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Mental health services use by melanoma patients receiving adjuvant interferon: association of pre-treatment mental health care with early discontinuation

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ABSTRACT

Background Although high-dose interferon (HD-IFN) is the sole approved adjuvant systemic treatment for melanoma in many jurisdictions, it is toxic. We sought to assess the population-level effects of HD-IFN toxicity, particularly neuropsychiatric toxicity, hypothesizing that such toxicity would have the greatest effect on mental health services use in advanced resected melanoma.

Methods This retrospective population-based registry study considered all melanoma patients receiving adjuvant HD-IFN in Ontario during 2008–2012. Toxicity was investigated through health services use compatible with HD-IFN toxicity (for example, mental health physician billings). Using stage data reported from cancer centres about a subset of patients (stages IIB–IIIC), a propensity-matched analysis compared such service use in patients who did and did not receive HD-IFN. Associations between early HD-IFN discontinuation and health services use were examined.

Results Of 718 melanoma patients who received HD-IFN, 12% were 65 years of age and older, and 83% had few or no comorbidities. One third of the patients experienced 1 or more toxicity-associated health care utilization events within 1 year of starting HD-IFN. Of 420 utilization events, 364 (87%) were mental health–related, with 54% being family practitioner visits, and 39% being psychiatrist visits. In the propensity-matched analysis, patients receiving HD-IFN were more likely than untreated matched controls to use a mental health service ($p = 0.01$), with 42% of the control group and 51% of the HD-IFN group using a mental health service in the period spanning the 12 months before to the 24 months after diagnosis. In the multivariable analysis, early drug discontinuation was more likely in the presence of pre-existing mental health issues (odds ratio: 2.0; 95% confidence limits: 1.1, 3.4).

Conclusions Stage IIB–IIIC melanoma patients carry a substantial burden of mental health services use whether or not receiving HD-IFN, highlighting an important survivorship issue for these patients. High-dose interferon is associated with more use of mental health services, and pre-treatment use of mental health services is associated with treatment discontinuation. That association should be kept in mind when HD-IFN is being considered.

Key Words Mental health, depression, high-dose interferon, melanoma, toxicity, adjuvant therapy, immunotherapy, population-based studies, health services research

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INTRODUCTION

A diagnosis of advanced melanoma (resected stages IIB–IIIC or lymph node recurrence) comes with uncertainties about the immediate and long-term effects of treatment on daily life, treatment logistics, and expected treatment outcomes[1]. The 5-year survival in stages IIB–IIIC melanoma varies substantially between subgroups, ranging from 38% to 78%[2]. The

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mental health needs of patients with various advanced cancers are known to potentially be substantial near the time of diagnosis, but the effects of a diagnosis of advanced resected melanoma and its treatment on patient mental health has been understudied[3].

A diagnosis of advanced melanoma typically means more surgery for a patient, including wide excision, sentinel lymph node biopsy, and sometimes a complete lymph node dissection and imaging. Surgery is followed by consideration of adjuvant systemic therapy for those without distant metastasis. High-dose interferon (HD-IFN) is the sole approved adjuvant systemic treatment for advanced melanoma in many jurisdictions. In randomized trials, HD-IFN has consistently been associated with a decrease in the risk of melanoma relapse[4]. That association has not consistently translated into a survival benefit, however, and controversy attends the use of HD-IFN in practice—and particularly which patients should be selected for treatment[4–6]. A full course of HD-IFN means a year of treatment.

High-dose interferon has substantial medical and neuropsychiatric toxicities. In the landmark Eastern Cooperative Oncology Group (ECOG) trials of HD-IFN, up to 50% of all patients experienced one or a combination of severe fatigue, fever, muscle aches, and nausea[7]. Dose modifications were required in up to 60% of patients because of myelosuppression. Of treated patients, 40% developed depression or other neuropsychiatric symptoms, and up to 10% of all patients required psychiatric evaluation and treatment, or dose modification[7]. Two French population-based studies reported on small groups of HD-IFN patients[8,9]; the study by Lévy-Sitbon *et al.* reported that 9 of 36 patients receiving HD-IFN stopped early because of toxicity. No further information about toxicity—such as its nature, timing, or management—was available for those cases.

An American study based on the MarketScan claims database (Truven Health Analytics, Ann Arbor, MI, U.S.A.) found substantial toxicity with the real-world use of IFN, with half of all patients discontinuing IFN within or after the 1-month intravenous (IV) induction phase[10]. The nature of the toxicities leading to discontinuation was not investigated. A Canadian post-marketing study similarly found that only 41% of 225 patients completed the 1-year course of HD-IFN[11].

