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MYELOPROLIFERATIVE NEOPLASMS (B STEIN, SECTION EDITOR)

# Integrative Approaches to Managing Myeloproliferative Neoplasms: the Role of Nutrition, Exercise, and Psychological Interventions

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## Abstract

**Purpose of Review** Myeloproliferative neoplasms (MPNs) have a high symptom burden that affects functional status, emotional well-being, and quality of life for patients. Symptom control continues to be a challenging therapeutic goal despite available pharmacologic interventions. The goal of this review is to detail recent efforts that have focused on non-pharmacologic interventions, such as wholistic or integrative medicine, as an adjunctive method to alter symptom burden in this population.

**Recent Findings** We discuss the ongoing physical, nutritional, and psychological interventional efforts which represent promising non-traditional interventions to date to help reduce symptom in MPN patients. In this article, we highlight the early promising data and importance of these various non-pharmacological interventions to dampen symptom burden and reduce disease-related inflammation.

**Summary** Nonpharmacologic interventions represent promising therapeutic strategies to alter traditional MPN treatment paradigms and improve MPN patient care.

**Keywords** Myeloproliferative neoplasms · Hematopoietic stem cells · Chronic inflammation · Symptom burden · Quality of life · Non-pharmacologic interventions · Integrative medicine

## Introduction

The myeloproliferative neoplasms (MPNs) are a group of chronic myeloid neoplasms characterized by hyperproliferation of clonal hematopoietic stem cells (HSCs) involving some or all myeloid lineages, depending on the subtype [1]. Classical Philadelphia chromosome negative MPNs include essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF). All three disorders result in an increased risk for thrombosis, variable rates of extramedullary hematopoiesis, and a possibility of transformation to myelofibrosis or acute leukemia at variable rates [1]. The majority of MPN disorders result from somatic mutations in hematopoietic stem cells (HSCs) with the most prevalent occurring in janus kinase gene (i.e., JAK2 V617F), followed by calreticulin (CALR) and myeloproliferative leukemia virus (MPL) genes [1].

Chronic inflammation plays a major role in MPN disease progression. Inflammation is a critical factor in the initiation or emergence of mutant hematopoietic stem cell clones, promotes myeloid malignancy progression, suppresses normal hematopoiesis, contributes to bone marrow fibrosis and extramedullary hematopoiesis, promotes thrombosis, and exacerbates symptom burden [2••]. Specific proinflammatory cytokines such as tumor necrosis factor-α, IL-6, IL-1, and IL-8 have shown to be related to patient symptoms [3••]. Symptom profiles differ due to different etiologies among myeloproliferative neoplasm (MPN) subtypes. The vast majority of MPN patients are symptomatic with a symptom severity that mirrors prognosis among MPN subtypes (ET < PV < MF) [4, 5]. Typical symptoms include (but not limited to) fatigue, pruritis, night sweats, loss of appetite, weight loss, abdominal pain, splenomegaly, anemia, and microvascular complications [6, 7]. Symptoms have also been found to vary by gender, disease phenotypes, and treatments (Geyer et al. JCO) [8]. The symptom burden in myeloproliferative

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neoplasms (MPNs) often leads to reduced overall quality of life with reduced ability to participate in physical, social functions along with inability to participate in daily living [9].

To date, there have been multiple methods of assessing symptom burden, the most common of which are the Myeloproliferative Neoplasm Symptom Assessment Form (MPN SAF) [5] and the Myeloproliferative Neoplasm Symptom Assessment Score Total Symptom Score (MPN-SAF TSS or MPN-10). These scores are patient-reported outcome tools that are used in both clinical practice and trial settings [4]. The MPN-10 has been recommended for assessment of MPN symptom burden and guides subsequent therapy decisions. This tool has been incorporated to National Comprehensive Cancer Network guidelines for treatment of ET, PV, and MF [4].

