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Depressive symptoms and suicidal ideation among symptomatic patients with a history of Lyme disease versus two comparison groups

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Abstract

Background—Depression has been reported in 8–45% of patients with post-treatment Lyme symptoms (PTLS), but little is known about suicidal ideation in these patients.

Method—Depression and suicidal ideation were assessed using the Beck Depression Inventory (BDI-II). Scores from the PTLS group (n=81) were compared to those from two other groups: HIV+ patients being treated for fatigue (n=70), and a non-patient comparison group (NPCG; n=44). ANOVA and T-tests were used to compare groups; logistic regression was used to identify the strongest correlates of suicidal ideation.

Results—Mean BDI-II scores fell in the mildly depressed range for PTLS and HIV+ patients, with both groups having higher depression scores than the NPCG. Suicidal ideation was reported by 19.8% of the PTLS patients and 27.1% of the HIV+ patients, a non-significant difference. Among those with mild or no depression, suicidal ideation was uncommon (6.5% PTLS & 11.9% HIV+). Among the patients with moderate-to-severe depression, suicidal ideation was more common (63.2% of 19 PTLS & 50%, of 28 HIV+); among these, 2 with PTLS and 1 with HIV+ expressed suicidal intent. 4.5% (n=2) of the NPCG had suicidal ideation, each had scores in the moderate-to-severe depression range. Higher scores on the cognitive-symptoms subscale of the BDI-II predicted greater likelihood of suicidal ideation across patient groups.

Conclusion—As expected, suicidal ideation is increased among patients who are depressed. The fact that one in five patients with PTLS reported suicidal ideation highlights the importance of screening for depression and suicidality to optimize patient care.

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Chronic Illness; Depression; Suicide; Lyme disease

Introduction

Lyme disease is a multi-systemic illness caused by the tick-borne bacterium *Borrelia burgdorferi*. The earliest presentation consists of an expanding skin rash (erythema migrans, [EM]), often accompanied by flu-like symptoms. Later presentations can involve one or more bodily systems, including the joints, heart, eyes, and peripheral and central nervous systems.¹

After treatment of Lyme disease with a course of antibiotics meeting Infectious Disease Society of America (IDSA) guidelines, approximately 5%-20% of patients have persistent or relapsing-remitting symptoms, most often affecting mood, pain, and cognition. The most commonly reported psychiatric symptoms among patients with either persistent symptoms after Lyme disease or chronic neurologic Lyme disease include depression and irritability. 2, 34, & 5

A prospective study of well-defined early Lyme disease however did not find an elevated rate of depressive symptoms among patients with Post Treatment Lyme Disease Syndrome (PTLDS) six months after acute infection compared to recovered patients.⁶ These patients – identified early after infection and optimally treated - not only had less depression but also had less severe functional impairment than reported in other studies of PTLDS.^{7 & 8} Because delayed treatment can lead to a more chronic course,⁹ the rapid treatment for early Lyme disease in this prospective study likely contributed to a more favorable outcome and possibly accounted for the lower likelihood of depressive symptoms. In contrast to the latter prospective study, a case-control study among antibiotic-treated patients with persistent symptoms after Lyme disease reported high levels of negative affect and depression; the rate of major depressive disorder was highest for those with well-defined past Lyme disease (45.2%) compared to those with recovered Lyme disease (5%).¹⁰

Despite reports of depression in PTLDS, little is known about the prevalence of suicidal ideation in this group. There have been isolated case reports of suicidal acts associated with Lyme disease^{11 & 12} or to the probability that one had persistent Lyme disease.^{13 & 14} Because of these case reports and because Lyme disease can be accompanied by factors that increase suicidal ideation and behavior, such as depressive comorbidity, economic stressors, and inflammation^{15, 16 & 17}, it is important to examine suicidal ideation among patients with PTLDS.