In the present report, we sought to assess the population-level effects of advanced melanoma and its treatment on mental health services use in Ontario. We hypothesized that HD-IFN toxicity, particularly neuropsychiatric toxicity, would have the greatest effect on mental health services use in advanced melanoma. By using matched analysis involving untreated advanced patients, and by measuring health services use compatible with HD-IFN toxicity for all melanoma patients receiving HD-IFN in the province of Ontario, we separated the estimated effect of HD-IFN toxicity from that of other mental health needs occurring in advanced melanoma. Importantly, we sought to build on earlier studies by identifying actionable predictors of HD-IFN toxicity, with a focus on the regimen's mental health toxicity.

METHODS

Primary Cohort

This retrospective population-based cohort study considered all cutaneous melanoma patients in Ontario who received HD-IFN between 2008 and 2012. In Ontario (population 14.2 million in 2017), medical care for melanoma—including surgery, radiotherapy, and IV cancer drugs—is provided under single-payer universal health coverage. Because patients dying of rapidly recurrent melanoma or unrelated severe medical conditions are likely to have patterns of health care utilization not entirely related to receipt of HD-IFN, patients dying within 18 months of their first HD-IFN treatment were excluded from the study cohort. During the study period, HD-IFN was approved for use for pT3b–pT4b, pN1a–pN3, and resected lymph node recurrences of melanoma[12].

Our project made use of data housed at the Institute for Clinical Evaluative Sciences (ICES), which is an independent not-for-profit organization that uses anonymously linked population-based data from individual patients in the province of Ontario to provide scientific insights into the Ontario health care system. Patients with melanoma were identified through the Ontario Cancer Registry, which contains data about stage and other tumour-related factors. The Ontario Cancer Registry is a population-based cancer registry known for its high level of completeness[13].

Patient demographics were determined based on data provided by the Ministry of Health and Long-Term Care through ICES. Receipt of HD-IFN was identified using provincial drug funding data. The Elixhauser comorbidity score[14] was determined using hospital admission data for the year before each patient started HD-IFN.

Toxicity of HD-IFN was investigated by measuring health services use compatible with HD-IFN toxicity. Mental health, hematologic, gastrointestinal, constitutional, and endocrine domains were considered. Occurrence of unintentional injury was searched for, given the potential for a patient to be distracted and inattentive while receiving HD-IFN. Mental health services use included psychiatric care, mental health emergency department and hospital admissions, and ambulatory family practitioner (FP) mental health visits. Mental health visits to a FP were identified using a validated algorithm[15] that relied on diagnostic codes in FP billings. A patient was counted as having a mental health event if 1 or more relevant uses occurred.

Propensity-Matched Analysis

To investigate the degree to which mental health services use related to HD-IFN toxicity, a propensity-matched analysis was undertaken to compare such use for confirmed stages IIB–IIIC melanoma patients who did and did not receive HD-IFN. Patients with other-stage melanoma at the time of diagnosis or with missing stage information were excluded.

Patients were included if the date of their melanoma diagnosis fell between 31 July 2007 and 30 June 2012. Those dates were chosen so that most patients treated with HD-IFN would have received it during 2008–2012. Because the date of IFN start was not applicable for the control group, the death exclusion was defined as 24 months from melanoma diagnosis, rather than 18 months from HD-IFN start, given the observed time lag between diagnosis and HD-IFN start in our sample.

The propensity score was based on age, Elixhauser comorbidity, sex, disease stage, and presence of mental

health services use within 1 year before the melanoma diagnosis. Greedy matching (1:1) with calipers of 0.3 was used. The remaining covariates were tested using standardized difference of the mean. Occurrence of mental health services use over time was measured using the product-limit method, depicted as 1 minus the Kaplan–Meier estimate. The McNemar test for paired data was used to test for differences at 24 months after diagnosis.

Subgroup Analysis: HD-IFN Duration

To further validate the association between mental health services use and HD-IFN toxicity, we looked at early discontinuation of HD-IFN, which was defined based on the median HD-IFN duration for patients whose duration was reported. Discontinuation of HD-IFN is recommended when dose adjustment is not sufficient to control side effects[16,17]. Significant mental health effects of IFN are a recognized reason for discontinuation[11,16,17]. "Duration" was defined as time on IV IFN plus time on subcutaneous (SC) IFN based on the date of the last SC IFN prescription plus the median time interval between prescription dates.

