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Multinational comparison of new antidepressant use in older adults: a cohort study

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ABSTRACT

Objectives We used an international pharmacosurveillance network to estimate the rate and characteristics of antidepressant use in older adults in countries with more conservative (UK) and liberal depression guidelines (Canada, USA).

Setting Electronic health records and population-based administrative data from six jurisdictions in four countries (UK, Taiwan, USA and Canada).

Participants A historical cohort of older adults (≥65 years) who had a new episode of antidepressant use between 2009 and 2014.

Outcome measures The age and sex-standardised cumulative incidence of new episodes of antidepressant use in older adults was measured. Descriptive statistics were used to compare the proportion of new users by the antidepressant prescribed, therapeutic class, potential treatment indication and country, as well as the characteristics of the first treatment episode (standardised daily doses, duration and changes).

Results The incidence of antidepressant use between 2009 and 2014 varied from 4.7% (Montreal and Quebec City) to 18.6% (Taiwan). Tricyclic antidepressants (TCAs) were the most commonly used class in the UK (48.8%) and Taiwan (52.4%) compared with selective serotonin reuptake inhibitors (SSRIs) in North American jurisdictions (42.3%–53.3%). Chronic pain was the most common potential treatment indication (41.2%–68.2%). Among users with chronic pain, TCAs were used most frequently in the UK and Taiwan (55.2%–60.4%), whereas SSRIs were used most frequently in North America (33.5%–46.4%). Treatment was longer (252–525 vs 169–437 days), standardised doses were higher (0.7–1.3 vs 0.5–1.0) and treatment was more likely to be changed (31%–46% vs 21%–34%) among patients with depression (9.1%–43%) than those with chronic pain.

Conclusion Antidepressant use in older adults varied 24-fold by country, with the UK, which has the most conservative treatment guidelines, being among the lowest. Chronic pain was the most common potential treatment indication. Evaluation of real-world risks of TCAs is a priority for future research, given high rates of use and the potential for increased toxicity in older adults because of potent anticholinergic effects.

Strengths and limitations of this study

- ► Uses an international pharmacosurveillance network to characterise antidepressant use across multiple jurisdictions.
- ► Despite data harmonisation efforts, measurement and reporting issues may lead to arbitrary differences between regions and countries.
- ► Treatment indication is unknown for all but one study cohort. Documentation of health problems in medical services billing data and electronic medical records was used as a proxy for treatment indication for remaining cohorts, which could have resulted in misclassification bias.
- ► While some cohorts represented total populations or representative samples, others were assembled from practices supported by specific information technology systems.

INTRODUCTION

Depression affects an estimated 300 million people worldwide.[1] In the past decade, many countries have reported a twofold to threefold increase in the use of antidepressant medications.[2] The primary increase has been in newer antidepressants such as selective serotonin reuptake inhibitors (SSRIs), which are considered to have better efficacy than older drugs, with fewer side effects.[3] Increasing prevalence of use of antidepressants has also been associated with an increase in the number of people started on therapy as well as its duration, with 40% of antidepressants being prescribed for more than 180 days.[4] Antidepressants now represent one of the most commonly prescribed medications,[5 6] especially among older adults, where the increase in use has been the greatest in the US population.[5 7]

The increasing use of antidepressants in older adults may be due to a number of factors. There has been long-standing advocacy for better recognition and treatment of depression in older adults.[8 9] In addition, individuals with multiple chronic conditions are more likely to experience depression. In Canada, 12% of

persons ≥65 years have two or more major chronic conditions compared with only 3.6% in younger adults; and 4% of adults with at least one major chronic disease have mood or anxiety disorders, which are other approved indications for antidepressant use.[10] While increasing prevalence of depression, anxiety and other mood disorders in older adults may account for increasing use of antidepressants, there is also evidence that antidepressants are prescribed for unapproved indications that may not be supported by scientific evidence of efficacy.[11–14] One recent study found that nearly 50% of antidepressants were prescribed for unapproved indications including chronic pain, tiredness and sleep disturbance,[11] which are also more common in older adults.[15]

Taken together, these factors have led to increasing concern about overuse of antidepressants, particularly in older adults.[16] This concern is heightened because of the reported association between antidepressant use and fall-related injuries, motor vehicle accidents, functional decline and mortality in older adults.[17–19] Clinical practice guidelines for the management of depression vary considerably in their recommendations for first-line treatment,[20–24] although most acknowledge the need to consider patient preferences (table 1). The UK NICE guidelines are the most conservative, recommending first-line treatment with psychotherapy such as cognitive behavioural therapy with pharmacotherapy added only if non-pharmacological therapy is unsuccessful.[24] At the other end of the spectrum, the Canadian 2009 guidelines list pharmacotherapy as a first-line treatment for major depressive disorder, including SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), mirtazapine or bupropion.[25–27] Of note, Canada ranks the third highest user of antidepressants among 23 Organisation for Economic Co-operation and Development countries, surpassed only by Australia and Iceland.[2]

However, few data are available regarding how national guidelines may contribute to differences in how antidepressants are used for older adults. We took advantage of an international pharmacosurveillance network[28] that uses electronic medical record (EMR) and population-based health administrative data to estimate the rate of antidepressant use in older adults in countries that had more conservative (UK) and lenient guidelines (Canada, USA, Taiwan). We evaluated differences in the choice of antidepressant, dose and duration of treatment, the prevalence of dose changes and switches in treatment of older adults with new episodes of antidepressant use, as well as differences in treatment approach for patients with a recorded diagnosis of depression, other mental health comorbidities and chronic pain.

