Preadmission antidepressant use and bladder cancer: a population-based cohort study of stage at diagnosis, time to surgery, and surgical outcomes

Research year report

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PREFACE

Some years must be shorter than others. The previous one certainly has been. It has only been a few weeks since I rode my bike up Randersvej heading for KEA for the first time. At least it feels that way. On the other hand, the last year has been full of so many great experiences, countless Stata syntaxes, and so much fun at 'flyverpladserne'—more than enough to fill several years.
Time is a tricky thing.[1]

Here, I will spend a bit of time saying thank you to, of course, Mette for her help and encouragement. Even in the busiest of times,[2] she would discuss the project and optimistically guide me on the right track. I must also express my thanks to Jørgen, who generously provided clinical knowledge and to Heidi for patiently answering all my questions about bladder cancer coding (in all its details). A special thanks to Mike and Cynthia who were overwhelmingly kind and invited me into their home and family for two months. I am deeply grateful for their hospitality, for the introduction to their version of American daily life, for our many interesting conversations about Danish and American culture, for experiencing the scientific environment at Regenstrief Institute, and for 'hyggelige' movie nights in the living room. Also, the last year would not have been the same without my fellow research year students. I am proud to have shared this year with such bright heads and happy that we could discuss both biostatistical issues and consolidate the tradition of cake at 'flyverpladserne'. Finally, a thank you to everyone at KEA for your help with practical, economical, and technical challenges, for academic guidance, and for great (so great, the best, really) times[3] after hours.

Ellen Hollands Steffensen, February 2017

[1] Also in statistical modelling.
[2] There it was again, time.
[3] !

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ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical
CCI	Charlson Comorbidity Index
CI	Confidence interval
CPR	Civil Registration Number
DDD	Defined daily dose
DNPR	The Danish National Patient Registry
HR	Hazard ratio
ICD	International Classification of Diseases
ICU	Intensive care unit
OR	Odds ratio
SES	Socioeconomic status

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ABSTRACT

Background: A history of psychiatric disease has been associated with worse survival after cancer. This could be due to differences in stage at diagnosis, in receipt of treatment, or in treatment complications.

Objective: To examine the associations between antidepressant use and cancer stage at diagnosis, rate of surgery, and surgical outcomes in patients with invasive bladder cancer.

Design and methods: We performed a register-based cohort study including all patients with incident invasive bladder cancer in Denmark 2005-2015. We defined use of antidepressants as redemption of two or more antidepressant prescriptions in the year before cancer diagnosis. We compared users and non-users with regard to cancer stage at diagnosis by logistic regression, postsurgical inpatient length of stay (LOS) by linear regression, and other surgical outcomes by Cox regression. Results were adjusted for age, sex, comorbidity, and marital status.

Results: Among 10,427 patients with bladder cancer, 10% were antidepressant users. At diagnosis, 51% of users and 52% of non-users had muscle-invasive disease (adjusted odds ratio 0.86; 95% confidence interval (CI) 0.74-0.99). Among patients with muscle invasive disease, fewer users than non-users had surgery within four months (15% vs. 25%, adjusted hazard ratio (aHR) 0.74; 95% CI 0.59-0.94).
Of 2532 patients undergoing surgery, 6% were antidepressant users. Median LOS did not differ between users (9 days) and non-users (10 days) (adjusted ratio of median LOS 1.02; 95% CI 0.93-1.12). The 30-day cumulative incidence of readmission was higher for users (41%) than non-users (33%) (aHR 1.33; 95% CI 1.05-1.67), while the 90-day cumulative incidence of reoperation for users was 44% and for non-users 38% (aHR 1.18; 95% CI 0.93-1.51). We found comparable one-year postsurgical mortality risk in users (15%) and non-users (14%) (aHR 0.96; 95% CI 0.63-1.46).

Conclusion: Use of antidepressants at or just before bladder cancer diagnosis was relatively common—this was not associated with advanced stage, but users had lower rate of surgery. Reassuringly, we found similar postsurgical one-year mortality in users and non-users despite higher readmission and reoperation rates.

DANSK RESUMÉ

Baggrund: Det er fundet, at kræftpatienter med tidligere psykiatrisk sygdom har dårligere overlevelse end øvrige kræftpatienter. Mulige forklaringer er forskelle i kræftstadie ved diagnose, behandlingsvalg eller behandlingskomplikationer.

Formål: At undersøge sammenhænge mellem brug af antidepressiv medicin og kræftstadie ved diagnose, tid til operation og postoperative komplikationer hos patienter med invasiv blærekræft.

Design og metoder: Vi gennemførte er registerbaseret kohortestudie af alle danske patienter med invasiv blærekræft diagnosticeret i 2005-2015. Brug af antidepressiva blev defineret som indløsning af mindst to recepter på antidepressiv medicin året forud for kræftdiagnose. Vi sammenlignede brugere og ikke-brugeres kræftstadie ved diagnose ved hjælp af logistisk regression, deres postoperative hospitalsindlæggelse med lineær regression og øvrige udfald med Cox regression. Alle resultater blev justeret for alder, køn, komorbiditet og ægteskabelig status.

Resultater: Blandt 10.427 blærekræftpatienter var 10% antidepressivbrugere. Ved diagnose havde 51% af brugere og 52% af ikke-brugere muskelinvasiv sygdom (justeret odds ratio 0,86; 95% konfidensinterval (CI) 0,74-0,99). Færre brugere end ikke-brugere blev opereret inden for fire måneder (15% vs. 25%, justeret hazard ratio (aHR) 0,74; 95% CI 0,59-0,94).
Af 2532 opererede patienter var 6% antidepressivbrugere. Indlæggelsesvarighed var ikke forskellig for brugere (median 9 dage) og ikke-brugere (median 10 dage) (justeret ratio 1,02; 95% CI 0,93-1,12). Den kumulerede incidens af 30-dags genindlæggelse var højere for brugere (41%) end ikke-brugere (33%) (aHR 1.33; 95% CI 1.05-1.67), mens 90-dags kumuleret incidens af reoperation hos brugere var 44% og hos ikke-brugere 38% (aHR 1,18; 95% CI 0,93-1,51). Vi fandt sammenlignelig etårs postoperativ dødelighed blandt brugere (15%) og ikke-brugere (14%) (aHR 0,96; 95% CI 0,63-1,46).

Konklusion: Brug af antidepressiv medicin ved eller umiddelbart før blærekræftdiagnose var relativt almindeligt. Dette var ikke associeret med avanceret stadie, men antidepressiva-brugere havde lavere operationsrate. På trods af højere reoperations- og genindlæggelsesrate havde brugere ikke øget etårs mortalitet efter operation.

MANUSCRIPT

Introduction

Bladder cancer is the 11th most commonly diagnosed cancer worldwide, with an age-standardized incidence rate of 12.4 per 100,000 person-years in northern Europe.[1] Recommended standard treatment for muscle-invasive and high-risk non-muscle-invasive tumors is radical cystectomy,[2] a procedure associated with 30-day complication rates between 24% and 73%.[3] Preexisting depression may be associated with higher risk of surgical complications.[4-6] This could be due to the elevated inflammatory level[7] and neuroendocrine alterations[8] seen in depression or a result of antidepressant side effects such as increased risk of bleeding.[9]

Increased risk of treatment complications may in part explain why depression diagnosed before cancer diagnosis is associated with elevated cancer-related mortality in various types of cancer.[10-16] In a recent Danish cohort study, patients with different cancers and a prescription for an antidepressant at the time of cancer diagnosis had a 30% higher one-year mortality than patients with cancer without a prescription for an antidepressant within three years before cancer diagnosis (hazard ratio 1.32; 95% CI 1.29-1.35).[17] Other mechanisms potentially explaining the elevated mortality are delay in cancer diagnosis resulting in advanced stage and lower probability of appropriate or definitive treatment. Yet, studies of delay in cancer diagnosis show conflicting results.[11,13,15,17] Prior antidepressant use was not associated with more advanced stage at cancer presentation among 5667 patients with invasive bladder cancer in the recent Danish work.[17] Although previous studies have reported a lower likelihood of appropriate treatment of patients with cancer and prior or existing depression,[10,13-16,18] this has not been investigated for bladder cancer. Altogether, little is known about the association between depression and stage at diagnosis and mortality in bladder cancer. No studies have investigated the association between depression and treatment for, or complications of, invasive bladder cancer.

As such, the aim of this nationwide population-based study was to investigate whether antidepressant use at or before invasive bladder cancer diagnosis, was associated with more advanced cancer at diagnosis or surgery, lower rate of cystectomy, a more complicated postoperative course, and higher one-year all-cause mortality.

