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Efficacy and associated neurotransmitters of digital cognitive behavior therapy for atopic dermatitis: A comparative effectiveness research

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Abstract

Background: Negative emotions are a major comorbidity of atopic dermatitis (AD). Evidence that supports the effectiveness of digital cognitive behavioral therapy (dCBT) as an adjuvant therapy for AD remains limited.

Objective: To investigate the preliminary efficacy of additional dCBT and potential neurotransmitter biomarkers for AD accompanied by negative emotions.

Methods: Thirty-two patients with AD were recruited and examined for clinical severity and negative emotions including insomnia, anxiety, and depression. Patients with mild-to-moderate negative emotions were divided into two groups that received standard care (N = 9) or mobile app-delivered CBT plus standard care (N = 11) for 12 weeks. Plasma levels of 40 neurotransmitters were determined using liquid chromatography tandem mass spectrometry pre- and post-treatment.

Results: Skin lesions, itch, and insomnia were significantly improved in both treatment groups. Improvements of itch (P = 0.0449) and insomnia (P = 0.0089) were more robust in the combination treatment group than those in the standard treatment group. Neurotransmitters that involve tryptophan, dopamine, and histidine pathways were markedly altered in patients with AD compared with healthy controls. Taurine levels were selectively increased following dCBT plus standard care (P = 0.0259). Baseline levels of L-tyrosine were negatively correlated with the reduction of skin lesions (r = -0.9073, P = 0.0334) and itch intensity (r = -0.9322, P = 0.0210) in the combination therapy group.

Conclusions: dCBT provides an efficacious supplementary approach for AD accompanied by negative emotions. Emotion-related neurotransmitters may contribute to AD and serve as indicators for treatment effects.

Key words: Atopic dermatitis, anxiety, depression, dupilumab, cognitive behavioral therapy, negative emotions, neurotransmitters.

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Introduction

Atopic dermatitis (AD) is a chronic and pruritic inflammatory skin disorder that affects up to 10% general population worldwide.[1] Due to its intense chronic itch and relapsing course, AD profoundly impairs quality of life of patients.[2] Although the novel targeted regimens like anti-IL-4Rα antibody dupilumab and Janus kinase inhibitors have promoted its treatment strategy to enter a new era, the effectiveness of these pharmaceuticals is still moderate,[3] most likely because of the disease heterogeneity. Therefore, it is essential to utilize novel approaches in addition to medications to enhance the therapy efficacy and improve disease outcomes.

Negative emotions are unpleasant and disruptive emotional reactions that manifest as a large range of negative feelings towards an event or person. In recent years, negative emotions such as anxiety, depression, and associated sleep disturbance have been increasingly recognized as non-allergic comorbidities of AD, and current investigators have routinely assessed them in clinical trials.[4-6] Furthermore, emotional factors have been found to contribute to AD exacerbations. Emerging evidence has shown that stress has a positive correlation with increased skin lesions and itch worsening in AD.[7] The avoidance of emotional stress has been listed as an approach to prevent AD flares across multiple international guidelines.[8-10] Despite this, whether the improvement of mental health will in turn lead to better outcomes of AD remains largely unclear.

Cognitive behavioral therapy (CBT) is a psychological intervention that aims to reduce symptoms of a range of mental conditions including depression, anxiety disorders, and insomnia. Evidence has mounted that CBT can enhance emotional functioning, modify dysfunctional behaviors, and improve quality of life.[11,12] Digital CBT (dCBT) is a contemporary method that delivers CBT via a computer and/or mobile devices with Internet connectivity. Although clinical evidence for the effectiveness of dCBT in treating emotion disorders has substantially increased over the last few years,[13] the application of dCBT in skin disorders with emotional comorbidities, remains quite limited.

Neurotransmitters are chemical compounds mostly released by neurons. They transmit messages between neurons or from neurons to other cells throughout the body.[14] A number of neurotransmitters are used by the body for different functions. Notably, dysregulated neurotransmitters are implied in psychiatric and neurological disorders. For instance, while norepinephrine exerts its effects on stress, the dopamine system is closely linked to depressive disorders.[15,16] Given this background, we hypothesized that neurotransmitter dysregulation may contribute to emotional conditions accompanied with AD.

The objective of this pilot study was to test feasibility and preliminary efficacy of smartphone-delivered dCBT as an adjuvant therapy for adult Chinese patients with AD. We hypothesized that dCBT combined with conventional medications would be acceptable and lead to significant decreases in skin symptoms and negative emotions associated with AD.

Material and Methods

Study design

From October 1, 2021 to June 2, 2022, we enrolled 47 adult patients with AD and 15 healthy controls. Assessments of skin symptoms and signs were performed in all patients at baseline. While 32 individuals with AD were examined for negative emotions, the other 15 patients as well as sex- and age-matched 15 healthy controls were tested for circulating neurotransmitters. Based on the results of emotion assessments, 20 patients were diagnosed with mild-to-moderate negative emotions. Next, these 20 patients were randomized in a 1:1 ratio to receive either a 12-week exposure-based CBT program provided via a mobile app in addition to standard treatment, or a control condition in which only standard treatment was administered. Measurements of skin lesion, itch intensity, negative emotions, and levels of circulating neurotransmitters were obtained prior to and following treatment.

All participants provided written informed consent and the study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University (IRB [2022] 047).

Participants

The AD cohort enrolled into this study had to meet the following criteria: (a) conformed diagnosis criteria for AD,[17] (b) be 18–70 years of age, (c) not have serious concurrent psychiatric problems (e.g. substance abuse, psychosis, severe depression) that could hinder participation in treatment, (d) not have concurrent psychological treatment for AD, and (e) not be pregnant. Patients were eligible for the intervention program if they owned and knew how to operate a smartphone. The 15 healthy controls were age- and sex-matched with 15 AD patients for the depiction of neurotransmitter profile.

