Journal of Pharmacy and Pharmaceutical Sciences

Lower Serum Cortisol Level After DST Predict Therapeutic Response and their Difference between Patients with Agitated and Retardation Depression

Jin Haiying[1], Xu Min[1], Gao Zhihan[2], Sun Fengli[3], Jin Weidong[4]*

[1]Department of Psychiatry, Zhejiang Chinese Medicine University, Hangzhou, China

[2]Department of Clinical Psychology, Zhejiang University School of Medicine, Hangzhou City, China

[3]Department of Psychiatry, Zhejiang Province Tongde Hospital, Hangzhou, China

[4]Zhejiang Province Mental Health Center, Hangzhou, China

Research Article

Received: 07-Oct-2024, Manuscript No. JPPS-24-149680; **Accepted:** 09-Oct-2024, Manuscript No. JPPS-24-149680; **Published:** 25-Nov-2024. Manuscript No. JPPS-24-149680.

***For Correspondence:**
Jin Weidong, Zhejiang Province Mental Health Center, Hangzhou, China

E-mail: wdjin@163.com

Citation: Haiying J, et al. Lower Serum Cortisol Level After DST Predict Therapeutic Response and their Difference between Patients with Agitated and Retardation Depression. J Pharm Pharm Sci. 2024;13:001

ABSTRACT

Background: Major Depressive Disorder (MDD) is one of the most common and debilitating mental disorders; however, its aetiology remains unclear. As for depression, retardation depression and agitated depression, which have different syndrome types and also maybe different in Hypothalamic-Pituitary-Adrenal (HPA).

Methods: 30 retardation depression patients and 30 agitated depression patients were involved. The Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA) were assessed in all depressive patients and Dexamethasone Suppression (DST) was completed at began of study. These all patients were observed for 4 weeks, during which the combination treatment of Traditional Chinese Medicine (TCM) and western medicine were carried out and symptom change with HAMA and HAMD.

Results: The bound cortisol of patients with agitated depression before dexamethasone were higher significantly than that of retardation depression. The suppression ratio of patients with agitated depression was lower than that of retardation depression.

HAMD, HAMA of patients with agitated depression was significantly different from that of retardation depression.

The suppression ratio negatively correlated significantly with HAMA relative change at 2nd weekend, HAMA relative change at 4th weekend.

Conclusion: The lower cortisol level after Dexamethasone Suppression Test (DST) indicate better the response to therapy, especially in patients with agitated depression. The two syndrome of depression was different in some

clinical symptom, response to treatment and Hypothalamic-Pituitary-Adrenal (HPA) regulation function.

Keywords: Depression; Retardation depression; Agitated depression; Hypothalamic-Pituitary-Adrenal (HPA)

Abbreviations: HPA: Hypothalamic-Pituitary-Adrenal; TCM: Traditional Chinese Medicine; MDD: Major Depressive Disorder; HAMD: Hamilton Depression Scale; HAMA: Hamilton Anxiety Scale; PMD: Psychotic Major Depression; XCHT: Xiaochaihutang; HPO: Hypothalamic Pituitary-Ovarianas; RDoC: Research Domain Criteria; DST: Dexamethasone Suppression Test; CRH: Corticotropin-Releasing Hormone; ACTH: Adrenocorticotropic Hormone; CORT: Corticosterone; CM: Childhood Maltreatment; EEG: Electroencephalo-Graph; MDD: Major Depressive Disorde; 5-HTTLPR: 5-Hydroxytryptamine Transporter Gene-linked Polymorphic Region; ERβ: Estrogen Receptor Beta; TPH2: Tryptophan Hydroxylase 2; OVX: Ovariectomies; CUMS: Chronic Unpredictable Mild Stressed.

