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Case Report

Mirtazapine and Bupropion Combined Treatment in Treatment-resistant Depression

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Abstract

Treatment-resistant depression is a difficult problem in clinical practice. Evidence for the efficacy of newer antidepressants, such as duloxetine and bupropion, is not yet well established. We present a case of treatment-resistant depression with full recovery where a combination of mirtazapine and bupropion was used after a failed response to combined mirtazapine and duloxetine treatment. (*Tzu Chi Med J* 2009;21(4):352–354)

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1. Introduction

Treatment-resistant depression (TRD) is a difficult problem for clinical psychiatrists. A definition used in the past is the absence of a clinical response to treatment with a tricyclic antidepressant at a minimum dose of 150 mg/day of imipramine (or an equivalent drug) for 4–6 weeks (1). However, there have been a number of different definitions of TRD used in various studies (2,3) and a consensus has yet to be reached. There is still a lack of adequate evidence to support any particular approach to TRD management in clinical practice. According to previous studies, switching, augmentation, combination, and non-pharmacological, that is psychosocial intervention, strategies have all been suggested (4–6). Numerous augmentation therapies, such as the use of steroids, buspirone, pindolol and atypical antipsychotics, have been suggested, but there is a lack of adequate double-blinded clinical trial evidence to support the use of any of these (7,8). In addition, the presence of various side effects, such as metabolic syndrome and endocrine system disturbance, would seem to render these agents relatively unsuitable. Lithium, even with the strongest evidence of efficacy as a first-line augmentation therapy (9), has well-known side effects, which include dry mouth, nephrotoxicity and neurotoxicity. When examined from a patient-centered perspective, these agents are not first-line options due to their possible side effects, which might affect patient compliance with medication. Combined treatment using different antidepressants, such as a selective serotonin reuptake inhibitor (SSRI) combined with a serotonin norepinephrine reuptake inhibitor (SNRI), norepinephrine

reuptake inhibitor and tricyclic antidepressant, have been published in a review of TRD therapeutic options [10]. Newer antidepressants, such as mirtazapine, duloxetine and bupropion, have, as yet, no clear roles in such treatment regimens. Here, we present a case of TRD in which combined therapy using these newer antidepressants was used.

2. Case report

A 54-year-old married man had his first episode of major depressive disorder about 5 years ago due to business-associated financial problems and the stress of working in the Republic of South Africa. He was treated with an SSRI initially, but then stopped treatment within 4 weeks because of poor response. His psychiatrist switched the prescribed antidepressant to mirtazapine in anticipation of a better response. Nevertheless, after 2 weeks of treatment with a dose of 60 mg/day, he continued to feel depressed; furthermore, he continued to harbor thoughts of suicide and suffered from generalized physical discomfort. At this point, he began to receive mirtazapine combined with duloxetine at a dose of 60 mg/day and his mood condition improved after 4 weeks. Finally, his depression achieved full remission after 6 months of treatment with mirtazapine and duloxetine. Over the next few years, no further depressive episodes were observed.

He returned to Taiwan about 1 year ago on his father's death. He began to suffer from depressed mood and showed lack of interest, lack of energy, restlessness, nervousness, anxiety, thoughts of suicide, and feelings of helplessness, hopelessness and worthlessness. There was also the presence of psychomotor retardation and overall generalized physical discomfort, including palm sweatiness, chills and fatigue. These had occurred over a 2–3-month period since his arrival in Taiwan. No systemic disease, substance dependence or substance abuse were noted. The feelings of physical discomfort did not fulfill the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) panic attack diagnostic criteria. His *Quick Inventory of Depressive Symptomatology–Self Report* (QIDS-SR) score was 40 (out of a total of 48), and his *Integral Inventory for Depression* (IID) score was 47 (out of a total of 60). At that time, he was initially treated with mirtazapine 60 mg/day, but his depression symptoms and somatic complaints were not relieved. In addition, he was unable to carry out many of his daily life activities, such as cooking. Combined treatment with duloxetine 60 mg/day was started due to the persistent depression. After another month of treatment, immobility for a large part of the day, depressed mood, general physical discomfort, difficulty remaining in a chair when sitting, and strong thoughts of suicide continued to be experienced. His QIDS-SR and IID scores were 35 and 46, respectively, at this time. After discussion with the patient and his wife, it was decided that the duloxetine dose would not be titrated but replaced with bupropion 300 mg/day.

Over the next 2 weeks, his mood improved and the patient demonstrated more energy in his usual activities, a greater motivation to interact with his family members, less palm sweating, less forehead sweating, less irritability and fewer ideas of suicide. On assessment, his QIDS-SR and IID scores had improved to 10 and 16, respectively, and no specific side effects were complained of. After 1 month of combined treatment with mirtazapine and bupropion, his depression had achieved near full remission (QIDS-SR, 3; IID, 5).

3. Discussion

The hypothetical biological pathogenesis model for major depressive disorder includes changes in three major neurotransmitters: serotonin, norepinephrine and dopamine [11]. All antidepressants currently in use are established on the basis of this "neurotransmitter model". In previously published articles, prescription suggestions for the treatment of TRD can be divided into two major categories, combined treatment and augmentation therapy. For combined treatment with two antidepressants, reports have usually suggested that an SSRI with an SNRI or a norepinephrine reuptake inhibitor be the first choice. In addition, as dopamine's role in depression has become more prominent over the last few years [12], a norepinephrine-dopamine reuptake inhibitor combination seems to have become another new choice. In this patient, a new SNRI, duloxetine, was combined with mirtazapine in anticipation that a serotonin receptor 5-hydroxytryptamine 1A agonist effect from mirtazapine [13] might elicit a better response than the single serotonin and norepinephrine reuptake inhibition effect of duloxetine. Even after a previous successful response to combined treatment with mirtazapine and duloxetine, the patient failed to respond to such a combination in the recent episode. The inadequate response might be related to one of the following: the absence of dopamine reuptake inhibition, a different episode with divergent symptoms, the dose level of duloxetine and/or the duration of therapy. In these circumstances, a different additional neurotransmitter strategy, targeting dopamine, might be considered an appropriate approach to this type of treatment-resistant condition.

The dopamine reuptake inhibition mechanism has been hypothesized as a new strategy for the treatment of major depression. A dopamine-deficiency animal

model has been reported to show symptoms similar to depression, including learned helplessness, immobility, decreased appetite and fear (14). Bupropion is a norepinephrine-dopamine reuptake inhibitor-type antidepressant, which has been reported to improve low energy symptoms in major depression (15). Our clinical experience with this patient suggests that we should consider combining all three neurotransmitters into our treatment strategies when tackling TRD.

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