Research report

Effects of antidepressant medication on emotion regulation in depressed patients: An iSPOT-D report

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ABSTRACT

Background: Antidepressant medication (ADM) is thought to reduce depressive symptoms by altering emotion-generative brain systems. However, it is unknown whether successful ADM treatment is associated with changes in psychobehavioral strategies used to regulate emotions. We examined depressive symptoms and emotion regulation strategies before and after ADM in the international Study to Predict Optimized Treatment in Depression (iSPOT-D).
Methods: The study enrolled 1008 adult patients with MDD (18–65 years old) from 18 primary and psychiatric care sites worldwide. Patients were randomly assigned to an 8-week course of escitalopram, sertraline, or venlafaxine-extended-release. We examined whether ADM is associated with changes in suppression, usually associated with maladaptive outcomes, and reappraisal, usually associated with adaptive outcomes. We also tested whether changes in emotion regulation predict changes in depressive symptoms following ADM.
Results: We observed more adaptive emotion regulation (decreased use of suppression and increased use of reappraisal) following ADM. Furthermore, the largest improvements in emotion regulation were associated with the best treatment outcomes.
Limitations: Because we assessed acute outcomes, it is not yet known if the effects of ADM on emotion regulation would persist over time.
Conclusions: ADMs are associated with acute, adaptive changes in the psychobehavioral strategies used to regulate emotions.

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1. Introduction

Major depressive disorder (MDD) is one of the most common and debilitating disorders, affecting 121 million people worldwide (World Health Organisation, 2001). A substantial number of individuals respond to antidepressant medication (ADM), which regularizes their problematic levels of negative and positive emotion. However, it is unclear which psychological processes characterize ADM′s mechanism of action.

One contributing factor to MDD is thought to be the generation of surplus negative emotion. Neuroimaging studies have observed increased activation in limbic and paralimbic regions, such as the amygdala, insula and subgenual anterior cingulate cortex in MDD (Drevets, 1999; Sheline et al., 2001; Siegle et al., 2006).

A second contributing factor is thought to be the ineffective use of emotion *regulation* to reduce negative emotion (Gratz and Roemer, 2004; Gross, 1998; Kanske et al., 2012). Expressive suppression—inhibiting the outward expression of felt emotions—is considered a maladaptive form of emotion regulation and its use is associated with more depressive symptoms (Gross and John, 2003; Moore et al., 2008; Nezlek and Kuppens, 2008). In contrast, cognitive reappraisal—re-thinking, reinterpreting or reframing the meaning of an emotional event to change subsequent emotion—is considered an adaptive form of emotion regulation and is associated with fewer depressive symptoms (Aldao et al., 2010; Gross and John, 2003).

What is not clear, however, is whether ADM works directly on emotion generation, on emotion regulation, or both. According to at least one prominent model (DeRubeis et al., 2005; DeRubeis et al., 2008) ADM works directly on emotion generation, and not on emotion regulation, but empirical evidence for this claim is lacking. In the present study, we focused on three possible models

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Model	Description	What the model predicts
Direct Impact	ADM are posited to act directly on emotion generation, dampening hyper-responsive subcortical representations of affect and leading to symptom alleviation (DeRubeis, Hollon et al., 2005; DeRubeis, Siegle & Hollon, 2008). Meta-analyses of neuroimaging data support the notion that ADMs have a more "bottom-up" influence on depressive symptoms through direct impact on subcortical functioning (Chiesa, Brambilla & Serretti, 2010; Quide et al, 2012).	Either no change in emotion regulation associated with ADM, or decreases in the use of all emotion regulation strategies associated with ADM, as there are weaker representations of negative emotions that require regulation.
Regulation Equilibrium	ADM causes a change on both sides of a negatively-coupled cortical-subcortical network, leading to changes in both emotion generation and regulation. Neuroimaging studies demonstrate that successful ADM treatment is associated with increased engagement of cortical regions (Kennedy et al., 2001, Zhong et al 2011), and (negative) coupling between cortical and subcortical regions (Anand et al., 2005; Chen et al., 2007), which is also characteristic of emotion regulation (Urry et al., 2006, Wager et al., 2008). Decreased activity in subcortical emotion generative regions triggers a reciprocal increase in cortical control regions.	Any attempts to use emotion regulation processes will be enhanced by ADM due to the negative feedback between cortically-dependent emotion regulation processes and subcortical representations of negative emotion.
Adaptive Regulation	ADM has an effect on depressive symptoms that paves the way for the selective use of more adaptive emotion regulation habits. Under this model, ADM has differential effects on different emotion regulation strategies, reducing the need for maladaptive strategies, like suppression, but promoting the use of more adaptive strategies, like reappraisal.	This model predicts opposing effects of ADM on the two types of emotion regulation, resulting in the most adaptive changes in emotion regulation.

