

Successful Use of Agomelatine in the Treatment of Major Depression in a Woman Taking Tamoxifen: A Case Report

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Abstract: The selective estrogen receptor modulator, tamoxifen, is extensively used for the endocrine treatment of all stages of hormone receptor–positive breast cancer. Tamoxifen is a mainly inactive prodrug, necessitating metabolism by the cytochrome P450 (CYP450) pathway, predominantly the Cytochrome P450 2D6 (CYP2D6), into the active metabolites 4-hydroxytamoxifen and, in particular, endoxifen to achieve its therapeutic effect. As several women treated with tamoxifen may experience depressive symptoms or may have a previous or actual major depressive episode with ongoing antidepressant treatment or need for a new-onset therapy, the coprescription of an antidepressant drug may be particularly problematic as several antidepressants are potent CYP2D6-inhibiting drugs. We herein report a case of a patient with major depression and concurrent tamoxifen therapy successfully treated with agomelatine monotherapy.

Key Words: agomelatine, tamoxifen, breast cancer, depression, anhedonia

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The selective estrogen receptor modulator, tamoxifen, is extensively used for the endocrine treatment of all stages of hormone receptor–positive breast cancer as it decreases breast cancer recurrence, mortality, and breast cancer risk in high-risk women.¹ Tamoxifen commonly causes a range of adverse effects and may also be linked to the development of major depressive (MD) episodes.² Nevertheless, it has been reported that women with more tamoxifen-related adverse effects are less likely to have a recurrence of breast cancer compared to women who have no adverse effects,³ but the development of a MD episode may expose the woman to a detrimental effect on quality of life and to an higher suicide risk, as such episodes may be severe.²

Agomelatine is a newly developed antidepressant drug with selective agonism for melatonergic MT1/MT2 receptors and antagonism for 5-HT_{2c} receptors.⁴ Efficacy of agomelatine in the treatment of MD has been widely demonstrated.⁵ Moreover, it has been reported that agomelatine may be beneficial in the treatment of several anxiety disorders, although data are more limited.⁶

We herein report a case of a patient with MD and concurrent tamoxifen therapy successfully treated with agomelatine monotherapy.

CASE REPORT

A 42-year-old married female teacher came to our observation in February 2012 at the outpatient facility of the Psychiatric Service of Diagnosis and Treatment of Teramo (Italy), after a consultation at the local emergency department due to a severe depressive episode. Her familiar psychiatric anamnesis was negative. She had experienced an adjustment disorder at the age of 33 years (due to reported work problems), successfully treated by a private psychiatrist with low doses of escitalopram and alprazolam, discontinued after almost 1 year of continuative treatment without recurrence. She was diagnosed 1 year before our first observation with estrogen receptor–positive intraductal carcinoma in situ, treated with surgery and tamoxifen, 20 mg/d. The patient reported that tamoxifen therapy was bothersome to her due to the presence of hot flashes, problems with sleep span (difficulty falling asleep, frequent awakenings during the night, and early morning wakefulness), and depressive symptoms that initially were reported as moderate and then worsened within 1 month after starting tamoxifen. She had previously consulted a private psychiatrist who prescribed escitalopram 20 mg/d for 3 months without benefits and after venlafaxine up to 300 mg with poor reported benefit on depressive symptoms. Moreover, she complained of a severe incapability to experience pleasure during such therapy and developed adverse effects such as weight gain and headache. For these reasons, the patient discontinued venlafaxine by herself after almost 6 months of therapy.

When observed in our outpatient facility, the patient was drug free for almost 2 months and was diagnosed with MD episode according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*⁷ (Hamilton Depression Rating Scale [HAM-D] score of 28), with severe anhedonia (Snaith-Hamilton Pleasure Scale [SHAPS] score of 11), sleep disturbances with early morning awakening, psychomotor retardation, and inability to work. The reintroduction of venlafaxine was proposed. However, the patient refused to take it again, as well as refused the introduction of mirtazapine (due to fear of weight gain and sedation). She also refused to immediately initiate a supportive psychotherapy. Therefore, agomelatine 25 mg/d at bedtime was prescribed in addition to tamoxifen, mainly due to the presence of marked anhedonia, sleep problems, and no effects on CYP2D6 and weight. Before prescribing agomelatine, a comprehensive physical examination and laboratory testing were carried out. Laboratory results (including tumor markers and liver enzymes), brain computed tomography, electrocardiogram, and chest radiograph did not show any relevant problem. Also, substance and alcohol use were ruled out on the basis of history taking and laboratory screening.

