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Anger attacks are associated with persistently elevated irritability in MDD: findings from the EMBARC study

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Original Article

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Abstract

Background. This report tests the association of self-reported symptoms of irritability with overt behavior of anger attacks (uncharacteristic sudden bouts of anger that are disproportionate to situation and associated with autonomic activation).

Methods. Participants of the Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care study who completed Massachusetts General Hospital Anger Attacks questionnaire were included ($n = 293$). At each visit, the 17-item Hamilton Depression Rating Scale and the 16-item Concise Associated Symptom Tracking scale were used to measure depression, anxiety, and irritability. In those with anger attacks present *v.* those without anger attacks, separate *t* tests and mixed model analyses compared afore-mentioned symptoms at baseline and changes with treatment respectively. As anger attacks may occur without aggressive behaviors, analyses were repeated based only on the presence of aggressive behaviors.

Results. At baseline, those with anger attacks ($n = 109$) *v.* those without anger attacks ($n = 184$) had similar levels of depression but higher levels of irritability [effect size (d) = 0.80] and anxiety ($d = 0.32$). With acute-phase treatment, participants with anger attacks experienced a greater reduction in irritability ($p < 0.001$) but not in depression ($p = 0.813$) or anxiety ($p = 0.771$) as compared to those without anger attacks. Yet, irritability levels at week-8 were higher in those with anger attacks ($d = 0.32$) than those without anger attacks. Similar results were found in participants with aggressive behaviors.

Conclusions. The presence of anger attacks in outpatients with major depressive disorder may identify a sub-group of patients with persistently elevated irritability.

Introduction

Irritability is an important yet understudied symptom domain in adult patients with major depressive disorder (MDD) (Fava et al., 2010; Judd, Schettler, Coryell, Akiskal, and Fiedorowicz, 2013). While it is reported by over half of adult patients with MDD (Fava et al., 2010; Judd et al., 2013), it is neither prominently highlighted by the NIMH Research Domain Criteria nor assessed by commonly used measures of depression severity (Kroenke, Spitzer, & Williams, 2001; Rush et al., 2003), reflecting its lack of inclusion as a diagnostic criterion symptom for MDD in adults (Association, 2013). Importantly, its presence or worsening is associated with earlier age of onset, greater disability, and poorer long-term clinical course (Fava et al., 2010; Jha, Minhajuddin, South, Rush, & Trivedi, 2018; Judd *et al.* 2013). A recent report highlighted the clinical utility of measuring irritability within the context of two separate 8-week long acute-phase antidepressant trials (Jha, Minhajuddin, South, Rush, & Trivedi, 2019). Authors found that irritability improved from baseline-to-week-4 and this improvement predicted remission (none or minimal depression) and no-meaningful-benefit (<30% reduction in depression) at week-8, both independent of baseline-to-week-4 improvement in depression (Jha, Minhajuddin, et al., 2019). This report addresses the central question those findings raised-of how patients' self-report of irritability symptoms associated with measures of overt behaviors such as anger attacks (Pine, 2019).

Anger attacks are bouts of anger that start suddenly, are disproportionate to the situation, are not part of the patient's usual behavior, and are associated with autonomic activation (Fava, Anderson, & Rosenbaum, 1990). In the Massachusetts General Hospital Anger Attacks Questionnaire (AAQ), Fava and colleagues operationalize the presence of anger attacks as patient's report of irritability and overreaction to minor annoyances in the past 6 months along with at least one episode of an anger attack in the past month that is accompanied

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by autonomic arousal and/or violent behavior (Fava et al., 1990, 1991, 1993). Typically, over a third of patients with MDD meet the criteria for the presence of anger attacks (Fava et al., 1991).

