Patterns of Opioid Consumption in Cancer Patients

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ABSTRACT: **Background:** Opioids are considered a cornerstone in the treatment of cancer pain.

Objectives: To assess opioid use during a 6 year period (2001–2006) among cancer patients served by Clalit Health Services, the largest health management organization in Israel.

Methods: Purchasing data of opioids authorized for use in Israel were obtained from the computerized databases of Clalit for the period 2001–2006. Patients' demographic and cancer morbidity data were extracted. The data were analyzed by translating the purchased opioids (fentanyl patch, oxycodone, buprenorphine, methadone, hydromorphone) to oral morphine equivalents (OME).

Results: During the study period 182,066 Clalit members were diagnosed with cancer; 58,443 (32.1%) of them died and 31,628 (17.3%) purchased opioids at least once. In 2001, 7.5% of Clalit cancer patients purchased opioids at least once within 5 years of the initial diagnosis. Between 2002 and 2006 this percentage increased consistently, reaching 9.9% in 2006. The average daily dose of opioids increased from 104.1 mg OME in the year 2001 to 115.2 mg OME in 2006 (11% increase). The average duration of opioid purchasing was 5.0 ± 8.3 months (range 1–84 months, median 2). During the study period 19,426 cancer patients who purchased opioids at least once died; only 14.3% (3274) were still alive 2 years after their first opioid prescription.

Conclusions: Opioid purchasing increased during the study period, especially during the final months of life. Children (0–18 years old) and elderly male patients (≥ 65 years) began opioid treatment later compared to other age groups. Only a few patients had an opioid early enough to relieve their pain.

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KEY WORDS: cancer patients, health management organization (HMO), opioids, consumption trends, pain

Pain is one of the most burdensome symptoms for cancer patients. Pooled prevalence of pain is at least 50% for all cancer types, with the highest prevalence occurring in head/neck cancer patients (70%), 60% in patients with metastatic or advanced disease, and 58% in patients undergoing anti-cancer treatment. More than one-third report their pain as moderate or severe [1]. One study of cancer patients in The Netherlands reported that 55% (n=786) of the 1429 respondents had experienced pain in the previous week. Of these patients, 44% (n=351) reported moderate to severe pain (≥ 4 on a scale of 0–10, where 0 = no pain and 10 = severe pain). Positive predictors of pain were low education level, advanced disease, and hematological (excluding non-Hodgkin lymphoma), gastrointestinal, lung and breast malignancies [2].

In 1986, the World Health Organization published the "WHO ladder for Cancer Pain Relief" [3]. Validation studies of the WHO ladder suggest that in up to 80% of patients with cancer the pain can be controlled using this approach [4,5]. One review article evaluating 20 years of use of the WHO ladder (1982–2004) found that analgesia was considered adequate in 45% to 100% of patients [6]. Opioids are considered a cornerstone in the treatment of cancer and non-cancer pain [7].

The WHO considers country-specific morphine consumption an important indicator of the quality pain control management available at the national level [8]. The International Narcotic Control Board (INCB) data based on government drug importation reports were used to evaluate opioid consumption for any given country.

Very few studies have evaluated opioid consumption based on actual purchasing patterns. The objective of our study was to assess opioid use during 6 years (2001–2006) among cancer patients insured by Clalit Health Services, the largest health management organization in Israel, based on actual purchasing data.

PATIENTS AND METHODS

The Israeli health system comprises four HMOs. At the time of this study, 54% of the Israeli population (3,774,600 enrollees) were insured in Clalit. Israeli citizens pay a progressive tax to the Social Security Institute which allocates the funds to the HMOs according to a capitation formula. Citizens receive medical services in accordance with a predefined health basket. This basket includes primary care services, hospitalizations, medications and diagnostic tests. Opioid medications are given free of charge to cancer patients.

WHO = World Health Organization
HMO = health management organization

STUDY POPULATION

The study population included all Clalit cancer patients who purchased opioids at least once after their cancer diagnosis during the 6 year study period 2001–2006 (31,628, 17.3% of 182,066 cancer patients).