Methods

We performed a nationwide registry based cohort study including all patients diagnosed with incident invasive bladder cancer in Denmark from 2005 through 2015. The entire Danish population, encompassing approximately 5.6 million inhabitants, has access to tax-supported healthcare, with free access to hospital-based and primary medical care provided by the Danish National Health Service.[19] At birth or upon immigration, all inhabitants in Denmark receive a unique ten-digit Civil Personal Register (CPR) number, which is recorded along with administrative and medical information in registries and databases.[20] It allows for person-specific linkage of information from multiple data sources.

Data sources

From the Danish National Patient Registry (DNPR), we retrieved diagnosis and procedure codes and their dates as well as additional administrative hospital data. The DNPR has tracked all somatic hospitalizations since 1977 and outpatient and emergency room visits to all public hospitals in Denmark since 1995. Recorded data include CPR numbers, dates of admission and discharge, and up to 20 diagnoses, classified according to the International Classification of Diseases, 8th revision (ICD-8) until 1993, and tenth revision (ICD-10) thereafter.[21] We ascertained information on tumor pathology from The Danish National Pathology Registry, which contains descriptions of pathological specimens using the Danish version of SNOMED codes from all pathology departments, yielding a coverage of almost 100%.[22] The registry was established in 1997, but data from earlier years have been added.[22] To define exposure status, we used prescription data from the Danish National Database of Reimbursed Prescriptions.[23] This registry encompasses information about all redeemed prescriptions from 2004 onwards, including date of redemption and Anatomical Therapeutic Chemical (ATC) code. All antidepressants intended for treatment of depression are subject to general reimbursement in Denmark.[24] Finally, the Danish Civil Registration System provided data on marital and vital status. This database, updated daily, contains nearly complete, demographic data, such as dates of birth and death, migration, and changes in marital status.[20]

Study population

We identified patients with incident, histologically verified invasive bladder cancer based on ICD-10 diagnosis codes (C67) and bladder cancer pathology. Date of diagnosis was defined as date of pathology requisition. To increase the probability of truly incident cases we excluded patients who fulfilled these criteria for a diagnosis of bladder cancer between 1995 and 2004. The algorithm defining the study population is provided in **supplemental table 1**.
For the surgical outcome analyses, we identified patients with bladder cancer and a recorded cystectomy. We excluded patients who received intended curative radiation therapy before cystectomy. NOMESCO Classification of Surgical Procedures codes defining radical cystectomy and intended curative radiation therapy are given in **supplemental table 1**.

Exposure

We defined individuals as exposed ('antidepressant users') if they filled two or more antidepressant prescriptions (ATC code N06A) on separate occasions in the year preceding bladder cancer diagnosis. Individuals filling one prescription or less are termed 'non-users'.

Outcome measures

We defined stage at diagnosis as muscle-invasive (pT2+) or non-muscle-invasive (pT1), and stage at cystectomy as organ confined (pT0-T2 and pN0) or non-organ confined (pT3-T4 or pN+).
Time to cystectomy was determined as the number of days from the first pathological description of muscle-invasive disease until date of surgery. We chose four months as a clinically relevant end of follow-up for this analysis.
Following surgery, we investigated outcomes expected to reflect a complicated postsurgical course: postsurgical length of stay (number of days in hospital after cystectomy), risk of treatment in an intensive care unit (ICU) within 30 days after cystectomy, acute readmission to a somatic hospital within 30 days after discharge from the primary admission, 90-day reoperation rate, and one-year all-cause mortality. We defined ICU treatment based on the procedure codes NABB (intensive care therapy) or NABE (intensive care observation), and reoperation as any invasive procedure within 90 days after cystectomy (NOMESCO Classification of Surgical Procedures codes 'K').

Covariates

Based on existing literature we included as potential confounders: age, sex, marital status at diagnosis, Charlson Comorbidity Index (CCI) score[25] (excluding bladder cancer), and any alcohol-related disorder. We determined CCI score and presence of alcohol-related disorders from ICD-10 codes in DNPR within ten years before cancer diagnosis.[26] The list of ICD-10 diagnosis codes for included comorbidities is provided in **supplemental table 2**.

Statistical methods

Patients' characteristics at bladder cancer diagnosis were summarized according to exposure groups.

We examined the association between antidepressant use and stage at diagnosis or surgery using logistic regression, adjusting for age at diagnosis (included as an unrestricted spline with four knots in the analysis of stage at diagnosis and squared in stage at surgery), sex, CCI score (0, 1-2, 3+), alcohol-related disorders (yes/no), and marital status at diagnosis (married/not married). We restricted the analysis of stage at surgery to patients without neoadjuvant chemotherapy. The algorithm to detect neoadjuvant chemotherapy in DNPR is found in **supplemental table 1**.

We performed two sensitivity analyses: 1) restricting the analysis of stage at diagnosis to patients diagnosed during 2011-2015, where the proportion of individuals with missing data was limited and 2) including the latest stage recorded before surgery if stage at surgery was missing in the analysis of stage at surgery.

In the analysis of time to surgery, we followed patients from the date on which muscle invasiveness was first detected until cystectomy, death, emigration, end of the four months of follow-up, or 11 April 2016, whichever came first. In the analysis of ICU treatment and reoperation, follow-up began at date of surgery; in the analysis of readmission, follow-up began at discharge. Follow-up for these events ended at event of interest, death, emigration, end of the 30-day or 90-day follow-up, or 11 April 2016, whichever came first.

The cumulative incidences of cystectomy and following surgery, ICU treatment, readmission, and reoperation were estimated by the Aalen-Johansen estimator, considering death—and, for the incidence of cystectomy, curative-intended radiation therapy—as competing risk. We investigated associations between antidepressant use and these outcomes using Cox proportional hazards regression models adjusting for age at diagnosis (squared), sex, CCI score (0, 1-2, 3+), alcohol-

related disorders (yes/no), and marital status at diagnosis (married/not married).
We performed multiple linear regression of log-transformed length of stay, to compute the ratio of median number of days admitted comparing antidepressant users to non-users. The regression included age (unrestricted spline, four knots), sex, CCI score (0, 1-2, 3+), alcohol-related disorders (yes/no), and marital status (married, widowed, divorced, never married).
For the mortality analysis, we followed patients from date of surgery until death, emigration, end of the one-year follow-up or 19 April 2016, whichever came first. Mortality after surgery was estimated using the Kaplan-Meier methods for exposure groups separately and compared using Cox regression adjusting as described for the other Cox regressions.
Additionally, we investigated whether neoadjuvant chemotherapy, stage at surgery (organ confined or not; missing values were replaced by the latest stage recorded before surgery), and type of surgery (open or robot assisted) mediated surgical outcome differences between exposure groups. The procedure codes for type of surgery are found in **supplemental table 1**.
For all Cox regressions, we assessed the assumption of proportional hazards by log-minus-log plots. All analyses were performed using Stata version 14 (StataCorp LP, College Station, Texas). The Danish Data Protection Agency approved the study (journal number 2014-54-0922).

Results

We identified 10,427 patients with incident invasive bladder cancer during 2005 through 2015 (**Figure 1**). In the overall cohort, 1079 (10.3%) filled at least two antidepressant prescriptions in the year preceding cancer diagnosis. In the cystectomized subgroup (n=2532), this number was 162 (6.4%). At presentation, antidepressant users were less likely to be married and had more comorbidity than non-users (**Table 1**).

Stage at diagnosis and at surgery

At diagnosis, the proportion of patients with muscle-invasive disease was 50.8% among antidepressant users and 52.1% among non-users, corresponding to an adjusted odds ratio of 0.86 (95% CI 0.74-0.99) for users (**Table 2**). This result is based on a complete case analysis of the 79% with pT stage information at diagnosis. Restricting the analysis to patients diagnosed during 2011 through 2015, where 93% had stage information, yielded an adjusted odds ratio of 0.87 (95% CI 0.71-1.05).

At surgery, a higher proportion of antidepressant users (62.2%) than non-users (56.5%) had non-organ confined disease. Comparing users to non-users, the adjusted odds ratio for non-organ confined disease was 1.16 (95% CI 0.78-1.74). Additionally adjusting for time from cancer diagnosis to surgery did not change estimates by more than 1% (results not shown). These analyses included patients with tumor-stage information at surgery (71%). Replacing missing values with the latest stage recorded before surgery increased the proportion with tumor-stage data to 97%, but the adjusted odds ratio for non-organ confined disease changed insignificantly to 1.19 (95% CI 0.84-1.69).

