Predicting chronic benzodiazepine use in adults with depressive disorder

Retrospective cohort study using administrative data in Quebec

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Abstract

Objective To identify predictive variables of incident chronic benzodiazepine (BZD) use that could be assessed by prescribing physicians.

Design Retrospective cohort study using public health and drug insurance administrative data.

Setting Quebec.

Participants New adult BZD users from January 1, 1999, to March 31, 2006, with a diagnosis of depressive disorder in the previous year were included. Chronic BZD use was defined as BZD availability at least 50% of the days between day 181 and day 365 following initiation.

Main outcome measures Potential associations between chronic BZD use and age; sex; drug insurance status; recent hospitalization; comorbidity; presence of chronic pain; use of psychotropic medication; mental health diagnoses; number, type, and duration of BZDs prescribed; and the prescribing physician's specialty.

Results Selection led to an exhaustive cohort of 13 688 patients aged 18 to 64 years, and 3683 aged 65 and older. For the 18 to 64 age group, the combination of disability insurance and more than 1 BZD increased the proportion of chronic users from 14.4% to 53.4%. For patients 65 and older, the main correlates of chronic BZD use included claiming more than 1 BZD (adjusted odds ratio 2.24, 99% CI 1.65 to 3.06) and recent hospitalization (adjusted odds ratio 1.70, 99% CI 1.38 to 2.10). Recently hospitalized older patients with a prescription duration of less than 8 days were the highest-risk group identified (57.8%).

Conclusion Physicians should be aware that patients are more likely to become chronic BZD users if they receive disability insurance or following a hospitalization. Combination of BZDs is a potentially problematic practice that could be increasing the risk of chronic use.

EDITOR'S KEY POINTS

- Benzodiazepines (BZDs) are among the most commonly prescribed psychotropic drugs and they are widely used in depression. Chronic (> 6 months) use has been linked to adverse events, including falls in the elderly and motor vehicle accidents. For established chronic users, attempted withdrawal is often unsuccessful; even the most targeted BZD interventions succeed for only a minority of patients.
- This study aimed to identify variables predictive of a higher risk of becoming a chronic BZD user for patients recently diagnosed with depressive disorder.
- Based on the significant predictors identified, the authors recommend that physicians prescribing a new BZD for a recently depressed patient should avoid a combination of BZDs, write a time-limited initial prescription, and consider alternatives for patients who were recently hospitalized or who receive disability insurance.

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Prédire l'usage chronique des benzodiazépines chez les adultes ayant un trouble dépressif

Étude rétrospective de cohortes à l'aide de données administratives au Québec

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Résumé

Objectif Cerner les variables permettant de prédire une utilisation chronique secondaire de benzodiazépines (BZD) que pourraient évaluer les médecins prescripteurs.

Conception Étude rétrospective de cohortes à l'aide de données administratives de la santé publique et des assurances-médicaments.

Contexte Québec.

Participants L'étude portait sur les nouveaux utilisateurs adultes de BZD, entre le 1er janvier 1999 et le 31 mars 2006, ayant reçu un diagnostic de trouble dépressif durant l'année précédente. L'utilisation chronique de BZD désignait la disponibilité de BZD au moins 50 % des jours entre le jour 181 et le jour 365 après l'amorce du traitement.

Principaux paramètres à l'étude Les associations potentielles entre l'usage chronique de BZD et les éléments suivants : l'âge, le sexe, la situation en matière d'assurances, les récentes hospitalisations, la comorbidité, la présence de douleurs chroniques, l'utilisation de médicaments psychotropes, les diagnostics de problèmes de santé mentale, le nombre, le type et la durée des BZD prescrits, de même que la spécialité du médecin prescripteur.

Résultats La sélection a permis de former une cohorte considérable de 13 688 patients âgés de 18 à 64 ans et de 3 683 de 65 ans et plus. Dans le groupe de 18 à 64 ans, la combinaison de prestations d'assurance invalidité et de plus de 1 BZD faisait passer la proportion d'utilisateurs chroniques de 14,4 à 53,4 %. Dans le groupe de patients de 65 ans et plus, les principaux corrélats précurseurs de l'usage chronique de BZD incluaient les demandes de remboursements pour plus de 1 BZD (rapport de cotes ajusté de 2,24, IC à 99 % de 1,65 à 3,06) et une hospitalisation récente (rapport de cotes ajusté de 1,70, IC à 99 % de 1,38 à 2,10). Les patients plus âgés récemment hospitalisés dont la prescription avait une durée de moins de 8 jours représentaient le groupe à risque le plus élevé (57,8 %).

Conclusion Les médecins devraient être au fait que les patients les plus susceptibles de devenir des utilisateurs chroniques de BZD sont ceux qui reçoivent des prestations d'assurance invalidité et ceux récemment hospitalisés. La combinaison de plusieurs BZD est une pratique potentiellement problématique qui pourrait accroître le risque d'un usage chronique.

POINTS DE REPÈRE DU RÉDACTEUR

- Les benzodiazépines (BZD) comptent parmi les médicaments psychotropes les plus fréquemment prescrits et ils sont largement utilisés pour la dépression. L'usage chronique (> 6 mois) a été associé à des événements indésirables, notamment des chutes chez les personnes âgées et des accidents de la route. Pour les utilisateurs chroniques établis, le sevrage échoue souvent; même les interventions les plus ciblées pour cesser les BZD ne réussissent que pour une minorité de patients.

- La présente étude avait pour but de cerner les variables permettant de prédire un risque plus élevé de devenir un utilisateur chronique de BZD chez les patients ayant reçu récemment un diagnostic de trouble dépressif.

