Suicide Risk Linked with Perceived Burdensomeness in Postural Tachycardia Syndrome

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Abstract

Background: Postural tachycardia syndrome (POTS) is a chronic, invisible illness characterized by orthostatic intolerance and excessive postural tachycardia. Aim: This study focused on the psychological factors underlying suicidal ideation in women with POTS. Method: 475 women with POTS completed the Beck Depression Inventory-1A, Interpersonal Needs Questionnaire, UCLA Loneliness Scale-Revised, and the Suicide Behaviors Questionnaire-Revised. Results: In this study, 64.6% of women with POTS scored in the high-risk group for suicide, 69.1% (328/475) had considered suicide in the past year, and 18.1% (86/475) had made at least one suicide attempt. In a hierarchical multiple regression analysis, perceived burdensomeness, depression, thwarted belongingness, and loneliness explained 34.4% of the variance in suicide scores, controlling for severity and duration of illness. Perceived Burdensomeness, the feeling of being a burden to others, was the strongest predictor of suicidal risk (β=0.46, p<0.001), followed by depression (β=0.17, p=0.006). Loneliness and Thwarted Belongingness did not make unique, significant contributions. Conclusion: Nearly two-thirds of our participants were in the high-risk group for suicide. Perceived burdensomeness was a major predictor of suicide risk, more so than depression, thwarted belongingness, or loneliness. Therapeutic interventions to prevent or diminish perceived burdensomeness could decrease suicidal ideation in those with POTS.

Keywords: Postural tachycardia syndrome (POTS); Suicide risk; Perceived burdensomeness; Thwarted belongingness; Depression

Introduction

Postural tachycardia syndrome (POTS) is a heterogeneous disorder [1] characterized by supine-to-standing heart rate increase of ≥ 30 beats per minute in adults and ≥ 40 beats per minute in adolescents in the absence of postural hypotension [2]. POTS generally affects young, well-educated women [3], but can occur in either gender at any age. Symptoms include neuropathic pain [2,4], chronic fatigue [5], headaches, palpitations, gastrointestinal disturbance, facial flushing [4,6], and orthostatic symptoms such as dizziness, light-headedness, and syncope [7]. POTS may be co-morbid with Ehlers-Danlos syndrome (EDS) [5,8], chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) [5], fibromyalgia [1], mast cell activation disorder [9], and Lyme disease [10].

Approximately 50% of people with chronic invisible illness are estimated to suffer from depression [11], a known risk factor for suicide. Many people with POTS have mild depression, but not at rates higher than the general population [12]. In contrast, one small study of 15 POTS participants found 86% had mild to moderate depression [13]. In these patients, chest discomfort and concentration problems correlated positively with depression [14].

Suicide is a major cause of death in many chronic illness communities where physical and emotional challenges persist. Physical illness and functional disability are known risk factors for suicide, particularly in older populations [15-17]. Increased risk of suicide has also been found in younger persons diagnosed with POTS [18,19], CFS/ME [20-22], fibromyalgia [23,24], and Lyme disease [25]. In previous studies of people with POTS, nearly 50% of respondents were at high-risk for suicide [18,19].

The interpersonal theory of suicide may be relevant to the chronic illness community. This theory proposes that people are at increased risk for suicide if they experience perceived burdensomeness (the perception that they are a liability to those around them) and thwarted belongingness (the perception that they do not belong in a social group) [26]. Distress related to perceived burdensomeness and thwarted belongingness has been investigated in populations with psychiatric disorders [27] but its contribution to predicting increased suicidal ideation among chronic illness patients is unknown.

The physical disability in POTS may contribute to feelings of loneliness [18]. For the 25% who are disabled and unable to work or go to school [3], loss of social interaction can increase isolation [28]. Loneliness is a known risk factor for suicide, even in the general population [29-31]. The complexity of POTS, combined with its invisible nature, may contribute to feelings of loneliness [18].

