation or chronic tension with the partner will result in some problem with sexuality.

Internal and external stimuli will stimulate the cortex and hence the limbic system, involving the affects and emotions, and then the hypothalamus where, it would appear, the integrating centre of all sexual stimuli is located. This originates the signals which, through the anterior cerebral medial bundle and the inferior thalamic peduncle, provoke genital response. The preoptic area, the lateral part of the hypothalamus, the tegument of the mesencephalon and the cingulate gyrus are also involved as essential parts of these neurobiological mechanisms.[22]

In general terms we can say that serotonin acts to inhibit the response while dopamine activates it. It is still unclear whether the differences known to exist, which depend on the different sub-types of pre and postsynaptic receptors in serotonin, result in disparities in the stimulation or inhibition of sexual desire and response. What we do know is that inhibition of the alpha-2 adrenoreceptors, 5HT1 agonism and/or 5HT2 antagonism are fundamental for arousal.[22] This is why antidepressants which respect these parameters present lower incidence of ASE.

Before we think about psychological hypotheses for SD, we must discard the presence of psychiatric disorders and organic causes. Diminished libido may be due to a hormonal cause (hypotestosterone, hyperprolactinaemia and low oestrogens); comorbid clinical disorders (like diabetes or degenerative neurological disorders), which frequently cause SD, since they affect the neurological pathways which control sexual response, with consequent anorgasmia, erectile dysfunction and/or ejaculation disorders; serious neurological or pelvic lesion, which can affect libido and sexual functioning; and physical affections (like burns or mastectomies) which may affect the individual's self-perception as an object of desire. Prostate problems in men can cause erectile dysfunction, particularly total prostatectomy (58% of cases);[23] it is less common after benign prostate hyperplasia surgery (13%).[24]

Sexual Dysfunction (SD) vs. Adverse Sexual Effects (ASE)

SD may be due to the ASE of a psychoactive drug, or it may be present prior to administration of the drug. Clinicians in general do not warn their patients of the risk of SD. Because they lack information, the patients become anxious when they notice that the treatment affects the quality of their sexual relations, and therefore abandon it.[25]

It is important to build up a detailed clinical history, including questions about the quality

of the individual's sexuality, prior to the administration of any drug. Clinical information like the presence of chronic conditions, surgery, cancer, menopause, pelvic traumas and neurological diseases must be taken into account.[25]

The minimum laboratory examinations to be assessed are glycaemia and insulin, thyroid and lipid profiles, prostate antigen, testosterone, oestrogens, FSH, prolactin, haemogram and renal function.[25]

When selecting an antidepressant, consideration must be given to the evidence on its effectiveness and action mechanism. The drug chosen should be the one with the lowest profile of adverse effects, which will not produce significant weight increase, sedation or chronic constipation, and has the lowest incidence of ASE (to maintain sexual functionality) in order to respect the patient's quality of life.[26]

Various families of antidepressants which could be useful for avoiding ASE have become widely known in recent years.

A classic group are the monoamine oxidase inhibitors (MAOI); although they can cause erection difficulties and an incidence of 20 to 40% of retarded ejaculation, in general they are known for not affecting this area in comparison with tricyclics.[27]

More modern antidepressants offer an advantage, bringing together all the requirements of first-line molecules in general: dual antidepressants, serotonin antagonist and reuptake inhibitors of the 5HT2 receptors (SARI), melatoninergic receptor agonists (MT1 and MT2)/ 5-HT2C antagonists (MelMM) and multimodal drugs.[28]

Before going into details, let us review what happens with the other antidepressant agents even more commonly used in our medium. SSRI are, by far, the antidepressants which cause most ASE, either due to diminution of the libido, difficulties in maintaining an erection or increased latency of orgasm. This is due to their agonist effects on the 5HT2 receptors. Paroxetine in particular also blocks cholinergic receptors and has inhibitory effects on nitric oxide synthase, causing even greater erectile dysfunction and failures in vaginal lubrication than the other SSRI. The reported frequency of ASE (diminished libido, retarded orgasm, anorgasmia and arousal problems) caused by these drugs are: paroxetine 70.7%; venlafaxine 67.3%; sertraline 62.9%; fluvoxamine 62.3%; fluoxetine 57.7%; mirtazapine 24.4% and moclobemide 3.9%.[29]

