Observational Study

Medicine

OPEN

Clinical efficacy and safety of low-dose doxepin in Chinese patients with generalized anxiety disorder

A before–after study

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Abstract

Clinical and animal studies have reported that low-dose doxepin may have positive effects on generalized anxiety disorder (GAD); however, its effectiveness and clinical safety are less well understood. This study is a before-after study and aims to investigate the effectiveness and side effects of low-dose doxepin by evaluating Hamilton Anxiety Scale (HAMA) scores, hormones, blood glucose, serum lipids, body weight, and body mass index (BMI) in patients with GAD. Forty-nine patients (20 males and 29 females) with GAD were randomly assigned to receive low-dose doxepin (6.25 mg–12.5 mg per day) for 12 weeks between February 2015 and March 2016. HAMA scores, fasting blood glucose (FBG) body weight, BMI, and some serum biochemical indexes, such as adrenocorticotropic hormone (ACTH), free triiodothyronine (FT3), total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDLC), and FBG, were assessed during pretreatment and post-treatment. Mean scores of HAMA decreased from 19.50 ± 1.22 to 8.50 ± 3.61 after low-dose doxepin treatment ($P < .01$). The serum levels of ACTH (4.33 ± 2.14 vs 6.12 ± 3.02 pmol/L), FT3 (4.78 ± 0.51 vs 5.15 ± 0.52 pg/mL), TC (4.55 ± 1.01 vs 5.93 ± 1.66 mmol/L), TG (1.69 ± 1.51 vs 3.39 ± 2.86 mmol/L), and LDLC (2.43 ± 0.88 vs 3.76 ± 1.25 mmol/L), and FBG (5.06 ± 0.43 vs 5.78 ± 0.81 mmol/L) were higher than that pretreatment with a significant difference ($P < .01$). Bodyweight (62.00 ± 7.45 vs 64.00 ± 6.44 kg, $P = .23$) and BMI (23.70 ± 2.35 vs 24.48 ± 2.11 kg/m^2, $P = .14$) had no difference after treatment. These results suggest that low-dose doxepin has beneficial clinical efficacy and safety. Low-dose doxepin can ameliorate anxiety in GAD patients and has some effects on neuroendocrine systems and the metabolic activity of serum glucose and lipid.

Abbreviations: ACTH = adrenocorticotropic hormone, BMI = body mass index, COR = cortisol, E2 = estradiol, FBG = fasting blood glucose, FT3 = free triiodothyronine, FT4 = free thyroxine, GAD = generalized anxiety disorder, HAMA = Hamilton Anxiety Scale, HDLC = high density lipoprotein cholesterol, HPA = hypothalamic adrenal axis, HPG = hypothalamic gonadal axis, HPT = hypothalamic thyroid axis, LDLC = low density lipoprotein cholesterol, PROG = progesterone, T = testosterone, TC = total cholesterol, TG = triglyceride, TSH = thyroid-stimulating hormone.

Keywords: clinical safety, doxepin, generalized anxiety disorder, metabolism, neuroendocrine systems

1. Introduction

Generalized anxiety disorder (GAD) is characterized by excessive worry and anxiety that are difficult to control, causing significant distress and impairment.[1] A meta-analysis, including 21 studies, indicated that the pooled current and lifetime prevalence of GAD in China were 5.17% (95% confidence interval: 3.72%–6.63%) and 4.66% (95% confidence interval: 3.17–6.14), respectively.[2] During the past decades, some drugs have been recommended for GAD treatment, such as selective serotonin reuptake inhibitors (SSRIs), and serotonin and noradrenaline reuptake inhibitors (SNRIs).[3] However, troublesome side effects, like delayed action, worsening of anxious symptoms, dizziness, nausea, serotonergic syndrome, and sexual dysfunction for SSRIs and SNRIs, are the reasons for treatment discontinuation and lack of desirable therapeutic outcome.[4] GAD patients with anxiety and/or depression often suffer more frequent relapses and require longer courses of treatment, the choice of an antianxiety is dictated by several factors that include efficacy, tolerability, and safety, not all patients with GAD could tolerate or respond to SSRI or other newer agents.[5,6] If an SSRI or other newer agents are not tolerated or responded to, the choice of agents will be a puzzling clinical problem. In clinical practice, tricyclic antidepressants (TCAs) drugs could remain an important option for many patients with anxiety and depression.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study was approved by the Ethics Committee of the Faculty of Pharmacy at Jinshan Hospital of Fudan University (NO.2017-23) and informed consent was obtained from all participants.

