Computerized Cognitive Behavioral Therapy for Patients with Post-Treatment Lyme Disease Syndrome

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COMPUTERIZED COGNITIVE BEHAVIORAL THERAPY FOR PATIENTS WITH POST-TREATMENT LYME DISEASE SYNDROME

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

July 2022

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Abstract

Lyme disease is the most common vector-borne illness in North America. Post-treatment Lyme disease syndrome is defined as a subset of patients appropriately treated for Lyme disease who continue to experience generalized symptoms, such as depression. However, treatment options for depressive symptoms in post-treatment Lyme disease syndrome largely remain unknown. The objective of this study is to examine whether computerized cognitive behavioral therapy, an internet-delivered form of traditional cognitive behavioral therapy, can reduce depressive symptoms in patients with post-treatment Lyme disease syndrome. Here, we conduct a parallel randomized controlled trial to evaluate whether computerized cognitive behavioral therapy can reduce depressive symptoms in this population. Insights into the effect of computerized cognitive behavioral therapy for these patients can help us develop more targeted therapeutic strategies for patients with post-treatment Lyme disease Syndrome in the future.
Chapter 1 - Introduction

1.1 Background

Lyme disease is the most common vector borne illness in North America.\textsuperscript{1-3} Between 2008-2015, a total of 275,589 cases of Lyme disease were reported to the Centers for Disease Control (CDC),\textsuperscript{4} although recent estimates suggest that the actual incidence may be tenfold higher.\textsuperscript{1,5} Lyme disease became a nationally notifiable health condition to the CDC in 1991.\textsuperscript{4,6} Subsequently, from 1992-2013, total case counts increased approximately 3-fold.\textsuperscript{1} Some of this change can be attributed to increased surveillance and recognition, but there is also evidence that the incidence of Lyme disease has increased and has expanded geographically.\textsuperscript{1}

Lyme disease is caused by the spirochete bacteria \textit{Borrelia burgdorferi} and is transmitted to humans by certain \textit{Ixodes} species of ticks.\textsuperscript{1,2} Lyme disease can cause a diverse array of symptoms that may occur at different stages throughout infection.\textsuperscript{1-3} In most cases, it presents with a pathognomonic rash resembling a bull’s-eye, known as erythema migrans.\textsuperscript{1,3} The rash is typically preceded by viral-like symptoms of fever, chills, headache, malaise, myalgias, and fatigue.\textsuperscript{1,3} If left untreated, Lyme disease can disseminate into other organ systems, causing neurological deficits, cardiac abnormalities, arthritis, and more.\textsuperscript{1-3} The majority of cases respond well to antibiotic therapy if detected early after infection.\textsuperscript{7}

Post-treatment Lyme disease syndrome (PTLDS) represents a subset of patients who continue to experience generalized symptoms such as depression, fatigue, myalgia, arthralgia, and cognitive dysfunction that persist for longer than six months after
completing the recommended antibiotic therapy for Lyme disease.\textsuperscript{7-10} Investigators have reported estimates ranging anywhere from 0 to 35\% for non-specific, persistent symptoms post-treatment.\textsuperscript{11-21} This variability in frequency may be due to the lack of a standardized case definition for PTLDS. Although PTLDS is formally recognized by the CDC, they do not provide guidelines on how to treat this disease.\textsuperscript{9} However, case definitions of PTLDS have been proposed by the Infectious Disease Society of America (IDSA) and the Swiss Society of Infectious Disease.\textsuperscript{7,22} They define PTLDS as a series of non-specific, subjective symptoms including musculoskeletal pain, fatigue, and cognitive impairment lasting greater than six months after completing standard antibiotic therapy.\textsuperscript{7,22}

The pathophysiological mechanism behind PTLDS remains elusive.\textsuperscript{7-10} Some animal studies have shown that parts of \textit{Borrelia burgdorferi} remain in animal models after treatment,\textsuperscript{23-25} but there is no evidence that \textit{Borrelia burgdorferi} remains in humans or is caused by the development of antibiotic resistance.\textsuperscript{8,26} Various hypotheses have been proposed including autoimmune dysregulation and hyperactivation of neural pathways following infection, but the exact pathogenesis remains unknown.\textsuperscript{26}

Although many symptoms of PTLDS are subjective and non-specific, various studies have suggested that anywhere from 23.5-50\% of patients with PTLDS experience depressive symptoms.\textsuperscript{20,27-29} This is compelling given the fact that in 2020, 8.4\% of United States adults had one or more depressive episode.\textsuperscript{30} Here, it is important to note that according to the IDSA case criteria for PTLDS, patients cannot be diagnosed with PTLDS if they have a previous psychiatric diagnosis, such as major depressive disorder.
Therefore, the percentage of PTLDS patients who experience depressive symptoms should exclude patients with previously-diagnosed MDD.

The exact mechanism surrounding the development of depressive symptoms and PTLDS remain unclear. Some researchers believe that the development of PTLDS may be due to the patients’ own perceptions about suffering from severe disease. Others believe that depressive symptoms may be due to the somatic effects of the disease as opposed to actual affective depressive symptoms. Lastly, some believe that patients with depressive symptoms and PTLDS already had premorbid psychological conditions. Despite this, it remains clear that depressive symptoms are common in patients suffering from PTLDS.

1.2 Statement of the Problem

Despite the link between PTLDS and depressive symptoms, there are no standardized treatment options for this population. Many treatment options have been proposed, but there is little to no scientific evidence on their efficacy. For example, many studies have shown that prolonged antibiotic use is not beneficial for these patients and can actually cause more harm.

Cognitive behavioral therapy (CBT) is one of the most well-studied treatments for depression, and there is overwhelming evidence that it is both a safe and effective treatment. Because of the symptom overlap between PTLDS and other chronic diseases such as fibromyalgia and chronic fatigue syndrome, non-pharmacological therapies such as counseling and CBT have been proposed. There are, however, no known studies to determine whether or not CBT would be an effective treatment for patients with PTLDS.
CBT has traditionally been delivered face-to-face, however, there has been an increasing desire to deliver CBT over the internet due to barriers to access associated with face-to-face CBT. These include geography, stigma around seeking help in person, cost, time, and precautions necessitated by COVID. Because of this, computerized cognitive behavioral therapy (CCBT) programs have been developed that can help address some of these barriers. Since PTLDS is a relatively rare disease, access to CCBT programs may improve outcomes for these patients.

1.3 Goals and Objectives

This study aims to investigate whether an internet-delivered version of CBT, one of the most effective treatments for depression, can also be effective for treating depressive symptoms in patients with PTLDS. Current data show that a clinically significant portion of patients with PTLDS experience symptoms of depression. However, there are minimal data to support effective treatment options for these patients. If CCBT is found to reduce depressive symptoms in PTLDS patients, it could expand treatment options and improve outcomes in the future.

1.4 Hypothesis

There will be a statistically significant difference in mean BDI-II score between PTLDS patients treated with CCBT compared to PTLDS patients receiving weekly telephone support calls after a period of six months.
1.5 References


Chapter 2 – Review of the Literature

2.1 Introduction

A comprehensive literature review was conducted between June 2021 and July 2022 to acquire the most up-to-date information on PTLDS, depressive symptoms, CBT and CCBT. Search engines such as PubMed, Cochrane, Ovid, and Scopus were used, and assistance was provided by librarians at the Yale School of Medicine. This review explores the prevalence of depressive symptoms in patients with PTLDS, possible etiologies of these symptoms, potential treatments for these symptoms, and the role of CBT in treating depression. Various combinations of the following search terms were used: Lyme disease, Lyme borreliosis, neuroborreliosis, post-treatment Lyme disease syndrome, borrelia burgdorferi, depression, major depressive disorder, depressive symptoms, cognitive behavioral therapy, and computerized cognitive behavioral therapy. The search included systematic reviews, meta-analyses, randomized control trials, cohort studies, cross-sectional studies, and case-control studies. This literature review aims to analyze the existing information surrounding PTLDS, depressive symptoms, cognitive behavioral therapy (CBT) and computerized cognitive behavioral therapy (CCBT) while exploring the various gaps that exist in the literature. ¹

2.2 Review of Empirical Studies

2.2.1 – Case Definitions and Prevalence of Post Treatment Lyme Disease Syndrome

Because the signs and symptoms of PTLDS are non-specific, overdiagnosis and overtreatment are major concerns. Because of this, both the Swiss Society of Infectious Disease and the Infectious Diseases Society of America (IDSA) have proposed case
definitions of PTLDS to help streamline the diagnosis and treatment of this disease. Both of these case definitions are summarized in Table 1.

In summary, both the Swiss Guidelines and IDSA guidelines define PTLDS as a complex disease consisting of non-specific and subjective symptoms, including musculoskeletal pain, fatigue, and cognitive impairment that persist greater than six months after appropriately treated Lyme disease infection. These symptoms cannot be caused by an active infection or another attributable disease. Additionally, both laboratory and clinical evidence of a former Lyme disease infection must be present for diagnosis. Clinical and laboratory evidence of a former infection must be well-documented and fit the appropriate diagnostic criteria for Lyme disease. It is important to note that laboratory evidence of prior Lyme disease infection without previous clinical manifestations of infection does not count. Furthermore, an appropriate timeline between Lyme disease infection and subsequent PTLDS symptoms must be demonstrated (i.e., Lyme disease infection treated appropriately followed by persistent or recurrent symptoms that began within six months of treatment and have persisted for more than six months). Lastly, all other possible etiologies of these symptoms must be excluded, including somatic, psychiatric, and behavioral etiologies.

