

Quetiapine Reduces Irritability and Risk of Suicide in Patients with Agitated Depression

Akiyoshi NISHIYAMA^{*1} and Hideo MATSUMOTO^{*2}

^{*1} Department of Psychiatry Tokai University Hachioji Hospital

^{*2} Department of Psychiatry Tokai University School of Medicine

(Received February 12, 2013; Accepted May 23, 2013)

Patients who suffer from agitated depression accompanied by psychomotor agitation and irritability are prone to suicidal ideation and attempts and must therefore be diagnosed and treated with utmost care. Clinically, there have been more than a few cases of suicidal attempts that seemed to have been provoked by careless prescription of antidepressant medication. In the present study, administration of quetiapine to 3 patients in the acute phase of agitated depression resulted in rapid improvement in irritability and alleviation of depression. Depression in these 3 patients was caused by chronic (persistent) anxiety and tension. During the acute phase, the patients evidenced psychomotor agitation and irritability, often experiencing a sudden, overwhelming urge to commit suicide. Findings from the present study suggest that treatment with quetiapine in patients with this type of agitated depression can quickly alleviate symptoms of anxiety and irritability and reduce the risk of suicide.

Key words: quetiapine, agitated depression, irritability, major depression, risk of suicide

INTRODUCTION

Agitated depression is a form of major depression accompanied by psychomotor agitation and irritability. Because patients with this type of depression are prone to suicidal ideation and are at high risk of suicide, they must be diagnosed and treated with utmost care. Several studies have shown that patients with agitated depression have a depressive mixed state [1]. Physicians should therefore take particular care in selecting appropriate treatment options for patients with agitated depression because careless prescription of antidepressants alone in an outpatient setting could increase the risk of suicide attempts. In the present study, it was observed that quetiapine was both safe and effective in alleviating the symptoms of agitated depression and in reducing the risk of suicide in a 49-year-old female patient as well as in 2 other patients under similar conditions. The 3 patients provided oral consent for the publication of this case report whose description has been slightly modified to protect the confidentiality of the patients' personal information, but only to an extent that does not compromise scientific integrity.

CASE REPORT

Patient A: 49-year-old female, married.

Major complaints: debilitating episodes of severe anxiety and suicidal ideation.

Past medical history: diagnosed with a uterine fibroid at the age of 39.

Family history: none in particular.

Life history: she was born in good health and had no developmental issues or disabilities. After graduating from a university, she found a job as an office

clerk. In her late 20s, she got married and became a housewife.

History of present illness: In Year X-10, she visited a local clinic complaining of heightened anxiety caused by some neighborhood problem and was diagnosed with acute stress reaction. She subsequently underwent 3 months of outpatient treatment at the same clinic. Unfortunately, she continued to have problems with her neighbors and she was constantly stressed out. At about this time, she began to notice not only a feeling of insecurity but also a tremor in her hands. In September, Year X-1, she was pushed to the limit when a serious problem occurred with the neighbors with whom she had had a falling-out before. Her anxiety and irritability worsened, and she began to have a very strong suicidal ideation. She also became extremely sensitive to external sounds, to the point of feeling as if all those sounds were occurring too close to her ears. Furthermore, she began to show signs of auditory hallucinations, often claiming that she could hear her neighbors out on the street speaking ill of her. She eventually started feeling that this world was better off without her, and she was soon consumed with feelings of guilt and total worthlessness that led to suicidal ideation. She even complained of squeezing sensation in the chest, which could be attributed to somatization disorder. In November, Year X-1, her anxiety and irritability symptoms worsened further, which made her feel restless. She became increasingly more suicidal, and in March, Year X, she attempted to stab herself in the chest with a knife but was stopped by her family who later on brought her to our clinic for consultation.

Initial findings: we found no impairment of consciousness or physical abnormality. Our neurological examination revealed tremor of the hands and fingers.

No other neurological abnormalities were present.