Fava et al. have previously reported that while levels of depressive symptoms were similar, patients with anger attacks had significantly higher levels of anxiety, somatization, and hostility symptoms than patients without anger attacks (Fava et al., 1993). Further, they found a greater reduction in hostility but not in depressive, anxiety, and somatization symptoms with antidepressant treatment in patients with anger attacks than those without anger attacks (Fava et al., 1993). Other groups have reported similar findings. For example, Painuly et al. previously found in a small study that depressed patients with anger attacks ($n = 20$) had significantly higher levels of irritability and anxiety than patients without anger attacks ($n = 20$) (Painuly, Sharan, & Mattoo, 2007). In a subsequent report with a larger sample size ($n = 328$), they replicated these findings of elevated irritability and anxiety in patients with anger attacks than those without anger attacks (Painuly, Grover, Gupta, & Mattoo, 2011). Additionally, they found that the frequency of anger attacks was positively correlated with irritability and aggression (Painuly et al., 2011). Taken together, these reports suggest that patients with anger attacks have similar levels of depression but higher levels of irritability and anxiety than patients without anger attacks (Fava, 1998). Additionally, the presence of anger attacks may be associated with greater reduction in irritability but not in depression or anxiety symptoms with acute-phase antidepressant treatment.

Aim of the study

Using a sample of convenience from the Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC) study, a double-blind placebo controlled randomized study of sertraline for 8-weeks, this report aims to evaluate the following specific questions:

(1) Do adult outpatients with MDD and anger attacks differ on levels of depression, anxiety, hostility, and irritability at baseline from those without anger attacks?
(2) If yes, do patients with a higher frequency of anger attacks have higher levels of these symptoms at baseline?
(3) Does the presence of anger attacks at baseline predict changes in depression, anxiety, and irritability with acute-phase antidepressant treatment?
(4) If yes, does treatment arm (sertraline *v.* placebo) affect this association?

Additional analyses evaluated the association of anger attack and irritability with depressive episode subtypes (melancholic or atypical) and with participants' self-reported feelings of hostility. As anger attacks may occur without overt aggressive behaviors and the first item assesses about the presence of irritability over the past 6 months, additional analyses were conducted based on the presence of overt aggressive behaviors. Hence, participants who reported aggressive behavior on AAQ were compared to those with no aggressive behaviors on measures of depression, anxiety, and irritability at baseline and with acute-phase antidepressant treatment. Findings of this report will elucidate the association among constructs of anger, hostility, and irritability, which while related are not completely redundant (Orri, Perret, Turecki, & Geoffroy, 2018).

Material and methods

Study design and participants

EMBARC study

As previously described (Trivedi et al., 2016, 2018), the EMBARC study (NCT01407094) enrolled 309 participants with MDD at four-sites. Of these, 10 were in a feasibility sample and 3 were randomized but were not eligible for the study (Trivedi et al., 2016). Of the 296 participants with MDD who were randomized either to sertraline or to placebo, 3 did not complete the AAQ at baseline. Thus, the modified intent to treat sample for this report includes $n = 293$ participants with MDD with $n = 149$ randomized to placebo and $n = 144$ randomized to sertraline. Institutional review boards at each site approved the study and all participants provided signed an informed consent prior to completing any study-related procedures. The inclusion and exclusion criteria have been described previously (Trivedi et al., 2016) and are listed in detail at https://clinicaltrials.gov/ct2/show/NCT01407094. Briefly, participants were 18–65 years of age, met criteria for current episode of MDD on Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First, Spitzer, Gibbon, & Williams, 2002), scored ⩾14 on Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) at both screening and randomization visits, did not meet criteria for any failed antidepressant trial in the current episode based on Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (Chandler, Iosifescu, Pollack, Targum, & Fava, 2010), and agreed to and were eligible for all biomarker procedures (electroencephalography, psychological testing, magnetic resonance imaging, and blood draws). Participants were excluded if they did not tolerate sertraline or bupropion in the past, were pregnant/breastfeeding/planning to become pregnant, were medically or psychiatrically unstable, met criteria for psychotic/bipolar disorder in lifetime or substance abuse in past 2 months or substance dependence in past 6 months, or were on prohibited concomitant medications (antipsychotic, anticonvulsant, mood stabilizers, central nervous system stimulants, daily use of benzodiazepines or hypnotics, or antidepressants).

