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Psychostimulant use for cancer-related fatigue in an oncology palliative care clinic: a retrospective cohort study

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Abstract

Purpose

Psychostimulants are prescribed for cancer-related fatigue (CRF), although data on real-world use are scant and trials have shown mixed results. We aimed to describe the prevalence and predictors of psychostimulant use in an oncology palliative care clinic (OPCC).

Methods

This retrospective cohort study included new patients seen in the OPCC at the Princess Margaret Cancer Centre, Toronto, Canada from 2022/6/4-2025/7/24, excluding those with prior psychostimulant use. We recorded demographic and clinical characteristics, including performance status, symptom scores, and outpatient psychostimulant prescriptions following the initial OPCC visit. We calculated the prevalence of subsequent psychostimulant prescription and evaluated factors associated with psychostimulant prescription using univariable and multivariable logistic regression. For psychostimulant recipients, we evaluated adherence and reported effects.

Results

Of 3,587 patients (age 66.5 ± 14.3 years, 49% female) with advanced solid tumours (92.0%) and hematologic malignancies (8.0%), 75.3% reported at least moderate (≥ 4/10) fatigue. Following the initial clinic visit, 193 (5.4%) received psychostimulant prescriptions; of these, 183 (94.8%) received methylphenidate. On multivariable analysis, psychostimulant receipt was associated with worse fatigue (OR 1.16, 95%CI 1.07–1.26), breast cancer diagnosis (OR 2.58, 95%CI 1.28–5.20 vs. thorax), and younger age (OR 0.97, 95%CI 0.96–0.99). Among 77 evaluable patients who received a psychostimulant from the OPCC and adhered to treatment (all received methylphenidate), CRF improved in 53 (68.8%); 3 (3.9%) reported non-serious adverse events.

Conclusion

Despite a high prevalence of CRF in outpatients receiving palliative care, few patients were treated with psychostimulants. Further research is needed to evaluate the efficacy of psychostimulants and understand prescribing practices.

Introduction

Cancer-related fatigue (CRF) is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is disproportionate to recent activity and interferes with usual functioning.[1] CRF is the most common symptom experienced by

patients with cancer at all disease stages and negatively impacts quality of life.[1–3] CRF is pervasive in the outpatient palliative oncology setting, with reported prevalence of moderate-to-severe fatigue ranging 66–84%.[4–7] Despite its high prevalence, CRF is underreported and undertreated, in part because it is often considered unavoidable, and in part due to perceived lack of effective treatments.[8]

The initial approach to managing CRF involves identifying and addressing treatable contributing factors, educating patients and family/caregivers, and counseling patients on self-monitoring of fatigue and energy conservation strategies.[1, 2] Exercise and psychosocial interventions are effective interventions, [9] although there is less evidence for their feasibility or effectiveness in patients with advanced disease. There are few proven pharmacotherapeutic options for treatment of CRF. Psychostimulants are the most frequently prescribed class of medications; however, there are conflicting guideline recommendations regarding their use,[1–3] reflecting the limited current evidence. In most randomized controlled trials (RCT) evaluating methylphenidate for CRF,[10–23] it was no more effective than placebo. Nevertheless, meta-analyses using pooled RCT data demonstrated a significant effect, with moderate effect sizes.[24–26] Importantly, psychostimulants remain widely used for CRF in patients with advanced cancer receiving palliative care, and remain interventions of interest.[24, 25, 27–29]

There are scant published data on the use of psychostimulants for CRF. A retrospective review of medical records explored the recorded effectiveness of methylphenidate for CRF in patients admitted to a palliative care unit and home palliative care service in Stockholm, Sweden.[30] Among 2,419 patients (with and without cancer) screened over 3 years, 112 received methylphenidate for CRF; it was generally effective and well-tolerated, though less beneficial in the last 4 weeks of life. Outpatient oncology palliative care clinics—where fatigue is common and patients typically have a higher performance status and longer life expectancy than those receiving inpatient or home-based palliative care—represent an obvious setting of interest for studying psychostimulants for CRF. However, to our knowledge, there have been no reports on the real-world use of psychostimulants in the outpatient oncology palliative care setting. We conducted a retrospective cohort study of patients in an oncology palliative care clinic to examine the prevalence and predictive factors of psychostimulant use for CRF, as well as the reported effects of psychostimulant treatment.