Recently, a retrospective chart review reported that 43% of psychiatric outpatients with a history of "Lyme and Associated Diseases" had suicidal tendencies.¹⁸ This report – representing an important first article on the topic - alerted clinicians to inquire about suicidality; the high rate of suicidality was alarming, and led to local and national media coverage in the United States.¹⁹ Several imitations of this study however make the results hard to interpret.¹⁸ Suicidality and depression were not assessed using standardized

validated measures. The term suicidality was not defined, so it was unclear whether these patients had suicidal thoughts, intent, or acts. Because the study does not delineate the criteria used to diagnose "Lyme and associated diseased", it is unclear how many would have met the standard CDC epidemiologic case definition. Finally, because a control comparison group was not included in the study, the reader cannot determine whether the rate among patients with Lyme & associated diseases is any different from another medically ill sample.¹⁸

Our study examines depression rating scale scores in an archived sample of individuals with Post-Treatment Lyme Symptoms (PTLS). We use the term PTLS rather than the more widely used term, Post Treatment Lyme Disease Syndrome (PTLDS), as the latter excludes individuals who develop major depression after Lyme disease diagnosis.²⁰ We chose two comparison groups. One was comprised of HIV+ patients participating in a treatment study for fatigue at the same institute. The second comparison group included medically healthy volunteers. Depressive symptomatology and rates of endorsement of suicidal ideation were compared among the groups.

The primary aim of this study was to report on depression severity and rates of endorsement of suicidal ideation between the two patient groups. A secondary aim was to examine whether the two subscales of the BDI (cognitive and somatic-affective) predict suicidal ideation.

Methods

Subjects

Suicidal ideation and depression were assessed among treatment-seeking individuals with a history of an infectious illness (PTLS n=81; HIV+ n=70) and among a medically healthy non-patient comparison group (NPCG n=44) (Table 1). PTLS patients and NPCG participants were drawn from samples screened for enrollment in an earlier placebo-controlled treatment study testing the efficacy of IV antibiotic therapy for post-treatment Lyme encephalopathy.^{8 & 21} HIV+ patients were drawn from a randomized placebo controlled trial of armodafinil for treatment of fatigue.²²

The PTLS patients met the rigorous epidemiologic case definition criteria established by the CDC for national surveillance²³. In addition, all patients had been treated previously with at least 3 weeks of intravenous antibiotic therapy, had a positive IgG Western blot for Lyme disease at the time of study screening, and reported persistent symptoms (including neurocognitive problems) that started within six months of diagnosis and treatment of Lyme disease. These self-reported neurocognitive problems ranged in severity from mild to severe; only half of the sample in this report had severe enough memory impairment on subsequent neurocognitive testing to be considered "memory impaired".^{21& 24}. The sample of patients with PTLS therefore in this report are typical of individuals with PTLDS in that it includes both those who do and those who do not have objective impairment on formal neurocognitive testing. By requiring not only past documentation of Lyme disease but also a current positive IgG Western blot for study inclusion, our sample exceeds the serologic requirements of the IDSA's definition of PTLDS and of most other articles published on this

topic. The NPCG sample were not ill and did not require treatment; they had been enrolled to enable us to control for the practice effect associated with repeated neurocognitive testing. They had no history of neurologic or psychiatric disorders, no history of Lyme disease or of a Lyme-like illness, and a negative Lyme Western blot antibody test.²¹

In the HIV+ sample, patients with untreated major depression [evaluated using the Structured Clinical Interview for Diagnostic (SCID) modules for depression] or with unstable medical illness and untreated conditions associated with fatigue were excluded. Even though patients with untreated Major Depressive Disorder (MDD) were excluded, those with MDD in partial remission and other Axis I depression diagnoses were included. Overall, 31 patients in this group had a SCID-defined depressive diagnosis.²²

These research studies took place at the NYS Psychiatric Institute and were approved by the Institutional Review Board. All participants signed informed consent for study participation.

Instruments

Depression—The Beck Depression Inventory-II is a validated 21-item self-report measure of depression. Each of the 21 items is rated on a 4-point scale ranging from 0–3.²⁵ The total score corresponds to different severity levels: 0–13 minimal, 14–19 mild, 20–28 moderate, 29–63 severe. Individuals with clinically significant depression typically score over 19.