- En se fondant sur les facteurs de prédiction significatifs cernés, les auteurs sont d'avis que les médecins qui prescrivent un nouveau BZD à un patient atteint de dépression depuis peu devraient éviter une combinaison de BZD, rédiger une ordonnance initiale à durée limitée et envisager d'autres options pour les patients récemment hospitalisés ou qui sont bénéficiaires d'une assurance invalidité.

Cet article a fait l'objet d'une révision par des pairs.
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Benzodiazepines (BZDs) are safe and effective for relieving common symptoms such as insomnia, anxiety, and muscle tension.[1] As such, BZDs are useful add-ons to first-line treatment in depression.[2-4] While effective in acute situations, no experimental data demonstrate effectiveness in depression beyond 6 to 8 weeks.[3] Nonetheless, long-term use of BZDs is common in clinical practice.[5-7]

Chronic (longer than 6 months) BZD use has been linked to adverse events, including falls in the elderly and motor vehicle accidents.[2,8] For established chronic users, attempted withdrawal is often unsuccessful; even the most targeted BZD discontinuation interventions succeed for only a minority of patients.[9,10]

To allow BZD initiation to be an informed decision for prescribing physicians, an individual's probability of future chronic use needs to be estimated. Studies on the predictors of incident chronic BZD use seldom provide separate data for populations with depression.[11-13] We did not find any study focusing on new BZD use in the context of depression in the general population.

The objective of the present study was to identify variables predictive of a higher risk of becoming a chronic BZD user for patients recently diagnosed with depressive disorder. Such information must be readily available to family physicians and other specialists at the time of prescription, and could be used to enhance the safety and appropriateness of BZD use for patients with depression.

METHODS

Design

We conducted a retrospective cohort study. All potential predictive variables were measured for the year up to and including the date of the first BZD claim, herein referred to as the *index date*.

Setting

In Quebec, public health insurance is administered by the Régie de l'assurance maladie du Québec (RAMQ).[14] Data were retrieved from an exhaustive secondary database including every adult with a diagnosis of mood disorder or schizophrenia registered by the RAMQ from 1996 to 2007 (N = 951 270).[15] Available information covers hospital stays, physician payment data, patient information, and public drug insurance data for eligible patients.

Coverage by a drug insurance plan has been mandatory in Quebec since 1997, but access to public drug insurance for people younger than 65 years of age is restricted to those unable to subscribe to private insurance coverage.[16] For people covered by public drug insurance in Quebec, drug information is comprehensive and valid.[17,18]

Patients

We selected adult patients with a new BZD use episode between January 1, 1999, and March 31, 2006. Inclusion criteria comprised the absence of a pharmacy BZD claim in the 2 years before BZD initiation and a diagnosis of depression (ICD-9 codes suggested by Health Canada[19]) in the year up to the index date. Exclusion criteria aimed at avoiding misclassification due to lack of information for either incomplete public drug insurance coverage during the observation period (from 2 years before BZD initiation to 1 year after) or for hospitalization of more than 7 days during the dependent-variable assessment period.

We separated our study population into 2 age cohorts (18 to 64 years of age and 65 years and older) to minimize the potential information bias from public drug insurance data, owing to different eligibility criteria for public insurance for people aged 65 and older.

Dependent variable

For this study, patients were defined as chronic users if they received enough BZD doses from the pharmacy to cover at least 50% of the days between day 181 and day 365 after the index date.

Independent variables

All variables were categorical except for age, which was used as a continuous variable within cohorts. Sex, age, and current drug insurance status were assessed at the index date. In both age cohorts, drug insurance status could be "regular" or linked to governmental "financial assistance," but only the 18- to 64-year-old participants could also be insured with a "disability" status.

Other independent variables included hospitalization within 30 days before the index date, comorbidity assessed with the Charlson-D'Hoore comorbidity index,[20,21] and the presence of chronic pain.[22] Mental health–related variables were either psychotropic medication classes available in the 90 days before the BZD's index date (antipsychotics, mood stabilizers, antidepressants) or a mental health diagnosis recorded within the year before the index date (psychotic, bipolar, anxiety, sleep, or substance use disorders). The time frame difference for assessing psychiatric drug use (90 days) or diagnosis (365 days) stems from the necessity of a physician visit for a diagnosis to be recorded in the database, while dispensed drug information is systematically collected from pharmacies for reimbursement.

In addition to patient information, other independent variables were the number of different BZDs dispensed at the index date, the duration of the prescription for the first BZD dispensed, the initial BZD molecule and dosage as calculated in equivalence to 1 mg of lorazepam,[23] and the prescribing physician's specialty.

Data analysis

Owing to the strong correlation between antipsychotic drugs and psychotic disorders on the one hand, and mood stabilizers and bipolar disorders on the other, it would have been inappropriate to include both in multivariate analysis. In our main model, we included the more reliable medication information rather than the diagnosis.

In bivariate analysis, we compared each independent variable according to chronic BZD use status, using Wald χ^2 tests for categorical variables and *t* tests for age, with $\alpha = .01$. We performed a multiple logistic regression including all independent variables in the main model, with $\alpha = .01$.

We performed regression tree analyses as published by Zhang et al,[24] using the RTREE software.[25] Regression tree analysis is a nonparametric method of recursive partitioning allowing identification of hierarchically organized risk factors for a dichotomous outcome. The relevance of this method to investigating mental health issues using RAMQ data has been demonstrated by Vanasse et al.[26]

Sensitivity analysis was performed by repeating the regression for each age group using 3 alternate models: the diagnostic model (psychotic and bipolar disorders replacing antipsychotics and mood stabilizers) and 2 alternate thresholds for the definition of chronic BZD use (40% and 60% instead of the original 50%). Apart from the tree-based regression, all data analysis was performed with SAS software, version 9.2.

Ethical approval

This study was approved by the Centre hospitalier universitaire de Sherbrooke ethics board and the Commission d'accès à l'information du Québec.