Treatment of MPNs primarily focuses on preventing thrombosis, bleeding, and reducing symptom burden to improve quality of life [10]. To date, pharmacological interventions remain the mainstay of treatment for MPN population and include cytoreduction, JAK inhibition, anemia-directed therapy, and allogenic stem-cell transplantation reserved for intermediate to high-risk PMF [10]. JAK inhibition therapy has improved the MPN symptom burden to some extent with reduction in inflammatory markers and splenomegaly, yet even in responders; unmet needs remain for challenging symptoms such as fatigue, mood-related symptoms, and insomnia despite pharmacotherapy [11].

Given the relationship of inflammation to symptom burden, inflammation represents a potential major treatment target in MPNs which may alter symptom burden [8, 12, 13]. However, given the chronicity of disease, therapies which alter the pro-inflammatory cascade of MPNs also need to take into consideration the level of risk with treatment. Although effective, pharmacologic therapies carry risk of immunosuppression, infections, and cytopenias. However, non-pharmacologic strategies represent a potential promising therapeutic venue that may improve symptom burden and reduce inflammation without elevated risk of adverse events. In this article, we discuss recent studies that evaluate exercise (including yoga), psychosocial interventions (i.e., acceptance and commitment therapy (ACT) and mindfulness), and nutrition that have revealed promising data to date in the alleviation of MPN-related symptoms and inflammation.

## Non-Pharmacologic Interventions in Myeloproliferative Neoplasms

As highlighted above, 84% of MPN patients report an impaired quality of life [5]. Lifestyle factors such as obesity, alcohol, and smoking are associated with myeloid malignancy development through promotion of chronic inflammation; thereby leading to MPN-related symptoms [14]. Of all MPN symptoms, fatigue stood apart as having the highest prevalence and is reported to be > 90% among patients with MPNs [2••].

Previous patient-centered research efforts have highlighted that non-pharmacologic therapies represent a potential venue for therapeutic intervention among MPN patients. A comprehensive understanding of fatigue in MPN patients has been conducted by Scherber et al. [2••]. In this international, 70-item, Internet-based survey developed by MPN investigators and hosted by Mayo clinic utilizing an online patient-reported questionnaire evaluated underlying confounding factors that can potentially contribute to worsening of fatigue [2••]. This study identified that although fatigue is multifactorial in nature, underlying contributing lifestyle factors and psychological symptoms were highly associated with fatigue.

Mood assessments were obtained among the participants using three questionnaires (PHQ-2, MHI-5, POMS-B). Approximately, 23% of respondents scored higher indicating a high probability of depressive symptoms. Patients frequently endorsed having been evaluated or diagnosed with depression (32%), anxiety (29.5%), stress (26.2%), and grief (15.0%) [2••].

One of the striking findings of this study was the demonstrated correlation between exercise and a reduction in fatigue. Individuals who were physically active reported less fatigue when compared to those with a sedentary lifestyle. This implication is that as fatigue level increases, it becomes more difficult to be physically active [2••]. Patients in this research survey have also endorsed self-medicating with anti-anxiety, anti-depressants, antihistamines, and prescription pain medications [2••]. These patients have utilized non-pharmacologic strategies such as scheduling activities during peak energy times, pacing activities, walking, setting priorities, labor-saving devices, relaxation/yoga, meditation, support groups, and sleep therapy by control of sleeping patterns [2••].

Interventions to reduce weight in MPNs in patients with high body mass index along with standard therapies to reduce symptoms may be an effective strategy based on research findings presented at European Hematology Association (EHA) in June 2018 [15]. In this analysis, individuals with significantly higher BMI (i.e., BMI in the overweight or obese range of > 25) demonstrated significantly higher high symptom burden compared to their normal weight counterparts. These findings highlighted the need for prospective research endeavors to better understand mechanisms and impact of which lifestyle modifications to help alleviate fatigue and other MPN-related symptoms [2••].

Numerous studies have evaluated the potential mechanisms for non-pharmacologic interventions in altering emotional, cognitive, and physical functioning. Figure 1 describes a theoretical model of symptom burden contributors that represent therapeutic targets for non-pharmacologic interventions.