Time to surgery

We identified 4953 patients with bladder cancer and muscle-invasive disease at or after cancer diagnosis. The cumulative incidence of cystectomy within four months was lower for antidepressant users (15.3%; 95% CI 12.3-18.6%) than non-users (25.2%; 95% CI 23.9-26.5%). The difference remained apparent after adjustment (adjusted hazard ratio 0.74 (95% CI 0.59-0.94), comparing antidepressant users to non-users) (**Table 4**).

Surgical outcomes

Table 5 presents unadjusted and adjusted estimates of associations between antidepressant use and surgical outcomes for the 2532 cystectomized patients.

Median length of postsurgical stay did not differ between antidepressant users and non-users.

Of all patients treated in an intensive care unit (ICU) within 30 days postoperatively (n=789, 31.2%), most (n=687, 87.1%) were admitted on the day of surgery. We found no difference in 30-day rate of ICU treatment between antidepressant users and non-users after adjustment.

With a cumulative incidence of 41.1% (95% CI 33.2-48.8%), antidepressant users were more likely to be acutely readmitted to a somatic hospital within 30 days after discharge from the primary admission, compared to non-users. The adjusted 30-day readmission hazard ratio was 1.33 (95% CI 1.05-1.67). We observed no substantial difference in the distribution of type of department for readmission between antidepressant users and non-users (results not shown). The primary diagnoses related to readmission were also similar among exposure groups and largely reflected postoperative complications (results not shown).

Antidepressant users' cumulative incidence of 90-day reoperation was 44.4% (95% CI 36.7-51.9%)

compared with 38.3% (95% CI 31.4-35.3%) among non-users. After adjustment, the hazard ratio for 90-day reoperation was 1.18 (95% CI 0.93-1.51) comparing users to non-users. The reoperation types were comparable among antidepressant users and non-users and mainly represented procedures related to the cystectomy or its complications (results not shown).
Overall one-year all-cause mortality after surgery was 14.5% (95% CI 13.1-15.9%) with no observed difference between antidepressant users and non-users (adjusted hazard ratio 0.94 (95% CI 0.61-1.43)).
Estimates did not change by more than 5% when we repeated all surgical outcome analyses additionally adjusting for neoadjuvant chemotherapy, stage at cystectomy, or type of surgery (**Supplemental table 3**).

Discussion

In this nationwide population-based cohort study, we found that patients with bladder cancer who filled at least two antidepressant prescriptions in the year before cancer diagnosis did not present with more advanced cancer when taking potential confounders into account. However, users had a lower rate of cystectomy in case of muscle-invasive disease. At surgery, users may have had a more advanced stage of disease. Following surgery, antidepressant users' length of stay was no longer and rate of ICU treatment no higher than that of non-users. The 90-day reoperation rate was nearly 20% higher among users, but the precision of this estimate was low. Users had higher rate of 30-day readmission, but their one-year all-cause mortality following surgery was not different from non-users. The observed differences did not appear to be mediated by differences in neoadjuvant chemotherapy, stage at or before surgery, or type of surgery.

Our finding of lower odds of muscle-invasive disease at presentation among antidepressant users is unexpected since depression has been associated with more advanced stage at cancer presentation.[13,15,17] A possible explanation for the result is an enhanced likelihood of cancer detection due to increased utilization of health care—including primary care—by depressed patients.[27] In addition, physicians may have a lower threshold for suspecting bladder cancer in depressed individuals because of their high smoking rate.[28] Study setting could be another explanatory factor: most Danish health care services are tax-funded providing free access to both primary and secondary care,[19] which minimizes the risk of patient delay in cancer diagnosis due to patients' financial situation or constraints.

At surgery, antidepressant users had an almost 20% higher odds of non-organ confined disease than non-users. We found no indication that time to surgery affected this difference. Still, we cannot rule out that the result is influenced by disparities in selection of antidepressant users and non-users for surgery. Additionally, the estimate is imprecise, limiting interpretation.

In accordance with previous studies of cancer patients with depression diagnosed before cancer diagnosis,[10,13-16,18] we observed a lower rate of cancer treatment among antidepressant users. Patient-related factors associated with decline of curative cancer treatment are: fear of surgery,[29] perceived low quality of communication between patient and physician,[30] concern about side effects,[31] and expected low quality of life after surgery.[30] These factors may be exaggerated in patients using antidepressants. We must emphasize, however, that we lacked information on clinical features contributing to treatment decision (such as renal function and performance status) that potentially differed between antidepressant users and non-users.

Higher readmission and reoperation rates among antidepressant users may suggest a more complicated postsurgical course, while the lack of difference in ICU treatment and length of stay speaks against any major difference. The antidepressant treatment may have contributed to surgical complications since selective serotonin re-uptake inhibitors increase the risk of bleeding[9]. In prior studies, surgical patients with depressive symptoms had impaired wound healing and higher risk of infections.[5,32,33] Our results are consistent with these findings, if antidepressant users had depressive symptoms at the time of surgery. Perhaps differences in development of postsurgical complications were not evident during the primary admission, explaining similarities in length of stay, and complications might not have impaired recovery to an extent that required ICU treatment.

We did not observe an association between antidepressant use and one-year all-cause mortality following cystectomy. Contrary to previous research, we investigated survival only in the subgroup of patients undergoing surgery—not among all patients diagnosed with bladder cancer. By this restriction, we eliminated receipt of treatment as a mediator of the potential effect of depression on survival. Nonetheless, differences in surgeons' selection of patients for cystectomy could have influenced our result if antidepressant users were selected more strictly than non-users. Another aspect to consider is severity of depression: generally, antidepressant users were probably less severely depressed than individuals included in earlier studies based on secondary psychiatric care data.[11,12] Finally, mortality might have been related to conditions other than depression in previous studies that were not able to control for differences in comorbidities other than depression.[10,11]

The study results must be interpreted bearing in mind a number of limitations. We lacked information on antidepressants administered to patients during their hospitalization. Yet, we do not expect this to affect results greatly due to the short mean admission time in the year preceding cancer diagnosis.

Our analyses did not take into account indications for acute readmission and reoperation, or cause of death. However, we only observed minor differences between antidepressant users and non-users in reoperation and readmission types. Furthermore, for both groups, most reoperation codes and diagnosis codes appeared to reflect complications related to cystectomy.

We were able to account for some potential confounders, but we lacked information on detailed clinical factors such as serum creatinine and presence of distant metastases as well as life style factors such as smoking and socioeconomic status (SES). However, we partially accounted for smoking and SES by including age, comorbidities, and marital status. The analysis of time to surgery was restricted to patients with muscle-invasive disease, but we cannot rule out the possibility that antidepressant users and non-users differed with regard to lymph node status and/or distant metastases. In an earlier study, smokers were more likely to present with muscle-invasive bladder cancer at diagnosis.[34] Accordingly, smoking probably did not explain our finding of less advanced stage at presentation among antidepressant users. In contrast, smoking is related to postsurgical complications in cancer patients,[35,36] and may in part confound our findings of readmission and reoperation. In one study, no clear association between SES and radical cystectomy was found[37] suggesting that SES is not a strong confounder in our analysis of time to surgery. Low SES has been associated with higher risk of complications,[38] but lower risk of readmission[39] after radical cystectomy, so the potential effects of including this factor in our analyses of readmission and reoperation are not clear. Further, in some analyses (length of stay, ICU treatment, readmission, and reoperation) estimates changed very little upon adjustment, leading us to believe that inclusion of unmeasured confounders would change results only minimally.

We defined exposure as redemption of two or more antidepressant prescriptions in the year before cancer diagnosis. This definition reduces the risk of misclassification due to non-compliance, which we expect to be higher among individuals filling just one prescription. Additionally, with typical package sizes, patients would need to fill more than one antidepressant prescription when treated according to guidelines for a single episode of depression or for anxiety.[40,41]

By using registry data, the current study did not rely on self-report of exposure and achieved

essentially complete follow-up. The prescription information is assumed to be highly valid since data are collected automatically when pharmacists scan bar codes on dispensed medication packages.[23] Additional strengths are the lack of selection of included patients and that the algorithms to define study population, intended curative radiation therapy, and neoadjuvant chemotherapy have been validated previously.[42]

We investigated associations between antidepressant use and stage of disease at bladder cancer diagnosis, time to cystectomy and surgical outcomes in a nationwide population-based study based on Danish registry data. Antidepressant use was associated with less advanced stage of bladder cancer at diagnosis, lower rate of cystectomy, and perhaps more advanced stage at surgery. After surgery, antidepressant users had higher rate of readmission and, potentially, reoperation, but not prolonged length of stay, higher risk of ICU treatment, or one-year all-cause mortality. Our findings stress the importance of considering mental health status in the diagnosis and treatment of somatic disease.