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How to cite this article: Zhang M, Huang F, Jiang F, Mai M, Guo X, Zhang Y, Xu Y, Zu H. Clinical efficacy and safety of low-dose doxepin in Chinese patients with generalized anxiety disorder: A before–after study. Medicine 2022;101:42(e31201).

Received: 23 June 2022 / Received in final form: 8 September 2022 / Accepted: 15 September 2022

http://dx.doi.org/10.1097/MD.0000000000031201

Doxepin belongs to the TCAs with a wide range of pharmacological mechanisms including: Inhibiting the reuptake of serotonin (5-HT) and norepinephrine (NE) in central nervous system, reducing sensory sensitivity of patients with GAD, exerting anxiolytic effect; Anti-H1 receptor effect, anticholinergic effect, blocking α1 adrenergic receptor， which are more manifested as adverse reactions. Given the wide and potential pharmacological effects of doxepin on the serotonergic, histisergic, cholinergic, adrenergic, and other neurotransmitter systems in central nervous system, the safety of doxepin is one of the key issues in the long-term treatment of doxepin.

In recent years, accumulating evidence demonstrated that doxepin may have potential biological effects on the function of the hypothalamic neuroendocrine axis, including hypothalamic adrenal axis (HPA), hypothalamic thyroid axis (HPT), and hypothalamic gonadal axis (HPG); and metabolic effects such as blood glucose, blood lipid, and body weight.[7] A large dose of doxepin intake was likely to cause obvious side effects, such as dry mouth, gastrointestinal side effects, hepatotoxicity, and weight gain, making it less tolerable compared with SSRIs and other newer antidepressants.[6] Nevertheless, some researches indicate that low-dose doxepin treatment has an anti-anxiety effect and can reduce side effects.[8–10] To explore the potential effect of low-dose doxepin on the hypothalamic neuroendocrine axis, we detected serum adrenocorticotropic hormone (ACTH) and cortisol (COR) levels to reflect the functional state of the HPA axis, serum thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) levels to reflect the functional state of the HPT axis, serum estradiol, progesterone (PROG), and testosterone (T) levels to reflect the functional state of HPG axis. In addition, the mechanism of doxepin treatment on the effects of blood glucose, blood lipids, body weight, and body mass index in patients with GAD is still unclear. Exploring the effect of low-dose doxepin on these metabolic indicators in patients with GAD through metabolic regulatory centers such as the hypothalamus is one of the important issues to evaluate their clinical safety.

In the present study, we used a before-after study by comparing the changes of Hamilton Anxiety Scale (HAMA) scores, neurohormone, blood glucose, blood lipid, body weight, and body mass index (BMI) in the process of low-dose doxepin treatment of GAD patients, to explore the optimal therapeutic dose of doxepin drugs, and to further evaluate the pharmacological effects and safety of low-dose doxepin in clinical application.

2. Materials and Methods

The study was approved by the Ethics Committee of the Faculty of Pharmacy at Jinshan Hospital of Fudan University (NO.2017-23) and informed consent was obtained from all participants. Patients met the DSM-5 diagnostic standard for generalized anxiety disorder, who went to the outpatient neurology department of Jinshan Hospital Affiliated with Fudan University between February 2015 and March 2016, were screened for inclusion in this study, including 20 males and 29 females. The inclusion criteria and exclusion criteria are listed in Table 1. Thirteen patients lost following-up prior to the end of the 12-week administration period. A total of 36 patients completed 12-week treatment, including 16 males (44.4%) and 20 females (55.6%) with an average age of 57.17 ± 11.59 years (range, 24–78 years).

