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DISCONTINUATION SYNDROME OF EXTENDED-RELEASE VENLAFAXINE DURING THE COVID-19 EPIDEMIC

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Dear editor,

Due to the epidemic of coronavirus disease 2019 (COVID-19) in the past a few months, many patients with major depressive disorder (MDD) had to discontinue antidepressants abruptly. And the abrupt interruption, as reported previously, will increase the risk of a wide range of antidepressants discontinuation symptoms (ADS), especially for venlafaxine, a serotonin-noradrenaline reputake inhibitors (SNRI) as well as a first-line antidepressant for depressio (Fava et al. 2018). During this particular period, however, features about ADS of extended-release (ER) venlafaxine and how to manage ADS both were little known.We aimed to further understand the discontinuation syndrome of ER venlafaxine and provide hospitals limited but increasing data for taking measures to prevent and treat ADS.

This is a single-center retrospective study conducted in Yongchuan Affiliated Hospital of Chongqing Medical University from Feb. 13 2020 to Jun. 18 2020. Patients who aged 18 years or older, met the diagnostic criteria of MDD in the ICD-10, had a 17-item Hamilton Depression Rating Scale (HAMD-17) total score of ≥ 14 (Hamilton 1960), had complete data, took the ER venlafaxine at a dose of 75-225 mg/d were enrolled. We obtained basic information (including age, sex, telephone number, address), diagnosis and treatment information by the use of electronic medical record system. Analyses were performed using SPSS 23.0 software (IBM SPSS Statistics, Armonk, NY). Continuous variables were expressed as mean with standard deviation (SD), and were compared using Student's t test. Categorical variables were expressed as percentage [number (%)], which was analyzed by the use of χ^2 test. A P value of < 0.05 was considered significant.

Finally, 418 outpatients and inpatients were enrolled in this study, with an average age (49.90±14.34) years. Among them, female patients accounted for 69.86% (292/418). We then investigated medication compliance and reasons for abrupt discontinuation of the 418 patients from telephone follow-up or clinical consultation. In our survey, total number of patients-driven abrupt discontinuations at any point during the 4 months was 130 (130/418, 31.1%). About 63.08% (82/130) patients discontinued ER venlafaxine due to the difficulty in purchasing medicine during the COVID-19 epidemic, the rest patients discontinued because of its adverse effect, its late and mild effectiveness, or prominent effectiveness in depressant symptoms. Of the 130 patients, 39.23% (51/130) patients discontinued abruptly after 6 weeks since the first dosage. Then the 51 patients received Discontinuation-Emergent Signs and Symptoms (DESS) scale to screen for discontinuation symptoms, 25.49% (13/51) patients met the diagnosis criteria of discontinuation syndrome (DS) and defined as DS group (Schatzberg et al. 1997), 74.51% (38/51) patients had not any discontinuation symptoms and defined as asymptomatic (AS) group. The characteristics and medication compliance of the 2 groups were shown in Table 1. There were no significant differences in sex and age, while the DS group had bigger maintaining dosage and longer period of maintenance treatment than AS group (P=0.017, P=0.026, P all > 0.05). Moreover, clinical manifestations of discontinuation syndrome in DS group were shown in Table 2. Headache, sleep disorder, irritability, anxiety and mood swings were the most common manifestations. And the discontinuation symptoms usually occur at 2-15 days after the last dosage. 4 patients gradually released from discontinuation symptoms without treatment within 3-15 days since the interruption. The rest 9 patients released from the trouble of discontinuation symptoms after restarting ER venlafaxine or Benzodiazepines.