SUPPLEMENTARY

Background

Bladder cancer

Bladder tumors are pathologically categorized according to depth of invasion as Tis (carcinoma in situ), Ta (non-invasive), T1-4 (invasive).[43] At diagnosis, about half of all tumors are invasive; of these, about half are muscle-invasive (T2-T4).[44] During the study period, 800-1,000 patients were diagnosed with invasive bladder cancer yearly in Denmark.[45,46] One- and five-year survival was approximately 70% and 35%, respectively.[47] Pathologic tumor-stage (T-stage) is the most important prognostic factor for survival; others are pathologic grade, the presence or absence of lymph node metastases or distant metastases, age, and comorbidity.[37]

The preferred treatment for patients with muscle-invasive bladder cancer is cystectomy if patients are free of multiple lymph node metastases or distant metastases and their performance status allows for surgery. A delay in cystectomy beyond three months is associated with poorer prognosis.[48,49] In men, radical cystectomy includes removal of the prostate and seminal vesicles in addition to the urinary bladder and regional lymph nodes, while in women removal of the uterus, cervix, ovaries, and parts of the vagina may be necessary.[43] A new urinary diversion—non-continent (ileal conduit) or continent (continent pouch or orthotopic neobladder)—is made from a bowel segment.[43] Common complications within 90 days after cystectomy are infectious (e.g. intra-abdominal abscess, sepsis, or wound infection), gastrointestinal (e.g. ileus), and genitourinary (e.g. urine leak).[50,51] Factors reported to affect the risk of complications are numerous, including: age, sex, comorbidity, smoking, receipt of neoadjuvant chemotherapy, experience of the surgeon, hospital volume, type of diversion, and intraoperative transfusion.[3,52]

Antidepressants

Antidepressants comprise various classes of drugs such as selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and tricyclic antidepressants. In general, antidepressants affect neurotransmitter signaling by elevating synaptic concentrations of serotonin and/or norepinephrine.[53]

Indications for antidepressants include depression, anxiety, neuropathic pain, social anxiety disorder, obsessive-compulsive disorder, bulimia, and post-traumatic stress disorder.[53] In the Netherlands during 1996-2012, antidepressants were increasingly prescribed for neuropathic pain,

anxiety, and sleeping disorders while depression-related indications decreased to 47% of prescriptions in 2012.[54] The overall use of antidepressants increased by a mean of 40 DDD/1000/day across Europe in the period 1980-2009.[55]

Antidepressant use is related to increasing age,[56] smoking,[57] poorer health,[57,58] physical impairment,[57,58] low educational level,[56] unemployment,[56,59] and low income.[56,57] As such, compared with the general population, antidepressant users on average carry a larger burden of unfavorable characteristics likely to worsen the course of somatic disease.

Methodological considerations

Study design

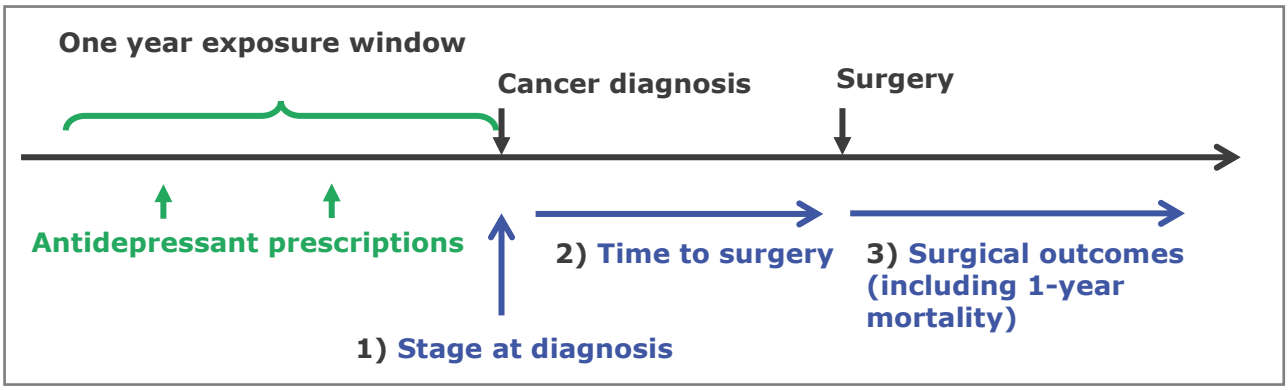
We conducted a cohort study using prospectively collected registry data to answer our research questions. Cohort studies are observational and include two or more groups of individuals defined by differences in exposure. Individuals are followed in time to investigate if the incidence of one or more events of interest differ by exposure groups.[60]

Another epidemiological design is the case-control design in which the study population is selected based on a certain outcome—cases have the outcome and controls, representing the population that gives rise to the cases, can be sampled by different techniques. One then compares the exposure in question between cases and controls.[60] This gives relative measures of association, but not directly absolute estimates, which instead are obtainable in cohort studies.[60] In some case-control studies, exposure data are recorded after the outcome occurred, which increases the risk of recall bias. This is not an issue in cohort studies, where data are recorded prospectively. Finally, the cohort design presents advantages compared to traditional case-control studies when (as in our case) many outcomes are of interest.

Neither the cohort nor the case-control design can exclude the risk of confounding. This is the advantage of the randomized controlled trial design: it randomizes study participants aiming for an even distribution of known and unknown confounders in each intervention group.[60] The goal is to compare groups that differ only by the exposure of interest. If we were to conduct a randomized controlled trial, we should have randomly assigned study participants to receive antidepressants or not, follow them in time to detect development of invasive bladder cancer, and then measure outcomes. This would be both virtually impossible, unethical, and very costly and time consuming.

Definition of exposure

We defined exposure as redemption of two or more antidepressant prescriptions in the year before cancer diagnosis (**Supplemental figure 1**).



Supplemental figure 1 Overview of exposure definition and study questions.

According to recommendations, a single episode of mild (ICD-10: F32.0) and in some cases moderate (ICD-10: F32.1) depression should not be medically treated.[41] In a Danish study of individuals suffering from depression according to the Major Depression Inventory, the proportion of patients using antidepressants were: 22.3% of mildly depressed, 29.8% of moderately depressed, and 50.0% of severely depressed (ICD-10: F32.3).[61] This implies that our cohort of antidepressant users is not representative of all depressed patients, but undersamples mildly depressed.

Time-to-event analysis and competing risk

We performed time-to-event analyses to compare rates of surgery and surgical outcomes. Two assumptions behind the analyses are briefly described in the following.

All time-to-event analyses assume independent censoring. In many follow up studies, some study participants are not followed until the event of interest occur—they are censored. When censoring is independent, the probability of being censored is not related to the risk of the event occurring.[62] For example, there would be dependent censoring in the analysis of time to surgery, if those censored were more comorbid and therefore at a lower risk of surgery compared with those remaining under observation. The assumption of independent censoring is modified when applying Cox regressions. Within the model, one assumes independent censoring conditional on the covariates.[63] Therefore, if participants are dependently censored due to differences in age, including age—sufficiently—in the model fulfills the assumption.

The second assumption, applied when using a Cox regression model, is the proportional hazards assumption—that is, the ratios of the instantaneous risks for study groups defined by the model parameters remain constant over the follow up period.[62] For example, if we study rate of death in antidepressant users and non-exposed adjusting for sex, we can form four groups by exposure status and sex. The risk of dying must be proportional between all groups at all times.

