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A CASE OF PERSISTENT DEPRESSIVE DISORDER WITH A SIGNIFICANT RESPONSE TO THE ADDITION OF LURASIDONE TO VORTIOXETINE

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INTRODUCTION

Persistent depressive disorder (PDD) is a combination of dysphoric mood and chronic major depressive episodes; major depressive disorder (MDD) may precede PDD or be present during PDD (Klein et al. 2017). Among the chronic depressions called PDD, dysthymia is particularly easily overlooked by clinicians and individuals, appears milder than other chronic depressions when viewed cross-sectionally, and can be difficult to distinguish from the patient's premorbid personality. Basically, dysthymia was introduced as a diagnosis for major depressive disorder that are chronic and low grade, and it represents the confluence of several older clinical constructs, including MDD and depressive personality, which overlap but have somewhat different meanings (Klein et al. 1993). According to DSM-5, PDD is added to the diagnosis of MDD on when it has persisted for more than two years (American Psychiatric Association 2013). PDD is a chronic mood disorder, more common than episodic MDD and often more severely disabling; in the DSM-5, the term encompasses several chronic depressive disorder (Schramm et al. 2020, NICE Evidence Reviews Collection 2022) . Although initially conceptualized as mild, most individuals with dysthymia far exceeded the minimum number of symptoms required for the diagnosis, and they have as much functional impairment and a poorer long-term course than patients with non-chronic MDD (Rhebergen et al. 2014). DSM-5 consolidated dysthymia and sever forms of chronic depression such as major depressive episodes superimposed on pre-existing dysthymia and chronic major depressive episodes, into the broader diagnostic category of PDD (American Psychiatric Association 2013). Only two studies have estimated lifetime prevalence rates for PDD; Murphy & Byrne (2012), using a nationally representative Australian sample as well as previous studies of dysthymia and chronic MDD representative sample and reported a prevalence of 4-6% for PDD. However, in a Swiss study of adults aged 35-66 years, Vandeleur et al. (2017) reported a prevalence of 18%. In clinical settings, the prevalence of chronic depression is considerably higher, accounting for 33-50% of patients with MDD (Schramm et al. 2020). In other words, many patients with medication-resistant depression are diagnosed with PDD. In other words, there is no robust evidence for drug treatment for PDD. Monoamine oxidase inhibitors (MAOIs) might be superior to tricyclic antidepressants (TCAs) in the treatment of PDD, although this needs to be more rigorously evaluated (Howland 1991) According to the network meta-analysis, fluoxetine, paroxetine, sertraline, moclobemide, imipramine, and amisulpiride can be considered as efficacious and acceptable for acute drug treatment for PDD (Kriston et al. 2014). In short, these is no robust evidence for drug treatment for PDD. Here, we report the case of a woman with PDD with psychotic features in which the patient had been continuously depressed for more than 8 years and had not responded adequately to a variety of antidepressants, mood stabilizers, and atypical antipsychotics. However, the patient responded well to the addition of lurasidone to vortioxetine.