All patients with GAD received doxepin (6.25–12.5 mg/day) for 12 weeks. HAMA was used to evaluate anxiety symptoms of patients pre-and post-treatment, and the reverse side-effects during the treatment were recorded with Treatment Emergent Symptom Scale (TESS). Blood samples were collected before treatment and at the end of the 12th week in each group. After extracting the venous blood at 8 AM, we detected the levels of serum ACTH, COR, FT3, FT4, TSH, estradiol (E2), PROG, and T, fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDLC), and high-density lipoprotein cholesterol (HDLC) in these outpatients before and after 12 weeks of the treatment to compare the changes of these indexes. Bodyweight and BMI were also recorded. All changes in clinical parameters before and after low-dose doxepin treatment of GAD patients were listed in Table 2. The safety concerns are measured by Treatment Emergent Symptom Scale (TESS) recording the adverse reactions of patients during treatment.

2.1. Statistical analyses

Quantitative variables were described using means and standard deviations (Mean ± SD). The Student *t* test was used to analyze differences between the 2 groups at each time point of the study. All statistical analyses were performed using SPSS statistical software (version 17.0, IL, CA). The analysis of image results was completed using GraphPad Prism 9 (GraphPad, CA). *P* value <.05 was considered statistically significant.

3. Results

3.1. Patients treated with low-dose doxepin exhibit improvements in anxiety

We first evaluated the efficacy of low-dose doxepin on anxiety. As shown in Figure 1, there are approximately 11 HAMA scores decreased after 12-week low-dose doxepin treatment, and a

Table 1

Inclusion criteria and exclusion criteria.

Inclusion criteria	• **20–80 yrs old** • **meets the diagnostic criteria for generalized anxiety disorder in the 10th edition of the International Classification of Diseases (ICD-10)** • **Hamilton Anxiety Scale scores ≥14**
Exclusion criteria	• secondary anxiety caused by physical diseases such as hyperthyroidism, coronary heart disease, diabetes, hypertension, cerebral infarction, myocardial infarction • anxiety caused by obsessive-compulsive disorder, space disorder, hypochondriasis, neurasthenia, mania, depression, schizophrenia and other mental diseases • withdrawal reactions from excitable drug overdoses, hypnotic sedatives or anti-anxiety drugs • endocrine metabolic diseases • allergies to doxepin tablets, or previous history of similar drug allergies; • pregnant or lactating women • take any drugs that affect glucose and lipid metabolism, thyroxine or sedative hypnosis for one month before enrollment • used antipsychotic drugs before

Table 2

Changes of clinical parameters before and after low-dose doxepin treatment of generalized anxiety disorder.

		Pretreatment	Post-treatment	*P* value*
HAMA scores		19.50 ± 1.22	8.50 ± 3.61	<.01
HPA axis function	ACTH (pmol/L)	4.33 ± 2.14	6.12 ± 3.02	<.01
	COR (nmol/L)	286.80 ± 104.47	334.20 ± 160.27	.18
HPT axis function	FT3 (pg/mL)	4.78 ± 0.51	5.15 ± 0.52	<.01
	FT4 (pmol/L)	18.33 ± 2.71	17.33 ± 1.07	.06
	TSH (pmol/L)	2.91 ± 0.76	3.17 ± 1.24	.33
HPG axis function	E2 (pg/mL)	61.66 ± 48.80	45.83 ± 41.48	.19
	PROG (ng/mL)	4.72 ± 3.40	3.48 ± 1.99	.09
	T (ng/mL)	1.95 ± 1.88	2.20 ± 1.98	.58
TG (mmol/L)		1.69 ± 1.51	3.39 ± 2.86	<.01
TC (mmol/L)		4.55 ± 1.01	5.93 ± 1.66	<.01
HDLC (mmol/L)		1.16 ± 0.34	1.17 ± 0.16	0.87
LDLC (mmol/L)		2.43 ± 0.88	3.76 ± 1.25	<.01
FBG (mmol/L)		5.06 ± 0.43	5.78 ± 0.81	<.01
Weight (kg)		62.00 ± 7.45	64.00 ± 6.44	.23
BMI (kg/m^2)		23.70 ± 2.35	24.48 ± 2.11	.14

*There is a significant difference ($P < .05$), compared to the pre-treatment by paired t test. Data are presented as mean ± SD.