Information about the duration of HD-IFN use was not available for all patients. Provincial drug reimbursement data contained information only about the initial 1-month IV phase of the drug regimen delivered through a cancer centre. The remaining months of the 12-month regimen are delivered by SC injection and are covered by public funding only for patients 65 years of age or older or for those receiving government assistance. Associations between early discontinuation of HD-IFN and health services use could be assessed only for the subgroup receiving publicly funded SC IFN prescriptions. Baseline subgroup characteristics were compared with the characteristics of the full study population. Backward-selection multiple logistic regression was used, with a cut-off p value of 0.3 being used to identify the most parsimonious model.

RESULTS

Primary Cohort Analysis

Of the 804 melanoma patients who received HD-IFN in Ontario during 2008–2012, 86 died within 18 months of their first HD-IFN treatment and were thus excluded for the purposes of the mental health services use analysis (Figure 1). Cause of death coded on the death certificate for those patients was melanoma for all but 11 patients. Cause of death for those 11 patients was either unknown or cannot be reported because of privacy rules governing the use of small cells of administrative data at ICES (≤5 patients in a group).

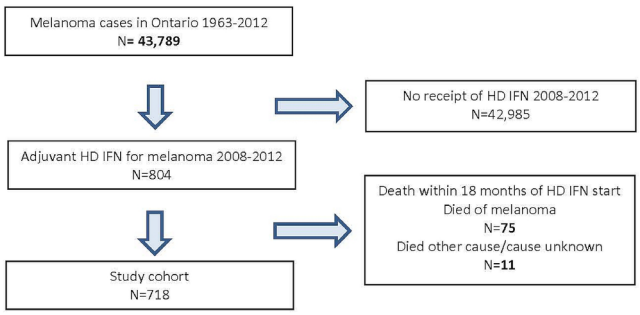

FIGURE 1 Identification of the study population for the primary cohort. HD IFN = high-dose interferon.

The study cohort thus consisted of 718 patients. Median age in the group was 52 years, and 87 patients (12%) were 65 years of age or older (Table I). A greater proportion of HD-IFN patients fell into higher neighborhood income quintiles than into lower quintiles (45% in quintiles 4–5 vs. 32% in quintiles 1–2). Of the patient cohort, 83% had little or no identified comorbidity (Elixhauser score 0 or 1). Stage information was available for 77% of patients, and 84% of the patients with stage information were staged as IIB–IIIC, with 16% being stage IIB (T3bN0M0, T4aN0M0), and 27% being stage IIIA (T1–4aM0 with 1–3 nodal micrometastasis found on sentinel node biopsy and completion dissection, if performed).

Figure 2 summarizes the occurrences of mental health services use in 3-month periods. Table II summarizes the diagnostic codes and events investigated for health services use associated with HD-IFN. Of the patients overall, 28% used mental health services within 12 months of HD-IFN start. Of 420 events of health services use during the period of interest, 364 uses were mental health–related (Table III). Of all HD-IFN patients, 7% required consultation with a psychiatrist, and 9% required ongoing care with a psychiatrist. Of the 52 patients who had consultations with a psychiatrist in the year after HD-IFN start, 84% had mood-related conditions recorded as the reason for the consultation. Notably, mental health services use was observed to rise starting 6 months before the start of HD-IFN treatment (Figures 2 and 3), indicating that mental health services use was not entirely attributable to HD-IFN.

Most of the remaining health care services use came as a result of injuries, with few events recorded in the remaining categories (Table III). Among patients with mental health events, 54% of all mental health services use involved mental health–related FP visits in the year after HD-IFN start; 39% involved receiving care from a psychiatrist; and the remainder involved emergency department visits or admissions to hospital or mental health facilities (Figure 3).

Propensity-Matched Analysis

In the propensity-matched analysis, a match was obtained for 389 of the 443 patients with a known stage IIB–IIIC diagnosis who received HD-IFN and who survived to 24 months after diagnosis. Table IV shows the characteristics of the matched cohort.

The occurrence of mental health services use before the melanoma diagnosis and in the early post-diagnosis period in patients who received HD-IFN was nearly the same as it was for stages IIB–IIIC patients not treated with HD-IFN (Figure 4). By 6 months after diagnosis, most patients would have started their HD-IFN, and a divergence in mental health services use was then observed, with significantly more use of services observed at 24 months for the patients treated with HD-IFN (p = 0.01). However, services use was high in both groups. Between 12 months before diagnosis and 2 years after diagnosis, 42% of patients with stages IIB–IIIC

TABLE I Patient and disease characteristics of 718 melanoma patients receiving high-dose interferon in Ontario, 2008–2012

