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CME Objective

After studying the article by Withers et al, you should be able to:

- Ask patients who present with depression with atypical features about traumatic events prior to and after depression onset, and consider the possible effects of mood on their experience and reporting of events

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Is Depression With Atypical Features Associated With Trauma History?

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ABSTRACT

Objective: Although studies have linked childhood trauma to depression resembling the atypical subtype, a majority of these studies did not use *DSM-IV* criteria for atypical features nor assess trauma both before and after depression onset. This study examined the relationship between atypical depression and lifetime trauma with the hypothesis that atypically depressed patients would report a higher number of trauma exposures than nonatypically depressed patients.

Method: Raters blind to depressive subtype investigated trauma history by reviewing the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders—Patient Edition (SCID-I/P) posttraumatic stress disorder modules and social history sections in charts of depressed outpatients who had participated in treatment studies between 1985 and 2010. Rates of trauma both before and after depression onset were compared for 292 depressed patients with and without *DSM-IV*-defined atypical features using χ^2 tests and binary logistic regressions. This chart review was conducted from 2009 to 2011.

Results: Lifetime trauma was reported significantly more often by depressed patients with atypical features than by those without ($P < .001$). Patients with atypical features reported significantly more traumatic experiences both prior to ($P = .012$) and following ($P = .015$) depression onset. When sex and age at onset or duration of depression were used as covariates, depressive subtype was a significant predictor of reported trauma both prior to ($P = .028$) and following ($P = .011$) depression onset.

Conclusions: These results suggest that a relationship exists between atypical depression and lifetime trauma that may be more complex than the etiologic pathways outlined in prior research. Rather, trauma and atypical depression may be interrelated throughout life.

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Trauma and depression are highly associated.^{1–5} However, few studies have examined the relationship between trauma and *DSM-IV* depressive subtypes, such as depression with atypical features, which is defined by mood reactivity and at least 2 of the following: significant weight gain or increased appetite, hypersomnia, leaden paralysis, and interpersonal rejection sensitivity. Atypical depression has been differentiated from other forms of depression in terms of its biology,^{6–8} treatment,^{9–11} and family history.¹²

Research has shown a possible link between trauma and atypical depression. Although 1 study associated severe childhood adversity with endogenous depression¹³ resembling the melancholic or nonatypical depression subtype, most have connected trauma with nonendogenous depression^{14,15} resembling the atypical depression subtype.^{16,17} Specifically, depression with reversed neurovegetative

features (oversleeping and overeating) was more strongly associated with childhood abuse than both depression without reversed neurovegetative features^{16,17} and normal controls.¹⁶ Trauma has also been associated with early onset of depression,^{4,18} chronicity of depression,^{3,19,20} and increased comorbidity.^{4,21} Since atypical depression is characterized by reversed neurovegetative features,^{6,12} early onset,^{12,22–24} chronicity,^{12,22,24} and increased comorbidity,^{6,23} it seems plausible that increased trauma may also be associated with this depressive subtype.

A second possible link between trauma and atypical depression comes from reports^{25,26} that both exhibit down-regulation of the hypothalamic-pituitary-adrenal (HPA) axis due to chronic stress. Cortisol levels are lowered in posttraumatic stress disorder (PTSD)²⁷ and hypersuppressed in childhood sexual abuse victims²⁸ and depressed trauma survivors.²⁹ Similarly, in atypical depressive patients, cortisol levels are lowered relative to both melancholic depressive patients³⁰ and healthy controls³¹ and hypersuppressed relative to healthy controls,³² especially for early-onset, chronic atypical depression.⁸ Thus, a hypoactive HPA axis characterizes trauma victims and atypical depression patients in contrast to the hyperactive HPA axis in melancholic depression.^{33,34}

Nevertheless, gaps remain in research linking atypical depression and trauma. First, prior studies^{16,17} did not use *DSM-IV* criteria for atypical depression but instead used reversed neurovegetative symptoms to infer atypical subtype. Second, the majority of studies required the presence of childhood maltreatment^{16,17,25} or PTSD rather than trauma in general.^{16,35} Though some studies take trauma events at any age into account, they still limit their purview to those that occurred prior to depression onset,¹⁴ assuming that early trauma predisposes one to later development of atypical depression.^{16,17} If trauma causes atypical depression, there should be increased trauma prior to depression onset but not necessarily once depression has occurred. Alternatively, association of trauma and atypical depression before and after depression onset would not disprove a causal connection but would indicate the possibility of a more complex relationship and require the consideration of additional factors.