ACTH = adrenocorticotropic hormone, BMI = weight (kg)/height^2 (m^2), BMI = body mass index, COR = cortisol, E2 = estradiol, FBG = fasting blood glucose, FT3 = free triiodothyronine, FT4 = free thyroxine, HAMA = Hamilton Anxiety Rating Scale, HDLC = high density lipoprotein cholesterol, HPA = hypothalamic adrenal axis, HPG = hypothalamic gonadal axis, HPT = hypothalamic thyroid axis, LDLC = low density lipoprotein cholesterol, PROG = progesterone, T = testosterone, TC = total cholesterol, TG = triglyceride, TSH = thyroid stimulating hormone.

comparison between pre-and post-treatment as regards the total scores of HAMA show a significant difference ($P < .01$) (Fig. 1). Therefore, low-dose doxepin has a distinct improvement in the anxiety of GAD patients.

3.2. Low-dose doxepin can affect neuroendocrine systems

Descriptive statistics of neuroendocrine systems for pre and post low-dose doxepin treatment groups are displayed in Figure 2. After 12 weeks of low-dose doxepin treatment, the serum ACTH level of patients significantly increased compared with pretreatment ($P < .01$). Serum COR levels tended to increase, but there was no significant difference between pre-and post-treatment (286.80 ± 104.47 vs 334.20 ± 160.27 nmol/L, $P = .18$). On the other hand, the serum FT3 level of patients after 12-week treatment was significantly higher than that before treatment with statistical significance (4.78 ± 0.51 vs 5.15 ± 0.52 pg/mL, $P < .01$). However, no differences were shown in the serum levels of FT4 (18.33 ± 2.71 vs 17.33 ± 1.07 pmol/L, $P = .06$) and TSH (2.91 ± 0.76 vs 3.17 ± 1.24 pmol/L, $P = .33$). E2 (61.66 ± 48.80 vs 45.83 ± 41.48 pg/mL, $P = .19$) and PROG (4.72 ± 3.40 vs 3.48 ± 1.99 ng/mL, $P = .09$) levels of GAD patients decreased after 12-weeks of treatment, but there was no statistical significance; while the serum testosterone level slightly increased after doxepin treatment, the difference was not statistically significant (1.95 ± 1.88 vs 2.20 ± 1.98 ng/mL, $P > .58$). From those data, we found that low-dose doxepin had effects on the HPA axis and HPT axis but the HPG axis.

3.3. Low-dose doxepin has different effects on serum lipid, blood glucose, body weight, and BMI

As shown in Figure 3, TG (1.69 ± 1.51 vs 3.39 ± 2.86 mmol/L), TC (4.55 ± 1.01 vs 5.93 ± 1.66 mmol/L), LDLC (2.43 ± 0.88 vs 3.76 ± 1.25 mmol/L), and FBG (5.06 ± 0.43 vs 5.78 ± 0.81 mmol/L) were higher than that pretreatment with a significant difference (all $P < .01$). Bodyweight (62.00 ± 7.45 vs 64.00 ± 6.44 kg, $P = .23$) and BMI (23.70 ± 2.35 vs 24.48 ± 2.11 kg/m^2, $P = .14$) had a moderate increase but had no statistical significance compared with pretreatment. HDLC had no obvious change in pre and post-treatment (1.16 ± 0.34 vs 1.17 ± 0.16 mmol/L, $P = .87$). These results suggest that low-dose doxepin may influence lipid and glucose metabolism and body weight.

3.4. Adverse reactions during treatment

There were 3 patients having side effects, 1 case of constipation, 1 case of facial flushing, and 1 case of daytime sleepiness, and the symptoms disappeared after the treatments were adjusted.