INTRODUCTION

Major Depressive Disorder (MDD) is one of the most common and debilitating mental disorders with unclear etiology. It has been hypothesized that genetic, immune-inflammatory and psychosocial factors and the presence of structural brain alterations might be the potential causes of depression [1,2]. Abnormality of Hypothalamic-Pituitary-Adrenal (HPA) are not only involved in chronic stress, inflammation, reduced neuroplasticity and network dysfunction, but also in depression [3]. Among them, HPA function plays a certain role in the occurrence and development of depression. The major depression with psychosis Psychotic Major Depression (PMD) patients had higher evening cortisol levels than did schizophrenic patients and heath controls [4]. It suggested that depression was accompanied by de-suppression [5]. Especially, antidepressant can improve this de-suppression of HPA, which also predict the response of antidepressant [5,6]. Also it was found that there was relationship between abnormal HAP and clinical symptom, cognition [8]. Xiaochaihutang (XCHT) can alleviate perimenopausal depression-like behaviors, restore 5-HT and hormones in OVX-CUMS mice, which may be related to normalizing the functions of HPA/HPO axis [9]. Depressed persons showed higher morning cortisol levels at awakening (T1) and a less dynamic awakening response compared to non-depressed older persons, which demonstrated a hypercortisolemic state and a diminished ability to respond to the stress of awakening among depressed older persons [10]. But it is possible that there are several different endophenotypes of depression with distinct pathophysiological mechanisms. Depressive disorders also are considered in the context pathological mechanisms at every translational level [3]. The studies have demonstrated a stronger association between the increased activation of HPA-axis and melancholic or endogenous depression subtype. Some findings indicate that there is a difference in the activity of the HPA-axis between melancholic and atypical depressive subtypes. However, these are more likely explained by hypercortisolism in melancholia. Further research should seek to distinguish a particular subtype of depression linked to HPA-axis abnormalities, based on symptom profile, with a focus on vegetative symptoms, neuroendocrine probes and the history of adverse childhood events [10]. The study also show that HPA axis dysregulation is related to environmental risk factors, such as childhood trauma [11]. It may mean that there were different HPA function between different type of depression. This suggests

that different depression subtypes may have different neurobiological basis, such as P300, neuropeptide and neuroendocrine [12,13].

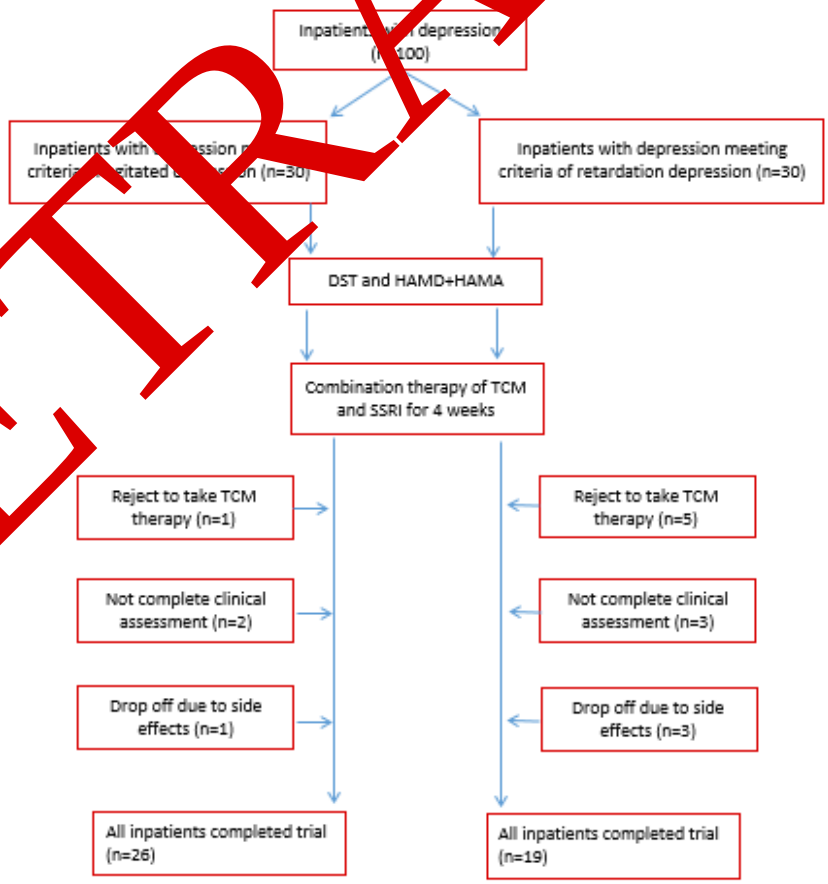
As for depression, we can divide into two different types according to the symptoms of depression patients. In the excess symptoms, the typical representative type was agitated depression, which was called as liver stagnation of liver qi in TCM and belong to the excess disease, the other typical representative type was retardation depression, which was called deficiency of heart and spleen in TCM and it belong to the asthenic disease. These indicated the different clinical traits of two syndrome of depression maybe related to existed the difference on pathology, such as neuroendocrinology. The reaction of HPA also related to combination of genetic variability, external factor and antidepressant [14]. All above help us put out a question that different syndrome of depression may had different HPA function status. This suggestion should be explained.

