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Could Modafinil Be an Option in the Treatment of Sexual Dysfunctions Due to Antidepressant Use in Women? Two Case Reports

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SUMMARY

Antidepressants are known to cause sexual dysfunctions. Sexual side effects due to antidepressants negatively affect compliance with treatment. Modafinil is a stimulant drug used for narcolepsy and some other sleep disorders. It is also used in treatment of resistant depression, chronic fatigue syndrome, attention deficit hyperactivity disorder, and cocaine addiction syndrome. In this article, two female patients whose depressive complaints improved with antidepressant treatment, but who applied to the psychiatry outpatient clinic with complaints of sexual dysfunction and daytime sleepiness, will be presented. Both patients had loss of sexual desire, arousal and orgasm difficulties. The sexual histories obtained from the patients suggested that there was no sexual dysfunction in the period before they started using antidepressants. Both patients stated that they did not want to change the current antidepressant treatment. Modafinil 100 mg/day was prescribed to the patients for daytime sleepiness. One month after the initiation of modafinil 100 mg/day in the 39-year-old patient, there was a marked decrease in the complaints of loss of sexual desire, decreased sexual arousal and orgasm difficulties. In the other patient, 43 years old, a slight improvement in sexual functions was observed after the initiation of modafinil. In this case, after the modafinil dose was increased to 200 mg/day, there was a significant improvement in sexual dysfunctions. In both cases, the improvement in sexual dysfunctions and possible mechanisms as a result of the addition of modafinil to the treatment will be discussed.

Keywords: Antidepressant, woman, sexual dysfunction, modafinil

INTRODUCTION

Antidepressant drugs are known to induce sexual dysfunction (Baldwin and Foong 2013, Segraves and Balon 2014). Sexual adverse effects of antidepressants affect adherence to treatment negatively (Kuloğlu et al. 2000). One study has shown that 36% of the patients receiving antidepressant treatment discontinued their medications due to sexual adverse effects (Montejo et al. 2001).

Modafinil is a stimulant used for the treatment of narcolepsy and some other sleep disorders (Broughton et al. 1997). It is also used for treatment-resistant depression, chronic fatigue syndrome, attention deficit hyperactivity disorder and cocaine dependence syndrome (Goss et al. 2013, Joos et al. 2010). Modafinil has been demonstrated to enhance glutamate activity while suppressing GABA activity (Ferraro et al. 1999). Additionally, modafinil increases dopamine in the synaptic cleft by blocking dopamine transporters (Minzenberg and Carter 2008).

In this report, cases of new-onset sexual dysfunction and daytime sleepiness that occurred in two female patients while receiving antidepressant treatment will be presented. Improvement of sexual dysfunction seen in both patients after adding modafinil to ongoing antidepressant therapy for the treatment of fatigue and daytime sleepiness will be discussed.

CASE 1

Z.A., a 43-year-old female, housewife, high school graduate, married for 24 years with one child. She was diagnosed with major depression and followed up at another healthcare center for three years. The patient presented to the psychiatric outpatient clinic with complaints of weakness and fatigue. She reported onset of depressive symptoms 3 years ago and

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use of several antidepressant drugs since then. During the previous year, she has been taking sertraline at a dose of 100 mg daily. The patient stated that her depressive complaints have improved almost completely for about a year, but she has been experiencing weakness, fatigue, and daytime sleepiness over the last few months. Her detailed history revealed loss of sexual desire that coincided with the initiation of antidepressant therapy. She reported experiencing similar sexual problems with all antidepressant medications and while her depressive symptoms improved with treatment, her sexual complaints persisted. She had no sexual complaints before she started taking antidepressants.

