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Attribution Retraining Group Therapy and SSRIs Affect Differing Facets of Anxiety Among Chinese Patients with Various Diagnoses: A Single-Center, Prospective Study

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Abstract

Background: The NIMH launched a Research Domain Criteria (RDoC) initiative, which encouraged researchers to shift from traditional categorical conceptions of mental disorders to process-oriented psychological functions described by constructs. As anxiety was chosen to be one of the constructs in RDoC, the present study aimed to compare different anxiety improvement pattern in clinical setting, because this was important for developing treatment strategies of anxiety under RDoC frame. The study compared potential differences in trajectory of anxiety symptoms improvement in patients with various diagnoses receiving attribution retraining group therapy (ARGT) and those undergoing first-line selective serotonin reuptake inhibitors (SSRI) in clinical care setting.

Methods: Participants were randomly assigned to ARGT (n = 63) or SSRI group (n = 66) group. Patients receiving ARGT had one session per week for 8 weeks. Hamilton Anxiety Scale (HAMA) was measured at 5 sequential time points during treatment.

Results: The results for the HAMA total scores showed only time effect was significant, showing that no significant differences in HAMA total score between ARGT and SSRI. Additionally, both groups over time reduced HAMA score significantly.

Conclusions: The results of the subscales analyses showed that both SSRI and ARGT group had effectively reduced anxiety symptoms. ARGT preferentially targeted on depressive symptoms and behaviour at interview. SSRI preferentially targeted on anxious emotions. Sequences of symptom improvement of two groups were different. Both ARGT and SSRI can effectively reduce anxiety symptoms of patients. The change process and underlying mechanism may differ in the two treatments.

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INTRODUCTION

Anxiety symptoms are very prevalent among patients of psychiatric hospitals in different mental disorders, such as major depressive disorders (MDD) and Obsessive compulsive disorder (OCD). Neuroscientists have found mental disorders share a common neurobiological substrate [1-3]. For example, it was shown in a recent meta-analysis that MDD, and OCD have more similar neural basis than substance use disorders, and bipolar disorder [3].

The NIMH launched a Research Domain Criteria (RDoC) project to create a framework for research on pathophysiology, which ultimately will inform future classification schemes [4]. The RDoC initiative encouraged researchers to shift away from the traditional categorical conceptions of mental disorders to process-oriented psychological functions described by the constructs deduced from bio-behavioural researchers [5, 6]. As a kind of potential threat, anxiety was chosen to be one of the constructs in negative valence systems domain in the RDoC matrix [6]. Research treatment outcome using the the RDoC frame can help further understanding and development of treatment strategies for anxiety.

Psychotherapy and medication are two well-established treatments for anxiety symptoms. Many studies have indicated the efficacy of SSRI and benzodiazepines in improving anxiety symptoms [7-12]. The first-line non-pharmacological treatment of the three mental illnesses is cognitive-behaviour therapy (CBT) [7-9]. Similar to SSRI, CBT has been shown to be an effective treatment on

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alleviation of anxiety symptoms [1, 13, 14].

Study has revealed the effectiveness of SSRIs on comorbid anxiety symptom in MDD patients and anxiety symptoms is related to treatment outcomes of depression [15]. Likewise, it has also been found that anxiety symptoms is also associated with OCD treatment outcome [16] in psychotherapies. Despite the intriguing roles of anxiety in treatment course of MDD and OCD, few studies have examined change patterns of anxious symptoms across these conditions. Also, transdiagnostic nature of anxious symptoms across MDD and OCD, it is interesting to compare session-by-session changed pattern of anxiety symptoms between CBT and medication, so as to develop strategy to better target anxious sub-symptoms in either single disorder or comorbid mental disorders.

Causal attribution about MDD affects many aspects of patients, such as seeking help and treatment preferences [17, 18]. Attribution retraining (AR) is one of a number of therapeutic approaches classified as CBT, which is designed to change maladaptive attributional styles to more adaptive ones [19]. We can try AR in psychotherapy to change the attributional style of depression patients which is not self-serving, thus improving patients' welling-being [20]. Attributional style is a crucial cognitive factor that associates with MDD and GAD patients [21-23]. By restructuring participants' self-defeating attribution tendency into a more self-helping one [19], AR treatments have been found to be effective for alleviating depression and anxiety symptoms [24-26].Wang and Zhang have developed and thus consistently demonstrated that ARGT is an effective treatment [24, 27] consistently shown that on anxiety symptom reduction, enhancement of psychosocial functioning, and neurological change among clinical outpatients with different diagnosis [24, 28].