Objectives

This is the first study of psychological factors that may lead to suicidal risk for women with POTS. To identify levels of suicide risk, we used standardized measures of depression, thwarted belongingness, perceived burdensomeness and loneliness in this chronically ill population. Also, we aim to understand the unique contributions of illness and self-report variables for explaining suicide risk.
Hypothesis

We hypothesized that suicide risk would increase as depression, loneliness, thwarted belongingness and perceived burdensomeness increased.

Method

Participants

Participants were recruited for an online survey about suicide risk via targeted campaigns through the Standing Up to POTS Facebook page and Facebook POTS support groups. People in these groups are motivated to find a community identity, and may be more disabled than the average POTS patient. Respondents included 561 females who were at least 18 years old and reported physician diagnosed POTS. Potential participants who had autoimmune illnesses including Addison’s disease, Crohn's disease, lupus, multiple sclerosis, and Sjogren’s syndrome were excluded (n=86). The remaining 475 participants were relatively young women (mean age=32.2 years, SD=10.7) who had suffered from POTS for a decade (\(\bar{x}=10.80\) years, SD=9.33). Self-reported comorbid diagnoses included 157 (33%) with CFS/ME, 154 (32%) EDS, 128 (27%) fibromyalgia, 80 (17%) mast cell activation disorder (MCAD), and 17 (4%) Lyme disease. Twenty (4%) participants reported having the cluster of POTS, EDS, MCAD and CFS/ME.

Procedure

Participants electronically read and agreed to the information in the informed consent form before opening the online survey. Initial survey items included demographic questions, number of years ill, symptoms, level of disability (Likert scale from 0-10), and physician-assessed medical diagnoses. We counted the total number of symptoms and total number of diagnoses reported by each participant. The women also completed the measures described below. In the debriefing statement at the end of the survey, all participants were given contact information for the National Suicide Prevention Lifeline (phone) and HOPELINE (text). The study protocol was approved by the Wittenberg University Institutional Review Board. All data were collected electronically via the StandingUptoPOTS.org website between January and April 2017.

Instruments

Beck Depression Inventory-1A (BDI; [32]). It is a 21 question, self-report measure that assesses depression severity. Participants rate emotions such as sadness, satisfaction, guilt, and disappointment on a 0 to 3 point scale. Other BDI items ask about physical symptoms such as tiredness, sleep, appetite, weight, and health worries. Scores range from 0 to 63, with scores between 31 and 40 indicating severe depression, and >40 describing extreme depression. The BDI is internally consistent (\(\alpha=0.895\)), has good test-retest reliability (\(r=0.82\)), and demonstrates adequate sensitivity and specificity [33].

Interpersonal Needs Questionnaire-15 (INQ; [34]). The 15-item INQ-15 uses six questions to measure Perceived Burdensomeness (e.g., “These days, I think I make things worse for the people in my life”) and nine questions to assess Thwarted Belongingness (e.g., “These days, I feel disconnected from other people”). Participants rate each statement on a one-to seven-point Likert scale; higher values indicate increased levels of perceived burdensomeness and thwarted belongingness. One study identified Perceived Burdensomeness scores ≥ 22 and Thwarted Belongingness scores ≥ 31 as indicating a “desire for suicide” [35]. In the current study, internal consistency reliabilities (Cronbach’s \(\alpha\)) for Perceived Burdensomeness scale and Thwarted Belongingness were .925 and .892, respectively. The INQ-15 demonstrates good screening validity for suicide risk in college students [34,35].

UCLA Loneliness Scale-Revised (ULS; [36]). The 10-item ULS-R assesses feelings of loneliness and social isolation on a four-point scale: Never (1), Rarely (2), Sometimes (3), or Often (4). Questions include “How often do you feel that you have no one to talk to?” and “How often do you feel shut out and excluded by others?” Total scores range from 10-40, with scores 25-29 indicating a high level of loneliness and scores ≥ 30 signifying very high loneliness. The ULS-R is internally consistent (\(\alpha=0.908\) in this study) and its test-retest reliability over one year was .73 for college students, nurses, teachers and the elderly [36].