Characteristic	Value [*n* (%)]
Age group at diagnosis	
0–24 Years[a]	27 (3.8)
25–34 Years	58 (8.1)
35–44 Years	118 (16.4)
45–54 Years	218 (30.4)
55–64 Years	210 (29.2)
≥65 Years	87 (12.1)
Sex	
Female patients	304 (42.3)
Male patients	414 (57.7)
Income quintile	
1 (poorest)	108 (15.0)
2	123 (17.1)
3	163 (22.7)
4	151 (21.0)
5 (richest)	172 (24.0)
Comorbidity (Elixhauser score[14])	
0/1	598 (83.3)
2+	120 (16.7)
Site	
Scalp and neck	50 (7.0)
Trunk	256 (35.7)
Upper limb	137 (19.1)
Lower limb	166 (23.1)
Other specified sites of skin or site unspecified	72 (10.0)
Other	37 (5.1)
Stage	
IA/IB	44 (6.1)
II/IIA	30 (4.2)
IIB	74 (10.3)
IIC	69 (9.6)
III	52 (7.2)
IIIA	125 (17.4)
IIIB	105 (14.6)
IIIC	38 (5.3)
IV	15 (2.1)
Missing	166 (23.1)
Histology	
Not otherwise specified	269 (37.5)
Nodular	204 (28.4)
Superficial spreading	198 (27.6)
Other	47 (6.5)

[a] Includes 5 or fewer patients less than 18 years of age.

disease not treated with HD-IFN had 1 or more events of mental health services use; in the HD-IFN–treated patients with stages IIB–IIIC disease, 51% had 1 or more events. The absolute difference between the groups was similar

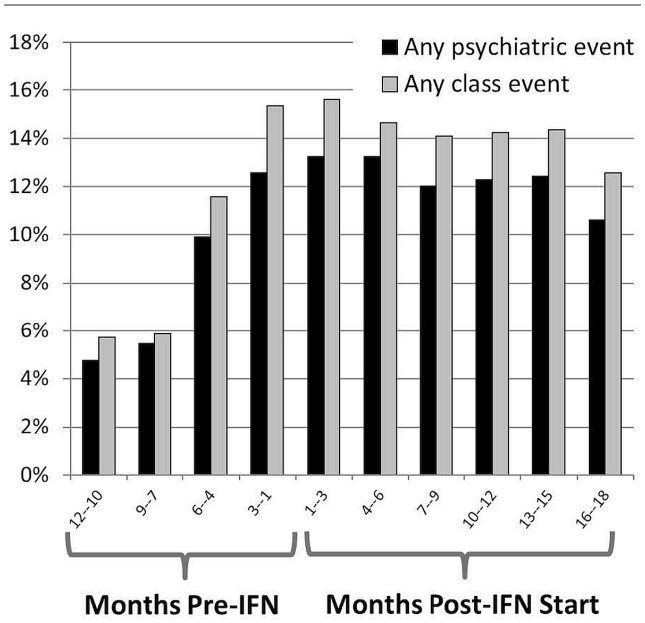

FIGURE 2 Health services use over time: proportion of 718 patients receiving high-dose interferon (IFN) and having 1 or more service events per time period.

in a sensitivity analysis in which mental health FP visits were excluded.

Subgroup Analysis: HD-IFN Duration

Information about duration of treatment was available for 280 of the 718 patients. Characteristics of that subcohort were similar to those of the full cohort, except that the median age was higher because of the public drug coverage inclusion criterion for patients 65 years of age and older (Table V). The proportion of patients with events of mental health services use was higher in the group of patients who discontinued treatment early. Notably, the steepest rise in the use of mental health services occurred in the year before HD-IFN was started, with more events occurring in the group of patients who discontinued HD-IFN early (31% vs. 17%). Little difference in new mental health services use was observed between the groups in the year after HD-IFN start (14% vs. 11%).

In multivariable logistic regression, after controlling for covariates, mental health services use before the start of HD-IFN was associated with early treatment discontinuation [odds ratio: 2.0; 95% confidence limits (CL): 1.1, 3.4; Table VI]. Mental health services use after HD-IFN start was not significantly associated with discontinuation (odds ratio: 1.3; 95% CL: 0.8, 2.3). No significant interaction between mental health services use before HD-IFN and after HD-IFN was started was observed in the model ($p = 0.98$).