RESULTS

Figure 1 shows the patient selection process. Chronic users made up 19.9% of the younger cohort and 33.0% of the older cohort, as shown in **Table 1**. Bivariate analysis indicated that most variables were significantly associated with chronic BZD use at $P < .01$ in at least 1 of the age cohorts.

Multiple logistic regression with the main model is shown in **Table 2**. For the 18- to 64-year-old cohort, significant predictors were disability status and more than 1 BZD molecule, followed by older age, receiving financial assistance, availability of an antipsychotic drug, prescription by a psychiatrist, a BZD initially dispensed for more than 21 days, recent hospitalization, being dispensed clonazepam, dosage equivalent to at least 2 mg of lorazepam, and availability of an antidepressant drug. For the 65 years and older cohort, significant predictors were more than 1 BZD molecule, recent hospitalization, availability of an antipsychotic drug, receiving financial assistance, and receiving a BZD initially for less than 8 days.

Figures 2 and **3** display the results of regression tree analyses. In the 18- to 64-year-old cohort, the risk of chronic use ranged from 53.4% in individuals who received disability drug insurance and more than 1 BZD to 3.6% in individuals aged 18 to 29 with regular or financial assistance drug insurance, who received only 1 BZD at the index date for 21 days or less from a prescription by a nonpsychiatrist. For the older cohort, the highest risk group (57.8%) includes individuals who were recently hospitalized and received an initial BZD prescription for 7 days or less. The lowest-risk group in this cohort (19.1%) were not recently hospitalized, did not recently receive an antipsychotic drug, and had an initial prescription for no more than 21 days.

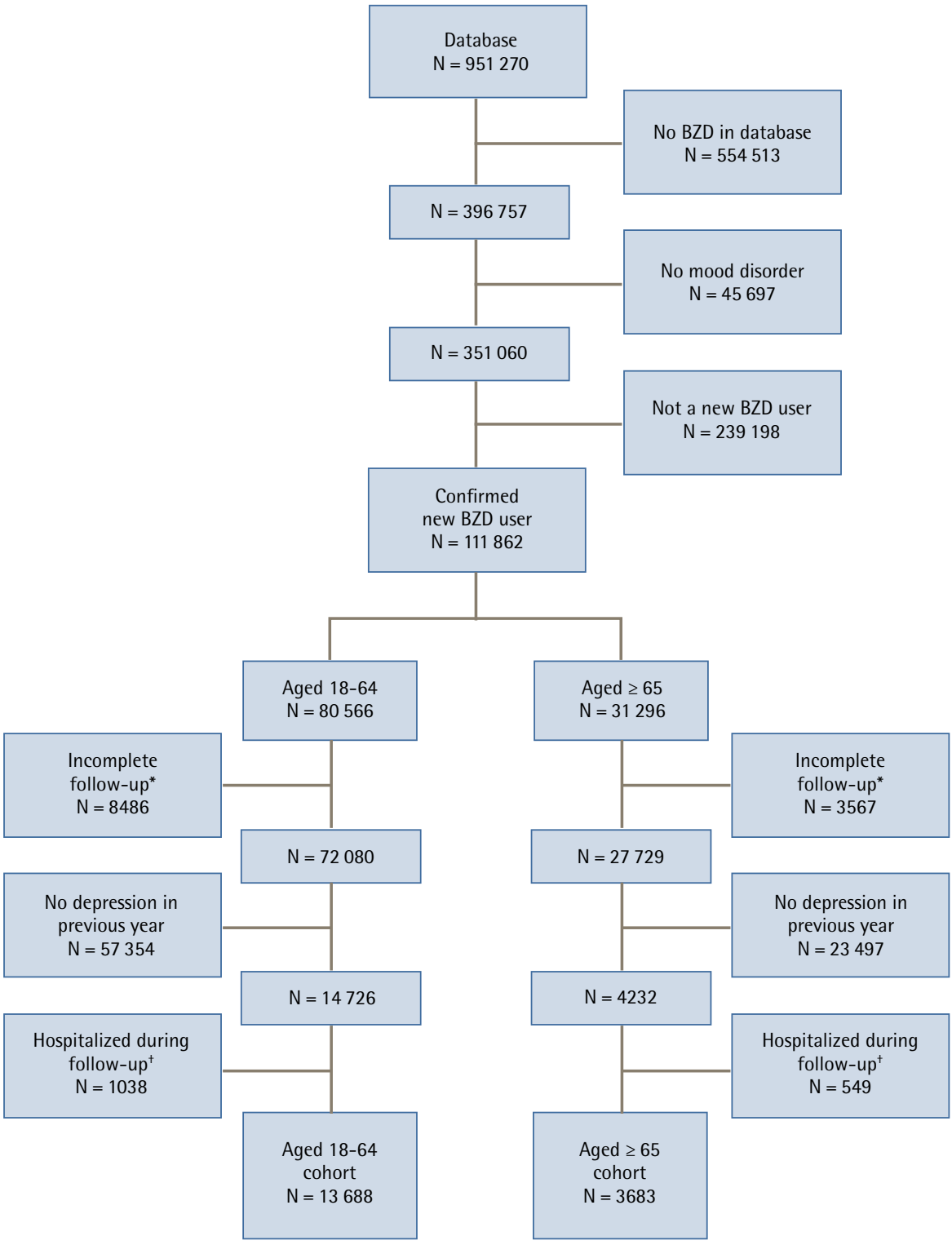
Sensitivity analysis (data not shown) suggested that chronic pain might be associated with chronic BZD use in the 18- to 64-year-old cohort; sensitivity analysis also revealed that it is unclear whether short-duration prescription (≤ 7 days) really is more strongly associated with chronic BZD use than long-duration prescription (≥ 22 days) is in the 65 and older cohort, but both remained strongly correlated with higher risk of chronic use compared with intermediate-duration prescription.