Assessments

AD clinical severity including skin lesions and itch intensity was assessed by eczema area and severity index (EASI) and worst itch numeric rating scale (WI-NRS). WI-NRS rates the weekly average of peak scores for pruritus on a numerical rating scale that ranges from 0 ("no itch") to 10 ("worst imaginable itch"). We examined negative emotions of the patients in terms of insomnia, anxiety, and depression by Pittsburgh Sleep Quality Index (PSQI), Generalized Anxiety Disorder Assessment-7 (GAD-7), and Patient Health Questionnaire-9 (PHQ-9), respectively. While mild AD is defined as EASI < 16, patients with EASI ≥ 16 were classified into moderate-to-severe forms. The severity of negative emotions is defined as none (0–4 scores), mild (5–9 scores), moderate (10–14 scores), and severe (≥ 15 scores). In this study, EASI scores were assessed by a single research nurse, whereas scales for itch and negative emotions were self-reported using the "AD good mood" smartphone app (Langgan Technology Co., Hangzhou, China) Each individual evaluation for negative emotions was further confirmed by a licensed psychiatrist.

Interventions

A 12-week dCBT was delivered by the smartphone app "AD good mood" for participants. The dCBT materials were organized into three categories that include sleeping problems, anxiety, and depression. Following a final diagnosis confirmed by psychiatrists, specific dCBT contents were launched to patients according to their assessment results of negative emotions. The app uses the principles of behavioral psychology to motivate patients and achieve behavior changes. There are three sections in each category of dCBT materials: introduction, training, and task completion. In addition to exercise and mindfulness, the application pays special attention to drug reminder, disease education, skin symptoms, itch sensation, cognitive reconstruction, sleep hygiene, relaxation training, relaxation music, and healthy lifestyle guidance. It prompts users to accomplish daily tasks in aforementioned areas.

For standard care, stepwise treatment according to the severity of AD was adopted according to the international guidelines.[8-10] All patients were instructed to use emollients at least twice per day to protect the skin barrier. In accordance with the standard treatment guidelines, participants were instructed to use anti-inflammatory treatments based on their disease severity, i.e. topical corticosteroids for mild AD and the monoclonal antibody against IL-4Rα (dupilumab) for moderate-to-severe AD.

To increase patient compliance in both groups, a study nurse was assigned to follow-up and monitor the therapeutics once a week utilizing virtual meeting tools.

Blood sample collection and neurotransmitters detection

A sample of peripheral blood (3 mL) was obtained from each subject and centrifuged at 1000 g for 10 min. Plasma were separated from cells within 1 h of collection, and 1-mL aliquots were stored at -80°C until being analyzed. Plasma samples were tested for 40 neurotransmitters that include 21 monoamines (noradrenaline, dopamine, and serotonin, etc.), 15 amino acids (excitatory neurotransmitters like glutamic acid and aspartic acid, and inhibitory neurotransmitters like glycine and taurine), and four others using liquid chromatography tandem mass spectrometry (LC-MS/MS) through neurochemical detection and analysis method package on Qtrap 6500 LC-MS/MS platform. Data were analyzed by SCIEX OS-MQ software (Sciex Company, America).

Statistical analysis

Data with normal distributions was described as mean ± standard deviation (SD) and statistical significance was determined using the two-tailed Student's t-test. If data were not normally distributed, median (interquartile range) was used and statistical significance was determined using the Wilcoxon-Mann-Whitney nonparametric test. Comparison between the measurements prior to and following treatment in the same group was determined by paired statistical tests, otherwise unpaired tests were used. Differences of incidence rate between two groups were compared by Fisher's exact test. Correlation between two variables was assessed using Pearson r correlation coefficient. All statistical tests were performed using GraphPad Prism software, version 9.0 (GraphPad Software, Inc, USA). *P* values lower than 0.05 were considered to indicate a statistically significant difference.

Results

Negative emotions are displayed by a large proportion of patients with AD

In those 32 patients with AD assessed for negative emotions including insomnia, anxiety, and depression (**Figure 1A**), 90.63% (29/32) of the patients exhibited at least one negative emotion (**Figure 1B**), with insomnia being the most common type (**Figure 1C**). Notably, among the three severity categories (mild, moderate, and severe) across negative emotions, the mild form represents the largest proportion (**Figure 1C**). Although 100% of the patients with moderate-to-severe AD (14/14) were accompanied by negative emotions, this incidence rate is not significantly different from that in patients with mild AD (15/18, 83.33%; $P = 0.2379$; **Figure 1D**). Collectively, these findings confirmed that regardless of AD severity, negative emotions are a common comorbidity of AD.

Additional dCBT to standard treatment effectively improves AD

In the cohort of 20 adult patients with AD accompanied by mild-to-moderate negative emotions, nine patients with AD received standard therapies, whereas the other 11 patients were treated with 12-week dCBT in addition to standard care (**Figure 2A**). We verified that demography and disease severity at baseline between the two groups were comparable (**Table 1**). All 20 patients with AD completed the 12-week interventions, leading to 100% treatment adherence in both groups. Following the standard treatment of 12 weeks, although the decreases from baseline in EASI scores (-6.4 [95%CI, -9.8 to -3.0], $P = 0.0025$; **Figure 2B**), WI-NRS scores (-2.7 [95%CI, -4.0 to -1.3], $P = 0.0017$; **Figure 2B**), and PSQI scores (-1.6 [95%CI, -2.7 to -0.5], $P = 0.0112$; **Figure 2C**) were statistically significant, alternations in either GAD-7 scores (-1.6 [95%CI, -3.3 to -0.2], $P = 0.0767$) or PHQ-9 scores (-1.4 [95%CI, -3.1 to 0.2], $P = 0.0761$) did not reach any significant difference (**Figure 2C**). On the contrary, patients who completed dCBT in addition to conventional therapy showed marked and significant improvement in both AD severity as measured by EASI scores (-14.0 [95%CI, -20.4 to -7.7], $P = 0.0006$) and WI-NRS scores (-4.5 [95%CI, -6.2 to -2.7], $P = 0.0002$; **Figure 2D**), and negative emotions including PSQI scores (-4.7 [95%CI, -6.3 to -3.1], $P = 0.0004$), GAD-7 scores (-3.6 [95%CI, -5.6 to -1.7], $P = 0.0018$), and PHQ-9 scores (-4.5 [95%CI, -6.5 to -2.4], $P = 0.0008$; **Figure 2E**). More importantly, the group receiving combination therapy displayed more significant improvements of itch intensity ($P = 0.0449$; **Figure 2F**) and insomnia ($P = 0.0089$; **Figure 2G**) than the standard treatment group.