Measurements

Anger attacks

At the baseline visit of the EMBARC study, participants completed the AAQ (Fava et al., 1990). Using this self-report questionnaire, participants were categorized as either with anger attacks or without anger attacks present per Fava et al.: '*classified as having anger attacks if they exhibited the following four criteria over the previous 6 months: (1) irritability, (2) overreaction to minor annoyances, (3) occurrence of anger attacks, at least one of which occurred within the past months, and (4) experience during at least one of the attacks of four or more of the following: tachycardia, hot flashes, chest tightness, paresthesia, dizziness, shortness of breath, sweating, trembling, panic, feeling out of control, feeling like attacking others, attacking physically or verbally, and throwing or destroying objects*' (Fava et al., 1993). Additionally, participants with anger attacks were asked to report the frequency of attacks in the past month as following categories: 0, 1–2, 3–4, 5–8, and 9 or more (⩾9). Those participants who responded with 'Yes' to AAQ items regarding 'physically or verbally attacking people' and/or 'throwing things around or destroying objects' were grouped as participants with aggressive behavior present while others were categorized as without aggressive behavior.

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Depression severity

Clinicians conducted the structured interview (Williams, 1988) for the 17-item Hamilton Depression Rating Scale (HAMD-17) to assess depression severity at each visit of the EMBARC study. Previous reports have found high concurrent validity of HAMD-17 with other measures of depression severity such as the 30-item Inventory of Depressive Symptomatology (Vittengl, Clark, Kraft, & Jarrett, 2005). During screening and baseline visits, patients also completed the 16-item QIDS-SR scale.

Anxiety

Participants completed the three-item anxiety domain of the Concise Associated Symptom Tracking scale (CAST-ANX) at each visit of the EMBARC study. Individual items included, 'I feel anxious all the time,' 'I am feeling restless, as if I have to move constantly,' and 'I cannot sit still.' These items were rated on a 5-point Likert scale with responses of 'strongly disagree,' 'disagree,' 'neither agree nor disagree,' 'agree,' and 'strongly agree' corresponding to scores of 1, 2, 3, 4, and 5 with a total score range of 3–15. Previous reports have found strong psychometric properties of the CAST-ANX domain (Jha et al., 2018; Minhajuddin, Jha, Chin Fatt, & Trivedi, 2020; Trivedi et al., 2011).

Irritability

Participants completed the five-item irritability domain of the CAST scale (CAST-IRR) as a measure of irritability at each visit of the EMBARC study and the CO-MED trial. Individual items included, 'I wish people would just leave me alone,' 'I feel very uptight,' 'I find myself saying or doing things without thinking,' 'Lately everything seems to be annoying me,' and 'I find people get on my nerves easily.' These items were rated on a 5-point Likert scale with responses of 'strongly disagree,' 'disagree,' 'neither agree nor disagree,' 'agree,' and 'strongly agree' corresponding to scores of 1, 2, 3, 4, and 5 with a total score range of 5–25. Previous reports have found strong psychometric properties of the CAST-IRR domain (Jha et al., 2018; Minhajuddin et al., 2020; Trivedi et al., 2011).

Hostility

Using a Visual Analogue of Mood Scales (VAMS) at baseline, participants rated their current mood as hostile—friendly on 250 mm horizontal lines (Pizzagalli et al., 2008; Trivedi et al., 2016). These responses were converted on a 100-point scale with lower scores indicating more hostile mood.

Presence of melancholic or atypical features

Clinicians completed current major depressive episode specifier module of SCID to identify the presence of melancholic or atypical features (First et al., 2002). The presence of melancholic features was determined by the affirmative response to either 'loss of pleasure in all, or almost all activities' or 'lack of reactivity to usually pleasurable activity' along with the presence of three or more of following: distinct quality of mood, depression worse in morning, early morning awakening, marked psychomotor retardation or agitation, significant anorexia or weight loss, and excessive or inappropriate guilt. The presence of atypical features were identified by the presence of mood reactivity (brightening of mood in response to an actual or potential positive event) along with of two or more of the following features: significant weight gain or increase in appetite, hypersomnia, leaden paralysis, and long-standing pattern of interpersonal rejection sensitivity.