Previous research comparing psychotropic medication intervention, particularly SSRI, and CBT haves focused on potential differences in efficacy [13, 29, 30] Here, the current research aimed to examine different characteristics and sequences of symptom change for the two treatment approaches. The objective was to understand the targets of each treatment across time, as such knowledge may inform a more personalized approach to clinical care for anxiety symptoms. Using symptoms measured by the seven subscales of HAMA, we hypothesized that ARGT and medication (SSRI or SSRI plus benzodiazepines) would preferentially target different subscale symptoms and have different sequences of symptom change.

METHODS

Ethics approval for this study was obtained from the ethics committee of Nanjing Brain Hospital (2012 Ethic review KY005), Nanjing Medical University (China) prior to recruitment. Written informed consent was also obtained from all participants at recruitment.

Participants

129 outpatients in a psychiatric hospital in Nanjing met the DSM-IV criteria for MDD (N=45), GAD (n=45) or OCD (N=39) based on Structured Clinical Interview for DSM-IV Axis I disorders, patient edition (SCID-I/P, Version 2.0, 29) were randomly allocated into the ARGT or the SSRI groups. Details of the subjects are shown in figure 1. The exclusion criteria were: 1) neurological disease; 2) severe physical illness (e.g. heart, lung, liver, kidney or blood system disease); 3) drug or alcohol abuse; 4) psychotic symptoms; 5) personality disorders; 6) pregnancy; 7) suicidal risk; 8) under antidepressants treatment or other psychotropic medicine within 6 months prior to the trial. The diagnoses were performed by consultant psychiatrist in the hospital.

The termination criteria were: 1) absence in psychotherapy or non-adherence to medicine treatment for two consecutive weeks or more; 2) serious adverse events due to the treatments; 3) suicide attempts in the past year; 4) serious physical illness or infectious diseases during the course of the treatment; 5) pregnancy; 6) withdrawal of informed consent.

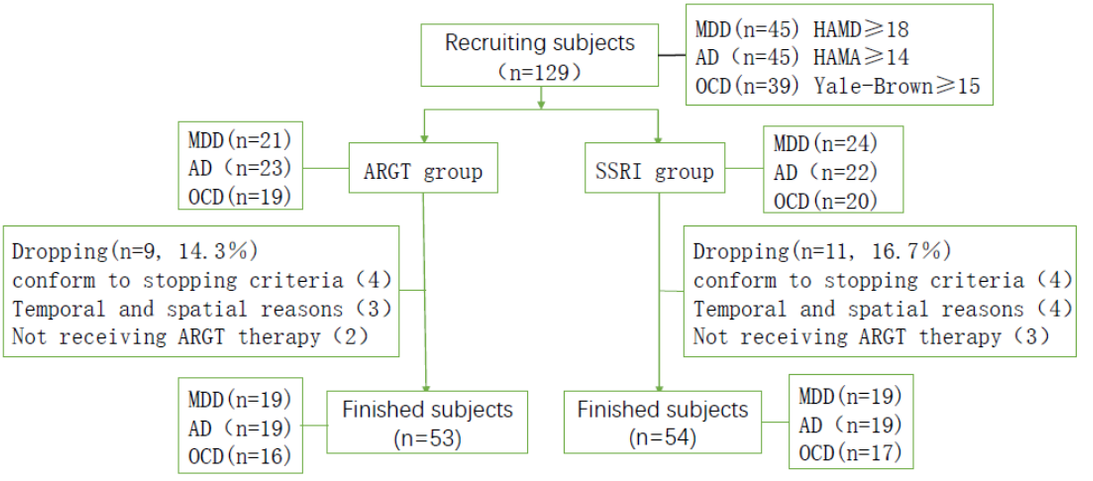

Figure 1. Flow chart of subjects

Design

A prospective case-control study design was used. Outpatients with MDD, GAD and OCD were sequentially allocated into the ARGT group or SSRI group by a block randomization with a block size of 8 (since there are 8 patients in each ARGT group). Response to treatment in subjects in both groups was assessed with symptomatology scales.

