Differential Change in Depressive Symptoms during Psychotherapy and Medication in Clinical Care

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ABSTRACT

The study aimed to compare potential differences in trajectory of depressive symptoms improvement between patients receiving attribution retraining group therapy (ARGT) and those undergoing first-line depression medication in clinical care. Participants were randomly assigned to ARGT (n = 63) and medication (n = 66) group. Patients in ARGT group received group therapy one session a week for 8 weeks, while patients in medication group took medication normally. Hamilton Depression Scale was measured for all participants at 5 sequential time points during the process. A mixed-effects linear model over 5 time points showed no significant differences between two treatments in the total depression scores. Both medication and ARGT had effectively reduced depressive symptoms. However, the pattern of symptoms improvement differed. In detail, ARGT preferentially targeted cognitive disturbance, retardation and hopelessness, while medication preferentially targeted factors related to diurnal variation, moreover, for ARGT, the pattern was weight and diurnal variation (week 2), sleep disturbance (week 4), anxiety, cognition disturbance, retardation and hopelessness (week 6), for medication, was sleep disturbance, anxiety, weight, and diurnal variation (week 2) cognition disturbance, retardation, hopelessness (week 8). The current finding showed ARGT reduced the depressive symptom and improved well-being in a different way, which may further benefit the advancement of precise treatment.

Key Words: Attribution Retraining Group Therapy, Selective Serotonin Reuptake Inhibitors, Depression, Hamilton Depression Scale, Processes of Depressive Symptoms Improvement

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Introduction

Major depressive disorder (MDD), generalized anxiety disorder (GAD) and obsessive-compulsive disorder (OCD) are among most prevalent psychiatric disorders, causing substantial personal or societal cost and increasing health care utilizing while impairing individual social and psychological function. Among commonalities, one shared by all these three conditions is depressive symptom, which is often assessed with Hamilton depression scale (HAMD). Psychotherapy and medication are two well-established treatments for depressive symptom, specifically, as well as the disorders, more broadly. The efficacy of selective serotonin reuptake inhibitors (SSRI) on improving depressive symptom has been largely proved (American Psychiatric Association, 2010; Nutt *et al*., 1999). Cognitive behavior therapy (CBT), as the first-line non-pharmacological treatment, has been empirically proved to be effective for various mental illnesses(American Psychiatric Association, 2010; American Psychiatric Association, 2013; The Canadian Anxiety Guidelines Initiative Group on behalf of the Anxiety Disorders Association of Canada, 2014), more specifically, large effect size for MDD, GAD, OCD (Butler *et al*., 2006).

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Attribution retraining (AR) is one of a number of therapeutic approaches classified as CBT. Attributional style is a crucial cognitive factor that associates with depression and anxiety (Luten *et al*., 1997; Ganellen, 1988). A number of studies have demonstrated a link between maladaptive attributional style and various psychological problems, including depression and anxiety (Haugen *et al*., 2002; Waikar *et al*., 1997; Luten *et al*., 1997). AR is designed to change maladaptive attributional styles to more adaptive ones (Försterling, 1985). By restructuring participants' self-defeating attribution tendency into a more self-helping one (Försterling, 1985), AR-related treatments have been found effective for alleviating depression and anxiety symptoms among various groups (Wang *et al*., 2011; Green-Emrich *et al*., 1991). Moreover, AR is not only regarded as a cognitive alteration, but also an integral part in hopelessness/self-esteem theory proposed by Abramson and associates (Metalsky *et al*., 1993).

Wang and Zhang have developed a group psychotherapy modality based on attribution retraining, which is attribution retraining group therapy (ARGT; Wang *et al*., 2008; Wang *et al*., 2011). ARGT can be classified as one kind of CBT that treats clients' maladjusted emotions and behaviors by changing their unhelpful explanations of life events as well as mitigating stressful symptoms. Several studies have provided supporting evidence for the efficacy of ARGT on depression and anxiety symptom reduction, enhancement of psychosocial functioning, and neurological change among clinical outpatients with MDD, GAD or OCD (Wang *et al*., 2011; Wang *et al*., 2013).