DISCUSSION

The key findings of the present study are a substantial burden of mental health services use by patients with stages IIB–IIIC melanoma, especially patients receiving HD-IFN, and an association between mental health services use before treatment with IFN and subsequent IFN

TABLE II Diagnostic codes and events investigated for health services use associated with high-dose interferon

Source	Intervention	Codes
From Ontario Health Insurance Plan billings		
	Psychiatric consultation	■ A195, A895, A190, A795, A695, A395, A196, A193, A194, A197,A198, A191, A192, C895, C190, C395, C196, C795, C695, K620, K623, K624, K629
	Ongoing psychiatric care	■ C193, C194, C192, C197, C199, C122, C123, C124, C142, C143, C121, C198 ■ K195,K196,K197,K198, K199, K196, K191, K190, K193, K208, K209, K203, K204, K205, K206, K210, K211, K200, K201, K202, K207, K192, K194
	Mental health–related general practitioner visits[a]	■ Service codes combined with ICD-10 mental health diagnosis codes: 295, 296, 297, 298, 300, 301,302, 306, 309, 311, 303, 304, 897, 898, 899, 900, 901, 902, 904,905, 906, 909 billed by a physician listed as a general or family practitioner, as a family practitioner/emergency medicine provider, or as community medicine/ public health.
From the Canadian Institute for Health Information's hospital admissions data and National Ambulatory Care Reporting System emergency department data		
	ICD-10 diagnoses	
	Psychiatric and neurocognitive diagnoses and conditions	■ Anxiety and related disorders (F40, F41, F42, F43, F44, F45,F48) ■ Depression (F32, F33) ■ Other or unspecified mood (affective) disorders (F38,F39) ■ Delirium (F05) ■ Other mental disorders (F06, F09, F59) ■ Personality or behavioral disorders attributable to brain disease, damage, or dysfunction (F07) ■ Psychosis, induced delusional disorder (F23, F24) ■ Mania (F30) ■ Bipolar disorder (F31) ■ Other or unspecified mood disorder (F38, F39) ■ Sleep disorder (F51) ■ Poisoning by drugs, medicines, and biologic substances (T36–T50) ■ Toxic effects of substances chiefly non-medicinal as to source (T51–65) ■ Intentional self-harm (X60–X84)
	Injury	■ Injury or trauma (S00–T32, T79) ■ Sequelae of injuries, poisoning and of other consequences of external causes (T90–T98) ■ Mechanisms of injury: transport accident (V01–V99, W00–W99, X00–X49) ■ Event of undetermined intent (Y10–Y34)
	Hematologic	■ Neutropenia (D70) ■ Thrombocytopenia (D69.5, D69.6) ■ Anemia (D64.9, D61.1, D63.0)
	Gastrointestinal	■ Hepatitis (K75.4–K75.9) ■ Toxic liver diseases (K71) ■ Liver failure (K72) ■ Nausea/Vomiting (R11) ■ Pancreatitis (K85)
	Constitutional	■ Anorexia (other than anorexia nervosa) and other symptoms and signs concerning food/fluid intake (R63) ■ Malaise and fatigue (R53) ■ Somnolence (R40.0)
	Thyroid disease	■ Hypothyroidism (E03) ■ Hyperthyroidism/thyrotoxicosis (E05) ■ Thyroiditis (E06)

[a] As defined by Steele *et al.,* 2004[15].

ICD-10 = *International Statistical Classification of Diseases and Related Health Problems,* revision 10.

TABLE III Health services use[a] for 718 patients receiving high-dose interferon, by time period

Domain of health services use	Months before interferon start				Months after interferon start					
	12–10	9–7	6–4	3–1	1–3	4–6	7–9	10–12	13–15	16–18
Mental health	4.7	5.4	9.9	12.5	13.2	13.2	12.0	12.3	12.4	10.6
Injury	1.1	≤0.7	2.1	1.8	≤0.7	0.8	1.3	1.4	1.8	1.7
Hematologic	0.0	0.0	0.0	≤0.7	0.8	0.0	≤0.7	0.0	≤0.7	≤0.7
Gastrointestinal	0.0	≤0.7	0.0	≤0.7	1.5	≤0.7	0.0	≤0.7	≤0.7	≤0.7
Constitutional	0.0	0.0	≤0.7	≤0.7	≤0.7	≤0.7	≤0.7	≤0.7	0.0	0.0
Thyroid disease	0.0	0.0	≤0.7	≤0.7	0.0	≤0.7	0.0	≤0.7	0.0	0.0
Any domain	5.7	5.8	11.6	15.3	15.6	14.6	14.1	14.2	14.3	12.5

[a] Shows the absolute percentage. Counts refer to the occurrence of 1 or more events per patient in a domain. Patients might have separately counted events in separate time periods or in separate domains. Counts in "Any domain" represent 1 or more events of any health services use domain per patient per time period. Not all patients were receiving high-dose interferon for the full 12-month course.

