Prescription patterns for psychotropic drugs in cancer patients; a large population study in the Netherlands

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Abstract

Background: Psychotropic drugs are commonly prescribed for various psychological complaints in cancer patients. We aim to examine the prescription pattern in cancer patients of three common psychotropic drugs: benzodiazepine, antidepressant and antipsychotic.

Methods: This is a retrospective case-control study. Data were extracted from the Agis Health Database. This insurance database contains the healthcare consumption of 1.3 million inhabitants of the Netherlands. We analyzed the use of psychotropics in cancer patients and an equally sized randomly selected control group of noncancer patients from 2006 to 2008. Odds ratio (OR) were adjusted for age, gender, immigrant status, neighborhood socio-economic status, and premorbid medical condition. Additionally, the numbers of new user in the 3 months after cancer was diagnosed and in the 3 months before death were compared.

Results: A total of 113 887 cancer patients and 121 395 control subjects were included. Cancer patients were significantly more often prescribed psychotropic drugs (adjusted OR: benzodiazepines = 1.70, CI = 1.67-1.74; antidepressants = 1.38, CI = 1.34-1.42; and antipsychotics = 1.70, CI = 1.62-1.77). Lower socio-economic status, immigrant, and premorbid chronic medical conditions were significantly associated with higher risk of psychotropic use. Odds for a new prescription for all three psychotropic drugs were significantly less in the first 3 months after cancer diagnosis than the 3 months before death (benzodiazepine, OR = 0.673, CI = 0.647-0.705; antidepressant, OR = 0.592, CI = 0.544-0.644; antipsychotic, OR = 0.177, CI = 0.165-0.190).

Conclusions: Psychotropic drug prescription is common in cancer patients, starts soon after diagnosis, and increases in the terminal stage. Prescription rates were significantly higher in patients from lower socio-economic group, immigrants, or with premorbid chronic medical condition.

Keywords: cancer; oncology; prescription; antipsychotic; psychotropic; antidepressant

Introduction

Cancer patients often experience psychological distress, closely related to fear and uncertainty about the illness and its progression as well as in response to treatment of cancer [1–5]. Previous studies reported psychiatric disorders in up to 50% of cancer patients. Adjustment disorder, major depressive disorder, and anxiety disorder are the most common psychiatric comorbidities in cancer patients [6–12], of which particularly the latter two disorders generally responding well to drug treatment.

Since their introduction in the 1950s, psychotropic drugs have gained huge popularity as a treatment for psychiatric complaints in all kinds of patients, reflected in a rapidly increasing number of prescriptions [13–19]. Psychotropics are also commonly used for many nonpsychiatric complaints in cancer patients. For instance, they are used in the treatment of fatigue, insomnia, and pain in cancer patients [20–24]. The relatively safe profile and minimal risk of serious adverse events further contribute to the widespread use of psychotropic drugs.

Although psychotropics have become common practice in oncology, the detailed rate of psychotropic prescriptions in cancer patients has remained unknown. A survey among 1579 cancer patients from five oncology centers in 1979 reported that 51% of the patients used at least one psychotropic drug. Hypnotics (48%), antidepressants (26%), and anxiolytics (25%) were the three most common psychotropic drugs prescribed [14]. Another survey presented psychotropic use in the last week of life in terminal cancer patients. The consumption of psychotropic drugs was much lower in this group of patients; about 16% of patients used benzodiazepines, 7% antipsychotic, and 2% antidepressive drugs [15]. A more recent study of 63 patients referred to a psycho-oncological treatment unit demonstrated that over 50% used psychotropics. The most common drugs prescribed were minor tranquilizers (51%) and antidepressants (25%) [17]. Another recent study found that antidepressants were more commonly prescribed in breast and prostate cancer patients especially in the terminal stage [18]. However, the generalizability of these results and
the power of the studies were limited because of the small sample size, selection of cancer types, the short period of time, and the lack of control group comparison.