DISCUSSION

Our study identified many predictors of chronic BZD use that could be of interest at the time of prescription. Predictors related to the patient included age, type of drug insurance plan, recent hospitalization, and antipsychotic drug use. Predictors related to the prescribing process were the number and type of BZD molecules dispensed, the dosage, and the duration of the initial BZD prescription. Particularly vulnerable subpopulations were identified using the regression trees. Patients with the lowest risk (< 5%) of chronic BZD use were the younger ones (18 to 29 years) who received only 1 BZD for 21 days or less prescribed by a nonpsychiatrist physician.

Like most previous authors, we found older age to be linked to chronic BZD use.[6,7,11-13,27-32] Similarly, while our sample comprised more female than male new BZD users, they were not at a greater risk of becoming chronic users.[7,11,12,30,31] Psychiatric comorbidity is a known predictor of chronic BZD use,[27,29,32,33] and we suspect that prescription by a psychiatrist and the availability of antipsychotic drugs are proxies for psychiatric comorbidity. We did not replicate previous findings on the association with anxiety disorders,[6,13] which we suspect is owing to underreporting of these conditions in the RAMQ database. Patients receiving disability insurance benefits are probably of lower socioeconomic

Figure 1. Patient selection from the database using RAMQ data



BZD—benzodiazepine, RAMQ—Régie de l'assurance maladie du Québec.
*Patient either withdrew from public drug insurance or died before 1 year of follow-up.
†Patients were excluded if they were hospitalized for more than 7 days during the chronic use assessment (days 181 to 365).

Table 1. Bivariate analyses for chronic BZD use in both age cohorts

	PATIENTS AGED 18-64 Y			PATIENTS AGED ≥65 Y		
CHARACTERISTICS	N	CHRONIC USERS, %	*P* VALUE	N	CHRONIC USERS, %	*P* VALUE
Total	13 688	19.9		3683	33.0	
Sex			<.01			.72
• Female	8739	18.6		2366	33.2	
• Male	4949	22.2		1317	32.7	
Age, y			<.01			<.01
• Mean (SD)	40.2 (11.7)	44.4 (11.1)		73.8 (6.1)	74.9 (6.6)	
• Median (IQR)	40 (31-49)	45 (37-53)		73 (69-78)	74 (69-80)	
Drug insurance coverage			<.01			<.01
• Regular	7607	14.3		1958	29.8	
• Financial assistance	3986	21.0		1725	36.6	
• Disability	2095	38.3		NA	NA	
Hospitalized in previous 30 d			<.01			<.01
• No	10 406	17.3		2034	26.5	
• Yes	3282	28.2		1649	41.1	
Charlson-D'Hoore comorbidity index score			<.01			<.01
• 0	10 642	18.3		1442	28.4	
• 1-2	2398	23.4		1157	33.6	
• 3-4	391	35.3		586	36.2	
• 5-6	138	35.5		254	44.5	
• ≥7	119	29.4		244	37.7	
Chronic pain (algorithm)			<.01			.06
• No	12 156	19.5		3143	32.5	
• Yes	1532	23.7		540	35.9	
Medication in previous 90 d						
• Antipsychotic			<.01			<.01
-No	11 777	17.7		3217	31.3	
-Yes	1911	33.5		466	44.6	
• Mood stabilizer			<.01			.22
-No	12 304	18.9		3373	32.7	
-Yes	1384	29.1		310	36.1	
• Antidepressant			.02			.83
-No	6846	19.2		1784	33.2	
-Yes	6842	20.7		1899	32.9	
Diagnosis (in previous 365 d)						
• Sleep disorder			.57			.12
-No	9699	19.8		2786	33.7	
-Yes	3989	20.2		897	30.9	

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Table 1 *continued from page e478*

CHARACTERISTICS	PATIENTS AGED 18-64 Y			PATIENTS AGED ≥65 Y		
	N	CHRONIC USERS, %	*P* VALUE	N	CHRONIC USERS, %	*P* VALUE
• Anxiety disorder			.01			.08
-No	13 351	19.8		3570	32.8	
-Yes	337	25.2		113	40.7	
• Substance use			<.01			<.01
-No	12 352	19.6		3491	32.5	
-Yes	1336	23.1		192	41.7	
No. of BZD molecules			<.01			<.01
• 1	11 797	17.6		3326	31.4	
• ≥2	1891	34.4		357	47.9	
Duration of initial prescription, d			<.01			<.01
• 1-7	2189	19.8		440	45.0	
• 8-14	2359	13.3		369	24.7	
• 15-21	2913	14.1		562	21.5	
• ≥22	6227	25.2		2312	34.9	
Initial dosage (in lorazepam equivalence), mg			<.01			.46
• <2	6573	16.5		2673	33.4	
• ≥2	7115	23.1		1010	32.1	
Molecule dispensed			<.01			<.01
• Alprazolam	1034	14.4		162	24.7	
• Bromazepam	401	13.2		93	21.5	
• Clonazepam	4290	23.2		598	30.4	
• Diazepam	267	15.0		57	19.3	
• Flurazepam	705	26.2		73	30.1	
• Lorazepam	3828	17.8		1277	31.5	
• Oxazepam	2061	19.1		1207	37.7	
• Temazepam	818	20.5		170	38.2	
• Other	284	22.5		46	41.3	
Prescriber specialty			<.01			<.01
• General practice	8989	16.8		2656	32.7	
• Psychiatry	3691	27.4		545	38.2	
• Other or unknown	1008	20.2		482	28.8	

BZD—benzodiazepine, IQR—interquartile range, NA—not applicable.