The BDI-II scores were prorated for the two patient groups. Since the HIV+ patients were enrolled in a treatment study of HIV+-related fatigue, prorated total scores without the 2 fatigue items (Loss of Energy & Tiredness or Fatigue) were calculated. Likewise, because the PTLS patients were screened for a treatment study focusing on cognitive difficulties after Lyme disease; prorated total scores without item 19 (Concentration Difficulty) were calculated. This was done to ensure that the total scores were not inflated for the two patient groups (Table 2).

Subscales—We dichotomized the BDI-II into somatic/affective and cognitive subscales based on prior research (Table 2).^{26 & 27}

Suicidal Ideation (Table 3)—Item 9 of the BDI-II inquiries about suicidal thoughts over the course of the last week. The scores range from 0 ('I don't have any thoughts of killing myself'), 1 ('I have thoughts of killing myself, but I would not carry them out'), 2 ('I would like to kill myself') to 3 ('I would kill myself if I had the chance'). In our study, suicidal ideation was considered present if the score was 1 or greater.

Statistical Analysis

Statistical analysis was conducted using SPSS Version 23, Chicago, IL. Chi-square tests were used to evaluate differences in proportions. Analysis of variance was used to explore BDI-II scores among the three groups. Mean, total, and subscale BDI-II scores were further compared with t-tests. A Bonferroni correction for multiple comparisons was applied with significance set at p .002. To clarify the contribution of depression to suicidal ideation, we reported scores for both depressed and non-depressed subgroups. Logistic regression was

conducted to identify predictors of suicidal ideation among the PTLS and HIV+ groups, control group was not included in the analysis.

Results

There were no significant group differences among groups in age or years of education. However, compared to the PTLS group, HIV+ patients were significantly more likely to be non-White and male (Table 1). Overall, 19.8% (n=16) of PTLS participants reported having suicidal ideation compared to 27.1% (n=19) of HIV+ participants and 4.5% (n=2) of healthy controls.

There were differences in the BDI-II depression scores among the three groups (Table 2). The mean score for both patient groups was higher than mean scores for NPCG. Within the mild range of depression severity characteristic of both groups, HIV+ patients had significantly higher mean scores than PTLS patients. Group differences were similar for both the Somatic-Affective and Cognitive subscales of the BDI-II. When the proportion of individuals in each group with moderate to severe BDI-II depression scores were compared, there was no difference between the two patient groups [χ^2 (1, N=47) = 2.25, p= .19].

Both PTLS and HIV+ patients were significantly more likely to report suicidal ideation without intent compared to NPCG (Table 3). Suicidal ideation was uncommon among those without clinically significant levels of depression, occurring among 6.5% (n=4) of the PTLS group and 11.9% (n=5) of the HIV+ group. Among patients with moderate or severe depression, the rate of suicidal ideation without intent was high in both groups; 52.63% (n=10) in the PTLS group and 46.43% (n=13) in the HIV+ groups. 2 patients in the PTLS group and 1 patient in the HIV+ group expressed suicidal ideation with intent, each of whom had moderate-severe depression. Overall, the difference in reported suicidal ideation between PTLS and HIV+ patients was not statistically significant.

Unlike the PTLS treatment study, depression was evaluated using the SCID in the HIV+ study.²² At the time of evaluation, 39 had no current diagnosis of a mood disorder, 7 had a diagnosis of dysthymia, 4 had sub-threshold depression, 11 had minor depression and the remaining 9 patients had major depression in partial remission. Based on SCID classification, rates of suicidal ideation among the non-depressed [10.25% (n=4)] and the depressed patients [48.38% (n=15)] were comparable to the rates of suicidal ideation reported above using a classification strategy based on dichotomizing depression according to the pro-rated BDI-II severity score (explained above).

To identify the strongest correlates of suicidal ideation, we computed a logistic regression with suicidal ideation (present vs. absent) as the outcome measure (Table 4). Ethnicity, gender, and the patient group were not significantly associated with suicidal ideation, nor was the Somatic-Affective subscale of the BDI-II. The BDI-II Cognitive subscale, however, was positively and significantly associated with suicidal ideation (odds ratio= 1.33, 95% confidence limits= 1.14, 1.55), independent of other factors.