Suicide Behaviors Questionnaire-Revised (SBQ; [37]). The four-question, self-report SBQ indexes suicide risk by assessing lifetime suicidal ideation and/or suicide attempts. The SBQ questions are: (1) “Have you ever thought about or attempted to kill yourself?” (six response options) (2) “How often have you thought about killing yourself in the past year?” (five options) (3) “Have you ever told someone that you were going to commit suicide, or that you might do it?” (five options) and (4) “How likely is it that you will attempt suicide someday?” (seven options). The SBQ total score was used to group participants by suicide risk. Scores ≥ 7 places participants into the high suicidal risk group and scores <7 in the low suicidal risk group. The American Psychiatric Association highlighted the SBQ as a valuable tool in the clinical assessment of suicide risk [38]. The internal consistency (\(\alpha=0.800\) in this study), reliability, and construct validity of the SBQ make it an effective measure for identifying suicide risk in population studies [39,40]. The SBQ demonstrated impressive screening validity in a study of psychiatric patients [37] and college students [39].

Statistical analyses

Using SPSS version 23, descriptive statistics were produced for all demographic variables and self-report scales. Bivariate correlations (Pearson) among all study variables were calculated. Next, setwise, hierarchical multiple linear regression analysis was run in which scores were entered as continuous variables. The hierarchical procedure allows...
assessment of the self-report scales’ contributions to predicting suicide risk, controlling for duration and severity of illness. Predictors were entered sequentially in two four-variable sets. Set 1 variables were number of years ill, total symptoms, level of disability, and total diagnoses, followed by the four self-report scales (Set 2). An Omnibus F test is reported for each set. The Set 2 F test indicates whether the self-report scales explain significant variance in suicide risk, controlling for the Set 1 variables. Standardized partial regression coefficients (βs), which are interpreted for a variable only if the Omnibus F for its predictor set is statistically significant, quantify the unique contribution of each variable for explaining suicide risk.

Results

Demographics

The participants' mean age was 32.2 (SD=10.7). These women were highly symptomatic (x̄=12.7 symptoms, SD=4.4) and had been ill for a decade (x̄=10.9, SD=9.3). They reported an average of 2.1 diagnoses (SD=1.0), and high levels of disability on a 0-10 Likert scale (Table 1; x̄=6.4, SD=1.9).

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Skew</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32.23</td>
<td>10.73</td>
<td>0.57</td>
</tr>
<tr>
<td>Total Diagnoses</td>
<td>2.13</td>
<td>1.05</td>
<td>0.64</td>
</tr>
<tr>
<td>Total Symptoms</td>
<td>12.71</td>
<td>4.40</td>
<td>-0.07</td>
</tr>
<tr>
<td>Years Ill</td>
<td>10.87</td>
<td>9.34</td>
<td>1.49</td>
</tr>
<tr>
<td>Extent of Disability</td>
<td>6.36</td>
<td>1.91</td>
<td>-0.55</td>
</tr>
</tbody>
</table>

Note: Extent of disability was self-rated on a scale ranging from 0 to 10

Table 1: Age and illness variable distributions (n=475).

Suicide risk in POTS

In this study, 64.6% (307/475) of POTS patients had total SBQ scores ≥7, placing them into the high-risk group for suicide (x̄=8.45, SD=3.94; Table 2). Sixty-nine percent (328/475) had considered suicide in the past year and 18.1% (86/475) had already made at least one suicide attempt. Additionally, 12.8% (61/475) reported that it was likely that they would attempt suicide in the future.

Table 2: Descriptive statistics for the self-report scales.

Self-report scales

Descriptive statistics for the self-report scales are presented in Table 2. All scale scores were normally distributed, but participants showed elevations on all measures: 23.8% (113/475) suffered from severe depression and 11.6% (55/475) were extremely depressed. Our POTS group reported moderate depression on the BDI (x̄=26.7, SD=10.9). Elevated INQ-15 Perceived Burdensomeness scores indicating desire for suicide were found in 33.7%
Bivariate correlations between self-report measures

There were statistically significant Pearson correlations between total SBQ scores and INQ-15 Perceived Burdensomeness \((r=0.61, p<0.001)\), BDI total scores \((r=0.53, p<0.001)\), INQ-15 Thwarted Belongingness \((r=0.45, p<0.001)\), and ULS-R total scores \((r=0.44, p<0.001)\). Also, INQ-15 Perceived Burdensomeness correlated with the BDI \((r=0.73, p<0.001)\), INQ-15 Thwarted Belongingness \((r=0.65, p<0.001)\), and the ULS-R (Table 3; \(r=0.60, p<0.001)\).