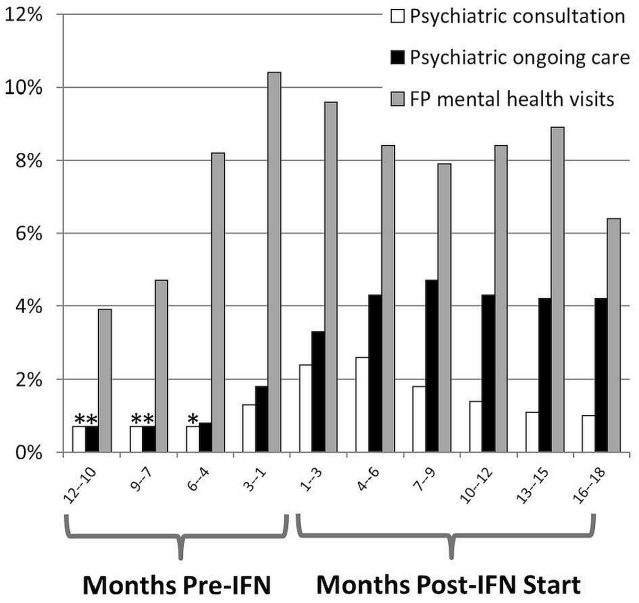

FIGURE 3 Mental health service type per time period: proportion of 718 patients receiving high-dose interferon and having 1 or more service events per time period. Individual patients could have separately counted events in separate time periods or separate service types. * Indicates data point of 0.7% or less (exact percentage suppressed per privacy regulations). Emergency department or hospital admissions with a psychiatric diagnosis and mental health facility admissions were 1.1% or less for all time periods and are therefore omitted. FP = family practitioner; IFN = interferon.

discontinuation. The association of early IFN discontinuation with use of mental health services before treatment constitutes an additional consideration for patients and clinicians who are undecided about HD-IFN use. For patients to whom IFN is offered, the association is relevant because it emphasizes the need for optimal mental health care to ensure that a full course of HD-IFN can be successfully delivered as planned.

Our observation that patients with mental health services use before HD-IFN start were more likely to discontinue HD-IFN early is in keeping with findings from other IFN studies[18,19]. Capuron and Ravaud[19] observed a clear correlation between depression scores on treatment day 1 and at 4 weeks. In the Dermatologic Cooperative Oncology Group randomized trial of low-dose IFN for melanoma[18], patients who had higher Beck Depression Inventory scores (≥5) before receiving IFN experienced increased odds, by a factor of 3, of early IFN discontinuation because of somatic or psychiatric effects (odds ratio: 3.09; 95% CL: 1.32, 7.27).

Limited evidence suggests that preventing early discontinuation of HD-IFN matters to outcome. A randomized phase II study conducted by Payne *et al.*[20] compared 4-week IV HD-IFN (IFN-α-2b 20 MIU/m^2 5 days per week for 4 weeks) with the same regimen followed by SC IFN (10 MIU/m^2 3 times per week for 48 weeks). A strong trend toward improved overall survival with long-course HD-IFN was observed. In multivariable analysis, long-course HD-IFN was associated with improved survival (hazard ratio: 0.59; 95% CL: 0.38, 0.92). In another trial evaluating the effect of IFN duration on outcome, Pectasides *et al.*[21] reported negative results, but their target dose was much less than the dose used in standard HD-IFN regimens. Although the supportive evidence is not robust, our observed association between pre-existing mental health care and early discontinuation of HD-IFN emphasizes, at minimum, the importance of optimizing the mental health care of patients who are to receive HD-IFN so as to ensure delivery of treatment per protocol.

We also found evidence of enduring mental health needs beyond the 1 year required for a full course of HD-IFN treatment. Use of mental health services by HD-IFN–treated patients continued to occur out to at least 16–18 months, never returning to the baseline levels seen 10–12 months before treatment (Figures 2 and 3). Our propensity-matched analysis suggests that temporal patterns of mental health services use demonstrate continued differences between patients having stages IIB–IIIC disease treated with and without HD-IFN. Those findings accord with observations from the randomized Sunbelt Melanoma Trial investigating adjuvant HD-IFN for melanoma staged by sentinel lymph node biopsy[22]. Self-reported quality of life and physical condition out to 5 years were reported. Only after 2 years did baseline quality of life in HD-IFN–treated patients approach that in patients receiving surgery without adjuvant therapy.

