Published in final edited form as:

Psychosomatics. 2018 ; 59(5): 472–480. doi:10.1016/j.psych.2018.01.006.

Associations of Physical and Psychologic Symptom Burden in Patients With Philadelphia Chromosome-Negative Myeloproliferative Neoplasms

Daniel C. McFarland, D.O.¹, Kelly M. Shaffer, Ph.D.², Heather Polizzi, R.N.³, John Mascarenhas, M.D.³, Marina Kremyanskaya, M.D.³, Jimmie Holland, M.D.², and Ronald Hoffman, M.D.³

¹Division of Network Services, Department of Medicine, Memorial Sloan Kettering Cancer Center, West Harrison, NY

²Department of Psychiatry and Behavioral Sciences, Memorial Sloan Kettering Cancer Center, New York, NY

³Division of Hematology/Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai Hospital, New York, NY

Abstract

Background—The physical symptom burden of patients with myeloproliferative neoplasms (MPNs) may endure for extended periods during their disease trajectories and lead to psychological distress, anxiety, and/or depression. This study evaluated the relationship between physical symptom burden captured by the Physical Problem List (PPL) on the Distress Thermometer and Problem List (DT&PL) and psychological outcomes (distress, anxiety, and depression) in the MPN setting.

Methods—Patients ($N=117$) with MPNs completed questionnaires containing the DT&PL and the Hospital Anxiety and Depression Scale (HADS) in a dedicated MPN clinic within an academic medical center. They reported symptoms from any of 22 physical problems on the PPL. Items endorsed by more than 10% of participants were assessed for their associations with distress (DT&PL), anxiety (HADS-A), and depression (HADS-D). The total number of endorsed PPL items per participant was also evaluated.

Results—Nine of 22 PPL items (fatigue, sleep, pain, dry skin/pruritus, memory/concentration, feeling swollen, breathing, and sexual) were reported by >10% of participants. In univariate analyses, all PPL items but one were associated with distress and depression, and all but two were associated with anxiety. In multivariate analyses, the total number of PPL items was associated with depression only ($p<.001$) when controlling for covariates.

Conclusion—Physical symptom burden in MPN patients was clearly associated with psychological symptoms. Depression was uniquely associated with overall physical symptom

burden. As such, the endorsement of multiple PPL items on the DT&PL should prompt an evaluation for psychological symptoms to improve MPN patients' overall morbidity and quality of life.

Introduction

Patients with myeloproliferative neoplasms (MPNs) experience high physical symptom burden (e.g., fatigue, pain, pruritus, insomnia) as documented with validated scales and assessments.^{1,2,3,4} However, the relationship between physical symptom burden and psychological symptoms such as distress, anxiety, and depression in patients with MPNs has not been well described. Physical symptom burden is highly prevalent in many cancers, especially in advanced cancer states, and tends to be associated with poor psychological outcomes such as anxiety and depressive disorders.^{5,6} A better understanding of which physical symptoms carry the highest risk of concurrent psychological symptoms would help address psychological symptoms for MPN patients with physical ailments and ultimately improve MPN patients' physical and psychological symptom control.

Chronic myeloid leukemia is an MPN that is characterized by the presence of the gene rearrangement *BCR-ABL*, the Philadelphia chromosome. MPNs without the Philadelphia chromosome, *BCR-ABL* negative MPNs, are composed of essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF).⁷ These *BCR/ABL* negative MPNs are associated with survival that exceeds a decade typically. There are additional forms of *BCR-ABL* negative MPNs that do not fit into these categories including chronic neutrophilic leukemia, chronic eosinophilic leukemia, mastocytosis, or an overlap condition with myelodysplastic syndrome.⁸ Both PV and ET display distinct patterns of clonal proliferation and may evolve into MF. Their symptoms profiles and disease trajectories vary considerably, although they each carry a risk of transformation to leukemia.⁹ Additionally, the *BRC/ABL* negative MPNs constitute a spectrum of considerable and unique symptoms such as erythromelalgia and aquagenic pruritus that patients suffer from for many years.¹⁰