In 2016, Nemeth et al. reviewed the 2005/2006 Swiss and US case definitions of PTLDS to determine if they were still valid in the context of new data. They reviewed the current scientific literature regarding PTLDS, including clinical history of Borrelia burgdorferi infection, proposed pathophysiology of PTLDS, prevalence of PTLDS, and current treatment options. The authors did not find any new data to suggest that these case definitions should be changed.
Despite the case definitions that currently exist, research studies have used different case definitions to describe PTLDS. Because of this, the prevalence of PTLDS varies greatly between studies.\textsuperscript{7,8} Investigators have reported estimates ranging anywhere from 0 to 35\% for non-specific, persistent symptoms post-treatment.\textsuperscript{9-19} This large range of estimates is likely due to the lack of consistency in enrollment criteria between studies and the fact there is no objective biomarker to diagnosis PTLDS, so physicians must rely on subjective measurements.\textsuperscript{9} Thus, it would be prudent for researchers to use a standardized case definition for PTLDS going forward.
Table 1: Swiss Society of Infectious Disease and Infectious Disease Society of America Case Definitions of Post-treatment Lyme disease syndrome (PTLDS)

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<tbody>
<tr>
<td>- Clinical and laboratory evidence for previous LD infection must be documented</td>
<td>- Adult or child with documented episode of LD infection that meets CDC criteria</td>
<td>- Adequate antibiotic therapy completed and documented</td>
</tr>
<tr>
<td>- Adequate antibiotic therapy completed and documented</td>
<td>- Treatment with accepted antibiotic regimen that stabilized or resolved LD signs/symptoms</td>
<td></td>
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<tr>
<td>- Recurrent or persisting symptoms including arthralgia, myalgia, fatigue, radicular pain, or cognitive dysfunction lasting &gt;6 months after antibiotic therapy</td>
<td>- Onset of the following subjective symptoms within 6 months of LD diagnosis and persistence of continuous or relapsing symptoms for &gt;6 post antibiotic therapy:</td>
<td></td>
</tr>
<tr>
<td>- Plausible timeline between <em>B. burgdorferi</em> infection and PTLDS symptoms (symptoms began within 6 months of completion of antibiotics, persist &gt;6 months)</td>
<td>- Fatigue</td>
<td></td>
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<tr>
<td>- Objective signs on physical exam not required</td>
<td>- Musculoskeletal pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Cognitive difficulties</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Subjective symptoms that interfere with occupational, educational, social, or personal activities</td>
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<table>
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<tr>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>- Evidence of active infection</td>
<td>- Active, untreated concurrent infection such as babesiosis</td>
</tr>
<tr>
<td>- Concurrent rheumatologic, neurological or psychiatric disease</td>
<td>- Objective abnormalities on physical exam that can explain symptoms</td>
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<tr>
<td></td>
<td>- Fibromyalgia or chronic fatigue syndrome diagnosed before LD</td>
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<tr>
<td></td>
<td>- History of undiagnosed or unexplained somatic symptoms before LD (musculoskeletal pain, fatigue)</td>
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<td></td>
<td>- Presence of another diagnosis that may explain patient’s symptoms</td>
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<tr>
<td></td>
<td>- Laboratory or imaging abnormalities that may suggest a disease process other than PTLDS</td>
</tr>
<tr>
<td></td>
<td>- Evidence of <em>Borrelia burgdorferi</em> infection via culture or PCR (Culture/PCR testing not required, but if done a positive result would be an exclusion)</td>
</tr>
</tbody>
</table>

Key: CDC = Centers for Disease Control; LD = Lyme disease; PCR = Polymerase chain reaction
2.2.2 - PTLDS and Depressive Symptoms

Multiple studies have demonstrated the presence of depression in patients with PTLDS. One case control study by Rebman et al. compared subjective symptoms, clinical laboratory results, and quality of life between patients with PTLDS (n = 61) and control participants (n = 26). PTLDS patients were defined as having confirmed or probable history of physician-documented Lyme disease, appropriate antibiotic treatment, and post-treatment symptoms associated with Lyme disease exposure that impacted daily functioning. Participants were excluded based on a self-reported history of various diagnoses that could alternatively explain symptoms, such as autoimmune disorders, HIV, hepatitis B/C, major depressive disorder, fibromyalgia, chronic fatigue syndrome, and substance use. It is important to note that although the inclusion criteria match the IDSA definition of PTLDS, the exclusion criteria were not as stringent. For example, the current study did not evaluate for the presence of co-infections such as babesiosis. They measured Beck Depression Inventory-II (BDI-II) scores in patients with PTLDS and compared them with those of control subjects. The BDI-II is a 21-item questionnaire that has scores from 0 to 63 indicating depression severity. A total score from 0-13 indicates minimal depression, 14-19 is mild depression, 20-28 is moderate depression, and 29-63 is severe depression (Appendix C).

Using t-tests, the study found that the PTLDS group self-reported significantly higher levels of depression than the control group (15.1 ± 7.7 vs 2.2 ± 3.2, p < .001). Additionally, the proportion of PTLDS patients reporting symptom severity above the cutoff for clinically relevant depression (BDI ≥ 14) was significantly higher than the control group (50.0% [30/60] vs 0.0% [0/26], p < .001). This study suggests that patients
with PTLDS may have higher levels of depression than the general population, and that screening tools like the BDI-II may be useful in evaluating and monitoring depressive symptoms in patients with PTLDS.

2.2.3 – Depression in PTLDS Versus Other Chronic Illnesses

Although there is evidence that depressive symptoms are common in patients with PTLDS, there is varying evidence as to whether or not rates of depression are higher in PTLDS compared with other chronic illnesses. For example, one study found higher rates of depressive symptoms in PTLDS patients compared with patients suffering from other various chronic illnesses.\(^{21}\) In contrast, another study found that depressive symptoms seem to be higher in PTLDS compared to healthy controls, but lower in PTLDS compared to other chronic illnesses, such as HIV.\(^ {22}\)

A cross-sectional study by Hassett et al. found higher rates of depressive symptoms in PTLDS compared to other chronic illnesses.\(^ {21}\) They compared patients with PTLDS (n = 31) to two additional groups of patients: one group who had recovered from Lyme disease in the past (n = 40) and another group who had a specific medical condition causing similar symptoms seen in Lyme disease, such as rheumatoid arthritis or multiple sclerosis (n = 42).\(^ {21}\) In this study, PTLDS was defined as patients who had met the CDC criteria for Lyme disease in the past, received adequate antibiotic treatment as defined by the IDSA, no longer had clinical evidence of current Lyme disease infection, attributed their current symptoms to Lyme disease, and had no symptom-free period greater than six months after initial infection.\(^ {21}\) Here, it is important to note that while the inclusion criteria for PTLDS are the same as the IDSA definition, there were no stringent exclusion criteria.\(^ {2,21}\)
In this study, all participants were screened for axis I psychiatric disorders (mood, anxiety, and somatoform disorders) using the Patient Health Questionnaire for mood, anxiety, somatoform, eating and substance use disorders.\textsuperscript{21} Patients who screened positive were then interviewed using the corresponding module(s) of the Structured Clinical Interview for DSM-IV to verify the diagnosis.\textsuperscript{21} Using logistic regression, the study found that rates of psychiatric disorders were significantly higher in the PTLDS groups than the comparison groups (p = .007, p = .02 with Holm correction, odds ratio 2.64, CI 1.30-5.35). Additionally, rates of depression were significantly higher in the PTLDS group than the comparison groups (45.2% in PTLDS, 5.0% in Lyme disease comparison group, 9.5% in other medical diagnosis comparison group, p-value .0099). The fact that 45.2\% of PTLDS patients in this study had depression was particularly compelling given that the rate of depression in the general population is estimated to be around 7.2\%-12.9\%.\textsuperscript{21} Additionally, the fact that the PTLDS group had much higher rates of depression than the group with other medical conditions (and no evidence of Lyme disease) suggests that depression in these patients may be due to the underlying pathophysiology of Lyme disease itself.

However, given the cross-sectional design of this study, the directionality of this relationship cannot be determined. It is possible that these patients had higher levels of depression before developing Lyme disease which helped facilitate the development of PTLDS. Additionally, it is important to note that the diagnosis of major depressive disorder at any point excludes the diagnosis of PTLDS.\textsuperscript{2} Furthermore, the researchers did not screen participants in the PTLDS group for the presence of additional co-infections, history of unexplained non-specific symptoms, or laboratory/imaging abnormalities that
could suggest a disease process other than PTLDS. Therefore, these patients did not necessarily meet the proposed IDSA criteria for PTLDS.

In contrast, a study by Doshi et al. found rates of depressive symptoms to be higher in PTLDS compared to healthy controls, but lower in PTLDS compared to HIV. In this study, the authors used the term PTLS instead of PTLDS because the latter excludes individuals with a past or current diagnosis of major depressive disorder. For inclusion in the PTLS group, patients had to have met CDC diagnostic criteria for Lyme disease, complete at least three weeks of antibiotics, have a positive IgG Western blot for Lyme disease at the time of study screening, and report persistent symptoms (including neurocognitive problems) that began within six months of diagnosis and treatment. Because study inclusion required both past documentation of a Lyme disease diagnosis and current positive IgG Western blot, their inclusion criteria were more strict than the IDSA case definition of PTLDS. However, this study did not exclude patients based on past or current diagnosis of major depressive disorder.

This study used the BDI-II to measure severity of depressive symptoms in PTLS patients and compared those values to those of HIV+ patients and medically healthy volunteers. They then compared rates of suicidal ideation between PTLS patients, HIV+ patients, and medically healthy volunteers. Using ANOVA to compare BDI-II scores among the three groups, mean BDI-II scores were greatest in HIV+ patients (19.0, SD 9.7) compared to PTLS (14.4, SD 8.5) and healthy volunteers (3.8, SD 6.8). BDI-II scores were also greater in PTLS patients compared to the healthy controls. Mean BDI-
II scores indicated a mild level of depression in both the PTLS and HIV+.\textsuperscript{22}

Categorically, 23.45% of PTLS patients reported moderate to severe depression, compared to 40% for patients with HIV and 4.5% for healthy controls.\textsuperscript{22} These differences were statistically significant with a p-value <.05.\textsuperscript{22}

Overall, the results of this study suggest that patients with PTLS have higher rates of depression than healthy participants but lower rates of depression than patients living with HIV. This study highlights the importance of screening for depression in PTLS patients. However, the results of this study do not suggest that patients with Lyme disease experience higher rates of depression than might be found in other chronic illnesses.