Fig. 1. Three plausible models that describe whether treatment with antidepressant medications is associated with changes in emotion regulation (Chen et al., 2007; Chiesa et al., 2010; Kennedy et al., 2001; Quidé et al., 2012; Wager et al., 2008; Zhong et al., 2011).

that describe whether treatment with ADMs results in a change of emotion regulation (Fig. 1).

Our first study goal was to determine whether ADM is associated with changes in emotion regulation. Our second goal was to test whether baseline levels of emotion regulation, changes in emotion regulation, or both are associated with change in symptoms following ADM. We measured depressive symptoms and the use of suppression and reappraisal before and after an 8-week course of ADM.

2. Methods

The measures reported here were collected as part of the international Study to Predict Optimized Treatment for Depression (iSPOT-D). The iSPOT-D protocol (Williams et al., 2011) and the clinical characteristics of the sample (Saveanu et al., in preparation) have been reported elsewhere. Because iSPOT-D is designed as a real-world effectiveness trial, a placebo arm was not included.

2.1. Participants

1008 adult patients (18–65 years old, mean=37.8 ± 12.6 years, 56.6% women) from 18 primary and psychiatric care sites worldwide were enrolled into the first phase of iSPOT-D. Of 6693 people screened by study staff, 1315 completed a baseline visit. Of these, 296 met exclusionary criteria, 7 refused to participate, and 5 were excluded on investigator discretion. Of the 1008 patients in the intent-to-treat sample, 286 were not present at follow up; 36 were discontinued due to intolerance. Participants had a diagnosis of a current single MDD episode or recurrent nonpsychotic MDD and an indication for ADM treatment. Participants completed testing at pre-treatment baseline and after 8 weeks of treatment.

2.2. Sites and practitioners

Seventeen "study management" sites in the United States, Netherlands, Australia/New Zealand and South Africa contributed data, to reflect the distribution of how ADMs are routinely managed across services and practices. Nearly all sites recruited participants from advertisements (Web, newspaper, television and radio) or from the study site's practice. Participants included those who had previously obtained care for depression in non-study-site settings and those for whom enrollment in the study was their first approach for treatment.

2.3. Inclusion and exclusion criteria

The Mini-International Neuropsychiatric Interview (MINI-Plus; Sheehan et al., 1998) was used to confirm DSM-IV criteria for current, nonpsychotic single or recurrent MDD. The 17-item Hamilton Rating Scale for Depression (HRSD$_{17}$; Hamilton, 1960) was used to confirm sufficient clinical symptom severity (HRSD$_{17}$ score ≥ 16). The other sections of the MINI-Plus assessed the following exclusion criteria: suicidal ideation (to the point of planning); a history of bipolar or psychotic disorder; or a current primary diagnosis of eating disorder, obsessive compulsive disorder, post-traumatic stress disorder, substance dependence or axis II personality disorders. Additional exclusion criteria were head trauma history with a loss of consciousness > 5 min, or sensory/motor impairments that precluded testing. Protocol drug exclusion criteria included the current receipt of, a known contra-indication to or a previous failure on study medications, a general medical condition that contraindicated one of the medications, or any non-protocol treatment that could not be washed out, including psychotherapy.

After a full explanation of procedures, participants gave written informed consent. Participants were compensated for each assessment (equivalent to $25/1-h assessment). This study received institutional review board approval prior to patient enrollment

and was conducted according to the principles of the Declaration of Helsinki 2008.

2.4. Procedure

Participants were administered either escitalopram (10–20 mg/day), sertraline (50–200 mg/day) or venlafaxine-extended release (75 to 225 mg/day). Randomization to ADM was carried out using PhaseForward's validated, Web-based Interactive Response Technology. The blocked randomization procedure (block size of 12) was undertaken at the Global Coordinating Center. Open treatment was used to ensure safety and represent clinical practice. Doses for ADMs were adjusted by the treating clinicians according to clinical routine. Treatments for concurrent general medical conditions, except medications contraindicated with the ADMs, were allowed and recorded. Psychotherapy was not allowed during the first 8 weeks of treatment.