In view of the high prevalence of psychological distress among cancer patients, it is of interest to examine the prevalence of psychotropic drug prescription and the choice of medications. Prescription patterns are a reflection of awareness of mental health in cancer patients and can be informative about the general approach taken toward mental health issues in this vulnerable group. We therefore studied the psychotropic prescription practice in cancer patients by using a population-based health care registration database. We assessed the prescription rates of three common psychotropic drugs among cancer patients, namely benzodiazepines, antidepressants, and antipsychotic drugs, and investigated prescription trends separately for each drug class after the cancer diagnosis is set and in the terminal phase of life. We hope that the findings of this study will draw attention from the public and healthcare decision makers toward the issues of psychological distress in cancer patients.

Methods

Data

This is a retrospective case-control study. The data used in this study were extracted from the Agis Health Database (AHD) anonymously. AHD is one of the main health insurance companies in the Netherlands. It provides healthcare coverage for about 1.3 million residents in the central part of the country. The database contains demographic and healthcare consumption data of the clients as well as extensive records of the pharmaceutical prescriptions. In the Netherlands, all inhabitants are, by law, obliged to have medical insurance coverage. The compulsory healthcare insurance covers all care for cancer patients and all psychotropic medication. Psychotropic drugs are available on doctor’s prescription only. The registration of prescriptions in the database is extensively controlled for the reason of financial reimbursement. It ensures the completeness and accuracy of the AHD [25]. Approval from the AHD research committee was obtained prior to accessing the data.

Cancer and control cases

Study subjects were identified in the AHD between 1 January 2006 and 31 December 2008. Selection was based on the presence of a diagnostic treatment combination code (DBC-codes in Dutch) for cancer (including nonmelanoma skin cancer). In the Dutch medical system, all cancer patients consult an oncologist. All diagnostic and treatment activities of these specialists will be paid by the insurance company. These activities are registered. Therefore, from 1 January 2006 to 31 December 2008, all new cases of cancer were identified as cases in this study. Only cancer patients with complete follow-up were included in the study (only allowed exit was death). In addition, a random sample of control patients without cancer was taken in the same period, matched by gender and age. Cancer cases were also determined by the date of diagnosis and, if applicable, by date of death.

Variables

Drug prescriptions were recorded according to the Anatomical Therapeutic Chemical classification system codes. The following Anatomical Therapeutic Chemical codes were included: NO5B, NO5C (benzodiazepine), N06A (antidepressant), and N05A (antipsychotic).

Psychotropic drug use was defined as at least one prescription of any of the psychotropic drugs during the study period. New user of each psychotropic drugs was defined as no use or use of less than 30 defined daily doses (DDD; assumed average dose per day) in the previous year. The numbers of new user among cancer patients in the 3 months after the cancer diagnosis and in the 3 months before death were calculated separately. Those who identified as new users will not be counted as new users again in the terminal stage.

The preexisting psychiatric and medical conditions were identified using the prescription patterns among the index and control patients in 2001–2007 as proxy indicator. Thus, psychiatric comorbidity was defined as the use of at least 90 DDD of psychotropic drugs in any of the 5 years before the diagnosis of cancer. For example, patients diagnosed of cancer in 2006 are screened for psychotropic use from 2001 to 2005, whereas patients diagnosed in 2008 are screened from 2003 to 2007. Similarly, the presence of comorbid chronic medical conditions was identified using the proxy indicator for any prescribed drugs starting with R03A, R03B, and R03D for pulmonary disease; A10A and A10B for diabetes mellitus; and C01A, C01B, C01D, C03, C07, C08, and C09 for cardiovascular disease. The use of more than 180 DDD of these drugs annually in 2005 and in subsequent years was taken as a cut-off point.