We know that the clinical guidelines place SSRI in the first line for treating MDD, but this recommendation has been seriously questioned since it is not evidence-based, and on occasions these drugs delay functional recovery.[30] Clinicians then face the dilemma of whether to switch the SSRI to eliminate the ASE or to add "antidotes", such as other antidepressants, to obtain functional recovery in this area. The two most frequent associations involve the addition of mirtazapine or bupropion.[31]

Mirtazapine stimulates serotoninergic and noradrenergic activity through their agonist effects on 5HT1a postsynaptic receptors and alpha2-adrenergic antagonism, associated with the antagonism of the 5HT2 and 5HT3 receptors; it thus prevents ASE principally by blocking 5HT2. It has this beneficial effect both alone and in association with mirtazapine, especially with SSRI and dual drugs. The effects are particularly marked after the fourth week of treatment with SSRI, but unfortunately the weight gain and over sedation rates caused create a serious obstacle to mass use.[32,33]

In a recent review, Zuilhof et al. found that the combination escitalopram/bupropion is superior to either of them in monotherapy for achieving remission.[34] In the case of bupropion, its effects on ASE and as an antidepressant enhancer when combined with another antidepressant are widely known;[35] however the literature is by no means conclusive on these effects in large samples.[36] In any case, this association induces a high rate of distal tremors, appearance of panic attacks, convulsive crises and associated anxiety[37] when bupropion is included. Furthermore, any association of two antidepressants always increases the costs and side effects compared to monotherapy.

Schweitzer et al., in 2009, reviewed the sexual side effects of the antidepressants then in use in Australia. They reviewed SSRI, venlafaxine, reboxetine, mirtazapine, duloxetine, bupropion, desvenlafaxine and agomelatine in double-blind, randomised comparative studies of these antidepressants, including evaluation of the

ASE with scored scales. Their findings were interesting: bupropion and duloxetine caused significantly lower ASE than SSRI in the short-term studies; reboxetine showed significantly lower rates of ASE in the short and long-term studies; bupropion and agomelatine caused significantly lower ASE than venlafaxine. There is a surprising lack of evidence that mirtazapine is preferable to SSRI in terms of the ASE that it generates, and there are no conclusive data for desvenlafaxine. Other conclusions are that greater efforts need to be made to evaluate the sexual function and its relation with depression directly, using reliable, validated scoring scales before and during treatment; and that studies which differentiate well between men and women in these aspects are still scarce.[38]

Reboxetine, a noradrenaline reuptake inhibitor (NRI), presents a low incidence of sexual effects,[39] especially compared with SSRI.[40] Unfortunately, its highly adrenergic profile generates anxiety, insomnia, urine retention, constipation, increased blood pressure and even reports of male impotence. Its profile and low antidepressant power have positioned it in second line use in normal practice, generally in enhancement strategies with SSRI.[41]

SARI antidepressants like trazodone have an antagonic effect on the 5-HT2A receptors; they stimulate areas habitually related with agitation, anxiety, sleep disorders and sexual dysfunction with moderate serotonin blocking.[42] They have also been used to reverse ASE caused by SSRI, with – in our opinion – timid results.[43] Their sedation profile, lack of antidepressant response in low and infrequent doses, and dangerous events of priapism in the male population have relegated these drugs also to the level of an adjuvant antidepressant.[44]

Tolerability and good antidepressant power in response

As we have said, a correct approach is needed from the start. Multimodal antidepressants (vortioxetine, vilazodone), some dual antidepressants (levomilnacipran, desvenlafaxine) and melatoninergic agonists (MT1 and MT2 receptors)/antagonists of 5-HT2C (MelMM) (agomelatine) play a major first line role.[45]