2.5. Measures

2.5.1. Hamilton rating scale for depression

Depressive symptom severity was assessed using the $HRSD_{17}$, which asks a clinician to indicate the severity of several depressive symptoms, which are then totaled. Inter-rater reliability was audited using an established video-based methodology (Saveanu et al., in preparation).

2.5.2. Emotion regulation questionnaire (ERQ)

Emotion regulation was measured using the ERQ (Gross and John, 2003), which consists of two subscales: 6 reappraisal items (e.g., "I control my emotions by changing the way I think about the situation I'm in.") and 4 suppression items (e.g., "I control my emotions by not expressing them."). Higher scores indicate more frequent strategy use.

2.6. Statistical analysis

All analyses were conducted using R 3.0.2 software (www.r-project.org). The overall retention rate was 68.6%, with no significant differences between treatment arms (range: 67.0–71.4%). All analyses were conducted per protocol (using patients with complete data only).

T-tests were conducted to examine differences between baseline scores and week 8 scores on suppression and reappraisal. To predict treatment outcome, baseline suppression and reappraisal scores and simple difference scores (week 8 minus baseline) of each were predictors in multivariate linear regression models. In all models, week 8 $HRSD_{17}$ scores were used as the primary outcome, and pre-treatment baseline $HRSD_{17}$ was included as a covariate. Demographic and treatment variables (gender, age and ethnicity, treatment arm [which ADM], and average daily dose) were included as covariates to ensure that emotion regulation predictors were not proxies for these variables. To assess clinical significance, we examined whether change in suppression and reappraisal was related to treatment response ($\geq 50\%$ reduction in depressive symptoms) and remission (≤ 7 on the $HRSD_{17}$ at 8 weeks).

The statistic of interest was the odds ratio (OR), which indicates the change in dependent variable ($HRSD_{17}$ at week 8) for each standard deviation of the independent variable (emotion regulation). ORs closest to 1 indicate the least influence of emotion regulation on treatment outcome, and those >1 indicate that treatment outcome is worse as the independent variable increases. Statistical significance was set at a p-value <0.01, corrected for testing three non-independent outcome variables in each analysis.
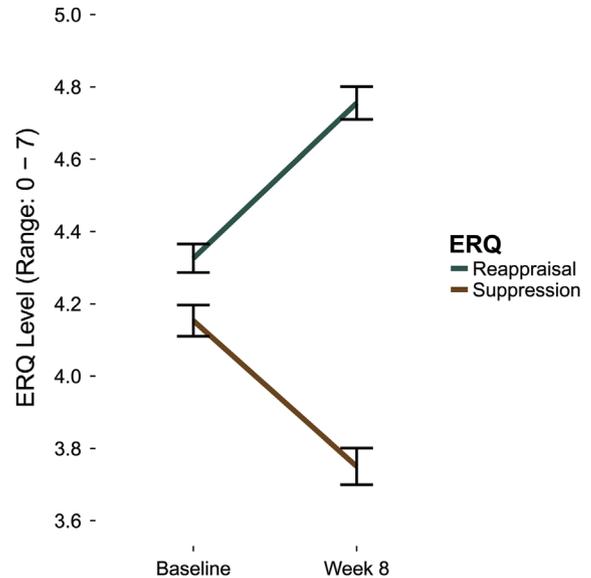

Fig. 2. Mean use of reappraisal (in green, on top) and suppression (in brown, on bottom) at baseline and week 8. Error bars represent standard error of the mean (SEM).

3. Results

Racial distribution (62% white, 17% black and 21% other) reflected the participating countries. For detailed clinical data on the sample, see Saveanu et al. (in preparation).

For the ERQ, alpha reliabilities were 0.75 and 0.85 for the suppression and reappraisal scales, respectively, at baseline and 0.79 and 0.88 at 8 weeks.

3.1. Does emotion regulation change with ADM?

We observed a significant decrease in the use of suppression from baseline to week 8 ($t= -7.69$, $df=674$, $p<0.001$; Fig. 2). We also observed a significant increase in the use of reappraisal ($t=8.53$, $df=674$, $p<0.001$; Fig. 2; Table 1). This observation is most consistent with the adaptive regulation model (see Fig. 1). To examine whether the changes in emotion regulation could be considered proxies for depressive symptoms, we examined the appropriate pairwise relationships at baseline ($rs=0.05$, -0.07, n.s., for suppression and reappraisal with depressive symptoms, respectively) and week 8 ($rs=0.20$, -0.23, $ps<0.001$, for suppression and reappraisal with depressive symptoms, respectively). The lack of baseline relationships indicate that we cannot consider them redundant measurements of depressive symptomology.