On mental state examination, the patient was conscious, fully cooperative, and oriented. She had normal self-care, euthymic mood, normal speech rate, coherent associations, and no signs of derailment. No delusions or hallucinations were detected. Apart from psychiatric treatment, comorbidities and concomitant medication use were absent. She reported that she did not smoke, use alcohol or any other substance. She scored 6 points on the Beck Depression Inventory (BDI) and 3 points on Hamilton Depression Rating Scale (HAM-D). Revised in 1967, the HAM-D is a 17-item questionnaire widely used by the clinicians to rate the severity of symptoms in patients with depression. Each item is assigned a score that ranges from 0 to 4 points. The HAM-D score levels of depression are as follows: 0 -13 points, not depressed; 14 to 27 points, mild depression; 28 to 41 points, moderate depression and 42 to 53 points, severe depression (Hamilton 1960, Hamilton 1967, Akdemir et al. 1996). The BDI is a self-report scale that enables the assessment of depressive symptoms in three domains, namely, physical, emotional and cognitive. The BDI does not intend to detect depression. Instead, it aims to objectively measure the intensity of depressive symptoms. There are four options for each of the 21 symptom categories. Each item is scored between 0 and 3 points and possible overall scores range from 0 to 63 points. Reliability and validity of the Turkish version were previously demonstrated, with a cutoff score of 17 determined for depression (Beck et al. 1961, Hisli 1989). The BDI and HAM-D scores of the patient indicated that the severity of her depressive symptoms was below the clinically significant level. Additionally, the patient was asked to complete the Arizona Sexual Experiences Scale (ASEX) to measure the severity of sexual dysfunction, yielding a total score of 25 points. The ASEX is a 5-item, self-rating scale that was designed to detect sexual dysfunction and monitor changes in sexual functioning in depressed patients (McGahuey CA et al. 2000, Soykan 2004). The ASEX is a rapid, easy-to-score scale which does not require special training to interpret. The female version of the scale contains five items that address sex drive, psychological arousal, vaginal lubrication, ability to reach orgasm and satisfaction from orgasm respectively. Each item is assigned a score between 1 to 6 points and possible total scores range from 5 to 30 points. A total ASEX score of 19 or higher and any one item with a score of 5 or higher indicate the presence of sexual dysfunction in that individual. In addition, 3 or more items with a score of >4 suggest that the individual might have a sexual problem (Soykan 2004). A review of the ASEX questionnaire completed by the patient at the initial examination showed that she scored 5 points on each item (very difficult/very weak), indicating problems in all three domains of sexuality: sex drive, arousal and orgasm.

In laboratory investigations, complete blood count (CBC), vitamin B12 and folate levels, ferritin, electrolytes, hepatic and renal function tests and thyroid hormones were within normal limits. As a result of clinical examination, the patient was diagnosed with antidepressant-related sexual dysfunction (sexual interest/arousal disorder combined with orgasmic disorder) according to the DSM-5 criteria based on aforementioned signs and symptoms. The patient was reluctant to reduce her current drug dose (sertraline 100 mg/day) or switch to another medication. Therefore, she was started on modafinil at a dose of 100 mg daily for daytime sleepiness and asked to return to the clinic one month later. During her follow-up visit, her mental state examination was normal. She reported partial improvement in the symptoms of weakness and daytime sleepiness. She stated that her sexual problems began to improve after starting treatment with modafinil 100 mg daily which was particularly beneficial for sex drive but her difficulties with orgasm improved only partially. The patient completed ASEX and scored a total of 19 points. A review of her ratings on repeat ASEX identified 4 points (somewhat weak) for the first question on sex drive, 3 and 4 points for the second and third questions on sexual arousal respectively, and 4 points each for the fourth and fifth questions on orgasm. Modafinil dose was increased to 200 mg daily and the patient was asked to return for follow-up.

During her follow-up visit 1 month later, fatigue and daytime sleepiness were found to resolve completely. In her sexual history, she reported her sex drive returning to the level she had 3 years ago but still experiencing some orgasm-related problems. The ASEX scale completed by the patient at that time revealed a total score of 13 points including 2 points each from first and second questions and 3 points from the other items. Clinical examination, recent history and latest ASEX scores showed improvement of her sexual functioning following modafinil treatment which was initiated for daytime sleepiness. Permission was obtained from the patient to use her data for this case report by explaining her that improvement of sexual function after modafinil treatment has not been previously reported in the literature.