Methods

The study took place at the Princess Margaret Cancer Centre (PM), a comprehensive cancer centre in Toronto, Canada, which is part of the University Health Network. PM is the largest tertiary cancer centre in Canada and has a robust palliative care program, including a stand-alone clinic that supports patients with advanced cancer longitudinally alongside their oncology care and sees approximately 1500 new patients per year.[31] We conducted a retrospective review of new consultations in the PM Oncology Palliative Care Clinic (OPCC) from June 4, 2022 to July 24, 2025. We excluded patients with prior psychostimulant use. Patients were identified from the OPCC database and their data were linked to the patient's electronic medical record (Epic) at the University Health Network.

Patient demographics (age, gender), primary cancer diagnosis, symptom measures, and performance status were extracted from the OPCC database. Performance status measures included the Palliative Performance Scale (PPS)[32] and the Eastern Cooperative Oncology Group performance status (ECOG) [33] completed by the palliative care physician during the initial consultation. Patients in the OPCC complete symptom screening at every visit, using the Edmonton Symptom Assessment System-revised version including constipation and sleep (ESAS-r-CS).[34] This validated questionnaire includes 11 items (pain, fatigue, drowsiness, nausea, anxiety, depression, appetite, dyspnea, well-being, constipation, and sleep). Patients rate each symptom on a scale of 0–10, where 0 indicates the absence of the symptom and 10 indicates the worst possible severity. The ESAS Distress Score (EDS) is calculated as the sum of 9 main ESAS items (with prorating of incomplete items when > 50% of items are complete),[35] and the Total Distress Score (TDS) is the sum of all 11 ESAS-r-CS items.[34]

If diagnostic information, ESAS-r-CS, PPS, or ECOG were missing from the OPCC database, they were extracted from Epic, which captures cancer diagnoses and questionnaire scores associated with clinic visits. We also examined data on clinician-estimated prognosis (less than 1/3/6/12/24 months or uncertain)—a mandatory field completed by the referring physician on the OPCC referral order in Epic. Data on outpatient psychostimulant prescriptions (prescribing service/clinic, date, specific medication, dose) were extracted from Epic.

The prevalence of incident psychostimulant prescription was calculated as: the number of individuals without current or previous psychostimulant use at the time of the initial OPCC consultation who received a psychostimulant prescription following this consultation, divided by the total number of new patients seen in the OPCC during that period (excluding those with current/prior psychostimulant use). A minimum follow-up period of 90 days after the initial consultation was used to ascertain prescription.

Among patients who received a prescription for a psychostimulant from the OPCC following the initial OPCC visit, a detailed chart review by 2 independent research team members was conducted to extract data on dosing and dose modifications, indication, adherence/reported use, patient-reported effectiveness, and adverse events.

This study was approved by the University Health Network Research Ethics Board (UHN-REB #25-5547).

Statistical analyses

Patient characteristics and prevalence of incident psychostimulant prescription were summarized descriptively for the entire cohort. The association between fatigue and psychostimulant prescription was analyzed in the cohort reporting their fatigue score on ESAS-r-CS at the initial consultation. Baseline 11 ESAS-r-CS item scores were compared using the two-sample t-test among patients who subsequently received a psychostimulant prescription versus those who did not. The association between psychostimulant receipt and demographic, clinical factors, physical and psychological symptom scores were evaluated using logistic regression. All p-values were 2-sided; $p < 0.05$ was considered statistically significant.

Results

Cohort characteristics and symptom burden

In total, 3,624 patients with advanced solid organ tumours or hematologic cancers had an initial consultation in the OPCC from June 4, 2022 to July 24, 2025, of whom 37 (1.0%) were excluded for prior psychostimulant use. The remaining 3,587 patients (mean age 66.5 ± 14.3 years, 49% female) comprised the study cohort, for whom demographic and clinical characteristics are shown in Table 1. The most common primary tumour sites were thoracic (18.8%), gastrointestinal (16.8%), head and neck (16.5%), gynecologic (12.3%), and genitourinary (9.6%).