In some follow up analyses, the occurrence of an event influences the risk of another event. In our case, when studying the rate of surgery, patients who die without being cystectomized are no longer 'at risk' of surgery and death is a competing event. Survival analysis using the Kaplan-Meier estimator would treat those who died as independently censored,[64] but this is not true, because their probability of cystectomy is zero. The Aalen-Johansen estimator, in contrast, appropriately determines the cumulative incidence of an event in a situation with competing risk(s).[64] Since the parameters in Cox regression models are hazard rate ratios (and the hazard rate is the probability of event within a short time period given the individual is at risk at the beginning of that period), Cox regressions are applicable in the presence of competing risk(s).[64]

Missing values

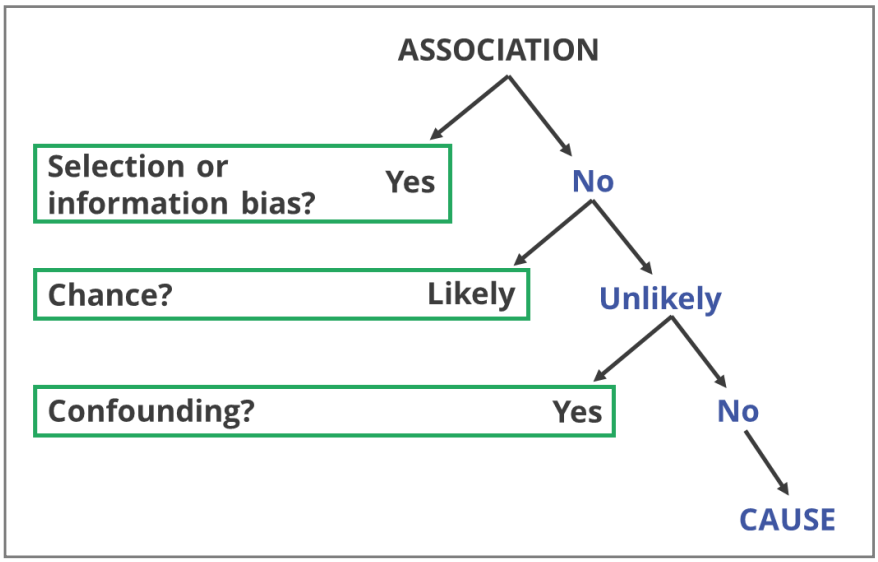
We lacked information on stage of disease at diagnosis and at cystectomy for 21% and 29% of the study population, respectively. The situation where some values are missing for a given variable can be characterized according to what the probability of values being missing depends on: if the probability is independent of observed and unobserved data, values are missing completely at random; if it depends on observed data only, values are missing at random; if it depends on unobserved data, values are missing not at random.[65] In our case, we found associations between missingness and observed values (see "missing value analysis"), leading us to believe that the stage data are missing at random or not at random.

Multiple imputation is a statistical technique that handles missing values under the assumption of data being missing at random or completely at random. In the process, a number of new datasets are generated in which missing observations are replaced by simulated values.[65] Each imputed dataset is analyzed separately and resulting estimates are combined into an overall estimate. However, when an outcome variable is the only variable with missing information (as in our case), multiple imputation presents no additional benefit over complete case analysis.[66] Therefore, we did not choose this method to handle the issue of missing data. Instead, we limited the analysis of stage at diagnosis to 2011 through 2015 assuming that the subgroup of patients diagnosed in this period was

a representative sample of the overall study population. For the analysis of stage at cystectomy, we included stage data recorded before surgery. Typically, these data originate from pathological examinations of specimens from transurethral resections. These specimens differ from surgical specimens in that the former cannot be used to assess lymph node status or distinguish T3+ from T2 tumors. As such, including prior records does not provide an entirely valid picture of tumor-stage at surgery. However, assuming comparable stage assessment procedures between antidepressant users and non-users, the analysis does to some extent estimate the association between antidepressant use and tumor invasiveness at surgery.

Additional strengths and limitations

The results presented in this report are observed associations subject to both random and systematic error. An observed association can be said to represent a causal relationship only if both errors are eliminated (**Supplemental figure 2**).



Supplemental figure 2 An association does not imply cause, if selection or information bias, chance (random error), or confounding influence study results. Adapted from Fletcher, Fletcher, and Fletcher (2014).[67]

Random error (chance in supplemental figure 2) is variability in the data that becomes less influential as the study size increases.[60] The confidence interval reflects the extent of random error of an estimate: a wide confidence interval indicates a large amount of random error and vice versa.[60] For example: the analysis of stage at diagnosis included more patients (n=8252) and the adjusted estimate had a more narrow confidence interval (0.74-0.99) than the analysis of stage at

cystectomy (n=1632 and confidence interval 0.78-1.74).

Traditionally, systematic error is classified as selection bias, information bias or confounding, together determinants of a study's internal validity. In the following, these terms will be explained in relation to the present work.

Selection bias

Bias can be introduced through selection of study participants at the level of entry into study or loss to follow up,[60] if the association between exposure and outcome differs between study participants and non-participants.[60] The complete case analysis of stage at diagnosis is a selective procedure (leaving out individuals with missing data) that could result in bias if antidepressant users with muscle-invasive disease were overrepresented among those with missing data.

Selection bias caused by loss to follow up is an almost non-existing issue in this study due to the Civil Registration System's level of completeness.[20]

Information bias

Another potential source of systematic error is information bias, which may be present when study participant's information on variables (exposures, covariates, or outcomes) is erroneous (misclassified).[60] The misclassification of a variable is non-differential, if it is unrelated to other study variables. Non-differential misclassification of a dichotomous exposure often bias estimates towards no association.[68] In contrast, misclassification is differential if the misclassification of a variable is related to values of other variables.

Non-compliance to the antidepressant treatment is a potential cause of misclassification in our study. We expect this source of information bias to be limited because: 1) filling a second prescription suggests that patients used up the first package and 2) the patient covers part of medication expenses indicating intention to use. Hypothetically, if noncompliant antidepressant users have higher mortality than compliant users, our result in the one-year all-cause mortality analysis would be an overestimate. But, as stated, we believe non-compliance to be a minor issue. On the other hand, 162 individuals classified as non-users filled a single prescription in the year before cancer diagnosis, and a number of non-users may have used antidepressants dispensed before that year. So it is likely that some in the non-user group used antidepressants. But, as described above, we intended to study patients taking antidepressants for a longer period of time, who were compliant, and who most likely had indications for antidepressant use. Also, including the 162 'one-time-redeemers' did not change estimates greatly (see *Sensitivity analyses* below).

Confounding

Confounding is a bias that occurs if, in the study of an exposure-outcome association, a third factor drives the association (or lack hereof). To do so, the confounder must be associated with the exposure *and* influence the presence or absence of outcome while not being an effect of the exposure.[60] An example in our setting is comorbidity: comorbidity increases the risk of developing a depression[53] and in severe cases contraindicates surgery.[2] Thus, if comorbidity is not taken into account, an association between antidepressant use and lower rate of surgery might be confounded by comorbidity. We included comorbidity using the Charlson Comorbidity Index (CCI) and diagnoses of alcohol-related disorders to avoid confounding, but there is still a risk of residual confounding due to diseases not considered.

In pharmacoepidemiological studies, confounding by indication is often an issue. When observing a drug-outcome association, the indication for the drug in question might cause the outcome without any effect of the drug itself—the disorder indicating drug use confounds the studied relationship.[60] In this study, we did not aim for an investigation of the sole 'pharmacological' effect of antidepressants. Instead, we wanted to study the subgroup of bladder cancer patients who used antidepressants and investigate if they experienced differences in diagnosis and treatment. As such, we were interested in both direct drug effects and effects of factors associated with antidepressant use such as indications. Therefore, confounding by indication is not a limitation in our study.

Sensitivity analyses

We performed a sensitivity analysis using a rule-out approach[69] to assess the extent of confounding by smoking needed to fully account for the observed associations in the analyses of readmission and reoperation. Assuming a 40% prevalence of smoking and the odds of smoking twice as high among antidepressant users as in non-users, smoking would have to increase the relative risk of readmission by 8.5 to fully explain the association between antidepressant use and readmission and the relative risk of reoperation by 2.5 to fully explain the association between antidepressant use and reoperation. Considering these high risks, smoking alone is unlikely to cause the observed associations, but it could in part confound them.

As additional sensitivity analyses, we repeated all analyses defining exposure as redemption of at least one antidepressant prescription in the year before bladder cancer diagnosis. In the study population, 11.9% filled at least one antidepressant prescription in the year prior to diagnosis of

invasive bladder cancer. This group of 'at least one prescription' antidepressant users had similar baseline characteristics as the antidepressant users in the main analyses (data not shown). Using the new definition of exposure, we observed comparable, but attenuated estimates compared to the original 'at least two prescriptions' definition (**Supplemental tables 4-7**). This points to the potential influence of the duration of antidepressant use.

Additionally, we examined the stage distribution at diagnosis using yet another, more restricted definition of exposure: redemption of at least two antidepressant prescriptions in the year preceding cancer diagnosis *and* at least one diagnosis of depression within five years before cancer diagnosis. We retrieved depression diagnoses (ICD-10: F32 and F33) from the Danish National Patient Registry, which contain information on in- and outpatient psychiatric hospital contacts from 1995 onwards.[21] In the analysis, variables were modeled as described for the analysis of stage at cystectomy in the main text. This definition did not lead to any difference in stage distribution between antidepressant users with a depression diagnosis and non-exposed (data not shown).