Measures

The 14-item Hamilton Anxiety Scale (HAMA) (1959) was used to measure severity of anxiety symptoms at five sequential time points during treatment, which are baseline, week 2, week 4, week 6 and week 8. HAMA is not only also widely used in China as other-rating scales in clinics and researches, but also developed seven new subscales. To assess different symptom cluster better, we developed seven subscales by exploratory and confirmatory factor analytic approaches [24]. The seven subscales by exploratory and confirmatory factor analytic approaches are: (1) anxious emotion including items1, 2, 3; (2) depressive symptoms including items 4, 5, 6; (3) somatic nervous symptoms including items 7, 8; (4) internal organ symptoms including items 9, 10, 11; (5) genito-urinary symptoms measured by item 12; (6) autonomic symptoms measured by item 13; and (7) behavior at interview measured by item 14 [24]. In current study, the inter-rater reliability of HAMA in Chinese version is 0.93 and the authenticity coefficient is 0.92.

The assessments were single blinded. Scores of HAMA were rated separately by two psychologists who did not know which group patients came from. All staff administering the assessments were provided with professional training specific to the assessments for more than 1 month prior to the commencement of the study. The Spearman correlation coefficient between the two psychologists was 0.835.

Demographic data (age, gender, marital status, education level, family environment) and clinical characteristics (onset, stressful life events, course of disease, psychotropic medications history, psychotherapy history, family history, physical illness history) were also collected at the time of recruitment.

TREATMENTS

ARGT Group

This group received two hour once a week of ARGT for consecutive 8 weeks according to a previously validated protocol [27]. Medications were withheld for the duration of the ARGT. Participants were allocated into different ARGT subgroups according to the sequence of enrollment into the study, with 7~8 patients allocated in each ARGT subgroup. Within a structured therapy protocol, each session focused on a specific topic. The topics were: 1) knowing and supporting each other and cognitive-behavioral model; 2) the meaning of symptoms and the effects of cognitive factors; 3) the role of attribution in psychology; 4) participants' upbringing and basic beliefs; 5) rebuilding attributional styles and practicing new behaviors; 6) consolidating new attribution styles and behaviors; 7) self-esteem, personality and attributions for positive events; 8) sharing future plans and discussing leaving. Relaxation training was used in each session [24, 27]. ARGT was performed by two qualified psychotherapists in each ARGT group. Each ARGT subgroup had a supervised session by one of the psychologist supervisors at least once every two weeks.

SSRI Group

Patients in the SSRI group were provided with the usual clinical pharmaceutical care only, with all patients prescribed one SSRI antidepressant, including fluoxetine, paroxetine, sertraline, citalopram or fluvoxamine. Choice of SSRI prescribed was based on patients' symptoms and tolerance. As part of the usual care, patients treated with SSRI may also have been prescribed benzodiazepine medication, including lorazepam, alprazolam and clonazepam; These data were unavailable regarding specific patients who may have been taking both SSRI and benzodiazepines. Thus, we considered the SSRI group to comprise patients taking SSRI or SSRI plus benzodiazepine. The medication was monitored by two psychiatrists experienced in the use of SSRI and anxiolytics. Participants in this group did not receive psychotherapy during the trial.

Statistical Analysis

All continuous variables were tested using Kolmogorov-Smirnov *Z* test for normal distribution and Levene test for homogeneity of variance. Non-parametric tests were used for non-normal and non-homogeneity variance data. Normal and homogeneity variance data were tested before *t* test. Linear mixed effect regression is used to test the interaction effect of group and time on HAMA. Reduction rates were calculated on each symptom of HAMA to examine the sequence of anxiety symptoms change in each group. A reduction rate = (subscale score at a given time point – subscale score at the last time point of this subscale) / subscale score at the last time point of this subscale. All analyses were performed in Statistical Package for the Social Sciences (SPSS) for Windows 15.0 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline Data

Among 129 subjects, 109 subjects completed the 8 weeks' treatment with 9 outpatients in ARGT group (14.3%) and 11 outpatients in SSRI group (16.7%) dropping out. The dropout rate between the two groups was not statistically significant (14.3% Versus 16.7%, x^2=0.139, p=0.709).