Table 1
Demographic and clinical characteristics of new patients seen in the oncology palliative care clinic from June 4, 2022-July 24, 2025 (N = 3,587)

Variable	**Mean ± SD or N (%)**
Age, years	66.5 ± 14.3
Female gender	1756 (49.0%)
Primary Cancer	
Breast	183 (5.1%)
CNS	158 (4.4%)
Gastrointestinal	599 (16.8%)
Genitourinary	342 (9.6%)
Gynecologic	437 (12.3%)
Head and neck	589 (16.5%)
Hematologic	286 (8.0%)
Sarcoma	110 (3.1%)
Skin	188 (5.3%)
Thorax	669 (18.8%)
ECOG Performance Status	
0	69 (5.2%)
1	545 (41.4%)
2	397 (30.1%)
3	290 (22.0%)
4	16 (1.2%)
Palliative Performance Scale	
20	2 (0.1%)
30	14 (0.8%)
40	92 (5.1%)
50	397 (21.8%)
60	523 (28.8%)
Missing/not documented: primary cancer, n = 26 (0.7%); ECOG, n = 2270 (63.3%); PPS, n = 1768 (49.3%); estimated prognosis, n = 185 (5.2%).	

Variable	Mean ± SD or N (%)
70	520 (28.6%)
80	193 (10.6%)
90	70 (3.8%)
100	8 (0.4%)
Estimated prognosis by referring clinician	
<6 months	830 (24.4%)
6–24 months	1000 (29.4%)
Uncertain	1572 (46.2%)
ESAS-r-CS distress score	33.9 ± 17.0 (n = 2060)
ESAS-r-CS total distress score	40.8 ± 20.0 (n = 2069)
Missing/not documented: primary cancer, n = 26 (0.7%); ECOG, n = 2270 (63.3%); PPS, n = 1768 (49.3%); estimated prognosis, n = 185 (5.2%).	

Of the 2,057 (57.3%) patients who completed the ESAS-r-CS at their initial OPCC visit and reported their fatigue score, 1,549 (75.3%) reported at least moderate fatigue (≥ 4/10); 859 (41.8%) reported severe (≥ 7/10) fatigue. Fatigue was the highest rated among all items on the ESAS (median 6.0 [interquartile range 3–8]; mean 5.5 [SD 2.7]). Characteristics of patients were similar among those with and without available baseline ESAS data (*Table S1*).

Psychostimulant prescription and reported use

Of the 3,587 patients comprising the study cohort, 193 (5.4%) patients received a psychostimulant prescription from any prescriber within PM after the initial palliative care clinic visit. Of these, 140 (3.9%) were prescribed a psychostimulant by an OPCC physician. Among the 193 patients, the median interval between the initial palliative care consultation and the first psychostimulant prescription was 114 (interquartile range 28–256) days. Among recipients of a psychostimulant prescription, 183 (94.8%) received methylphenidate immediate release (IR), all at an initial total daily dose ≤ 10 mg.

For the 140 patients prescribed a psychostimulant by an OPCC physician, all prescriptions were for the indication of improving CRF and 139 (99.3%) were for methylphenidate IR. Among these patients, 7 (5.0%) had their dose increased to a maximum of 20 mg/day, and only 1 patient eventually exceeded this dose, reaching a maximum of 60 mg/day. Of the 77 patients who adhered to methylphenidate treatment and had follow-up notes reporting effects, 53 (68.8%) reported improved fatigue; 12 (15.6%) no benefit; and 12 (15.6%) had conflicting notes regarding effectiveness (Fig. 1). Of these 77 patients, 3 (3.9%) reported non-serious adverse events that were felt to be related to methylphenidate, 2 leading to its discontinuation (anxiety, nausea), and 1 that was dose-limiting (insomnia).