Previous research comparing psychotropic medication intervention, specifically SSRI and CBT has focused on potential differences in efficacy (Butler *et al*., 2006). Here, the current research aimed to identify 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 treatment approach in clinical care for mitigating depressive symptoms. By employing the sub-terms from Hamilton depression scale (HAMD), we hypothesized that ARGT would preferentially target cognitive and related symptoms, including cognitive disturbance and hopelessness, which would be followed by improvements in somatic symptoms (top-down), such as weight change and sleep disturbance. We predicted that first-line depression medication (SSRI, or SSRI plus benzodiazepines, particularly in the case of comorbid anxiety) would first improve somatic symptoms, followed by later improvements in cognitive symptoms (bottom-up).

Method

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

Participants

Participants were clinical outpatients aged 16 to 50 years who met the DSM-IV criteria for MDD, GAD or OCD based on Structured Clinical Interview for DSM-IV Axis I disorders, patient edition (SCID-I/P, Version 2.0, 29). Patients were recruited from a psychiatric hospital in Nanjing, China. The inclusion criteria: 1) MDD group: Scores ≥ 18 on the 24-item version of the Hamilton Rating Scale for Depression (HAMD , Hamilton M, 1960), 2) GAD group: Scores ≥ 14 on the 14-item version of the Hamilton Rating Scale for Anxiety (HAMA, Hamilton M, 1959), 3) OCD group: Scores ≥ 16 on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; Goodman *et al*., 1989), 4)Willing to participate in the study.

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; 9) more than one target diagnosis (e.g., comorbid MDD and GAD or comorbid MDD and OCD).

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) Needs of other special interventions, such as appearance of suicide ideation; 4) serious physical illness or infectious diseases during the course of the treatment; 5) pregnancy; 6) wrong diagnosis; 7) withdrawal of informed consent.

Design

A prospective case-control study design was used. Outpatients with MDD, GAD and OCD were

sequentially allocated into the ARGT group or medication group by a block randomization with a block size of 8 (since there are 8 patients in each ARGT group). Symptomology scale was employed to assess the changes in depressive symptoms that appeared to both groups.

Assessments

The following scales were used to evaluate symptoms:

(1) The 24-item version of HAMD (Hamilton M, 1960) was used for measuring severity of depressive symptoms for MDD, GAD and OCD subjects at five sequential time points during treatment, which are baseline, week 2, week 4, week 6 and week 8. Internal consistency of HAMD in Chinese version is 0.88~0.99 and the authenticity coefficient (reflecting the severity of clinical symptoms) is 0.92. HAMD includes 7 subscales: anxiety, weight, cognition disturbance, diurnal variation, retardation, sleep disturbance, hopelessness. Most of the items of HAMD score 0 to 4 and a small number of items score 0 to 2. The total score of HAMD is the sum of each item score. Different diagnosis (MDD, OCD and GAD) was measured in the same way with the same HAMD.

(2) The 14-item HAMA (Hamilton M, 1959) M and the Y-BOCS (Goodman *et al*., 1989) was used to measure severity of anxiety and obsessive-compulsive symptoms before they enrolled in the study.

The assessments were single blinded. They were rated separately by two professionals who did not know which group the patient 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 coefficients (HAMD, HAMA) between the two psychologists were 0.832 and 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.

Treatment

Patients randomized to the ARGT group were provided with ARGT once a week according to a previously validated protocol (Wang *et al*., 2008). Anti-depressant medications were withheld during the treatment for ARGT group. Each ARGT session lasted two hours and was provided weekly for 8 weeks. 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.

