Trazodone Add-on in COVID-19-related Selective Serotonin Reuptake Inhibitor-resistant Post-traumatic Stress Disorder in Healthcare Workers: Two Case Reports

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COVID-19 represents a significant stress factor for all people worldwide due to several factors, including quarantine, lockdowns, fear of contagion, deaths, and other traumatic events. However, the healthcare workers (HCWs) have paid the higher price of this pandemic in terms of fatalities, contagions, and psychological well-being. Studies suggest that this particular population is at increased risk of developing a severe post-traumatic stress disorder (PTSD). The early diagnosis and timely treatment of PTSD in HCWs may restore well-being and significantly impact health services functioning, reducing burnout, days spent far from work, disrupted personal and team empowerment, and worse job performances. In the present article, we reported on two cases of HCWs directly involved in the treatment of COVID-19 patients who showed selective serotonin reuptake inhibitor-resistant PTSD, which was successfully treated with extended-release trazodone TRZ Contramid® add-on.

KEY WORDS: Healthcare workers; COVID-19; PTSD; Serotonin uptake inhibitors; Trazodone; Add-on.

INTRODUCTION

COVID-19 represents a significant stress factor for all people worldwide [1,2]. However, healthcare workers (HCWs) paid the higher price of this pandemic in terms of deaths, contagions, and psychological well-being [3]. The trauma-related stress symptoms in HCWs are common [4], and several studies investigated the impact of post-traumatic stress on HCWs [5], suggesting that they are at high risk of developing post-traumatic stress disorder (PTSD), adjustment disorders, and other trauma-related disorders [6,7].

PTSD is a severe psychiatric disorder [8,9] and is particularly insidious in HCWs as, and surprisingly, they are reluctant to seek help [10]. Moreover, during the pandemic, HCWs experienced significantly great fear, ongoing arousal symptoms, and job dissatisfaction [11]. The selective serotonin reuptake inhibitors (SSRIs) are the gold standard in the pharmacological treatment of PTSD patients, but they sometimes do not respond to SSRIs [12].

Trazodone (TRZ) is a different class of antidepressants (serotonin-2 antagonist/reuptake inhibitors), approved for the treatment of major depression [13]. It is somewhat useful in treating PTSD, but the evidence is minimal [14,15]. TRZ selectively inhibits neuronal reuptake of serotonin and is an antagonist of 5-HT2A. Other TRZ actions include antagonism at several different receptors, including 5-HT2B, 5-HT2C, adrenergic α1, and partial agonism at 5-HT1A [16]. TRZ Contramid® (Angelini, Rome, Italy) once-a-day is an extended-release, once-daily formulation of TRZ, designed to optimize antidepressant action with the anxiolytic/hypnoregulation effect [16,17].

We reported, following the CARE (for CAse REports)
guidelines [18], two cases of HCWs involved in treating COVID-19 patients who showed SSRI-resistant PTSD, which was treated with TRZ Contramid® add-on. We followed the CARE guidelines.

**CASE**

**Case 1**

**Symptoms**
A 33-year-old male nurse with no personal or family history of mental illness requested help from an outpatient facility in Teramo (Italy). He worked in an Intensive Therapy Unit and developed symptoms highly suggestive of PTSD. He reported hyperarousal, the feeling to be detached from his life and loved ones, avoiding trauma-related symptoms (the patient did not work anymore as it was on sick leave), hopelessness and depressive symptoms, re-experiencing of traumatic experiences, and disturbing nightmares regarding the deaths he saw and to be infected and intubated. He took escitalopram (ESC) 20 mg prescribed by his general practitioner in March 2020 with partial benefits on hopelessness and depressive symptoms and lower hyper-arousal and detachment. However, especially the nightmares were reported very disturbing, with frequent awakenings that disrupted his sleep.

**Diagnosis**
We made a diagnosis of PTSD confirmed by the Mini-International Neuropsychiatric Interview [19], and the Davidson Trauma Scale (DTS) yielded a frequency score (FS) of 49, a severity score (SS) of 57, and a total score (TS) of 107.