Further prospective studies have been conducted to assess the efficacy of non-pharmacologic interventions in alleviating MPN symptoms, by utilizing methods such as yoga,

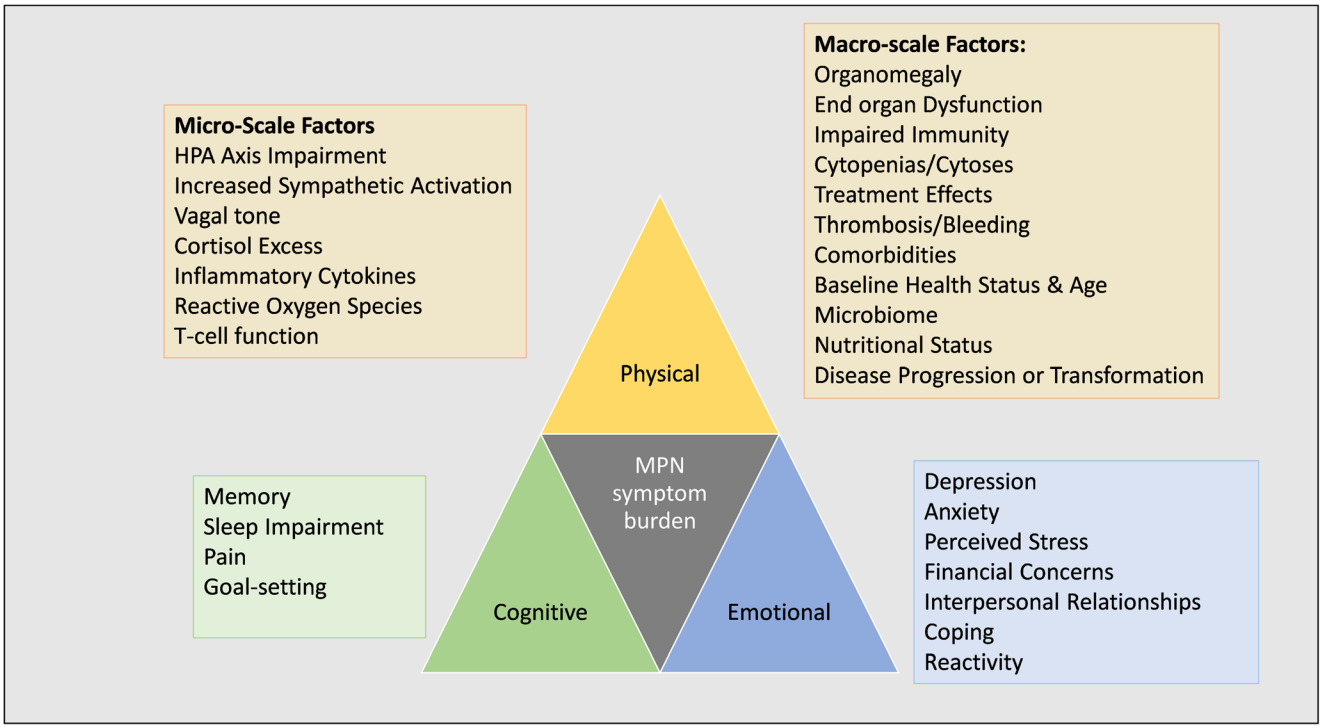


**Fig. 1** Theoretical model of therapeutic targets for non-pharmacologic interventions in MPN populations. [3••, 16, 17, 18••]

meditation/mindfulness, and nutrition. Table 1 summarizes the non-pharmacologic interventional efforts to date for MPN patients.

## Yoga

Yoga used as non-pharmacologic therapy has been shown to be efficacious for improving symptoms such as depression, anxiety, fatigue, and insomnia in other cancer populations including hematological malignancies [11]. Two prospective studies have been conducted so far to examine the effects of online yoga intervention for fatigue and quality of life in MPN patients.