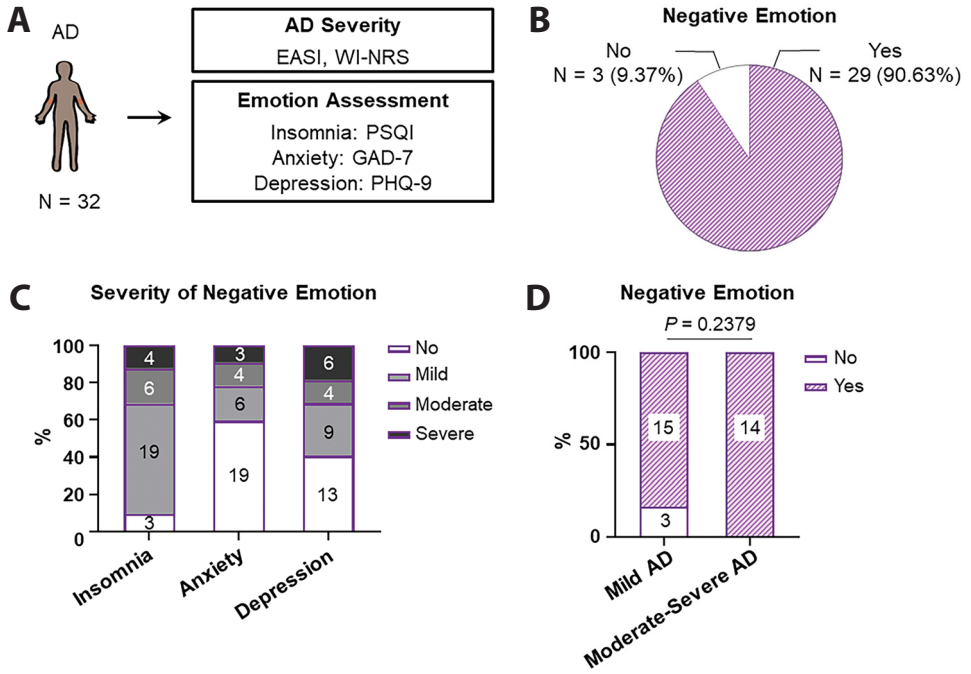


Figure 1. Negative emotions are displayed by a large proportion of patients with atopic dermatitis (AD). (A) Schematic of assessments for clinical severity and negative emotions in a cohort of patients with AD (N = 32). (B) Pie chart depicting the percentage (%) of patients that were positive or negative for emotional conditions. (C) Percentage (%) of patients (N = 32) that exhibited none, mild, moderate, and severe negative emotions including insomnia, anxiety, and depression. The patient number in each group was listed in each section of the column chart. (D) Frequency composition of patients who exhibited negative emotions out of all patients with mild (N = 18) or moderate-to-severe AD (N = 14). The patient number in each group was shown in each section of the column chart. EASI, eczema area and severity index; WI-NRS, worst itch numeric rating scale; PSQI, Pittsburgh Sleep Quality Index; GAD-7, Generalized Anxiety Disorder Assessment-7; PHQ-9, Patient Health Questionnaire-9.

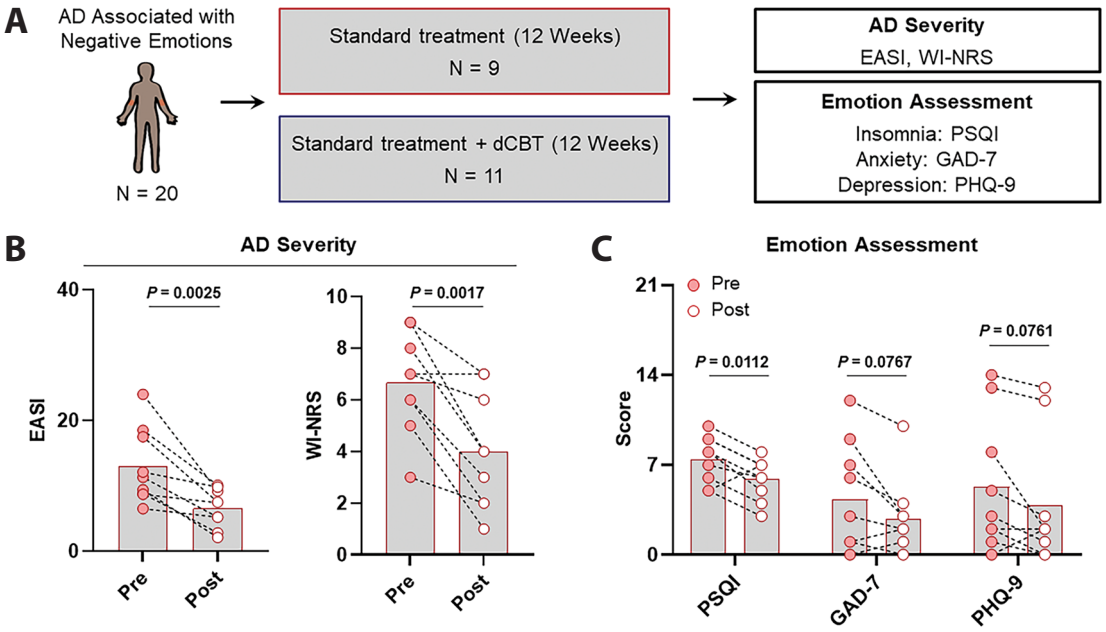


Figure 2. Additional dCBT to standard treatment effectively improves AD outcomes. (A) Schematic of treatment for patients with AD accompanied by negative emotions (N = 20). AD severity and negative emotions were assessed at baseline and following 12-week treatment. Comparison of (B) AD severity (EASI and WI-NRS) and (C) negative emotions (insomnia, anxiety, and depression) before and after standard treatment. Comparison of (D) AD severity (EASI and WI-NRS) and (E) negative emotions (insomnia, anxiety, and depression) before and after treatment with dCBT plus standard care. Comparison of decrease in (F) AD severity and (G) negative emotions between patients that received standard treatment and those treated with dCBT plus standard care.