Covariates

The following information about the cancer and control patients was gathered: age, gender, non-Western immigrant, and socioeconomic status. The age of the cancer patients was determined on the date of the cancer diagnosis. The age of the control group was taken on 1 January 2006. Subpopulations according to cultural background were analyzed separately. The first generation of non-Western immigrants, which consists of Moroccan, Turkish, and Surinamese patients, is registered in the AHD. The subsequent generations were identified by matching the surname and by visual control of the surnames. The socioeconomic status of the subjects was based on the postal code of the neighborhood.
Socioeconomic status was dichotomised into subjects from deprived and non-deprived areas.

Analyses

The prevalence of psychotropic use for the cancer and control groups was calculated for the study period (1 January 2006 to 31 December 2008). The number of psychotropic drugs used in the cancer and the control groups was compared. The difference in the average monthly use of the psychotropic drugs (based on DDD) between the cancer and control groups was determined with the independent Student t-test. A logistic regression model was used to analyze the determinants of psychotropic drug use in cancer patients, reported in adjusted odds ratios. The mean numbers of new users and average monthly use of each psychotropic drug for the users for the 3 months after the cancer diagnosis and 3 months before death were compared. All tests were two-sided at the alpha level of 0.05.

Results

After removing cases with incomplete dataset and repeated cases, a total of 113 887 cancer patients and 121 395 control subjects were included in this study (Table 1). The two groups did not differ in age and gender (two-sided t-tests, \( p > 0.9 \)); the mean age for both groups was around 60 years (cases were about 1.5 years older than the controls), 62% were women, and about 9.5% were non-Western immigrants from Turkish, Moroccan, and Surinamese origin. About 13%–15% of the subjects were from low socioeconomic status group (based on the area of residential).

As compared with patients without cancer, a significantly higher percentage of cancer patients was prescribed at least one psychotropic drug during the study period. Benzodiazepine was the most commonly prescribed psychotropic drug to cancer patients (28.5%). More than 1 in 10 cancer patients (10.9%) were prescribed antidepressant drugs, which resulted in an odds of 1.47. Although the percentage of cancer patients with antipsychotic drug prescriptions was relatively low (4.7%), it was significantly higher than in the control group (Table 2).

The comparison of the average monthly use of psychotropic drugs (measured in DDD as assumed average dose per day) among cancer and control patients demonstrates that cancer patients used higher amounts of benzodiazepine (10.20, SD = 0.14 vs. 8.95, SD = 0.23; 95% CI for the mean difference = 0.77, 1.74, \( p < 0.01 \)) but lower amounts of antipsychotics as compared with the control group (6.67, SD = 0.32 vs. 9.00, SD = 0.53; 95% CI for the mean difference = -3.46, -1.20, \( p < 0.01 \)). The amount of antidepressant drug prescription did not differ significantly between the cancer (17.31, SD = 0.78) and control groups (16.59, SD = 1.76; 95% CI for mean difference = -2.75, 4.20, \( p = 0.68 \)). The results demonstrate that cancer patients older than 60 years used more benzodiazepines and antipsychotics but less antidepressant drugs. Male cancer patients used much less benzodiazepines and antidepressant but slightly more antipsychotics as compared with female cancer patients. Immigrants with cancer used more of all types of psychotropic drugs than the cancer patients with a Dutch background. Although the crude prevalence of all types of psychotropic drug use was lower for cancer patients from deprived areas, the odds of prescription was higher after adjustment for other variables. The presence of comorbid chronic medical conditions was associated with a higher prescription rate of any psychotropic drugs in cancer patients (Table 3).

Co-prescription of one or two psychotropic drugs to patients with cancer was more frequent than in the control group (OR = 1.658, 95% CI = 1.624–1.693). There were significantly more patients in the control groups with co-prescription of all three types of psychotropic drugs (OR = 0.552, 95% CI = 0.542–0.562).

The chance of cancer patients being prescribed a psychotropic drug for the first time was higher in the terminal disease stage (3 months before death) than in the first 3 months after the cancer diagnosis, especially for antipsychotic. However, the average dose used was lower in the terminal stage for antidepressant and antipsychotic drugs. There was no difference in the average dose used for benzodiazepine in the two disease stages.