We sought to answer the following questions: (1) Does a relationship exist between trauma and *DSM-IV*-defined atypical depression? (2) Do rates of trauma differ before and after onset of depression? and (3) Are any individual atypical features associated with trauma?

We hypothesized that atypical depression patients would report more lifetime traumatic experiences than nonatypical depression patients. We also predicted that certain characteristic features of atypical depression, particularly mood reactivity and rejection sensitivity, might mediate the relationship between reported trauma and atypical depression, perhaps by making individuals more sensitive to negative events.

METHOD

Description

A chart review of depressed patients was conducted between 2009 and 2011 to assess presence or absence of trauma, with

- History of trauma appears more likely in patients with atypical depression than other depressive subtypes.
- Patients with atypical depression report more traumatic experiences both prior to and following depression onset.
- Individual symptoms of atypical depression do not appear to be associated with trauma history; the association may be present only when multiple symptoms co-occur to form the distinct syndrome of atypical depression.

particular focus on the timing of any reported trauma. This research was approved by the Institutional Review Board (IRB) of the New York State Psychiatric Institute.

Participants

Patients who had participated in various psychopharmacologic research studies at the Depression Evaluation Service of the New York State Psychiatric Institute from 1985 to 2010 were randomly selected from a pool of several thousand Depression Evaluation Service patients until a sample of 300 patients was obtained. Criteria for inclusion were current diagnosis of a unipolar mood disorder (ie, major depressive disorder, dysthymic disorder, or depressive disorder not otherwise specified) and determination of presence or absence of both atypical features and trauma history. There was insufficient documentation of trauma history for 6 patients and depressive diagnosis for 2 patients, so 8 were removed from the analysis, resulting in 292 patients. Because of exclusion criteria from prior Depression Evaluation Service studies, no participant had a history of psychosis, current substance abuse or dependence, and/or other medical conditions or medications that were known to induce psychiatric disorders at the time of intake. Most Depression Evaluation Service studies excluded individuals with histories of bulimia or anorexia nervosa because of antidepressant-associated seizure risk. Informed consent was obtained for the initial Depression Evaluation Service studies and the New York State Psychiatric Institute IRB granted a waiver of consent for the present research.

Diagnosis

At intake, a research psychiatrist completed an interview including the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders–Patient Edition (SCID-I/P)³⁶ and a written social history, with particular focus on depressive subtype. For this study, all diagnoses past and present were taken into account and patients were grouped into those who had experienced an atypical episode and those who had not.

Sources of Trauma Information

The SCID-I PTSD module was reviewed for any traumas listed, followed by the written social history for any additional traumas.

Types of Trauma

Trauma was defined as in *DSM-IV* as physical abuse, sexual abuse, experiencing a serious accident or disaster, witnessing severe violence, and experiences that threatened death, serious injury, or threat to the physical integrity of self or others. We considered severe verbal/emotional abuse by a caregiver toward a dependent child to be a threat to physical integrity, but vague statements, such as “the patient had a traumatic home environment” or “the patient’s mother would yell at him,” were not included as trauma.

Trauma Raters

Two raters (J.M.T. and A.C.W.) blind to depressive subtype documented all potentially traumatic events (213) from intake records. Both raters then judged each event as either fitting or not fitting the definition of trauma above, achieving high interrater reliability ($\kappa = 0.75$). All discrepancies (11) between judges were resolved by consensus with a third judge (J.W.S.). Thirty-six events were deemed nontraumatic, resulting in 177 traumatic events. Patients were then coded for whether they experienced trauma throughout their lifespan (“lifetime trauma”). Following completion of trauma coding, presence and dates of traumas were merged with a database that included demographics, Axis I diagnoses, depressive subtype, and age at depression onset.