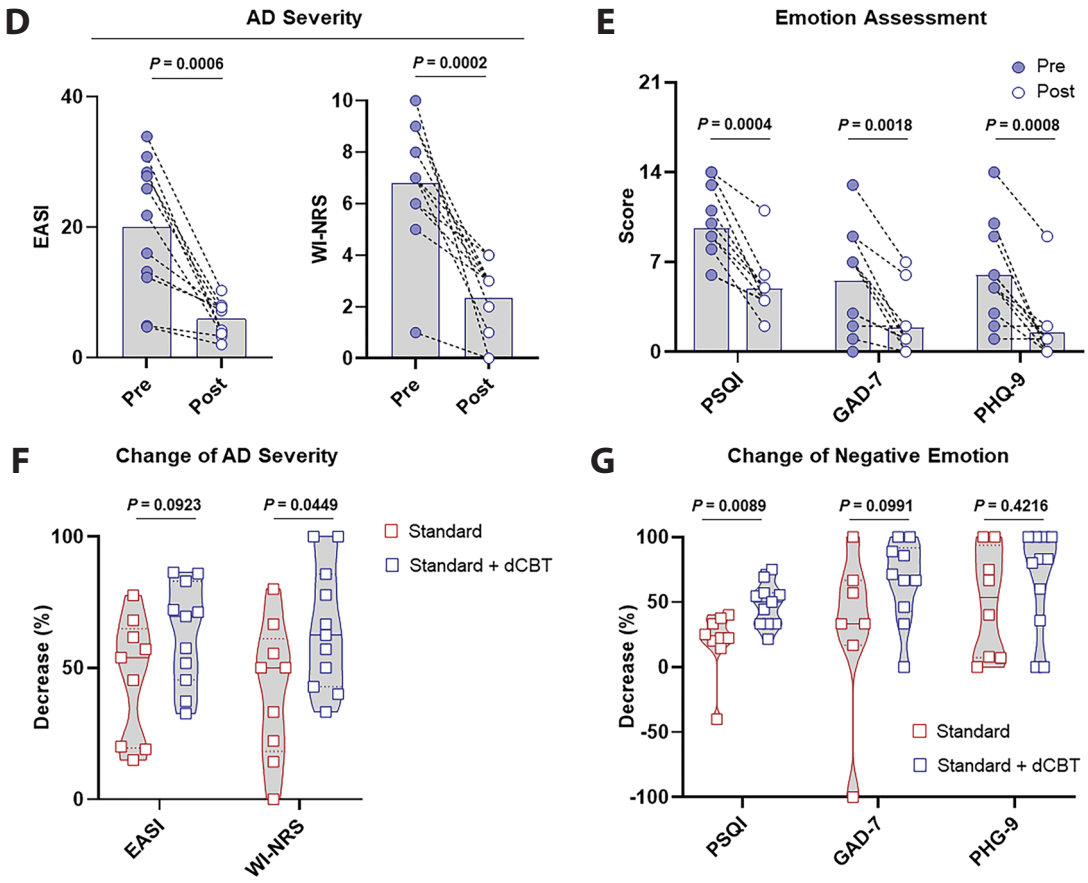


Figure 2. (Continued)

Table 1. Baseline comparison of patients with negative emotions that received standard treatment or standard treatment plus dCBT in the context of AD.

Group	Standard treatment (N = 9)	Standard treatment plus dCBT (N = 11)	$P^{\$}$
Mean age (yrs, mean ± SD)	27.67 ± 7.51	30.91 ± 8.02	0.3395
Female/male, N	4/5	8/3	0.3618
[a]Severity of AD			
Mild, N	3	7	0.3698
Moderate-to-severe, N	6	4	0.3698
EASI (mean ± SD)	12.98 ± 5.44	19.97 ± 9.83	0.1119
WI-NRS (mean ± SD)	6.67 ± 1.83	6.82 ± 2.33	0.7571
[b]Negative emotions			
Insomnia (PSQI, mean ± SD)	7.44 ± 1.81	9.64 ± 3.08	0.0760
Anxiety (GAD-7, mean ± SD)	4.33 ± 4.11	5.55 ± 3.85	0.4175
Depression (PHQ-9, mean ± SD)	5.33 ± 5.20	6.00 ± 3.59	0.7433

Table 1. (Continued)

Group	Standard treatment (N = 9)	Standard treatment plus dCBT (N = 11)	*P*[§]
Standard treatment for AD			
Emollients, N	9	11	> 0.9999
Topical steroids, N	3	7	0.3698
Dupilumab, N	6	4	0.3698

[§]Student's t-test was used in comparison of mean age, EASI, WI-NRS, GAD-7, PSQI, and PHQ-9. Fisher's exact test was applied to compare sex distribution and patient number in each severity and treatment group.
[a]AD severity is classified based on the EASI scores. While mild disease is defined as EASI < 16, moderate-to-severe forms are defined as EASI ≥ 16.
[b]Negative emotions are classified into insomnia, anxiety, and depression, which were assessed by Pittsburgh Sleep Quality Index (PSQI), Generalized Anxiety Disorder Assessment-7 (GAD-7), and Patient Health Questionnaire-9 (PHQ-9), respectively.
Abbreviations: AD, atopic dermatitis; dCBT, digital cognitive behavioral therapy; EASI, eczema area and severity index; IQR, interquartile range; WI-NRS, worst itch numeric rating scale.

