Concomitant medication use and its implications on the hazard pattern in pharmacoepidemiological studies: example of antidepressants, benzodiazepines and fracture risk

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ABSTRACT

BACKGROUND: Antidepressants and benzodiazepines are often co-prescribed and both associated with an increased fracture risk, albeit with distinctive hazard patterns. Timing of initiation of one with respect to the other and duration of use may influence the combined fracture hazard.
The objective of our study was to describe patterns of concomitant use of benzodiazepine and antidepressants in terms of timing of initiation and duration and to illustrate the potential impact of various scenarios of timing of co-use on hip fracture hazard.
METHODS: Patients initiating antidepressant therapy (2002-2009) were identified from the Netherlands Primary Care Research Database. Concomitant benzodiazepine use was assessed according to the start time of benzodiazepine with respect to antidepressant therapy start. Duration of concomitant use was estimated relative to the length of antidepressant treatment episode.
RESULTS: Among 16,087 incident antidepressant users, 39.0% used benzodiazepines concomitantly during their first antidepressant treatment episode. The time of initiation of benzodiazepine use was variable (64.4% starting before, 13.7% simultaneous and 21.9% after antidepressants). Duration of concomitant use in the three groups varied.
CONCLUSION: Co-prescribed medications with a common adverse event, may not only require accounting for concomitant use, but also the timing of start and duration of use as the overall hazard may vary accordingly.

Key words: antidepressants, benzodiazepines, concomitant use, duration of use, hazard pattern, hip fracture, timing of use

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INTRODUCTION

Poly-pharmacy is often unavoidable in daily clinical practice, but may be associated with additional risks of adverse events. Several examples of frequently combined medications with the same adverse event have been described: aspirin and clopidogrel and the risk of bleeding[1] anti-rheumatic agents and methotrexate and the risk of hepatotoxicity [2] and angiotensin converting enzyme (ACE) inhibitors and non-steroidal anti-inflammatory drug (NSAID) use and renal impairment [3]. When hazard patterns of drug-adverse event vary over time, the risk of an adverse event may differ at the initiation of a therapy compared to during continuous use or even after termination of therapy. Timing of start of concomitant medication use may hence modify the combined effect.

Electronic health care databases are often used for observational research on adverse effects of medications [4, 5]. The availability of longitudinally recorded data allows for a detailed characterization of both the exposure to medication and the outcome of interest. In more recent drug-adverse event studies, we observe elaborated definitions of the main exposure of interest but rarely of the concomitant medication use as a confounding or effect modifying factor. It is important to account for concomitant medication use in more detail, as two medications may be associated with the same adverse event, albeit with different hazard patterns over time.

To elaborate this, we portray the example of concomitant use of benzodiazepines among antidepressant users and the hazard for fracture as the common adverse event. Concomitant use of antidepressants and benzodiazepines is proven to be effective to treat the acute phase of depression [6] and hence are often co-prescribed in routine clinical practice [7]. The use of antidepressants [8-14] and benzodiazepines [15-20] have both been associated with an increased risk of fractures. The hazard patterns for fracture have been reported to be different for these two classes of medications. Studies have reported high risk of fracture for antidepressant use (both selective serotonin re-uptake inhibitors and tricyclic antidepressants) starting three to six months after continuous use followed by a lower but persistent risk up until in the fourth to fifth year of continuous use [9, 12, 21]. In contrast, fracture risk is highest immediately after initiation of benzodiazepine use and there is a marked decrease in the risk upon continuous use as reported in various studies [18, 20, 22]. Accordingly, fracture hazard for antidepressant use is high long after initiation of therapy with bone mineral density alteration as the potential mechanism of action, whereas the more acute risk for fracture associated with benzodiazepine use is thought to be related to an increased risk of falls. Assuming at least an additive effect of concomitant use and the approximate patterns of fracture hazard for antidepressant and benzodiazepine use roughly derived from risk estimates reported in previous studies as noted above, different timings of benzodiazepine use start may modify the combined risk for fracture. This is shown in Figure 1, where different scenarios of combined risk patterns for concomitant use are depicted. Scenario 1A represents the situation in which patients use antidepressants but do not use benzodiazepines and hence bear the potential risk pattern associated with antidepressant use only. Further, scenarios 1B, 1C and 1D represent situations in which patients start using benzodiazepine concomitantly before, simultaneous and after the initiation of antidepressant use, respectively. As shown, the coexisting and/or overlapping risk patterns, assuming at least an additive effect, for these three groups are different.

