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BUPROPION AND PSYCHOTHERAPY IN THE TREATMENT OF THE SEXUAL SIDE EFFECTS OF ANTIDEPRESSANTS

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Sexual dysfunction is a common side effect with many antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs). While the effects of the SSRIs are often very helpful in the treatment of depression, anxiety and OCD, sexual side effects are common but often not asked for by the prescriber. Two main strategies can be effective in treating sexual dysfunction. One is to add another medication, such as the dopamine and norepinephrine reuptake inhibitor bupropion. Another is to use psychotherapy, particularly one that is focused on communication. Psychotherapy is not used often in this context, although its effectiveness for sexual dysfunction in general has been established, and even cases of medication induced sexual dysfunction are frequently multifactorial.

Keywords: sexual dysfunction, selective serotonin reuptake inhibitor, SSRI, serotonin, dopamine, antidepressants, bupropion, medication, psychotherapy, psychiatry

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Introduction

A significant number of patients undergoing treatment with selective serotonin reuptake inhibitors (SSRIs) report sexual dysfunction. However, sexual dysfunction is also a common symptom of the underlying condition the medication is used for, such as depression and anxiety.

SSRI-induced sexual dysfunction can significantly lower the quality of life of the patient. SSRIs alleviate symptoms of depression primarily by selectively inhibiting the reuptake of serotonin in the central nervous system. An increase in serotonin may, however, affect other hormones and neurotransmitters, such as testosterone and dopamine. This may lead to side effects of sexual dysfunction, as testosterone may affect sexual arousal and dopamine plays a role in achieving orgasm.

The most common sexual side effect is delayed ejaculation. Other types of sexual side effects include reduced sexual desire, reduced sexual satisfaction, anorgasmia, and impotence. A prospective, descriptive clinical study of 344 subjects found that the incidence of sexual side effects was highest with paroxetine, followed by fluvoxamine, sertraline, and fluoxetine. The incidence of sexual dysfunction was similar between fluoxetine and escitalopram. (Jing & Straw-Wilson, 2016)

The best clinical evidence supports starting treatment with an antidepressant that has a better adverse sexual effect profile, such as bupropion or mirtazapine, particularly in patients concerned about their sexual functioning and in those with sexual dysfunction at baseline. (T. Lorenz et al., 2016) However, bupropion usually helps little in clinical practice against anxiety, or may even worsen it, which is often comorbid with depression.

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Bupropion

Bupropion has been used as an antidepressant for decades, though its use as an antidepressant is generally not considered first-line. It has a unique pharmacology, inhibiting the reuptake of noradrenaline and dopamine, potentially providing pharmacological augmentation to more common antidepressants such as selective serotonergic reuptake inhibitors (SSRIs). Preclinical and clinical data show that bupropion acts via dual inhibition of norepinephrine and dopamine reuptake and is devoid of clinically significant serotonergic effects or direct effects on postsynaptic receptors. (Stahl et al., 2004)

Bupropion undergoes metabolic transformation to an active metabolite, 4-hydroxybupropion, through hepatic cytochrome P450-2B6 (CYP2B6) and has inhibitory effects on cytochrome P450-2D6 (CYP2D6), thus raising concern for clinically-relevant drug interactions. Common side effects are nervousness and insomnia. Nausea appears slightly less common than with the SSRI drugs and sexual dysfunction is probably the least of any antidepressant. (Foley et al., 2006)

Several large multi-medication trials, most notably STAR*D, also support a therapeutic role for bupropion. It demonstrated similar effectiveness to other medications, though this literature highlights the generally low response rates in refractory cohorts. Bupropion is generally well tolerated, it has very low rates of sexual dysfunction, and is more likely to cause weight loss than gain. (Patel et al., 2016)

Bupropion as an Add-On

Bupropion is used in clinical practice quite frequently as an add-on to a serotonergic antidepressant therapy if sexual side effects due to the latter drug emerge. There is support for this prescribing strategy in the literature. However, there are also some contradictory findings, which may be due to the complexity of human sexuality and the diverse manifestations of sexual dysfunction. In a literature review, Zisook and colleagues found that controlled and open-label studies support the effectiveness of bupropion in reversing antidepressant-associated sexual dysfunction, whereas open trials suggest that combination treatment with bupropion and an SSRI or SNRI is effective for the treatment of MDD in patients refractory

to the SSRI, SNRI, or bupropion alone. (Zisook et al., 2006) In a later literature review, Valeska and colleagues found that most of the studies have noted that bupropion has the advantage of a lower impact on sexual functioning, and that it is effective, when combined with other antidepressants, in treating emergent sexual dysfunction. (M. Pereira et al., n.d.) There were also some studies indicating that bupropion enhanced sexual functioning in general.