**Interventions**
He refused to introduce a benzodiazepine to improve sleep and the introduction of melatonin as he took it without benefits. We suggested adding a low dosage of TRZ Contramid® once-a-day (75 mg at bedtime) to strengthen ESC’s response and improve sleep, and the patient accepted. After one week of treatment, he reported improved sleep quality and a slight reduction in DTS scores (FS = 40, SS = 39, TS = 79). After the other three weeks of treatment, the patient told us that the nightmares were almost disappeared and the symptoms were significantly relieved (DTS: FS = 20, SS = 21, TS = 41). We decided to keep the TRZ at 75 mg/day, lowering ESC to 10 mg/day. After two weeks of continuous improvement, the patient showed a remarkable response without adverse effects (DTS: FS = 0, SS = 11, TS = 23), with the disappearance of nightmares. He decided to go back to work.

**Outcomes**
The last visit was carried out in October 2020, and the patient was fully remitted (DTS: FS = 3, SS = 5, TS = 8). He took ESC 10 mg/day and TRZ Contramid® 75 mg/day without adverse effects. His remarkable comment was that “when my nightmares began to be less invasive, I felt better.” No adverse effects were reported, and he agreed to begin a trauma-focused cognitive-behavioral therapy (TF-CBT).

**Case 2**

**Symptoms**
A 44-year-old female nurse with no personal or family history of mental illness requested help from an outpatient facility in a Central Italy region. She worked in an Infectious Disease Unit and sought our assistance due to the development of PTSD symptoms. She experienced an intense burnout feeling due to depressive symptoms, fear of contagion of self and beloved ones, anhedonia, hyperarousal, and unwanted and intrusive thoughts about the COVID patients who saw. She avoided places that reminded her of the COVID, and she was absent from work for almost 40 days before our first visit. Moreover, despite being at home, she was having disturbing nightmares concerning the virus, the contagion, and the sensation to be in a biocontainment unit and suffocate, which caused her to miss many hours of sleep each night. She reported that repeated sudden awakenings during the night had also disturbed her husband and son’s sleep, and she preferred to sleep on the couch. She was taking low paroxetine (PAR) dosage (20 mg) prescribed by a private psychiatrist in April 2020, without benefits.

**Diagnosis**
At the time of our first assessment, we diagnosed PTSD that was confirmed by the administration of the Mini-International Neuropsychiatric Interview [19], and the DTS scores were remarkably high (FS = 59, SS = 61, TS = 120). She told us that "sleeping is a trouble for me as
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nightmares of being sick and suffocate are my main concerns”.

**Interventions**

We prescribed mirtazapine 15 mg at bedtime and increased PAR to 40 mg/day. However, after two weeks, the patient dropped mirtazapine due to excessive drowsiness and no benefits over nightmares. She continued to take PAR due to a slight effect on depressive symptoms. Her DTS scores were still high (FS = 51, SS = 52, TS = 103), and the nightmares were always compelling. However, she refused to add other medication, trusting in a positive PAR effect titrated to 40 mg/day. After another three weeks of no improvement, the patient again asked us for help, and we prescribed TRZ Contramid® 75 mg at bedtime, in addition to PAR. She did not report substantial benefits after one week of combined therapy except for a slight improvement in sleep quality. We decided to increase the TRZ dosage to 150 mg. After two weeks, she reported a slight improvement in overall PTSD scores on DTS (FS = 40, SS = 32, TS = 72). We lowered PAR to 20 mg/day and continued with TRZ 150 mg. After one month of continuous improvement (mostly on sleep and nightmares), she achieved a response (DTS: FS = 26, SS = 23, TS = 49) without adverse effects. After another month, she decided to go back to work and begin psychological counseling (DTS: FS = 12, SS = 10, TS = 22).

**Outcomes**

The last visit was made in October 2020, and she was fully remitted (DTS: FS = 7, SS = 6, TS = 13), always taking PAR 20 mg and TRZ Contramid® 150 mg. No adverse effects were observed. Similar to Case 1, she told us that “...improvement of sleep and disappearance of nightmare was the game changer!”. Both patients gave us a written informed consent to report their cases.

**DISCUSSION**

To date, this is the first paper that reported a successful combination of SSRIs/TRZ Contramid® therapy in the treatment of SSRI-resistant PTSD in HCWs. In both cases, we diagnosed PTSD with a clinical assessment and HCWs interviews as routinely made in the “real world” clinical practice, with the help of the Mini-International Neuropsychiatric Interview and the DTS to quantify the severity of symptoms and monitor follow-up.