Additional results

Description of redeemed antidepressants

Among antidepressant users, the ten most commonly prescribed antidepressants accounted for 95% of all prescriptions filled (**Supplemental table 8**). Citalopram and mirtazapine alone accounted for 55% of all prescriptions. Of antidepressant users, 9% and 7% solely filled prescriptions for tricyclic antidepressants and serotonin–norepinephrine reuptake inhibitors, respectively.

Individuals with missing values

Among the 2175 individuals with missing stage at diagnosis, 219 (10.1%) were antidepressant users. Of all patints with missing stage, 827 (38.0%) had a stage recorded at a later point in time. Of these, 444 (53.7%) had muscle-invasive disease (T2+) in that recording. Among the 62 antidepressant users with a later recording of stage, 32 (51.6%) were staged T2+.

Additional discussion and perspectives

The inspection of individuals with missing stage information did not indicate selection to cause bias in the analysis of stage at diagnosis, since antidepressant use was not associated with missing stage

and T2+ was not greatly overrepresented among those with a later stage recorded or among antidepressant users with a later stage.

Although antidepressants in many cases are prescribed for depression,[54] some antidepressant users probably had other indications. Tricyclic antidepressants and serotonin–norepinephrine reuptake inhibitors are among first line choices for treatment of neuropathic pain.[70] Our inspection of redeemed drug types suggests that only few antidepressant users had this indication. In a Danish setting, two studies examined the association between antidepressant use and prevalent depression. Thielen et al.[71] report a specificity of antidepressant prescription registry data for a prevalent depression of 94-97%, while Ellervik et al.[61] found a specificity of self-reported antidepressant use for current depression of 95%. These results suggest that a substantial proportion of antidepressant users received medication for depression. However, to investigate the role of psychiatric disorders further, information on the indications for antidepressants are needed. Due to a limited number of individuals with a prior psychiatric diagnosis, we were only able to include earlier depression diagnoses in the analysis of stage at presentation. The observed no difference in odds of muscle-invasive disease is potentially explained by a combination of increased health care utilization (leading to earlier diagnosis) and more severe depression (resulting in patient delay) by patients with a prior depression diagnosis.

To investigate antidepressant drug effects in greater detail, dose-response correlations could be explored by quantifying antidepressant exposure (using DDD and redemption dates). Data from the Danish Transfusion Database would allow one to study associations between antidepressant use and blood transfusions, if antidepressant side effects, such as the risk of postoperative bleeding, were of special interest. It would also be interesting to further investigate determinants of cystectomy. This requires additional information on patient and/or physician related factors. If antidepressant users have more postsurgical complications, and this is confirmed in other studies, our results form the basis for intervention studies aimed at preventing complications in antidepressant users.

Altogether, this study suggests that patients with bladder cancer using antidepressants before diagnosis may be a subgroup worth special attention—especially in relation to receipt of treatment and postsurgical course. Our findings raise the possibility that antidepressant users do not receive appropriate treatment implying that treatment choice for a substantial proportion of bladder cancer patients perhaps should be revised. Following surgery, our findings point to the importance of differentiated clinical care according to individual needs.

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TABLES AND FIGURE

Table 1 Characteristics at diagnosis for patients with incident invasive bladder cancer (n=10,427) during 2005 through 2015 according to use of antidepressants before cancer diagnosis.

	Non-users		AD users	
	n	%	n	%
Total	9348	89.7	1079	10.3
Median age (IQR) (years)	72.5	66.0-79.8	74.4	67.8-82.3
Age group (years)				
18-49	224	2.4	22	2.0
50-59	814	8.7	85	7.9
60-69	2554	27.3	235	21.8
70-79	3475	37.2	378	35.0
80-	2281	24.4	3539	33.3
Sex				
Male	7036	75.3	647	60.0
Female	2312	24.7	432	40.0
Marital status				
Married	5549	59.4	532	49.3
Widowed	1836	19.6	320	29.7
Divorced	1233	13.2	145	13.4
Never married	730	7.8	82	7.6
Charlson Comorbidity Index score				
Low (0)	4703	50.3	334	31.0
Medium (1-2)	3124	33.4	437	40.5
High (3+)	1521	16.3	308	28.5
Mean number of days spent in hospital in the year before diagnosis (SD)	4.9	9.6	7.8	14.3
Alcohol-related disorders	191	2.0	68	6.3
Year of cancer diagnosis				
2005-2007	2563	27.4	271	25.1
2008-2010	2555	27.3	283	26.2
2011-2013	2527	27.0	314	29.1
2014-2015	1703	18.2	211	19.6
Intended curative radiation therapy	1145	12.3	114	10.6

AD users: filled at least two antidepressant prescriptions in the year before bladder cancer diagnosis.
Non-users: filled no, or one, antidepressant prescription in the year before bladder cancer diagnosis.
IQR: interquartile range. SD: standard deviation.

Table 2 Odds ratios for muscle-invasive bladder cancer at diagnosis comparing antidepressant users to non-users. Results of complete case analysis (2005-2015) and when restricting the analysis to 2011 through 2015.

	Complete case analysis						2011-2015	
	Muscle-invasive (pT2+)		Non-muscle-invasive (pT1)		Unadjusted odds ratio (95% CI)	Adjusted* odds ratio (95% CI)	Unadjusted odds ratio (95% CI)	Adjusted* odds ratio (95% CI)
	n	%	n	%				
Non-users (n=7392)	3854	52.1	3538	47.9	Ref.	Ref.	Ref.	Ref.
AD users (n=860)	437	50.8	423	49.2	0.95 (0.82-1.09)	0.86 (0.74-0.99)	0.96 (0.79-1.16)	0.86 (0.71-1.05)

AD users: filled at least two antidepressant prescriptions in the year before bladder cancer diagnosis.
Non-users: filled no, or one, antidepressant prescription in the year before bladder cancer diagnosis.
CI: confidence interval.
*Adjusted for age, sex, CCI, alcohol-related disorders, and marital status.

Table 3 Odds ratios for non-organ confined bladder cancer at cystectomy comparing antidepressant users to non-users. Results of complete case analysis and when replacing missing values for cancer stage with the latest stage observed before surgery.

	Complete case analysis						Including prior stages	
	Non-organ confined (pT3-T4 or pN+)		Organ confined (pT0-T2 and pN0)		Unadjusted odds ratio (95% CI)	Adjusted* odds ratio (95% CI)	Unadjusted odds ratio (95% CI)	Adjusted* odds ratio (95% CI)
	n	%	n	%				
Non-users (n=1521)	859	56.5	662	43.5	Ref.	Ref.	Ref.	Ref.
AD users (n=111)	69	62.2	42	37.8	1.27 (0.85-1.88)	1.16 (0.78-1.74)	1.29 (0.92-1.81)	1.19 (0.84-1.69)

AD users: filled at least two antidepressant prescriptions in the year before bladder cancer diagnosis.
Non-users: filled no, or one, antidepressant prescription in the year before bladder cancer diagnosis.
CI: confidence interval.
*Adjusted for age, sex, CCI, alcohol-related disorders, and marital status.

Table 4 Cumulative incidence and hazard ratio of cystectomy within four months from the first time muscle-invasive disease was detected comparing antidepressant users to non-users.

	Cystectomized, n	Four months cumulative incidence, % (95% CI)	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Non-users (n=4443)	1120	25.2 (23.9-26.5)	Ref.	Ref.
AD users (n=510)	78	15.3 (12.3-18.6)	0.60 (0.47-0.75)	0.74 (0.59-0.94)

AD users: filled at least two antidepressant prescriptions in the year before bladder cancer diagnosis.
Non-users: filled no, or one, antidepressant prescription in the year before bladder cancer diagnosis.
HR: hazard ratio. CI: confidence interval.
*Adjusted for age, sex, CCI, alcohol-related disorders, and marital status.

Table 5 Surgical outcomes by antidepressant use before cancer diagnosis: length of stay, 30-day ICU treatment, 30-day acute readmission, 90-day reoperation, and one-year all-cause mortality after cystectomy. The analysis of acute readmission excludes patients with a primary admission longer than 30 days (n=140).