MATERIALS AND METHODS

Study design

The trial was designed in two groups. One group was agitated depression. The other group was retardation depression. At base line of begin of study, the HAMD and HAMA were assessed in all depressive patients. The DST was also completed at began of study. The all patients were observed for 4 weeks, during which the combination treatment of TCM and western medicine were carried out and symptoms change with HAMA and HAMD. The study schedule was to see in Figure 1.

Figure 1. Schedule of clinical trial and assessment



Sample

All samples were 100 patients with depression which meet the criteria of depression in ICD-10. The criteria of inpatients involved were include:

- The inpatients meet the ICD-10 diagnostic criteria for depression.
- The age of inpatients is greater than or equal to 18 years old, less than or equal to 60 years' old.
- The inpatients had not brain organic diseases and mental disorders caused by organic diseases.
- The inpatients had not dependence on psychoactive substances and mental disorders caused by them.
- The inpatients had not some diseases for the presence and taking of hormones.
- The inpatients informed consent of taking combination therapy.
- The guardian of patients informed consent of trials.
- The inpatients meet diagnostic criteria for agitated depression or retardation depression. But all patients do not meet criteria of agitated or retardation depression.

Randomization

The two study groups were randomly given Selective Serotonin Reuptake Inhibitors (SSRI) and TCM decoction after dividing group according diagnostic criteria of retardation depression or agitated depression [15,16]. The TCM decoction was given according to TCM syndrome. The patients were received both therapy of SSRI and TCM decoction.

Main index

The first index was blood cortisol, suppression ratio and positive ratio of DST. The second index were HAMD, HAMA and their changes. HAMD, HAMA were assessed by two psychiatrists with medium-degree or high-degree professional title at least. The pair two psychiatrists had better reliability in assessment of HAMD, HAMA.

Treatment method

All patients receipted combination of TCM and western medicine, which was one drug of SSRI that be considered suitable to the patients. The patients in group of agitated depression were given Chaihu-Shugan-San (CSS) decoction [15]. The patients in group of retardation depression were given Gui Pi decoction [16].

Blood cortisol determination and DST

Blood cortisol was measured by radioimmunoassay in laboratory of Zhejiang Province Tongde Hospital. At 11:00 pm of the day, 1 mg of dexamethasone was taken orally. Blood was drawn at 8:00 am and 4:00 pm next day to check the cortisol again. In one case, the plasma cortisol concentration exceeded 5 ug/dl, which was defined as DST positive but it was old way. The new positive way was that ratio of cortisol level after dexamethasone at 8:00 am/cortisol level before dexamethasone at 8:00 am was lager 50%, which was called suppression ratio that mean higher suppression ratio represented poor regulation of HPA [17,18].