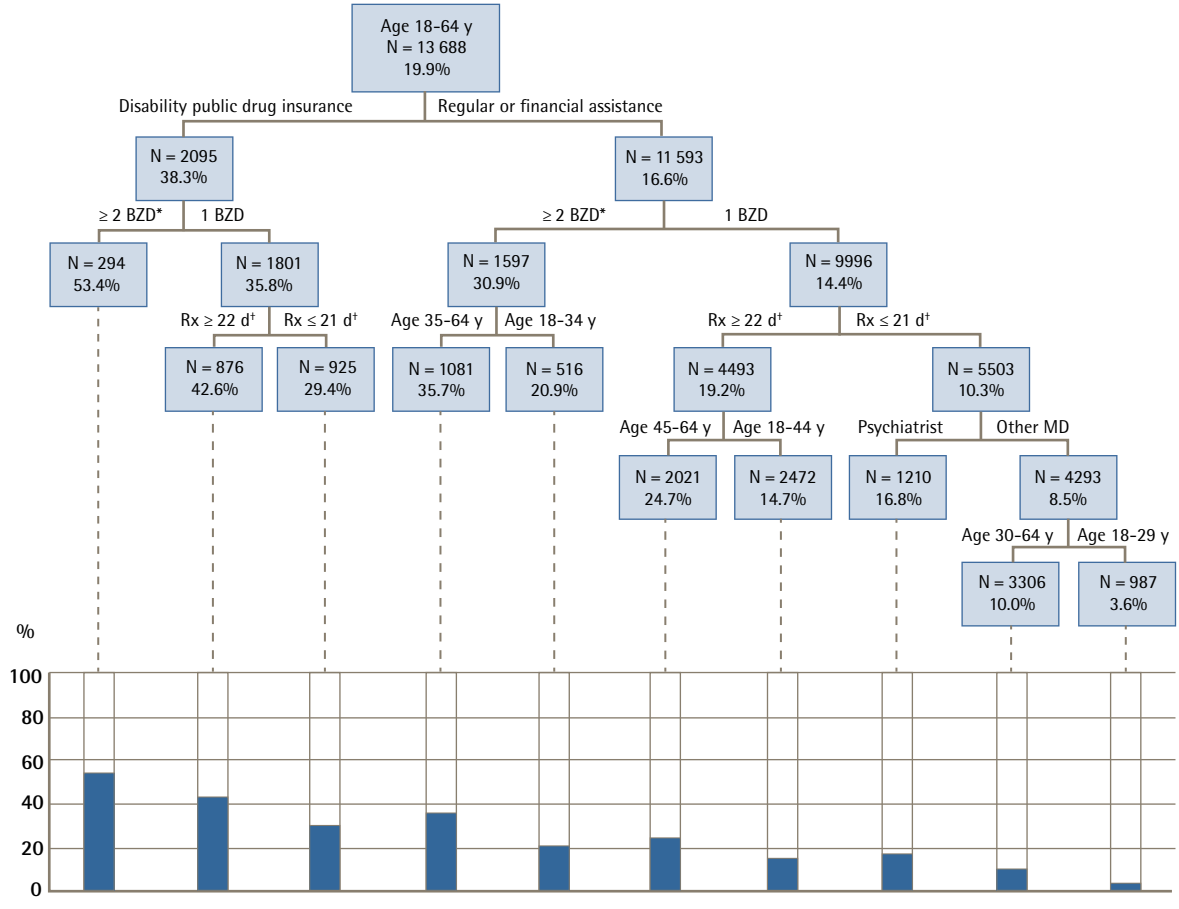
status and have lower education levels compared with the rest of the 18- to 64-year-old cohort, and these are 2 chronic BZD use predictors.[6,7,32,34] Somatic disorders and chronic pain were found to be linked to incident chronic BZD use in the elderly by Luijendijk et al,[31] findings not convincingly replicated in our study. One explanation is that this association does not remain in the depressed population, but it is noteworthy that these authors used self-reported data for comorbidity, which might differ from administrative data. Hospitalization is known to be a time window where BZD initiation frequently leads to chronic use,[33,35] even though most chronic use begins from ambulatory visits.[35] Finally, we found that a first BZD prescription for a duration of 7 days or less was an important predictor of chronic use for the 65 and older cohort, which is counterintuitive. However, van