<table>
<thead>
<tr>
<th>Variable</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Years ill</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>2. Symptoms</td>
<td>0.097</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Disability</td>
<td>0.109</td>
<td>0.362</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4. Diagnoses</td>
<td>0.263</td>
<td>0.361</td>
<td>0.238</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5. SBQ</td>
<td>0.077</td>
<td>0.147</td>
<td>0.213</td>
<td>0.126</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6. BDI</td>
<td>-0.065</td>
<td>0.210</td>
<td>0.340</td>
<td>0.094</td>
<td>0.533</td>
<td>-</td>
<td></td>
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<tr>
<td>7. INQ-PB</td>
<td>-0.033</td>
<td>0.210</td>
<td>0.334</td>
<td>0.140</td>
<td>0.613</td>
<td>0.732</td>
<td>-</td>
<td></td>
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</tr>
<tr>
<td>8. INQ-TB</td>
<td>0.016</td>
<td>0.140</td>
<td>0.236</td>
<td>0.090</td>
<td>0.451</td>
<td>0.656</td>
<td>0.642</td>
<td>-</td>
<td></td>
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<tr>
<td>9. ULS-R</td>
<td>-0.033</td>
<td>0.162</td>
<td>0.245</td>
<td>0.067</td>
<td>0.445</td>
<td>0.667</td>
<td>0.592</td>
<td>0.744</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 3: Bivariate correlations between all variables.**

Hierarchical multiple regression analyses

Because high correlations among the self-report predictor variables suggested that multicollinearity might be a problem, we first ran collinearity diagnostics on the independent variables. The resulting tolerance (ranging from 0.361 to 0.912) and variance inflation factor values (all under 3.0) indicated no evidence of multicollinearity [41].

Omnibus F tests for both sets of suicide risk predictors were significant \(\text{Set 1 } F(4, 465)=6.821, p<0.001; \text{ Set 2 } F(8, 465)=38.1, p<0.001\). The Set 1 variables explained 5.6\% \((R^2=0.056)\) of the variance in suicide risk scores, with level of disability the only significant predictor (Table 4; \(\beta=0.46, p<0.001\)). Set 2 explained an additional 34.4\% \((\Delta R^2=0.344)\) of the variance, with Burdensomeness making the largest unique contribution to explaining suicide risk \((\beta=0.46, p<0.001; \text{ CI } =0.861-1.419)\), followed by Depression \((\beta=0.17, p=0.006, \text{ CI } =0.017-0.103)\). Loneliness \((\beta=0.08, p>0.05, \text{ CI } =-0.024-0.116)\) and INQ-15 Belongingness \((\beta=-0.007, p<0.05, \text{ CI } =-0.378-0.335)\) did not make significant unique contributions to explaining suicide risk (Table 4). A post hoc power analysis produced a value of 1.0 for the addition of Set 2 variables to the analysis, indicating that the non-significant regression coefficients for ULS-R and INQ-15 Belongingness were not attributable to a lack of power [42].