During the consultation, the patient exhibited symptoms of anxiety and irritability. Although she managed to remain seated, she remained restless throughout the consultation. Furthermore, the patient suffered from loss of appetite, weight loss of 20 kg during the last 6 months, decreased physical activity, and sleep disorder. Her suicidal ideation persisted, and she was constantly thinking about how to kill herself. She was easily excitable, and showed persistent instability of mood that could potentially cause sudden, unexpected behavior. We suspected that she had agitated depression on the basis that she not only met the DSM-IV-R criteria for major depressive disorder but also presented with anxiety, irritability, and persistent frustration which put her at a risk of engaging in dangerous behavior. She met none of the diagnostic criteria for manic and hypomanic episodes. Although we strongly advised the patient and her family that she should undergo inpatient treatment to avoid the risk of further suicidal behavior, the patient refused to admit herself for inpatient treatment due to personal reasons. We therefore had no choice but to initiate drug therapy in an outpatient setting, asking the patient to return a week later for a follow-up and making her promise not to engage in any suicidal behavior in the meantime. We also ensured that her family was fully informed on how to deal with her at home. She showed no signs of crowded or racing thoughts or talkativeness at the initial visit.

Course of treatment: we decided that administration of antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), was highly likely to trigger dangerous behavior in this patient. The treatment that could help resolve insomnia and relieve anxiety and irritability as quickly as possible was the key to reducing the risk of suicide. We therefore started the patient on 50 mg quetiapine plus 1 mg ethyl loflazepate and 8 mg ramelteon as adjunctive therapy.

By the time she returned for a follow-up visit a week later, she was sleeping much better and she no longer suffered from hypersensitivity to sound. As a result, she became free of anxiety and irritability and exhibited lower levels of suicidal ideation. These findings suggest that a week-long administration of quetiapine was effective in alleviating the symptoms of agitated depression. Because the patient felt that taking quetiapine at a dose of 50 mg made her feel slightly groggy, we reduced the dose to 25 mg and continued her on this drug. On the other hand, the feeling of insecurity, negative thoughts, and loss of motivation and energy persisted. Three weeks after treatment initiation, although the feeling of insecurity still persisted, her appetite improved and she became active enough to do household chores. When she visited us 5 weeks later for a follow-up, she occasionally showed a smile, and all the symptoms observed during the initial visit were almost gone, except for a few moments of insecurity. In addition, she gained 10 kg of weight. We evaluated the improvement of the state of depression in 17-item Hamilton Depression Scale (HAM-D17). The score that was 33 points at the first visit was improved to nine points in three weeks after initiation of therapy.

The clinical course of this patient, who initially exhibited agitated depression accompanied by anxiety, irritability, and overwhelming suicidal ideation, suggests that quetiapine treatment at a dose ranging from 25 mg to 50 mg could have an immediate effect in suppressing suicidal impulses and in removing the risk of further suicide attempts by alleviating the symptoms of insomnia and irritability. The characteristics of this patient were as follows: she had been in a constant state of insecurity and fear, which made her stressed out and caused a gradual heightening of anxiety, eventually exhibiting panic-like anxiety and irritability that were so overwhelming that she felt that death was her only escape. By nature, she was always serious and nervous.

Patient B, a woman in her 50s, attempted to commit suicide several years ago. She had been under significant psychological distress caused by persistent financial concerns and a stressful family environment. On top of this, she became physically ill. Shortly afterwards, she committed suicide. She was subsequently brought to a general hospital without a psychiatric ward by ambulance. Immediately afterwards, a physician who examined the patient found that she was suffering from a feeling of despair due to role loss. She also exhibited frustration, severe suicidal ideation, depressed mood, loss of interest, insomnia, and a feeling of worthlessness, and met the DSM-IV-R criteria for major depressive disorder. The presence of both irritability and psychomotor agitation led to the diagnosis of agitated depression. She was started on quetiapine at a dose of 25 mg, which was increased to 75 mg 3 days later. This helped reduce suicidal ideation, and 9 days later, her suicidal ideation resolved completely. Quetiapine dose was gradually increased up to 150 mg. One month after treatment initiation, the patient achieved remission from depression. The score of HAM-D17 that was 32 points at the first visit was improved to nine points in four weeks after initiation of therapy.