Table 2. Multiple logistic regression for chronic BZD use in both age cohorts

	PATIENTS AGED 18-64 Y (N = 13 688)			PATIENTS AGED ≥65 Y (N = 3683)		
CHARACTERISTICS	OR (CRUDE)	ADJUSTED OR	99% CI	OR (CRUDE)	ADJUSTED OR	99% CI
Male sex	1.25*	1.03	(0.91-1.16)	0.98	0.90	(0.73-1.10)
Age (+ 1 y)	1.03*	1.03*	(1.03-1.04)	1.03*	1.02†	(1.00-1.03)
Drug insurance coverage						
• Regular	Reference			Reference		
• Financial assistance	1.59*	1.71*	(1.49-1.96)	1.36*	1.32*	(1.09-1.59)
• Disability	3.71*	2.81*	(2.39-3.30)	NA	NA	NA
Hospitalized in previous 30 d	1.87*	1.48*	(1.28-1.70)	1.93*	1.70*	(1.38-2.10)
Charlson-D'Hoore comorbidity index score						
• 0	Reference			Reference		
• 1-2	1.37*	1.07	(0.92-1.25)	1.28†	1.07	(0.84-1.36)
• 3-4	2.44*	1.47	(1.08-2.01)	1.43*	1.09	(0.82-1.47)
• 5-6	1.86†	1.08	(0.62-1.90)	2.02*	1.48†	(1.00-2.20)
• ≥7	2.46*	1.34	(0.80-2.22)	1.52†	1.17	(0.78-1.74)
Chronic pain (algorithm)	1.29*	1.16	(0.97-1.39)	1.16	1.06	(0.82-1.39)
Antipsychotic (in previous 90 d)	2.34*	1.51*	(1.28-1.79)	1.77*	1.64*	(1.24-2.17)
Mood stabilizer (in previous 90 d)	1.76*	1.06	(0.88-1.28)	1.16	1.02	(0.72-1.45)
Antidepressant (in previous 90 d)	1.10	1.26*	(1.12-1.42)	1.02	1.14	(0.94-1.38)
Sleep disorder (in previous 365 d)	1.37	1.19	(0.83-1.70)	1.41	1.38	(0.81-2.34)
Anxiety disorder (in previous 365 d)	1.03	1.00	(0.88-1.14)	0.88	0.89	(0.71-1.11)
Substance use disorder (in previous 365 d)	1.24†	0.92	(0.75-1.13)	1.48†	1.19	(0.78-1.80)
≥2 BZD dispensed	2.46*	2.48*	(2.13-2.89)	2.01*	2.24*	(1.65-3.06)
Duration of initial prescription, d						
• 1-7	Reference			Reference		
• 8-14	0.62*	0.75†	(0.60-0.94)	0.40*	0.47*	(0.31-0.71)
• 15-21	0.67*	0.87	(0.71-1.08)	0.34*	0.40*	(0.27-0.58)
• ≥22	1.36*	1.49*	(1.25-1.77)	0.65*	0.70†	(0.53-0.93)
Initial dosage equivalent to ≥2 mg of lorazepam	1.52*	1.38*	(1.22-1.56)	0.94	0.96	(0.77-1.21)
Molecule delivered						
• Alprazolam	0.78	0.97	(0.74-1.27)	0.71	0.82	(0.49-1.38)
• Bromazepam	0.71	0.82	(0.54-1.25)	0.60	0.67	(0.33-1.36)
• Clonazepam	1.40*	1.46*	(1.24-1.71)	0.95	1.05	(0.78-1.41)
• Diazepam	0.82	0.85	(0.53-1.39)	0.52	0.71	(0.29-1.78)
• Flurazepam	1.65*	1.11	(0.85-1.45)	0.94	0.94	(0.46-1.92)
• Lorazepam	Reference			Reference		
• Oxazepam	1.09	1.15	(0.95-1.40)	1.32†	1.25†	(1.00-1.58)
• Temazepam	1.20	1.27	(0.98-1.66)	1.35	1.53	(0.96-2.41)
• Other	1.35	1.17	(0.78-1.77)	1.53	1.67	(0.74-3.78)
Prescriber specialty						
• General practice	Reference			Reference		
• Psychiatry	1.86*	1.49*	(1.30-1.71)	1.27	1.24	(0.94-1.64)
• Other or unknown	1.25†	1.03	(0.82-1.31)	0.83	0.79	(0.59-1.05)

BZD—benzodiazepine, NA—not applicable, OR—odds ratio.
*$P < .001$.
†$P < .01$.

Figure 2. Regression tree for chronic BZD use: *Patients aged 18 to 64 years (N = 13 688).*



BZD—benzodiazepine, MD—medical doctor, Rx—prescription.
*≥ 2 BZD indicates a combination of BZD molecules at initiation.
†Rx ≥ x d or ≤ x d indicates the initial BZD was dispensed for more or less than x days.

Hulten et al found that a shorter episode of BZD use was linked to higher BZD consumption over time and higher risk of relapse.[30] A very short initial prescription might be insufficient for appropriate symptom relief but, to our knowledge, this hypothesis has not been tested rigorously in clinical trials.