The Distress Thermometer and Problem List (DT&PL) is endorsed by the National Comprehensive Cancer Network (NCCN) for the identification of psychological distress in patients with cancer as a practical means to triage patients to appropriate psychosocial resources in the cancer community.¹¹ It is a one-item measure with proven acceptability in busy oncology clinics and is the most broadly utilized measure of distress internationally.¹² The Problem List that accompanies the DT&PL is meant to be a convenient tool to identify pertinent real-time issues in the clinic.^{13,14} The DT&PL Physical Problem List (PPL) variables have not been explored for their associations with distress, anxiety, or depression in patients with *BCR/ABL* negative MPNs. Distress screening with the DT&PL or another tool is mandated by accrediting agencies, it is still not uniformly performed across institutions.^{15,16}

While any physical symptom may be distressing or ultimately lead to increased anxiety or a depressive disorder, certain physical symptoms may be more likely to coincide with significant psychological issues, especially in patients with MPNs. These relationships should be understood by the consultant psychiatrist and primary oncology team in order to

facilitate the management of concomitant psychological and physical symptoms. The PPL provides unique information about patients' perceived bother by individual physical symptoms and is used routinely in many oncology clinics; as such, it should be assessed to understand the full range of its clinical utility. Therefore, this study examines specific physical symptoms as identified by the PPL category of the DT&PL and their individual associations with distress, anxiety, and depression. Given the known relationship between physical and psychological symptoms, we hypothesize that collective and individual physical symptoms will be associated with distress, anxiety, and depression.

Methods and Materials

Details for the current study have been previously reported and are reviewed in brief here.¹⁷ The Mount Sinai Hospital Institutional Review Board approved this study and all participants provided informed consent prior to participation. Data were collected from May 2015 to October 2015.

Participants

Men and women with documented BCR/ABL negative MPNs were screened based on inclusion criteria consisting of a confirmed tissue diagnosis of an MPN as identified by the treating physician. Patients selected their disease designation based as ET, PV, MF, or Other. Exclusion criteria consisted of another cancer diagnosis as identified by the patient. New and established patients were recruited to participate in the survey.

Procedure

Participants were asked to participate by either a clinic receptionist or treating staff (e.g., nurse practitioner, hematologist). Available psychological services were listed in the survey and patients were asked to bring up any concerns with clinic staff and, in particular, to tell a staff member if they felt significantly depressed or had suicidal ideation. A board-certified psychiatrist oversaw the study and was available for consultation.

Measures

Patient demographic and medical characteristics—Patients completed demographic information including age, race/ethnicity, gender, marital and working status, disease type (ET, PV, MF, other), and length of time with disease (under 1 year, 1–3 years, 3–5 years, 5–10 years, over 10 years).

Distress, anxiety, and depression—Patients completed the Distress Thermometer (DT) to assess for distress and the Hospital Anxiety and Depression Scale (HADS) to assess for anxiety and depression. The DT has been used widely by cancer institutions to meet the Commission on Cancer distress-screening mandate for accreditation in 2015.^{18,19} The DT is a one-item measure of distress and has a range of scores from 0 to 10 and a distress screening cut-off of 4 or greater.

The HADS is a 14 question psychometric measure that was developed to identify 'caseness' (e.g., possible and probable cases) of anxiety and depressive disorders among patients in

hospital clinics.²⁰ Physical symptoms are excluded. The HADS is divided into an anxiety subscale (HADS-A) and a depression subscale (HADS-D). Responses are scored 0 to 3 points such that each individual HADS (i.e., HADS-A and HADS-D) may garner between 0 and 21 points. A cut-off of 8 and over on a respective subscale is most commonly used to identify caseness of both depression and anxiety with a sensitivity and specificity of 0.80 on average.^{20,21}

Physical Problems—Patients reported whether a physical symptom had been a problem for them over the past week using the PPL accompaniment to the DT. Problem List items are potentially modifiable depending on clinic needs. We utilized the standard PPL, which contains 22 separate items (see Table 2 for items) to which patients endorse whether or not a particular physical symptom has been a problem for them in the past week.

Statistical Analysis

The primary outcome of this study was the association of 22 PPL items with the psychological symptoms of distress, anxiety, and depression. Associations with distress, anxiety, and depression were examined if at least 10% of patients endorsed that particular physical symptom (to ensure adequate power). Independent t-tests were used to assess the bivariate associations between patient psychological symptoms and endorsement of physical problems. A Bonferroni correction was performed to protect against a type I error for the multiple comparisons assessed in this study.