ARGT was performed by two qualified psychotherapists in each ARGT group. The primary psychotherapist led all subgroups and was a registered clinical and counseling psychologist in Professional Organizations and Individual Practitioners in Clinical and Counseling Psychology, Chinese Psychological Society. Various qualified co-psychotherapists assisted the primary group leader in each subgroup. The research objectives were unknown to all co-therapists. Moreover, 4 supervisors who were registered psychologist supervisors in Chinese Psychological Society supervised treatment sessions. Each ARGT subgroup had a supervised session by one of the psychologist supervisors at least once every two weeks. To maintain treatment integrity, the co-psychotherapist also recorded each step of the intervention plan and reported to the main psychotherapist to check prior to the following session.

Patients in medication group were only provided with usual clinical pharmaceutical care, 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. Medications were prescribed from the minimum effective doses up. The initial doses of SSRI were based on recommended minimal effective doses, and were 10mg, 10mg, 50mg, 10mg, and 50mg for each antidepressant, respectively. Dose was re-evaluated at week 2 and adjusted based on clinician's evaluation. After the whole treatment, the average maximum

doses among participants of SSRI were: 20.00±0.00 mg, 24.67±6.40 mg, 87.5±29.46 mg, 26.36±6.74 mg, and 91.07±23.22 mg in order. As part of usual care, patients treated with SSRI may also have been prescribed benzodiazepine medication, including lorazepam, alprazolam and clonazepam; data were unavailable regarding specific patients who may have been taking both SSRI and benzodiazepines. Thus, we consider the medication group to comprise patients taking SSRI or SSRI plus benzodiazepine. The medication was monitored by two clinicians experienced in use of SSRI and anxiolytics. Participants in medication group were not to receive psychotherapy during the whole trial.

Statistical analysis

Baseline demographic data of each group were compared by using χ^2 test for nominal variables and independent-samples *t* test for continuous variables (after Kolmogorov-Smirnov *Z* test and Levene test). All scores of 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. The paired-samples *t* test was used to compare the scores at baseline and week 8 in each group. The independent-samples *t* test was used to compare reduction scores between two groups. Linear mixed effect regression is used to test the interaction effect of group and time on HAMD. Reduction rates were calculated on each symptom of HAMD to identify the sequence of depressive 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 tests were two-tailed with 0.05 as an indication for statistical significance. 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 Date

A total of 129 eligible outpatients with MDD (*n*=45), GAD (*n*=45) or OCD (*n*=39) were enrolled into the study. 63 subjects were randomized to the ARGT group and 66 into the medication group. Of the 129 enrolled subjects, 109 subjects completed the 8 weeks treatment with 9 outpatients in ARGT group (14.3%) and 11 outpatients in medication group (16.7%) dropping out. The dropout rate between the two groups was not statistically significant (14.3% versus 16.7%, χ^2=0.139, *p*=0.709).

Demographic and clinical characteristics of the 109 outpatients were collected when enrolling in this study and compared at baseline (ARGT group to medication group). Results showed that two groups were well matched on all the characteristics examined, 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 HAMD and HAMA of two groups showed no significant difference (*p*>0.05).

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

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

Covariance matrix of fit statistics of model is shown in Table 1. Results of fixed effects from the mixed-effects linear model are shown in Table 2. The results revealed no significant difference in HAMD total scores between two groups after controlling baseline scores and course of disease.

The mixed-effect linear regression of each subscale of HAMD was also performed by using data from ARGT group and medication group at each timepoint. As shown in Table 3, scores on cognition disturbance, retardation, and hopelessness symptoms were significantly lower in patients from ARGT group compared to those in medication group. Patients from medication group had significantly lower scores on diurnal variation than those from ARGT group. We referred to cognition disturbance, retardation, and hopelessness symptoms as “overall preferential factors” of ARGT and diurnal variation as “overall preferential factor” of medication.