3.2. Does pre-treatment emotion regulation relate to treatment outcomes?

We tested for an effect of baseline (pre-treatment) scores on treatment outcome, defined as symptoms rated dimensionally, and by categorical thresholds for response and remission. The multivariate model using baseline ERQ as the primary predictor, including covariates mentioned above, explained more variance in week 8 $HRSD_{17}$ than a model without baseline ERQ ($R^2=0.14$ vs $R^2=0.13$, $p=0.03$). In this model, however, pre-treatment baseline levels of suppression and reappraisal were not significantly predictive of week 8 symptoms rated dimensionally on the $HRSD_{17}$ at the $p<0.01$ threshold (suppression, $OR=0.94$, $p=0.09$; reappraisal, $OR=0.93$, $p=0.05$), nor significantly related to $HRSD_{17}$ response ($OR=1.13$, $p=0.15$ and $OR=1.07$, $p=0.44$, respectively) or $HRSD_{17}$ remission ($OR=1.15$, $p=0.09$ and $OR=1.14$, $p=0.12$, respectively).

Table 1
Mean ERQ suppression, ERQ reappraisal and HRSD$_{17}$ scores by time, remission, and treatment arm.

Remission Status	Measure	All (N=675)		Escitalopram (N=233)		Sertraline (N=239)		Venlafaxine-XR (N=203)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
All	Baseline Suppression	4.13	1.35	4.14	1.40	4.23	1.31	4.00	1.33
	Baseline Reappraisal	4.34	1.20	4.42	1.23	4.27	1.16	4.34	1.20
	Baseline HRSD$_{17}$	21.87	4.13	21.96	4.19	22.14	4.20	21.44	3.96
	Week 8 Suppression	3.76	1.34	3.73	1.37	3.77	1.39	3.79	1.27
	Week 8 Reappraisal	4.76	1.21	4.74	1.25	4.73	1.17	4.81	1.21
	Week 8 HRSD$_{17}$	9.64	6.37	9.47	6.75	9.61	6.01	9.89	6.35
Remission	Baseline Suppression	4.20	1.34	4.19	1.37	4.24	1.33	4.17	1.33
	Baseline Reappraisal	4.43	1.20	4.52	1.22	4.37	1.18	4.40	1.22
	Baseline HRSD$_{17}$	20.96	3.93	21.48	4.17	21.29	4.10	19.93	3.20
	Week 8 Suppression	3.49	1.29	3.49	1.27	3.38	1.39	3.60	1.21
	Week 8 Reappraisal	5.01	1.16	4.86	1.27	5.11	1.08	5.06	1.09
	Week 8 HRSD$_{17}$	4.07	2.04	3.68	2.13	4.39	1.95	4.16	1.98
No remission	Baseline Suppression	4.07	1.35	4.09	1.42	4.22	1.30	3.86	1.32
	Baseline Reappraisal	4.27	1.19	4.32	1.24	4.19	1.14	4.30	1.18
	Baseline HRSD$_{17}$	22.62	4.15	22.39	4.18	22.84	4.17	22.62	4.11
	Week 8 Suppression	3.99	1.34	3.94	1.42	4.08	1.31	3.94	1.30
	Week 8 Reappraisal	4.55	1.21	4.62	1.22	4.41	1.15	4.62	1.26
	Week 8 HRSD$_{17}$	14.32	4.80	14.74	4.96	13.91	4.66	14.36	4.80

Abbreviations: HRSD$_{17}$, 17-item Hamilton rating scale for depression; ERQ, Emotion Regulation Questionnaire.