The effect of psychosocial distress variables on total number of items endorsed from the PPL was tested using negative binomial regression, as the outcome variable (total PPL items) represents a count variable, which was over-dispersed (i.e., Pearson's chi square value for the model using Poisson regression $\chi^2/df = 1.61$).²² Demographic and disease-related factors that were found to be significantly related to endorsement of specific physical problems in our prior work²³ were included as covariates. Statistical procedures were performed using the SPSS version 24 software (SPSS, Chicago, IL 2013) and statistical tests were two-tailed with a 5% significance level.

Results

One hundred and seventeen participants completed the survey with a response rate of 78%. The average age was 57.7 years (SD 14.8) and 69 (60.5%) were female. The majority of participants were White (76.1%), partnered (65.2%), and working (55.8%). Thirty-four (31.2%) had PV, 31 (28.4%) had ET, 31 (28.4%) had MF, and 13 (11.9%) had another type of MPN (Table 1). The duration of disease ranged from under 1 year (7.5%) to over 10 years (29.2%). The average distress score (DT) was 3.14, anxiety (HADS-A) 5.54, and depression (HADS-D) 3.40.

Nine out of 22 PPL items were endorsed by over 10% of the patients (Table 2). Eight of the nine most prevalent PPL variables were associated with at least two of three psychological outcomes (Table 3). In other words, distress was associated with every PPL variable except "Feeling Swollen" and depression was associated with every PPL variable except "Skin Dry/

Itchy”. Anxiety was associated with every PPL variable except for “Tingling” and “Skin Dry/Itchy”.

A Bonferroni correction was performed for the 27 comparisons that are presented in Table 3 (i.e., 9 symptoms $\times$ 3 psychological variables). The corrected α was 0.00185 ($p=0.05/27$). For simplicity, the corrected α was rounded down to $p<.001$ and can be seen in Table 3 as any association denoted by ***. After the Bonferroni correction, 6 of the 9 PPL variables were associated with at least one psychological symptom (Fatigue, Sleep, Tingling, Memory/Conc, Feeling Swollen, and Sexual) and Pain, Skin Dry/Itchy, and Breathing were not associated with a psychological variable. While PPLs associations for Distress were brought from eight to one (Memory/conc) and seven to three for Anxiety (Memory/Conc, Feeling Swollen, Sexual), Depression retained the majority of its associations-eight to five (Memory/Conc, Fatigue, Sleeping, Tingling, and Sexual).

Table 4 shows results from the hierarchical negative binomial regression analysis predicting the number of physical problems endorsed. Results did not differ in terms of significance or direction when models were run without outliers (2 respondents endorsing 15 and 20 physical problems, respectively); as such, results are reported with all data analyzed. The level of depressive symptoms was the only variable that related to total number of problems endorsed. Controlling for covariates, distress, and anxiety, patients who endorsed more depressive symptoms also tended to endorse more physical problems.

Discussion

This study demonstrated that the most commonly endorsed physical symptoms in patients with MPNs were also associated with at least one psychological variable. This relationship is striking to consider because diagnosing psychological symptoms, especially depression, can be difficult. But, the presence of physical symptom burden on this commonly used measure of distress may lead a clinician to more strongly consider these psychological manifestations. That is, the presence of numerous physical complaints should alert the clinician to consider an underlying psychological disorder, especially depression. Notably, depression appears to be uniquely associated with the number of physical symptoms that are endorsed as problematic by patients on multivariate analysis.

This is a significant finding because psychological symptoms such as depression can be difficult to diagnose and are not addressed for other reasons as well; insufficient use of a screening tool, limited or inadequate psychosocial resources. For these and a multitude of other reasons, depression remains frequently unrecognized and untreated.^{24,25} Depression and anxiety have both been associated with long term morbidity.^{26,27} The presence of depression specifically has been associated with mortality but this association disappears when depression in the cancer setting is treated appropriately.^{28–30} Physical symptom burden should provoke the care provider to evaluate closely for the presence of a concomitant psychological disorder in patient with MPNs. The reverse is also true. Depression, anxiety, and distress are associated with physical symptom burden in the MPN setting. Depression is most strongly linked to mounting physical symptoms. In other words, addressing physical symptom burden is critical to allaying psychological suffering.³¹

While the link between physical symptom burden and psychological symptoms is established, it has not been evaluated in patients with MPNs nor using the DT&PL as a measure of physical symptom burden. It is a convenient and universally available tool from which to glean the amount of physical symptom burden present. The consultant psychiatrist or primary oncology team should be able to use the DT&PL to track patients' psychological and physical symptom trajectories in clinic. This use of the DT&PL should be further explored.