The aim of this study was to estimate concomitant use of benzodiazepine among antidepressant users and characterize the timing of benzodiazepine start with respect to antidepressant therapy start and the duration of concomitant use. Secondly, we aimed to illustrate scenarios of timing of initiation and duration of concomitant benzodiazepine use among antidepressant users and discuss potential scenarios and implications on the estimation of the combined hazard for hip fracture.

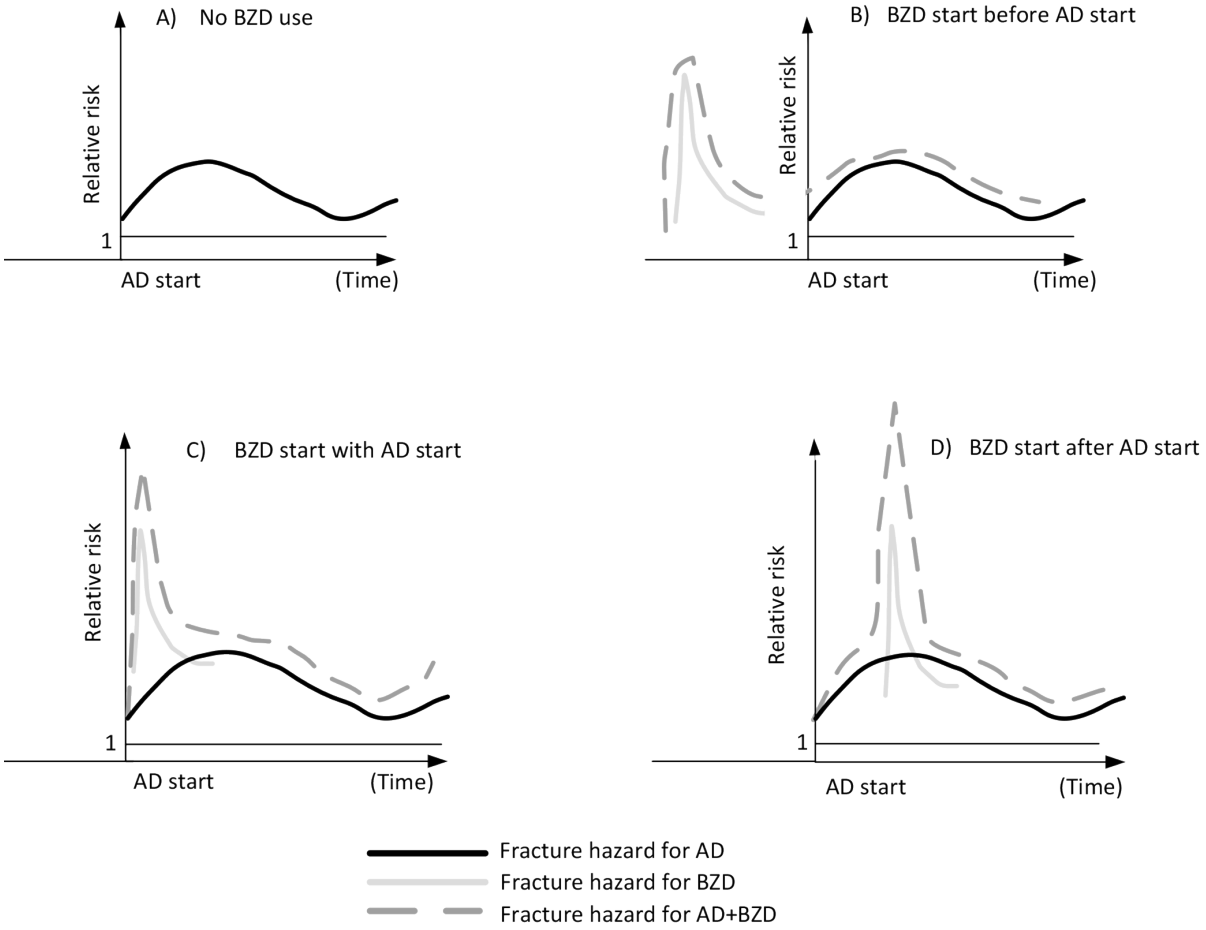
METHODS

Setting

Data were obtained from the Netherlands Primary Care Research Database (NPCRD)[23], a database from general practices that register data on morbidity, drug prescriptions and referrals

FIGURE 1

FOUR SCENARIOS OF TIMING OF BENZODIAZEPINE INITIATION AMONG NEW ANTIDEPRESSANT USERS AND THEIR RESPECTIVE HAZARD FUNCTIONS FOR HIP FRACTURE OVER TIME



in electronic medical records on a continuous basis. The NPCRD includes more than 350,000 patients registered at 85 practices. Prescription data are classified according to Anatomical Therapeutic and Chemical (ATC)[24] classification and morbidity is coded using the International Classification of Primary Care (ICPC)[25].

Study population

All patients with a first prescription for an antidepressant drug (ATC N06A) enrolled in practices, which are registered in the database between 2002 and 2009 were identified. The date of the first antidepressant prescription was considered to be the start date. Patients aged 18 years and older at the time of the start date with at least one year of enrollment history in NPCRD and at least 90 days of follow-up available were eligible for inclusion. We included only new users, defined as patients who had their first AD prescription (start date) during the study period without any AD prescription in the year preceding the start date.

Definition of antidepressant use

For each patient starting an antidepressant, all prescriptions for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MOAIs) were identified. Treatment episodes were constructed according to the method previously applied by Gardarsdottir et al. [26]. In short, a treatment episode