Patient C, a woman in her early 40s, had been under constant distress due to her inability to manage the household budget. Her family would often blame her for being irresponsible, which made her feel miserable and at the same time angry with her family for not acknowledging her efforts. Because it became too stressful to be at home all the time, she took a part-time job and worked 3 days a week. One day, after being confronted by her family about her problems, she became extremely restless and attempted self-harm by drug overdose. Shortly after this incident, she visited our clinic for help. During the consultation, she seemed restless and frustrated. She exhibited suicidal impulses and had a specific plan on how to kill herself. She also suffered from sleep disorder and exhibited depressed mood, insomnia, feelings of guilt, loss of concentration, and fatigability, and met the DSM-IV-R criteria for major depressive disorder. On the basis of severe irritability and anxiety, she was diagnosed with agitated depression. We strongly advised her to undergo inpatient treatment but the patient adamantly refused to admit herself for treatment. We thus made her promise not to attempt suicide and agreed to initiate treatment in an outpatient setting. She was started on

25 mg quetiapine and 1.5 mg lorazepam. A week later, the patient was able to sleep much better. Although she still had some suicidal ideation, she was no longer at imminent risk of suicide. A month later, her suicidal ideation resolved completely and she achieved remission from depression. The score of HAM-D17 that was 25 points at the first visit was improved to eight points in four weeks after initiation of therapy.

DISCUSSION

The above-mentioned cases describe patients suffering from feelings of anxiety and tension, which seemed to be the cause of their depression. The symptoms of psychomotor agitation and irritability were probably triggered by constant anxiety and tension, which eventually led to severe suicidal ideation that drove them to the acts of self-harm and attempted suicide. None of the patients, however, exhibited a manic or hypomanic state characterized by crowded or racing thoughts or talkativeness, which, according to many research studies, are often observed in patients in a mixed state [2]. Although we recommended inpatient treatment in a psychiatric ward for the 3 patients to avoid further risk of suicide attempts, none of them consented to this treatment plan. Thus, we made them promise not to attempt suicide and initiated treatment in an outpatient setting for Patients A and C. Patient B was treated at a general clinic to address both her physical and psychological conditions. Although loss of interest and motivation was observed in all patients, none of them showed signs of psychomotor retardation. Their inability to function normally in daily life was caused by an overwhelming sense of anxiety that triggered insomnia, tension, and restlessness. In this type of patients, initiation of treatment with antidepressants alone, such as SSRIs or TCAs, was only likely to increase the risk of suicide attempts, with little effect on depressive symptoms. Any serious risks of self-harm and suicide must be avoided when treating patients in an outpatient setting or using a liaison approach. Because patients with depression who suffer from anxiety, agitation, and insomnia are at a high risk of attempting suicide within a week or two of treatment initiation, removing anxiety and irritability as quickly as possible is key to treatment success. None of the 3 patients had diabetes. Quetiapine was chosen for the treatment of the 3 patients on account of the fact that it has a beneficial side effect profile, particularly with regard to extrapyramidal symptoms. Previous research has shown that adjunctive quetiapine treatment in agitated depression is associated with a two-fold higher remission rate compared with antidepressants alone [3]. Furthermore, quetiapine has an early onset of action and sleep-improving effect, both of which are crucial in decreasing suicide risk [4]. We wanted to provide the treatment in safety. Therefore, we determined that it was better to use antidepressant after irritability was improved. And we started the treatment with quetiapine monotherapy for this purpose in the introduction of the treatment. However, the depressed mental state was improved with the regression of the suicidal ideation, too. Therefore, the pharmacotherapy of 3 patients became quetiapine monotherapy as the result, because all of the 3 patients improved depression be-

fore using antidepressants. The 3 patients in the present study did in fact experience alleviation of irritability a week after treatment initiation, which resulted in a reduction in suicidal ideation. In another 4 weeks, all patients achieved improvement in depression. The pharmacotherapy of 3 patients became quetiapine monotherapy as the result, because 3 patients also improved depression before using antidepressants.