The relevant physical problems were similar to the validated Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom (MPN-SAF TSS) but with lower overall prevalence.¹⁰ This is likely due to the dichotomous (yes/no) structure of the PPL of the DT&PL that asks about *bother* and not just the presence or experience of a symptom. The MPN-SAF TSS uses a likert scale to capture the presence of physical symptoms in addition to bother or discomfort.

This is the first study to evaluate specific PPL variables for their associations with multiple psychological symptoms in MPN patients; however, our findings fit with past literature among other cancer patient populations. A previous study found that of the general DT&PL problem list items, 'financial', 'worry', 'nervousness', 'getting around', and 'sleep' were associated with distress.³² Another study found that 'worry' and 'fatigue' were associated with distress in a general outpatient oncology population.³³ Other cancer settings have revealed the predominance of depression symptoms associated with physical symptom burden, to the exclusion of other psychological symptoms. For example, a large study of 487 general cancer patients had a synergistic relationship between depression and the presence and severity of physical symptoms that was independent of cancer type, functional status, chemotherapy, or survival.⁵ Another study found that fatigue, pain, insomnia, and gastrointestinal issues were associated with anxiety and depression in patients with breast cancer³⁴ while an additional study found that depression was most commonly associated with memory and concentration along with appetite problems in a population of general cancer patients.³⁵ Our study fit this pattern. It revealed a predominant association of depression with physical symptoms but was focused on the MPNs and controlled for relevant issues within this disease group.

That *depression* was the psychological variable most significantly associated with the number of PPL variables endorsed might be related to several factors. For one, distress and anxiety are frequently associated with comorbid underlying depression.³⁶ That is, a primary depressive disorder may masquerade as anxiety or an abnormal adjustment to a stressor (e.g., distress).³⁷ Also, living with chronic disability caused by an MPN-related physical impairment may lead to demoralization and hopelessness, key cognitive factors of depression.³⁸ Lastly, some physical symptoms such as fatigue, pain, or insomnia have putative underlying biological etiologies.^{39–41}

It is interesting to note that underlying biological correlates, markers of inflammation mostly, have been discovered for physical symptoms that arise in patients with MPNs.⁴² These biological markers of inflammation (e.g., IL-6, TNF- α) correlate with the severity of physical symptoms and also with disease characteristics. For example, specific cytokine

profiles have been studied that may be used to predict survival and monitor treatment response in patients with MF.⁴³ Also, TNF- α has been shown to facilitate clonal expansion of JAK2 V617F positive cells in patients with MPNs.⁴⁴

These same inflammatory markers are also elevated in depressive states and chronic emotional stress (e.g., having experienced early childhood adversity)^{45,46}, and are thought to play a role in the development and perpetuation of psychological states such as depression.^{42,47,48} Therefore, it is likely that both physical and psychological symptoms, especially depression, contribute to the deterioration of quality of life standards among patients with MPNs.

A limitation to this study is the use of a non-validated tool for measuring symptom burden. However, the rationale was to evaluate the use of the DT&PL in this regard since it is already so commonly in use in clinics and has proven clinical utility. Further study should validate the use of the DT&PL to assess physical symptom burden, perhaps using the MPN-SAF TSS scale. In addition, physical symptoms, such as those seen in patients with MPNs, with an underlying biological correlate may uncover a similar correlate that is involved in the biological underpinning of a psychological process as well. Therefore, it is of considerable importance to evaluate the association between physical and psychological symptoms in patients with MPNs and other cancer states with associated inflammation.

In summary, this study of patients with BCR/ABL negative MPNs provides evidence for an association between physical symptom burden using the DT&PL and psychological symptoms, most significantly depression. This association warrants further exploration given the clinical importance of detecting depression and other psychological symptoms and addressing concomitant physical symptom burden in MPN patients. The presence of either high physical or psychological symptom burden should alert treating clinicians to the presence of the other. These data help substantiate the need for psychologic/psychiatric care among MPN patients with high physical symptom burden.