Timing of Trauma

When documented, age at each traumatic event was recorded. For discrete events (eg, witnessing violence), a single age was recorded. For ongoing or chronic events (eg, abuse throughout childhood), ages at both onset and offset of the event were recorded. By using the ages at which the traumatic events occurred and the age at first depression onset, each patient was identified as having experienced trauma prior to depression onset, following depression onset, or both. Some patients provided the life period (eg, childhood, adolescence, adulthood) when the trauma occurred rather than a specific age. When it was possible to determine the order of events, the before and after depression onset trauma categories were coded. For example, someone who was sexually abused “throughout early childhood,” became depressed “after college,” and then was attacked at knifepoint “during middle age” would be coded as having trauma both before and after depression onset. However, if both depression onset and trauma occurred “in childhood,” the relative order could not be determined. Likewise, because depression chronology and trauma history were probed separately, events that occurred at the same age or co-occurred were not assigned a relative order, and such traumas were captured only under the lifetime trauma category. Twenty-nine patients had trauma history that could not be established as occurring before or after depression onset and therefore were included in analyses of lifetime trauma but not of onset-relative trauma.

Statistics

Analyses of variance were used to compare atypical depression and nonatypical depression diagnostic groups on

age at intake, age at earliest depression onset, age at earliest trauma, and number of years from first depression onset. Sex ratio, comorbidity, and lifetime trauma rates between diagnostic groups were compared between diagnostic groups with $2 \times 2 \chi^2$ tests. We expected to find that female patients would have higher rates of both atypical depression^{23,24,37} and trauma,³⁸ so an additional $2 \times 2 \times 2 \chi^2$ test compared lifetime trauma rates by sex and diagnostic group.

To account for the fact that there is more opportunity for trauma to occur over longer periods of time, all time-relative trauma rates (ie, trauma before and after depression onset) were assessed by using binary logistic regressions covaried for the duration of the time period in years. This method corrects for potential effects of expected differences in age at onset between the 2 diagnostic groups. The duration of the period before depression onset was measured as the age at first depression onset. The duration of the period after depression onset was measured as the difference between the current age at intake and the age at first depression onset. Binary logistic regressions were run for each time period, with trauma presence as the categorical dependent variable, sex and depressive subtype as categorical predictors, and duration of time period as a continuous predictor. Thus, while it was expected that female gender and longer duration would both be significantly associated with increased trauma rates in each time period, the question of interest was whether atypical depression remained a significant predictor of higher trauma rates while sex and duration were included as covariates. This analysis was meant to confirm the hypothesis that atypical depression is associated with increased trauma rates in the period preceding first depression onset and to test whether atypical depression patients have similar or different trauma rates in the period following depression onset.

To examine whether individual atypical depression features account for any atypical depression-trauma associations, similar binary logistic regressions were run for each life period using all 5 atypical depression features as simultaneous categorical predictors in place of depressive subtype.

RESULTS

Demographic Characteristics

The sample of 292 depressed individuals consisted of 96 (32.9%) atypical depression and 196 (67.1%) nonatypical depression patients, with 169 (57.9%) female and 123 (42.1%) male patients. Mean age at intake was 37.2 years ($SD = 11.4$) and at earliest depression onset was 18.7 years ($SD = 13.0$). Mean number of years from earliest depression onset was 18.4 ($SD = 14.0$). Of the 292 patients, 283 (96.9%) had sufficient data to determine lifetime psychiatric comorbidity. Specifically, criteria were met for substance dependence (past only) by 10.6%, PTSD by 7.1%, other anxiety disorders by 33.6%, somatoform disorders by 5.7%, and eating disorders (primarily binge eating disorder) by 8.2%. Overall, 135 patients (47.7%) met diagnostic criteria for at least 1 comorbid disorder.