CASE 2

T.Y., a 39-year-old female, high school graduate, housewife, married for 19 years with 3 children. The patient presented

to the psychiatric outpatient clinic with complaints of loss of sexual interest, weakness and sleeping too much. Her medical history noted that she started antidepressant treatment after being diagnosed with major depression two years ago. Since then, she has been receiving several antidepressants the names of which she could not recall. For the past 4 months, she had been taking venlafaxine 75 mg daily. She reported complete resolution of her depressive symptoms after starting venlafaxine 75 mg/day treatment but has been experiencing weakness and daytime sleepiness in the previous month. She stated that loss of sexual interest developed after starting antidepressant therapy two years ago and similar side effects occurred with all antidepressants that she used. She reported having no sexual problems before taking psychiatric drugs.

During mental state examination, she was conscious and fully cooperative and oriented. She had normal self-care, normal speech rate, euthymic mood with no loose associations and no signs of derailment. Perception examination was normal. She did not have any comorbidities or nor used concomitant medication apart from psychiatric treatment. Smoking, alcohol use or substance abuse was absent in her history. She scored 6 points on the BDI and 4 points on the HAM-D; thus, the intensity of her depressive symptoms was lower than the clinically significant level. Additionally, the ASEX scale was used to measure the severity of sexual dysfunction, producing a total score of 22 points. A review of the ASEX form completed by the patient revealed the following scores: 5 points for the first question (very weak sex drive), 4 points for the second question, 3 points for the third question and 5 points for the fifth question. These scores indicated that she experienced problems in all three aspects of sexuality including sex drive, arousal and orgasm. Laboratory workup showed that CBC, vitamin B12 and folate levels, ferritin, electrolytes, hepatic and renal function tests and thyroid hormones were within normal ranges. Based on clinical evaluation of these findings and her symptoms, the patient was diagnosed with antidepressant-related sexual dysfunction (sexual interest/arousal disorder combined with orgasmic disorder) according to the DSM-5 criteria. The patient was unwilling to make any changes in her treatment because she considered that among all the drugs that she had taken for the last 2 years, the only medication that improved her depressive symptoms was venlafaxine. Thus, the patient was started on modafinil 100 mg daily for the treatment of daytime sleepiness and asked to return for follow-up.

One month later, no psychopathological findings were observed on her mental state examination. The patient reported improvement of her complaints of fatigue and loss of sexual interest. At that visit, her overall ASEX score was 14 points including 3 points each for questions 1, 2 and 5, 1 point for question 3 and 4 points for question 4. Modafinil dosage was escalated to 200 mg daily to obtain greater efficacy. At the follow-up visit 2 weeks later, she reported complete resolution of her complaint of decreased sex drive. During that visit, the patient scored a total of 12 points on the ASEX scale including 2 points for Items 1 and 2, 1 point for Item 3, 4 points for Item 4 and 3 points for Item 5. Collectively, clinical assessment, history and ASEX scores of the patient indicated improvement of sexual functioning after modafinil treatment. The patient was explained about the lack of any data on improvement of sexual functioning with modafinil and her permission was obtained to use her data for this case report.

DISCUSSION

Patients with depressive disorder often experience reduced sexual activity (Laurent and Simons 2009). However, available antidepressants used for the treatment of depression mostly cause sexual dysfunction (Baldwin and Foong 2013, Segraves and Balon 2014). Sexual adverse effects of antidepressant drugs have been associated with reduced quality of life and impaired interpersonal relationships and functioning. Antidepressant-related sexual adverse effects are among the leading causes of treatment discontinuation and recurrence of depression (Kennedy and Rizvi 2009, Rosen et al. 1999).