Table 1. Clinical and demographic differences in EMBARC study participants with and without anger attacks

	No anger attacks		Anger attacks present	
	184		109	
Categorical variables	*N*	%	*N*	%
Sex				
Male	62	61.4	39	38.6
Female	122	63.5	70	36.5
Race				
White	118	62.1	72	37.9
Black	34	58.6	24	41.4
Other	32	71.1	13	28.9
Site				
New York	54	62.1	33	37.9
Boston	30	61.2	19	38.8
Michigan	41	69.5	18	30.51
Texas	59	60.2	39	39.80
Current MDE specifier				
Neither melancholic, atypical nor catatonic	57	60.0	38	40.0
Melancholic features	72	63.2	42	36.9
Atypical features	55	67.1	27	32.9
Catatonic features	0	0.0	1	100.0
Hispanic ethnicity	33	60.0	22	40.00
Employed at baseline[a]	104	65.0	56	35.0
Onset of depression before age 18	74	67.9	35	32.1
Continuous variables	Mean	s.d.	Mean	s.d.
Age in years	37.03	13.54	36.97	12.90
Years of education	15.12	2.70	15.00	2.48
HAMD-17	18.43	4.25	18.70	4.57
QIDS-SR	17.93	2.65	18.26	2.95
Irritability (CAST-IRR)[b]	15.23	3.83	18.19	3.46
Anxiety (CAST-ANX)[b]	8.52	2.64	9.37	2.63
Hostility – Friendly Visual Analogue of Mood Scale	74.39	20.62	66.93	22.61

HAMD-17 is 17-item Hamilton Depression Rating Scale, QIDS-SR is 16-item Quick Inventory of Depressive Symptomatology Self-Report, CAST-IRR and CAST-ANX are irritability and anxiety domains respectively of Concise Associated Symptom Tracking Scale.
[a]Missing $n = 4$.
[b]Missing $n = 1$.

Statistical analysis plan

As reported earlier, the modified intent to treat sample includes all EMBARC study participants who were randomized to sertraline or placebo and completed AAQ at baseline ($n = 293$). Independent sample t tests and χ^2 tests were used to compare continuous and categorical features, respectively, between participants with anger attacks and those without anger attacks at

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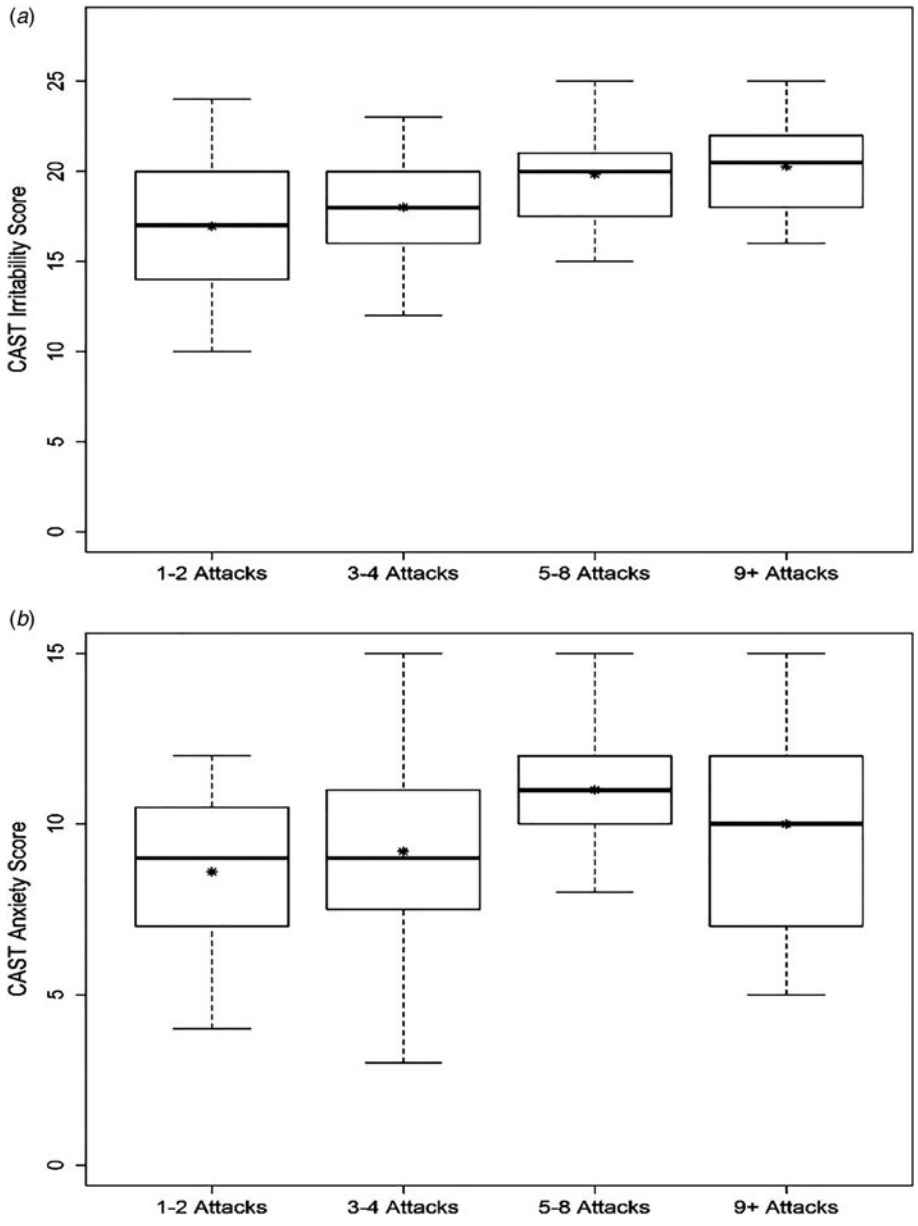