The 3 patients were middle-aged women in their 40s to 50s used to living a well-adjusted life without any history of developmental or personality disorders that could give rise to adjustment issues. Their depression was caused by a chronic state of anxiety and tension, which, during the acute phase, progressed into agitated depression. Their symptoms were characterized by anxiety, irritability, insomnia, and suicidal ideation. Patients with these symptoms are prone to suicide attempts during the acute phase, thus quick alleviation of symptoms is essential to avert a worst-case scenario. Quetiapine proved to be effective in this respect. Once the patients got over the acute phase, they achieved improvement in depression in about a month. These findings suggest that initiation of appropriate treatment is key to successful treatment of agitated depression.

Research evidence suggests that agitated depression is often associated with the presence of concomitant depressive mixed state. Depressive mixed state is defined as major depression plus at least 3 concurrent non-euphoric hypomanic symptoms [5]. Agitated depression is associated with the presence of certain hypomanic symptoms. Experts claim, in fact, that many patients with agitated depression also present a depressive mixed state. According to Akiskal *et al.* [1], 20% of patients with unipolar major depression are diagnosed as having agitated depression. Recent studies suggest that agitation is the consequence of hypomanic symptoms and support the view that agitated depression in unipolar patients indicates bipolar spectrum disorder [6, 7]. In view of these facts, agitated depression can be broadly categorized into the following two types: agitated depression as a depressive mixed state and agitated depression as a result of unipolar major depression. There is still much controversy over whether or not these two types of agitated depression belong to the bipolar spectrum. The patients presented in this case report had no hypomanic symptoms. They suffered from unipolar major depression accompanied by irritability and agitation, which eventually progressed into agitated depression. Quetiapine treatment proved to be effective in achieving remission of symptoms in these patients.

CONCLUSION

Some types of agitated depression are caused by persistent anxiety and tension, which, during the acute phase, produce symptoms such as psychomotor agitation and irritability accompanied by a sudden, overwhelming urge to commit suicide. Findings from the present study suggest that treatment with quetiapine in patients with this type of depression can quickly alleviate symptoms of anxiety and irritability and reduce the risk of suicide.

ACKNOWLEDGMENT

Dr Matsumoto has received grant support from Yoshitomiyakuhin, GlaxoSmithKline, Dainippon Sumitomo, Pfizer, Meiji Seika, Janssen, Mitsubishi Tanabe, and Otsuka as well as honoraria from Lilly, Novartis, Yoshitomiyakuhin, GlaxoSmithKline, Dainippon Sumitomo, Pfizer, Meiji Seika, Otsuka, and Janssen. Dr Nishiyama have no conflicts of interest.

REFERENCES

- 1) Agitated “unipolar” depression re-conceptualized as a depressive mixed state: implications for the antidepressant-suicide controversy. Akiskal HS, Benazzi F, Perugi G, Rihmer Z. *J Affect Disord.* 2005 Apr; 85(3): 245-58.
- 2) Various forms of depression. Benazzi F. *Dialogues Clin Neurosci.* 2006; 8(2): 151-61. Review.
- 3) Adjunctive antidepressant treatment with quetiapine in agitated depression: positive effects on symptom reduction, psychopathology and remission rates. Dannlowski U, Baune BT, Bückermann I, Domschke K, Evers S, Arolt V, Hetzel G, Rothermundt M. *Hum Psychopharmacol.* 2008 Oct; 23(7): 587-93. doi: 10.1002/hup.963.
- 4) Antidepressive efficacy of quetiapine XR in unipolar major depression—the role of early onset of action and sleep-improving effect in decreasing suicide risk. Rihmer Z. *Neuropsychopharmacol Hung.* 2009 Dec; 11(4): 211-5.
- 5) The importance of depressive mixed states in suicidal behaviour. Rihmer A, Gonda X, Balazs J, Faludi G. *Neuropsychopharmacol Hung.* 2008 Mar; 10(1): 45-9. Review.
- 6) The dual factor structure of self-rated MDQ hypomania: energized-activity versus irritable-thought racing. Benazzi F, Akiskal HS. *J Affect Disord.* 2003 Jan; 73(1-2): 59-64.
- 7) Agitated “unipolar” major depression: prevalence, phenomenology, and outcome. Maj M, Pirozzi R, Magliano L, Fiorillo A, Bartoli L. *J Clin Psychiatry.* 2006 May; 67(5): 712-9.