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Ifenprodil for the Treatment of Flashbacks in Adolescent Female Posttraumatic Stress Disorder Patients with a History of Abuse

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A recent meta-analysis study showed that a history of abuse is associated with an increased risk for a lifetime diagnosis of multiple psychiatric disorders, such as posttraumatic stress disorder (PTSD), anxiety disorders, depression, eating disorders, sleep disorders, and suicide attempts [1]. In particular, PTSD is highly prevalent among women with a history of childhood abuse. Re-experiencing the event through intrusive flashbacks is one of the key diagnostic criteria for PTSD using ICD-10 [2], although the precise mechanisms for flashbacks are currently unknown [3]. Several lines of evidence suggest that glutamatergic neurotransmission via the N-methyl-D-aspartate (NMDA) receptor plays a role in certain behavioral manifestations common to PTSD, including dissociation and perceptual alterations [4, 5]. There are currently no standard therapeutic agents for treating flashbacks associated with PTSD.

Ifenprodil (brand name Cerocral), a neuroprotective agent that binds to the GluN2B subunit of the NMDA receptor [6], is used as a cerebral vasodilator in a limited number of countries including Japan and France. Here, we report on 3 cases where ifenprodil proved effective in treating the flashbacks of adolescent female PTSD patients with a history of abuse. Written informed consent was obtained from the patients and their parents for publication of this case report.

Ms. A. was a 16-year-old Japanese female diagnosed with PTSD (F43.1) and other depressive episodes (F32.8), according to ICD-10 criteria [2]. In junior high school, she was physically and sexually assaulted by a classmate for approximately 6 months. She subsequently suffered repetitive flashbacks, depressive episodes and irritation. Treatment with ifenprodil (20 mg) was initiated, and after 3 weeks, the number of flashbacks was reduced by more than 60%. The frequency of her flashbacks changed from 'frequently' (4) to 'rarely' (2), using the Likert five-point frequency scale. No side effects were reported in this patient.

Ms. B. was a 17-year-old Japanese female diagnosed with PTSD (F43.1) and other bipolar affective episodes (F31.8), according to ICD-10 criteria [2]. In junior high school, classmates physically assaulted her for approximately 2 months. She subsequently suffered repetitive flashbacks, depressive episodes and irritation. Treatment with blonanserin (8 mg) and fluvoxamine (50 mg) failed to reduce the incidence of flashbacks. New treatment with ifenprodil (20 mg) was initiated and, after 2 weeks, her flashbacks were markedly reduced by more than 80%. The frequency fell from 'very frequently' (5) to 'rarely' (2) using the Likert scale. Ms. B. also showed slight improvement in her dissociative symptoms. Her only reported side effect was a mild headache.

Ms. C. was a 19-year-old Japanese female, diagnosed with PTSD (F43.1) and other bipolar affective episodes (F31.8), according to ICD-10 criteria [2]. In elementary school, she was sexually assaulted by her uncle. She suffered flashbacks, depressive episodes and irritation for more than 10 years. She was treated with several drugs, including fluvoxamine, carbamazepine, valproate sodium, risperidone, blonanserin, quetiapine, and aripiprazole, and underwent psychotherapy, but none were effective in treating her flashbacks. Ifenprodil (20 mg) was added to the regimen and after 2 weeks, the number of flashbacks was reduced by more than 50%. Flashback frequency fell from 'very frequently' (5) to 'occasionally' (3), using the Likert scale. In this patient, the only reported side effect was nausea.

None of these cases had a history of phencyclidine, ketamine, methoxetamine or tiletamine use. Nor was there use of any other recreational drug known to block glutamatergic neurotransmission via the NMDA receptor.

Ifenprodil was well tolerated in these 3 PTSD patients with histories of abuse. The depressive symptoms and irritation in 2 patients were first treated with antidepressants or atypical antipsychotics. Although their depression and irritation improved, the occurrence of flashbacks remained unchanged. Treatment with ifenprodil dramatically reduced the incidence of flashbacks in all patients. To our knowledge, this is the first report demonstrating the beneficial effect of ifenprodil for treating flashbacks in adolescent female subjects. Recently, Kishimoto et al. [7] reported that ifenprodil showed beneficial effects in the treatment of flashbacks, in female PTSD patients with a history of childhood sexual abuse. However, the precise mechanisms underlying this effect are unclear. It is also reported that ifenprodil is a potent agonist at endoplasmic reticulum chaperone sigma-1 receptors, which play a role in neuronal plasticity in the brain [8, 9]. With its high affinity for both the NMDA and sigma-1 receptors, it is likely that ifenprodil acts, at least partially on these receptors, to alleviate flashbacks in PTSD patients, although further detailed studies are needed [7]. While selective serotonin reuptake inhibitors are effective in treating PTSD in children, adolescents and young adults [10], there is an increased risk of attempted suicide [11]. In contrast, there are no reports of an increased suicide risk in patients using ifenprodil.

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It seems likely therefore, that ifenprodil may be an effective and safe drug for the treatment of flashbacks associated with PTSD in children and adolescents.

In conclusion, ifenprodil therapy may prove to be an effective alternative treatment for flashbacks in adolescent female patients with PTSD, since this drug is already in clinical use. Nonetheless, more detailed randomized, double-blind studies are needed to confirm its efficacy.

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