Factors associated with psychostimulant prescription

The baseline symptom scores for patients who subsequently received, or did not receive, a psychostimulant prescription are presented in Table 2. Patients with a higher symptom burden at the initial consultation were more likely to receive a psychostimulant ($p < 0.01$ for both EDS and TDS). Specifically, psychostimulant recipients had worse baseline ESAS-r-CS scores for fatigue ($p < 0.01$), drowsiness ($p = 0.01$), depression ($p = 0.02$), anxiety ($p < 0.01$), well-being ($p < 0.01$), and insomnia ($p < 0.01$).

Table 2
Baseline symptom scores by psychostimulant receipt following initial oncology palliative care clinic consultation (N = 2,057)

ESAS-r-CS symptom item	**Received psychostimulant prescription**		**P***
	No (n = 1940)	**Yes (n = 117)**	
	Mean ± SD	*Mean ± SD*	
Pain	4.7 ± 3.1	4.7 ± 3.0	0.99
Tiredness	5.5 ± 2.7	6.4 ± 2.4	0.0004
Drowsiness	3.6 ± 2.9	4.3 ± 3.0	0.01
Nausea	1.7 ± 2.5	1.9 ± 2.3	0.40
Appetite	4.2 ± 2.9	4.2 ± 2.7	0.95
Shortness of breath	2.5 ± 2.8	3.0 ± 2.8	0.13
Depression	3.1 ± 2.9	3.8 ± 3.0	0.02
Anxiety	3.4 ± 2.9	4.2 ± 3.0	0.004
Wellbeing	4.8 ± 2.5	5.6 ± 2.3	0.003
Constipation	2.8 ± 3.1	2.7 ± 2.9	0.81
Problem sleeping	4.4 ± 2.9	5.3 ± 2.8	0.003
*Two-sample t-test.			
Missing/not documented: pain, n = 29 (1.5%) no, n = 2 (1.7%) yes; drowsiness, n = 45 (2.3%) no, n = 2 (1.7%) yes; nausea, n = 42 (2.2%), all no; appetite, n = 42 (2.2%) no, n = 1 (0.9%) yes; shortness of breath, n = 55 (2.8%) no, n = 6 (5.1%) yes; depression, n = 70 (3.6%) no, n = 7 (6.0%) yes; anxiety, n = 82 (4.2%) no, n = 3 (2.6%) yes; wellbeing, n = 116 (6.0%) no, n = 5 (4.3%) yes; constipation, n = 77 (4.0%) no, n = 9 (7.7%) yes; problem sleeping, n = 97 (5.0%) no, n = 3 (2.6%) yes.			
Abbreviations: ESAS-r-CS, Edmonton Symptom Assessment System-revised version with Constipation and Sleep; SD, standard deviation.			

The results of the univariable and multivariable logistic regression analyses for psychostimulant receipt are shown in Table 3. In univariable analyses, older age was associated with a lower likelihood of

psychostimulant prescription (odds ratio [OR] 0.97, 95%CI 0.96–0.99) and breast cancer diagnosis was associated with a higher likelihood of psychostimulant prescription (OR 2.93, 95%CI 1.48–5.80 vs. thoracic primary). Patients with worse baseline ESAS-r-CS scores for fatigue, drowsiness, depression, anxiety, and insomnia had increased odds of receiving a psychostimulant. There were no significant associations for gender, baseline dyspnea score, or estimated prognosis by the referring clinician. In the multivariable analyses, a breast cancer diagnosis (OR 2.58, 95%CI 1.28–5.20 vs. thorax) and more severe fatigue (OR 1.16, 95%CI 1.07–1.26) were associated with a greater likelihood of psychostimulant receipt, while older age was associated with a lower likelihood of psychostimulant receipt (OR 0.97, 95%CI 0.96–0.99) (Table 3).