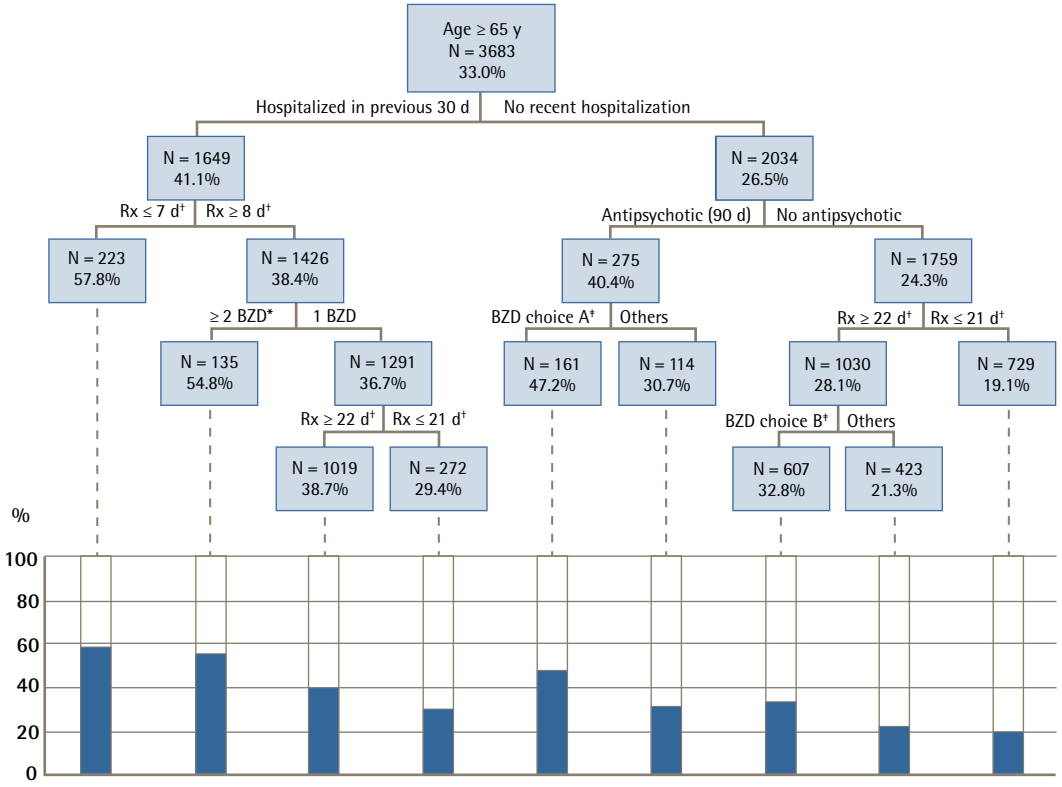
Limitations

Our study faced limitations inherent to research using administrative databases. For instance, data on the reasons for prescriptions or relevant psychological characteristics were not available in the RAMQ database, and socioeconomic factors could not be assessed directly. The diagnoses in the database were collected for billing purposes with ICD-9 codes, which limits their sensitivity regarding symptomatic complaints such as insomnia. Although the sample in this study is limited to public drug insurance beneficiaries, this population covers most family practice patients in Quebec.[36] However, external generalization is limited by exclusions for lack of information, which we nevertheless deemed necessary to preserve internal validity.

Strengths

Among the strengths of our study, the sample size makes it unlikely that a statistically significant relationship has been missed for lack of power. The range of variables used in the analyses included both patient- and prescription-related predictors, which was important for the purposes of our study. Moreover, we studied an exhaustive sample from real-life practice in Quebec, and we maintained a clinical perspective at all steps of the study, which is expected to ease interpretation and application of important results by clinicians. Finally, the comparison of regression trees and logistic regression helps to identify which predictors should be prioritized in future clinical-setting investigations.

Figure 3. Regression tree for chronic BZD use: *Patients aged 65 years and older (N = 3683).*



BZD—benzodiazepine, Rx—prescription.
*≥ 2 BZD indicates a combination of BZD molecules at initiation.
†Rx ≥ x or ≤ x d indicated that the initial BZD was dispensed for more or less than x days.
‡Choice A BZDs include alprazolam, clonazepam, oxazepam, and temazepam. Choice B BZDs include lorazepam, oxazepam, or other.

Conclusion

Benzodiazepines are effective for short-term symptomatic relief in depression, but many patients become chronic users. Our recommendations for physicians prescribing a new BZD for a recently depressed patient are to avoid a combination of BZDs, an independent predictor of future chronic use, in the absence of evidence-based benefit; to write a time-limited initial prescription, with 2-week intervals seeming more prudent than typical monthly prescriptions; and to consider alternatives for patients recently hospitalized or receiving disability benefits, as these factors predict future chronic BZD use. On a more positive note for younger patients, if these recommendations are followed, BZD use is relatively unlikely to become chronic in adults younger than 30 who do not have serious comorbidities. Future studies should seek to replicate and expand our conclusions to help provide safe and appropriate care to depressed patients by family physicians and other specialists.

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Contributors

Dr Vanasse had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. **Drs Carrier, Courteau,** and **Vanasse** contributed to the study concept and design. **Drs Courteau** and **Vanasse** contributed to data acquisition. **Drs Carrier** and **Courteau** contributed to data cleaning and analysis, and to statistical analysis. **Drs Carrier, Roberge,** and **Vanasse** contributed to data interpretation. **Dr Carrier** contributed to drafting the manuscript. **Drs Courteau, Roberge,** and **Vanasse** contributed to critical revision of the manuscript for important intellectual content.