Acknowledgments

Funding sources: Writing of this manuscript was supported by the NIH/NCI Cancer Center Support Grant P30 CA008748 (PI: Craig Thompson). Dr. Shaffer was supported by the NCI T32 CA009461 (PI: Jamie Ostroff).

References

1. Scherber R, Dueck AC, Johansson P, et al. The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF): international prospective validation and reliability trial in 402 patients. *Blood*. Jul 14; 2011 118(2):401–408. [PubMed: 21536863]
2. Tefferi A, Hudgens S, Mesa R, et al. Use of the Functional Assessment of Cancer Therapy--anemia in persons with myeloproliferative neoplasm-associated myelofibrosis and anemia. *Clin Ther*. Apr 01; 2014 36(4):560–566. [PubMed: 24636526]
3. Mesa RA, Niblack J, Wadleigh M, et al. The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international Internet-based survey of 1179 MPD patients. *Cancer*. Jan 1; 2007 109(1):68–76. [PubMed: 17123268]
4. McFarland DC, Polizzi H, Mascarenhas J, Kremyanskaya M, Holland J, Hoffman R. Psychological Symptoms Among Patients With BCR-ABL-Negative Myeloproliferative Neoplasms. *J Natl Compr Canc Netw*. Dec; 2016 14(12):1563–1570. [PubMed: 27956541]

5. Fitzgerald P, Lo C, Li M, Gagliese L, Zimmermann C, Rodin G. The relationship between depression and physical symptom burden in advanced cancer. *BMJ supportive & palliative care*. Dec; 2015 5(4):381–388.
6. Cella D, Nowinski CJ, Frankfurt O. The impact of symptom burden on patient quality of life in chronic myeloid leukemia. *Oncology*. 2014; 87(3):133–147. [PubMed: 25012261]
7. Tefferi A, Pardanani A. Myeloproliferative Neoplasms: A Contemporary Review. *JAMA oncology*. Apr; 2015 1(1):97–105. [PubMed: 26182311]
8. Haferlach T, Bacher U, Kern W, Schnittger S, Haferlach C. The diagnosis of BCR/ABL-negative chronic myeloproliferative diseases (CMPD): a comprehensive approach based on morphology, cytogenetics, and molecular markers. *Annals of hematology*. Jan; 2008 87(1):1–10. [PubMed: 17938925]
9. Vannucchi AM, Guglielmelli P, Tefferi A. Advances in understanding and management of myeloproliferative neoplasms. *CA: a cancer journal for clinicians*. May-Jun; 2009 59(3):171–191. [PubMed: 19369682]
10. Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Nov 20; 2012 30(33):4098–4103. [PubMed: 23071245]
11. NCCN practice guidelines for the management of distress 2015. 2015 [Accessed December 22, 2015]
12. Mitchell AJ. Pooled results from 38 analyses of the accuracy of distress thermometer and other ultra-short methods of detecting cancer-related mood disorders. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Oct 10; 2007 25(29):4670–4681. [PubMed: 17846453]
13. Tuinman MA, Gazendam-Donofrio SM, Hoekstra-Weebers JE. Screening and referral for psychosocial distress in oncologic practice: use of the Distress Thermometer. *Cancer*. Aug 15; 2008 113(4):870–878. [PubMed: 18618581]
14. Snowden A, White CA, Christie Z, Murray E, McGowan C, Scott R. The clinical utility of the distress thermometer: a review. *British journal of nursing*. 20(4):220–227. [Feb 24–Mar 9 2011] [PubMed: 21471860]
15. Lazenby M, Tan H, Pasacreta N, Ercolano E, McCorkle R. The five steps of comprehensive psychosocial distress screening. *Current oncology reports*. 2015; 17(5):447. [PubMed: 25824699]
16. Lazenby M, Ercolano E, Grant M, Holland JC, Jacobsen PB, McCorkle R. Supporting commission on cancer-mandated psychosocial distress screening with implementation strategies. *Journal of oncology practice*. May; 2015 11(3):e413–420. [PubMed: 25758447]
17. McFarland DC, Shaffer KM, Polizzi H, et al. Prevalence of Physical Problems Detected by the Distress Thermometer and Problem List in Patients With Myeloproliferative Disorders. *Journal of the National Comprehensive Cancer Network : JNCCN*. Dec; 2017 15(12):1503–1508. [PubMed: 29223988]
18. Bower JE, Bak K, Berger A, et al. Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jun 10; 2014 32(17):1840–1850. [PubMed: 24733803]
19. Pirl WF, Fann JR, Greer JA, et al. Recommendations for the implementation of distress screening programs in cancer centers: report from the American Psychosocial Oncology Society (APOS), Association of Oncology Social Work (AOSW), and Oncology Nursing Society (ONS) joint task force. *Cancer*. Oct 1; 2014 120(19):2946–2954. [PubMed: 24798107]
20. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res*. Feb; 2002 52(2):69–77. [PubMed: 11832252]
21. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. Jun; 1983 67(6):361–370. [PubMed: 6880820]
22. Cameron ACTP. *The Regression Analysis of Count Data*. Second. Cambridge: 2013.