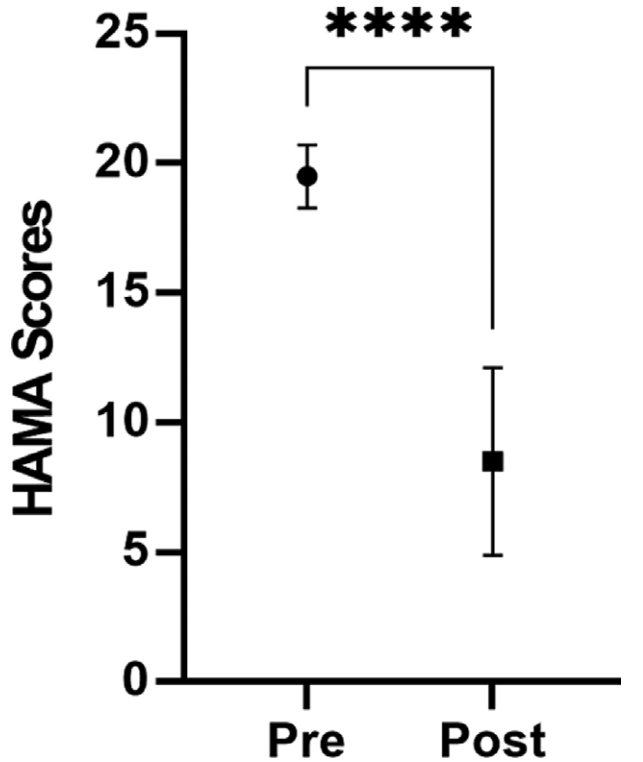

Figure 1. HAMA scores of GAD patients with low-dose doxepin treatment in the pre-and post-treatment period. Quantitative analysis of the results. (n = 36; Mean ± SD; ****$P < .0001$, compared to the pretreatment by paired *t* test). GAD = generalized anxiety disorder, HAMA = Hamilton Anxiety Rating Scale, Post = post-treatment, Pre = pretreatment.