It is also important to note that there are some limitations to this study’s generalizability. The sample of HIV+ patients was selected from HIV+ patients who were seeking treatment for chronic fatigue, so it is possible that this sample experienced higher levels of depression than the overall population of HIV+ patients.\textsuperscript{22} Furthermore, the sample of PTLS patients all reported some type of neurocognitive complaint, so it is possible that they suffered higher levels of depressive symptoms prior to study entry.\textsuperscript{22}

\textit{2.2.4 – Driving Factors for Depression in PTLDs}

Despite the fact that depressive symptoms appear to be more prevalent in PTLDs, the driving mechanism behind the development of depressive symptoms remains elusive. One hypothesis in the literature is that depression may be a driving factor for developing PTLDs.\textsuperscript{23} However, studies have found that depressive symptoms do not develop until patients develop PTLDs.\textsuperscript{8,18,23} Furthermore, the characteristics of depression seem to be different in PTLDs compared to major depressive disorder (MDD), suggesting that there
may be a separate neurological pathway driving depression in PTLDS compared to MDD.\textsuperscript{24}

A prospective cohort study by Aucott et al. found that depressive symptoms did not develop until patients developed PTLDS.\textsuperscript{18} The study followed a set of patients with early, untreated Lyme disease in order to characterize their symptoms over time, both pre- and post-treatment.\textsuperscript{18} The study enrolled 63 patients with erythema migrans rash, systemic symptoms consistent with early Lyme disease, and positive two-tier antibody testing for \textit{Borrelia burgdorferi}.\textsuperscript{18} Patients were excluded based on the exclusion criteria for the IDSA case definition of PTLDS.\textsuperscript{18} Patients were then treated for Lyme disease using a three-week course of doxycycline.\textsuperscript{18} Participants reported subjective symptoms and completed a copy of the BDI-II at each visit: before treatment, four weeks post-treatment, three months post-treatment, and six months post-treatment.\textsuperscript{18}

At the end of the six-month period, participants were classified as either PTLDS-positive or PTLDS-negative based on the IDSA case definition.\textsuperscript{18} Differences in number of total symptoms and BDI-II scores between PTLDS status (PTLDS-positive or PTLDS-negative) were analyzed using Chi-square and independent sample t-tests.\textsuperscript{18}

They found that at six months, 35\% of the sample (21 out of 63) met the IDSA case definition for PTLDS.\textsuperscript{18} Demographic characteristics were not significantly different between the PTLDS-positive (n = 21) and the PTLDS-negative (n = 42) groups.\textsuperscript{18} Furthermore, at the initial visit, the PTLDS-positive group did not have a significantly higher BDI-II score than the PTLDS-negative group (M = 3.68, SD = 3.31, t(28) = -1.69, p = .10), but the PTLDS-positive group had a significantly higher BDI-II score than the PTLDS-negative group at six months (p = .0002).\textsuperscript{18} Additionally, less than 10\% of the
sample self-reported new-onset depressive symptoms throughout the study.\textsuperscript{18} This is reflected by BDI-II scores, as less than 8\% of the sample had a BDI-II score greater than 13 at any point in the study.\textsuperscript{18} The study did not report the mean BDI-II scores of the PTLDS-positive group versus PTLDS-negative group.

As a prospective study, the authors were able to better characterize the development of PTLDS as well as explore functional health outcomes associated with PTLDS. The prospective design of this study also reduced bias compared to a retrospective design because the sample did not solely include those who sought treatment after developing worse outcomes after Lyme disease infection. It has also been hypothesized that depression could be a risk factor for the development of PTLDS.\textsuperscript{21,25,26} However, in this study, mean BDI-II scores did not differ significantly between PTLDS-positive and PTLDS-negative groups pre-treatment, suggesting this is not the case.\textsuperscript{18} Furthermore, even though the PTLDS-positive group had significantly higher BDI-II scores than the PTLDS-negative group at six months, only less than 10\% of the whole sample reported new-onset depressive symptoms.\textsuperscript{18} These low rates could be due to exclusion of participants with depression from the study, but it may also indicate that depressive symptoms do not play a major role in PTLDS within the first six months.\textsuperscript{18} Limitations of this study include small sample size, self-reported symptoms, lack of matched control group, and patient presentation limited to EM rash and early Lyme disease.

Similar to the previous findings, an additional prospective cohort study by Bechtold et al. found that depressive symptoms did not develop until after PTLDS.\textsuperscript{23} They evaluated depressive symptoms in early Lyme disease patients throughout a six-
month post-treatment period compared to healthy controls. Similar to the previous study by Aucott et al., patients were included who had an EM rash and evidence of systemic Lyme disease. They were excluded based on exclusion criteria from the IDSA case definition of PTLDS, but were not excluded for common medical conditions (diabetes, thyroid disease, hypertension) that were controlled. Participants were then treated with three weeks of oral doxycycline and completed BDI-II pre-treatment, three weeks post-initiation of treatment, and six months post-treatment. Control participants were matched to cases based on age, sex, and the presence of well-controlled medical conditions. At six months, cases were considered PTLDS-positive based on IDSA criteria. Based on this, three groups were formed: PTLDS-positive (n = 6), PTLDS-negative (n = 101), and controls (n = 26). PTLDS-positive made up 5.6% of the sample (6 out of 101).

Using ANCOVA and post-hoc analyses, they found that pre-treatment, PTLDS-positive and PTLDS-negative groups had significantly higher levels of depressive symptoms than controls (PTLDS-positive: 11.8 ± 9.5 (0.0-25.0), PTLDS-negative: 4.8 ± 4.9 (0.0-21.0), control: 2.3 ± 2.7 (0.0-9.3), p = .005). Three weeks post-initiation of treatment, PTLDS-positive patients had higher levels of depressive symptoms than both PTLDS-negative and controls (PTLDS-positive: 10.2 ± 6.6 (1.0-20.0), PTLDS-negative: 4.3 ± 4.1 (0.0-18.0), control: 2.3 ± 2.7 (0.0-9.3), p = .004). Similarly, at six months post-treatment, PTLDS-positive patients had higher levels of depressive symptoms than both PTLDS-negative and controls (PTLDS-positive: 13.8 ± 8.8 (5.0-25.0), PTLDS-negative: 2.1 ± 2.3 (0.0-12.0), control: 2.3 ± 2.7 (0.0-9.3), p = .0003).
the PTLDS-positive group had a mean BDI-II score of 13.8, which indicates clinically-relevant depression.\textsuperscript{23}

The results of this study suggest that PTLDS-positive patients experience higher rates of depressive symptoms than both PTLDS-negative patients and the general population, and that their depressive symptoms are clinically relevant. Furthermore, depression is not a driver for PTLDS, as the PTLDS-positive patients did not develop depressive symptoms until after treatment for Lyme disease.\textsuperscript{23} This suggests that there may be a separate neurological pathway that drives depressive symptoms in PTLDS as compared to MDD. Furthermore, this study suggests that it is important to screen PTLDS patients for depression. The PTLDS sample was well-defined and paralleled the IDSA case definition.\textsuperscript{23} Limitations to this study include a small sample of PTLDS patients (n = 6) and a small control group, limiting sample to patients who presented with EM rash, and only including patients who were treated early and appropriately for Lyme disease.\textsuperscript{23}

Building on the previous study, Weinstein et al. studied the same cohort of patients from the previously mentioned study by Bechtold et al.\textsuperscript{8,23} However, instead of only following these patients for six months post Lyme disease diagnosis, this study followed these patients for one year.\textsuperscript{8} At the one-month mark, they measured depressive symptoms using the BDI-II.\textsuperscript{8} As described above, the cohort consisted of three groups: PTLDS-positive (n = 6), PTLDS-negative (n = 101), and controls (n = 26).\textsuperscript{8} Using Mann-Whitney U-tests to compare depressive symptoms between the PTLDS-positive group and non-PTLDS groups with a significance level of p < .05, they found that at the one-year mark, PTLDS patients had significantly greater cognitive-affective depressive symptoms than non-PTLDS participants measured with the BDI-II (PTLDS-positive:
At the one-year mark, five out of the six PTLDS-positive participants endorsed clinically significant, yet mild, levels of depression. This study suggests that PTLDS patients may develop clinically-relevant depressive symptoms. This could be due to emotional distress secondary to having an illness or perhaps that PTLDS inherently causes depressive symptoms as part of the illness. Similar to the previous study, limitations include small sample size (n = 6), limiting sample to patients who presented with EM rash, and only including patients who were treated early and appropriately for Lyme disease.

These studies suggest that not only do depressive symptoms seem to develop after PTLDS, but depressive symptoms in PTLDS seem to be different than MDD, suggesting a separate underlying neurological pathway. A study by Keilp et al. compared depression severity and neurocognitive dysfunction between patients with PTLDS and major depressive disorder (MDD) in order to elucidate similarities and differences in neuropsychological mechanisms between the two disorders. PTLDS patients all met current diagnostic criteria for the IDSA case definition of PTLDS. First, the PTLDS group (n = 81), MDD group (n = 92), and healthy comparison (HC) group (n = 97) were compared based on depression severity using the BDI-II. Mean BDI-II scores were significantly higher in the MDD group compared to the PTLDS group (MDD 33.0 (11.2), PTLDS 14.7 (8.1), p < .001). However, mean BDI-II scores were significantly higher in the PTLDS group compared to the HC group (PTLDS 14.7 (8.1), HC 2.6 (5.1), p < .001). Depressive symptoms in the PTLDS group were characterized as mild by the BDI-II, whereas depressive symptoms in the MDD group were characterized as severe.
Secondly, the PTLDS and MDD groups were compared based on neuropsychological performance using the standard factor-derived index scores from the Wechsler Adult Intelligence Scale, Third Revision (WAIS-III) and selected subtests from the Wechsler Memory Scale, Third Revision (WSM-III), including Faces Memory I & II, Logical Memory I & II, Letter-Number Sequencing, and Spatial Span. All WAIS-III scores and WSM-III scores were then converted into T-scores that adjusted for age, sex, and education effects on test performance, which allowed for direct comparison of scores between groups. WAIS-III t-scores and WMS-III t-scores were then compared in omnibus fashion between groups using a General Linear Model. If an overall significant omnibus test was found, the individual scores were then examined using ANOVA with Student-Newman Keuls post hoc procedure.

Among WAIS-III index scores, PTLDS patients had lower Working Memory (F[2,267] = 6.91, p = .001) and Verbal Comprehension Index scores (F[2,267] = 9.91, p < .001) than both the MDD and HC groups. Among WMS-III scores, PTLDS patients performed worse on Logical Memory I (F[2,266] = 25.07, p < .001) and Logical Memory II (F[2,266] = 26.19, p < .001) than both MDD and HC participants.

Overall, the results of this study suggest that PTLDS patients tend to present with mild to moderate depressive symptoms, while MDD patients present with severe depressive symptoms. Furthermore, while PTLDS patients are less depressed than MDD patients, they have a greater level of difficulty on memory-related tasks. These findings may help clinicians better distinguish between patients with PTLDS and patients who present with MDD alone. Additionally, these findings suggest that there may be a separate neurological pathway leading to depressive symptoms in patients with PTLDS.
as compared to MDD. However, it is important to note that as a retrospective study, the severity of depressive symptoms may be overestimated.