Discussion

In this study, we compared the prescription of psychotropic drugs in 113 887 cancer patients and 121 395 controls extracted from a population-based insurance register in the Netherlands between 2006 and 2008. We found that 28.5% of cancer patients were prescribed benzodiazepine at least once, 10.9% were prescribed antidepressants, and 4.7% antipsychotics. All classes of psychotropic drugs were more frequently prescribed to cancer patients than to the controls. To our best knowledge, this is the largest population-based study on this topic. According to a result of a prospective study on the prevalence of psychiatric disorder in the Dutch population, 23.3% experience at least once DSM-III-R disorder in the preceding year where one-year prevalence of depression was 5.8% [26].

Cancer patients from deprived areas, immigrants, and those with comorbid chronic medical conditions had a significantly higher prescription rate for any type of psychotropic drugs. The odds of being prescribed a

Table 1. Baseline characteristics of the cancer patients and control group

<table>
<thead>
<tr>
<th></th>
<th>Cancer patients (( N = 113 \ 887 ))</th>
<th>Control group (( N = 121 \ 395 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD)</td>
<td>60.45 (18.27)</td>
<td>58.90 (19.65)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>71 293 (62.6)</td>
<td>75 265 (62.0)</td>
</tr>
<tr>
<td>Non-Western immigrant (%)</td>
<td>10 819 (9.5)</td>
<td>11 290 (9.3)</td>
</tr>
<tr>
<td>Deprived area (%)</td>
<td>17 425 (15.3)</td>
<td>16 146 (15.3)</td>
</tr>
</tbody>
</table>
The use of psychotropic drugs in cancer and control subjects, mean difference (95% CI)

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Cases N = 113 887</th>
<th>Control N = 121 395</th>
<th>Crude OR (95%CI)</th>
<th>Adjusted OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any drug</td>
<td>37 450 (32.9)</td>
<td>25 842 (21.3)</td>
<td>1.81 (1.78–1.85)</td>
<td>1.67 (1.64–1.71)</td>
</tr>
<tr>
<td>Benzodiazepine (%)</td>
<td>32 458 (28.5)</td>
<td>21 487 (17.7)</td>
<td>1.85 (1.81–1.88)</td>
<td>1.70 (1.67–1.74)</td>
</tr>
<tr>
<td>Antidepressant (%)</td>
<td>12 414 (10.9)</td>
<td>9 347 (7.7)</td>
<td>1.47 (1.43–1.51)</td>
<td>1.38 (1.34–1.42)</td>
</tr>
<tr>
<td>Antipsychotic (%)</td>
<td>5 353 (4.7)</td>
<td>3 278 (2.7)</td>
<td>1.77 (1.69–1.85)</td>
<td>1.70 (1.62–1.77)</td>
</tr>
</tbody>
</table>

Adjusted OR = Odds ratio adjusted for gender, immigrant status, neighborhood socio-economic status, age and premorbid chronic medical conditions (diabetic, cardiovascular, and pulmonary conditions).

The presence of premorbid chronic medical condition is defined as the use of more than 180 DDD of the proxy indicator medication in subsequent years from 2005 backwards to 2005. The use of psychotropic drugs is defined as at least once prescription during the study period (2006–2008).

Associated factors for psychotropic drug use in cancer patients from the logistic model for each of the covariates