Statistical methods

All data were processed by Statistical Package for the Social Sciences (SPSS) 18.0 statistical software and the measurement data between groups were tested by mean t test, $p<0.05$ was statistically significant. And Analysis of Variance (ANOVA) were tested by mean F test, $p<0.05$ was statistically significant. Correlation relationship were tested by correlation analysis (r).

RESULTS

The information of all patients was listed in Table 1.

Table 1. General information of two group with depression.

-	Retardation depression	Agitated depression
Case	19	26
Gender	Male: 4, female: 15	Male: 5, female: 21
Age (years)	18 ~ 60 (31.3 ± 13.6)	18 ~ 60 (32.5 ± 14.8)
Duration (month)	1-1.5 (0.81 ± 0.21)	1-2 (0.85 ± 0.32)
Education (years)	6-14 (9.4 ± 3.8)	5-15 (9.8 ± 4.2)
Marriage	Unmarried: 3, married: 10, divorce: 6	Unmarried: 10, married: 16
Family history	Positive: 15; negative: 4	Positive: 7; negative: 19
Drug	Sertraline: 10; escitalopram: 5; fluxetine: 4	Sertraline: 8; escitalopram: 10; fluxetine: 1; paroxetine: 7
TCM	Guipi decotion	Chaihushugansan decotion
Note: TCM: Traditional Chinese Medicine; Guipi decotion: A TCM soup from decotion for treatment of retardation depression; Chaihushugansan decotion: A TCM soup from decotion for treatment of agitated depression.		

The cortisol level after and before dexamethasone and DST

The both blood cortisol of patients with agitated depression at 8:00 am and 4:00 pm before dexamethasone were higher significantly than that of retardation depression. But no difference after dexamethasone, seen in Table 2. The relative change of blood cortisol in patients with agitated depression at 8:00 am was higher significantly than that of retardation depression, seen in Table 2. The suppression ratio of patients with agitated depression was lower than that of retardation depression, seen in Table 2. There was no difference in DST positive rate between two groups, also see in Table 2.

Table 2. The blood cortisol and their changes in two groups.

-	Retardation depression (n=19)	Agitated depression (n=26)
First day (μg/dl) at 8 am	14.12 ± 8.41[a]	28.07 ± 10.95[a]
First day (μg/dl) at 4 pm	12.08 ± 8.35[a]	22.67 ± 11.25[a]
Second day (μg/dl) at 8 am	3.36 ± 5.86	3.01 ± 4.83
Second day (μg/dl) at 4 am	1.96 ± 0.21	2.11 ± 0.33
Relative change at 8 am	0.76 ± 0.28[b]	0.90 ± 0.15[b]
Relative change at 4 am	0.80 ± 0.12	0.82 ± 0.22
Suppression ratio	0.24 ± 0.28[a]	0.10 ± 0.15[a]
DST positive ratio	4/15[#]	1/25[#]
Note: (a) p<0.01; (b) p<0.05; #: DST (Dexamethasone Suppression Test) positive ratio.		

The HAMD, HAMA and their changes

The HAMD, HAMA of patients with agitated depression at base line were not different from than that of retardation depression. But HAMD of patients with agitated depression was significantly different from that of retardation depression at fourth weekend and HAMA of patients with agitated depression was significantly different from that of retardation depression at second weekend, given by Table 3.

Table 3. The HAMD and their changes in two groups.

-	Retardation depression (n=19)	Agitated depression (n=26)
HAMD at base line	33.68 ± 7.12	35.00 ± 6.19
HAMD at first weekend	30.89 ± 7.03	32.15 ± 5.62
HAMD at second weekend	24.53 ± 7.41	21.69 ± 6.04
HAMD at forth weekend	21.26 ± 6.98[a]	9.54 ± 3.60[a]
HAMD relative change at first weekend	0.08 ± 0.11	0.07 ± 0.13
HAMD relative change at second weekend	0.27 ± 0.19	0.37 ± 0.17
HAMD relative change at forth weekend	0.37 ± 0.17[a]	0.72 ± 0.12[a]
Note: (a) p<0.01.		