The action mechanism of multimodal drugs like vortioxetine in sexuality and MDD is thus very important. The action of vortioxetine on the different serotoninergic sub-receptors gives us an optimum balanced profile for powerful treatment of depression without causing serious damage in the sexual sphere. Understanding these mechanisms is fundamental for understanding the action profile of this drug. 5HT1A agonism avoids the reduction in sexual desire generated by antagonism; the absence of an effect on 5HT2A avoids the anorgasmia of antagonism; 5HT3 antagonism produces an antidepressant, anxiolytic effect; 5HT7 antagonism avoids the ataraxy and anhedonic distance of agonism. All these effects combined with an action on SERT (not comparable with that of SSRI), and the interactions with glutamatergic and GABAergic neurons by 5HT1a stimulation and 5HT1b blocking, trigger the liberation of dopamine (DA), noradrenaline (NA), histamine (HA) and acetylcholine (ACh) in the prefrontal cortex and the hippocampus as a secondary effect, giving a good profile in this area.[46,47] The blocking of auto-regulator systems (5HT1b, 5HT1d, 5HT7) is also interesting, as it allows the negative feedback presented by drugs like SSRI and dual drugs to be braked, limiting their action especially in the sexual area.[48,49]. All these mechanisms explain why several randomised works with placebo in adults with major depression showed that the ASE with vortioxetine are similar to those with placebo.[50] A double-blind, randomised study showed that switching from an SSRI (sertraline, citalopram, paroxetine) to vortioxetine in patients with MDD with clinical remission was associated with an improvement of ASE and maintenance of the effect obtained.[51]

Although dual antidepressants (serotonin and noradrenaline reuptake inhibitors) do not have these mechanisms found in multimodals, low ASE rates are reported in the meta analysis, with a good antidepressant profile and cognitive recovery. With drugs in this group, however, the greater the antidepressant and anxiolytic effect, the lower the safety profile. Thus venlafaxine at dual dose levels has rates of diminution of desire and retarded orgasm of 60%, similar to SSRI.[52] Milnacipran, which has a more adrenergic than serotoninergic effect, presents rates of 56% for improvement of sexual desire, with a

strong antidepressant response rate;[53] in general however, dual antidepressants present high rates of sexual dysfunction.[54] Although duloxetine presents good ASE rates,[17] the best are found with levomilnacipran[45] and desvenlafaxine; there is good evidence for the latter, especially in low doses,[55] in naturalistic prospective studies[56] and in some meta analyses.[57] Although this effect appears only at low doses, no study has yet assessed sexual function using appropriate sexual function questionnaires. One report grouped the data from two similar studies which compared desvenlafaxine (200 to 400 mg/day) with venlafaxine and a placebo; the incidence for desvenlafaxine was 9%, similar to venlafaxine at a dose of 75 to 150 mg.[58]

Jacobsen used the ASEX scale to compare emergent ASE with vortioxetine, duloxetine and a placebo, in six studies with MDD and one with GAD, finding a significantly higher incidence for duloxetine (5.7%) compared to vortioxetine; the latter presented no differences from the placebo at any dose. We may note here that the percentage tends to increase with the dose of vortioxetine, reaching 2.6% at a dose of 20 mg, which is compatible with our clinical experience.[59]

Finally we must mention agomelatine, an MT1 and MT2 agonist and 5HT2C antagonist; with this novel action mechanism, a good profile in this area can plausibly be expected. There are small comparative studies of this drug with paroxetine[60] and venlafaxine,[61] which show that agomelatine is better at preventing ASE.

CONCLUSIONS

A virtuoso approach to balance good antidepressant power with a profile of low sexual side effects is the best approach to treating a depressed patient with or without SD, since the relation between SD and MDD is bi-directional.

Early, thorough, integral evaluation of the patient allows suitable diagnosis and treatment of each individual.

The new multimodal drugs, agomelatine and some latest generation dual drugs produce integral improvement in the patient, with a good antidepressant effect and avoiding discontinuation due to tolerability problems, with a good profile in the sexual sphere. By avoiding discontinuation, we improve the prognosis and integrate sexuality as a very important aspect of human life – which is little considered by clinicians in general, but is of great interest to our patients. Although strategies like adding bupropion, trazodone or mirtazapine may be effective, it is always preferable to take an integral approach from the start.

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