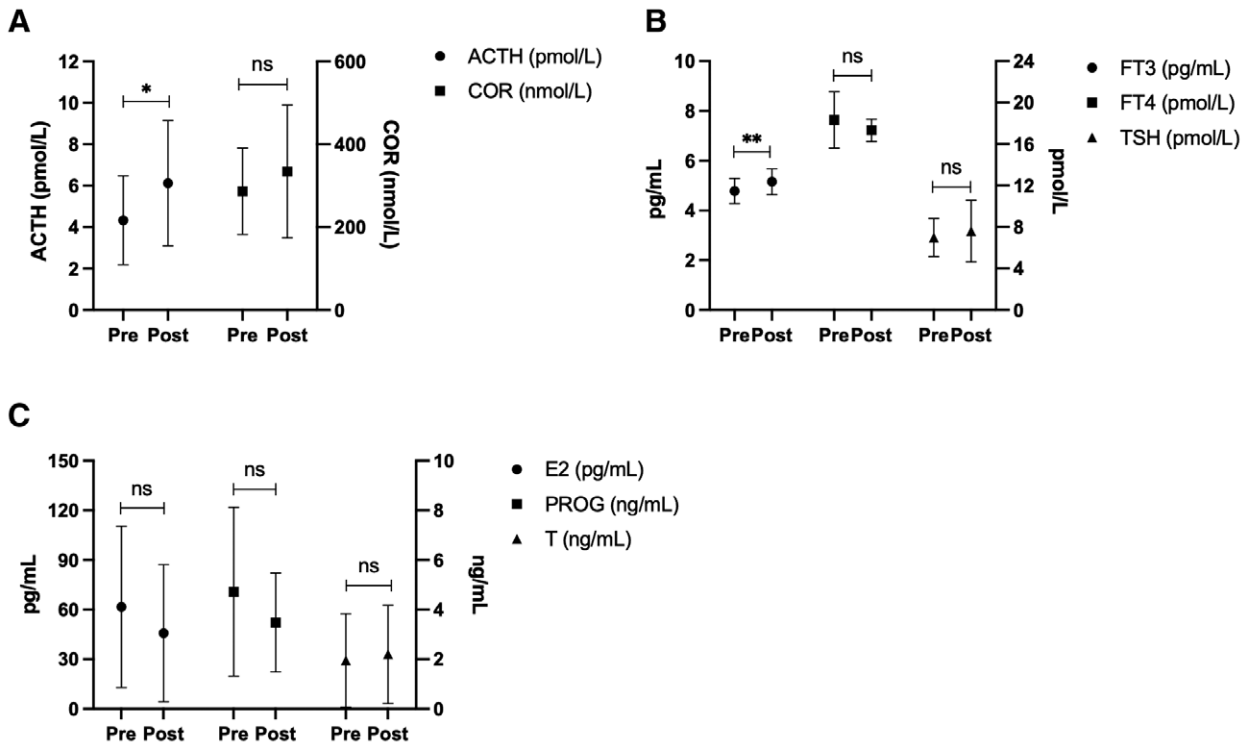

Figure 2. Low-dose doxepin effects on neuroendocrine systems. (A) Serum levels of ACTH and COR pre-and post-treatment. (B) Serum levels of FT3, FT4, and TSH pre-and post-treatment. (C) Serum levels of E2, PROG, and T pre-and post-treatment. (n = 36; Mean ± SD; *$P < .05$, **$P < .01$, ns: no significance, compared to the pretreatment by paired *t* test). ACTH = adrenocorticotropic hormone, COR = cortisol, E2 = estradiol, FT3 = free triiodothyronine, FT4 = free thyroxine, Post = post-treatment, Pre = pretreatment, PROG = progesterone, T = testosterone, TSH = thyroid-stimulating hormone.

4. Discussion

GAD is a common clinical mental illness that diminishes the quality of life, impairs the role of daily function, and leads to high healthcare costs.[11] Some medications are efficacious in the treatment of GAD, including SSRIs, and SNRIs. However, in some trials of the medications above, a significant proportion of GAD patients fail to improve or have residual symptoms.[12] Besides, the early onset of side effects often leads to non-adherence to pharmacological therapy in the case of antianxiety.[13] There is also a paucity of data available to compare the efficiency and safety of those medications for GAD.[14]

Doxepin was primarily approved to treat depression in 1969, nevertheless, with a wide variety of receptors to block, doxepin had been approved for insomnia and anxiety by the US Food and Drug Administration.[15] Anecdotal reports have shown that patients taking higher doses of doxepin are more likely to have anticholinergic effects, increased appetite, and weight.[16] On the contrary, low-dose doxepin does not show significant anticholinergic effects or results in severe adverse reactions.[17] In the present study, we found that 12-week treatment with low-dose doxepin (6.25–12.5 mg/day) had significant efficacy with regards to improvement from baseline in the assessment of anxiety, which is consistent with previous studies.[18]

Although some intrinsic pathological relationships between doxepin and neuroendocrine systems have previously been illustrated, evidence for the exact impact is still limited. Previous studies found that selective serotonin reuptake inhibitors (SSRIs) and other antianxiety agents also had effects on the HPA axis.[19] In our study, serum ACTH increased ($P < .01$), and COR levels showed a slight increase, but had no statistical significance ($P > .05$) compared to pretreatment in patients with GAD. Furthermore, Lewis found that serotonin (5-hydroxytryptamine or 5-HT) can stimulate ACTH release,[20] while doxepin can inhibit 5-HT reuptake and increase 5-HT concentration in the synaptic space, thus promoting the increase in serum ACTH level, which is consistent with our findings. However, some studies indicated that doxepin can activate the 5-HT receptor and promote the release of thyrotropin-releasing hormone (TRH), thus increasing the serum TSH level.[21] In the present study, we also evaluated the effect of low doxepin on the HPT axis. We found that the serum level of FT3 increased significantly ($P < .01$), TSH increased slightly and serum FT4 decreased, but there was no significant difference compared with pretreatment ($P > .05$). The increase in serum TSH levels in the physiological range may be considered that the increased concentration of 5-HT in the synaptic space induced by low-dose doxepin was not enough to cause significant changes in serum TRH. Furthermore, serum FT3 increased after treatment, which may be due to the fact that low-dose doxepin relieved inhibition of deiodinase activity and restored the transformation function of T4 to T3. In addition, sexual dysfunction secondary to anxiolytics and antidepressants is also often underestimated.[22] Increasing data suggest that SSRIs-induced sexual dysfunction occurs in both men and women, and the incidence is approximately 50%.[23,24] In the present study, we found that low-dose doxepin treatment had no significant effect on serum E2, PROG, and T secretion in patients with GAD ($P > .05$). It was consistent with a previous study that lower doses of antidepressants, including second-generation antidepressants and tricyclic antidepressants, may reduce the incidence of sexual dysfunction.[25]