### Online-Streamed Yoga Study

The first yoga study was a feasibility trial of home-based, single arm phase I online-streamed yoga conducted by

**Table 1** Overview of non-pharmacologic interventions [11, 19]

| Non pharmacologic interventions | | Study design | Results |
|---|---|---|---|
| Yoga | Online-streamed yoga study | 12-week yoga intervention with weekly online yoga videos | In total symptom burden (ES = − 0.36, $p = 0.004$), anxiety (ES = − 0.67, $p = 0.002$), fatigue (ES = − 0.58, $p = < 0.01$) sleep(ES = -0.38, $p = 0.04$)In NIH PROMIS QoL at week12 (ES = 0.7, $p = 0.03$)significant decrease in TNF-α and no change in CBC or IL-6 N |
| | Pilot study on online yoga | 60 min/week of 12-week online yoga | |
| Mindfulness meditation | Acceptance and commitment therapy | Online video intervention that utilizes weekly ACT videos for 8 weeks | Under Investigation |
| | Calm app | Novel, feasible, smart phone-based mobile application with 10-min guided meditation to improve adherence, uptake, and reach | Early Investigation |
| Nutrition | NUTRIENT Study | Phase I | Determines dietary needs and requirements, involves focus groups Under Investigation |
| | | Phase II | To assess feasibility and adherence to dietary intervention |
| | Supplement use | N-acetylcysteine, aminoacids | Restores blood parameters |
| | | | Reduces symptom score |

Huberty et al. [11]. Two hundred forty-four patients completed the eligibility survey and were asked to complete 60 min of online-streamed yoga weekly for 12 weeks which included MPN-specific videos. MPN patients who enrolled ($N = 38$) were asked to complete the 12-week yoga intervention. The majority of patients were diagnosed with PV ($N = 16$) and ET ($N = 16$) while MF was a less common diagnosis ($N = 8$) [11]. Yoga participation averaged 50.8 min/week. Overall, 68% of patients were satisfied or very satisfied, and 75% felt that it was very helpful for coping with MPN symptoms. Yoga intervention showed significant improvements in total symptom burden (effect size ES = − 0.36, $p = 0.004$), anxiety (ES = − 67, $p = 0.002$), sleep (ES = − 0.58, $p < 0.01$), fatigue (ES = − 0.33, $p = 0.04$) [11]. The sample size of this study is very small and has no control group warranting further randomized, controlled trials in this setting [11].

### Pilot Study on Online Yoga

MPN Yoga II Pilot Study was a phase II study designed and conducted in late 2017 by Eckert et al. [19] with the aim to examine the effects of 60 min/week of the 12-week online yoga study. This study evaluated fatigue and quality of life as compared to wait-list control group as well as remote assessment of biomarkers such as CBC, IL-6, and TNF-α by collecting blood samples at baseline (week 0) and post intervention (week 12). Wait-list control group were asked to maintain their normal level of activity [19] until approximately week 12, when they were then asked to complete the online yoga intervention.

All participants completed self-report surveys which included measures such as demographics, MPN SAF, and NIH PROMIS (National Institutes of Health Patient Reported Outcomes Measurement Information System) and were administered at baseline (week 0), mid intervention (week 7), and post intervention (week 12) [19]. Two hundred sixty patients completed the eligibility and 48 patients completed the full 12-week intervention. Objective yoga averaged 40.8 min/week whereas self-reported yoga averaged 56.1 min/week [19].

There was no significant difference at week 12 in MPN SAF fatigue or MPN SAF QoL groups; however, NIH PROMIS QoL was significantly better in the yoga group at week 12 (ES = 0.7, $p = 0.03$). There was a significant decrease in TNF-α from week0 to week 12 but no significant differences in CBC or IL-6 [19]. Again, significant improvements in fatigue were not seen due to small sample sizes. Therefore, a large sample size is required for further investigation. Efforts are also underway to investigate this intervention in other settings including bone marrow transplantation survivors and other hematologic malignancies.

## Meditation/Mindfulness

Mindfulness-based interventions have proven to be effective non-pharmacologic approaches in chronic conditions such as fibromyalgia, chronic fatigue, chronic pain, and malignancies as breast cancer and CNS tumors, by reducing inflammation, thereby alleviating cancer-related symptoms such as emotional, psychological, and sleep disturbances [20–24].