Table 3
Univariate and multivariable logistic regression for receipt of psychostimulant following initial oncology palliative care clinic consultation (N = 2,057)

Variable	Univariate				Multivariable			
	Odds Ratio	95% CI		P	Odds Ratio	95% CI		P
		Lower	Upper			Lower	Upper	
Age (years)	0.97	0.96	0.99	< .0001	0.97	0.96	0.99	0.0001
Gender (F vs. M)	1.17	0.81	1.71	0.40				
Primary Cancer	.	.	.	0.005	.	.	.	0.04
Thorax	Ref				Ref			
Breast	2.93	1.48	5.80	0.002	2.58	1.28	5.20	0.008
CNS	1.16	0.43	3.16	0.77	0.83	0.29	2.34	0.72
Gastrointestinal	1.00	0.53	1.87	0.99	0.95	0.50	1.80	0.88
Genitourinary	0.84	0.38	1.87	0.67	0.91	0.41	2.02	0.81
Gynecologic	1.20	0.62	2.30	0.59	1.13	0.58	2.18	0.72
Head and neck	0.61	0.29	1.27	0.18	0.57	0.27	1.21	0.14
Hematologic	0.81	0.34	1.94	0.64	0.76	0.32	1.83	0.54
Sarcoma	2.44	0.99	6.00	0.05	1.70	0.67	4.34	0.27
Skin	0.67	0.23	1.99	0.47	0.73	0.24	2.17	0.57
Estimated prognosis	.	.	.	0.67				
6–24 months	Ref							
<6 months	0.94	0.56	1.57	0.80				
Uncertain	0.82	0.52	1.28	0.38				
ESAS-r-CS scores								
Tiredness	1.15	1.06	1.24	0.0004	1.16	1.07	1.26	0.0002

All demographic and clinical factors as well as physical and psychological symptom scores with $p < 0.25$ were included in variable selection. The multivariable logistic model included all variables with $p < 0.10$. An odds ratio > 1 indicates a higher likelihood for receipt of psychostimulant.

Abbreviations: ESAS-r-CS, Edmonton Symptom Assessment System-revised version with Constipation and Sleep; CI, confidence interval.

Variable	Univariate				Multivariable			
	Odds Ratio	95% CI		P	Odds Ratio	95% CI		P
		Lower	Upper			Lower	Upper	
Drowsiness	1.09	1.02	1.16	0.01				
Shortness of breath	1.05	0.99	1.12	0.13				
Depression	1.08	1.01	1.15	0.02				
Anxiety	1.10	1.03	1.17	0.005				
Problem sleeping	1.10	1.03	1.18	0.003				
All demographic and clinical factors as well as physical and psychological symptom scores with $p < 0.25$ were included in variable selection. The multivariable logistic model included all variables with $p < 0.10$. An odds ratio > 1 indicates a higher likelihood for receipt of psychostimulant.								
Abbreviations: ESAS-r-CS, Edmonton Symptom Assessment System-revised version with Constipation and Sleep; CI, confidence interval.								

Discussion

Among patients with advanced cancer receiving outpatient palliative care, psychostimulant use was relatively uncommon, despite a high prevalence of CRF. Patients with higher symptom burden, younger age, and a diagnosis of breast cancer were more likely to receive a psychostimulant prescription. Among the patients who received a psychostimulant from the OPCC, most reported subjective improvement in fatigue; adverse events were infrequent and non-serious. To our knowledge, this study represents the largest description of real-world psychostimulant use for CRF in the outpatient oncology palliative care setting.

Despite moderate-to-severe fatigue among 75% of patients who completed symptom screening, only 5% received a psychostimulant prescription following their initial consultation. Interestingly, a retrospective study of in-patients and home palliative care patients in Sweden also reported that 5% received a psychostimulant.[30] This relatively low observed rate of psychostimulant use likely has several explanations. CRF is a multifactorial symptom with many potential provoking and contributing factors.[9] In many cases, initial psychostimulant therapy might not have been appropriate, as clinicians and patients may have wished to first address underlying causes of CRF. Similarly, the perception that fatigue is an expected and unavoidable symptom associated with cancer and/or its treatments may also have led to its under-treatment.[8] Prescribing restraint could also have stemmed from the fact that psychostimulants are not strongly endorsed as an intervention for CRF in any current guideline,[1–3] a reflection of the conflicting evidence regarding their effectiveness from RCTs.[10–26] Despite the

relative safety demonstrated in these trials, there could also have been concern about stimulant-related adverse effects among prescribers as well as patients.