Demographic data are shown by diagnostic group (Table 1). At intake, atypical depression patients were significantly

Table 1. Demographic Variables of Depressive Subtypes

Variable	Atypical Depression (n = 96)		Nonatypical Depression (n = 196)		Statistic
	Mean	SD	Mean	SD	
Age at intake, y	35.2	11.7	38.1	11.1	$F=4.470, P=.035$
Age at depression onset, y	17.6	12.1	19.3	13.4	$F=1.142, P=.286$
No. of years depressed at intake	17.6	12.6	18.8	14.6	$F=0.476, P=.491$

Table 2. Reported Presence of Lifetime Trauma by Depressive Subtype

Variable	Atypical Depression		Nonatypical Depression		Statistic	
	n/n	%	n/n	%		
Sex						
Male	26/95	27.1	97/195	49.5	$\chi^2_1=13.27, P<.001$	
Female	70/95	72.9	99/195	50.5		
Comorbidity						
Substance dependence	6/95	6.3	24/188	12.8	$\chi^2_1=2.77, P=.096$	
Posttraumatic stress disorder	9/95	9.5	11/188	5.9	$\chi^2_1=1.26, P=.261$	
Other anxiety disorders	38/95	40.0	57/188	30.3	$\chi^2_1=2.65, P=.103$	
Somatoform disorders	9/95	9.5	7/188	3.7	$\chi^2_1=3.91, P=.048$	
Any comorbid diagnosis	51/95	53.7	84/188	44.7	$\chi^2_1=2.05, P=.152$	
Trauma						
Lifetime trauma present	50/95	52.6	60/195	30.8	$\chi^2_1=12.97, P<.001$	
Before depression onset	23/84	27.4	26/180	14.4		$\chi^2_1=6.34, P=.012$
After depression onset	25/85	29.4	30/182	16.5		$\chi^2_1=5.92, P=.015$

Table 3. Reported Presence of Lifetime Trauma by Depressive Subtype and Sex

Sex	Atypical Depression			Nonatypical Depression			Statistic
	Total, n	Trauma, n	%	Total, n	Trauma, n	%	
Male	26	13	50.0	97	24	24.7	$\chi^2_1=6.219, P=.013$
Female	69	37	53.6	98	36	36.7	

Table 4. Presence of Trauma Before and After Depression Onset

Predictor	Trauma Present Before Depression Onset					Trauma Present After Depression Onset				
	β	SE	Wald	df	P	β	SE	Wald	df	P
Sex	-1.076	0.387	7.745	1	.005	-0.255	0.342	0.557	1	.455
Subtype	-0.767	0.350	4.810	1	.028	-0.863	0.340	6.444	1	.011
Duration	0.046	0.012	13.917	1	<.001	0.054	0.011	21.793	1	<.001

Abbreviation: SE = standard error.

Table 5. Presence of Lifetime Trauma by Individual Features of Atypical Depression

Predictor	β	SE	Wald	df	P
Mood reactivity	-0.048	0.401	0.014	1	.905
Weight gain/appetite increase	-0.589	0.306	3.696	1	.055
Hypersomnia	-0.115	0.352	0.107	1	.743
Lead paralysis	-0.381	0.297	1.641	1	.200
Rejection sensitivity	-0.495	0.275	3.228	1	.072
Sex	-0.494	0.285	3.006	1	.083
Duration (age at intake)	0.026	0.012	4.813	1	.028

Abbreviation: SE = standard error.

younger than nonatypical depression patients ($P=.035$). No significant difference was found between atypical depression and nonatypical depression patients in terms of number of years depressed ($P=.491$) and age at onset ($P=.286$), an unexpected result since atypical depression has been associated with an earlier age at onset relative to depressive subtypes.^{12,22-24} Although age at onset was not signifi-

cantly different, atypical depression patients in our sample still had an earlier onset, so this discrepancy appears to result from an earlier than usual onset for nonatypical depression patients versus prior literature.