The HAMD relative changes of patients with agitated depression was significantly higher than that of retardation depression at fourth weekend and the HAMA relative changes of patients with agitated depression was significantly higher than that of retardation depression at fourth weekend, also seen in Table 4.

Table 4. The HAMA and their changes in two groups.

-	Retardation depression (n=19)	Agitated depression (n=26)
HAMA at base line	23.5 ± 8.15	19.12 ± 8.69
HAMA at first weekend	22.74 ± 8.69	17.96 ± 7.58
HAMA at second weekend	19.89 ± [a]	12.00 ± 4.67[a]
HAMA at forth weekend	16.53 ± 6.28	2.47 ± 0.48
HAMA relative change at first weekend	0	0.05 ± 0.10
HAMA relative change at second weekend	0.15 ± 0.12[a]	0.35 ± 0.18[a]
HAMA relative change at forth weekend	29 ± 0.15	0.17 ± 0.03
Note: (a) p<0.01.		

The correlation between cortisol level, cortisol changes and mental symptoms, their changes

The both of 1st day 8 am blood cortisol level and 1st day 4 pm blood cortisol level positively correlated significantly with HAMD relative change at 4th weekend and negatively with HAMD at 4th weekend, HAMA at 2nd weekend, HAMA at 4th weekend. The suppression ratio negatively correlated significantly with HAMA relative change at 2nd weekend, HAMA relative change at 4th weekend. The both cortisol relative change at 4 pm and 8 am positively correlated significantly with HAMA relative change at 2nd weekend, at 4th weekend see in the Table 5.

Table The relationship between blood cortisol, their changes and symptoms.

	1st day 8 am blood cortisol	1st day 4 pm blood cortisol	2nd day 8 am blood cortisol	2nd day 4 pm blood cortisol	Suppression ratio	Cortisol relative change at 4 pm	Cortisol relative change at 8 am
HAMD at base line	0.113	0.151	0.107	0.111	0.006	0.005	-0.006
HAMD at 1st WK	0.15	0.197	0.009	0.012	-0.097	0.129	0.097
HAMD at 2nd WK	-0.089	-0.029	-0.096	-0.087	0.095	-0.078	-0.095
HAMD at 4th WK	-0.395*	-0.302*	-0.012	-0.022	0.238	-0.171	-0.238

HAMD relative change at 1st WK	-0.066	-0.061	0.151	0.203	0.149	-0.067	-0.149
HAMD relative change at 2nd WK	0.165	0.121	0.158	0.17	-0.129	0.203	0.129
HAMD relative change at 4th WK	0.432**	0.349*	0.045	0.065	-0.25	0.164	0.25
HAMA at base line	-0.271	-0.239	-0.134	-0.155	-0.012	-0.048	-0.012
HAMA at 1st WK	-0.279	-0.226	-0.089	-0.066	0.016	-0.011	-0.016
HAMA at 2nd WK	-0.428**	-0.345*	-0.003	-0.01	0.198	-0.146	-0.198
HAMA at 4th WK	-0.436**	-0.345*	0.023	0.019	0.229	-0.233	-0.[illegible]
HAMA relative change at 1st WK	0.016	-0.039	-0.121	-0.123	-0.069	0.109	0.069
HAMA relative change at 2nd WK	0.265	0.169	-0.229	-0.226	-0.336*	0.356*	0.366*
HAMA relative change at 4th WK	0.218	0.215	-0.21	-0.211	-0.310*	0.330*	0.[illegible]*

Note: WK=Weekend,**p<0.01,*p<0.05.