The demographic and clinical characteristics of the 109 outpatients at baseline were collected and compared between ARGT group and SSRI group (table 1.). The two groups were comparable in all variables, including age, gender, marital status, educational level, diagnosis, onset of illness, stressful life events, course of disease, psychotropic medications history, psychotherapy history, family history as well as physical illness history (all p>0.05). Baseline scores of HAMA of two groups showed no significant difference (p>0.05).

Table 1. Demographic and clinical characteristics of ARGT and SSRI groups

	ARGT(*n*=54)	SSRI (*n*=55)	Statistics	*p* value
Age, years			0.087[a]	0.768
	29.31±9.78	30.95±10.18	-0.853[b]	0.396
Gender, *n*				
Males	24(44.4%)	26(47.3%)	0.088[c]	0.767
Females	30(55.6%)	29(52.7%)		
Marital status, *n*				
Married	23(42.6%)	29(52.7%)	1.632[d]	0.547
Never married	29(53.7%)	23(41.8%)		
Divorced or Widowed	2(3.7%)	3(5.4%)		
Educational level, *n*				
<9 years	3(5.6%)	8(14.5%)	4.304[c]	0.230
9-12 years	12(22.2%)	15(27.3%)		
12-16 years	33(61.1%)	24(43.6%)		
>16 years	6(11.1%)	8(14.5%)		
Diagnosis, *n*				
MDD	19(35.2%)	19(34.5%)	0.021[c]	0.989
GAD	19(35.2%)	19(34.5%)		
OCD	16(29.6%)	17(30.9%)		
Onset, *n*				
First	38(70.4%)	30(54.5%)	2.908[c]	0.088
Recurrence	16(29.6%)	25(45.5%)		
Stressful life events, *n*				
Yes	44(81.5%)	43(78.2%)	0.184[c]	0.668
No	10(18.52%)	12(21.8%)		
Course of disease, *n*				
≤1 year	13(24.1%)	24(43.6%)	5.047[c]	0.080
1~10 years	33(61.1%)	23(41.8%)		
≥10 years	8(14.8%)	8(14.5%)		
Psychotropic medications history, *n*				
Yes	24(44.4%)	27(49.1%)	0.236[c]	0.627
No	30(55.6%)	28(50.9%)		
Psychotherapy history, *n*				
Yes	12(22.2%)	8(14.5%)	1.072[c]	0.301
No	42(77.8%)	47(85.5%)		
Family history, *n*				
Yes	13(24.1%)	10(18.2%)	0.074[c]	0.785
No	41(75.9%)	45(81.8%)		
Physical illness history, *n*				
Yes	16(29.6%)	15(27.3%)	0.568[c]	0.451
No	38(70.4%)	40(72.7%)		

a: Levene test; b: *t* test; c: Pearson Chi-Square test; d: Fisher's exact test; MDD: major depressive disorder; AD: anxiety disorder; OCD: obsessive-compulsive disorder; ARGT: Attributional retraining group therapy; SSRI: Selective serotonin reuptake inhibitors

Linear mixed-effect modeling of HAMA scores in five time-points

Linear mixed-effect model is based on restricted maximum likelihood (REML) methods. Treatment methods (group), time-points and interaction of group and time (group*time) were treated as fixed effects on outcomes, baseline scores and differences in courses of psychiatric conditions between two groups were covariates and random variables.

The Results of mix-effect linear model test of fixed effects are shown in Table 2. The results revealed no significant difference of HAMA total scores between the two groups after controlling baseline scores and course of disease.

Table 2. Mixed effect on total scores of HAMA

Time points	ARGT		Medication		*F* (group)	*F* (time points)	*F* (group × time points)
	n	$\bar{x}\pm s$	*n*	$\bar{x}\pm s$			
Baseline	63	19.89±7.08	66	20.33±5.59	0.384 (*P*=0.536)	222.535 (*P*=0.000)	1.071 (*P*=0.372)
2 weeks	60	14.52±5.43	64	12.13±5.74			
4 weeks	57	9.46±4.77	61	8.49±4.58			
6 weeks	56	5.57±3.67	59	5.92±3.50			
8 weeks	54	2.93±2.37	55	4.36±3.48			
EMM	10.474		10.233				

HAMA: Hamilton anxiety scale; EMM: mixed effect model

Table 3. Mixed –effect linear model on scores of each subscales at post-treatment