### Acceptance and Commitment Therapy

ACT is an evidence-based psychological intervention that targets emotions, thoughts, and behavior [25]. ACT has been shown to improve quality of life in chronic conditions as fibromyalgia, chronic pain and chronic fatigue, and malignancies as breast cancer and brain tumors. ACT works by alleviating symptoms such as pain, pain disability, anxiety, depression, insomnia, and fatigue and improving quality of life [20–24]. My ACT (acceptance and commitment therapy) study is an ongoing, feasible, randomized, online video intervention employed to assess symptom control with primary target being fatigue, utilizing weekly ACT videos up to 8 weeks with eight weekly video topics namely introduction, acceptance, defusion, being present, self as context, values, committed action and conclusion.

Up to 190 MPN patients were enrolled in the study, randomized based on age and Brief Fatigue Index Score (4–6, 7–10). All patients completed baseline surveys and Fitbit was assessed weekly for surveys. Patients were randomized in 1:1 fashion, 95 patients in intervention group utilized weekly ACT videos up to 8 weeks and 95 patients in the wait-list group were monitored for similar duration without any intervention. Fitbit was assessed weekly, and surveys were conducted in both the groups at week 4 and week 8, followed by washout period in the intervention group from week 8 in order to eliminate the effects of the treatment. Crossovers were employed on wait-list group with weekly ACT videos with surveys to be conducted at week 20 in both the groups. Results of this study are not yet available at the time of publication of this manuscript and will need a close follow-up.

### Mindfulness/Meditation

Mindful interventions are limited in several ways as they require in-person delivery, limiting uptake, especially for MPN patients who face many demands and stressors including fatigue, pain, transportation, and scheduling difficulties along with required delivery by a trained provider and attendance to a specific schedule, further limiting adherence, uptake, and reach [26]. Mobile applications (apps) represent a novel approach to the delivery of mindfulness meditation by bypassing the barriers to care delineated above. Calm app is a novel, feasible, consumer, smartphone-based meditation mobile

application that utilizes 10-min, guided meditations that teaches users on the basics and integration of mindfulness into their daily lives. Early efforts are underway to investigate the efficacy of daily meditation delivered via Calm app with aim to control MPN symptom burden.

## Nutrition and Supplement Use

Cachexia, weight loss, and malnutrition are important contributors of adverse outcomes especially in MPN patients due to chronic inflammation with cytokine release and associated nutritional deficiencies such as hypocholesterolemia and hypoalbuminemia have been associated with decreased survival in PMF patients [27]. As other non-pharmacologic interventions such as yoga and mindfulness, inflammation continued to be the main target for dietary modifications in MPNs.

Results of Prospective study by Mitrou et al. [27], included participants from the National Institutes of Health American Association of Retired Persons (NIH-AARP), has provided strong evidence for a beneficial effect for higher conformity with Mediterranean diet on the risk of death from all causes (Men: HR 0.79 with 95% CI 0.76–0.83, Women: HR 0.80 with 95% CI 0.75–0.85), including deaths due to cancer with statistically significant decreased risk of cancer by 12% [28].

The ATTICA study was performed by Chrysohoou et al. to understand the mechanisms by which Mediterranean diet reduces all-cause mortality. This study has shown that adherence in Mediterranean diet attenuates inflammation including where indicated process with 20% lower CRP ($p = 0.015$) and 17% lower IL-6 ($p = 0.025$) [29, 30]. Also, the study has shown statistically significant reduction in coagulation markers including as 15% lower homocysteine levels ($p = 0.031$), 14% lower white blood cell counts ($p = 0.001$), and 6% lower fibrinogen levels ($p = 0.025$) [29].

Diets emphasizing anti-inflammatory properties have demonstrated good efficacy when utilized in nutritional intervention for high-inflammation disease states such as inflammatory bowel disease. An intervention among patients with IBD expressed ($N = 40$) and up to 60% had "good" or "very good" response in IBD severity after 4 weeks of dietary compliance [31].