Based on the literature, there is evidence that depressive symptoms may be present in patients with PTLDS. Not all studies reported the prevalence of depression in patients with PTLDS. Of the four studies that reported statistics, depression was prevalent from anywhere from 23.5% to 50%.\textsuperscript{18,20-22} Despite this, the exact mechanism driving depression in PTLDS remains elusive. One hypothesis in the literature is that depression may be a risk factor for developing PTLDS.\textsuperscript{23} However, in some studies, depressive symptoms do not develop until patients develop PTLDS.\textsuperscript{8,18,23} Furthermore, other studies have suggested that the depressive symptoms are associated with greater cognitive difficulties in PTLDS compared to MDD, suggesting that there is a separate neurological pathway driving depression in PTLDS compared to MDD.\textsuperscript{24} Lastly, while some studies have found rates of depressive symptoms to be higher in patients with PTLDS compared to patients living with other chronic illnesses,\textsuperscript{21} other studies have not found this to be the case.\textsuperscript{22}

2.2.5 – PTLDS Diagnosis and Treatment

The diagnosis and treatment of PTLDS poses some challenges because objective signs and symptoms have been difficult to document.\textsuperscript{9,27-30} Furthermore, since there are no objective physiological biomarkers to aid in diagnosis, it is primarily a clinical diagnosis that is based off of laboratory and clinical evidence of prior Lyme disease infection as well as patient-reported symptoms after adequate treatment.\textsuperscript{23,27,29,30} Because of this, it is important to review prior testing to ensure the initial diagnosis of Lyme disease was correct, take the timeline of symptoms into account, and determine whether
or not PTLDS symptoms could be due to other diseases such as fibromyalgia, chronic fatigue syndrome, or other medically-unexplained symptoms. Ultimately, PTLDS is a diagnosis of exclusion and requires a thorough evaluation of other possible underlying conditions that could explain the patient’s complaints.

There are currently no recommendations for specific treatment of PTLDS by the Food and Drug Administration (FDA), Infectious Disease Society of America (IDSA), or the Ad Hoc International Lyme Disease Group. Several randomized control trials in patients with a history of Lyme disease who report PTLDS symptoms have not found prolonged antibiotic therapy to be effective. Furthermore, many serious adverse effects are associated with prolonged antibiotic therapy and the long-term use of intravenous catheters. Because of the similarities between conditions like fibromyalgia and chronic fatigue syndrome, it has been proposed that it may be helpful to treat patients with similar therapeutic strategies such as cognitive behavioral therapy and low impact exercise.

2.2.6 – Beating the Blues: Internet-Delivered CBT for Depression

Cognitive behavioral therapy (CBT) is one of the most well-studied treatments for depression, and there is overwhelming evidence that it is both safe and effective. CBT is a form of psychotherapy that helps patients recognize how their underlying negative thoughts, attitudes, beliefs, and expectations contribute to feelings of sadness and anxiety. Once these thoughts are recognized, patients can work to question and change underlying beliefs that contribute to depression. CBT has traditionally been delivered face-to-face, but recently, there has been increasing interest in delivering CBT via the internet due to the barriers associated with face-to-face CBT. These include
geography (distance to CBT provider), a lack of available therapists, stigma around seeking help in person, time, cost, and COVID.\textsuperscript{36,37} Because of this, alternative methods of CBT, called computer-assisted cognitive behavioral therapy (CCBT) have been developed that are delivered over the internet and require minimal therapist involvement.\textsuperscript{36,38,39} A recent meta-analysis examined 40 RCTs that studied CCBT for treating depression.\textsuperscript{40} The study found that the random effects weighted mean effect size for CCBT compared to controls at posttreatment was $g = 0.502$ (SE = 0.057, 95\% CI, 0.390 to 0.614, $P < .001$), which is a moderate to large effect size.\textsuperscript{40} Similarly, another meta-analysis reported that compared to usual care, CCBT significantly improves symptoms for mild to moderate major depression ($M = 0.83$, 95\% CI, 0.59 – 1.07).\textsuperscript{36}

Beating the Blues (BtB) is an interactive, computer-based CBT program that has been shown to reduce depression and anxiety symptoms in primary care patients.\textsuperscript{38,39,41,42} It consists of a 15-minute introductory videotape followed by eight therapy sessions that last each last 50 minutes (Appendix H).\textsuperscript{41} Each 50-minute session is customized to the patient’s specific needs and contains interactive menus, advice, and personalized feedback to engage and motivate patients.\textsuperscript{41} There are also video vignettes of patients practicing CBT strategies to give participants concrete examples on how to employ CBT techniques.\textsuperscript{41} Physicians are provided with progress reports after each session.\textsuperscript{41} BtB has been shown in clinical trials to reduce depressive symptoms more than treatment as usual for patients in primary care and community treatment settings.\textsuperscript{38,39,41,42} has similar outcomes to face-to-face CBT,\textsuperscript{39} and is a cost-effective method for treating depressive symptoms.\textsuperscript{43}

2.2.7 – \textit{Beating the Blues: Evidence for Reducing Depressive Symptoms}
One randomized control trial examined the effects of BtB for treating depression in adult primary care patients compared to treatment as usual (TAU). Participants were recruited from several primary care offices and included based on an International Classification of Diseases -10 (ICD-10) diagnosis of depression. Participants were randomized to either receiving BtB (n = 55) or TAU from their primary care provider (n = 66). Participants in the BtB group underwent weekly BtB sessions at their primary care office plus standard treatment. Participants in the TAU group were either referred to counseling/support services or received psychotropic medications. The study measured BDI-II scores of patients pre-treatment, post-treatment, and at one, three, and six months. Using a series of mixed effects regression models, the authors found a significantly greater reduction of 5 points in the BDI-II scores of the BtB group compared to TAU (95% CI, 2 – 9, P < .05) at all post-treatment visits with a moderate effect size of \( d = 0.54 \). Furthermore, after treatment with BtB, the mean BDI-II scores for depression fell to the near normal range (M = 12.04, SD = 10.45, P < .05). These findings were persistent whether or not participants received pharmacotherapy. These results suggest that BtB is more effective than TAU for treating depression in primary care patients. One limitation to this study is the high attrition rate: in the BtB group, 35% of patients did not complete the full BtB program. Although these dropout rates are similar to those reported in trials of face-to-face therapy, other studies have found attrition rates to be higher in CCBT.

Another study was a continuation of the Proudfoot et al. 2003 BtB randomized control trial described above. They continued to enroll participants from the previous study who had depression based on the ICD-10 diagnostic criteria. Similar to the study...
above, participants were randomized to either the BtB (n = 146) or TAU (n = 128) group. They then measured average changes in depressive symptoms with the BDI-II pre-treatment, post-treatment, and at one, three, and six months. Using linear mixed effects models, they found that while mean BDI-II levels decreased for both BtB and TAU, they decreased more in the BtB group (Pre-treatment, BtB: M = 24.9 (10.8) TAU: M = 24.7 (9.2). Post-treatment, BtB: M = 9.3 (8.5) TAU: M = 14.9 (11.3) with a moderate effect size of d = 0.47. The results of this study suggest that BtB may reduce depressive symptoms in primary care patients more than TAU. The attrition rates in the BtB group were similar to the previous study (37%) and to the TAU group (34%).

A naturalistic, open trial examined the efficacy of BtB for depression in routine care settings (eight primary care and three mental health centers). Health care providers identified patients as having depression based on their clinical judgement. Participants then completed the BtB course. After each weekly session, the participants were asked to rate their depression on nine point scale, with zero being not at all depressed and nine being extremely depressed. Using t-tests, they found a significant reduction of 1.85 in self-reported depression between the first and last BtB session (P < .001), with an uncontrolled pre-post effect size of 0.87. 62% of patients completed the entire BtB program, similar to the Proudfoot et al studies. This study is limited in that there is no control group, making it difficult to interpret the treatment effect given the possibility of spontaneous remission or the effects of other treatments. It is also limited by the lack of a depression rating scale. That said, given the previous data from the Proudfoot et al studies that compared BtB to TAU, it contributes to the growing evidence that BtB may be effective for treating depression.
2.3 Review of Relevant Methodology

2.3.1 – Study Design

The proposed study will be a parallel-group RCT investigating the effect of CCBT delivered via the BtB program compared to a weekly phone call intervention on depressive symptoms in patients with PTLDS. The study will recruit PTLDS patients from all over the United States using targeted advertisement campaigns, online flyers, and physician referrals (described in detail in Chapter 3).

An RCT design was chosen based off of previously conducted studies that examined the effects of CCBT on depression compared to a control group. Some studies compared the effects of CCBT to a waitlist control. Although waitlist control groups can be an ethically sound design because participants are still offered the intervention after study completion, it could cause participants to alter their behavior knowing they will eventually receive the intervention. Alternatively, one study compared BtB versus a self-help CBT workbook to treat patients with mild to moderate depression. However, this study did not find a significant difference in changes in depression between the two groups. Lastly, one study examined the use of a CCBT program versus weekly telephone support calls for treating depression. It found that participants receiving the CCBT intervention had a greater reduction in depressive symptoms than the group receiving weekly support calls. Therefore, we will compare the BtB program to weekly telephone support calls to examine changes in depressive symptoms between these two groups.
Participants with PTLDS will be recruited from all over the country using targeted advertisement campaigns both on the internet and in medical settings. A full description of recruitment methods is outlined in Chapter 3.

2.3.2 – Selection Criteria

Participants will be selected who meet the proposed IDSA case definition of PTLDS. Inclusion and exclusion criteria will directly mirror the IDSA inclusion and exclusion criteria as listed in Table 2. In summary, participants must have clinical and laboratory evidence of a prior Lyme disease infection, completed the appropriate antibiotic treatment, and developed a constellation of non-specific symptoms beginning within six months of treatment that cannot be explained by other somatic or psychiatric etiologies.

2.3.3 – Potential Confounding Variables

There are confounding variables that may diminish the validity of the proposed study. Based on review of previous studies that examined depression and PTLDS patients, these include age, sex, education, and total time living with PTLDS. We will measure these variables at baseline and control for them using multivariate analysis.

2.3.4 – Intervention

The intervention will be Beating the Blues (BtB), a computer-based CBT program for primary care patients described above and in Appendix H. BtB is a nine-session internet-based CBT program consisting of a 15-minute introductory video followed by eight, 50-minute interactive online sessions. BtB has been shown in RCTs to be more effective than TAU for reducing depression and anxiety symptoms in primary care patients with depression and/or anxiety. Additionally, in a pilot study, participants
rated their therapeutic alliance with BtB positively, suggesting that BtB may be a favorable option for patients. In terms of cost, studies have also indicated that BtB may be a cost-effective method for treating depression and anxiety in the primary care population. Lastly, CCBT programs have been shown to reduce barriers to and increase access to psychotherapy services for patients with mental health disorders. Because PTLDS is a rare condition and sufferers may be scattered throughout different regions, it is important to use an accessible intervention.