Sequences of improved symptoms in ARGT group and medication group

To examine the sequence of depressive symptoms improving for each group, reduction rates were

Table 1. Covariance Matrix of fit Statistic of Mixed Model with Repeated Measures on Overall and Subscale Scores

Variables	-2 Log Likelihood	AIC	AICC	CAIC	BIC
Overall score	3642.768	3652.768	3652.872	3679.627	3674.627
Anxiety	296.563	306.563	306.666	333.421	328.421
Cognition disturbance	152.722	162.722	162.826	189.580	184.580
Retardation	674.567	684.567	684.670	711.425	706.425
Sleep disturbance	423.402	433.402	433.505	460.260	455.260
Hopelessness	947.856	957.856	957.960	984.714	979.714
Weight	201.156	213.156	213.301	245.386	239.386
Diurnal variation	429.396	439.396	439.500	466.254	461.254

Table 2. Mixed Effect on Total Scores of HAMD

Time points	ARGT		Medication		*F* (group)	*F* (time points)	*F* (group ×time points)
	n	*x±s*	*n*	*x±s*			
Baseline	63	23.27±8.23	66	25.77±7.04	2.652 (*P*=0.104)	284.355 (*P*=0.000)	2.080 (*P*=0.084)
2 weeks	60	18.17±6.89	64	17.42±6.48			
4 weeks	57	13.25±6.29	61	12.18±5.41			
6 weeks	56	7.23±3.92	59	8.86±4.77			
8 weeks	54	3.89±2.61	55	4.84±2.92			
EMM	13.061		13.815				

Table 3. Mixed – Effect Linear Model on Scores of Each Subscales at Post-Treatment

Variables	*EMM* (ARGT)	*EMM* (Medication)	*F* (Group)	*F* (Time)	*F* (Group * time)
Anxiety	0.662	0.625	2.018	156.929***	2.148
Cognition disturbance	0.463	0.523	6.932**(1<2)	146.001***	2.640
Retardation	0.710	0.839	14.155***(1<2)	128.681***	1.994
Sleep disturbance	0.315	0.288	0.836	40.663***	1.189
Hopelessness	0.829	0.954	7.594**(1<2)	96.378***	2.275
Weight	0.058	0.095	2.434	18.342***	1.175
Diurnal variation	0.299	0.138	27.986***(1>2)	27.899***	5.667***

Note. 1: ARGT, 2; Medication

calculated on each sub-symptom of HAMD. 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 reduction rates of two groups and Mann-Whitney *U* test. Results indicated that at week 2, reduction rates of some symptoms for patients in medication 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 medication group and others made no significant difference between the two groups (Table 4).

To further identify the differences in depressive symptom improving in each group, criteria were used to identify "primarily improved symptoms" of each treatment, which included 1) reduction rate>30%; 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 (weight and diurnal variation symptoms); 4) excluding symptoms which have already met criteria 1), 2) and 3) in another group (sleep disturbance and anxiety of ARGT group and cognition disturbance, retardation and hopelessness of medication group).

Based on these criteria, results showed that "primarily improved symptom" of ARGT group were cognition disturbance, retardation and hopelessness at week 6. "Primarily improved symptom" of medication group were anxiety and sleep disturbance at week 2 (underlined in Table 5). Results displayed in Table 5 also showed sequences of depressive symptom improvement in each group respectively: weight, diurnal variation (week 2), sleep disturbance (week 4) and anxiety, cognition disturbance, retardation, hopelessness (week 6) for ARGT group; sleep disturbance, anxiety, weight, diurnal variation

Table 4. Comparison between Two Groups on Reduction Rates of Subscale Scores of HAMD (%)