DISCUSSION

Abnormal HPA axis function in depression

Our study also found that in all cases, 5 cases appeared DST positive, indicating that some patients with depression did have the phenomenon of HPA axis inhibition, which can indicate that hyperactivity of the HPA axis may lead to depression. Some of the results in the study of neuroendocrine, inflammatory factors and other changes in rats induced by chronic paradoxical sleep deprivation showed that the levels of CRH, ACTH and CORT in serum of depressed rats were significantly increased (p<0.05) as signals of highly activated HPA axis [19]. The effects of agarwood essential oil on the ACTH and CORT concentrations of bound stress-induced depressed mice were shown. the addition of agarwood essential oil significantly reduced the levels of ACTH and CORT in the serum of mice, thus improving the hyperactivity of the HPA axis [20].

The regulation of HPA also was presented as suppression ratio and relative change of cortisol. The suppression ratio is used to represent the regulation function of the HPA axis, the more the suppression ratio is higher, the worse the adjustment function. This result found that there is a relationship between the suppression ratio and the effective rate of anxiety. The pearson correlation coefficient of the Hamilton Anxiety Scale (HAMA) and the suppression ratio is -0.336 (p<0.05) and the Hamilton Anxiety Scale (HAMA) The pearson correlation coefficient between the four weeks and the inhibition rate was -0.[illegible]0 (p<0.05), but it was not found to be related to the effective rate of depression. These conclusions are different from the results of other scholars. This shows that the depression is getting better at the same time, the improvement of anxiety symptoms is more closely related to the HPA axis, which also shows that the degree of adjustment of the HPA axis function may to some extent predict the anxiety improvement level of patients with depression. Some research also found that hair cortisol sharply increased with stressor onset, decreased as internship continued and rose again at year's end. Depressive symptoms rose significantly during internship but were not predicted by cortisol levels [21]. In the paper summarized by caroline normann, genetic variation in four HPA-axis genes may influence the effects of TCM in depression [22]. This also indirectly explains the relationship between HPA and depression.

Differences of clinical manifestations and HPA function between two subgroup

In this study, we separated depression into two subtypes based on its symptoms, which conclude two opposite subgroup of agitated depression, retardation depression. This study found HAMD, HAMA were significantly higher than those of agitated depression (p<0.01). There are HAMD and HMMA differences between the two syndromes in

different clinical stages. Although there are few studies comparing the differences between agitated depression and retardation depression.

This study used multi-temporal evaluation and relative symptom changes to reflect the efficacy of different time points. We found that Hamilton Depression scale (HAMD) was measured after the fourth week, Hamilton Anxiety Scale (HAS) after the second week, Hamilton Depression scale (HAMD) after the fourth week relative change rate, Hamilton Anxiety Scale (HAMA) after the second week relative change rate, agitated depression and retardation depression in clinical efficacy ($p<0.01$). During the study of acupuncture and moxibustion on depression, the results showed that the two most common syndromes of depression syndrome were agitated depression and retardation depression and there was significant difference in therapeutic effect ($p<0.01$) [23].

This study also found the difference on the regulation between two groups. There is a difference in the cortisol level before treatment between the agitated depression and the retardation depression ($p<0.01$) and the relative change of 8 am before and after treatment ($p<0.05$) and the inhibition rate of the two groups are different ($p<0.05$). This indirectly indicates that there are differences in HPA between different syndrome types. These difference in HPA regulation between two group maybe beneficial for classification of the two syndrome of depression.