Fig. 1. Baseline irritability and anxiety in EMBARC study participants with anger attacks ($n = 108$ (Among participants with anger attacks ($n = 109$), one participant with 3–4 anger attacks in the past 1 month had missing data for irritability and anxiety domains of Concise Associated Symptom Tracking scale (CAST) in the EMBARC study)) based on the frequency of attacks in past 1 month.

baseline. For symptoms that differed significantly, analyses of variance (ANOVA) were used to compare their levels based on the frequency of anger attacks in the past month (categorized as 1–2, 3–4, 5–8, and ⩾9). When applicable, Cohen's d effect size (d) was estimated to convey the magnitude of differences in levels of symptoms (depression, anxiety, hostility, and irritability). To evaluate if baseline anger attacks predicted changes in depression, anxiety, and irritability, repeated measures mixed model analyses were used with depression, anxiety, and irritability as the dependent variable in separate models, along with anger attacks, time, and time-by-anger attacks interaction as key independent variables of interest, and select baseline variables (age, sex, site, race, and ethnicity) as covariates. As repeated-observations for VAMS were not available, hostility was not included as an outcome in mixed model analyses. For symptoms with a significant time-by-anger attacks interaction, mixed model analyses were repeated and included a three-way interaction term (time-by-anger attacks-by-treatment arm) for time, anger attacks, and treatment arm (sertraline or placebo) to evaluate if treatment arms moderated the association between baseline anger attacks and changes in symptom levels. To evaluate if the presence of aggressive behaviors affected our analyses, we also compared depressed patients with aggressive behavior to those without aggressive behavior.

All analyses were conducted using SAS 9.4 and threshold of significance was set at $p < 0.05$.

Results

Baseline characteristics of EMBARC study participants with (37.2%, 109/293) and without (62.8%, 184/293) anger attacks are reported in Table 1. Of those participants with anger attacks, 40.4% (44/109), 29.4% (32/109), 17.4% (19/109), and 12.8% (14/109) reported 1–2, 3–4, 5–8, and ⩾9 attacks in past 1 month, respectively. The proportion of participants with melancholic or atypical features was similar in those with anger attacks

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Table 2. Mixed model analyses of changes in depression, anxiety, and irritability based on the presence of anger attacks at baseline

	Depression		Anxiety		Irritability	
	F value (df)	*p**	*F* value (df)	*p**	*F* value (df)	*p**
Anger attacks	0.31 (1, 285)	>0.99	5.19 (1, 286)	0.207	18.92 (1, 288)	<0.001
Week	95.23 (6, 1487)	<0.001	18.82 (6, 1425)	<0.001	48.79 (1, 1426)	<0.001
Week-by-anger attacks	0.49 (6, 1487)	>0.99	0.55 (6, 1425)	>0.99	3.09 (6, 1426)	0.045

*p** is the *p* value after Bonferroni adjustment (three independent variables of interest in these three mixed model analyses). All mixed model analyses were adjusted for age, sex, race, ethnicity, and site.

and those without anger attacks, see Table 1. Similarly, levels of irritability were similar in participants with melancholic features [mean = 16.27, standard deviation (S.D.) = 4.01], atypical features (mean = 16.35, S.D. = 3.77), or neither (mean = 16.36, df = 4.12).