Some studies have found that antidepressants can increase the level of TC.[26] In our research, we showed that after 12-week treatment, serum TG, TC, and LDLC of GAD patients was significantly increased (all $P < .05$), while HDLC had no difference between pretreatment and post-treatment. It may be because

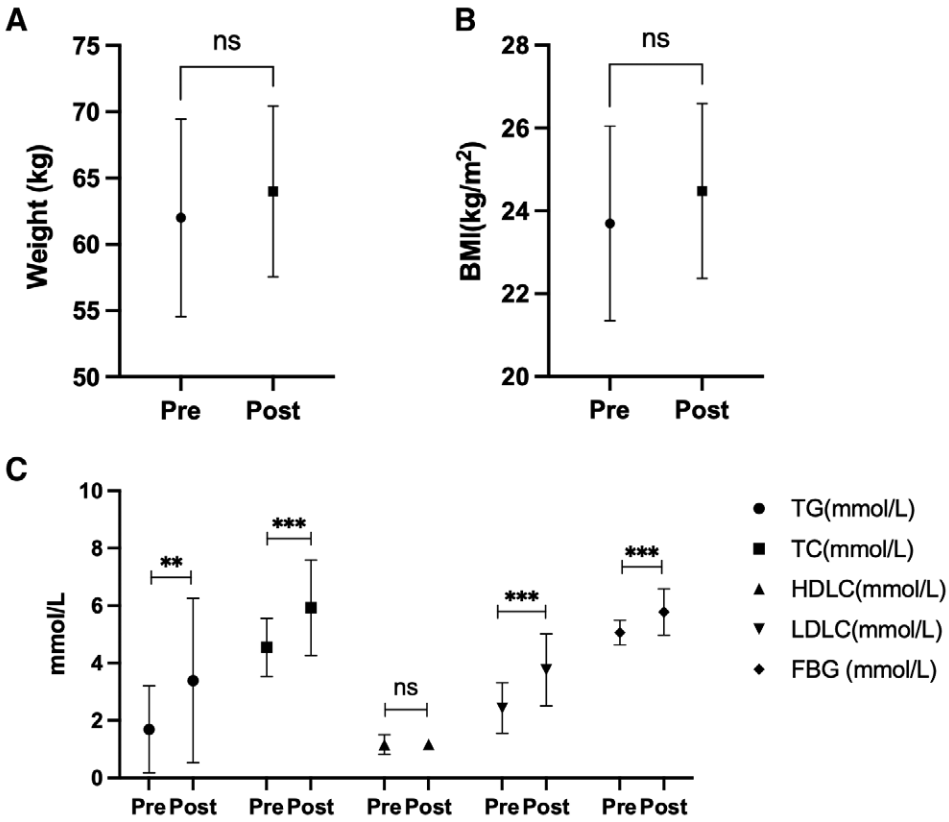

Figure 3. Low-dose doxepin affects serum lipid, blood glucose, body weight, and BMI. (A) Low-dose doxepin effects on weight pre- and post-treatment. (B) Low-dose doxepin effects on BMI pre-and post-treatment. (C) Serum levels of TG, TC, HDLC, LDLC, and FBG pre-and post-treatment (n = 36; Mean ± SD; ***$P < .001$, **$P < .01$, ns: no significance, compared to the pretreatment by paired *t* test). BMI = body mass index, BMI = weight (kg)/height^2 (m^2), FBG = fasting blood glucose, HDLC = high density lipoprotein cholesterol, LDLC = low density lipoprotein cholesterol, Post = post-treatment, Pre = pretreatment, TG = triglyceride, TC = total cholesterol.