Many studies examining the effects of CCBT have used a waitlist control group. However, even though waitlist control groups can be an ethically sound method because participants are still receiving treatment after the study, there are drawbacks. For example, it has been proposed that participants may alter their behavior knowing they will eventually receive treatment. Therefore, the control intervention in the proposed study will be weekly telephone calls by research personnel to discuss experiences in participants’ lives that may have contributed to feelings of depression. The structure of these phone calls will be based off the 2004 study by Christensen et al., which compared changes in depressive symptoms between participants using a CCBT program to a control group receiving weekly phone calls. The study reported that the CCBT program was more effective in reducing depressive symptoms than weekly phone calls, with the CCBT group having a significantly greater mean decline in Center for Epidemiologic Studies depression score of 3.6 compared to the control group (SD = 0.8-6.3, CI = 95%). The structure of these phone calls will be described in further detail in Chapter 3.

2.3.5 – Randomization Techniques
The randomization techniques used in this study will be similar to previous studies examining the efficacy of CCBT for treating depression. After participants are deemed eligible, they will complete their baseline assessments. Once baseline assessments are completed, participants will be block-randomized using an online research randomizer on a 1:1 basis to either the intervention or control group. This will control for equal representation and minimize the effects of potential confounding variables (age, sex, education, total time living with PTLDS) between both the intervention (group receiving CBT) and control (group receiving weekly telephone calls).

Similar to previous studies, interviewers will be randomly allocated to one of two groups: one group of interviewers will contact the intervention group and the other group of interviewers will contact the control group. For the intervention group, interviewers will contact participants weekly by phone to provide instructions on accessing the BtB program. Interviewers will be provided with an instruction booklet that outlines word-for-word instructions to give the participants for accessing the BtB program. A separate group of interviewers will contact participants in the control group weekly by phone to discuss various topics that may contribute to depression. They will also be provided with an instruction booklet with verbatim questions to ask participants.

Interviewers will be blinded to the study hypothesis and details of the other intervention. It is impossible to blind the experimental group to the intervention they are receiving, but they will be blinded to the study hypothesis and details of the other intervention. The control group will be blinded to the study hypothesis and details of the other intervention. Research personnel responsible for administering questionnaires and analyzing data will be blinded to the group they are analyzing.
2.3.6 – Primary and Secondary Outcomes

The primary outcome of this study will be average change in depressive symptoms using the BDI-II. The BDI-II is a standardized and validated rating scale that is widely used to measure depressive symptoms in clinical and research settings. The BDI-II has 21 items with scores ranging from 0 to 63, with a higher score indicating a higher level of depression. The cutoffs for the BDI-II are as follows: 0-13 indicates minimal depression, 14-19 indicates mild depression, 20-28 indicates moderate depression, and 29-63 indicates severe depression. The BDI-II assesses 21 symptoms and attitudes including mood, sense of failure, guilt feelings, sense of punishment, irritability, social withdrawal, distortion of body image, loss of appetite, somatic preoccupation, self-dislike, self-accusation, suicidal wishes, crying, loss of libido, fatiguability, and work inhibition. A copy of the BDI-II can be found in Appendix C.

Many studies have demonstrated the validity and reliability of the BDI-II in a variety of populations and settings. One study found the internal consistency reliability of the BDI-II to be high with a Cronbach’s alpha of 0.92 for the outpatient population. Not only does the BDI-II have high validity and reliability, but it is also a straightforward and easy to self-administer, instructing participants to rate symptoms occurring within the past two weeks. Lastly, the BDI-II has been widely used to evaluate depressive symptoms in our population, patients with PTLDS.

The secondary outcome measures will be average change in fatigue using the Fatigue Severity Scale (FSS), average change in pain using the Short-Form McGill Pain Questionnaire (SF-MPQ) and average change in quality of life using the Short-Form Health Survey, Version 2 (SF-36). These standardized surveys have been widely used to
characterize symptoms in both clinical and research settings. The FSS is a 9-item questionnaire that measures levels of fatigue, with scores ranging from nine to 63. Higher scores indicate worse fatigue, and a score ≥ 36 indicates clinically relevant fatigue (Appendix D). The SF-MPQ is a 15-item questionnaire that measures levels of pain, with scores ranging from 0 to 45. Higher scores indicate worse pain, and a score ≥ 4 indicates clinically significant pain (Appendix E). Lastly, the SF-36 is a 36-item questionnaire that measures both physical and mental quality of life, with higher scores indicating higher quality of life (Appendix F). These measures have been used in previous research to characterize fatigue, pain, and quality of life in PTLDS patients.

2.3.7 – Sample Size and Statistical Significance

We will calculate our sample size from two previous studies: one that used CBT as an intervention and measured average change in depression using the BDI-II, and one that measured average changes in BDI-II scores in a cohort of prospectively followed Lyme disease patients. The study using CBT reported a mean difference of 3.5 in total BDI-II scores between baseline and at a one-year follow up with intention to treat analysis. The study of patients with Lyme disease found a mean difference of 1.3 in total BDI-II scores between baseline and at one-year follow up. The standard deviation was 4.9.

We will maintain a power of 80%, alpha of 0.05, and two tails. The 2004 study by Christensen et al. which compared a CCBT program to weekly telephone calls had an attrition rate of 15%. Because our proposed study has a very similar design, we will also account for 15% attrition. This results in a sample size of 182, with 91 participants in the control and intervention group.
2.4 Conclusion

This literature review demonstrates that depressive symptoms are common in patients with PTLDS, yet there is still little known about effective treatment options for these patients. With CBT as one of the best studied, least invasive, and most effective treatment options for depression, it is possible that CBT could also be beneficial for reducing depressive symptoms in patients with PTLDS. Furthermore, because PTLDS is a rare disease and there are many barriers to accessing mental health services, CCBT programs, such as Beating the Blues, may be a favorable treatment option for these patients. Our proposed study is a RCT studying the effects of a CCBT program, Beating the Blues, on depressive symptoms in patients with PTLDS, compared to a weekly phone call intervention. The results of this proposed study could inform providers how to safely and effectively manage depressive symptoms in this patient population.

2.5 References


58. Wormser GP, McKenna D, Shaffer KD, Silverman JH, Scavarda C, Visintainer P. Evaluation of selected variables to determine if any had predictive value for, or


Chapter 3 – Methods

3.1 Study Design

The following study will be a parallel-group randomized controlled trial conducted over a period of 12 months. The study will be conducted by researchers at Yale University and will recruit patients by both an advertisement campaign directed towards patients who have been treated for Lyme disease in the past as well as physicians who currently treat patients with Lyme disease. The study population will include participants who are over 18 years of age, meet the specific IDSA criteria for PTLDS, and are not pregnant.

Participants will be randomized to one of two groups. Participants randomized to the intervention group will undergo the Beating the Blues (BtB) online cognitive behavioral therapy program. This program consists of a 15-minute introductory video followed by eight therapy sessions. One session will be completed per week, with each session lasting about 50 minutes. As described in Chapter 2, each session is built upon the previous and tailored to each patient’s specific needs. A description of the BtB program can be found in Appendix H. Participants randomized to the control group will receive six weeks of weekly telephone support calls to discuss factors that may contribute to depression. The structure of these phone calls will be based off of the 2004 study by Christensen et al,¹ and are as follows: Week 1: artistic and physical activities; Week 2: hobbies and education; Week 3: social, financial, and family structure; Week 4: work and stress; Week 5: physical health, medications, and pain; and, Week 6: nutrition and alcohol.
Each primary and secondary dependent variable will be measured at baseline (zero months), two months, and at one-, three-, and six-months follow-up. The control group will follow the same schedule.

3.2 Study Population and Sampling

The study population will consist of participants who meet the Infectious Disease Society of America’s (IDSA) case definition for PTLDS. The inclusion and exclusion criteria mirror the IDSA case definition and are described in Table 2. Participants must also be able to read and understand English at an eighth-grade level or higher. Lastly, participants must not be pregnant.

Yale University researchers will be responsible for the recruitment of patients who may meet the IDSA criteria for PTLDS. Participants will be enrolled in the study continuously during a six-month enrollment period. Interested patients will first undergo preliminary screening via a secure, standardized online survey. The survey will include screening questions to include or exclude patients based on the IDSA PTLDS criteria. Specifically, patients must self-report at least one symptom of fatigue, musculoskeletal pain, or neurocognitive complaints that began within six months of Lyme disease diagnosis. These symptom(s) must also have been present for at least six months, be continuous or relapsing, and interfere with quality of life. Additionally, patients who self-report that they are diagnosed with any of the conditions listed in Table 2 under “exclusion criteria” will be excluded.

If eligible based on screening, participants will be asked if they are still interested in proceeding with the study and would like to be contacted by research staff. If they
agree, they will be contacted by the research assistant via telephone. They will then be asked to sign a consent form that permits researchers to perform a review of their medical records. Specifically, the medical record review will examine prior Lyme disease diagnosis, signs and symptoms of prior LD infection, results of two-tier serologic tests, antibiotic treatment, the presence of any active, untreated co-infections (e.g. Bartonella, Babesia), the presence of any conditions listed under “exclusion criteria” in Table 2, and evidence of fatigue, musculoskeletal pain, or neurocognitive complaints that began within 6 months of LD diagnosis. After this process, patients will be eligible if they meet the IDSA criteria for PTLDS, are 18 years and older, are not currently pregnant, and can read and understand at least an eighth grade level of English.