Surgical outcome	Non-users	AD users
Length of stay		
Days admitted, median (IQR)	10 (7-13)	9 (8-13)
Unadjusted ratio of median duration (95% CI)	Ref.	1.03 (0.95-1.13)
Adjusted* ratio of median duration (95% CI)	Ref.	1.02 (0.93-1.12)
30-day ICU treatment		
Total, n	2370	162
Admitted, n	742	47
Cumulative incidence, % (95% CI)	31.3 (29.5-33.2)	28.4 (21.6-35.6)
Unadjusted HR (95% CI)	Ref.	0.92 (0.69-1.24)
Adjusted* HR (95% CI)	Ref.	0.94 (0.70-1.27)
30-day acute readmission		
Total, n	2241	151
Readmitted, n	747	62
Cumulative incidence, % (95% CI)	33.4 (31.4-35.3)	41.1 (33.2-48.8)
Unadjusted HR (95% CI)	Ref.	1.36 (1.08-1.71)
Adjusted* HR (95% CI)	Ref.	1.33 (1.05-1.67)
90-day reoperation		
Total, n	2370	162
Reoperated, n	908	72
Cumulative incidence, % (95% CI)	38.3 (36.4-40.3)	44.4 (36.7-51.9)
Unadjusted HR (95% CI)	Ref.	1.19 (0.93-1.51)
Adjusted* HR (95% CI)	Ref.	1.18 (0.93-1.51)
One-year all-cause mortality		
Total, n	2370	162
Deaths, n	330	24
Cumulative incidence, % (95% CI)	14.4 (13.1-16.0)	15.0 (10.3-21.6)
Unadjusted HR (95% CI)	Ref.	1.05 (0.69-1.58)
Adjusted* HR (95% CI)	Ref.	0.96 (0.63-1.46)

AD users: filled at least two antidepressant prescriptions in the year before bladder cancer diagnosis. Non-users: filled no, or one, antidepressant prescription in the year before bladder cancer diagnosis. IQR: interquartile range. ICU: intensive care unit. CI: confidence interval. HR: hazard ratio. *Adjusted for age, sex, CCI, alcohol-related disorders, and marital status.

Supplemental table 1 Algorithm to define invasive bladder cancer based on pathology and diagnosis codes; Health Care Classification System procedure codes to identify cystectomies; algorithm to define intended curative radiation therapy; algorithm to define neoadjuvant chemotherapy.

Invasive bladder cancer	**SNOMED codes in description of pathological specimen**		**ICD-10 diagnosis codes**	
	Topography: Urinary bladder *and* Malignant tumor	T74 M80xx3-M84xx3	Malignant neoplasm of bladder *excluding* Malignant neoplasm of urachus Malignant neoplasm of urachus with metastases Locally recurrent malignant neoplasm of urinary bladder	C67 C67.7 C67.7M C67.9X
	SNOMED codes must co-occur in the same pathological description and be dated within 365 days before, or 90 days after, a hospital contact with C67. Date of diagnosis is the first date of pathology in this window.			
Cystectomy			**Procedure codes**	
	Open cystectomies		KKCC00, KKCC10, KKCC20, KKCC30, KKCC96	
	Robot assisted cystectomies		KKCC01, KKCC11, KKCC21, KKCC31, KKCC97, KZXX00	
Intended curative radiation therapy	**Treatment code**		**ICD-10 diagnosis codes**	
	External radiation therapy	BWGC	Malignant neoplasm of bladder	C67
	At least 15 radiation treatments with C67 as indication at one of the five treatment centers in Denmark. The BWCG codes must not be preceded by a cystectomy.			
Neoadjuvant chemotherapy	**Treatment code**			
	Cytostatic treatment	BWHA		
	One to eight cytostatic treatments within 24 weeks. The last treatment must be succeeded by a cystectomy within 12 weeks.			

Supplemental table 2 ICD-10 codes defining Charlson Comorbidity Index (CCI) diseases and alcohol-related disorders.

CCI disease category	Score	ICD-10 code
Myocardial infarction	1	I21-23
Congestive heart failure	1	I50, I11.0, I13.0, I13.2
Peripheral vascular disease	1	I70-74, I77
Cerebrovascular disease	1	I60-69, G45-46
Dementia	1	F00-03, F05.1, G30
Chronic pulmonary disease	1	J40-47, J60-67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2-3
Connective tissue disease	1	M05-06, M08-09, M30-36, D86
Ulcer disease	1	K22.1, K25-28
Mild liver disease	1	B18, K70.0-70.3, K70.9, K71, K73-74, K76.0
Diabetes mellitus	1	E10.0-10.1, E10.9, E11.0-11.1, E11.9
Hemiplegia	2	G81-82
Moderate to severe renal disease	2	I12-13, N00-05, N07, N11, N14, N17-19, Q61
Diabetes with end organ damage	2	E10.2-8, E11.2-11.8
Any tumor	2	C00-26, C30-41, C43-58, C60-66, C68-75
Leukemia	2	C91-95
Lymphoma	2	C81-85, C88, C90, C96
Moderate to severe liver disease	3	B15.0, B16.0, B16.2, 19.0, K70.4, K72, K76.6, I85
Metastatic solid tumor	6	C76-80
AIDS	6	B20-24

	ICD-10 code
Alcohol-related disorders	F10.1-10.9, G31.2, G62.1, G72.1, I42.6, K29.2, K86.0, Z72.1

AIDS: acquired immune deficiency syndrome.
ICD-10: International Classification of Diseases, Tenth Revision.

Supplemental table 3 Surgical outcomes by antidepressant use with additional adjustment for neoadjuvant chemotherapy, stage of cancer at cystectomy, and type of surgery.

Surgical outcome	Non-users	AD users
Length of stay, ratio of median duration (95% CI)		
Model 1	Ref.	1.02 (0.93-1.12)
Model 2	Ref.	1.02 (0.93-1.11)
Model 3	Ref.	1.01 (0.92-1.10)
Model 4	Ref.	1.01 (0.92-1.10)
30-day ICU treatment, HR (95% CI)		
Model 1	Ref.	0.94 (0.70-1.27)
Model 2	Ref.	0.94 (0.70-1.27)
Model 3	Ref.	0.90 (0.66-1.22)
Model 4	Ref.	0.93 (0.69-1.25)
30-day acute readmission, HR (95% CI)		
Model 1	Ref.	1.33 (1.05-1.67)
Model 2	Ref.	1.28 (0.99-1.67)
Model 3	Ref.	1.33 (1.02-1.74)
Model 4	Ref.	1.30 (1.00-1.69)
90-day reoperation, HR (95% CI)		
Model 1	Ref.	1.18 (0.93-1.51)
Model 2	Ref.	1.18 (0.93-1.51)
Model 3	Ref.	1.18 (0.92-1.51)
Model 4	Ref.	1.19 (0.93-1.52)
One-year all-cause mortality, HR (95% CI)		
Model 1	Ref.	0.96 (0.63-1.46)
Model 2	Ref.	0.96 (0.63-1.47)
Model 3	Ref.	0.91 (0.59-1.39)
Model 4	Ref.	0.94 (0.62-1.44)

AD users: filled at least two antidepressant prescriptions in the year before bladder cancer diagnosis.
Non-users: Filled no, or one, antidepressant prescription in the year before bladder cancer diagnosis.
ICU: intensive care unit. CI: confidence interval. HR: hazard ratio.
Model 1: adjusted for age, sex, CCI, alcohol-related disorders, and marital status.
Model 2: as model 1 + receipt of neoadjuvant chemotherapy.
Model 3: as model 1 + stage at surgery (non-organ confined/organ-confined).
Model 4: as model 1 + type of surgery (open/robot assisted).

Supplemental table 4 Odds ratio for muscle-invasive bladder cancer at diagnosis. One-prescription users filled at least one antidepressant prescription in the year before cancer diagnosis, while non-users did not. Results of complete case analysis and when restricting the analysis to 2011-2015.

	Complete case analysis						2011-2015	
	Muscle-invasive (pT2+)		Non-muscle-invasive (pT1)		Unadjusted odds ratio (95% CI)	Adjusted* odds ratio (95% CI)	Unadjusted odds ratio (95% CI)	Adjusted* odds ratio (95% CI)
	n	%	n	%				
Non-users (n=8120)	3783	52.0	3486	48.0	Ref.	Ref.	Ref.	Ref.
One-prescription users (n=132)	508	51.7	457	48.3	0.99 (0.86-1.13)	0.90 (0.78-1.03)	0.99 (0.83-1.18)	0.90 (0.75-1.08)

CI: confidence interval.
*Adjusted for age, sex, CCI, alcohol-related disorders, and marital status.

Supplemental table 5 Odds ratios for non-organ confined bladder cancer at cystectomy. One-prescription users filled at least one antidepressant prescription in the year before cancer diagnosis, while non-users did not. Results of complete case analysis and when replacing missing values for cancer stage with the latest stage observed before surgery.