Sex and comorbidity are compared by diagnostic group (Table 2). Significantly more female patients were in the atypical depression group than in the nonatypical depression group ($P<.001$). No significant difference was shown in any comorbid disorder ($P=.152$), comorbid PTSD ($P=.261$), other anxiety disorders ($P=.103$), or substance dependence ($P=.096$), but significantly more comorbid somatoform disorders were in atypical depression than in nonatypical depression patients ($P=.048$) (Table 2).

Trauma Rates

Basic trauma rates were compared with χ^2 tests (Table 2). Atypical depression patients reported significantly more traumatic experiences than nonatypical depression patients for the lifetime ($P<.001$), before depression onset ($P=.012$), and after depression onset ($P=.015$) periods.

Lifetime trauma was reported significantly more often by 43.7% of female patients (73/167) versus 30.1% of male patients (37/123) ($\chi^2_1=3.11, P=.009$). A $2 \times 2 \times 2$ χ^2 test confirmed that atypical depression was associated with lifetime trauma, regardless of sex (male patients: $P=.013$; female patients: $P=.030$) (Table 3).

In the binary logistic regressions for the period before depression onset, sex ($P=.005$), subtype ($P=.028$), and duration (ie, age at onset) ($P<.001$) were all significant predictors of reported trauma, such that female gender, atypical depression, and longer duration were all associated with more frequent reports of trauma before depression onset (Table 4). For the period after depression onset, subtype ($P=.011$) and duration (ie, age – age at onset) ($P<.001$) were significant predictors, such that atypical depression and longer duration were associated with more frequent reports of trauma after depression onset; however, sex was not a significant predictor of trauma rates after depression onset ($P=.455$) (Table 4).

In the binary logistic regressions with the 5 atypical depression features, sex, and duration as simultaneous predictors of trauma presence, no atypical depression features were significant predictors of reported lifetime trauma (Table 5).

DISCUSSION

To our knowledge, this is the first study utilizing *DSM-IV* criteria for atypical depression while measuring trauma in the

life periods both before and after depression onset. These results confirm the hypothesis that atypical depression patients report more traumatic experiences than nonatypical depression patients. Moreover, our findings are in line with prior studies¹⁴⁻¹⁷ that associated depression resembling atypical depression with early trauma. The data go further, however, in demonstrating that increased trauma also occurs after depression onset.

Various possibilities could explain this relationship between trauma and atypical depression. First, the findings could be coincidental, so they require replication. Second, it is possible that atypical depression patients may not actually incur more traumatic events than nonatypical depression patients, but they may report events differently. Compared to melancholic nonatypical depression patients, atypical depression patients are characterized by a mood state that may make them more likely to initially experience an event as traumatic. Also, research has shown that mood state affects both encoding and recall of memories.³⁹⁻⁴² Amygdala activity during emotional arousal causes increased memory consolidation in the hippocampus, leading to sustained memory enhancement over time.^{43,44} This observation suggests that the emotional tone of an event might influence later recall of *whether* the event occurred at all. It is also possible that the various depressive subtypes include presentations that cue interviewers to probe differently, resulting in varying reports of trauma history.

Third, a possible explanation for the observed relationship to atypical depression patients actually incurring more traumatic events than nonatypical depression patients. It remains possible that early trauma has a causal influence on later development of atypical depression. However, this does not explain increased trauma following depression onset. Alternatively, other factors, such as a chaotic environment, anxious-ambivalent attachment styles,⁴⁵ and personality pathology, determining poor relationship choices and interpersonal problems could be associated with both increased trauma and depressive illness. It is also possible that trauma and atypical depression have a complex and potentially bidirectional relationship. For instance, trauma may induce atypical depression features through adaptive responses of the central nervous system,^{8,25-32} chromosomal changes,^{46,47} and interplay with genes,⁴⁸⁻⁵⁰ while atypical depression may make one more prone to trauma through its characteristic mood state. Any of these possibilities would be consistent with findings that victims of trauma are more likely than nonvictims to experience subsequent traumas.^{35,51}

Although we predicted that rejection sensitivity and mood reactivity would partially mediate the relationship between trauma and atypical depression, this was not the case in our sample. It seems that the 5 atypical depression features combine into a phenomenologically distinct disorder that accounts for more variance in trauma reporting than any of the features alone. This finding should be replicated with more detailed documentation of trauma. For example, it is possible that certain atypical depression features are

associated with particular types of trauma, such as those that are interpersonal in nature.