**Table 2: Study Inclusion & Exclusion Criteria (Based of IDSA Definition²)**

<table>
<thead>
<tr>
<th><strong>Inclusion Criteria</strong></th>
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<tr>
<td>- Adult (18+) with documented episode of Lyme disease (LD) infection that meets CDC criteria</td>
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<tr>
<td>- Treatment with accepted antibiotic regimen that stabilized or resolved LD signs/symptoms</td>
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<tr>
<td>- Onset of the following subjective symptoms within 6 months of LD:</td>
</tr>
<tr>
<td>- Fatigue</td>
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<tr>
<td>- Musculoskeletal pain</td>
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<tr>
<td>- Cognitive difficulties</td>
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<tr>
<td>- Subjective symptoms that interfere with occupational, educational, social, or personal activities</td>
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<tr>
<th><strong>Exclusion Criteria</strong></th>
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<tbody>
<tr>
<td>- Active, untreated concurrent infection such as babesiosis</td>
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<tr>
<td>- Objective abnormalities on physical exam that can explain symptoms</td>
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<tr>
<td>- Presence of another diagnosis that may explain patient’s symptoms (BMI ≥ 45, sleep apnea, narcolepsy, uncontrolled autoimmune diseases, uncontrolled cardiopulmonary or endocrine disorders, malignant conditions within 2 years besides for skin cancer, liver disease, major depressive disorder, bipolar disorder, schizophrenia, delusional disorder, dementia, anorexia nervosa, bulimia nervosa)</td>
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<tr>
<td>- Laboratory or imaging abnormalities that may suggest a disease process other than PTLDS</td>
</tr>
<tr>
<td>- Evidence of <em>Borrelia burgdorferi</em> infection via culture or PCR (Culture/PCR testing not required, but if done a positive result would be an exclusion)</td>
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</table>
3.3 Recruitment

Participants in both the control and intervention groups will be recruited in various ways. First, patients may be referred to the study by physicians who treat patients with Lyme disease. Research staff will send out study information by email and/or by mail to infectious disease, primary care, emergency department, and internal medicine physicians throughout the United States. They will be encouraged to refer patients who they believe may meet the IDSA criteria for PTLDS. Second, an advertising campaign will be created that is specifically directed towards patients who have been treated for Lyme disease in the past. Online flyers will be posted on popular social media websites such as Facebook and Instagram, including Lyme disease-focused Facebook groups. Online flyers will also be sent to Lyme disease information sites and online newsletters of medical practices. Online flyers will also be posted on the Yale New Haven Hospital website. Additionally, paper advertisements will be sent to physicians who treat patients with Lyme disease, and physicians will be encouraged to post these flyers in their medical offices. Lastly, information about the study will be sent to academic hospitals nationwide so they can also recruit their patients to the study.

Each flyer will contain a link to the primary online screening survey. If patients are eligible based on the screening survey, they will be asked if they would like to submit their contact information so that they can be contacted by a member of the research staff. If they agree, their contact information will be sent to the research assistant via the eligibility website. The research assistant will then contact each potential participant via
telephone call to explain more about the study goals, i.e., to improve treatment options for patients living with PTLDs. The research assistant will then explain the potential risks and benefits of participating in the study, what participating in the study entails, and a description of informed consent. If the participant verbally acknowledges that he/she understand the possible study risks, gives informed consent, and agrees to proceed with the study, he/she will be sent an electronic PDF document via email. The document will thoroughly state the study goals, risks, and requirements, as well as an explanation of informed consent. It will also grant researchers permission to review the participant’s medical records and will explain what information researchers are specifically going to obtain. Both of these forms must be signed and returned electronically for participants to enter the next phase of the study.

After consent is obtained, research staff will review each potential participant’s medical record to determine if he/she is eligible to proceed with the study. When participants are eligible based on their medical records, they will be randomly allocated to either the control group or the experimental group. They will immediately be sent a secure, online survey containing a copy of the Beck Depression Inventory-II (BDI-II), Fatigue Severity Scale (FSS), Short-Form McGill Pain Questionnaire (SF-MPQ) and Short-Form Health Survey, Version 2 (SF-36), which they will complete promptly. This BDI-II score will signify their baseline levels of depressive symptoms severity, fatigue, pain, and quality of life. After this process is complete, they will be randomized to their treatment group.

3.4 Study Variables and Measures
The independent variable will be whether participants receive BtB or telephone support calls. Participants in the experimental group will be assigned to complete the internet-based, self-guided BtB program. They will watch a 15-minute introductory video, and then undergo one session of BtB per week, for a total of eight weeks. The participants in the control group will receive weekly telephone support calls for six weeks (described in Section 3.1). Each participant will complete standardized electronic assessments (listed below) at baseline just after randomization (zero months), two months, and at one-, three-, and six-months follow-up.

The primary dependent variable will be the average change in depressive symptoms throughout the study using the Beck Depression Inventory Second Edition (BDI-II) (Appendix C). The BDI-II is a self-administered questionnaire that measures current depressive symptoms and depressive symptoms that were present in the preceding two weeks. The BDI-II is composed of 21 questions. Each question is scored on a scale from 0-3 points. The cutoffs for the BDI-II are as follows: 0-13 indicates minimal depression, 14-19 indicates mild depression, 20-28 indicates moderate depression, and 29-63 indicates severe depression. Each participant will complete a standardized electronic copy of the Beck Depression Inventory measured at baseline just after randomization (zero months), at two months, and at one-, three-, and six-months follow-up visits.

The secondary dependent variables will be average change in fatigue, pain, and global health. Average changes in fatigue will be measured by the Fatigue Severity Scale (Appendix D). Average changes in pain will be measured by the Short-Form McGill Pain Questionnaire (Appendix E). Lastly, average changes in quality of life will be
measured by the Short-Form Health Survey, Version 2 (Appendix F). Each participant will receive a standardized electronic copy of these questionnaires. Like the primary dependent variable, each of these variables will be measured at baseline (zero months), two months, and at one-, three-, and six-month follow-up visits.

The covariates will be sex, age, education, and total time living with PTLDS. These will be recorded at baseline and adjusted for in the multivariate analysis.

3.5 Randomization and Assignment

After eligibility is confirmed and informed consent is completed, each participant will undergo randomization. Each participant will be block randomized on a 1:1 basis to either the control group or the experimental group. Randomization will be performed using Research Randomizer (randomizer.net). Research Randomizer is a free, online randomization tool that will assign each participant a six-digit number and randomly assign them to either the control group or the intervention group. All research personnel responsible for data analysis will be blinded to the identity of each participant using the randomly assigned six-digit code. Lastly, the research personnel involved in data analysis will be masked to the treatment group they are analyzing.

3.6 Data Collection

All surveys will be located on REDCap. REDCap is a secure, web-based application that manages online surveys. Each participant will receive each survey on their password-protected REDCap account. They will receive a survey at baseline, two months, and at one-, three-, and six-months follow-up visits. Each participant will submit
each survey using only their six-digit code so their identity is blinded from research personnel. Participants will have one week to complete each survey after it is sent. They will receive an email notification as soon as each survey is sent, and they will receive an email reminder each day the survey is not completed until the survey is due.

3.7 Sample Size Calculation

The sample size was calculated using the online calculator Power and Precision 4. First, we used data from previous studies to estimate the population mean and standard deviation for both the control and intervention group. We entered these data into the T-test with Two Independent Samples calculator, estimating a 15% attrition rate. The calculator estimated that we will need a sample size of 182, with 91 participants in each group. The full sample size calculation can be found in Appendix G.

3.8 Statistical Analysis

All baseline characteristics will be presented using descriptive statistics. All of the mean between-group differences will be analyzed using an intention-to-treat analysis, meaning that all participants who were randomized will be analyzed in the group in which they were originally assigned. Mean differences in primary and secondary outcomes will first be analyzed at the level of each individual patient using paired t-tests. Secondly, mean differences in primary and secondary outcomes will then be analyzed between the control group and the experimental group using a student t-test. If there is a significant difference between the control group and the experimental group, a linear
regression will be performed using covariates such as sex, age, and total time living with PTLDS. A p-value less than .05 will be considered statistically significant.

3.9 Subject Protection and Confidentiality

The current proposal will be sent to the Yale University Human Research Protection Program (HRPP) to undergo review by the Yale Institutional Review Board (IRB). The proposed study will not begin until all aspects of the proposal are approved by the HRPP and IRB. Before study commencement, all research personnel must complete HRPP training relevant to their role, as described in IRB Procedure 800 PR1 Human Research Protection Training, Orientation, and Continuing Education. Research personnel will not be able to participate in the study until they provide documented proof of completion.

During recruitment, all subjects will begin the process of informed consent in accordance with IRB Policy 410 Recruitment. All potential participants will be accurately informed of the study's nature, purpose, risks and benefits.

Before enrollment in the study, participants must complete an Informed Consent Form in accordance with IRB Policy 400 Privacy and Confidentiality of Human Research Information. This form will be written in simple English and will accurately describe the nature of the study, study procedures, potential risks and benefits, alternatives to participation, subject confidentiality, and voluntary participation. Participants will be informed that they may withdraw from the study at any time without repercussions. Finally, they will be informed that withdrawal from the study will not affect their eligibility for participation in future research.
Lastly, all protected patient information will be securely stored in accordance with federal and state law. All patient information will be stored on password-protected computers and will only be accessed via a secure, password-protected electronic database. Researchers will only obtain and store the minimum information necessary for study completion. All research personnel will sign and submit a confidentiality agreement.

3.10 Timeline and Resources

In accordance with the Thesis Guidelines, this study will be carried out to completion within a maximum two-year time frame. Within this two-year time frame, all aspects of the study such as recruitment, data collection, follow-up, and data analysis will be completed. The following study timeline is listed below:

- Recruitment of study personnel and organization: August 2022 - November 2022
- Participant recruitment and enrollment: December 2022 - December 2023
- Data analysis: May 2023 - July 2023

Of note, subject recruitment will occur over the span of a year on a rolling basis. Participants will be enrolled in the study for a total of six months.

3.11 References:


Chapter 4 – Conclusion

4.1 Advantages and Disadvantages

This study will be the first RCT comparing internet-delivered CBT to an attention control group for treating depressive symptoms in patients with PTLDS. With the prevalence of Lyme disease continuing to rise\(^1\), there will inevitably be more patients developing PTLDS who are in need of care. Therefore, it is important to investigate safe and effective treatment options for this growing population. One advantage of our study is its clear inclusion and exclusion criteria, which mirror the proposed IDSA case definition of PTLDS. This will increase generalizability of our results to other patients living with PTLDS.\(^2\) Many studies in the past have failed to stringently define PTLDS, which may have reduced the generalizability of their results. Another advantage is its RCT design, which will help minimize bias through controlling for confounding variables. Additionally, patients will be recruited from various parts of the country, which will increase sample size and promote generalizability of our results to many populations. Using CCBT will also help improve access to care, as patients are able to access therapy on their own time from any location they chose, without having to work around the schedule of a therapist.

There are some limitations to our study which we must consider. First, previous studies using CCBT have had high attrition rates.\(^3\) While we do attempt to mitigate these effects with our sample size calculation, it is impossible to predict the extent of this issue. We also hope to promote adherence with weekly telephone calls to participants to monitor adherence and answer questions that may come up along the way. Lastly, PTLDS is a rare disease, and our study uses stringent inclusion and exclusion criteria so
that our participants meet the IDSA case definition for PTLDS. While this is beneficial because it will increase generalizability, it could also make it more difficult to enroll patients who meet these rigid criteria. We hope to diminish these effects by enrolling participants from many areas of the country. The use of CCBT will also allow for patients to participate from many different geographical locations.