comprised a series of subsequent antidepressant prescriptions, irrespective of switching between different types of antidepressant and changes in dose regimen. As prescribing records in NCPRD did not provide information on the dosing regimen, the prescription length for each antidepressant was considered to be 90 days, consistent with the maximally allowed dispensing duration in the Netherlands. In case a subsequent antidepressant prescription with the same drug was collected before the theoretical end date of a previous antidepressant prescription, the number of overlapping days was added to the theoretical end date of the subsequent antidepressant prescription. If a subsequent prescription was another antidepressant, the patient was considered to have switched therapy and any remaining days from the previous type of antidepressant were disregarded.

A new treatment episode was assumed when an interval of 30 days or more occurred between the theoretical end date of a prescription and the next prescription for the same patient. For all patients, only the first treatment episode was assessed.

Concomitant use of benzodiazepines

Among patients with a first episode of antidepressant use, all prescriptions for benzodiazepines (ATC codes N05BA), benzodiazepine derivatives (ATC N05CD) and benzodiazepine related drugs (ATC N05CF) were identified.

As information on the dosing regimen for benzodiazepine was not available, the length of a benzodiazepine prescription was assumed to be 30 days, based on the common prescribing practice for benzodiazepines in the Netherlands. To assess concomitant use of benzodiazepines ('co-use') during the first episode of antidepressant use, we calculated the number of days that benzodiazepines were used within this period. If a benzodiazepine prescription was issued prior to the start of antidepressants or the theoretical end date of a prescription was after the end date of the antidepressant treatment episode, only the days within the antidepressant episode were taken into account.