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Benzodiazepine</th>
<th>Antidepressant</th>
<th>Antipsychotic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>Crude OR (95%CI)</td>
<td>Adjusted OR (95%CI)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60</td>
<td>23.6 (0.65)</td>
<td>0.77</td>
<td>1.13</td>
</tr>
<tr>
<td>&gt;60</td>
<td>32.3 (0.63–0.66)</td>
<td>0.75–0.78</td>
<td>1.24</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24.4 (0.72)</td>
<td>0.60</td>
<td>0.86</td>
</tr>
<tr>
<td>Female</td>
<td>30.9 (0.70–0.74)</td>
<td>0.60–0.61</td>
<td>0.74</td>
</tr>
<tr>
<td>Immigrant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>29.4 (1.67)</td>
<td>1.15</td>
<td>1.01</td>
</tr>
<tr>
<td>No</td>
<td>32.3 (1.60–1.76)</td>
<td>1.11–1.20</td>
<td>0.84</td>
</tr>
<tr>
<td>Deprived area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>28.8 (1.10)</td>
<td>0.94</td>
<td>0.95</td>
</tr>
<tr>
<td>Yes</td>
<td>26.8 (1.06–1.14)</td>
<td>0.91–0.96</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Adjusted OR = Odds ratio adjusted for gender, immigrant status, neighborhood socio-economic status, age and premorbid chronic medical conditions (diabetic, cardiovascular, and pulmonary conditions).

Premorbid chronic medical condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>%</th>
<th>Crude OR (95%CI)</th>
<th>Adjusted OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric chronic condition</td>
<td>39.6 (1.76)</td>
<td>1.80</td>
<td>1.54</td>
</tr>
<tr>
<td>No</td>
<td>27.2 (1.69–1.83)</td>
<td>1.74–1.86</td>
<td>1.63</td>
</tr>
<tr>
<td>Diabetic condition</td>
<td>32.1 (1.21)</td>
<td>1.05</td>
<td>1.25</td>
</tr>
<tr>
<td>No</td>
<td>28.1 (1.16–1.26)</td>
<td>1.01–1.08</td>
<td>1.25</td>
</tr>
<tr>
<td>Cardiovascular condition</td>
<td>34.8 (1.62)</td>
<td>1.80</td>
<td>1.20</td>
</tr>
<tr>
<td>No</td>
<td>24.8 (1.58–1.67)</td>
<td>1.76–1.85</td>
<td>1.45</td>
</tr>
</tbody>
</table>

The presence of premorbid chronic medical condition is defined as the use of more than 180 DDD of the proxy indicator medication in previous years (2001–2005).

adjusted OR = Odds ratio adjusted for gender, immigrant status, neighborhood socio-economic status, age and premorbid chronic medical conditions (diabetic, cardiovascular, and pulmonary conditions).

Our results demonstrate that psychotropic prescription in cancer patients is also associated with a lower socio-economic status (deprived areas). Antidepressant and benzodiazepine prescription in cancer patients is also associated with immigrant status. The higher prescription of psychotropic drugs to immigrants may be explained by higher levels of stress related to suffering from a chronic illness such as cancer in a cultural different context. Previous studies in the general population showed that both Turkish and Moroccan immigrants had increased risk of depressive symptoms as indicated in the increased risk of antidepressant and antipsychotic drug prescription in the immigrant population [27]. Patients with lower socio-economic status may have limited capacity in coping with chronic diseases such as cancer. This may lead to more psychological distress. Another interesting finding was the significantly increased rate of psychotropic drug prescriptions in patients with comorbid chronic medical conditions. It suggests that the debilitating effect of cancer and adverse events of the treatment are higher in patients with preexisting morbidity of chronic disease. Female cancer patients were prescribed more often with benzodiazepine and antidepressants. This probably reflects the higher prevalence of depressive symptoms and anxiety in women. The higher rates of antipsychotic and benzodiazepine prescription in older cancer patients are most likely...
related to the higher risk of acute organic symptoms and anxiety in this group of cancer patients [28].