In a study by Ashton and colleagues with 47 patients receiving 75 mg or 150 mg of bupropion 1–2 hrs before sexual activity, bupropion successfully reversed a variety of sexual dysfunctions caused by SRIs in 31 (66%) patients. Side effects of anxiety and tremor led to discontinuation of bupropion in 7 patients. Otherwise, bupropion was well tolerated. (Ashton & Rosen, 1998) However, in another study by Clayton and colleagues, patients were randomly assigned to receive either bupropion SR 150 mg b.i.d. or placebo for four weeks in addition to the SSRI. The difference in global sexual functioning, based on the total Changes in Sexual Functioning Questionnaire (CSFQ) score, was not statistically significant between the two groups at week four, nor were differences in orgasm, desire and interest as measured by sexual thoughts, or self-reported arousal. There was a statistically significant difference between the two groups at week four in desire as measured by self-report feelings of desire and frequency of sexual activity. Desire and frequency showed a significantly greater improvement among those patients receiving bupropion SR compared with placebo. Frequency was significantly correlated to total testosterone level at baseline. (Clayton et al., 2004)

Bupropion has shown effectiveness in both sexes. However, as sexual side effects can manifest differently it is informative to look at individual populations. In a study by Sararinejad with 218 women (25–45 years old), who were randomized to receive 12 weeks of double-blind fixed dosed treatment with bupropion sustained release 150 mg b.i.d. or placebo, the mean for Female Sexual Function Index total score was higher in the bupropion sustained release group than in the placebo group ($p = 0.001$). Mean Clinical Global Impression Scale score for the bupropion group was significantly lower than that for the placebo group ($p = 0.001$). At the end of the trial the mean scores for desire, arousal, lubrication, orgasm, and satisfaction were significantly higher in the bupropion group. The highest improvement was observed in sexual desire, followed by lubrication. (Safarinejad, 2011) In a randomized clinical trial was performed on 40 schizophrenic patients, participants were randomly divided into two experimental and control groups.

The study group was medicated with bupropion 150 mg/day and the control group was given placebo for one-month. The study group showed significant improvement in sexual function, leading to significant change in the score of sexual desire, erection and orgasm. (Rezaei et al., 2018)

Psychotherapy

Many approaches have been adopted for management of patients with sexual dysfunction associated with antidepressant treatment, including waiting for the problem to resolve, behavioural strategies to modify sexual technique, individual and couple psychotherapy, delaying the intake of antidepressants until after sexual activity, reduction in daily dosage, 'drug holidays', use of adjuvant treatments, and switching to a different antidepressant. (Baldwin, 2004) Unfortunately, the potential benefits of psychotherapy are often overlooked. Given that sexual activity is sensitive to many psychological factors and based primarily on communication if experienced with another person, psychotherapy should be a primary therapeutic approach for sexual dysfunction, whether caused by a medication or otherwise.

In clinical experience, sexual dysfunction is rarely due to a single factor, even in many patients who are on a medication that can cause sexual dysfunction. It is thus important to look at the treatment of sexual dysfunction from a more global perspective. Psychological interventions usually place a significant emphasis on communication, which is at the heart of sexual functioning, whether in the form of internal or external communication. (Haverkampf, 2010b) In a systematic review and meta-analysis of all available studies on psychological interventions for sexual dysfunction from 1980 to 2009, the overall post-treatment effect size for symptom severity was d = 0.58 (95 % CI: 0.40 to 0.77) and for sexual satisfaction d = 0.47 (95 % CI: 0.27 to 0.70). Psychological interventions were shown to especially improve symptom severity for women with Hypoactive Sexual Desire Disorder and orgasmic disorder, and evidence seemed to vary considerably across different disorders. (Frühauf et al., 2013)

Attitudes towards Sex

In a study of sexually functional males and females from the general population (43 males, 102 females) and clients attending a university clinic for the treatment of sexual dysfunction (1 14 males, 84 females), all groups of dysfunctional respondents were more likely than the functional group to report current negative attitudes towards sex. All groups of dysfunctional females were also more likely to experience deficits in both the sexual and non-sexual aspects of their current relationship, most particularly in relationship quality and range of sexual experiences. (McCabe & Cobain, 1998) This can raise the question whether sexual dysfunction leads to a more negative attitude towards sex or the negative attitude towards sex to greater sexual dysfunction. But maybe it is important to acknowledge that a clear line between sexual dysfunction and thoughts about sex does not exist. As mentioned above, sexual activity can be viewed as a form of communication (Haverkampf, 2010b), which is sensitive to many factors within and in the interaction with others. Messages containing meaningful information have a significant impact on a person's thinking, feeling, and behaviours. (Haverkampf, 2010a) Communication-Focused Therapy®, for example, takes an approach that promotes awareness, reflection, and experimentation with respect to a patient's communication patterns.