DATA SOURCES

The data included all opioids authorized and available for use during the study period in Israel and included fentanyl (transdermal, ampules), buprenorphine (tablets), methadone (solution), morphine (tablets: immediate/controlled release, ampules), oxycodone (tablets: immediate/controlled release, syrup), and hydromorphone (ampules). Meperidine was rarely purchased and was excluded from the analysis since it is not indicated in the treatment of chronic pain and is usually used for hospitalized patients.

The data included all opioids prescribed at primary care clinics, outpatient clinics, community pharmacies, and by home care units. The data did not include opioids administered during hospitalizations. Opioid purchasing data were obtained from Clalit pharmacy databases. In addition, patients' demographic information (gender, age, address, country of birth) and cancer diagnosis (excluding benign skin tumors) were also extracted.

DATA ANALYSIS

Morphine is the prototype and gold standard of comparison for opioid analgesics [9]. In order to compare patients' use of opioids, data were analyzed by converting all opioid consumption into oral morphine equivalents [10,11]. The study population included active cancer patients, cured cancer patients, and patients in remission. In the treatment of most cancers, 5 year survival defines clinical cure. In an attempt to isolate active cancer patients, when calculating annual purchasing rates we included the total number of cancer patients who purchased opioids at least once in the numerator, and the total number of annual cancer patients who were alive ≤ 5 years after the diagnosis in the denominator.

DEFINITIONS

- *Total OME (mg):* Total annual amount of opioids purchased converted into oral morphine equivalents
- *OME (mg) per prescription:* Total annual amount of opioids purchased converted into oral morphine equivalents and then divided by the number of prescriptions
- *OME (mg) per patient:* Total annual amount of opioids purchased converted to oral morphine equivalents divided by the total number of prescribed patients
- *Duration of opioid consumption:* Total number of months during which cancer patients purchased opioids
- *Average daily opioid dose:* OME (mg) per prescriptions divided by days (represents the average daily dose of opioids for one cancer patient who purchased an opioid at least once)
- *Continuous opioid purchasing:* Patients who purchased opioids continuously every month without a break over the course of their entire opioid consumption period
- *Alternate opioid purchasing:* Patients who purchased opioids alternately during their opioid consumption period
- *Up to 5 years survival:* Clalit cancer patients alive up to 5 years after initial diagnosis (cancer patients living longer than 5 years after diagnosis were excluded).

The study received Institutional Review Board approval from the Meir Medical Center, Kfar Saba, Israel (approval number 0057-2010K).

RESULTS

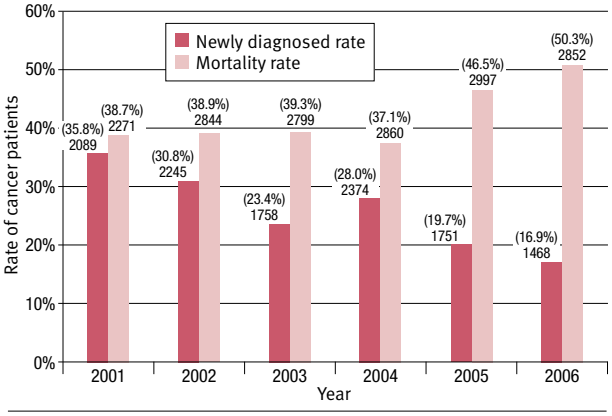
During the study period 182,066 Clalit cancer patients were diagnosed and enrolled. Of them, 57.7% were women, 60.8% were aged 65 and above (average age 67.4 ± 17.9), and 32.1% succumbed to their disease. Approximately 17.3% of Clalit cancer patients (31,628) purchased an opioid at least once. Of them, 55.0% were women, 67.6% aged ≥ 65 (average age 69.6 ± 14.1), and 19,426 (61.4%) died during the study period. The annual distribution of cancer patients who received an opioid prescription at least once is shown in Figure 1.

TRENDS IN OPIOID PURCHASING

The average daily dose of opioids increased from 104.1 mg OME in 2001 to 115.2 in 2006 (11% increase).