Competing interests

None declared

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References

1. Neutel CI. The epidemiology of long-term benzodiazepine use. *Int Rev Psychiatry* 2005;17(3):189-97.
2. Dell'osso B, Lader M. Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal. *Eur Psychiatry* 2013;28(1):7-20. Epub 2012 Apr 20.
3. Furukawa TA, Streiner D, Young LT, Kinoshita Y. Antidepressants plus benzodiazepines for major depression. *Cochrane Database Syst Rev* 2001;(2):CD001026.
4. Kennedy SH, Lam RW, Parikh SV, Patten SB, Ravindran AV. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. *J Affect Disord* 2009;117(Suppl 1):S1-2. Epub 2009 Aug 13.
5. Bijlsma MJ, Hak E, Bos J, De Jong-van den Berg LT, Janssen F. Assessing the effect of a guideline change on drug use prevalence by including the birth cohort dimension: the case of benzodiazepines. *Pharmacoepidemiol Drug Saf* 2013;22(9):933-41. Epub 2013 Jun 3.
6. Cunningham CM, Hanley GE, Morgan S. Patterns in the use of benzodiazepines in British Columbia: examining the impact of increasing research and guideline cautions against long-term use. *Health Policy* 2010;97(2-3):122-9. Epub 2010 Apr 21.
7. Préville M, Bossé C, Vasiliadis HM, Voyer P, Laurier C, Berbiche D, et al. Correlates of potentially inappropriate prescriptions of benzodiazepines among older adults: results from the ESA study. *Can J Aging* 2012;31(3):313-22. Epub 2012 Jul 17.
8. McIntosh B, Clark M, Spry C. *Benzodiazepines in older adults: a review of clinical effectiveness, cost-effectiveness, and guidelines.* Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2011.
9. Gould RL, Coulson MC, Patel N, Highton-Williamson E, Howard RJ. Interventions for reducing benzodiazepine use in older people: meta-analysis of randomised controlled trials. *Br J Psychiatry* 2014;204(2):98-107. Erratum in: *Br J Psychiatry* 2014;205(4):330.
10. Mugunthan K, McGuire T, Glasziou P. Minimal interventions to decrease long-term use of benzodiazepines in primary care: a systematic review and meta-analysis. *Br J Gen Pract* 2011;61(590):e573-8. Erratum in: *Br J Gen Pract* 2013;63(606):12.
11. Holzbach R, Jahn H, Pajonk FG, Naber D. Benzodiazepines in addition to antidepressants in the treatment of severely depressed inpatients—how often does it lead to long-term intake? *Ger J Psychiatry* 2008;11(4):134-40.
12. Li YH, Xiang YT, Su YA, Shu L, Yu X, Kilbourne AM, et al. Long-term benzodiazepine use in patients with major depressive disorder in China. *Perspect Psychiatr Care* 2014;50(3):149-54.
13. Pfeiffer PN, Ganoczy D, Zivin K, Valenstein M. Benzodiazepines and adequacy of initial antidepressant treatment for depression. *J Clin Psychopharmacol* 2011;31(3):360-4.
14. Régie de l'assurance maladie du Québec. *Données et statistiques*. Quebec, QC: Régie de l'assurance maladie du Québec. Available from: **www.ramq.gouv.qc.ca/fr/donnees-statistiques/Pages/donnees-statistiques.aspx**. Accessed 2015 Mar 13.
15. Vanasse A, Courteau J, Fleury MJ, Grégoire JP, Lesage A, Moisan J. Treatment prevalence and incidence of schizophrenia in Quebec using a population health services perspective: different algorithms, different estimates. *Soc Psychiatry Psychiatr Epidemiol* 2012;47(4):533-43. Epub 2011 Mar 29.
16. Gouvernement du Québec. *Loi sur l'assurance-maladie du Québec (A-29.01)*. Quebec, QC: Gouvernement du Québec; 2016. Available from: **www2.publicationsduquebec.gouv.qc.ca/dynamicSearch/telecharge.php?type=2&file=/A_29/A29.html**. Accessed 2016 Jul 13.
17. Assayag J, Forget A, Kettani FZ, Beauchesne MF, Moisan J, Blais L. The impact of the type of insurance plan on adherence and persistence with antidepressants: a matched cohort study. *Can J Psychiatry* 2013;58(4):233-9.
18. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Québec. *J Clin Epidemiol* 1995;48(8):999-1009.
19. Health Canada. *Rapport sur les maladies mentales au Canada*. Ottawa, ON: Health Canada; 2002.
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-83.
21. D'Hoore W, Bouckaert A, Tilquin C. Practical considerations on the use of the Charlson comorbidity index with administrative data bases. *J Clin Epidemiol* 1996;49(12):1429-33.
22. Tian TY, Zlateva I, Anderson DR. Using electronic health records data to identify patients with chronic pain in a primary care setting. *J Am Med Inform Assoc* 2013;20(e2):e275-80. Epub 2013 Jul 31.
23. Canadian Pharmacists Association. *CPS. Compendium of pharmaceuticals and specialties*. Ottawa, ON: Canadian Pharmacists Association; 2013.
24. Zhang H, Holford T, Bracken MB. A tree-based method of analysis for prospective studies. *Stat Med* 1996;15(1):37-49.
25. Zhang H, Singer B. *Recursive partitioning in the health sciences*. New York, NY: Springer; 1999.
26. Vanasse A, Courteau J, Lesage A, Fleury MJ, Grégoire JP, Moisan J, et al. Inégalités de santé des troubles de l'humeur selon la défavorisation matérielle et sociale du quartier de résidence. *Can J Psychiatry* 2012;57(12):772-81.
27. Ayalon L, Gross R, Yaari A, Feldhamer E, Balicer RD, Goldfracht M. Patients' and physicians' characteristics associated with the purchase of benzodiazepines by older primary care patients in Israel. *Adm Policy Ment Health* 2013;40(2):117-23.
28. Bramness JG, Sexton J. The basic pharmacoepidemiology of benzodiazepine use in Norway 2004-9. *Nor Epidemiol* 2011;21(1):35-41.
29. Manthey L, Giltay EJ, van Veen T, Neven AK, Zitman FG, Penninx BW. Determinants of initiated and continued benzodiazepine use in the Netherlands study of depression and anxiety. *J Clin Psychopharmacol* 2011;31(6):774-9.
30. Van Hulten R, Teeuw KB, Bakker A, Leufkens HG. Initial 3-month usage characteristics predict long-term use of benzodiazepines: an 8-year follow-up. *Eur J Clin Pharmacol* 2003;58(10):689-94. Epub 2003 Feb 7.
31. Luijendijk HJ, Tiemeier H, Hofman A, Heeringa J, Stricker BH. Determinants of chronic benzodiazepine use in the elderly: a longitudinal study. *Br J Clin Pharmacol* 2008;65(4):593-9. Epub 2007 Dec 17.
32. Zandstra SM, Van Rijswijk E, Rijnders CA, Van De Lisdonk EH, Bor JH, Van Weel C, et al. Long-term benzodiazepine users in family practice: differences from short-term users in mental health, coping behaviour and psychological characteristics. *Fam Pract* 2004;21(3):266-9.
33. Fang SY, Chen CY, Chang IS, Wu EC, Chang CM, Lin KM. Predictors of the incidence and discontinuation of long-term use of benzodiazepines: a population-based study. *Drug Alcohol Depend* 2009;104(1-2):140-6. Epub 2009 Jun 9.
34. Fortin D, Préville M, Ducharme C, Hébert R, Trottier L, Grégoire JP, et al. Factors associated with long-term benzodiazepine use among elderly women and men in Quebec. *J Women Aging* 2007;19(3-4):37-52.
35. Halme AS, Beland SG, Preville M, Tannenbaum C. Uncovering the source of new benzodiazepine prescriptions in community-dwelling older adults. *Int J Geriatr Psychiatry* 2013;28(3):248-55. Epub 2012 May 8.
36. Duhoux A, Fournier L, Nguyen CT, Roberge P, Beveridge R. Guideline concordance of treatment for depressive disorders in Canada. *Soc Psychiatry Psychiatr Epidemiol* 2009;44(5):385-92. Epub 2008 Oct 22.