23. McFarland DCSK, Polizzi H, et al. Prevalence of physical problems detected by the Distress Thermometer and Problem List in patients with myeloproliferative disorders. *JNCCN*. 2017
24. Passik SD, Dugan W, McDonald MV, Rosenfeld B, Theobald DE, Edgerton S. Oncologists' recognition of depression in their patients with cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr; 1998 16(4):1594–1600. [PubMed: 9552071]
25. McDonald MV, Passik SD, Dugan W, Rosenfeld B, Theobald DE, Edgerton S. Nurses' recognition of depression in their patients with cancer. *Oncology nursing forum*. Apr; 1999 26(3):593–599. [PubMed: 10214600]
26. Mitchell AJ, Ferguson DW, Gill J, Paul J, Symonds P. Depression and anxiety in long-term cancer survivors compared with spouses and healthy controls: a systematic review and meta-analysis. *The Lancet. Oncology*. Jul; 2013 14(8):721–732. [PubMed: 23759376]
27. McFarland DC, Holland JC. The management of psychological issues in oncology. *Clinical advances in hematology & oncology : H&O*. Dec; 2016 14(12):999–1009. [PubMed: 28212362]
28. Satin JR, Linden W, Phillips MJ. Depression as a predictor of disease progression and mortality in cancer patients: a meta-analysis. *Cancer*. Nov 15; 2009 115(22):5349–5361. [PubMed: 19753617]
29. Mols F, Husson O, Roukema JA, van de Poll-Franse LV. Depressive symptoms are a risk factor for all-cause mortality: results from a prospective population-based study among 3,080 cancer survivors from the PROFILES registry. *Journal of cancer survivorship : research and practice*. Sep; 2013 7(3):484–492. [PubMed: 23677523]
30. Giese-Davis J, Collie K, Rancourt KM, Neri E, Kraemer HC, Spiegel D. Decrease in depression symptoms is associated with longer survival in patients with metastatic breast cancer: a secondary analysis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Feb 01; 2011 29(4):413–420. [PubMed: 21149651]
31. Trivedi MH. The link between depression and physical symptoms. *Primary care companion to the Journal of clinical psychiatry*. 2004; 6(Suppl 1):12–16.
32. VanHoose L, Black LL, Doty K, et al. An analysis of the distress thermometer problem list and distress in patients with cancer. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*. May; 2015 23(5):1225–1232. [PubMed: 25315367]
33. Clover KA, Oldmeadow C, Nelson L, Rogers K, Mitchell AJ, Carter G. Which items on the distress thermometer problem list are the most distressing? *Support Care Cancer*. Nov; 2016 24(11):4549–4557. [PubMed: 27260016]
34. Breen SJ, Baravelli CM, Schofield PE, Jefford M, Yates PM, Aranda SK. Is symptom burden a predictor of anxiety and depression in patients with cancer about to commence chemotherapy? *The Medical journal of Australia*. Apr 06; 2009 190(7 Suppl):S99–104. [PubMed: 19351303]
35. Akechi T, Nakano T, Akizuki N, et al. Somatic symptoms for diagnosing major depression in cancer patients. *Psychosomatics*. May-Jun; 2003 44(3):244–248. [PubMed: 12724506]
36. Greenberg DB. Barriers to the treatment of depression in cancer patients. *Journal of the National Cancer Institute. Monographs*. 2004; 32:127–135.
37. Ramasubbu R, Taylor VH, Samaan Z, et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and select comorbid medical conditions. *Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists*. Feb; 2012 24(1):91–109. [PubMed: 22303525]
38. Robinson S, Kissane DW, Brooker J, Burney S. A systematic review of the demoralization syndrome in individuals with progressive disease and cancer: a decade of research. *Journal of pain and symptom management*. Mar; 2015 49(3):595–610. [PubMed: 25131888]
39. Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. *Neuroscience*. Aug 29; 2013 246:199–229. [PubMed: 23644052]
40. Sephton S, Spiegel D. Circadian disruption in cancer: a neuroendocrine-immune pathway from stress to disease? *Brain Behav Immun*. Oct; 2003 17(5):321–328. [PubMed: 12946654]
41. Jones SG, Benca RM. Circadian Disruption in Psychiatric Disorders. *Sleep Med Clin*. Dec; 2015 10(4):481–493. [PubMed: 26568124]
42. Geyer HL, Dueck AC, Scherber RM, Mesa RA. Impact of Inflammation on Myeloproliferative Neoplasm Symptom Development. *Mediators Inflamm*. 2015; 2015:284706. [PubMed: 26538823]