Using a fixed duration of 30 days for a benzodiazepine prescription can inflate the number of days use in case the prescriptions were e.g. issued on a weekly basis or were used in a higher frequency. Therefore, we created a rule that the number of days of co-use could not be larger than the difference between the last theoretical end date of a benzodiazepine prescription and the start of benzodiazepine/ start of the antidepressant treatment episode, whichever came last. As an antidepressant episode can potentially last for years, we applied the above mentioned rule taking into account clusters of benzodiazepine use, where a difference of 182 days between the end date of one benzodiazepine prescription and a subsequent one marked a new cluster. This prevented a scenario where intensive co-use at the beginning and at the end of an antidepressant episode would overestimate the number of days of co-use. Concomitant use of benzodiazepines within the first antidepressant episode was further defined in two dimensions: First, we assessed the timing of benzodiazepine start with respect to the start of the antidepressant treatment episode (T=0). Three subgroups of patients were identified according to the timing of concomitant benzodiazepine start: 1) patients who start using benzodiazepines before, 2) those who start using benzodiazepine simultaneously (on the same day) and who have no benzodiazepine prescription in the 182 prior to the start day and 3) patients who start using benzodiazepine after the start of the antidepressant treatment episode.

Second, the duration of concomitant use in days was plotted relative to the length of the antidepressant treatment episode in days.

Data Analysis

The cohort of new antidepressant users was described for sex, age, major indications (footnote Table 1), length of antidepressant treatment episode and type of antidepressant use. Mean, median and standard deviation were calculated. The frequency of concomitant use of benzodiazepine was determined according to the definitions described above. Results were stratified by timing of benzodiazepine start. Duration of concomitant benzodiazepine use was compared with respect to antidepressant treatment episode length. Data analyses were performed using SPSS for Windows 20.0 (SPSS Inc, Chicago, IL).

RESULTS

A total of 16,087 patients initiated antidepressant treatment between 2002 and 2009 (Table 1). The majority (63.0%) was female and the mean age was 50 years (SD 18) at the start of antidepressant treatment. The most frequently recorded indications were depression/depression related disorders (35.5%), followed by anxiety/anxiety related disorders (11.0%). The range of the antidepressant episode lengths was wide (between 90 and 2920 days) and the mean and median were 295 and 166 days, respectively. About one third (34.0%) of the patients had the minimum antidepressant treatment length (3 months), corresponding to a single antidepressant prescription. The majority of the patients were SSRI users (54.2%) and only one third of the patients were TCA users.

More than one third (39.0%) of the new antidepressant users were concomitant users of benzodiazepines (Figure 2) at least once during their antidepressant treatment episode. The majority (64.4%) of these patients initiated benzodiazepine use before antidepressant therapy start. In total 21.9% of concomitant users started using benzodiazepine after initiation of antidepressant therapy, and 13.7% started the use of benzodiazepines and antidepressants simultaneously.

Figure 3 shows the duration of the concomitant benzodiazepine use versus total antidepressant treatment episode length overall, as well as for those who start benzodiazepine use before, simultaneous and after antidepressant treatment initiation separately. Figure 3A shows regular periods of 30, 60 and 90 days of benzodiazepine co-use during the antidepressant treatment episode in addition to some other lengths of periods of concomitant benzodiazepine use. Figures 3B and 3C indicate relative long duration of concomitant use of benzodiazepine among the subgroups of antidepressant users who start using benzodiazepine before and simultaneous compared with the duration of concomitant use for those who start using benzodiazepine after antidepressant initiation (figure 3D) which was relatively shorter. Comparing the scatter plot of prescriptions in figures 3B, 3C and 3D, we notice more density of prescriptions clustered in a diagonal line indicating a positive correlation between the length of co-use and the length of antidepressant treatment episode in figure 3B and to a lesser extent in figure 3C compared to figure 3D. This indicates a more regular benzodiazepine co-prescribing at intervals of 30, 60 and 90 days during antidepressant treatment episode in figure 3D which does indicates a less relative increase of co-use duration compared to figures 3B and 3C.