Do adult outpatients with MDD with anger attacks differ on levels of depression, anxiety, hostility, and irritability at baseline from those without anger attacks?

Yes, but only on levels of anxiety, hostility, and irritability. Levels of depression, as measured by HAMD-17 ($t = -0.50$, df = 214, $p = 0.620$) and QIDS-SR ($t = -0.94$, df = 208, $p = 0.350$), did not differ between participants with anger attacks and those without anger attacks (Table 1). Participants with anger attacks had significantly higher levels of anxiety ($t = -2.66$, df = 225, $p = 0.008$, $d = 0.32$), hostility ($t = -2.82$, df = 211, $p = 0.005$, $d = 0.35$), and irritability ($t = -6.80$, df = 243, $p < 0.0001$, $d = 0.80$), also see Table 1. Higher scores on irritability were associated with greater hostility (Pearson's $r = 0.34$, $p < 0.0001$).

Do patients with higher frequency of anger attacks have higher levels of irritability and anxiety at baseline?

Yes. Among participants with anger attacks, there was a statistically significant difference in levels of irritability ($F = 5.74$, df = 3, 104, $p = 0.001$; Fig. 1, Panel A) and anxiety ($F = 4.41$, df = 3, 104, $p = 0.006$; Fig. 1, Panel B) on the basis of the frequency of anger attacks in the past month. In *post hoc* tests, the magnitude of difference between participants with 5–8 and ⩾9 attacks in levels of irritability ($d = 0.16$) and anxiety ($d = 0.42$) was small (Cohen, 2013). However, participants with 5–8 attacks had higher levels of irritability than those with 3–4 ($d = 0.64$) and 1–2 ($d = 0.87$) attacks. Similarly, participants with ⩾9 attacks had higher levels of irritability than those with 3–4 ($d = 0.80$) and 1–2 ($d = 1.01$) attacks. Participants with 5–8 attacks also had higher levels of anxiety than those with 3–4 ($d = 0.71$) and 1–2 ($d = 1.08$) attacks. Anxiety in participants with ⩾9 attacks was either of similar magnitude or moderately higher than those with 3–4 ($d = 0.28$) or 1–2 ($d = 0.56$) attacks.

Does the presence of anger attacks at baseline predict changes in depression, anxiety, and irritability with acute-phase antidepressant treatment?

Yes, but only for changes in irritability. There was no significant week-by-anger attacks interaction for depression (unadjusted $p = 0.813$) and anxiety (unadjusted $p = 0.771$) symptoms with acute-phase antidepressant treatment, see Table 2. There was a significant week-by-anger attacks interaction for irritability ($p = 0.045$ after Bonferroni adjustment). While participants with anger attacks experienced greater reduction in irritability, their irritability levels remained significantly higher than those of participants without anger attacks throughout the acute-phase antidepressant treatment period (Fig. 2, Panel A). The observed mean (S.D.) scores of CAST-IRR at week-8 in participants with ($n = 87$) anger attacks and those without anger attacks ($n = 146$) were 14.22 (5.08) and 12.76 (4.33) respectively ($d = 0.32$). In contrast, anxiety levels were no longer different at week-8 (Fig. 2, Panel B) between participants with and without anger attacks.