Table 5 presents the frequency of depressive symptoms and suicidal ideation in the PTLS and HIV+ samples by gender and race. The impact of the substantial differences in the demographic makeup are addressed in the discussion.

In a supplemental item-analysis, scores on each item of the BDI-II were compared among the three groups. PTLS and HIV+ patient scores were significantly higher on all items compared to NPCG scores. Pairwise comparisons of PTLS and HIV+ groups were conducted. A Bonferroni correction was applied and results are reported at .002 level of significance. There were no differences between the groups on the following items-mood, pessimism, self-criticalness, suicide, crying, agitation, indecisiveness, worthlessness, sleep, loss of energy, sleep, tiredness or fatigue, and sex. On the remaining 8 items, HIV+ patients scores were higher on all items except item 17, that assesses irritability, which in turn was significantly higher for the PTLS patients.

Discussion

We found that one-fifth of all PTLS patients reported suicidal ideation and nearly onequarter reported moderate-to-severe levels of depression. While suicidal intent was not common in the PTLS group (2 of 81), the high rate of suicidal ideation is of concern. The vast majority of individuals with suicidal ideation in both the PTLS and HIV+ groups also had moderate-severe depression. Among the subgroup of PTLS individuals with significant depression, nearly two-thirds reported suicidal ideation compared to only 6.5% of those without significant depression. The results suggest that primary care providers who see chronically symptomatic patients with a history of Lyme disease should screen for depression, as that would lead to more rapid treatment of the depressive symptoms and alert the clinician to probe for suicidal ideation and refer to a mental health provider. Treatment of depression would likely also lead to improved energy and cognition – symptoms characteristic of both depression and PTLS.

Overall, the mean level of depression was mild in the two groups of patients – those with PTLS and those with HIV+. When considered categorically, 23.45% of PTLS patients reported moderate-to-severe symptoms of depression. This rate is lower than the 45.2% reported in a study of PTLDS recruited from a Lyme Disease referral center in a rheumatology clinic,⁹ but comparable to rates of depression reported in a recent study of patients with acute disseminated Lyme borreliosis.²⁸ Whether high levels of depression among patients with PTLS are related to the immune response triggered by the microbe, aspects of the illness itself (e.g., pain, relapsing-remitting symptoms), psychologic sequelae (e.g., hopelessness and fear), economic stressors (e.g., loss of job, health care expenses) or all of these remains an open question that requires a future study to clarify.

For the PTLS group, approximately 20% reported suicidal ideation. Our results are lower than the 43% rate for suicidal tendencies reported recently from a clinical series of patients diagnosed with Lyme and other associated diseases.¹⁸ Referral bias may have increased the rate of suicidality in the published clinical series, given that these patients were drawn from a psychiatric practice with a specialty in neuropsychiatric Lyme disease. Our study, by making a distinction between suicidal ideation and suicidal intent, suggests that the vast

majority of patients endorsing suicidal ideation do not have the intention or plan to kill themselves. Our findings however, do highlight the psychological distress experienced by a subgroup of patients with PTLS. Their rate of suicidal ideation is similar to that reported for patients with chronic pain,²⁹ and similar to the rate among the HIV+ patients with fatigue in our study.

Slightly over one-quarter of the HIV+ patients in our study reported suicidal ideation; as noted, this was primarily among those with moderate to severe depressive symptoms. Other studies among HIV+ patients that have used item 9 of the BDI to assess suicidal ideation revealed rates ranging from 19% to 40%.^{30, 31 & 32} It is important to note however, that of the 31 patients in the HIV+ sample with a SCID-defined depression diagnosis; 25 were on antidepressants at the time of study enrollment.²² Excluding patients with untreated major depression and including patients on anti-depressant medication may have led to an underestimate of the level of depressive symptoms and suicidal ideation within the HIV+ group in this study.