Variables	*EMM* 1	*EMM* 2	*F* (group)	*F* (time)	*F* (group * time)
Anxious emotion	1.129	0.940	18.075***(1>2)	121.146***	4.843**
Depressive symptoms	0.885	0.981	4.869*(1<2)	141.429***	1.779
Behavior at interview	0.685	0.805	8.001**(1<2)	118.006***	1.926
Somatic nervous symptoms	0.557	0.600	0.686	60.556***	2.143
Internal organ symptoms	0.449	0.446	0.004	60.649***	0.131
Genito-urinary symptoms	0.408	0.324	3.098	31.152***	0.752
Autonomic symptoms	0.431	0.494	1.630	37.489***	1.888

1: ARGT group, 2: Medication group; *p<0.05, ** p<0.01, ***p<0.001; EMM: mixed effect model

The mix-effect linear regression of each subscale of HAMA was also performed by using all data from each timepoint. The results are presented in Table 3. As shown seen in Table 3, group effect was significant on scores of depression symptoms and behavior *at interview* suggesting that these two symptoms were significantly lower in patients from ARGT group compared to those in the SSRI group at post treatment. The results from the anxious symptoms showed significant group, time and group x time effects (see table 3) showing that Patients from SSRI group had significantly lower scores on anxious emotion at week 8 than those from ARGT group. We refer to depressed symptom and behavior at interview as "overall preferential factors" of ARGT and anxious emotion as "overall preferential factor" of medication.

Sequences of Improved Symptoms in Argt Group and SSRI Group

To examine the sequence of anxiety symptoms change in each group, reduction rates were calculated on each symptom of HAMA. A reduction rate = (subscale score at a given time point – subscale score at the last time point of this subscale) / subscale score at the last time point of this subscale. *T* test was used to compare the difference of reduction rate between two groups. Kolmogorov-Smirnov *Z* test and Levene test were adopted before independent *t* test on reducing rates of two groups and Mann-Whitney *U* test. The results are presented in table 4. As can be seen in table 4 that at week 2, reduction rates of symptoms for patients in SSRI group were significantly higher than that of patients in ARGT group and other symptoms made no significant difference between the two groups. However, at week 6 and week 8, patients in ARGT group reported significant reduction rates in some symptoms when compared with that of SSRI group and others made no significant difference between the two groups (Table 4).

To further differentiate various anxiety symptoms changes by each group, the following criteria were used to identify "primarily improved symptoms" of each treatment. They were: 1) reducing rates>30% (The rate is self-defined to show statistic changes of each syndrome which is not identical to clinically significant improvement); 2) symptoms which met criteria 1) at the first time in each group; 3) excluding symptoms which met criteria 1) and 2) in both groups at the same time (internal organ symptoms and genito-urinary symptom); 4) excluding symptoms which have already met criteria 1), 2) and 3) in another group.

Based on these criteria, the results showed that no "primarily improved symptoms" emerged in the ARGT group. "Primarily improved symptoms" of SSRI group are anxiety, insomnia, anxious emotion, depression, behavior at interview, somatic and autonomic symptoms at week 2 (underlined in Table 5). The results displayed in Table 4 also showed sequences of anxiety symptom improvement of each group respectively: internal organ symptoms, genito-urinary symptoms (week 2), anxious emotions, depressive symptoms, behavior at interview, autonomic symptoms (week 4), somatic nervous symptoms (week 6) for ARGT group and all seven symptoms improved together at week 2 for SSRI group.

Table 4. Comparison between two groups on reducing rates of subscale value scores of HAMA (%)