A distinct neurotransmitter profile is exhibited in AD

To depict the fundamental neurotransmitter profile of AD, we tested plasma levels of 40 neurotransmitters in 15 patients with AD and 15 healthy subjects (**Figure 3A**). In the detectable 28 neurotransmitters, patients with AD displayed a distinct pattern in contrast to healthy controls (**Figure 3B**), and the pattern is strongly associated with mental health issues like drug addiction and neurotransmitter metabolism (**Figure 3C**). Particularly, the metabolic pathways of tryptophan and dopamine respectively encompass five (**Figure 3D**) and three members (**Figure 3E**) that were robustly altered. However, only L-histidine in the histidine metabolic pathway exhibited lower levels in patients with AD than that in the healthy controls (**Figure 3F**). Collectively, these results indicate that AD has a unique neurotransmitter profile from healthy individuals.

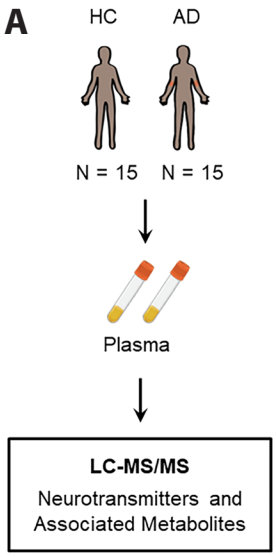
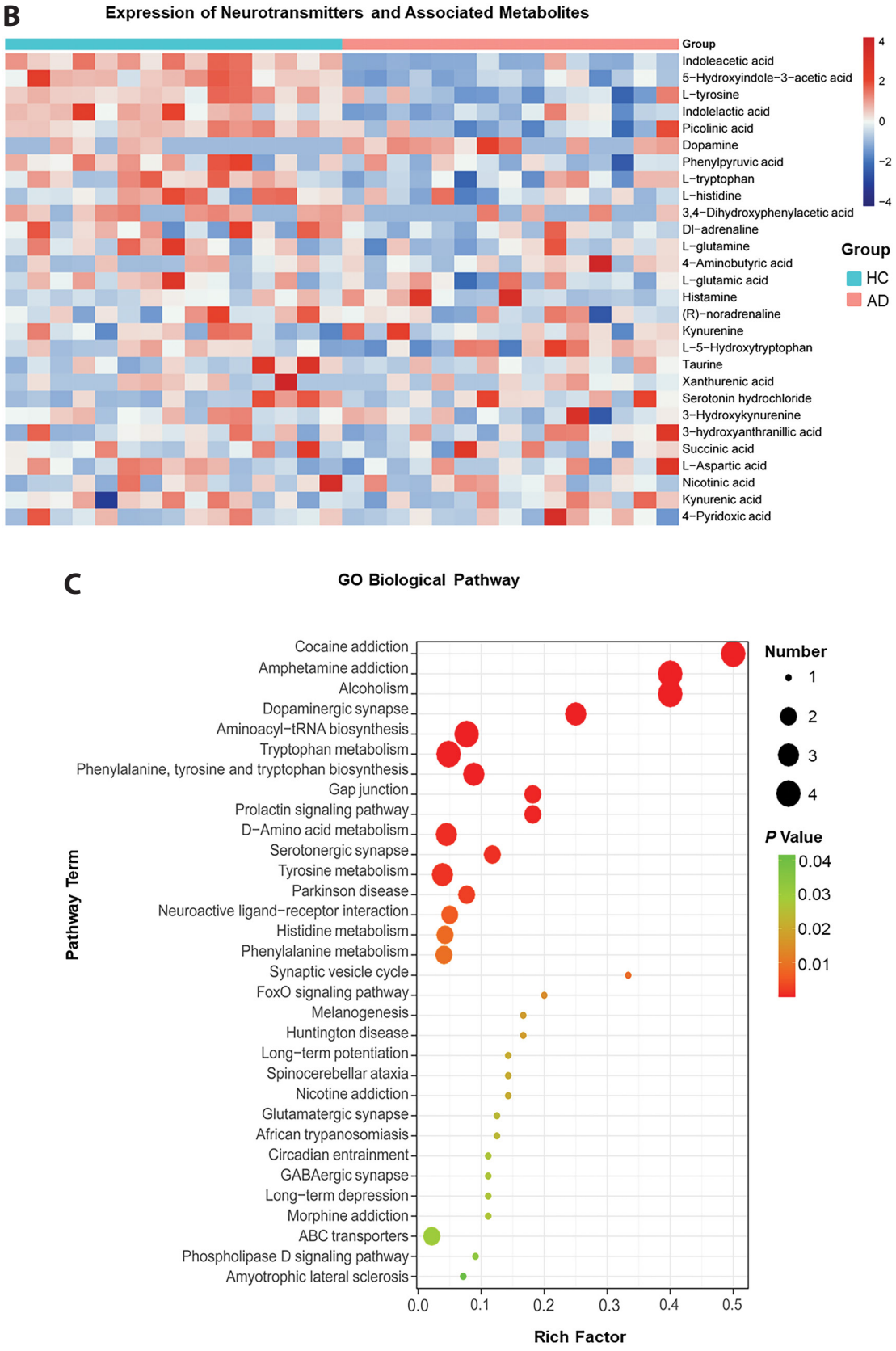


Figure 3. Patients with AD exhibit a distinct neurotransmitter profile. (A) Schematic of liquid chromatography tandem mass spectrometry (LC-MS/MS) tests for plasma neurotransmitters and associated metabolites from healthy controls (HC; N = 15) and patients with AD (N = 15). (B) Heatmap analyses of 28 detectable neurotransmitters and associated metabolites in HC and patients with AD. (C) Biological pathway enrichment based on Gene Ontology (GO) analyses. The dot size indicates neurotransmitter numbers and the color indicates the corresponding significance of *P* values. Comparison of levels of plasma (D) tryptophan associated metabolites, (E) dopamine associated metabolites, and (F) L-histidine between HC and patients with AD. 5-HIAA, 5-hydroxyindole-3-acetic acid; PPA, phenylpyruvic acid.