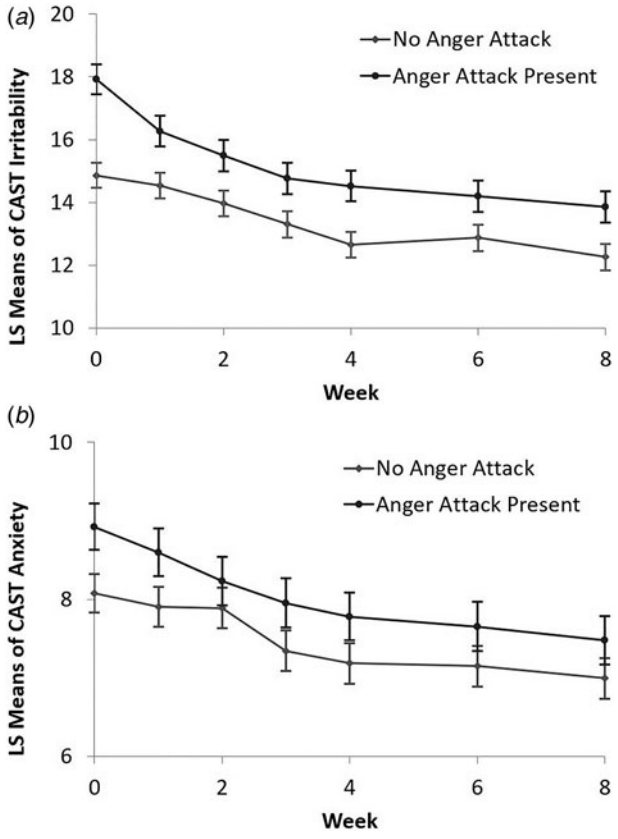


Fig. 2. Changes in irritability and anxiety among participants with and without anger attacks in the EMBARC study. Legends: EMBARC is the Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care study. LS means are least square means obtained from repeated measures mixed model analyses. CAST is Concise Associated Symptom Tracking scale.

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Does treatment arm (sertraline v. placebo) affect the association between baseline anger attacks and changes in irritability with antidepressant treatment?

No. The three-way interaction of week-by-anger attack-by-treatment arm was not significant in predicting changes in irritability ($F = 0.50$, df = 1, 1401, $p = 0.835$).

Exploratory analyses with aggressive behaviors

Of the 293 participants, 84 (28.5%) reported physically/verbally attacking people, 55 (18.8%) reported throwing things around/destroying objects, and 96 (32.8%) reported either one or both aggressive behaviors. Of the 96 participants with aggressive behavior, 86 (89.6%) met criteria for anger attacks. Participants with aggressive behavior had higher irritability (mean = 18.35, S.D. = 3.55; $t = -6.55$, df = 290, $p < 0.0001$, $d = 0.82$) than those without aggressive behaviors (mean = 15.33, S.D. = 3.77). Levels of anxiety ($p = 0.075$) and depression ($p = 0.510$) at baseline did not differ on the basis of aggressive behaviors. Furthermore, there was no significant week-by-aggressive behaviors interactions for changes in depression (unadjusted $p = 0.760$) and anxiety (unadjusted $p = 0.642$) during acute-phase antidepressant treatment. While participants with aggressive behaviors experienced greater reduction in irritability, their irritability levels remained significantly higher than those of participants without aggressive behaviors even after acute-phase antidepressant treatment (see online Supplementary Table ST2 and Fig. SF1).

Conclusions

In this report of a large sample of adult outpatients with MDD, we extended the clinical utility of measuring irritability by demonstrating its association with overt behavior of anger attacks. In our sample, over a third of patients met criteria for anger attacks. These patients had significantly higher levels of irritability and anxiety as compared to those without anger attacks. While anxiety levels were no longer different after acute-phase antidepressant treatment, patients with anger attacks continued to report higher levels of irritability than those without anger attacks even after 8 weeks of treatment. When only the presence of aggressive behaviors was considered, those with these behaviors had significantly higher levels of irritability at baseline than those without aggressive behavior, and this difference persisted even after acute-phase antidepressant treatment. The association between baseline anger attacks and persistently elevated irritability post-treatment was not moderated by the treatment arm (sertraline *v.* placebo).

Our findings of elevated levels of anxiety and irritability in adult depressed patients with anger attacks are consistent with previous reports (Fava et al., 1993; Painuly et al., 2007). Additionally, our findings of greater reduction in irritability but not in depression and anxiety among patients with anger attacks compared to those without anger attacks is consistent with the report of Fava et al. (Fava et al. 1993) where patients with anger attacks experienced greater reduction in hostility, a construct related to irritability, but not in depression or anxiety symptoms with fluoxetine treatment. These findings argue for systematic assessment of irritability as part of a measurement-based care protocol for the treatment of depression Trivedi et al. (2019), which may allow validation of these findings in real-world clinics (Jha, Grannemann, et al., 2019) and further enhance their generalizability.