	Week 2		Week 4		Week 6		Week 8	
	$\bar{x}\pm s$	Z / t	$\bar{x}\pm s$	Z / t	$\bar{x}\pm s$	Z / t	$\bar{x}\pm s$	Z / t
Reduction rate of anxious emotions								
1	0.16±0.25	-4.357***	0.33±0.34	-0.545*	0.36±0.36	-1.541	0.39±0.53	-2.518*
2	0.37±0.32		0.27±0.41		0.21±0.52		0.00±0.96	
Reduction rate of depressive symptoms								
1	0.25±0.23	-2.597*[a]	0.38±0.30	-1.811	0.74±0.43	-4.113***	0.67±0.49	-1.475
2	0.38±0.28		0.24±0.45		0.10±0.49		0.37±0.56	
Reduction rate of behavior at interview								
1	0.20±0.26	-0.732	0.31±0.44	-0.857	0.46±0.41	-3.058**	0.63±0.52	-1.557
2	0.51±0.40		0.23±0.41		0.20±0.59		0.45±0.42	
Reduction rate of somatic nervous symptoms								
1	0.28±0.35	-4.320***	0.21±0.64	-1.183	0.43±0.45	-1.882	0.65±0.44	-2.853**
2	0.61±0.37		0.35±0.50		0.16±0.55		0.32±0.42	
Reduction rate of inter organ symptoms								
1	0.37±0.34	-1.027	0.40±0.45	-0.049	0.56±0.41	-0.164	0.50±0.49	-0.254
2	0.46±0.49		0.29±0.75		0.56±0.46		0.40±0.65	
Reduction rate of genito-urinary symptoms								
1	0.33±0.40	-0.933	0.42±0.56	-0.844	0.46±0.46	-2.265	0.70±0.48	-1.130
2	0.44±0.54		0.54±0.58		0.86±0.32		0.83±0.58	
Reduction rate of autonomic symptoms								
1	0.25±0.41	-1.637	0.43±0.54	-0.596	0.47±0.51	-0.101	0.64±0.50	-1.300
2	0.42±0.48		0.38±0.48		0.46±0.50		0.81±0.49	

1: ARGT group, 2: Medication group; *p<0.05, ** p<0.01, ***p<0.001; Z: Kolmogorov-Smirnov Z test; t: Independent-Samples T Test

Table 5. Reducing rates of HAMA subscales – Identification of "relatively primarily effected symptoms" of two groups(%)

	ARGT group ($\bar{x}\pm s$)				SSRI group ($\bar{x}\pm s$)			
	Week 2	Week 4	Week 6	Week 8	Week 2	Week 4	Week 6	Week 8
Anxious emotions		0.33±0.34			0.37±0.32			
Depressive symptoms		0.38±0.30			0.38±0.28			
Behavior at interview		0.31±0.44			0.51±0.40			
Somatic-nervous symptoms			0.43±0.45		0.61±0.37			
Internal organ symptoms	0.37±0.34				0.46±0.49			
Genito-urinary symptoms	0.33±0.40				0.44±0.54			
Autonomic symptoms		0.43±0.54			0.42±0.48			

Underline indicates that the symptom of this subscale in HAMA is the relatively primarily effected symptoms

DISCUSSION

The main findings of the article are as follows: (1) SSRI group showed significantly greater symptom improvement than ARGT group at week 2. However, the reverse trend was observed occurred at week 6 and week 8 (Table 3). (2)"Overall preferential factors" of ARGT group were depressive symptoms, behavior at interview. Anxious emotions were identified as "overall preferential factors" by SSRI (Table 2). (3) No "Primarily improved symptoms" was identified in ARGT group. Symptoms of anxious emotions, depressive symptoms, behavior at interview, somatic nervous symptoms, autonomic symptoms were identified as "Primarily improved Symptoms" by SSRI (Table 4). (4) Sequences of anxiety symptoms improvement by ARGT were internal organ symptoms, genito-urinary symptoms (week 2); anxious emotions, depressive symptoms, behavior at interview, autonomic symptoms (week 4); somatic nervous symptoms (week 6). Sequences of symptoms improvement by SSRI: all seven symptoms are improved at week 2 (Table 4.)

Consistent with previous studies, our results showed the effects of SSRI, particularly SSRI on anxiety symptoms

in patients with MDD, GAD, OCD [7-12]. And our findings indicated that the treatment effect of ARGT was equivalent to SSRI, further supporting the efficacy of ARGT on anxiety symptoms in MDD, AD, OCD patients [24, 25, 31]. However, the current study contributed new information regarding the differential symptom targets and change sequences of the two treatments over time.