In 2001, 7.5% of Clalit cancer patients purchased opioids at least once within 5 years of the initial diagnosis. Between 2002 and 2006, this percent increased consistently, reaching 9.9% in 2006. Figure 2 depicts the annual specific rates of

Figure 1. Annual death rate and newly diagnosed rate of Clalit Health Services cancer patients who received a prescription for opioids at least once (2001–2006)



OME = oral morphine equivalent

cancer patients alive within 5 years of the initial diagnosis who purchased opioids at least once during the study period, adjusted by gender and age group. The gender-adjusted specific rate of these patients was higher among men, and the age-adjusted specific rate was highest among patients aged ≥ 65 and lowest among patients aged 0–18.

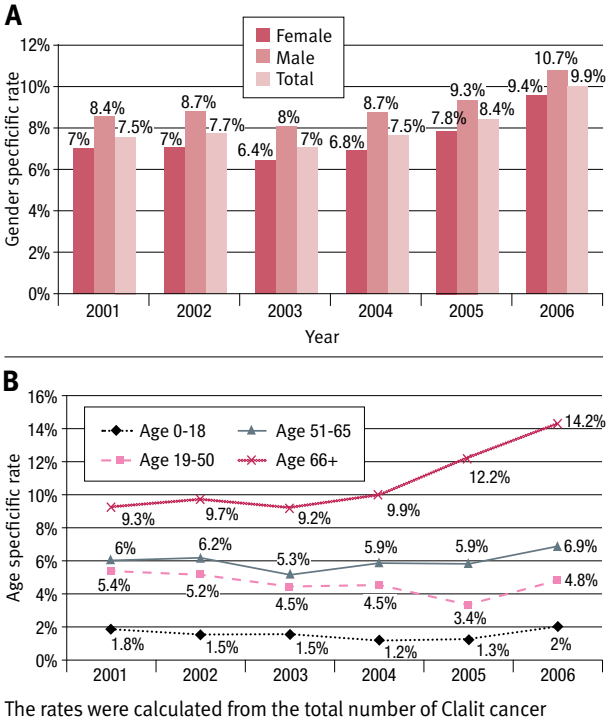
OPIOID CONSUMPTION BEFORE DEATH

Figure 3 shows the average patient opioid consumption during 24 months before death converted to OME (data were calculated in 3 month periods). The average daily dose of opioids increased from 159.8 mg OME at 22 to 24 months before death to 218.4 mg during the 4 to 6 months before death (37% increase). Gender adjustment shows that women received lower OME (mg) per patient and per daily dose during all the periods before death.

DURATION OF OPIOID CONSUMPTION

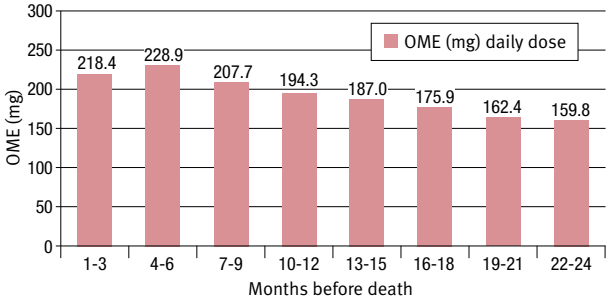
Approximately 37.3% (n=11,782) of the cancer patients purchased opioids for only one month, and 9.3% (n=2951) purchased opioids for more than 12 months. The average opioid purchasing duration for the entire study cohort was 5.2 ± 8.6 months (range 1–84 months, median 2).

Figure 2. Annual **[A]** gender- and **[B]** age-specific rates of patients alive within 5 years of the initial diagnosis who purchased an opioid prescription at least once



The rates were calculated from the total number of Clalit cancer patients alive within 5 years of the initial diagnosis (cancer patients living longer than 5 years after diagnosis in this figure were excluded)

Figure 3. Average daily dose OME (mg) purchasing during the months before death



For patients purchasing opioids for longer than 1 month (19,846), we designated the consumption pattern as either continuous or alternate. Thirty-nine percent (n=7841) purchased opioids continuously. On average, patients using opioids continuously were older (69.9 ± 13.2 vs. 68.8 ± 14.4, $P < 0.0001$), and women used opioids alternately more often than men (63.0% vs. 57.5%, $P < 0.0001$).