43. Tefferi A, Vaidya R, Caramazza D, Finke C, Lasho T, Pardanani A. Circulating interleukin (IL)-8, IL-2R, IL-12, and IL-15 levels are independently prognostic in primary myelofibrosis: a comprehensive cytokine profiling study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Apr 01; 2011 29(10):1356–1363. [PubMed: 21300928]
44. Fleischman AG, Aichberger KJ, Luty SB, et al. TNFalpha facilitates clonal expansion of JAK2V617F positive cells in myeloproliferative neoplasms. *Blood*. Dec 08; 2011 118(24):6392–6398. [PubMed: 21860020]
45. Irwin MR, Miller AH. Depressive disorders and immunity: 20 years of progress and discovery. *Brain Behav Immun*. May; 2007 21(4):374–383. [PubMed: 17360153]
46. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends in immunology*. Jan; 2006 27(1):24–31. [PubMed: 16316783]
47. Mondet J, Hussein K, Mossuz P. Circulating Cytokine Levels as Markers of Inflammation in Philadelphia Negative Myeloproliferative Neoplasms: Diagnostic and Prognostic Interest. *Mediators Inflamm*. 2015; 2015:670580. [PubMed: 26525644]
48. McFarland DC, Shen MJ, Polizzi H, et al. Psychological Manifestations of Early Childhood Adversity in the Context of Chronic Hematologic Malignancy. *Psychosomatics*. Jan-Feb;2017 58(1):46–55. [PubMed: 28010748]

Table 1MPN Sample Demographics and Characteristics (*N*=117)

	<i>Mean</i>	<i>SD</i>
Age	57.7	14.8
Distress (DT&PL)	3.14	2.83
Anxiety (HADS-A)	5.54	4.37
Depression (HADS-D)	3.4	3.4
	<i>N</i>	%
Race/Ethnicity		
White	86	76.1
Non-White	27	23.9
Gender		
Female	69	60.5
Male	45	39.5
Married		
Yes	73	65.2
No	39	34.8
Employed		
Yes	63	55.8
No	50	44.2
Disease Type		
PV	34	31.2
ET	31	28.4
MF	31	28.4
Other	13	11.9
Time with MPN		
<1 year	8	7.5
1–3 years	21	19.8
3–5 years	25	23.6
5–10 years	21	19.8
>10 years	31	29.2

Note: where sum = 117, patients did not report data.

Abbreviations: DT&PL, Distress Thermometer and Problem List; HADS-A, Hospital Anxiety Depression Scale-Anxiety; HADS-D, Hospital Anxiety Depression Scale-Depression; ET, Essential Thrombocythemia; MF, Myelofibrosis; MPN, Myeloproliferative Neoplasm; PV, Polycythemia Vera.