TABLE IV Propensity-matched cohort of patients with stages IIB–IIIC melanoma, based on treatment with high-dose interferon (HD-IFN)

Variable	Treated with HD-IFN		*p* Value
	No	Yes	
Patients (*n*)	389	389	
Age at diagnosis (years)			
Mean	53.43±12.88	54.09±12.02	0.46
Median	54	56	
IQR	45–62	47–62	
Comorbidity by Elixhauser score[14] [*n* (%)]			
0–1	381 (97.9)	376 (96.7)	0.269
2+	8 (2.1)	13 (3.3)	
Sex [*n* (%)]			
Female patients	137 (35.2)	151 (38.8)	0.299
Male patients	252 (64.8)	238 (61.2)	
Use of mental health services before melanoma diagnosis [*n* (%)]			
No	309 (79.4)	311 (79.9)	0.859
Yes	80 (20.6)	78 (20.1)	
Stage [*n* (%)]			
II	176 (45.2)	151 (38.8)	0.069
III	213 (54.8)	238 (61.2)	

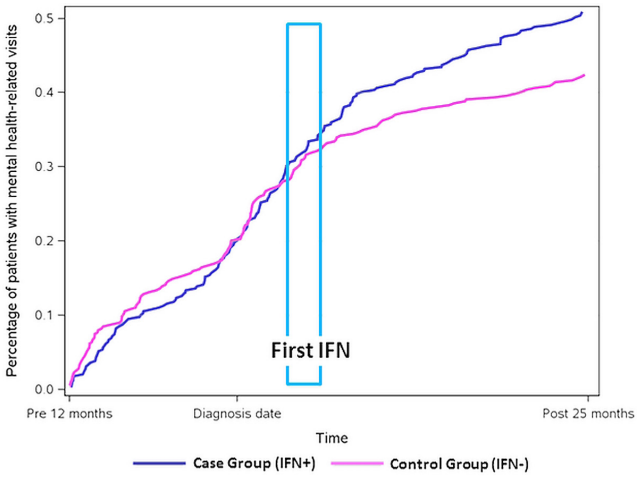

FIGURE 4 Propensity-matched analysis of mental health services use by patients with stages IIB–IIIC melanoma, by whether they received (*n* = 389) or did not receive (*n* = 389) high-dose interferon. The rectangle represents the interquartile range from time of diagnosis to interferon (IFN) start for patients treated with high-dose IFN.

Given the limited efficacy of HD-IFN and its substantial toxicity, alternatives are eagerly anticipated. Adjuvant immunotherapy with anti–PD-1 or anti-CTLA4 agents could prove to be more efficacious, although mature results comparing them directly with HD-IFN are not yet available. Patient-reported outcomes in a trial comparing placebo with high-dose adjuvant ipilimumab suggest a lesser, more transient effect on neurocognitive function[23]. Results from the use of anti–PD-1 agents in the metastatic setting suggest a favourable effect on quality of life[24,25]. Serious mental health or constitutional symptoms directly attributable to treatment appear to be rare[26,27]. However, we have demonstrated use of mental health care services even before drug treatment, which could be related to illness adjustment. If proven alternatives to HD-IFN are adopted, the needs of melanoma patients for mental health care will remain important to address, as is true for other malignancies[3].

A broad approach will most likely be required to most effectively meet the mental health care needs of melanoma patients. For example, peer-to-peer support has been promoted as a relational solution tailored to the individual's experience and the help being requested[28]. Notably, the Melanoma Network of Canada is pioneering such a model of support. Further work is also required to investigate the interactions of FPs with melanoma patients, given that a patient's mental health visits were often made to FPs. Given the infrequency with which a FP is likely to have to counsel a patient receiving a new advanced melanoma diagnosis about what to expect in terms of treatment and outcomes, those practitioners probably have a substantial information need.

Our study has a number of important strengths. The sample was population-based, providing insights emerging from an unselected group of Canadian patients. It is the largest and most comprehensive population-based study of HD-IFN toxicity to date. We used administrative data sources known for their completeness and population coverage. The sources captured events significant enough to warrant a physician assessment. Stage data reported from all cancer centres in Ontario allowed for an investigation of patients with stages IIB–IIIC melanoma

TABLE V Patient-related and tumour-related characteristics of the 280 patients in the Ontario Drug Benefit subcohort

Characteristic	Value [*n* (%)]
Age group at diagnosis	
0–24 Years	20 (7.1)
25–34 Years	24 (8.6)
35–44 Years	44 (15.7)
45–54 Years	59 (21.1)
55–64 Years	74 (26.4)
≥65 Years	59 (21.1)
Sex	
Female patients	122 (43.6)
Male patients	158 (56.4)
Income quintile	
1	58 (20.7)
2	49 (17.5)
3	65 (23.2)
4	53 (18.9)
5	55 (19.6)
Comorbidity (Elixhauser score[14])	
0/1	218 (77.9)
2+	62 (22.1)
Site	
Scalp and neck	16 (5.7)
Trunk	99 (35.4)
Upper limb	54 (19.3)
Lower limb	64 (22.9)
Other specified sites of skin or site unspecified	26 (9.3)
Other	21 (7.5)
Stage	
IA/IB	14 (5.0)
II/IIA	10 (3.6)
IIB	29 (10.4)
IIC	30 (10.7)
III	17 (6.1)
IIIA	45 (16.1)
IIIB	44 (15.7)
IIIC	15 (5.4)
Missing/IV	76 (27.1)
Histology	
Not otherwise specified	96 (34.3)
Nodular	84 (30.0)
Superficial spreading	81 (28.9)
Other	19 (6.8)

by receipt or non-receipt of HD-IFN. We were thus able to consider whether an association was evident between HD-IFN treatment and increased use of mental health services.