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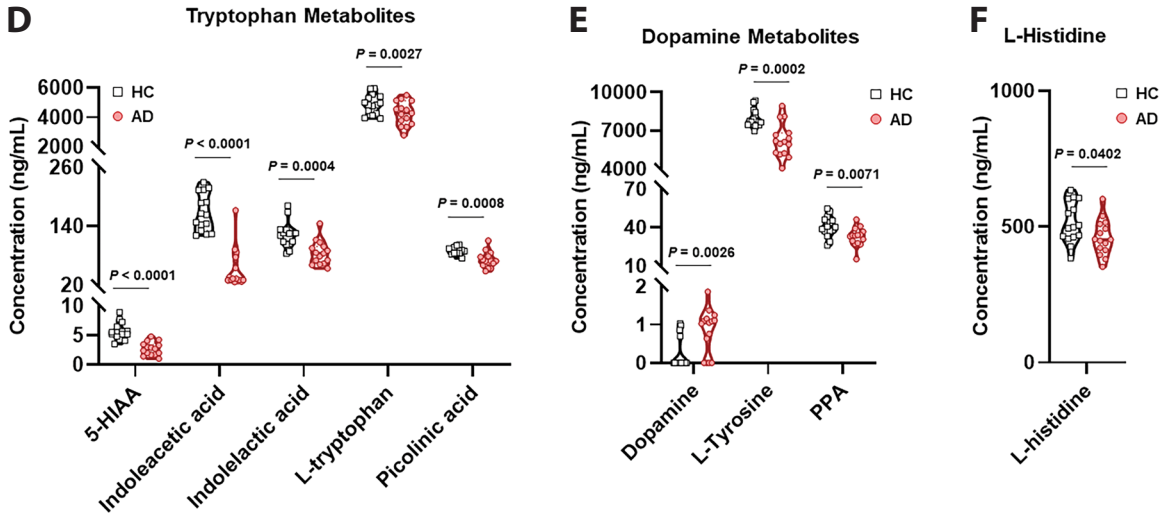


Figure 3. (Continued)

Neurotransmitters are associated with outcomes of AD

Given that neurotransmitters represent a distinctive feature of AD, we hypothesized that specific neurotransmitters may indicate the effects of dCBT. We compared levels of neurotransmitters pre- and post-treatment in those AD patients with mild-to-moderate negative emotions (**Figure 4A**). In the cohort receiving standard treatment (N = 9), unlike tryptophan metabolites (**Figure 4B**), only levels of dopamine displayed a substantial decline from baseline (P = 0.0204; **Figure 4C**). No significant change of L-histidine levels was observed following standard treatment (**Figure 4D**). On the contrary, dCBT plus standard care did not yield any significant alteration in the levels of tryptophan metabolites (**Figure 4E**), dopamine metabolites (**Figure 4F**), or L-histidine (**Figure 4G**). However, the levels of taurine exhibited a robust increase following additional dCBT plus standard treatment (P = 0.0259; **Figure 4G**). This dynamic change of taurine levels was not found in the standard treatment group (**Figure 4D**), implying that different therapeutic approaches may result in various dynamic changes of neurotransmitters in AD.

Specific neurotransmitters may indicate poor responses following additional dCBT in AD

We further did correlation analyses between neurotransmitter concentrations and disease severity of AD. Despite distinct changes observed in neurotransmitter levels at the post-treatment stage, no significant correlation was found between the alteration of dopamine levels or taurine levels and the decreases of EASI or WI-NRS scores in either group. Strikingly, although baseline levels of L-tyrosine were not correlated with the improvement of EASI (r = 0.4736, P = 0.1978; **Figure 5A**) or WI-NRS scores (r = 0.6391, P = 0.8702; **Figure 5B**) in the standard treatment group, L-tyrosine at its baseline exhibited a negative correlation with the reduction of EASI (r = -0.9073, P = 0.0334; **Figure 5C**) and WI-NRS scores (r = -0.9322, P = 0.0210; **Figure 5D**) following the combined treatment. Taken together, these results suggest that L-tyrosine is probably linked to the poor responses in the additional dCBT for AD.