The patient characteristics associated with psychostimulant receipt mostly align with expected prescribing behaviour. Psychostimulant receipt was associated with worse baseline fatigue, as well as with symptoms that often co-occur with fatigue, such as drowsiness, sleeplessness, depression, and anxiety.[8, 36] The inverse association with age may reflect greater clinician caution regarding cardiovascular and neuropsychiatric risks with stimulant use in older patients.[37] The 2.5-fold greater likelihood of receiving a psychostimulant among patients with breast cancer than with a thoracic primary may reflect their different disease trajectories. Patients with metastatic breast cancer often have a longer expected survival, which affords greater opportunity for symptom-directed prescribing.[38, 39] Of note, the early methylphenidate trials were also conducted in breast cancer populations,[19, 20, 22] including the largest trial demonstrating benefit from this intervention.[19] Fatigue is also a common toxicity of systemic therapies for breast cancer, particularly CDK4/6 inhibitors combined with endocrine therapy, which are the current first-line standard in hormone receptor-positive metastatic disease.[40] Further studies are needed to understand the underlying reasons for prescription of psychostimulants in specific populations.

Among the minority of patients who were prescribed a psychostimulant by an OPCC physician and took it as prescribed (methylphenidate in all cases), more than two-thirds reported improvement in fatigue—a higher proportion than the 46% judged to have benefited in the Swedish cohort.[30] This difference may reflect the outpatient setting: our patients had better performance status and longer expected survival than patients receiving inpatient or home-based palliative care, and methylphenidate was less effective in the Swedish study when started in the last month of life.[30] Reported adverse events were also less frequent in our cohort (3.9% vs. 23%); although this may in part reflect under-ascertainment inherent to retrospective chart review, it may also relate to the conservative dosing in the OPCC—all methylphenidate prescriptions began at a total daily dose of 10 mg or less and few were escalated. These observations should nonetheless be interpreted cautiously, in that we recorded patient-reported improvement in CRF in a retrospective, open-label, uncontrolled setting.

Limitations

This study has limitations. The study took place at a single academic cancer centre and its results may not be generalizable to other oncology palliative care programs. Data were incomplete for several variables, including ESAS-r-CS and performance status; however, characteristics were similar between patients with and without baseline symptom scores (*Table S1*). ESAS-r-CS scores were recorded at the initial consultation, which preceded the first psychostimulant prescription by a median of 114 days; baseline scores may therefore not reflect symptom severity at the time of prescribing. However, fatigue in advanced cancer is typically chronic, and the observed associations were consistent across fatigue and related symptoms. As psychostimulant prescriptions were identified from Epic orders only, prescriptions issued elsewhere would not have been captured. Finally, the retrospective design meant

that indication, adherence, effectiveness, and adverse events were ascertained from clinical documentation; reported effects were therefore susceptible to ascertainment bias.

Conclusion

In this large retrospective cohort of patients with cancer referred to an outpatient palliative care clinic, fatigue was highly prevalent and frequently severe, yet only 5% of patients received a psychostimulant prescription following their initial consultation. Factors associated with psychostimulant use included younger age, a breast cancer diagnosis, and greater fatigue and symptom burden. Most patients who adhered to treatment reported improvement in CRF, with few adverse events. The discordance between real-world uptake and subjective benefit underscores the need for future studies to understand prescribing practices for psychostimulants and to clarify which patients have the potential to derive a meaningful benefit.

Abbreviations

ECOG
Eastern Cooperative Oncology Group
PPS
Palliative Performance Scale
ESAS-r-CS
Edmonton Symptom Assessment System-revised version with Constipation and Sleep
SD
standard deviation.

Declarations

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Competing interests: The authors have no competing interests to declare.

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Consent to participate: A waiver of individual consent was granted given the retrospective nature of the study.

Data availability: The data underlying this article are available from the corresponding author on reasonable request.

Author Contribution

NCY, BH, and CZ designed the study. NCY, BH, TC, CC, and AH collected the data. NCY and LL performed statistical analyses. NCY, BH, LL, and CZ interpreted the data. NCY drafted the manuscript. All authors critically revised the manuscript for content and approved the final version.