We found in our sample that higher frequency of anger attacks was linearly associated with irritability but not with anxiety. While irritability and anxiety often exist together and are correlated, recent reports from the developmental literature suggest that their neural mechanisms may be distinct (Kircanski et al., 2018; Stoddard et al., 2017). To our knowledge, similar studies have not been done in adults. Findings of this report also elucidate association among constructs of anger attacks, aggressive behavior, hostility, and irritability. Aggressive behavior was common among those with anger attacks with 78.8% (86/109) reporting either one or both aggressive behaviors. The range of irritability and hostility levels in participants with anger attacks partially overlapped with that of participants without attacks. Furthermore, while higher levels of irritability were associated with greater hostility, the two measures had a shared variance of 12.5% only. Future studies should comprehensively evaluate these symptoms and behavior constructs to determine their shared *v.* unique variance and include assessments from clinicians and other observers in patients' lives such as family members or co-workers. Findings from our report also argue for systematic screening of anger attacks as it may identify a group of adult patients with MDD who experience persistently elevated irritability, which in turn has been associated with poorer long-term outcomes (Judd et al., 2013).

Earlier work by Fava and colleagues suggests that patients with anger attacks may have distinct biological underpinnings of their illness. They have previously shown a blunted prolactin response to both thyrotropin-releasing hormone stimulation (Rosenbaum et al., 1993) and fenfluramine challenge (Fava et al., 2000) in patients with anger attacks, which they linked to dysregulation of serotonergic neurotransmission (Fava et al., 2000). However, it may also be related to aberrant dopaminergic neurotransmission, given dopamine's inhibitory effect on prolactin secretion (Fitzgerald & Dinan, 2008). Consistent with this notion, Dougherty et al., found evidence for down-regulation of dopamine receptors in the striatum of patients with MDD and anger attacks as compared to healthy controls (Dougherty et al., 2006).

The additional biological relevance of anger attacks may be found in its association with cardiovascular and metabolic pathology. Fava et al. had initially observed that patients with anger attacks had higher cholesterol levels than those without anger attacks (Fava, Abraham, Pava, Shuster, and Rosenbaum, 1996). A subsequent study validated the association between anger attacks and elevated cholesterol levels and additionally found higher prevalence of smoking for >11 years among patients with anger attacks (Fraguas et al., 2007). Furthermore, in patients with MDD and anger attacks, plasma homocysteine levels correlated with length of current depressive episode and severity of symptoms, but no such association was seen MDD patients without anger attacks (Fraguas et al., 2006). Reflecting this higher cardiovascular burden, Iosifescu et al. found that patients with anger attacks had higher severity of white matter hyperintensities overall and in subcortical regions as compared to those without anger attacks (Iosifescu et al., 2007). Future studies should systematically evaluate the role of hypothalamic-pituitary-adrenal (HPA) axis dysfunction in patients with anger attack and irritability (Van Praag, 2001). Emerging evidence points bidirectional association (Gold & Kadriu, 2019) between the HPA axis and lateral habenula, a key brain region in reward circuit that has been shown to modulate aggressive behavior in pre-clinical models (Flanigan et al., 2019; Golden et al., 2016).

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There are several limitations of this report. Findings of this report were obtained by unplanned secondary analyses, and as such they may not be adequately powered and should be considered preliminary. The presence of anger attacks was ascertained only at baseline. Thus, we cannot estimate the proportion of participants who no longer met criteria for anger attacks after 8 weeks of antidepressant treatment. The assessments of anger attacks, aggression, hostility, and irritability were restricted to a self-report measure which differs from studies in youths where it is common to include assessments from parent/teacher(s) (Brotman, Kircanski, Stringaris, Pine, & Leibenluft, 2017). As anger attack questionnaire explicitly asked for the presence of irritability in past 6 months, it may explain in part the overlap between the presence of anger attacks and irritability. However, additional analyses based on aggressive behaviors produced similar findings. Finally, the inclusion and exclusion criteria of our studies may make the findings of our study less generalizable to all MDD patients (Zimmerman, Balling, Chelminski, & Dalrymple, 2019).

In conclusion, in this large sample of adult outpatients with MDD, we found that irritability is an important symptom domain which is associated with overt presentation of anger attacks. Additionally, the presence of anger attacks in adult patients with MDD may identify a sub-group of patients who have persistently elevated irritability despite acute-phase antidepressant treatment.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291720000112.

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