There are some limitations of this study that merit consideration. The type of patient who presents for participation in free medication studies may represent 1 subtype of depressed individuals, in terms of both exclusion criteria imposed by the researchers and motivation for treatment. For instance, few patients had bulimia or anorexia nervosa and none had bipolar disorder in our sample, which helps control potentially confounding variables⁵²⁻⁵⁵ but also limits the generalizability of our findings. Further, personality disorders are associated with both trauma^{56,57} and atypical depression,^{58,59} but their influence could not be examined, as they are not assessed at the Depression Evaluation Service. However, we found an association of somatoform diagnoses with atypical depression, which confirms prior findings of high rates of somatization disorder in atypical depression.⁶⁰ Although somatoform disorders have been associated with trauma,^{61,62} they were found in only 5.7% of our sample, so it is unlikely that this variable accounts for our main finding. Nevertheless, larger and more inclusive samples are needed to fully examine the role of comorbidity in the relationship between trauma and atypical depression and to generalize our findings to a broader population of depressed individuals.

Further, an important limitation is that although each patient was systematically asked about trauma history during administration of the SCID-I and social history interview, a comprehensive list of specific event types was not consistently probed for. This unstandardized assessment of trauma made it difficult to evaluate trauma in terms of type, severity, and duration, any of which could be important, so future studies should utilize validated trauma scales.

Finally, self-reported trauma history that relied on retrospective recall makes it possible that subjectivity and recall bias were more pronounced in atypical depression patients than nonatypical depression patients. It may be helpful to attain independent corroboration of traumatic events to minimize recall bias.

Because of these limitations, our results can speak only to differences in reporting of trauma during interviews; however, reporting of trauma may be a critically important variable itself, as it can be an indicator of a patient's own life experience. Indeed, corroboration of reported events is often unavailable to clinicians. Therefore, the unstandardized collection of trauma history used in this study may reflect clinical practice better than more sophisticated measures. Thus, when clinicians encounter depressed patients who also report both atypical features and histories of trauma, we suggest (1) keeping in mind the possible effects of mood on the initial experience of events, recall bias, and reporting of events; (2) considering traumatic events throughout the lifespan; and (3) maximizing the standardization of information collection between varying types of patients by using validated, self-rated trauma history questionnaires.

Despite several limitations, our study confirms a link between lifetime trauma and atypical depression and thus

justifies the need for further research into this observed relationship. Our findings suggest that the relationship may be more complex than previously accounted for and that studies limiting trauma inquiries to childhood or life periods before depression may be leaving out half of the picture.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

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POSTTEST

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1. In this sample, which of the following characteristics was significantly less common in the group with atypical depression than in the group with nonatypical depression?
 - a. Male gender
 - b. Posttraumatic stress disorder
 - c. Substance dependence
 - d. Somatoform disorders
2. In this sample, patients with atypical depression reported trauma occurring after the onset of depression ___ those with nonatypical depression.
 - a. Less often than
 - b. As often as
 - c. More often than
3. Which of the following patients is most likely to report having experienced trauma before depression onset, according to the results of this study?
 - a. Mr A, who has depression with mood reactivity
 - b. Ms B, who has depression with increased appetite and weight gain
 - c. Mr C, who has depression with rejection sensitivity and hypersomnia
 - d. Ms D, who has all 5 features of atypical depression
4. To follow recommendations by these authors, what would you do when evaluating depressed patients for traumatic events?
 - a. Always obtain independent corroboration of traumatic events to minimize recall bias
 - b. Maximize standard information collection among patients by always using a validated trauma history questionnaire
 - c. Limit trauma histories to childhood and life periods before the onset of depression