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Figures

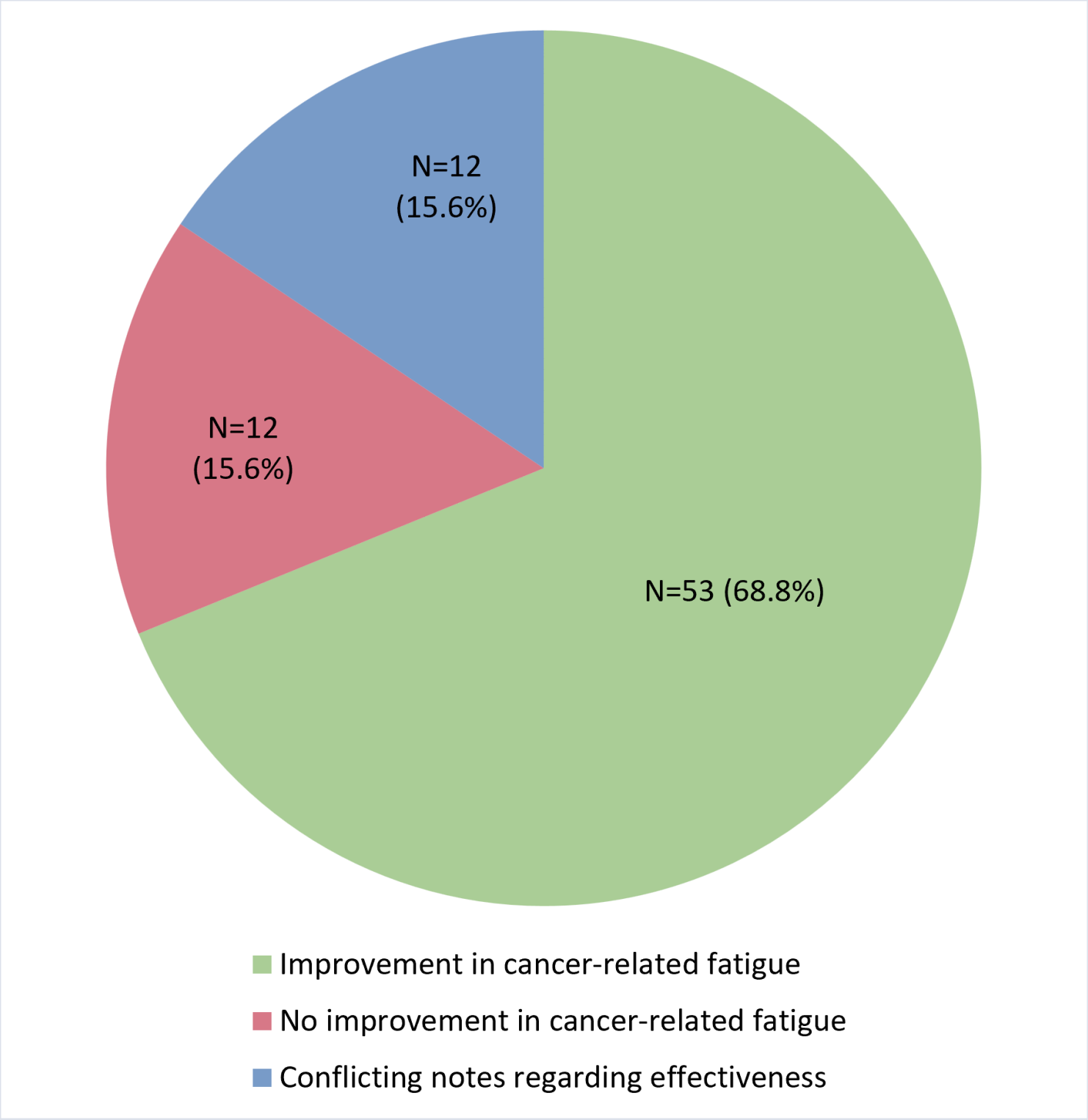


Figure 1

Reported effects of methylphenidate for cancer-related fatigue among evaluable patients who received a prescription from the oncology palliative care clinic (N=77)

Supplementary Files

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