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Unstandardized Coefficients</th>
<th>95% Confidence Interval for B</th>
<th>Standardized Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(b)</td>
<td>SE</td>
<td>Lower</td>
</tr>
<tr>
<td><strong>Step 1 ((R^2=0.056))</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years ill</td>
<td>0.015</td>
<td>0.020</td>
<td>-0.024</td>
</tr>
<tr>
<td>Total symptoms</td>
<td>0.054</td>
<td>0.046</td>
<td>-0.036</td>
</tr>
<tr>
<td>Disability level</td>
<td>0.340</td>
<td>0.101</td>
<td>0.142</td>
</tr>
<tr>
<td>Total diagnoses</td>
<td>0.263</td>
<td>0.189</td>
<td>-0.109</td>
</tr>
<tr>
<td><strong>Step 2 ((R^2=0.344))</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>BDI</td>
<td>0.060</td>
<td>0.022</td>
<td>0.017</td>
</tr>
<tr>
<td>INQ-PB</td>
<td>1.140</td>
<td>0.142</td>
<td>0.861</td>
</tr>
<tr>
<td>INQ-TB</td>
<td>-0.022</td>
<td>0.181</td>
<td>-0.378</td>
</tr>
<tr>
<td>ULS-R</td>
<td>0.046</td>
<td>0.036</td>
<td>-0.024</td>
</tr>
</tbody>
</table>

Bolded predictors are statistically significant; BDI: Beck Depression Inventory-1A; INQ-PB: Interpersonal Needs Questionnaire-Perceived Burdensomeness; INQ-TB: Interpersonal Needs Questionnaire-Thwarted Belongingness; ULS-R: UCLA Loneliness Scale-Revised

**Table 4: Setwise hierarchical regression analysis results.**
Discussion

In this study, nearly 65% of women diagnosed with POTS reported scores indicating high-risk for suicide, and 18% had already made at least one attempt. Additionally, 13% stated that it was likely that they would attempt suicide in the future, 33% had elevated Perceived Burdensomeness scores, 35% conveyed severe to extreme depression, 71% reported Thwarted Belongingness, and 76% described high or very high levels of loneliness. However, the Perceived Burdensomeness score was a stronger predictor of suicide risk than depression, Thwarted Belongingness, or loneliness.

These results are consistent with those from previous studies showing that people with POTS have an increased suicide risk. In those studies, nearly 50% of people with POTS who were surveyed were placed into the high-risk category for suicide based on SBQ scores [18,19]. In this study, which assessed psychological factors involved in this increased risk, 65% of women with POTS were at high-risk for suicide. This elevation in number might be from a self-selection bias as the advertised topic of this survey was suicide. Perhaps those who had considered suicide participated at higher rates than those who had not.

Perceived Burdensomeness was the strongest predictor of suicide risk in this study of POTS patients. POTS significantly decreases quality of life [3,13,18,43,44]. Nearly 25% of POTS patients are so disabled that they cannot work or attend school and have a quality of life similar to patients with congestive heart failure or chronic obstructive pulmonary disorder [3]. The high level of disability experienced by many POTS patients may lead to feelings of perceived burdensomeness. In one study, 97% of POTS patients were limited by their illness and 30% required assistance for basic personal care [18]. Perceived burdensomeness is also elevated in chronic pain populations [45-48]. Because more than 50% of people with POTS have chronic neuropathic pain [2,4], it is likely that perceived burdensomeness could generalize to the POTS population. The clinical cut-offs for INQ-15 Perceived Burdensomeness, proposed by Mitchell et al. [27] for inpatient psychiatric patients and used in this study, may not generalize to the chronic illness community. Only 33% of our sample had elevated Perceived Burdensomeness scores according to that scale cut-off, while nearly twice that many fell into the high-risk group for suicide.

Among the physically ill, suicidal thinking is sometimes a symptom of depression, often a response to suffering from chronic illness, and at times viewed as a mechanism to permanently relieve physical and emotional misery [49]. In people with chronic pain, suicide risk was more related to psychosocial factors such as perceived burdensomeness, thwarted belongingness, and hopelessness than physical factors [50]. Interestingly, perceived burdensomeness made a larger unique contribution to explaining suicidal risk in this chronically ill sample. This may be a result of the BDI over-diagnosing depression. This chronically ill sample suffers from physical symptoms like fatigue, insomnia, and poor appetite [18]. A high proportion of our participants fell into the moderately depressed category on the BDI – this is possible if they simply agreed with the most extreme response for the seven somatization questions (ability to work, sleep, fatigue, appetite, weight change, worry about health, and interest in sex) that potentially related to their physical illness. If the BDI does over-diagnose depression among the chronically ill, it may explain why depression was outperformed by perceived belongingness in this study. One way to view these findings is from a longitudinal perspective: Chronically ill persons perceive themselves as a burden to others, which leads to depression and, ultimately, suicide risk. Prospective studies are needed to test this hypothesis. In the meantime, those who perceive themselves as a burden on others should be evaluated for suicide risk.