	Week 2		Week 4		Week 6		Week 8	
	$x\pm s$	Z/t	$x\pm s$	Z/t	$x\pm s$	Z/t	$x\pm s$	Z/t
Reduction rate of anxiety								
1	0.23±0.23	-2.815**[a]	0.18±0.39	-1.975*	0.35±0.29	-1.012	0.38±0.43	-0.284
2	0.37±0.30		0.32±0.31		0.26±0.47		0.32±0.57	
Reduction rate of cognition disturbance								
1	0.17±0.23	-2.176*	0.29±0.34	-0.628	0.46±0.45	-2.932**	0.74±0.38	-3.059**
2	0.26±0.32		0.21±0.47		0.24±0.46		0.52±0.35	
Reduction rate of retardation								
1	0.18±0.27	-2.623**	0.28±0.31	-0.299	0.46±0.41	-2.621**	0.63±0.52	-2.643**
2	0.27±0.23		0.27±0.41		0.20±0.59		0.45±0.42	
Reduction rate of sleep disturbance								
1	0.28±0.35	-4.208***	0.49±0.51	-1.140	0.53±0.52	-1.179	0.29±0.43	-1.342[a]
2	0.61±0.37		0.64±0.42		0.36±0.59		0.57±0.62	
Reduction rate of hopelessness								
1	0.20±0.27	-1.087	0.23±0.33	-0.526	0.42±0.50	-3.236**	0.63±0.44	-2.065*
2	0.22±0.29		0.18±0.37		0.19±0.44		0.43±0.44	
Reduction rate of weight								
1	0.53±0.51	-0.309	0.71±0.49	-0.786	1.00±0.00	1.581[a]	0.50±0.71	0.000[a]
2	0.58±0.49		0.53±0.52		0.67±0.52		0.50±0.71	
Reduction rate of diurnal variation								
1	0.36±0.53	-0.208	0.48±0.51	-1.611	0.75±0.43	-1.540	0.86±0.38	-0.845
2	0.39±0.48		0.72±0.45		0.45±0.50		0.67±0.50	

Notes. [a] *t* test; 1: ARGT, 2: Medication

Table 5. Reduction rates of HAMD Subscales - Identification of "Relatively Primarily Effected Symptoms" of Two Groups (%)

	ARGT group ($x\pm s$)				Medication group ($x\pm s$)			
	Week 2	Week 4	Week 6	Week 8	Week 2	Week 4	Week 6	Week 8
Anxiety			0.35±0.29		0.37±0.30			
Cognition disturbance			0.46±0.45					0.52±0.35
Retardation			0.46±0.41					0.45±0.42
Sleep disturbance		0.49±0.51			0.61±0.37			
Hopelessness			0.42±0.50					0.43±0.44
Weight	0.53±0.51				0.58±0.49			
Diurnal variation	0.36±0.53				0.39±0.48			

(week 2) and cognition disturbance, retardation, hopelessness (week 8) for medication group.

Summary of results (Fig. 1):

(1) Medication group showed significantly greater symptom improvement than ARGT group at week 2. However, the reverse trend was observed at week 6 and week 8 (Table 4).

(2) "Overall preferential factors" of ARGT group were cognition disturbance, retardation and hopelessness and "overall preferential factors" of medication group were diurnal variation subscales (Table 3).

(3) "Primarily improved symptoms" of ARGT group were cognition disturbance, retardation and hopelessness. Symptoms of sleep disturbance and anxiety were identified as "Primarily improved symptoms" by medication (Table 5).

(4) Sequences of depressive symptoms improvement by ARGT were weight, diurnal variation (week 2) → sleep disturbance (week 4) → anxiety, cognition disturbance, retardation, hopelessness (week 6). Sequences of symptoms improvement by medication: sleep disturbance, anxiety, weight, diurnal variation (week 2) → cognition disturbance, retardation, hopelessness (week 8) (Table 5)

Discussion

Consistent with an extensive body of researches from clinical psychopharmacology, our findings further proved the efficacy of medication, more specifically, SSRI, on MDD, GAD, OCD (American Psychiatric Association, 2010; American Psychiatric Association, 2013; The Canadian Anxiety Guidelines Initiative Group on behalf of the Anxiety Disorders Association of Canada, 2014; Nutt *et al.*, 1999; Ballenger, 2002).