Relationship between HPA axis and efficacy of antidepressant and its prediction

The correlation analysis in this study shows that, the patient with a good HPA axis, the pearson correlation coefficient of 8 am on the first day with Hamilton Depression Scale (HAMD) was -0.395 ($p<0.01$), The Pearson correlation coefficient of blood cortisol 4 pm after the fourth week of Hamilton Depression Scale (HAMD) was -0302 ($p<0.05$). The pearson correlation coefficient between 8 am on the first day and the fourth week of Hamilton Depression scale (HAMD) was 0.432 ($p<0.01$), the pearson correlation coefficient between blood cortisol and the relative rate of Hamilton Depression scale (HAMD) was 0.349 ($p<0.05$). The pearson correlation coefficient of blood cortisol was an -0.428 am ($p<0.01$), The pearson correlation coefficient of blood cortisol after the second week of Hamilton Anxiety Scale (HAMA) was -0.345 ($p<0.05$). The pearson correlation coefficient of 8 am on the first day with Hamilton Anxiety Scale (HAMA) was -0.436 ($p<0.05$), The pearson correlation coefficient between blood cortisol and Hamilton Anxiety Scale (HAMA) was -0.345 ($p<0.05$). Which suggests a relationship between plasma cortisol levels and symptomatology. In Kabir et al study that in particular lower evening cortisol levels may predict poorer course in MDD. So this finding may prove clinical implications that a lower cortisol awakening response is a predictor of a worse prognosis of depression [24]. Fiksdal et al found that symptoms of anxiety and depression among individuals without a psychiatric diagnosis are associated with blunted and exaggerated cortisol responses to and recovery from stress. Such patterns could indicate increased risk for unhealthy HPA axis dysregulation, allostatic load and disease [25]. It also indicates lower cortisol level after DST, higher cortisol level before DST, higher cortisol awakening response maybe related more effective in treatment.

CONCLUSION

The study highlights the role of the Hypothalamic-Pituitary-Adrenal (HPA) axis in the pathophysiology of Major Depressive Disorder (MDD), emphasizing that different subtypes of depression, such as agitated and retardation depression, may exhibit distinct HPA function statuses. Findings indicate that abnormalities in the HPA axis are not only linked to depression but also to its subtypes, with hypercortisolism playing a significant role, particularly in melancholic depression.

LIMITATIONS

First, the number of cases in the study is too small. The all sample only are 45 cases, who is a lack of representativeness. Second, the intervention drugs are not uniform, which conclude both SSRI and Chinese herb. Third, the HPA axis function is affected by external and internal factors and the resulting may be uncertain.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

1.1 Ethic certificate of Zhejiang Province Tongde Hospital Ethics Committee (V1.0/20170120).

1.2 Consent Form (V1.0/20170120: V1.0).

Title: study on the difference between depressive patients with stagnation of liver qi and deficiency of heart and spleen.

All participants agree to publish their data.

CONSENT FOR PUBLICATION

All authors agree to publish our paper and no conflict in any interests.

AVAILABILITY OF DATA AND MATERIA

The current study data are not publicly available, but are available from the corresponding author on need.

COMPETING INTERESTS

There were not any financial and non-financial competing interests. All authors do not have any conflicts in all benefits.

AUTHOR'S CONTRIBUTION

Our authors have different contributions to this article. Dr. J participated in trial and the writing of the article, XM, GZH participated in the trial, Prof. SFL and Prof JW participated in the design and statistical processing and participated in the design, statistical processing and the final revision of the article.

FUNDING

This study was supported by funding of Peak Subject of Psychiatry, Zhejiang Province Mental Health Center (PSP-2023-001) in design, literature collection and statistic and quality assessment.

ACKNOWLEDGMENT

We thank Xing Baoping give us study idea and Zhu Jian Feng help us in literature retrieval. We thank Wang Zhiqiang help us in the final revision of the article. We also thank laboratory support of Zhejiang Province Tongde Hospital.

REFERENCES

1. Solaro C, et al. Depression in multiple sclerosis: Epidemiology, aetiology, diagnosis and treatment. CNS Drugs. 2018;32:117-133.
2. Kim YK, et al. The role of pro-inflammatory cytokines in neuroinflammation, neurogenesis and the neuroendocrine system in major depression. Prog Neuropsychopharmacol Biol Psychiatry. 2016;64:277-284.
3. Dean J, et al. The neurobiology of depression: An integrated view. Asian J Psychiatr. 2017;27:101-111.
4. Cherian K, et al. HPA axis in psychotic major depression and schizophrenia spectrum disorders: Cortisol, clinical symptomatology and cognition. Schizophr Res. 2019;213:72-79.