Communication-Focused Approaches

Communication with others can in itself have an antidepressant effect, depending also on the meaningfulness of the interactions. Since sex and intimacy are built on communication, both internal and external, they are very sensitive to changes in communication patterns. Depression can lead to less interactions, which then can also maintain the depression in a vicious cycle. Women with depressive symptoms, for example, have reported greater desire for sexual activity alone (masturbation) than the nondepressed women. (Frohlich & Meston, 2002) Thus, depression itself may be a barrier to the kind of communication that may be important for the enjoyment and initiation of fulfilling sexual activity with a partner.

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Sexual activity occurs within a web of meaningful messages within and without the individual. A communication-focused approach means creating greater awareness in the patient for the communication patterns that have a large bearing on whether own needs, values, and spirations are satisfied or not. In one study investigating a community sample with 53 women and 34 men in long-term, heterosexual relationships, a majority of the men and women reported that they had experienced one or more sexual concerns or problems in the past 18 months. Both better communication in general, and disclosure of specific sexual likes and dislikes in particular, were between sexual problems and concerns and sexual satisfaction. (*The Relationships between Sexual Problems, Communication, and Sexual Satisfaction - ProQuest*, n.d.)

The artificial distinction between sex therapy and communication therapy has fortunately vanished to a large extent. If they are viewed separately, they can lead to conflicting effects. In an earlier study from 1981 on sex therapy and communication therapy, the experience of sexual interaction and the orgasmic experience improved in males and females in sex therapy, and in females in communication therapy. The male experience of sexual interaction deteriorated in communication therapy, while the male orgasmic experience initially increased and subsequently diminished again. Satisfaction with the total relationship increased in the males in communication therapy, and in the females in sex therapy. (Everaerd & Dekker, 1981) However, it must be remembered that a large part of sex therapy can be subsumed within the wider range of communication-focused approaches. Sex with another person happens within the framework of the interactions in a relationship. The quality of the communication between the partners has a significant effect on all areas of the relationship, but particularly on intimacy, which is very sensitive to flows of meaningful messages. In another study, male and female partners from 76 heterosexual couples independently completed measures of their own and their partners' sexual preferences, as well as measures of sexual and general relationship adjustment, sexual difficulties, marital role preferences, depression, and social desirability. Results indicated that sexual satisfaction in both partners was associated with men's understanding of their partner's preferences and agreement between their preferences. General relationship adjustment of both partners was associated with women's understanding of men's marital role preferences. (Purnine & Carey, 1997)

A communication-focused is not a quick fix. New communication patterns and insights have to be practiced and engrained as part of daily life. This also requires an openness to changes in communication patterns. Often, rigidity in a problematic relationship dynamic and the fear to address issues within the relationship causes an exacerbation and entrenchment of the relationship difficulties and any sexual dysfunction that goes with them. In a study, couples who reported less relationship adjustment prior to treatment showed greater overall gains in coital orgasmic frequency than couples who reported better relationship adjustment. (Kilmann et al., 1986) The treatment conditions consisted of a communication skills format, a sexual skills format, and one of two combination formats.

Behavioural and Cognitive-Behavioural Approaches

Psychotherapy often focused primarily on the underlying condition rather than the sexual dysfunction. In a study by Hoyer and colleagues with 451 outpatients treated with CBT, sexual dysfunctions improved in a significant number of patients but only after successful treatment for the psychological disorder. Results for patients suffering primarily from depression were similar to those who suffered from other psychological disorders. (Hoyer et al., 2009) When patients are treated with an antidepressant, whether with an SSRI or otherwise, it is important to keep in mind that the depression can also lead to sexual dysfunction, and that it may not be easy to distinguish whether it is pharmacologically induced or a manifestation or by-product of the underlying condition. In a study with 55 male and 79 female patients with major depression, over 40% of men and 50% of women reported decreased sexual interest. (Kennedy et al., 1999)

In a review of the literature, Berner and Günzler found that twelve out of 20 trials in men used either a concept derived from Masters and Johnson or a cognitive-behavioural treatment program. Overall, psychosocial interventions improved sexual functioning. In men with premature ejaculation, behavioural techniques proved to be effective. Most of the compared interventions proved to be similarly effective. (Berner & Günzler, 2012) The results of a study of 23 couples, in which the wife was suffering from secondary orgasmic dysfunction, indicated that a cognitive-behavioural sex therapy program was

effective in changing a wide range of subjective satisfaction and behavioural measures. (Libman et al., 1984)

In a study by Lorenz and colleagues, exercise immediately prior to sexual activity significantly improved sexual desire and, for women with sexual dysfunction at baseline, global sexual function. Scheduling regular sexual activity significantly improved orgasm function; exercise did not increase this benefit. Neither regular sexual activity nor exercise significantly changed sexual satisfaction. (Tierney Ahrold Lorenz & Meston, 2014) In another study by the same authors, exercise prior to sexual stimuli increased genital arousal. Women reporting greater sexual dysfunction had larger increases in genital arousal post-exercise. For women taking SSRIs, genital arousal was linked to SNS activity. (Tierney A. Lorenz & Meston, 2012)

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