4.2 Clinical Significance

With the prevalence of Lyme disease steadily increasing throughout the country,¹ there will be an increasing number of patients who develop PTLDS. Additionally, it has been shown that depressive symptoms occur more in these patients than in the general population.⁴ Currently, there are no safe or effective treatment options for these patients. It has been repeatedly shown that chronic antibiotic use in these patients is not beneficial and carries many more risks than benefits.⁵⁻⁸ Thus, it is important that we investigate alternative treatments that may help alleviate symptoms of depression in this population. With CBT as one of the most highly regarded treatment options for depression⁹ and with CCBT increasingly being used to improve access to care,³ it is possible that CCBT may not only reduce depressive symptoms in PTLDS, but it may also improve access to care. Overall, the results of this study could provide insight into safe and effective treatment options for a growing number of patients suffering from PTLDS.

4.3 References


APPENDICES

Appendix A: Participant Consent Form

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE

Study Title: Computerized Cognitive Behavioral Therapy for Patients with Post-Treatment Lyme Disease Syndrome
Principal Investigator: Amir Garakani
Co-Investigator: Katherine Fry
Funding Source: Pending

Invitation to Participate and Description of Project

You are invited to participate in a research study investigating potential treatments for patients with post-treatment Lyme disease syndrome (PTLDS). The goal of this study is to investigate whether an online therapy program called Beating the Blues can be helpful for treating symptoms of PTLDS. You have been asked to participate because you meet the diagnostic criteria for PTLDS, are an adult over the age of 18, and are not currently pregnant.

In order for you to decide if you would like to participate in the study, you must be informed of all the potential risks and benefits. The goal of this consent form is to give you detailed information about the possible risks and benefits of participating in this study, so you can decide if you would like to participate. A research staff member should also discuss this information with you. You should understand the goal of this study, study procedures, potential risks and benefits of participating in the study, and alternative treatments. Once you understand the study, you can agree if you would like to participate or not. If you would like to participate, you will sign the consent form at the end of this document.

Description of Procedures

If you are interested in participating in this study, you will first be asked screening questions about your health. This will determine if you are eligible for the study. Information will be collected about your age, past medical history, Lyme disease history, and overall health. If you are eligible, you will be asked to fill out several surveys before starting the study. These surveys will ask you about current depression symptoms, fatigue, pain, and quality of life. After completing these surveys, you will begin the study.

If you agree to participate in the study, you will be randomly assigned to one of two groups. Both groups will receive weekly telephone calls from research staff. However, one group will also complete an online program that explores your emotions and beliefs.
in addition to these telephone calls. Random assignment means that you have a 50/50 chance of ending up in one group over the other. You will be randomly assigned using a computer program.

Throughout the study, you will complete surveys that ask about depression symptoms, fatigue, pain, and quality of life. You will complete these surveys before you begin the study, two months into the study, and at one, three, and six months after the study. You will receive emails from research personnel with secure links to the surveys you will complete.

Medical Record Access:
If you decide to participate in this study, research staff will ask for permission to access your medical records. Research staff will review information about your Lyme disease history (results of laboratory testing, antibiotics used to treat Lyme disease), results of laboratory studies (complete blood count, liver and kidney tests, thyroid hormone levels), and any other medical diagnoses you have. This information will be used to determine if you are eligible for the study.

Risks and Inconveniences
We do not anticipate major risks of participating in this study. Both groups will be asked about their emotions and life experiences that may have contributed to their emotions. This may be upsetting to some individuals. Research staff will call participants once a week to discuss negative emotions and provide outside referrals, if necessary.

The measurement tools we use may include personal information about psychological and physical symptoms. Some of these questions may make you uncomfortable to answer. You only have to provide as much information as you feel comfortable answering.

Lastly, because you are completing these surveys that contain personal information, there may be a risk of breach of confidentiality about your health status. However, this is unlikely to occur. All research staff will be trained and certified in the privacy of research studies.

Benefits
The benefits of participating in this study may include learning techniques to manage mental health symptoms, learning how to prevent recurrence of mental health symptoms, learning how to cope with negative feelings, and learning ways to manage emotions.

Treatment Alternatives
The alternative to participating in this study is to decline participation. If you decide not to participate, you will work with your current health care provider(s) to manage your symptoms.
Confidentiality and Privacy

All identifiable information collected in this study will remain confidential and will only be disclosed with your written permission or as required by US or State law. Information that is legally required to report to the government includes abuse of a child, elderly person, or a cognitively impaired person.

Your data will be de-identified by using a unique study code instead of your name. All of your information will be stored in a password-protected database using your unique study code instead of your name. Only research staff, who are thoroughly trained and certified in privacy regarding research studies, will have access to this data. After data analysis is complete, all of your data will be destroyed.

Health Insurance Portability and Accountability Act (HIPAA) standards will be maintained while accessing and storing your information from your medical record. Only approved information that is necessary to complete the study will be obtained from your medical record. Information that is not relevant to the study will not be obtained from your medical record. Data auditing will be performed at random points throughout the study to ensure that there is no inappropriate viewing or disclosure of your health information. Once data is analyzed, all of your health information will be destroyed.

As this study takes place at Yale University, representatives from Yale University, the Yale Human Research Protection Program, and the Yale Human Investigation Committee are able to access study records to ensure that subject health records and information are stored and maintained as required by US and State law. Each representative is required by US and State law to keep your information confidential.

Voluntary Participation and Withdrawal

You are able to decide if you do not want to participate in this study. At any point during the study, you are free to withdraw for any reason. If you would like to withdraw from the study, please contact a member of the research team at your earliest convenience. Refusing to participate in the study or choosing to withdraw will not result in any form of punishment. You will always be entitled to receiving standard of care treatment for your medical condition, whether or not you choose to participate in the study.

You do not give up any of your legal rights by signing this form.

Questions

This consent form contains some technical terms. If you do not understand any part of this consent form, please contact a member of the research team who will clarify for you. Please take as much time as you need to thoroughly read this form and make your decision as to whether or not you would like to participate in this research study.

Authorization and Permission
I have read (or someone has read to me) this consent form and have decided to participate in the research study as described above. The general purposes, the particulars of my involvement, and the possible hazards and inconveniences of participation have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject: _______________________

Signature: _____________________________ Date: _________________

Relationship: ___________________________ Date: _________________

______________________________________ Date: _________________

Signature of Principal Investigator
or

______________________________________ Date: _________________

Signature of Person Obtaining Consent

If you have any further questions about this project or have research-related problem, you may contact the co-Principal Investigator, Katherine Fry. If you would like to discuss a research-related problem with anyone other than the researchers, you may contact the Yale Human Investigation Committee at (203) 785-4688.

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at (203) 432-5919
Appendix B: Preliminary Screening Survey

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
YALE UNIVERSITY SCHOOL OF MEDICINE

Study Title:  
Principal Investigator: Amir Garakani

Screening Form Information:  
We are researchers at Yale University School of Medicine studying potential treatment options for patients living with post-treatment Lyme disease syndrome (PTLDS). The following survey includes questions about your previous health history that will determine if you may be eligible for our study. Some questions may be sensitive in nature. You do not have to answer any questions that you do not wish to answer.

At the end of the survey, you will be immediately told whether or not you may be eligible. If you are not eligible, all of the information you entered will be destroyed immediately. If you are eligible, you will be asked if you would like to provide your contact information (name and telephone number) so a member of our research team can call you to tell you more about the study. If you do not wish to send us your contact information, all of the information you entered will be destroyed immediately.

Do you wish to complete this online survey to see if you are eligible for our study?  
- Yes  
- No

[Informed consent for online screener]

How old are you?  
- Enter here

What gender do you identify as?  
- Enter here

What state do you currently reside in?  
- Enter here

Have you been diagnosed with Lyme disease in the past?  
- Yes  
- No  
  - If they enter no, survey will end

If yes, did you have a rash that looks like this picture? (insert picture of erythema migrans rash)  
- Yes
• No

How were you diagnosed with Lyme disease?
• Blood testing
• No blood testing (ex – you were bitten by a tick then developed a rash)
• Other
  o Describe here

Did you take antibiotics to treat the Lyme disease?
• Yes
• No

Did you complete the course of antibiotics prescribed to you?
• Yes
• No

Did you feel better immediately after taking the antibiotics?
• Yes
• No

Within six months after completing the course of antibiotics prescribed to you to treat your Lyme disease, did you experience any of the following symptoms?
• Excessive fatigue
  o Yes
  o No
• Musculoskeletal pain
  o Yes
  o No
• Cognitive difficulties (ex – trouble remembering, trouble completing tasks that you were normally able to complete without an issue)
  o Yes
  o No

Did these symptoms cause you to have difficulties in your work, educational, social, or personal activities?
• Yes
• No

Were you diagnosed with fibromyalgia before having Lyme disease?
• Yes
• No

Were you diagnosed with chronic fatigue syndrome before having Lyme disease?
• Yes
• No

Did you have a history of unexplained and undiagnosed symptoms before having Lyme disease (ex – musculoskeletal pains, excessive fatigue)?
  • Yes
  • No

How tall are you?
  • Answer here

How much do you weigh?
  • Answer here

Are you diagnosed with any medical conditions?
  • Yes
    o List here
  • No

Do you take any medications?
  • Yes
    o List here
  • No

Have you had cancer within the past two years?
  • Yes
    o List here
  • No

Have you ever been diagnosed with any psychiatric conditions (ex – major depressive disorder, bipolar disorder, schizophrenia, anorexia nervosa, bulimia, etc.)?
  • Yes
    o List here
  • No
Appendix C: Beck Depression Inventory-II

The BDI-II contains 21 questions, each answer being scored on a scale value of 0 to 3. The cutoffs used differ from the original: 0–13: minimal depression; 14–19: mild depression; 20–28: moderate depression; and 29–63: severe depression. Higher total scores indicate more severe depressive symptoms.