doxepin has an anti-H1 receptor effect, stimulating appetite regulation center in the hypothalamus, and increasing appetite and calorie intake, leading to the increase of serum lipid level.[27,28] Our findings showed that low-dose doxepin can significantly increase FBG, but didn't meet the criteria for diabetes. Similarly, a nested case-control study found that the use of moderate to high daily doses of SSRIs increased the risk of developing diabetes mellitus,[29] and some reports have suggested that the long-term use of SSRIs may be associated with significant weight gain.[28,30] Most antidepressants appear to produce a 3 kg to 4 kg weight gain after 6 to 12 months of therapy.[31] Our results showed that the body weight and BMI of patients increased slightly but had no statistical differences after low-dose doxepin treatment ($P > .05$). So far, the mechanism by which these metabolic abnormalities are produced by anti-anxiety is not entirely clear, and it may relate to the specific medication, drug dose, length of treatment, as well as individual genetic differences.

Our previous study found that the incidence of adverse reactions to low-dose doxepin was lower than that of citalopram.[18] In this study, we also found that the incidence of adverse reactions was very low (8.3%), including constipation, facial flushing, and daytime sleepiness using low-dose doxepin treatment, suggesting that low-dose doxepin treatment has good clinical safety, which is consistent with other studies.[9,32] On the other hand, intake high-dose doxepin (average 75–300 mg/day) was prone to having more adverse effects.[33] Based on the data on high-dose doxepin treatment, there might be an excess of admissions and poisons for the patients with anxiety or depression, so a low dose of doxepin may be necessary to reduce drug toxicity in clinical practice.

5. Conclusion

Our study indicates that low-dose doxepin has *good therapeutic* efficacy and *tolerability, as well as a very low* incidence of adverse reactions in the treatment of generalized anxiety disorder. However, we also found that low-dose doxepin exerts some metabolic adverse effects on generalized anxiety disorder patients, including serum glucose, lipid, body weight, and body mass index, which is somewhat similar to SSRIs and other antidepressants.[29] Certainly, adverse side effects still need to be recognized and managed in the treatment of low-dose doxepin. Hence, good therapeutic efficacy and tolerability, and lack of important adverse effects make low-dose doxepin a unique, rational drug for the treatment of generalized anxiety disorder patients.

6. Limitation

This study has some limitations. First, the sample size is relatively small, which limits the ability of statistical analysis and reduces the credibility of the study. Second, there is no detailed hierarchical analysis of each age group. The elder patients may sense to side effect. Third, lack of detailed stratified of each gender group. Hormone secretion levels vary by sex and age, and changes in sex hormones after antidepressant therapy are also different. Fourth, lack of placebo control and a short duration of the follow-up. Future investigations are necessary to validate the kinds of conclusions that can be drawn from this study. In future research, a larger sample is needed to study the differences in hormone levels and clinical safety in patients with different gender and age. We also should set a placebo control and enlarge the following-up time.

This study was funded by grants from the Shanghai Municipal Commission of Health and Family Planning (Grant No. 201740209) and the Shanghai Jinshan District Key Medical Foundation (Grant No. JSZK2015A05).

Author contributions

Mengqi Zhang and Fengmin Huang examined and evaluated the patients and wrote the manuscript draft. Mengqi Zhang, Fengmin Huang, Feiyu Jiang, Meiting Mai, Xiaorou Guo, and Ying Zhang contributed to the acquisition, analysis, and interpretation of clinical data. Hengbing Zu and Ying Xu designed the study and supervised the finalization of the manuscript. All authors have read and approved the final version of the manuscript.

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