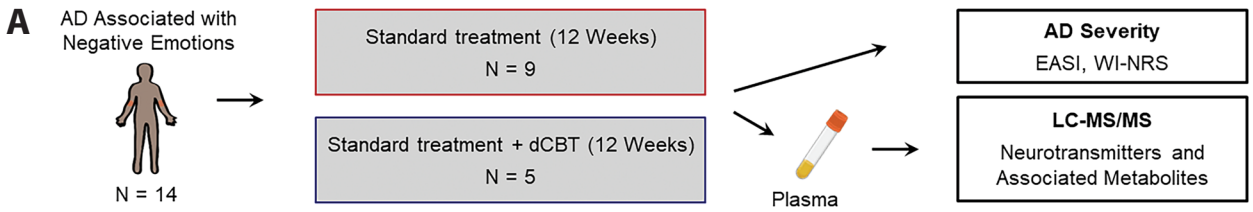
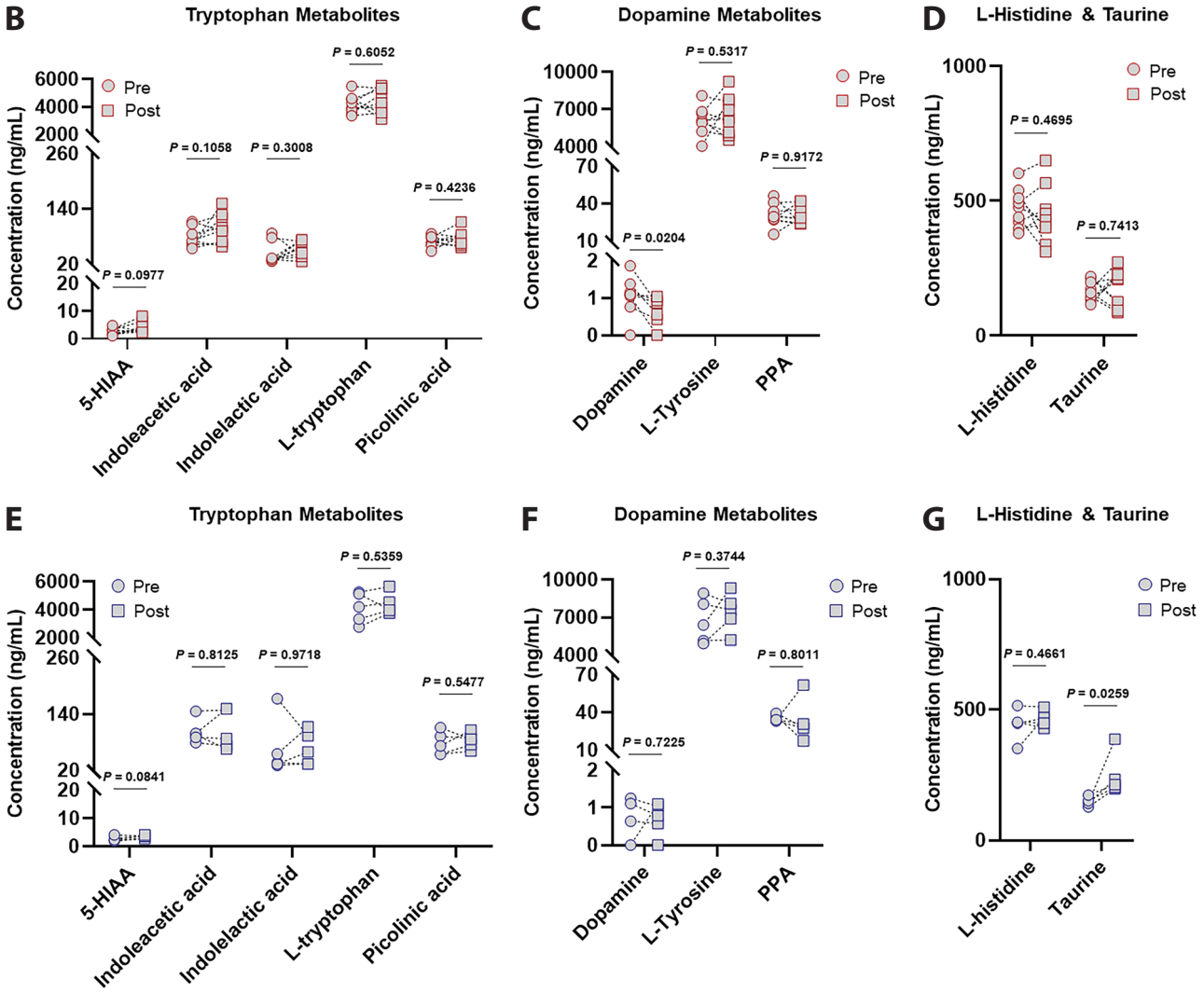


Figure 4. Neurotransmitters are associated with outcomes in AD. (A) Schematic of LC-MS/MS tests for plasma neurotransmitters and associated metabolites from AD patients with negative emotions that received either standard treatment (N = 9) or dCBT plus standard treatment (N = 5). AD severity (EASI and WI-NRS) and neurotransmitters were assessed at baseline and following 12-week treatment. Comparison of levels of plasma (B) tryptophan associated metabolites, (C) dopamine associated metabolites, and (D) L-histidine and taurine in AD patients with negative emotions prior to and following standard treatment. Comparison of levels of plasma (E) tryptophan associated metabolites, (F) dopamine associated metabolites, and (G) L-histidine and taurine in AD patients with negative emotions prior to and following dCBT plus standard treatment.



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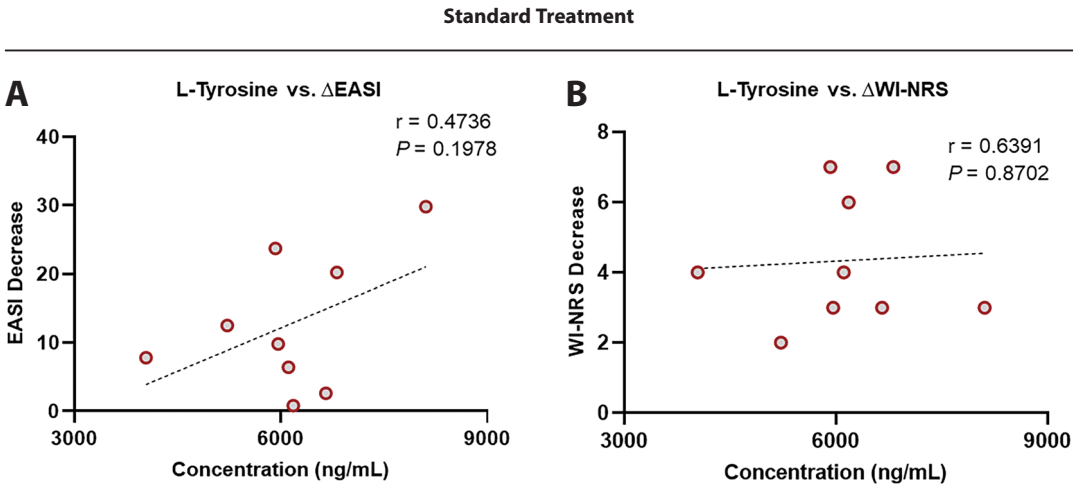

Figure 5. Specific neurotransmitters are linked poor responses of additional dCBT. Correlations between baseline levels of L-tyrosine and the decrease of (A) EASI and (B) WI-NRS following standard care. Correlations between baseline levels of L-tyrosine and the reduction of (C) EASI and (D) WI-NRS in the group that received dCBT plus standard care. The decrease of EASI was calculated by baseline EASI minus post-treatment EASI. The decrease of WI-NRS was calculated by baseline WI-NRS minus post-treatment WI-NRS.