Other studies have shown that perceived burdensomeness can be more important than thwarted belongingness [51,52] and associated loneliness [35] as risk factors for suicide. Our results support this assertion in a sample of chronically ill women. In our study, perceived burdensomeness exceeded both thwarted belongingness and loneliness as predictors of suicide risk. A study in military veterans with a history of depression found that perceived burdensomeness was a more significant factor in suicidal thinking than thwarted belongingness or social support [53].

Fortunately, there are opportunities to identify and help POTS patients at high-risk for suicide before they make an attempt. Psychological factors associated with suicide risk in chronic illness can be altered by targeted intervention [50], giving practitioners the opportunity to prevent suicide. If perceived burdensomeness is indeed a major factor in suicide risk in POTS, healthcare practitioners and psychologists can make great strides in suicide prevention within the POTS community by identifying individuals at risk and working with caretakers to make interactions more positive [16] and decrease feelings of perceived burdensomeness. Providing positive life events - such as playing board games, making a favorite snack, or sharing a movie at home - that meet the physical needs of the chronically ill person and increase social belonging can be beneficial in decreasing both perceived burdensomeness and suicide risk [29]. The healthcare community, in particular, could decrease suicide risk for those with POTS through compassionate care and routine screening for suicide risk. Of those who attempt suicide, 64% visit a healthcare facility in the month prior to the attempt and 38% visit the week prior [54].

Limitations of the Study

Our data were from online self-report measures, rather than objective medical testing or direct physician diagnosis, and shared method variance may have inflated the predictor/criterion correlations. Also, participants reported physician diagnosed POTS, but some disclosed co-morbid diagnoses of CFS/ME, EDS, fibromyalgia, mast cell activation disorder and/or Lyme disease that could worsen their symptomology and increase suicidal risk. We did not measure pain, sleep disturbance, or other physical symptoms that may be related to suicidal risk. In addition, participants were told in advance that the survey included questions about suicidal thinking, and some self-selection may have occurred that increased our reported percentage of POTS patients who have considered suicide. Further, we did not ask about medications or other treatments taken by participants. Finally,
because our participants were solicited from online support groups, they may not be representative of all POTS patients. Many in these support groups have more debilitating POTS symptoms than the average POTS patient, which may overestimate the percentage of POTS patients at high-risk for suicide.

Conclusions

In this study, nearly 65% of participants with POTS had thoughts of suicide, thoughts best explained by their feelings of being a burden on others. Further, 18% of those in this study had already made an attempt and 13% reported that were likely to make an attempt in the future. Efforts to decrease perceived burdensomeness and increase positive interactions might decrease suicide risk in this chronically ill and currently underserved population.

Recommendations

Practitioners should actively screen POTS patients for suicide risk. Many physicians have their patients’ complete online questionnaires, and a short suicide survey could be added to these assessments. Asking patients during appointments if they are suicidal is also appropriate. Most people who die by suicide see a physician in the previous year. Not asking about suicidal thoughts is a missed opportunity for meaningful intervention. Having a protocol in place to address suicidal risk and/or behavior when it is discovered is of paramount importance. This might include having contact information for local social workers, counselors, and suicide support groups that understand the specific vulnerabilities of the chronically ill. In larger clinics or hospitals, training mental health staff to address issues surrounding perceived burdensomeness, depression, thwarted belongingness and loneliness experienced by the chronically ill could go a long way to decreasing suicidal risk.

Ethical Standards

The study protocol was approved by the Wittenberg University Institutional Review Board and has been performed in accordance with the ethical standards described in the 1964 Declaration of Helsinki. All participants gave informed consent prior to their inclusion in this research study.

Conflict of Interest

The authors state that there is no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References


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