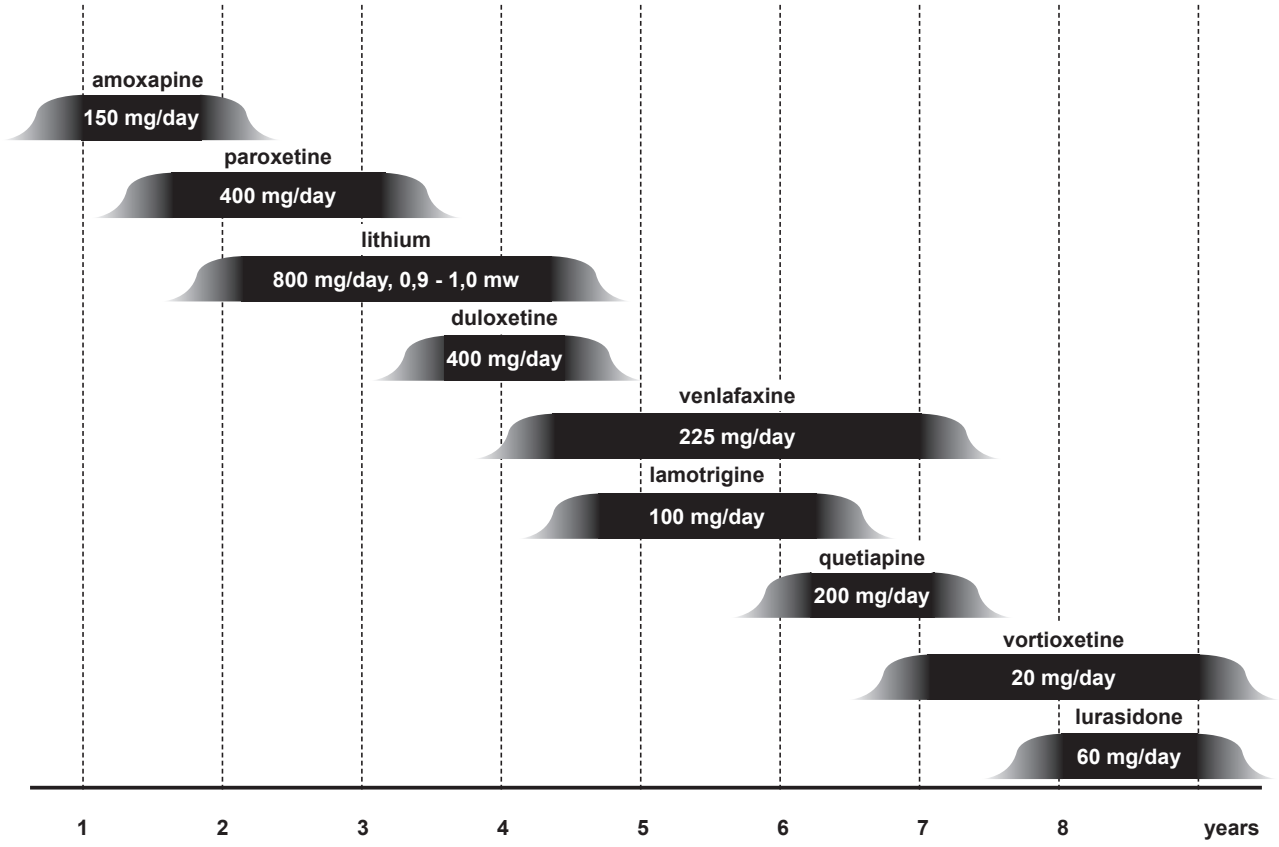
CASE REPORT

The patient made her first visit to our department at the age of 34, presenting with depression, anxiety, agitation, difficulty concentrating, self-doubt, insomnia, headache, paranoia (insecticide being sprinkled on her clothes), and auditory hallucinations (hearing a voice saying "poor you" with a miserable face). The initial diagnosis was depression with psychotic features and the patient was prescribed the following medicines: amoxapine (maximum dose 150 mg), paroxetine (maximum dose 40 mg), paroxetine (maximum dose 40mg) and lithium (maximum dose 800 mg, blood concentration 1.0 mM), duloxetine (maximum dose 40 mg), duloxetine (maximum dose 40 mg) and lithium (maximum dose 800 mg, blood concentration 0.9 mM), venlafaxine (maximum dose 225 mg), venlafaxine (maximum dose 225 mg), venlafaxine (maximum dose 225 mg) and lamotrigine

(maximum dose 100 mg), venlafaxine (maximum dose 225 mg) and quetiapine (maximum dose 200 mg). Depressive symptoms showed mild improvement at times, but fluctuated. The same was true for hallucinations and delusions. The score of 17-item Hamilton Rating Scale for Depression (HAM-D-17) (Hamilton 1960) was 28 at the point. The patient was treated with venlafaxine (maximum dose 225 mg) and quetiapine (maximum dose 200 mg) with the addition of vortioxetine (maximum dose 20 mg). Four weeks later, the patient experienced a decline in depressed mood and anxiety/agitation. Venlafaxine was tapered off, and the patient was maintained on quetiapine (200 mg) and vortioxetine (20 mg) for another 6 weeks. There was some improvement in self-doubt and concentration, and the patient began to watch daytime television shows. The HAM-D-17 score was 21 at the point. However, there was little change in her hallucinations and delusions. Therefore, 20 mg of lurasidone was prescribed in addition to vortioxetine (20 mg). Since the patient was non-responsive, the dose was increased to 60 mg, and two weeks later the hallucinations and delusions were almost completely absent. The HAM-D-17 score was 7 at the point. The combination of vortioxetine (20 mg) and lurasidone (60 mg) was effective and the patient is now able to do all household chores by herself and started working part-time. The HAM-D-17 score was 2 at the point. She has been on this prescription for one year and has remained in remission without any side effects.