SNRI has been reported to produce similar types of discontinuation symptomatologies as serotonin serotonin reuptake inhibitors (SSRI). A systematic review of 30 RCT and open trials about the discontinuation symptoms of SNRI reported that, the incidence of discontinuation symptoms was variable in different SNRI, including venlafaxine, duloxetine, milnacipran, and levomilnacipran (Fava et al. 2018). However, the rate of discontinuation symptoms appeared to be higher after discontinuation of venlafaxine, ranging from 23 to 78%. While it was lower in duloxetine (6-55%), milnacipran (13-30%), and levomilnacipran (9-10%). In our survey, the prevalence (31.1%) of abrupt discontinuation was frequent. Among them, patients diagnosed with ADS accounted for 25.49%, though it is generally considered that ER venlafaxine is rare to produce discontinuation symptoms due to its longer half-life. The high rate of cessation in our study mainly explained by the increasing difficulty in purchasing ER venlafaxine, such as the regulation of administration that residents should stay at home, the suspension of public transport and hospital's protective measures for infection prevention and control. Moreover, hospital's little attention and limited measures to ADS, patients' little knowledge to ADS also contributed to the high abrupt cessations rate.

Despite the symptoms after abrupt discontinuation of ER venlafaxine in our study were fewer compared with other reports (Liebowitz et al. 2009; Baboolal 2004). The influence discontinuation symptoms have had on patients in our survey were great and, resulting some patients failing to keep on working even producing suicidal thought, which is different from common viewpoint that ADS tends to be self-limitation and mild in severity. So, we considered that some measures should be taken to manage the discontinuation symptoms during this particular period. Prevention is always prior to treatment. But a majority psychiatrists had not attach importance to ADS until

Table 1. Characteristics and Medication compliance of DS and AS groups

	Female, n(%)	Age, years (mean±SD)	Dosage, mg/d (mean±SD)	Duration, weeks (mean±SD)
DS (n=13)	10 (76.92)	47.38±15.22	132.69±32.89	34.77±28.57
AS (n=38)	25 (65.79)	48.79±14.23	104.61±37.15	14.42±12.37
P value	0.46	0.764	0.017	0.026

Abbreviation: DS: discontinuation syndrome group; AS: asymptomatic group; SD: standard deviation

Table 2. Clinical Manifestations of Discontinuation Syndrome of ER Venlafaxine

Discontinuation symptom	Number of patients
Nervousness or anxiety	6
Irritability	5
Mood swings	5
Trouble sleeping, insomnia	6
Increased dreaming or nightmares	2
Shaking, trembling	1
Fatigue, tiredness	2
Headache	5
Dizziness, lightheadedness, or sensation of spinning	2
Nausea	1
Burning, numbness, tingling sensations	3
Ringing or noises in the ears	1
Suicidal thought	1

it occurs. Firstly, as recommended in the early time, clinicians should advise all patients starting antidepressant medication to be aware of the risk of ADS after sudden cessation of treatment (Anderson et al. 2008). Secondly, although the half-life of antidepressants is considered to be stronger correlation with discontinuation symptoms, gradual tapering and short duration play a minor role in preventing discontinuation symptoms (Tint at al. 2008). However, our study shows that patients with higher maintenance dose and longer duration are more vulnerable to ADS. Thus, under the guidance of psychiatrists via various online consultation and telehealth support, gradually tapering to a relatively small dose before final cessation maybe a practicable means for preventing ADS. Thirdly, our limited but increasing data add the necessity of this advise that, administration could open online antidepressants prescription authority in some particular periods. Patients have been diagnosed with MDD could get antidepressants more conveniently and safely in the local community health service with the online prescription prescribed by accredited psychiatrists. Lastly, when patients had discontinuation symptoms unfortunately, online consultation conducted by experienced psychiatrists could play a role in patients with mild ADS. Patients with severe ADS, however, had to restart medicines such as SNRI or SSRI.

The methods of antidepressants purchase, monitoring of adverse effect, and management of ADS are challenged during the COVID-19 pandemic. In this particular period, our data and advises mentioned above maybe serve to manage ADS.

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Competing Interests: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Availability of data and materials: if necessary, we can provided the original data.

Conflict of interest: None to declare.

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