5. Gao ZH, et al. Antidepressants and HPA function in patients with depression. Herald of Medicine. 2017;36: 659-664.
6. Scherf CM, et al. Extent of cortisol suppression at baseline predicts improvement in HPA axis function during antidepressant treatment. PNEC. 2020;114:104590.
7. Fischer S, et al. Hypothalamic-Pituitary-Adrenal (HPA) axis functioning as predictor of anti-depressant response-Meta-analysis. Neurosci Biobehav Rev. 2017;83:200-211.
8. Keller J, et al. HPA axis in major depression: Cortisol, clinical symptomatology and genetic variation predict cognition. Mol Psychiatry. 2017;22:527-536.
9. Zhang K, et al. Antidepressant-like effects of xiaochaihutang in perimenopausal mice. J Ethnopharmacol. 2020;10:112318.
10. Juruena M, et al. Atypical depression and non-atypical depression: Is HPA axis function a biomarker? A systematic review. J Affect Disord. 2018;233:45-67.
11. Murri BM, et al. The HPA axis in bipolar disorder: Systematic review and meta-analysis. Psycho neuroendocrinology. 2016;63:327-342.
12. Shen Y, et al. How about P300 in patients with depression in China: Review of results from some Chinese meta-analysis. NeuroQuantology. 2019;17:46-50.
13. Sun FL, et al. Differences in neurobiology of different syndrome of melancholia in the viewpoint of TCM. NeuroQuantology. 2019;17:76-80.
14. Ancelin M, et al. Heterogeneity in HPA axis dysregulation and serotonergic vulnerability to depression. Psycho neuroendocrinology. 2017;77:90-94.
15. Jin WD, et al. Meta-analysis of clinical efficacy of Xiaochaihu shuganshu in treatment of depression. J Tradit Chin Med. 2009;7:1397-1399.
16. Ma YC, et al. Preliminary observation on treating depression in the integrative medicine. J Chin Clin Med. 2011;3:6-7.
17. Gan N, et al. Dexamethosone suppression test in inpatients with unipolar or bipolar disorder: A comparison study. Chin J Neuromed. 200[illegible]:113[illegible]
18. Hongwei L, et al. Relationship of Hypothalamus-Pituitary-Adrenal (HPA) axis function and suicidal behavior in patients with depression. Shanghai Arch Psychiatry. 2013;1:32-39.
19. Ma W, et al. Chronic paradoxical sleep deprivation-induced depression-like behavior, energy metabolism and microbial changes in rats. Life Sci. 2019;15:88-97.
20. Wang S, et al. Agarwood essential oil ameliorates restrain stress-induced anxiety and depression by inhibiting hpa axis hyperactivity. Int J Mol Sci. 2018;19:3468.
21. Mayer S, et al. Chronic stress, hair cortisol and depression: A prospective and longitudinal study of medical internship. Psychoneuroendocrinology. 2018;92:57-65.
22. Normann C, et al. Gene-environment interactions between HPA-axis genes and childhood maltreatment in depression: A systematic review. Acta Neuropsychiatr. 2020;6;1-11. [Crossref] [Google Scholar] [PubMed]
23. MacPherson H, et al. Acupuncture for depression: Patterns of diagnosis and treatment within a randomised controlled trial. eCAM. 2013;2013:1-9.
24. Kabia FM, et al. The predictive value of cortisol levels on 2-year course of depression in older persons. Psycho neuroendocrinology. 2016;63:320-326.
25. Fiksdal A, et al. Associations between symptoms of depression and anxiety and cortisol responses to and

recovery from acute stress. Psycho neuroendocrinology. 2019;102:44-52.