TABLE 1

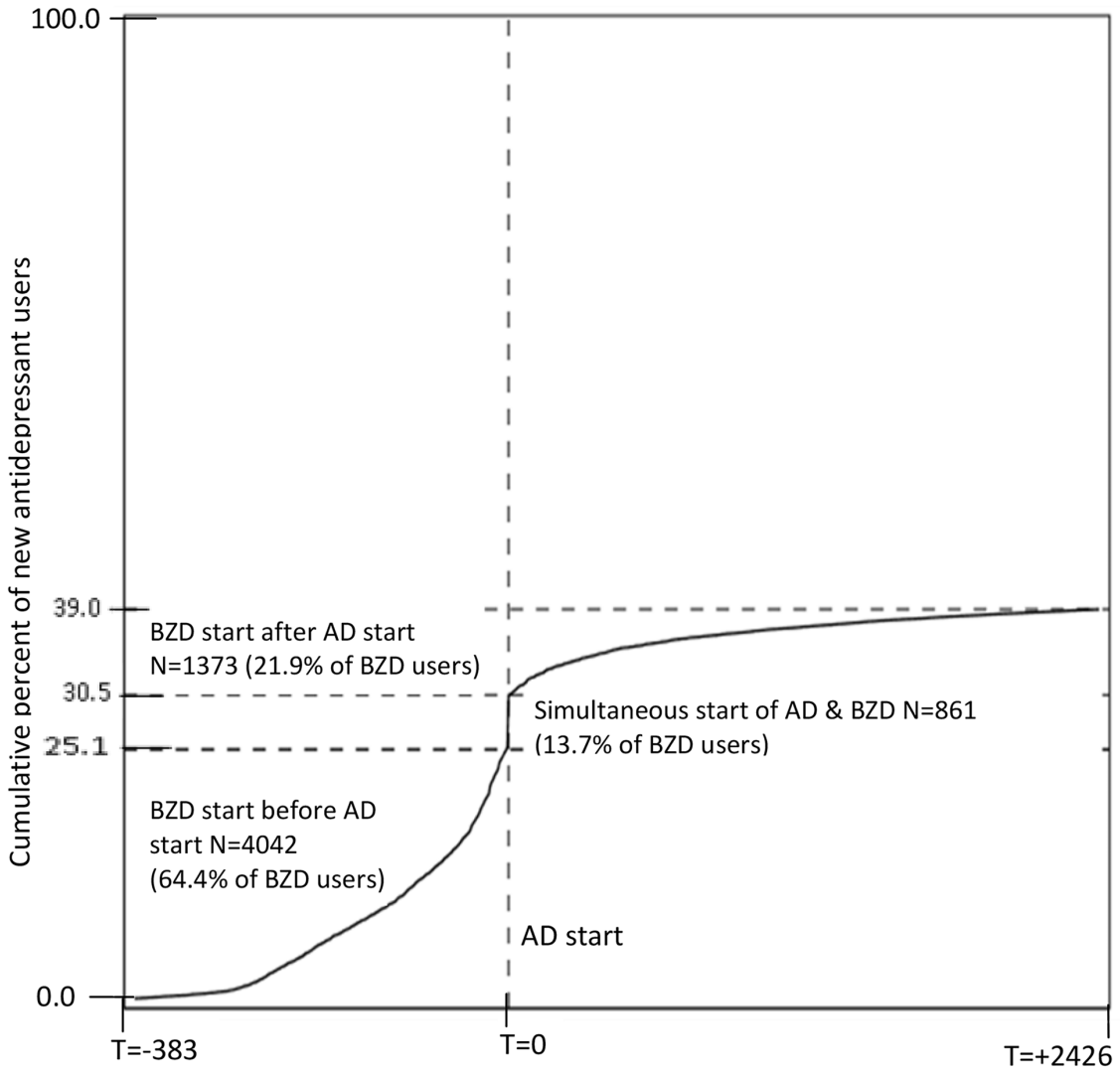
CHARACTERISTICS OF ANTIDEPRESSANT THERAPY INITIATORS

ANTIDEPRESSANT THERAPY INITIATORS N=16,087	N	%
Female	10,207	63.4
Mean age (standard deviation)	50	(18)
Indication of use		
Depression	5713	35.5
Anxiety	1775	11.0
Sleeping disorder	382	2.4
Unspecified	473	2.9
Other	5226	32.4
Unknown	2518	15.7
Antidepressant episode duration in days		
Mean (Standard deviation)	295	(345)
Median	166	
Minimum	90	
Maximum	2920	
25th percentile	90	
75th percentile	344	
3 month	5480	34.1
>3-6 months	3295	20.5
6-12 months	3608	22.4
>12 months	3704	23.0
Only selective serotonin re-uptake inhibitors use	8714	54.2
Only tricyclic antidepressants use	5386	33.5
Only other antidepressant use	1987	12.3

Depression: depression and related disorders (ICPC code P76, P03)
Anxiety: anxiety and related disorders (ICPC codes: P01, P74)
Sleeping disorder (ICPC code: P06)
Unspecified: no diagnosis determined by the general practitioner
Unknown: missing data.

FIGURE 2

DISTRIBUTION OF CONCOMITANT BENZODIAZEPINE USE AMONG NEW ANTIDEPRESSANT USERS, ACCORDING TO TIMING OF BENZODIAZEPINE START WITH RESPECT TO ANTIDEPRESSANT TREATMENT EPISODE START (T=0)