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the one statement in each group that best describes the way you have been feeling during the past two weeks, including today. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

<table>
<thead>
<tr>
<th>1. Sadness</th>
<th>6. Punishment Feelings</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 I do not feel sad.</td>
<td>0 I don't feel I am being punished.</td>
</tr>
<tr>
<td>1 I feel sad most of the time.</td>
<td>1 I feel I may be punished.</td>
</tr>
<tr>
<td>2 I am sad all the time.</td>
<td>2 I expect to be punished.</td>
</tr>
<tr>
<td>3 I am so sad or unhappy that I can't stand it.</td>
<td>3 I feel I am being punished.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Pessimism</th>
<th>7. Self-Dislike</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 I am not discouraged about my future.</td>
<td>0 I feel the same about myself as ever.</td>
</tr>
<tr>
<td>1 I feel more discouraged about my future than I used to.</td>
<td>1 I have lost confidence in myself.</td>
</tr>
<tr>
<td>2 I do not expect things to work out for me.</td>
<td>2 I am disappointed in myself.</td>
</tr>
<tr>
<td>3 I feel my future is hopeless and will only get worse.</td>
<td>3 I dislike myself.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Past Failure</th>
<th>8. Self-Criticism</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 I do not feel like a failure.</td>
<td>0 I don't criticize or blame myself more than usual.</td>
</tr>
<tr>
<td>1 I have failed more than I should have.</td>
<td>1 I am more critical of myself than I used to.</td>
</tr>
<tr>
<td>2 As I look back, I see a lot of failures.</td>
<td>2 I criticize myself for all of my faults.</td>
</tr>
<tr>
<td>3 I feel I am a total failure as a person.</td>
<td>3 I blame myself for everything bad that happens.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Loss of Pleasure</th>
<th>9. Suicidal Thoughts or Wishes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 I get as much pleasure as I ever did from the things I enjoy.</td>
<td>0 I don't have any thoughts of killing myself.</td>
</tr>
<tr>
<td>1 I don't enjoy things as much as I used to.</td>
<td>1 I have thoughts of killing myself, but I would not carry them out.</td>
</tr>
<tr>
<td>2 I get very little pleasure from the things I used to enjoy.</td>
<td>2 I would like to kill myself.</td>
</tr>
<tr>
<td>3 I can't get any pleasure from the things I used to enjoy.</td>
<td>3 I would kill myself if I had the chance.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Guilty Feelings</th>
<th>10. Crying</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 I don't feel particularly guilty.</td>
<td>0 I don't cry anymore than I used to.</td>
</tr>
<tr>
<td>1 I feel guilty over many things I have done or should have done.</td>
<td>1 I cry more than I used to.</td>
</tr>
<tr>
<td>2 I feel quite guilty most of the time.</td>
<td>2 I cry over every little thing.</td>
</tr>
<tr>
<td>3 I feel guilty all of the time.</td>
<td>3 I feel like crying, but I can't.</td>
</tr>
</tbody>
</table>

[Continued on Back]
Beck Depression Inventory

11. Agitation
   0 I am no more restless or wound up than usual.
   1 I feel more restless or wound up than usual.
   2 I am so restless or agitated that it's hard to stay still.
   3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest
   0 I have not lost interest in other people or activities.
   1 I am less interested in other people or things than before.
   2 I have lost most of my interest in other people or things.
   3 It's hard to get interested in anything.

13. Indecisiveness
   0 I make decisions about as well as ever.
   1 I find it more difficult to make decisions than usual.
   2 I have much greater difficulty in making decisions than I used to.
   3 I have trouble making any decisions.

14. Worthlessness
   0 I do not feel I am worthless.
   1 I don't consider myself as worthwhile and useful as I used to.
   2 I feel more worthless as compared to other people.
   3 I feel utterly worthless.

15. Loss of Energy
   0 I have as much energy as ever.
   1 I have less energy than I used to have.
   2 I don't have enough energy to do very much.
   3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern
   0 I have not experienced any change in my sleeping pattern.
   1a I sleep somewhat more than usual.
   1b I sleep somewhat less than usual.
   2a I sleep a lot more than usual.
   2b I sleep a lot less than usual.
   3a I sleep most of the day.
   3b I wake up 1-2 hours early and can't get back to sleep.

17. Irritability
   0 I am no more irritable than usual.
   1 I am more irritable than usual.
   2 I am much more irritable than usual.
   3 I am irritable all the time.

18. Changes in Appetite
   0 I have not experienced any change in my appetite.
   1a My appetite is somewhat less than usual.
   1b My appetite is somewhat greater than usual.
   2a My appetite is much less than before.
   2b My appetite is much greater than usual.
   3a I have no appetite at all.
   3b I crave food all the time.

19. Concentration Difficulty
   0 I can concentrate as well as ever.
   1 I can't concentrate as well as usual.
   2 It's hard to keep my mind on anything for very long.
   3 I find I can't concentrate on anything.

20. Tiredness or Fatigue
   0 I am not more tired or fatigued than usual.
   1 I get more tired or fatigued more easily than usual.
   2 I am too tired or fatigued to do a lot of the things I used to do.
   3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex
   0 I have not noticed any recent change in my interest in sex.
   1 I am less interested in sex than I used to be.
   2 I am much less interested in sex now.
   3 I have lost interest in sex completely.
Appendix D: Fatigue Severity Scale

**FATIGUE SEVERITY SCALE (FSS)**

<table>
<thead>
<tr>
<th>Read and circle a number.</th>
<th>Strongly Disagree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. My motivation is lower when I am fatigued.</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>2. Exercise brings on my fatigue.</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>3. I am easily fatigued.</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>4. Fatigue interferes with my physical functioning.</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>5. Fatigue causes frequent problems for me.</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>6. My fatigue prevents sustained physical functioning.</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>7. Fatigue interferes with carrying out certain duties and responsibilities.</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>8. Fatigue is among my most disabling symptoms.</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
</tr>
<tr>
<td>9. Fatigue interferes with my work, family, or social life.</td>
<td>1 2 3 4 5 6 7</td>
<td></td>
</tr>
</tbody>
</table>

Please circle the number between 1 and 7 which you feel best fits the following statements. This refers to your usual way of life within the last week. 1 indicates “strongly disagree” and 7 indicates “strongly agree.”
Appendix E: Short-Form McGill Pain Questionnaire

SHORT-FORM (McGILL) PAIN QUESTIONNAIRE

PATIENT’S NAME: __________________________ DATE: ___/___/___

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>NONE</th>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Throbbing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Shooting</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Stabbing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Sharp</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cramping</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Gnawing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Hot-Burning</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>Aching</td>
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<td>2</td>
<td>3</td>
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<td>Heavy</td>
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<tr>
<td>Tender</td>
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<td>3</td>
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<td>Splitting</td>
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<tr>
<td>Tiring-Exhausting</td>
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<td>Sickening</td>
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<td>Fearful</td>
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<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>Punishing-Cruel</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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</tbody>
</table>

Please indicate on the line below where your pain level is by marking with an X.

WORST POSSIBLE PAIN

Please indicate what your present pain intensity is right now by checkmarking.

0 NO PAIN
1 MILD
2 DISCOMFORTING
3 DISTRESSING
4 HORRIBLE
5 EXCRUCIATING
Appendix F: Short-Form Health Survey, Version 2

SF-36 QUESTIONNAIRE

Name:_________________________ Ref. Dr._________________________ Date:_____

ID#: ______________ Age: ______ Gender: M / F

Please answer the 38 questions of the Health Survey completely, honestly, and without interruptions.

GENERAL HEALTH:
In general, would you say your health is:
☐ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor

Compared to one year ago, how would you rate your health in general now?
☐ Much better now than one year ago
☐ Somewhat better now than one year ago
☐ About the same
☐ Somewhat worse now than one year ago
☐ Much worse than one year ago

LIMITATIONS OF ACTIVITIES:
The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Lifting or carrying groceries
☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Climbing several flights of stairs
☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Climbing one flight of stairs
☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Bending, kneeling, or stooping
☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Walking more than a mile
☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Walking several blocks
☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Walking one block
☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all
Bathing or dressing yourself
- Yes, Limited a Lot
- Yes, Limited a Little
- No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities
- Yes
- No

Accomplished less than you would like
- Yes
- No

Were limited in the kind of work or other activities
- Yes
- No

Had difficulty performing the work or other activities (for example, it took extra effort)
- Yes
- No

EMOTIONAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities
- Yes
- No

Accomplished less than you would like
- Yes
- No

Didn't do work or other activities as carefully as usual
- Yes
- No

SOCIAL ACTIVITIES:
Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
- Not at all
- Slightly
- Moderately
- Severe
- Very Severe

PAIN:
How much bodily pain have you had during the past 4 weeks?
- None
- Very Mild
- Mild
- Moderate
- Severe
- Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?
- Not at all
- A little bit
- Moderately
- Quite a bit
- Extremely
ENERGY AND EMOTIONS:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?
☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

Have you been a very nervous person?
☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

Have you felt so down in the dumps that nothing could cheer you up?
☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

Have you felt calm and peaceful?
☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

Did you have a lot of energy?
☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time
Have you felt downhearted and blue?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel worn out?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a happy person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel tired?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

SOCIAL ACTIVITIES:
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?
- All of the time
- Most of the time
- Some of the time
- A little bit of the time
- None of the Time
GENERAL HEALTH:
How true or false is each of the following statements for you?

I seem to get sick a little easier than other people
☐ Definitely true  ☐ Mostly true  ☐ Don't know  ☐ Mostly false  ☐ Definitely false

I am as healthy as anybody I know
☐ Definitely true  ☐ Mostly true  ☐ Don't know  ☐ Mostly false  ☐ Definitely false

I expect my health to get worse
☐ Definitely true  ☐ Mostly true  ☐ Don't know  ☐ Mostly false  ☐ Definitely false

My health is excellent
☐ Definitely true  ☐ Mostly true  ☐ Don't know  ☐ Mostly false  ☐ Definitely false
Appendix G: Sample Size Calculation

15% Attrition:

\[(1.15)(158) = 181.7\]

\[N = 182 \text{ participants, 91 per group}\]
### Appendix H: Structure of Beating the Blues CBT Program

<table>
<thead>
<tr>
<th>Session</th>
<th>Cognitive Components</th>
<th>Behavioural Components</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>How to use Beating the Blues</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Getting Started About Anxiety &amp; Depression Define your Road to Recovery statement</td>
<td>What We Think Pleasurable Events</td>
</tr>
<tr>
<td>2</td>
<td>Understanding how your thoughts affect your behaviour and mood</td>
<td>Setting Goals Recognise and record automatic unhelpful thoughts Problem Solving</td>
</tr>
<tr>
<td>3</td>
<td>Distraction Techniques Identifying Thinking Errors</td>
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<tr>
<td>4</td>
<td>Challenging Unhelpful Thinking</td>
<td>Choose another “doing technique” Activity Scheduling; Task Breakdown; Sleep Management; Graded Exposure</td>
</tr>
<tr>
<td>5</td>
<td>Identifying and challenging unhelpful Beliefs</td>
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<td>6</td>
<td>Understanding your Attributional Style and how this impacts your mood and behaviour</td>
<td>Choose another “doing technique”</td>
</tr>
<tr>
<td>7</td>
<td>How to change your Attributional Style to improve confidence and self esteem</td>
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</tr>
<tr>
<td>8</td>
<td>Review of Program and Goals Planning for the Future</td>
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</table>