DISCUSSION

In this case report, a patient with PDD who had an inadequate response to various antidepressants, mood stabilizers, and atypical antipsychotics, had an excellent response to the combination of vortioxetine and lurasidone. Information on the causes of PDD including dysthymia, is scarce, but the causes are likely multifactorial. Early research efforts have implicated serotonergic abnormalities in the biology of PDD, including lower maximum rate of platelet serotonin uptake, decrease urinary serotonin metabolite 5-hydroxy-indoleacetic acid concentration, and decreased platelet monoamine oxidase concentration in patients with PDD compared with people who are healthy. Recent research demonstrated that dysregulation of the immune system has also been implicated, for example increased CD16 or CD56, or both, increased CD4/CD8 ratio, elevated basal IL1B concentration, and increased concentration of CXCL10 in patients with PDD compared with people who are healthy. Some studies point to neuroendocrine abnormalities, such as increased baseline concentrations of plasma corticotropin-releasing hormone and cortisol concentrations in patients with PDD compared with patients who are healthy. Additionally, psychophysiological alterations and sleep-associated physiological impairments might be involved in PDD (Howland et al. 1991, Griffiths et al. 2000). Recent findings suggested that elevated levels of inflammation are contributory to treatment resistance (Strawbridge et al. 2015, Cowen 2017). Interestingly, lurasidone was inadequate at 20–40 mg but produced a complete remission at 60 mg. However, a partial response was already seen at 20 mg (32% improvement in HAM-D-17 score), but no further improvement was seen. It has been reported that supratherapeutic doses of vortioxetine (30–40 mg) are relatively well-tolerated and effective in patients with treatment-resistant depression (Cuomo et al. 2022). However, the maximum dose permitted in Japan is 20mg. Why did the combination of vortioxetine plus lurasidone result in improvement of depressive symptoms? Lurasidone is a successful drug for bipolar depression, but its efficacy in unipolar depression has not been demonstrated. Recently, open and double-blind studies have reported that lurasidone is effective for unipolar anxiety/agitation and mixed states (Suppes et al. 2016, Swann et al. 2017). In this case, mixed states were absent as far as we know, while anxiety and agitation were present. Thus, it might be possible, the present case was bipolar depression, but not completely ruled out. It is common for hypomanic episodes to be missed during the long course of the disease. Vortioxetine is a 5-HT3, 5-HT7 and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist and serotonin transporter inhibitor[19]. Vortioxetine influences noradrenergic, dopaminergic, cholinergic, histaminergic and glutamatergic as well as serotonergic neurotransmission via above 5-HT receptors in major depressive disorder (Sanchez et al. 2015). On the other hand, lurasidone exhibits both an antipsychotic and antidepressant action. Based on its pharmacodynamics profile, it is believed that the drug's clinical action is mediated mainly through the D2, 5-HT2A and 5-HT7 receptors inhibition (Jaeschke et al. 2016). The pharmacologic mechanism of why the combination of vortioxetine and lurasidone worked so well in this case is unknown, but the profiles of these drugs suggest that their potent effects on not serotonin and dopaminergic neurons but other neurons might be involved. Alternatively, it is possible that this drug combination exerted its effectiveness through anti-inflammatory effects (Rossetti et al. 2016, Tomaz et al. 2020). As this is a case report, the efficacy of lurasidone addition to vortioxetine needs to be proven in future randomized control trials. In conclusion, the combination of vortioxetine and lurasidone may be effective for persistent depressive disorder that is resistant to various medications.



Ethical considerations: This followed the Declaration of Helsinki, and the relevant Ethics Committee of University of Occupational and Environmental Health, Japan approved the protocol. Informed consent was obtained from all participants, and we assigned each patient an arbitrary identification number to protect their privacy.

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