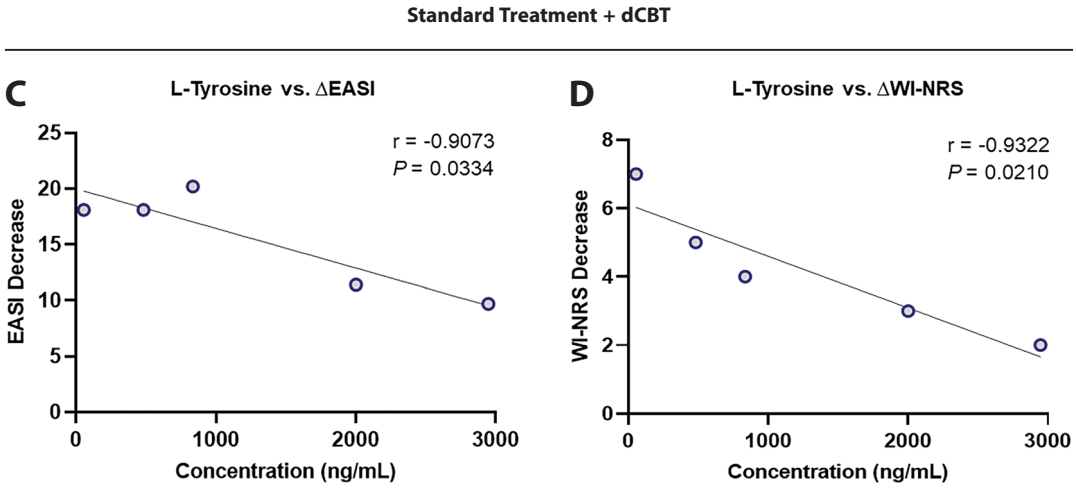

Figure 5. (Continued)

Discussion

Compelling epidemiologic evidence shows that comorbidities of AD include the illnesses other than merely allergic conditions.[18] It has been revealed that the early onset of AD is a risk factor for patients to develop a broad spectrum of neuropsychiatric conditions such as autism, attention deficit disorder, anxiety, depression, and even suicidal ideation.[19,20] Therefore, management of emotional issues accompanied with AD is of great significance to improve the disease outcomes. More recently, a study conducted by Hedman-Lagerlöf et al. found that internet-delivered CBT in addition to standard care appears to be efficacious to reduce the symptoms including itch intensity, perceived stress, sleep problems, and depression.[21] We confirmed these findings in the present study on Chinese patients with AD. It should be noted that the small sample size of our study may lead to high uncertainty around the effect estimates. However, due to the consistency of our study and others, we speculate that dCBT delivered by either computer or mobile devices may become an effective adjunct therapy for AD to achieve substantial improvements. Meanwhile, the effectiveness of dCBT combined with a variety of medications beyond topical steroids and dupilumab should be examined in future to increase the extensibility of this new treatment strategy.

The feature of chronicity of AD requires a long and adhered management. Notably, a recent study from Dr. Silverberg's team shows that digital interventions are advantageous for patients with AD and led to higher levels of medication adherence and clinical improvement.[22] Given that medical resources are sometimes limited, particularly in China with a large patient population, digital interventions would be more supportive for patients in illness self-management. Furthermore, the patient compliance of dCBT in our study is much greater compared with those previously published studies.[13,21] This is likely due to the modest cohort size and the contribution of our research nurse who did routine follow-up. It would be fascinating to investigate whether alternative approaches, in addition to routine monitoring, could improve treatment adherence for such combination therapy strategies.

Emerging evidence has revealed that neuroimmunology contributes to AD mechanisms.[23] Indeed, itch biology in the context of AD specifically highlights the integration of immunologic pathways with identified itch-sensory circuits.[24,25] Meanwhile, various neuropeptides like substance P and calcitonin gene related peptide released from peripheral nervous system are sufficient to activate skin resident mast cells.[26-28] These neuroimmune interactions have demonstrated a significant role in mechanism research and drug development for AD.[3] Despite this, how those emotion-related neurotransmitters regulate skin inflammation and itch in AD remains largely unknown. It has been found that low levels of serum serotonin, a tryptophan-derived neurotransmitter, are highly linked to depression.[29] Although we did not find any difference of serotonin levels between the AD group and the control group, other altered metabolites in tryptophan pathway suggest that this network may be involved in the pathogenesis of AD. Dopamine and its metabolites are well studied as emotion-related neurotransmitters.[16] However, a recent research shows that dopamine also acts as an important regulator of immune function.[30] In the present study, we found that patients with AD exhibited elevated levels of circulating dopamine and its levels decreased following anti-inflammation treatment. Therefore, the role of dopamine in the neuroimmune mechanisms of AD would be an interesting inquiry for further investigations.

So far, the relevant biomarkers of dCBT are poorly identified. Taurine is a classic neuromodulator that protects the nervous system.[31] Circulating taurine has been found dramatically decreased in depression and dementia.[32-34] We observed that additional dCBT yield elevated levels of taurine, suggesting that taurine might be a potential biomarker for dCBT application in the context of AD. L-tyrosine is a precursor to produce dopamine. It has been found that L-tyrosine can help improve cognitive performance under stress conditions.[35] However, although

we revealed that levels of L-tyrosine were significantly decreased in patients with AD compared with healthy controls, the high levels of L-tyrosine appear to imply poor responses of additional dCBT. Taken together, more research is still needed to establish the role played by specific neurotransmitters in adjuvant dCBT for AD treatment. Meanwhile, in addition to those classical neuropeptides like B-type natriuretic peptide and substance P that contribute to itch biology and immune regulation, it would be intriguing to do fundamental and translational studies on the function of emotional-related neurotransmitters in AD.

In conclusion, dCBT in addition to standard anti-inflammation therapy for patients with AD significantly improved emotional distress and itch intensity. dCBT provides an acceptable and efficacious supplementary approach for AD accompanied by negative emotions. Emotion-related neurotransmitters likely contribute to AD and may serve as indicators for the treatment effects. However, to confirm the effectiveness of dCBT for skin diseases in a wide patient population, more large-scale clinical trials are still required.

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Author contributions

- WZ, HM and FW designed and conceptualized the studies and provided administrative, technical, or material support.
- RT, YG and HS assisted in statistical analysis and technical support.
- WZ and FW wrote the manuscript, performed data analysis and had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
- FW acquired funding and supervised the research program.
- All of the authors have critically revised the manuscript for data acquisition, analysis, and interpretation.

Conflict of interest

All authors declare that they have no relevant conflicts of interest.

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