A striking result of our study is the fact that the risk of new user of any psychotropic drugs in cancer patients was higher in the terminal stage (last 3 months before death) than in the early disease stage (first 3 months after cancer diagnosis). This finding is similar with the reports by Khan et al. where antidepressants and benzodiazepine were more often prescribed for breast and prostate cancer patients who died [18]. It may reflect higher level of psychological distress in the terminal stage of cancer. It is consistent with reports of significant increase in distress and pain and a significant decrease in well-being in the period before death [29] and several other studies reporting that pain, fatigue, loss of appetite, anxiety, and depression are commonly encountered in the terminal cancer patients [30–34]. Alternatively the higher prescription rate in the terminal stage may be related to delay in recognition and treatment of mental health problems. The increased new use of antipsychotics in the terminal stages is likely to be due to increased prevalence of the organic psycho syndrome in the terminal cancer stage. Despite the noticeable prevalence of antipsychotic drug prescription (4.8%), it was much lower compared to earlier reports by Derogatis et al in 1979 (13.3%) [14]. In the survey on terminal cancer patients by Goldberg and Mor in 1985, the consumptions of antipsychotic drugs was 7% [15]. Antipsychotic drugs are frequently used as antiemetic, which is a highly prevalent symptom in patients with terminal cancer. In the survey conducted by Derogatis et al reported more than 90% of the psychotropic drugs were prescribed because of nausea and vomiting [14]. In this study, we found that a relatively high prevalence of cancer patients were prescribed with antipsychotic drugs for the first time in the last 3 months of life (8%). In addition to the control of gastro-intestinal symptoms it is likely that antipsychotic drugs are being used to control the sudden change in behavior due to acute organic psycho syndrome or psychosis such as hallucination and delusion during the terminal phase in these patients [28]. These symptoms are often related to the progression of cancer, brain metastasis, electrolytes imbalance and effects of cancer treatment.

In this study the prevalence of benzodiazepine users was 28.5%. Although benzodiazepines are for many decades the most frequently prescribed psychotropic drug in cancer patients the benzodiazepine prescription in this sample is slightly higher compared to previous studies in which the rate of benzodiazepine prescription in cancer patients ranged from 24.5% to 28.3% [14,17].

The prevalence of antidepressant prescription in cancer patients was about 10.9% in this study, which matches the estimates from our recent meta-analysis [35]. It is known that antidepressants are often prescribed not only for depression but also various other indication such as pain control, insomnia, panic attacks and appetite stimulation. As it is not possible to retrieve the actual depression prevalence it remains possible that a proportion of cancer patients with depression actually remain untreated. We also found that the risk for co-prescription of all three types of psychotropic drugs was lower among cancer cases (OR = 0.55, CI:0.542-0.562), but the meaning of that remains unknown.

Other limitations of this study include the fact that the study period was restricted to the first three years after the diagnosis of cancer. Patients who received psychotropic prescription after the study period are not identified. This may underestimate the prescription rates in these patients although it is not likely that the prescription rates differ in the patient group that exceeded our analysis time-frame, bias cannot be ruled out. As the study does not follow up all the cases until the end of life, the study on prescription in the terminal cancer phase was confined to the patients who deceased during the study period. These patients were mostly likely to be in advanced and more aggressive disease stages, resulting in a possible overestimation of prescription to all cancer patients. Social and family support which may help the patients to cope with their psychological problem was not measured in this study. Different types of psychotropic have their own safety and efficacy profile. The types of antidepressants, benzodiazepine and antipsychotics prescribed were not available in this study. In the current study we selected those patients that were in the database for the whole period, the only allowed exit for the database was death. It is highly unlikely that there was a systematic bias in those that terminated their insurance during the index period although this cannot be ruled out. Lastly, clinical data, such as cancer stage and physical disability were not documented in the database. These factors might confound the result in the analysis of psychotropic drugs prescription rates.

In conclusion, the prescription pattern among cancer patients that we observed suggest extensive use of psychotropic drugs in daily clinical practice starting soon after illness onset and an increase of new prescriptions in the terminal phase of cancer. The increased use of antidepressant drugs in the last 3 months before death raises the question whether these prescription are related to somatic symptom relief, late onset depression or alternatively to delayed diagnosis of depression. In general the highly frequent use of psychotropic drugs seems to be a reflection of the high levels of psychological distress among cancer patients. Further studies are needed to evaluate and to optimize psychotropic drug prescription in cancer patients.

**Conflict of interest**

The authors have declared that there is no conflict of interest.

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