During the study period 19,426 cancer patients of those who had purchased opioids at least once succumbed to their disease. Of them, 67% (13,055) were alive 3 months after their first opioid prescription, 30% (5875) were alive after 1 year, and 13.8% (2682) were still alive after 2 years. Figure 4 shows the percentage of cancer patients still alive at defined intervals since their initial opioid prescription, adjusted by gender and age group. Children aged 0–18 purchased their first opioid prescription closer to death compared with adults and older cancer patients. Furthermore, women purchased their first opioid prescription earlier than men did.

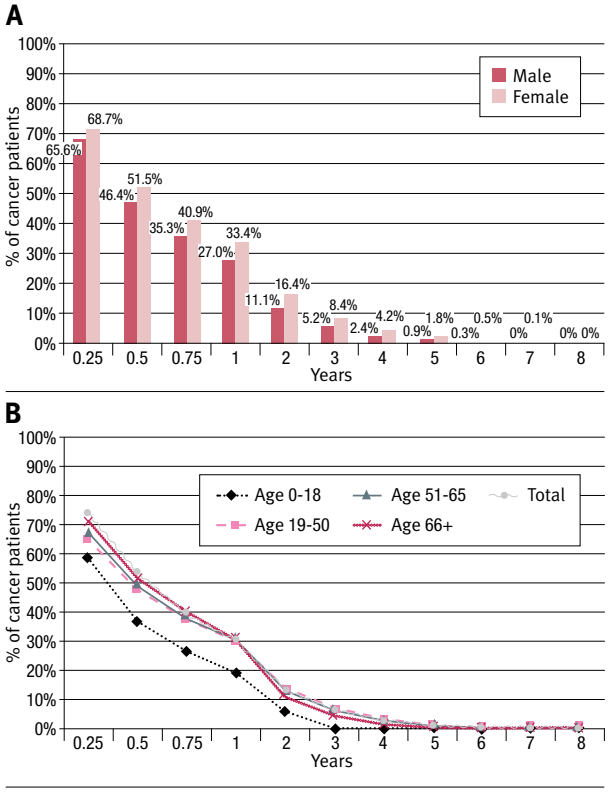
DISCUSSION

In 1991, 57% of all morphine was consumed by 10 countries with the highest per capita consumption for several years. Together, the top 20 countries (all developed countries) account for 86% of worldwide morphine consumption. The remaining 14% of morphine was consumed in 100 other countries that make up the majority of the world's population. In Israel, morphine consumption increased from 2 kg in 1984 to 20 kg in 1991 (900%) [12].

In previous studies, we found an impressive increase in opioid consumption in all Clalit members, from 56.4 kg in 2000 to 94.5 kg in 2004 (68% increase) [13] and to 110.6 kg in 2006 (96% increase) [14]. The OME per capita increased from 15.7 mg in 2000 to 29.3 mg in 2006 [14].

Other studies have described trends in opioid consumption in Israel (2000–2008), drawing from the database maintained by the Israel Ministry of Health pharmaceutical administration's database. Consumption of the five strongest opioids (requiring a special prescription) increased by 47%, from 2.46

Figure 4. Percent of cancer patients still alive after first-time opioid purchase (n=19,426): **[A]** gender- and **[B]** age-adjusted specific rates



defined daily dose/1000 inhabitants per day in 2000 to 3.61 DDD/1000 inhabitants per day in 2008 [15].

The present study evaluated 6 years of opioid consumption among Clalit cancer patients only. The total OME (mg) per patient increased during the months before death, with the highest dose taken 4 to 6 months before death (4673.6 OME mg/patient). An apparent decrease in opioid consumption was seen in the 3 months before death. One of the explanations may likely be that the patients were hospitalized, since only outpatient consumption was evaluated in our study. A Danish study analyzed the change in opioid use between 1994 and 1998 in a cohort of cancer patients (24,190) and found that overall consumption of opioids increased from 20 kg to 37 kg OME per year. The annual proportion of cancer patients who received at least one opioid prescription within the period of observation increased from 17% to 20% [16].

We found that only 7.5–9.9% of the cancer patients alive within 5 years of the initial diagnosis purchased an opioid at least once during the years 2001–2006. These numbers appear to be low; however, an increasing trend can be observed over time. The study population included all Clalit patients with a cancer diagnosis and thus, in addition to active cancer patients, also included patients in remission (those who were cured). In order to overcome this bias, we narrowed our analysis to consider only the population of cancer patients who were alive within 5 years of the diagnosis. In the present analysis we included only those patients alive within 5 years of the diagnosis who purchased opioids at least once. Analysis of all cancer patients in all trajectory stages (including patients in remission) yielded significantly lower purchasing rates as expected.