Firstly, the effect of SSRI on anxiety symptom reduction occurred earlier than ARGT. the benefit of ARGT occurred at the end of week 6 and 8, when the overall symptom score in ARGT was reduced to the same level as that observed in the SSRI group (see figure 2). The different courses of each treatment can be attributed to the quick and direct effect of SSRI on 5 – HT and benzodiazepines on GABA, as well as other neurotransmitters relevant to anxiety symptoms. While therapeutic process of ARGT is more gradual. During the first four weeks, ARGT focused more on rapport as well as psycho-education instead of other more interventional elements, which were foci of following sessions. Therefore, the effect of ARGT became more apparent at the end of week 6 and 8, which may be explained by pertinent interventions on individuals' cognition and behaviour during weeks 5 and 6. In fact, varied study have identified reduced intolerance of uncertainty and cognitive diffusion as active treatment components for anxious symptoms in psychotherapies [32, 33].

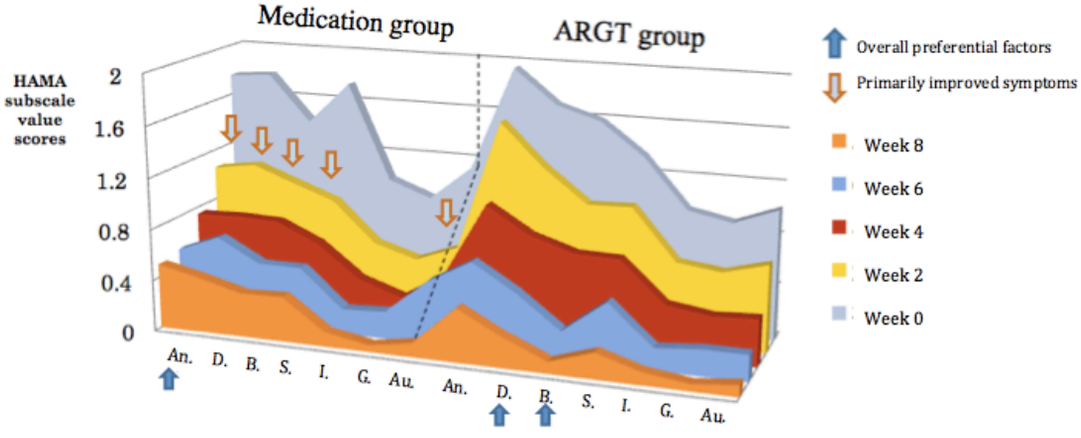

Figure 2. This area graph shows the changes of the HAMA subscale value scores for different symptoms with time by medication and ARGT. For illustration purposes, subscales were standardized for comparison (calculated as subscale ratio score = subscale score / total score of this subscale). The vertical axis is the HAMA subscale value scores and the horizontal axis is subscales of two groups: An = Anxious emotions, D=Depressive symptoms, B= Behavior at interview, S= Somatic-nervous symptoms, I= Internal organ symptoms, G= Genito-urinary symptoms, Au = Autonomic symptom. Different color shows different time from week 0 to week 8.

Secondly, ARGT preferentially targeted on depressive symptoms and behaviour at interview, while SSRI targeted on anxious emotions comparatively. Specifically, depressive symptoms included depressed mood, insomnia and cognitive symptoms. Behaviour at interview indicated overall mental illness state and cognitive functioning when patients' presenting themselves in front of doctors. Since ARGT focuses on cognitive and behaviour modification, it was easy to understand why it preferentially targeted on symptoms related to cognitive and behaviour. This finding was consistent with an extensive body of research on CBT for depression, for example large effect size was found for depression symptoms [13]. It is widely acknowledged that prefrontal lobe plays an important role in cognitive function [34]. The dorsolateral prefrontal and anterior cingulate cortex is viewed the main centre of cognitive control [35, 36]. Effects of CBT was predicted by enhanced pre-treatment activation in dorsal anterior cingulate cortex, and dorsal prefrontal cortex during threat processing [37, 38]. Our previous research supported CBT may work via up – regulation function of cognitive control system in brain [39].

Comparatively, medication preferentially targeted on anxious emotions. The core limbic regions, such as amygdala and ventral striatum, response immediately to a potential threat [40-42], which will lead to anxious emotion directly. Research suggests that SSRI act on raphe nuclei, locus coeruleus, hippocampus and hypothalamus preliminarily, followed by changes in the cortex [43]. Neuroimaging studies also support changes from subcortex to cortex by SSRI [44]. By comparing preferential symptoms of two treatments, it can be postulated that effect of ARGT may involve brain regions that of frontal lobe cortex and medication may target limbic system, a crucial part of emotional response.