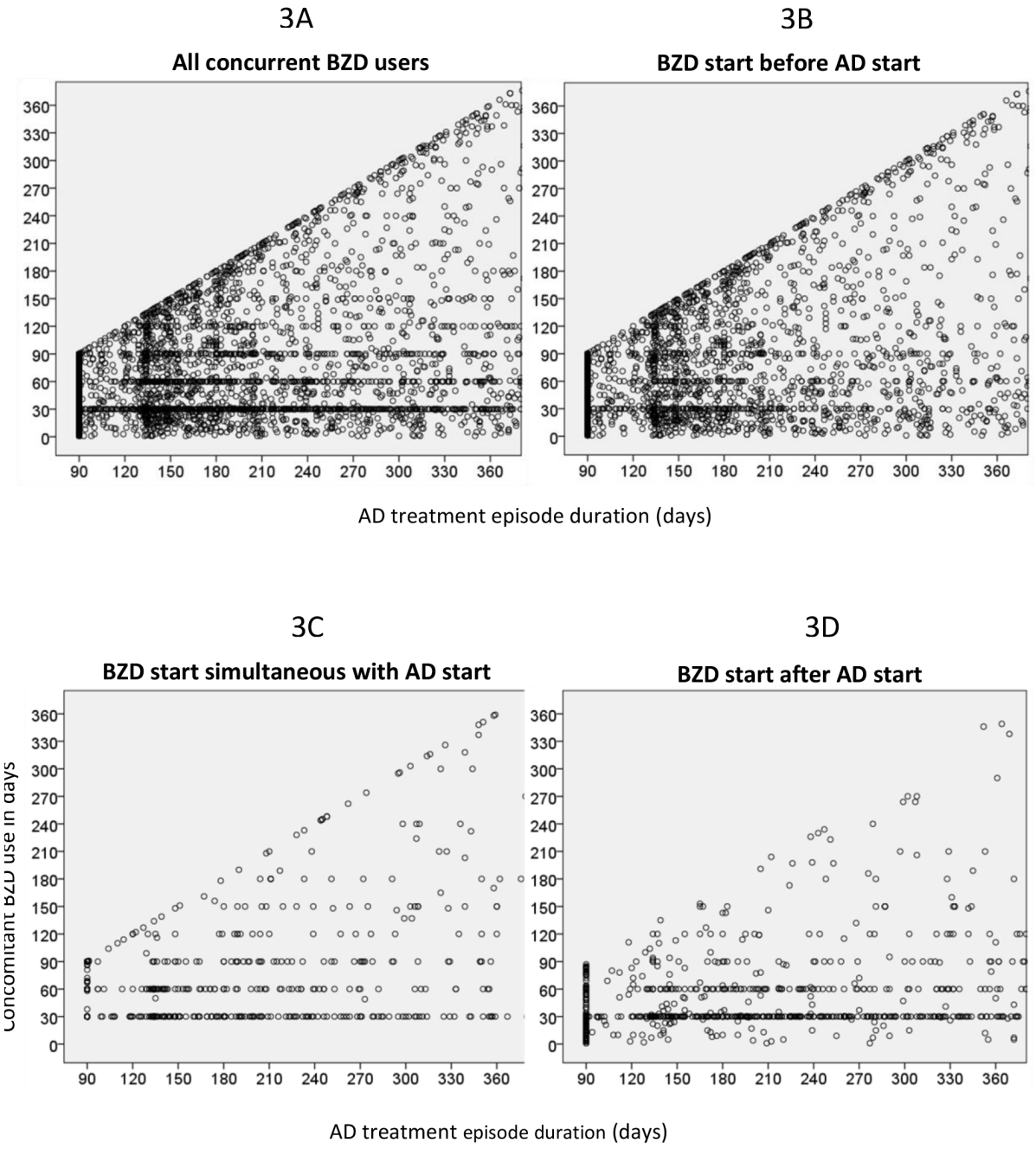


DISCUSSION

In our study population of incident antidepressant users, 39% of patients were concomitant benzodiazepine users. This is in line with the proportion of co-use reported in several recent studies on psychotropic polypharmacy from Canada (49.3%) [27], Japan (36.7%) [7] and the Netherlands (40.1%) [28]. Among the concomitant users, timing of start of benzodiazepine use varied. The majority of concomitant users (64.4%) started using benzodiazepines before the start of the antidepressant therapy. Moreover, 13.9% of concomitant users initiated benzodiazepine use on the same day as the antidepressant start day. The duration of concomitant use varied also among these patient groups with different timing of benzodiazepine start. In general, the duration of concomitant use was longer for patients who started using benzodiazepine before and simultaneous to antidepressant therapy start compared with patients who started using benzodiazepine after antidepressant treatment initiation. The highest fracture risk of concomitant co-use is

FIGURE 3

DISTRIBUTION OF DURATION OF CONCOMITANT USE OF BENZODIAZEPINE WITH RESPECT TO THE DURATION OF ANTIDEPRESSANT TREATMENT EPISODE: OVERALL (3A) AND IN THREE DIFFERENT PATIENT GROUPS IN TERMS OF TIMING OF BENZODIAZEPINE START (3B-3D)



expected when a benzodiazepine is initiated 3 to 6 months after start of antidepressant therapy (figure 1D). Approximately 10% of our study population falls in this category (figure 2). We are not aware of any publications describing the concomitant use of benzodiazepines among antidepressant initiators in this level of detail with respect to timing and duration of co-use.

Antidepressants and benzodiazepines are widely used medications and are prescribed for a broad range of indications. Despite the wide range of indications for prescribing antidepressants [29], the most frequently recorded indications are depression-/related

indications and anxiety-/related indications [30, 31]. Patients diagnosed with depression or anxiety related morbidities are advised to continue using antidepressants for at least a year to prevent relapse [32]. On the other hand, benzodiazepines are advised to be prescribed for shorter periods [33-35] as they may be highly addictive [36] and may have higher chance for misuse and associated risks such as falls especially in elderly [37, 38]. Long term use of benzodiazepines has been reported to be problematic in several studies [36, 39, 40]. Concomitant use of antidepressants and benzodiazepines is proven to be effective to treat the acute phase of depression [6]. Considering guidelines for prescribing and reports of utilization studies of both medications and the prevalence of their co-prescription [41], a more detailed characterization of the dynamics of concomitant use when evaluating a common adverse event is imperative. The main motive for this, as shown in scenarios 1B, 1C and 1D, is the combined hazard patterns, which may be different for different timing of benzodiazepine start.