Some could wonder what the real rates are of cancer patients suffering pain. Most of the recent studies have shown under-treatment of cancer pain [17-19]. Usually patients suffer pain during the diagnosis process, active treatment and terminal phase. The WHO has defined opioid consumption as an indicator of quality of pain treatment. According to these studies about 90% of cancer patients in the terminal stage suffer from severe pain. During our study period about 32% of the cancer patients died [Figure 1]. Only 32% of those who died had at least one opioid prescription. Thus, it can be assumed that the majority of cancer patients who died should have been prescribed an opioid prescription at least once

In order to evaluate if opioids are given to cancer patients early enough during the course of their illness we calculated the percentage of cancer patients who were still alive after their first opioid was prescribed. Only 30% patients were alive 1 year after their first opioid was purchased, and 13.8% after 2 years.

Another Danish study that evaluated a cohort of cancer patients during the years 1997–2003 found that opioid treatment was initiated close to the date of diagnosis in 20% of patients. Most incident users (57%) were not terminal when they began using opioids, and 44% survived the first treatment cycle. Of those who died, 70% received opioids in the terminal phase. The incidence rates of new opioid users were inversely related to the 5 year cancer survival period and no statistically significant differences in opioid use were found between men and women [20].

Over the course of the study period, the age and gender-adjusted specific rates of patients purchasing opioids were higher among men and among patients ≥ 65 years old. Children aged 0–18 years purchased their first opioid prescription closer to the time of death when compared with adults, and women purchased their first opioid prescription earlier in their disease course than men. Further age regression analysis shows that older patients (≥ 65) purchased the lowest total OME (mg) per patient and per prescription in the 48 months before death.

Our data analysis is population based and was extracted from the patient databases of the largest HMO in Israel, which insures 54% of the Israeli population. On average, patients insured by Clalit are older and of a lower socioeconomic status when compared with the rest of Israel. However, since Clalit covers nearly 3,800,000 members, we can assume that they serve as a representative population of patients receiving opioids in Israel.

DDD = defined daily dose

Cherny and colleagues from the European Association for Palliative Care (EAPC) and European Society of Medical Oncology (ESMO) have documented the current status of access to opioids for pain relief in Europe, yet warn that some of their data may have deficits due to the survey selective bias [21,22]. The Pain and Policy Studies Group (PPSG) has also described global opioid consumption trends using government consumption reports [22,23]. Two studies reported on opioid consumption, pooling statistics from the databases of seven European countries [24,25]. Most of these databases are founded on cumulative sales of opioid medications as reported by wholesalers and do not consider consumption on the patient level. Previous studies on the opioid consumption of cancer patients have used cohorts that do not necessarily represent the population at large. For this reason, taken collectively, data from the existing literature are not sufficiently representative of the true amount of opiods consumed in practice by patients, as we have tried to represent in our study [24,25].

STUDY LIMITATIONS

We assumed that most of the patients diagnosed with cancer who purchased opioids during the study period purchased them because of cancer-related pain. Although one could argue that cancer patients can also be prescribed opioids for non-cancer-related pain, we assume this was a very small minority of patients. Our basic assumption was that patients who purchased opioids and had been diagnosed with cancer received the opioid treatment for cancer pain, especially since we included only the opioids purchased after the cancer diagnosis date. Even assuming that this may lead to a bias, the situation would be even worse than described in this article.

Unfortunately, since the study is based on computerized databases we were not able to distinguish between the opioid use by cancer patients treated for cure and those receiving only palliative care. We assumed that the 36% of patients who died during the study period had been treated as palliative care patients for a while.

The results of our investigation of the opioid purchasing patterns of cancer patients indicate progress in pain management and further point to the need to improve pediatric and geriatric pain management protocols. In addition, our findings show that opioids are often prescribed too late in the course of the patient's disease. Increased investment in medical education and an increase in patient awareness of proper pain management may lead in the future to an increase in opioid use for pain control in cancer patients.

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