Finally, this study found different sequences of anxiety

symptoms improvement for ARGT and SSRI. Seven anxiety symptoms improved together at week 2 in SSRI group. This rapid effect was given by the direct effects of the pharmaceuticals on physiological pathways, including the 5-HT and GABA activity. While ARGT group showed a gradual improvement process with internal organ symptoms, genito-urinary symptoms (week 2), followed by anxious emotions, depressive symptoms, behaviour at interview, autonomic symptoms (week 4), and then somatic nervous symptoms (week 6).

The components of ARGT may explain these findings. First, relaxation training and other behavioural skills were implemented in ARGT in the first session and practiced throughout treatment course. Previous studies have indicated that relaxation training can improve heart rate and blood pressure in patients with anxiety disorders [45]. Additionally, at week 2, participants discussed attribution of physical symptoms. Physical attribution is common among patients with somatic symptoms, which can worsen the psychological experiences of symptoms and lead to escalatinge fear of disease and resistance against somatic symptoms [46]. Interventions targeted at physical sensory attribution may play important role in reducing anxiety [47]. Psychotherapists encouraged participants to find psychological meaning in physical symptoms while paying less attention on them. This could explain why ARGT reduced somatic symptoms at week 2. Cognitive and behavior skills were intensively used during the third and fourth weeks. Thus, it was not surprising that emotion and behavior symptoms improved at week 4. Although slower than SSRI, most symptoms were effectively reduced at week 4 in ARGT group. Somatic nervous symptoms, involving muscular system and sensory system, reduced significantly until week 6. We speculated that was because symptoms in peripheral nerves system improved followed by improvement of prefrontal lobe cortex, on which ARGT targeted mainly as we discussed above.

Thus, these findings indicated clinical implications that Medication (SSRI, benodiazepines) and CBT (ARGT) may have different effectiveness for different patients with different symptoms. Patients characterized primarily by depressive symptoms and behavior at interview may be most benefitted by CBT, whereas patients whose anxiety were characterized primarily by anxious emotions may be benefitted most by antidepressants and/or anxiolytics. Findings also indicated that depending on patients' primary complaints, temporal ordering of combined treatment (SSRI and CBT) may be worth considering.

Noteworthy in this study, we investigated anxiety symptoms in patients with various diagnoses under the RDoC frame. This design by no means influenced effect or study aims whether for psychotherapy or medication. In fact, clinicians did not choose treatments for anxiety based on diagnoses, but on clinical characteristics in clinical care. CBT, ARGT, SSRI and benodiazepines were all used in MDD, GAD and OCD generally. Imaging researches found mental disorders share a common neurobiological substrate [1-3]. Further, a recent meta-analysis showed MDD, GAD, OCD have more similar neural basis than psychotic disorder, substance use disorders, and bipolar disorder [3]. Imaging outcomes matched with clinical treatments strategies, which both supported that clinical implications from transdiagnostic data are meaningful.

One limitation of the current study was that we did not have information regarding how many patients were using both SSRI and benzodiazepines. In this study, we considered the SSRI group to comprise patients taking SSRI or SSRI plus benzodiazepine. Thus, it was unclear to what extent benzodiazepine influenced outcomes, in particular, regarding the faster effect of medication. Another limitation was restricted measures of anxiety (behavior unit of analysis in DRoC matrix) used in this study. We only used the anxiety scale to investigate changes in anxiety symptoms in the three groups of patients, but did not explore their corresponding brain mechanisms. Therefore, the corresponding mechanism in neurological level (circuit unit of analysis in DRoC matrix) cannot be confirmed. Hence, other units of analysis are required in further study to understand anxiety and develop treatment Strategy.

In summary, this study confirmed that both ARGT and SSRI were effective in reducing anxiety symptoms of patients with MDD, GAD or OCD. The present results indicated that the change processes and underlying mechanisms differed in the two treatments. SSRI effect was more rapid and ARGT group experienced a gradual treatment course. ARGT preferentially targeted on depressive symptoms and behavior at interview, and SSRI targeted on anxious emotions comparatively. Greater attention to symptom improvement sequences and primary targets by psychotherapies and SSRIs may help tailor treatments to improve psychiatric treatment efficacy.

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