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After 1 week of therapy, the patient reported a little improvement (HAM-D, 26) especially on sleep quality and the agomelatine was increased to 50 mg/d. After 3 weeks of gradual but continuous improvement, the patient achieved response (HAM-D, 15) with a significant reduction of anhedonia (SHAPS, 5) and sleep normalization. After another 4 weeks, the patient gained full symptom remission (HAM-D, 5) with disappearance of anhedonia (SHAPS, 1) and was motivated to go back to work. Then, she was followed up once monthly in our outpatient facility and maintained complete recovery during time, initiating also a supportive psychotherapy in June 2012.

The last observation was made in July 2013: the patient was taking agomelatine 50 mg/d and tamoxifen 20 mg/d with a good compliance, maintaining full remission (HAM-D, 2; SHAPS, 0) without adverse effects. No switch into manic or hypomanic episodes was ever observed. The routinely monitored liver parameters were always normal during the whole period of agomelatine therapy. Her breast cancer had been monitored regularly on an outpatient basis and no recurrence had been detected. She regularly works as a teacher and attends activities of daily living.

The patient provided informed consent to present this report.

DISCUSSION

To date, this was the first report that evaluated the efficacy and tolerability of agomelatine in a woman in therapy with tamoxifen. Specifically, the patient treated with tamoxifen developed an MD episode with severe anhedonia that remitted with agomelatine monotherapy after failure of other antidepressants.

When treating depression in women under tamoxifen therapy the major concern is relative to pharmacological interactions between antidepressants and tamoxifen.⁸ Tamoxifen is a mainly inactive prodrug, necessitating metabolism by the cytochrome P450 (CYP450) pathway, predominantly the CYP2D6, into the active metabolites 4-hydroxytamoxifen and in particular, endoxifen, to achieve its therapeutic effect.⁹ Therefore, the main problem of tamoxifen coprescription is that drug-induced CYP2D6 inhibition can critically disrupt the formation of active tamoxifen metabolites, thus interfering with the efficacy in the treatment of breast cancer.¹⁰ As several women during tamoxifen treatment may experience depressive symptoms or may have a history or an actual MD with ongoing treatment or need for a new-onset therapy, the coprescription of an antidepressant drug may be particularly problematic as several antidepressants are potent CYP2D6-inhibiting drugs.¹¹ Approximately 90% of agomelatine is metabolized by CYP1A2 (hydroxylation) and approximately 10% by CYP2C9 (demethylation) isoforms. At higher serum concentrations, CYP2C19 is also involved in metabolism. As agomelatine has no clinical effects on CYP2D6,¹² it may be considered a useful option to treat MD during tamoxifen therapy, as seen in the present case.

Moreover, the patient showed a severe anhedonia as part of a depressive clinical picture that was not relieved by either escitalopram or venlafaxine. In the present case, agomelatine remarkably reduced anhedonia and this finding is in line with the result of previous studies.^{13,14} In fact, it has been demonstrated that agomelatine may increase dopamine (DA) and noradrenaline (NA) levels in the frontal cortex, also stimulating cell proliferation and neurogenesis¹⁵ and these effects may be related to the improvement of anhedonia.¹⁶

It has been suggested that tamoxifen-induced MD may be due to an inhibition of protein kinase C (PKC), a family of enzymes widely present in the brain, which plays a crucial role

in regulating both presynaptic and postsynaptic neurotransmission.¹⁷ Inhibition of PKC induced by tamoxifen may reduce the release of DA and NA, neurotransmitters implicated in the development and maintenance of MD.¹⁸ This action of tamoxifen on such neurotransmitters has stimulated researchers to evaluate it, with positive results, as adjuvant therapy of acute bipolar mania, where increases in DA and NA have been observed.¹⁹ In the present case, through the blockade of 5-HT_{2c} receptors,⁴ agomelatine may have restored the release of both DA and NA at the frontocortical dopaminergic and noradrenergic pathways, improving tamoxifen-induced MD episode and related anhedonia.

In conclusion, the present article supports the notion that agomelatine may be coprescribed in women with MD and concomitant tamoxifen treatment, especially in presence of severe anhedonia and sleep disturbances. However, although encouraging, this is only a case report and, therefore, prospective studies on larger samples are undoubtedly needed.

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