Until recent, no studies evaluated the nutritional needs or preferences among MPN patients as regards to dietary change. The NUTRIENT Study was designed to determine the nutritional needs and preferences that will help inform the creation of a tailored MPN dietary intervention [32].

Part 1A of the NUTRIENT Study, completed in April 2017, was a prospective, online, Internet-based survey hosted by Mayo Clinic Survey Research Cancer Center and was promoted on multiple MPN-based forums, website, and Facebook pages during February 2017. This study included two parts; Part-I involved two efforts with first being a 55-item questionnaire ($N = 1329$) that included assessment of dietary needs, symptoms, nutritional habits, and supplement intake; and the second, involving focus groups [32]. Part II assessed feasibility and adherence. Over 30 % of patients who responded to the survey endorsed using dietary interventions to help control MPN symptoms. 96.2% of MPN patients endorsed being willing to restrict their diet if it helped to control symptoms; 98% of patients were willing to restrict their diet to stabilize or reduce the risk of MPN progression. Foods/intolerances/restrictions associated with worsened symptom score (MPN-10) included diabetic diet ($p < 0.0001$), lactose intolerance ($p = 0.0422$), fried and fast foods ($p = 0.0198$, 0.0015), soda ($p < 0.0001$), pre-made snack foods ($p = 0.0296$), refined sugars ($p = 0.0139$), and tacos ($p = 0.0277$) while alcohol ($p < 0.0001$), rice ($p = 0.0452$), baked foods ($p = 0.0212$), diary other than cheese (milk, cream) ($p = 0.0240$), and pasta ($p = 0.0183$) correlate with improved symptom score.

This survey also investigated patient use of supplements among MPN patients. Overall, 72% of MPN respondents reported use of over-the-counter supplements. Use of N-acetylcysteine ($p = 0.002$) and amino acid supplements ($p = 0.002$) were significantly associated with improved symptom burden among respondents. Given that a previous study found N-acetylcysteine treatment in murine models engrafted with JAK2 V617FKI bone marrow cells resulted in restores blood parameters, reduced DNA damage, and double-stranded breaks along with decrease in splenomegaly with reduction in frequency of JAK2 V617F progenitors in bone marrow and spleen [16]; N-acetylcysteine supplement use appeared to be a promising potential therapeutic approach to improve MPN-related symptom burden as well.

Part 1B of the NUTRIENT survey involved focus groups. [33] MPN participants were recruited from the "We are MPN" participant conference in Irvine, California April 2017 ($N = 13$, 77% female). MPN patients frequently reported food restrictions or intolerances that are related to their MPN disease course and symptoms. Participants were enthusiastic regarding participation and execution of a dietary intervention and express concern over the lack of resources regarding diet. Patients desired the ability to connect among peers and with researchers and desired a tailored dietary intervention which addresses their needs and preferences. [33]

Based on these results, the NUTRIENT Study Part 2 is an ongoing research prospective trial to assess the feasibility and adherence to Mediterranean dietary intervention, where an anticipated 30 patients will be enrolled and followed over the course of a dietary intervention with the Mediterranean diet. Early efforts are also ongoing to open a Southwest Oncology Group (SWOG) trial with the primary objective of assessing the effects N-acetylcysteine on MPN symptom burden. Although these still represent early efforts, nutrition and supplement use remain promising low-risk adjunct non-pharmacologic therapy options that could be combined with medicinal therapies to alleviate MPN-related symptoms.

## Conclusions

Overall, patients with MPNs experience disabling symptoms with significant impairment in quality of life. Despite traditional medicinal therapies, symptom burden remains challenging for patients and for physicians to treat. Recently published preliminary data on the role of non-pharmacologic interventions primarily targeting chronic inflammation have shown significantly promising results with easy feasibility and adherence among patients with very low-risk side effect profile. Further research needs to be focused on these non-pharmacologic treatment modalities to help formulate a comprehensive treatment approach in MPN patients.

### Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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