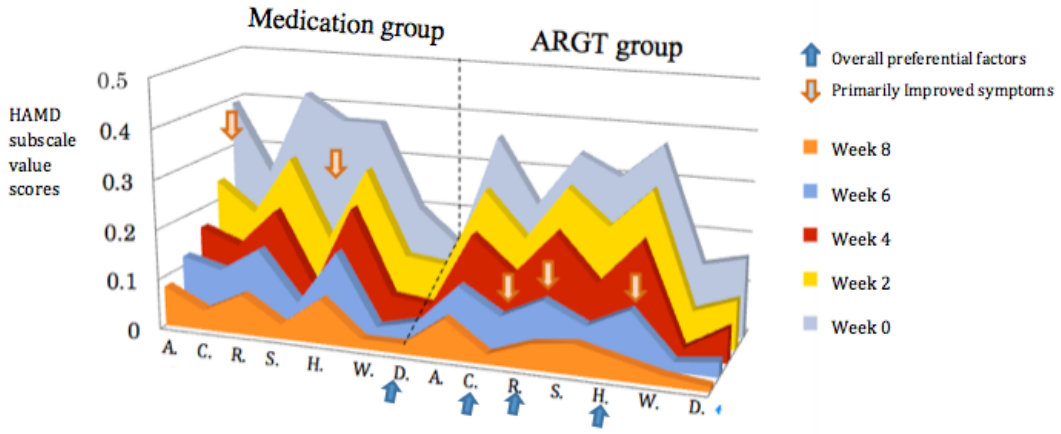

Figure. 1 This area graph shows the changes of the HAMD subscale ratio scores for different symptoms with time by medication and ARGT. For illustration purposes, subscales were standardized for comparison (calculated as subscale ratio score = subscale score / total score of this subscale). The vertical axis is the HAMD subscale ratio scores and the horizontal axis is subscales of two groups: A. = Anxiety, C. = Cognition disturbance, R. = Retardation, S. = Sleep disturbance, H. = Hopelessness, W. = Weight, D. = Diurnal variation. Different color shows different time from Week 0 to Week 8

More importantly, our findings also supported that a comparable efficacy of CBT, more specifically, ARGT, on reducing depressive symptom for patients with MDD, GAD or OCD (Wang *et al*., 2011; Green-Emrich *et al*., 1991; Dieser *et al*., 2002; Zhang *et al*., 2010). Other than that, the current study contributed a brand-new insight concerning the depressive symptom improvement pattern of ARGT and medication.

First of all, although the overall symptom score in ARGT group was reduced to the same level as that for in medication group, the effect of medication on depressive symptom reduction occurred earlier than that of ARGT. Specifically, medication group showed significantly greater symptom improvement at week 2, while for ARGT group, that occurred at week 6 and week 8. The temporal difference brought by two treatments may likely reflect on the differential mechanism that underlies each treatment. In detail, medication directly modulated the level of 5-HT and other depressive symptoms-related neurotransmitters, while ARGT is a more gradual process. ARGT focused more on bonding as well as psycho-education in the first four weeks, instead of other more interventional elements, which are foci in following sessions. So it was reasonable that the effect of ARGT became more apparent at the end of week 6 and 8 than that at week 2, which can be explained by pertinent interventions on individuals' cognition and behavior during week 5 and week 6.

Secondly, in consistency with our hypothesis, ARGT preferentially targeted cognition disturbance, retardation and hopelessness symptoms, and medication targeted diurnal variation symptoms. Cognition disturbance and retardation are both related to the cognitive function and ARGT is characterized by turning the maladaptive attributional styles into more adaptive ones, associating with changes at cognition level. So the effect brought by ARGT on cognition level was likely due to the key feature of ARGT. Moreover, cognition is significantly associated with prefrontal cortex (PFC) (Gläscher *et al*., 2012), Neuroimaging studies suggest that CBT acts on cerebral cortex and PFC (Clark *et al*., 2010; Tan *et al*., 2014). Since AR is based on hopelessness/self-esteem theory (Metalsky *et al*., 1993), it was no wonder hopelessness was one of ARGT's target. Diurnal variation symptom is associated with circadian rhythm, especially different cortisol concentrations during a day (Parker *et al*., 2003), which typically characterizes endogenous depression. Thus, it was not surprising that medication targeted diurnal variation more so than ARGT, given the direct effects of the pharmaceuticals on physiological pathways, including the 5-HT and γ-aminobutyrate activity.