3.3. Do changes in emotion regulation relate to treatment outcome?

We asked whether the change in emotion regulation (week 8 level minus baseline level) related to treatment outcome (depression symptom changes from baseline to week 8). The model using change in ERQ as the primary predictor explained a greater portion of the variance than the model using baseline ERQ ($R^2=0.23$, $p < 0.001$, difference in $R^2=0.09$, $p < 0.001$). In this model, we observed a significant effect of change in suppression from baseline to week 8 ($OR=1.33$, $p < 0.001$) such that individuals who showed the smallest decreases in suppression showed the greatest depressive symptoms at week 8 (covarying for baseline symptoms). We also observed a significant effect of change in reappraisal use on treatment outcome ($OR=0.86$, $p < 0.001$) such that individuals who showed the largest increases in reappraisal from baseline to week 8 showed the fewest depressive symptoms at week 8 (covarying for baseline symptoms). These effects were independent of one another, as the suppression and reappraisal change scores were not significantly correlated ($r=0.04$, $p=0.31$).

Additionally, the change in suppression was related to both response ($\geq 50\%$ reduction on the HRSD$_{17}$; $OR=0.62$, $p < 0.001$) and remission (≤ 7 on the week 8 HRSD$_{17}$; $OR=0.54$, $p < 0.001$). The change in reappraisal also related to response, ($OR=1.44$, $p < 0.001$) and remission ($OR=1.31$, $p < 0.01$). See Fig. 3.

3.4. Demographic and treatment variables

It is clear from Tables 2 and 3 that the effects of emotion regulation that we report are not proxies for age, gender, ethnicity, treatment arm (type of ADM administered) and average daily dose of ADM.

4. Discussion

During an 8-week course of ADM, we observed improvements in emotion regulation, characterized by decreases in suppression and increases in reappraisal. Both of these improvements related to treatment outcome, taking into account baseline depression symptoms. These findings suggest that ADM is associated with a shift toward more adaptive emotion regulation habits.

4.1. Implications for models of treatment for depression

We tested hypotheses derived from three competing models (see Fig. 1): (1) ADM reduces depressive symptoms *without impacting emotion regulation*, (2) treatment-related decreases in negative affect leads to *increases in both types of emotion regulation*, and (3) ADM leads to *decreases in maladaptive emotion regulation (suppression) and increases in adaptive emotion regulation (reappraisal)*. Our findings were most consistent with the third model.

These findings provide behavioral, psychosocial evidence that is consistent with neurochemical evidence that ADMs influence subcortical (Anand et al., 2007; Windischberger et al., 2010) and cortical (Anand et al., 2007, 2005) pathways. More specifically, ADMs have been shown to involve down-regulation of the subcortical limbic system, alleviating affective symptoms (Newhouse et al., 2000; Shapiro et al., 1999; Thase, 1997), and to up-regulate activation in frontal pathways, alleviating cognitive and psycho-motor symptoms (Entsuah et al., 1995; Hindmarch and Bhatti, 1988; Newhouse et al., 2000). These results are consistent with reports of changes in personality variables following ADM (Bagby et al., 1999) but focus in upon specific behavioral and psychological strategies individuals use in the face of negative emotion.

Our results cannot speak to the causal direction between the change in depressive symptoms and the changes in emotion regulation. It is possible that during ADM, the alleviation of depressive symptoms occurs first, and only then do patients who have fewer depressive symptoms begin to change their emotion regulation habits. Another possibility is that the initial effects of ADM decrease negative affect, but patients who then change their emotion regulation habits adaptively can amplify the initial effects of ADM, and therefore show the greatest ultimate alleviation of depressive symptoms.