Increased levels of serotonin due to antidepressant use adversely affect all aspects of sexuality (i.e., sex drive, arousal and orgasm) by causing a reduction in dopamine levels in the central nervous system (Rosen and Marin 2003, Zajecka 2001). Our patients did not have a history of comorbid conditions or concomitant medication use and experienced sexual dysfunction after taking antidepressant medication. All laboratory tests were normal. Both patients were diagnosed with sexual dysfunction since their sexual complaints persisted despite improvement of depressive symptoms.

The primary approach for the management of antidepressant-related sexual dysfunction includes lowering the drug dose, considering a drug holiday or switching to another medication with a lower frequency of sexual adverse effects (Doğan 2001). Since both of our patients expressed their unwillingness to reduce the dose of their antidepressant drugs or change their medication, modafinil was initiated for complaints of daytime fatigue, weakness and sleepiness. A significant improvement was observed in sexual functioning of our patients after starting modafinil therapy. While improved sexual functioning was achieved after increasing modafinil dose to 200 mg/day in the first case, a low dose (100 mg/day) seemed sufficient to obtain a clinical response in the second case. Modafinil is used for treatment-resistant depression (Goss et al. 2013). Therefore, it may help resolve sexual dysfunction seen in individuals with major depression by improving depressive symptoms. However, there were no findings suggestive of depression in our patients at the initial

mental state examination. In addition, their BDI and HAM-D scores were low. Thus, it is considered that improvement of sexual functioning after treatment with modafinil cannot be attributed to its antidepressant effects.

There are no clinical studies on the impact of modafinil on sexual functions However, clinical improvement was observed in erectile dysfunction after adding modafinil to antidepressant treatment in a 39-year-old male patient with major (Karaş and Kaşer 2019). Two cases of hypersexuality associated with modafinil use were reported (Bulut et al. 2015, Sahoo et al. 2016). Moreover, modafinil may cause spontaneous orgasm (Uca and Altaş 2014). Modafinil is involved in the modulation of a number of neurotransmitters including orexin, hypocretin, glutamate, GABA, norepinephrine and histamine (Ferraro et al. 1999, Gass and Olive 2008, Scammell et al. 2000). On the other hand, modafinil increases dopamine in the synaptic cleft by inhibiting dopamine transporters (Minzenberg and Carter 2008). It has been suggested that modafinil may cause sexual arousal in males by inducing dopaminergic activity in the medial preoptic area (Dominguez and Hull 2005). The mesolimbic dopaminergic pathway is primarily involved in sex drive. Dopamine is the most important neurotransmitter known to be involved in the formation of sexual desire, arousal, fantasies and motivation (Stahl 2000). The improvement of sexual interest/arousal disorder observed in our patients occurred most probably due to increased dopamine in the synaptic cleft via inhibition of dopamine transporters by modafinil. Also, descending spinal noradrenergic fibers and noradrenergic sympathetic innervation of the genital area facilitate orgasm (Stahl 2000, İncesu 2004). In rats, modafinil increases noradrenaline levels in the prefrontal cortex and hypothalamus (Makela et al. 2003). Modafinil produces increased noradrenaline levels in the synaptic cleft by binding to noradrenaline transporters (Minzenberg and Carter 2008). Partial improvement of orgasmic disorder in our patients after modafinil use may be related to an increase in noradrenaline levels. On the other hand, GABA is known to have an inhibitory effect on sexual functioning (İncesu 2004). Modafinil decreases the levels of GABA, the main inhibitory transmitter, while increasing glutamate levels, an excitatory neurotransmitter, in certain parts of the brain (Minzenberg and Carter 2008). Therefore, improved sexual functioning experienced by our patients after using modafinil may be related, in part, to a reduction in GABA.

The cases presented here suggest that modafinil may be used as an alternative therapeutic option for the management of sexual dysfunction in patients with major depression receiving antidepressant drugs. Although the exact cause-effect relationship could not be demonstrated, this possible effect merits further controlled studies.

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