Thirdly, sequence of depressive symptom improvement by ARGT was: in order, weight and diurnal variation (week 2), sleep disturbance (week 4), and anxiety, cognition disturbance, retardation, and hopelessness (week 6), comparatively, Sequence of depressive symptom improvement by medication was: sleep disturbance, anxiety, weight, and diurnal variation (week 2) cognition disturbance, retardation, hopelessness (week 8). Sequence of symptom improvement by medication is consistent with our hypothesis and supported the "bottom-up" mechanism (from subcortex to cortex) of medication, particularly SSRI (Mayberg *et al*., 2000; Goldapple *et al*., 2004). Researches have suggested that SSRI acts

on raphe nuclei, locus coeruleus, hippocampus and hypothalamus preliminarily, followed by changes in the cortex (Mayberg *et al*., 2000).

In contrast with our hypothesis, this study did not find "top - down" regulation by ARGT (Goldapple *et al*., 2004). We hypothesized that ARGT would improve cognitive, somatic and emotional symptoms in order. On the contrary, improvements brought by ARGT in cognition disturbance, retardation, hopelessness were not apparent until week 6, then followed improvements in somatic symptoms. The components of ARGT may explain these findings. First, relaxation training and other behavioral skills were implemented in the first session and practiced throughout the whole treatment course. Previous studies have suggested that relaxation training can improve heart rate and blood pressure in patients with anxiety disorders (Conrad *et al*., 2007). Additionally, at week 2, participants discussed attribution of physical symptoms. Psychotherapists encouraged participants to find psychological meaning attached to physical symptoms, hence reducing excessive focus on them. These could explain why ARGT reduced somatic symptoms at week 2 and week 4. For cognition disturbance, retardation, hopelessness improved at week 6-8, it was speculated that those symptoms' improvements were due to various cognitive and behavioral skills that used. Improvement brought by ARGT is a comprehensive course, although those symptoms are the main targets of ARGT. Although these speculations require further study, they underscore a need to isolate the features of psychotherapy interventions that target specific symptoms over time. As such, treatments may be better tailored to patients.

Thus, these findings suggested clinical implications: Medication (SSRI, benodiazepines) and CBT (ARGT) took effect on depressive symptom reduction in a different way. Patients characterized primarily by cognition disturbance, retardation, and hopelessness may benefit more from CBT, whereas patients whose depressive symptoms are characterized primarily by somatic disturbances, such as sleep disturbance and diurnal variation may benefit more from antidepressants and/or anxiolytics. Findings also suggested that depending on patients' primary complaints, temporal ordering of combined treatment (medication and CBT) may be worth considering.

One limitation of this current study was the smaller subgroups of patients with different diagnoses, precluding analysis by psychiatric disorder. Thus, the effects of medication versus CBT on the symptom improvement process remained to be further studied to optimize treatment protocols. Another limitation was that we did not have information regarding how many patients were using both SSRI and benzodiazepines. Thus, it was unclear to what extent benzodiazepine influenced the outcomes. Future work should address specific somatic symptoms targeted by concurrent use of SSRI and benzodiazepines, as these medications are commonly used in clinical care when depression and anxiety are comorbid.

Conclusion

In summary, this study confirmed that ARGT and medication can each in isolation effectively reduce depressive symptoms of patients with MDD, GAD or OCD, however, in a different pattern, specifically, ARGT preferentially targeted cognitive and related symptoms and medication preferentially targeted physical symptoms. Medication effects suggested a "bottom - up" process: from subcortex at week 2 to cortex at week 8. ARGT outcomes may reflect a different "bottom-up" process: subcortex at week 2 and week 4 to cortex improvement at week 6. Greater attention to symptom improvement sequences and primary targets by psychotherapies and psychopharmaceuticals can help to tailor treatments to improve psychiatric treatment efficacy.

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