	Complete case analysis						Including prior stages	
	Non-organ confined (pT3-T4 or pN+)		Organ confined (pT0-T2 and pN0)		Unadjusted odds ratio (95% CI)	Adjusted* odds ratio (95% CI)	Unadjusted odds ratio (95% CI)	Adjusted* odds ratio (95% CI)
	n	%	n	%				
Non-users (n=1503)	849	56.5	654	43.5	Ref.	Ref.	Ref.	Ref.
One-prescription users (n=129)	79	61.2	50	38.8	1.22 (0.84-1.76)	1.11 (0.76-1.61)	1.25 (0.91-1.72)	1.19 (0.86-1.64)

CI: confidence interval.
*Adjusted for age, sex, CCI, alcohol-related disorders, and marital status.

Supplemental table 6 Cumulative incidence and rate of cystectomy within 4 months from the first time muscle-invasive disease was detected. One-prescription users filled at least one antidepressant prescription in the year before cancer diagnosis, while non-users did not.

	Cystectomized, n	Four months cumulative incidence, % (95% CI)	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Non-users (n=4361)	1106	25.4 (24.1-26.7)	Ref.	Ref.
One-prescription users (n=592)	92	15.5 (12.8-18.6)	0.60 (0.49-0.74)	0.76 (0.61-0.94)

CI: confidence interval. HR: hazard ratio.
*Adjusted for age, sex, CCI, alcohol-related disorders, and marital status.

Supplemental table 7 Length of stay, 30-day ICU treatment, 30-day acute readmission, 90-day reoperation, and one-year all-cause mortality after cystectomy. One-prescription users filled at least one antidepressant prescription in the year before cancer diagnosis. Non-users did not fill a prescription in that year. The analysis of acute readmission excludes patients with a primary admission longer than 30 days (n=140).

Surgical outcome	Non-users	One-prescription users
Length of stay		
Days admitted, median (IQR)	10 (7-13)	9.5 (8-13)
Unadjusted ratio of median duration (95% CI)	Ref.	1.02 (0.94-1.11)
Adjusted* ratio of median duration (95% CI)	Ref.	1.01 (0.93-1.10)
30-day ICU treatment		
Total, n	2344	188
Admitted, n	734	55
Cumulative incidence, % (95% CI)	31.3 (29.5-33.2)	28.7 (22.4-35.4)
Unadjusted HR (95% CI)	Ref.	0.93 (0.71-1.22)
Adjusted* HR (95% CI)	Ref.	0.95 (0.72-1.26)
30-day acute readmission		
Total, n	2217	175
Readmitted, n	737	72
Cumulative incidence, % (95% CI)	33.3 (31.3-35.2)	41.1 (33.8-48.3)
Unadjusted HR (95% CI)	Ref.	1.29 (1.01-1.64)
Adjusted* HR (95% CI)	Ref.	1.27 (0.99-1.63)
90-day reoperation		
Total, n	2344	188
Reoperated, n	899	81
Cumulative incidence, % (95% CI)	38.4 (36.4-40.4)	43.1 (35.9-50.0)
Unadjusted HR (95% CI)	Ref.	1.13 (0.90-1.42)
Adjusted* HR (95% CI)	Ref.	1.13 (0.90-1.42)
One-year all-cause mortality		
Total, n	2344	188
Deaths, n	326	28
Cumulative incidence, % (95% CI)	14.4 (13.1-16.0)	15.1 (10.7-21.1)
Unadjusted HR (95% CI)	Ref.	1.06 (0.72-1.56)
Adjusted* HR (95% CI)	Ref.	0.97 (0.65-1.44)

IQR: interquartile range. ICU: intensive care unit. CI: confidence interval. HR: hazard ratio.
*Adjusted for age, sex, CCI, alcohol-related disorders, and marital status.

Supplemental table 8 The ten antidepressants most commonly redeemed among patients who filled at least two prescriptions in the year before cancer diagnosis.

Antidepressant (generic name)	**ATC code**	**Pharmacological subgroup**	**Number of prescriptions**, n (%)
Citalopram	N06AB04	Selective serotonin reuptake inhibitors	2253 (38.1)
Mirtazapin	N06AX11	Other antidepressants	1020 (17.3)
Escitalopram	N06AB10	Selective serotonin reuptake inhibitors	529 (8.9)
Venlafaxin	N06AX16	Other antidepressants	473 (8.0)
Sertralin	N06AB06	Selective serotonin reuptake inhibitors	337 (5.7)
Amitriptylin	N06AA09	Non-selective monoamine reuptake inhibitors	292 (4.9)
Mianserin	N06AX03	Other antidepressants	250 (4.2)
Nortriptylin	N06AA10	Non-selective monoamine reuptake inhibitors	200 (3.4)
Paroxetin	N06AB05	Selective serotonin reuptake inhibitors	172 (2.9)
Duloxetin	N06AX21	Other antidepressants	117 (2.0)

ATC: Anatomical Therapeutic Chemical.

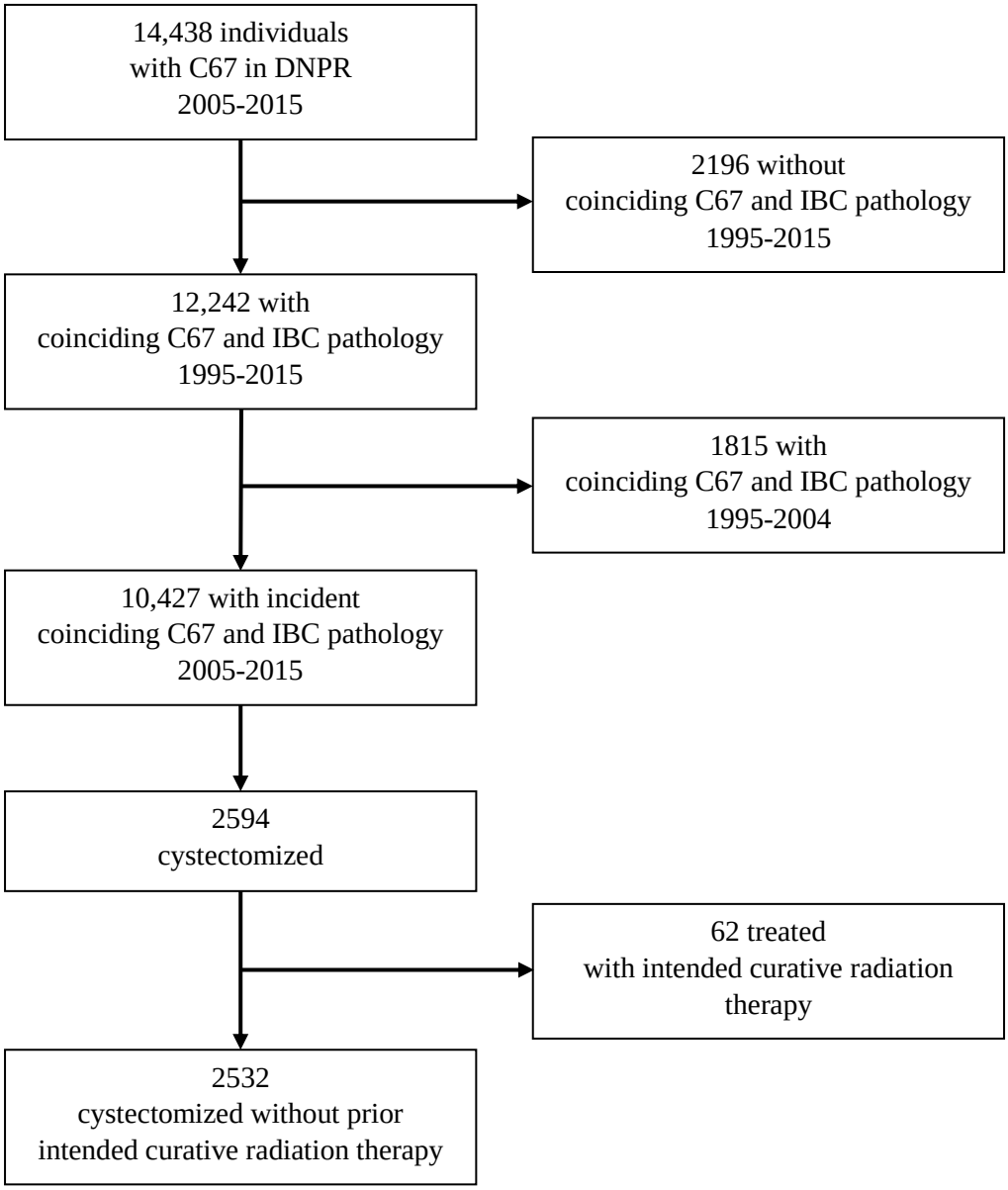

Figure 1 Flow diagram of the study population.
DNPR: The Danish National Patient Registry. IBC: invasive bladder cancer.

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