4.2. Emotion regulation in treatment for depression

Our results indicate that ADM is associated with a shift toward more adaptive emotion regulation. In addition to psychotherapeutic improvement as a result of direct instruction (Fava et al., 1998; Pampallona et al., 2004), unprompted changes in emotion regulation during ADM administration are associated with better treatment outcomes. The independent effects on reappraisal and suppression
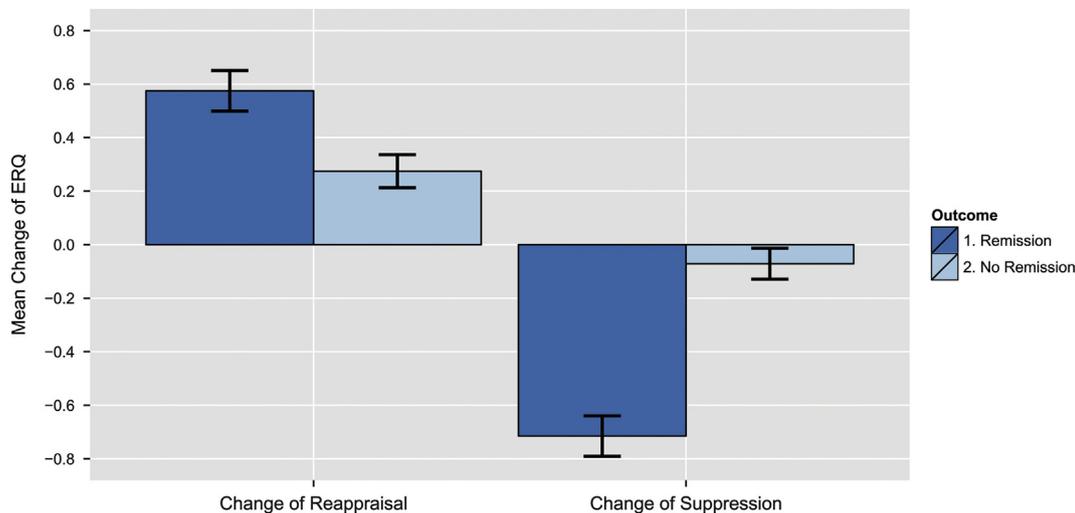
Fig. 3. Mean change (week 8 minus baseline) in reappraisal (left) and suppression (right) in patients who achieved remission (≤ 7 on the HRSD$_{17}$ at week 8, dark blue) and did not (> 7 on the HRSD at week 8, light blue). Error bars represent SEM. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Regression analysis predicting week 8 depressive symptoms (HRSD$_{17}$ scores) from baseline ERQ scores.

Predictor	OR	p-value
Age	1.130	0.001
Gender	0.926	0.318
Race	–	0.053
Treatment arm	–	0.720
Mg per day	1.130	0.407
Baseline depressive symptoms	0.926	< 0.001
Baseline reappraisal	1.130	0.051
Baseline suppression	0.926	0.086

Note: Odds ratios from a linear regression predicting week 8 HRSD$_{17}$. OR=odds ratio per 1 standard deviation increase of predictor.
Abbreviations: HRSD$_{17}$, 17-item Hamilton rating scale for depression; ERQ, Emotion Regulation Questionnaire, OR=odds ratio.

Table 3
Regression analysis predicting week 8 depressive symptoms (HRSD$_{17}$ scores) from the change in ERQ scores.

Predictor	OR	p-value
Age	1.102	0.007
Gender	0.945	0.426
Race	–	0.032
Treatment arm	–	0.693
Mg per day	1.054	0.277
Baseline depressive symptoms	1.413	< 0.001
Change in reappraisal	0.865	< 0.001
Change in suppression	1.326	< 0.001

Note: Odds ratios from a linear regression predicting week 8 HRSD$_{17}$. OR=odds ratio per 1 standard deviation increase of predictor.
Abbreviations: HRSD$_{17}$, 17-item Hamilton rating scale for depression; ERQ, Emotion Regulation Questionnaire, OR=odds ratio.

underscore that successful treatment corrects not only under-regulated affect, but also *mis*-regulated affect (Campbell-Sills and Barlow, 2007).

It is important to note that although baseline depressive symptoms, age, gender, ethnicity, treatment type and average daily dose may influence emotion regulation, the relationship between changes in emotion regulation and treatment outcome was evident after considering these important sources of variation.

In addition, the effects we report are not due to the baseline use of these strategies. Ultimately, the best model demonstrated that participants with the greatest decreases in suppression use and/or increases in reappraisal use showed better treatment outcomes. However, we did observe trend-level effects of baseline suppression and reappraisal, which, if replicated, may have clinical utility because they are available before treatment.

4.3. Strengths, limitations and future directions

The present study is the first to use a before-and-after design to examine changes in emotion regulation associated with ADM. This study's strengths include a large sample, which may also lead to statistically significant findings that are relatively small (albeit robust) effects. Our study was designed to test outcomes in real world settings, which necessarily include contributions from physician rapport, ADM effects, placebo responding and other motivational factors. Future studies might test different questions about mechanisms of change in emotion regulation with additional control conditions.

In addition, we cannot speak to the direction of causality between changes in emotion regulation and depressive symptoms following ADM. Future studies might employ denser sampling of measures, with the hope that a lag–lead relationship elucidates the most likely causal relationship.

5. Conclusion

The present findings highlight the importance of emotion regulation in depression, even when examining a treatment (ADM) that is frequently not conceptualized as targeting emotion regulation. The present results also speak to a need to distinguish between emotion generation and regulation when considering changes following treatment for mood and anxiety disorders.

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