The study also has some limitations. Our estimates of mental health needs are conservative for a number of reasons. The algorithm we used did not capture informal counselling. We could not observe mental health events managed solely by dose modification. Treatment duration and SC dose information were not available for all patients, limiting our ability to evaluate the toxic effects of IFN managed by dose modification or discontinuation. Missing duration information also limited our ability to assess causality for health services use, although we performed a propensity-matched analysis of untreated patients for comparison. Because we measured the toxicities of HD-IFN using trends in health services use, we were not able to directly compare the magnitude of the toxic effects with standard clinical trial toxicity scales. Notably, the original ECOG trials of HD-IFN used varying definitions of neuropsychiatric toxicity, and accordingly found varying effects of HD-IFN on neurocognitive status[7]. In the ECOG 1684 trial, the presence of depression was reported in 40% of treated patients, with 2%–10% of patients in cooperative group trials showing side effects that warranted a psychiatric assessment and treatment or dose modification[7]. The occurrences of those psychiatric assessments and modifications might be more comparable with our findings. However, our observations point to a greater burden of mental health need in the population setting than was reported in the ECOG randomized controlled trials.

CONCLUSIONS

Stages IIB–IIIC melanoma patients show a substantial burden of mental health services use that is relevant regardless of the choice of adjuvant therapy. For patients receiving HD-IFN, mental health services use before treatment start was associated with treatment discontinuation. That observation constitutes an additional consideration for patients and clinicians who are undecided about HD-IFN use. For patients to whom HD-IFN is offered, the association is relevant in that it emphasizes the need for providing optimal mental health care so that a full course of HD-IFN can be successfully delivered to the patient as planned.

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TABLE VI Factors associated with early discontinuation of high-dose interferon (IFN) in 280 patients, by logistic regression analysis

Factor	Comparator	Model					
		Univariate		Multivariable			
		OR	95% CL	Unselected		Backward selection	
				OR	95% CL	OR	95% CL
Age	Per year	1.001	0.985, 1.017	1.003	0.986, 1.020		
Mental health care							
Before interferon start	Yes vs. no	1.976	1.152, 3.378	1.828	1.030, 3.236	1.957	1.131, 3.390
After interferon start	Yes vs. no	1.572	0.955, 2.591	1.328	0.777, 2.268		
Female sex	Vs. male sex	1.013	0.631, 1.628	1.016	0.612, 1.687		
Comorbidity (Elixhauser score[14])	0–1 vs. 2+	0.738	0.419, 1.298	0.744	0.409, 1.353	0.710	0.396, 1.275
Income quintile	1 vs. 5	1.049	0.499, 2.206	1.054	0.489, 2.275		
	2 vs. 5	1.460	0.674, 3.166	1.553	0.698, 3.457		
	3 vs. 5	0.977	0.474, 2.017	1.047	0.493, 2.226		
	4 vs. 5	1.069	0.500, 2.284	1.228	0.556, 2.716		
Stage	I–II vs. III	0.816	0.466, 1.428	0.910	0.508, 1.631	0.912	0.514, 1.619
	NA vs. III	0.479	0.265, 0.866	0.484	0.263, 0.891	0.489	0.268, 0.892

OR = odds ratio; CL = confidence limits.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: TB has had a consulting or advisory role with Bristol–Myers Squibb, Roche, Novartis, and Gilead Sciences; JX was employed by Ventana Medical Systems; CCE had a consulting or advisory role with UnitedHealthcare, and patents, royalties, or other intellectual property with UpToDate; TMP received honoraria from Roche Canada, Merck, Novartis Canada Pharmaceuticals, and Bristol–Myers Squibb, and an immediate family member received honoraria from Astellas Pharma, Abbvie, AstraZeneca, Bayer, and Janssen; TMP also had a consulting or advisory role with Roche, Merck, Novartis, and Bristol–Myers Squibb, and an immediate family member had a consulting or advisory role with Janssen, Abbvie, AstraZeneca, Bayer, and Astellas Pharma; TMP further received research funding from Roche Canada and Merck. The remaining authors have no conflicts to disclose.

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