4.5% (n=2) of the NPCG had suicidal ideation, each of whom reported depressive symptoms in the moderate-to-severe range. As these medically healthy controls were community volunteers, this rate is not surprising as this rate is comparable to what has been reported in a study that used a single question to assess suicidal ideation in the general US population³³; this is also similar to what has been reported by the CDC.³⁴

Rates of self-reported moderate to severe depression did not differ between PTLS and HIV+ patients, and in both groups the presence of suicidal ideation was associated with elevated scores on the cognitive symptoms subscale of the BDI-II. This is consistent with previous factor analyses of the BDI-II,^{35 and} with previous findings that the subjective symptoms of depression are the strongest correlates of suicidal thinking.³⁵ Thus, a common mechanism for the emergence of suicidal thinking appear to be operative across these two infectious diseases.

Our study used item-9 of the BDI-II to assess suicidality as have other studies conducted among patients with medical diseases. Although other more comprehensive assessments of suicidality are available, item-9 of the BDI is a useful quick screen of suicide risk. It has been shown to be a valid predictor of suicide among inpatients³⁶ and of repeat suicide attempts and suicide among 5200 psychiatric outpatients followed prospectively for up to 20 years.³⁷ These studies demonstrated that each successive severity rating on item-9 of the BDI-II conferred greater suicidal risk. Future studies should use a more comprehensive evaluation of suicidality such as the Columbia-Suicide Severity Rating Scale.³⁸

Primary care clinicians may wish to add the PHQ-9 to their assessment of patients with chronic symptoms after Lyme disease; this provides a rapid screen of both depression and suicidal thoughts.³⁹ Patients with mild to severe symptoms of depression may then be asked further about suicidal thoughts, guided by a tool such as the Suicide Assessment Five-step Evaluation and Triage (SAFE-T).⁴⁰

One of the key limitations of this study relates to the use of a convenience medical sample for comparison. In this study, as shown in Table 1, the race and gender makeup of the two

patient groups differed considerably; this may have affected our study findings. We chose the HIV+ patients because this comparator group shared the similar features of seeking treatment in a placebo-controlled clinical trial at the same research facility for distressing symptoms in the context of an infectious disease. Nevertheless, the race and gender make-up of these two samples differed; nearly twice as many patients in the PTLS group were white and four times as many were female. How might these differences have affected the results? Table 4 indicates that neither gender, ethnicity, or group were predictors of suicidal ideation; the only significant predictor of suicidal ideation using data from both the PTLS and HIV+ patients was the cognitive subscale of the BDI-II. Table 5 shows the impact of gender and race; the gender differential suggests that our Lyme sample is biased toward a higher rate of depression and suicidal ideation than would be expected in the more male-dominated HIV+ sample while the race differential suggests that our Lyme sample is biased toward a lower rate of depression and suicidal ideation than would be expected in the more racially diverse HIV+ sample. Therefore, the differential impact of race and gender appear to balance each other out. We emphasize however that it is necessary to replicate our study findings with a more demographically similar medically ill control group.

Other limitations to this study include the following. First, the two patient groups were recruited into different studies; all comparisons are based on archived data. We chose the HIV+ patients because this comparator group shared a number of features: a) participation in a treatment research study at the same institution; and b) have another primary infectious illness often associated with chronicity. However, because the HIV+ patients were seeking treatment in a randomized placebo-controlled study, they may not be representative of the larger group of those without fatigue, those who are not healthy enough or motivated enough to seek help, or those who are unwilling to accept the possibility of placebo treatment. An additional limitation is the restrictive criteria for patients with PTLS. While this was a rigorously diagnosed sample of patients with well-documented prior Lyme disease, patients were restricted to those with neuropsychological complaints; possibly, these individuals would have had different rates of depression or suicidality than those without such complaints. Similarly, as mentioned above the HIV+ patients' data used in this study had to have prominent fatigue; this sample is therefore not representative of the larger sample of those with HIV+ infection. To enhance generalizability, a future replication study would benefit by recruitment of samples recruited from medical clinics rather than a research center.

In conclusion, the fact that nearly two-thirds of depressed patients with PTLS reported suicidal ideation in this study highlights the importance of screening for depression and suicidality to optimize patient care. However, the results of this study do not support the hypothesis that Lyme disease is associated with a higher rate of suicidal ideation than might be found in another illness associated with pain and/or fatigue.