SSRIs and TF-CBT are the first-line treatments of PTSD, but several patients may remain symptomatic and functionally impaired despite treatments [20,21]. Therefore, targeting these symptoms is critical in the beneficial treatment of resistant PTSD [22]. Most specialists approve that PTSD and obstinate nightmares should not be regarded as treatment-refractory unless it has had an adequate prazosin trial [23-25]. However, prazosin, an α1-blocker, isn’t available in Italy, and we considered an alternative strategy.

Low dose TRZ Contramid® (i.e., dosages ≤ 150 mg/day) acts at 5-HT2A, H1, and, primarily, α1 receptors, working also as a sedative-hypnotic medication [26]. The α1 receptors’ action may explain the positive effect of TRZ add-on in the two cases. This action may somewhat resemble that of prazosin, improving nightmares, and leading to symptoms remission [27]. In both case reports, nightmares were the most disturbing and marked symptoms, which might explain TRZ’s beneficial action. Moreover, TRZ has an overall beneficial effect on sleep architecture than SSRIs, restoring slow-wave sleep, improving REM sleep, and improving sleep continuity [28]. This may also explain the positive results seen. The presence and severity of sleep disturbances in PTSD are associated with increased risk of substance abuse, more severe daytime PTSD symptoms, increased risk of suicidal ideation, and worse quality of life and subjective well-being [29]. The treatment with a drug as TRZ that targets sleep disturbances might be crucial for better PTSD treatment outcomes. This action of TRZ is essential because several studies showed that benzodiazepines (BZDs) should be considered relatively contraindicated for patients with PTSD or recent trauma [30,31]. Moreover, persons with PTSD may quickly develop substance-related problems, particularly with BZDs and z-pills, and, therefore, their administration should be avoided [32].

Moreover, the dosage of TRZ Contramid® 75 – 150 mg may further enhance SSRIs’ action on the dorsolateral prefrontal cortex (dIPFC), dorsomedial PFC, ventrolateral PFC (vIPFC), and the ventromedial PFC, brain regions implicated in PTSD pathophysiology, restoring serotonin and noradrenaline imbalance [33]. It is possible to hypothesize that TRZ Contramid®, due to extended-release, may also effectively inhibit the 5-HT2A and 5-HT2C receptors and block the serotonin transporter than immedi-
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It is also unlikely that a pharmacokinetic interaction may explain the SSRI/TRZ combination's positive effect. TRZ is extensively metabolized by cytochrome P450 3A4, whereas ESC is a negligible inhibitor of the same cytochrome, and PAR is mainly metabolized by CYP2D6 [35].

In conclusion, these cases highlight the TRZ Contramid® potential benefit when associated with SSRIs. Subjects with more prominent sleep disturbances and nightmares may be more susceptible to achieve a good response with this combination, but further studies are needed. Moreover, we firmly believe a global effort must be made to timely diagnose stress-related disorders and PTSD in HCWs [36-39]. Improving the well-being and preventing psychiatric disorders in such persons implicitly means improving healthcare systems worldwide [40,41]. Besides, COVID-19 reducing stigma strategies must be another concomitant priority to not repeat the errors made with HIV infection [42].

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

**Author Contributions**

Conceptualization: Domenico De Berardis, Michele Fornaro, Antonio Ventriglio, Federica Vellante. Cases acquisition and description: Domenico De Berardis, Federica Vellante, Antonio Ventriglio. Cases discussion: Domenico De Berardis, Michele Fornaro, Antonio Ventriglio, Alessandro Valchera, Federica Vellante, Mauro Pettoruso, Giovanni Martinotti, Silvia Fraticelli, Massimo Di Giannantoni. Supervision: Mauro Pettoruso, Giovanni Martinotti, Silvia Fraticelli, Massimo Di Giannantoni. Writing—original draft: Domenico De Berardis, Michele Fornaro, Antonio Ventriglio, Alessandro Valchera, Federica Vellante. Writing—review & editing: Domenico De Berardis, Mauro Pettoruso, Giovanni Martinotti, Silvia Fraticelli, Massimo Di Giannantoni.

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