Table 2

Frequency of Physical Problems Endorsed

Physical Problem List Variables	<i>N</i>	%
Fatigue	38	35.5
Sleep	29	27.1
Pain	23	21.5
Skin dry/itchy	20	18.7
Tingling	19	17.8
Memory/Concentration	18	16.8
Feeling swollen	12	11.2
Breathing	11	10.3
Sexual	11	10.3
Mouth Sores	10	9.3
Appearance	9	8.4
Constipation	9	8.4
Diarrhea	9	8.4
Getting around	9	8.4
Nose dry	9	8.4
Eating	7	6.5
Indigestion	6	5.6
Nausea	5	4.7
Change in urination	4	3.7
Bathing	2	1.9
Fevers	2	1.9
Substance abuse	2	1.9

Table 3

Associations of Distress, Anxiety, and Depression with the Most Commonly Endorsed Physical Problems.

	Distress (DT&PL)		Anxiety (HADS-A)		Depression (HADS-D)	
	M (SD)	t	M (SD)	t	M (SD)	t
Fatigue	Yes 4.50 (3.2)	3.403**	7.47 (5.0)	3.153**	5.36 (3.5)	4.804***
	No 2.28 (2.2)		4.73 (3.7)		2.14 (2.5)	
Sleep	Yes 4.78 (3.2)	3.421**	7.89 (4.4)	3.397**	5.07 (3.4)	3.723***
	No 2.48 (2.6)		4.52 (4.3)		2.48 (2.8)	
Pain	Yes 5.32 (3.4)	3.605**	7.27 (4.1)	2.342*	5.32 (3.5)	3.605**
	No 2.61 (2.9)		4.80 (4.4)		2.61 (3.0)	
Skin Dry/Itchy	Yes 4.67 (3.1)	-2.631*	7.26 (4.1)	-1.904	4.74 (2.9)	-1.826
	No 2.78 (2.6)		5.19 (4.4)		3.17 (3.5)	
Tingling	Yes 4.82 (3.1)	-2.815**	7.00 (4.9)	-1.553	6.50 (3.8)	-4.460***
	No 2.77 (2.7)		5.27 (4.2)		2.85 (3.1)	
Memory/Conc	Yes 5.38 (2.8)	-3.701***	9.65 (4.8)	-4.565***	6.59 (3.7)	-4.431***
	No 2.68 (2.6)		4.81 (3.9)		2.87 (3.1)	
Feeling Swollen	Yes 4.08 (2.5)	-1.244	9.82 (1.8)	-6.769***	6.55 (3.3)	-3.292**
	No 3.00 (2.9)		5.08 (4.3)		3.10 (3.3)	
Breathing	Yes 5.18 (2.9)	-2.631*	9.20 (3.7)	-2.861**	6.30 (4.3)	-2.844**
	No 2.87 (2.7)		5.19 (4.3)		3.16 (3.2)	
Sexual	Yes 5.50 (2.6)	3.213**	12.10 (5.2)	5.912***	8.80 (2.2)	7.106***
	No 2.62 (2.6)		4.48 (3.7)		2.52 (2.7)	

Abbreviations: DT&PL, Distress Thermometer and Problem List; HADS-A, Hospital Anxiety Depression Scale-Anxiety; HADS-D, Hospital Anxiety Depression Scale-Depression;

* p<.05,

**

p<.01,

p<.001

Table 4

Hierarchical Negative Binomial Regression Analysis Predicting Total Items Endorsed on the Physical Problem List

	B	Std Error	Exp(B)	95% CI for Exp(B)	p
Covariates					
Race/Ethnicity	0.09	0.21	1.09	0.72 – 1.64	.69
Married	0.26	0.19	1.30	0.89 – 1.88	.17
Disease Type					
PV	0.17	0.28	1.18	0.69 – 2.04	.55
MF	0.09	0.28	1.09	0.63 – 1.90	.76
Other	0.43	0.29	1.54	0.87 – 2.71	.14
Psychosocial Distress Variables					
Distress Thermometer	0.06	0.04	1.07	0.98 – 1.16	.14
Depressive Symptoms	0.13	0.03	1.14	1.07 – 1.21	<.001
Anxiety Symptoms	0.03	0.03	1.03	0.97 – 1.10	.31

Note. Race/ethnicity: 0 = Race/ethnicity other than white, 1 = white; Married: 0 = No, 1 = Yes; Disease Type: effect compared to ET.