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Table 1

Demographic characteristics of PTLS and HIV+ patients and NPCG

	PTLS patients n=81	HIV+ patients n=70	NPCG n=44
Mean Age (SD)	46.5 (12.2)	45.8 (8.4)	44.1 (9.8)
Mean Years of Education (SD)	14.6 (2.5)	14.6 (2.7)	15.1 (2.6)
Gender (% female)*	59.3%	12.9%	50%
Ethnicity			
White (%)	96.3%	48.6%	93.2%
African American	_	27.1%	2.3%
Hispanic	2.5%	21.4%	4.5%
Other	1.2%	2.9%	-

* p<.001; HIV patients vs PTLS patients; HIV+ patients vs NPCG

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Psychosomatics. Author manuscript; available in PMC 2019 September 01.

Since Item 9 (suicidal thoughts and wishes) was an outcome variable in our study and is included in the computation of the cognitive subscale score, data regarding the cognitive subscale are reported both with and without this item.

*** The somatic/affective subscale was computed by responses on remaining items-loss of pleasure, crying, agitation, loss of interest, indecisiveness, loss of energy, changes in sleep pattern, irritability,

changes in appetite, concentration difficult, tiredness or fatigue and loss of interest in sex.

Table 3

Suicidal ideation among PTLS and HIV+ patients and NPCG *

		ITA	LS n=81	HIV	'+ n=70	NP(CG n=44
Ité	em 9 of BDI-II	Depressed (n=19)	Non-Depressed (n=62)	Depressed (n=28)	Non-Depressed (n=42)	Depressed (n=2)	Non-Depressed (n=42)
0	No Ideation	7 (36.84%)	58 (93.55%)	14 (50%)	37 (88.1%)	I	42 (100%)
-	Ideation	10 (52.63%)	4 (6.45%)	13 (46.43%)	5 (11.9%)	1 (50%)	I
7	Ideation and Intent	1 (5.26%)	I	1 (3.57%)	Ι	1 (50%)	I
3	Strong intent to kill self	1 (5.26%)	I	I	I	Ι	I
De *	pression severity assessed b	y prorated BDI-	-II scores.				

repression sevenity assessed by protation DDT II scores.

 $\overset{*}{}_{\rm r}$ ldeation v
s No-Ideation-Lyme v
s HIV+, ns; Lyme vs Control <.05; HIV+ vs Control <.05

Table 4

Predictors of Suicidal Ideation in PTLS and HIV+ patients

	Adjusted odds ratio	(95% confidence limits)	p-value
Gender-Male (Reference Group-Female)	1.30	(0.42–4.01)	.647
Ethnicity–Non-White (Reference Group-White)	0.49	(0.14–1.69)	.258
Group-HIV+ (Reference Group-PTLS)	1.05	(0.29–3.79)	.940
BDI-II Somatic -Affective subscale	1.07	(0.93–1.23)	.375
BDI-II Cognitive subscale	1.33	(1.14–1.55)	<.001*

* p<0.05

Table 5

Frequency of Depression Severity and Suicidal Ideation in the Patient Group Broken Down by Gender and Ethnicity

Cender					
Gender					
	Lyme		H	IIV+	
	Male	Female	Male	Female	
Depression					
Minimal-Mild Depression	81.82%	72.92%	50.82%	33.33%	
Moderate-Severe Depression	18.18%	27.08%	49.18%	66.67%	
Suicide Ideation					
Absent	87.88%	75%	72.13%	77.78%	
Present	12.12%	25%	27.87%	22.22%	
Ethnicity					
	Lyme		H	IIV+	
	White	Non-White	White	Non-White	
Depression					
Minimal-Mild Depression	81.94%	66.67%	55.88%	41.67%	
Moderate-Severe Depression	24.36%	33.33%	44.12%	58.33%	
Suicide Ideation					
Absent	80.77%	66.67%	70.59%	75%	
Present	19.23%	33.33%	29.41%	25%	