Studies on the association of antidepressants and fractures have, almost always, considered benzodiazepine use as confounding to the main exposure and subsequently adjusted for. This is irrespective of study type (case-control or cohort or other), source of data used (survey or electronic health care database) and/or definition of the confounder variable. However, previous association studies have not corrected for timing of start of the confounder with respect to the main exposure. A literature search showed eight cohort studies [10, 13, 42-47] on antidepressant use and fracture risk. Five of those studies used interview generated information on medication use. Because of the relative simplicity of these medication data, advanced assessment of co-prescription is not possible. Of the three studies [13, 45, 47] that have used electronic health care databases, only two included benzodiazepine use as a potential confounder. Coupland et al used a simple adjustment for use of hypnotics/anxiolytics at baseline [45]. Abbing et al took into account timing of co-use, by adding benzodiazepine exposure to the multivariate model as a time-dependent covariate [47]. However, duration of benzodiazepine use was not taken into account simultaneously. This implies that the hazard is assumed constant over time, hence neglecting the specific hazard functions for benzodiazepine-induced fracture risk as depicted in figure 1. In our present study, we found that more than half of the concomitant users started benzodiazepines more than 2 weeks before antidepressant initiation (figure 2). For those patients, concomitant benzodiazepine should in fact no longer be regarded a potential confounder, as the hazard of fracture has already disappeared (figure 1B).

The recent multi-country study from our group [47] showed different risk estimates for fracture per country, despite applying common methods for defining antidepressant use as the main exposure and benzodiazepine use as co-medication. Considering different scenarios of hazard patterns and magnitudes of concomitant use discussed in figure 1 hypothesize that residual confounding because of insufficient adjustment of timing and duration of co-use may have played a role. The three cohorts might have different distributions of patients with respect to timing of benzodiazepine start (more prevalent users in cohorts where the risk estimate is lower – acute risk of benzodiazepine absent) and hence different magnitudes of overall risk found in their study. Specifically, when antidepressant treatment start is the T0 – exposure window of interest, the cohort with higher risk estimate in our previous study may have a larger patient group with scenarios in figures 1C and 1D as more relevant compared to the cohorts with lower risk estimates where figure 1B may be more relevant.

Our study has some limitations. First, information on the prescribed dose was not available in the database and assumptions on prescription length for antidepressant and benzodiazepine had to be made. However, the assumed prescription lengths were based on the common prescribing practices in the Netherlands. Second, patients starting with benzodiazepine use after the initiation of antidepressant therapy can, by definition, not have duration of concomitant benzodiazepine use that is equal to the duration of antidepressant use. This may introduce bias when comparing the duration of concomitant use between the subgroups based on timing of benzodiazepine start (before starters / simultaneous starters / after starters). Third, the combined hazard scenarios depicted in figure 1 were simplified for illustration purposes and were not based

on empirical data, hence ignoring aspects like dose and possible drug-drug interaction. In addition, we were not able to test whether our hypothesis on a fluctuating cumulative fracture hazard function associated with combined antidepressant and benzodiazepine use is true. A general limitation for such studies can be the unavailability of patient compliance information which may differ not randomly in the three groups. Future studies, which include fracture endpoints, are needed to fill this knowledge gap.

CONCLUSION

The frequency of concomitant benzodiazepine use among antidepressant users is considerable and the timing of concomitant benzodiazepine start is highly variable. When studying a common adverse event associated with medications that are often co-prescribed, as in the example of antidepressants, benzodiazepines and hip fracture, it is important to take into account not only the presence of concomitant medication use, but also the timing of start and duration of co-use as the overall hazard may vary accordingly.

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