METHODS

Study design and population

To characterise antidepressant use in older adults, a cohort of individuals who were ≥65 years of age and had a new episode of antidepressant use between 1 January 2009 and 31 December 2014 following 2 years during which they had no prescription or dispensation of an antidepressant was assembled. Eligible patients were identified from EMR or population-based registries in a total of six jurisdictions in four countries (Canada, USA, UK and Taiwan).

Data sources

Canada

Quebec EMR cohort

Data were extracted from the Medical Office of the 21st Century (MOXXI) EMR, which includes a real-time linkage to the Quebec insurance agency, the Régie de l'assurance maladie du Québec (RAMQ) databases. This linkage provides historical and daily updates of patients' received medical services (diagnosis, procedure, date, location, provider), prescriptions dispensed from community pharmacies for persons who are publicly insured (prescriber, pharmacy, drug, dose, dispensing date, duration, refills) and mortality. Approximately 110 primary care physicians in Quebec use MOXXI for approximately 90 000 of their patients, representing approximately 25% of the patients in the practice, and approximately 5% of the Quebec population in primary care practices.

Quebec administrative data cohort

Data were retrieved from the Montreal Population Health Record, a population-based 25% random sample of the 4.1 million residents of Montreal, Canada's second largest city, which is dynamically updated each year to account for in and out-migration. Beneficiary characteristics were measured by linking the RAMQ beneficiary database (age, sex, postal code) with Statistics Canada's census file (postal code level measures of socioeconomic status) and the Institute of Statistics birth and death registry (date of birth and death). From this population-based dataset, we identified all non-institutionalised persons ≥65 years of age between 2009 and 2014. All medical services (date, diagnosis, procedure), hospitalisations (admission and discharge date, primary and secondary diagnoses, in-hospital procedures) and medications (prescriber, pharmacy, drug, dose, dispensing date, duration, refills) received by members of the cohort were retrieved from the RAMQ database and those of the Quebec Ministry of Health.

Ontario administrative data cohort

Data were extracted from the Institute for Clinical Evaluative Sciences population-based repository of health records for the 13.6 million Ontario residents. The data are provided by the Ontario Ministry of Health and Long-Term Care, which pays for all essential health services. For the 2 053 588 Ontario non-institutionalised residents who were ≥65 years between 2007 and 2014, we randomly sampled 20% and extracted age, sex and date of death from the beneficiary registrants database, all billing claims for medical services provided by Ontario physicians (date of service, diagnosis, procedure code, physician provider), all claims for medications dispensed in the community by Ontario pharmacies (drug, date dispensed, prescriber,

Table 1 Summary of depression guidelines

	US—APA guidelines (2010)	UK—NICE guidelines (2009)	Canada—CANMAT (2009)	Taiwan—Taiwan Association Against Depression (2012)
First-line treatment	Antidepressant medications for patients with mild, moderate or severe MDD, especially patients with a history of prior positive response, moderate to severe symptoms, significant sleep or appetite disturbances, agitation, patient preference, etc. Psychotherapy for patients with mild/moderate MDD, especially in the presence of significant psychosocial stressors, intrapsychic conflict, interpersonal difficulties, a co-occurring Axis II disorder, treatment availability or patient preference. The combination of psychotherapy and antidepressant medication for patients with moderate to severe MDD, as well as in milder cases for patients with psychosocial or interpersonal problems, intrapsychic conflict, or co-occurring Axis II disorder.	For patients with persistent subthreshold depressive symptoms or mild to moderate depression, first-line treatment is low-intensity psychosocial interventions. Antidepressants should be considered only for patients with a past history of moderate or severe depression, initial presentation of symptoms that have been present for a long period (at least 2 years)or subthreshold depressive symptoms or mild depression that persists after other interventions. For patients with persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions, an antidepressant or a high-intensity psychological intervention should be considered. For patients with moderate or severe depression, a combination of antidepressant medication and a high-intensity psychological intervention should be provided.	Second-generation antidepressants are first-line treatments for patients with a major depressive episode of moderate or greater severity. First-line treatments for individuals with depression of mild severity include CBT and IPT. Psychotherapy should be considered for patients with treatment-resistant depression.	Pharmacotherapy (preferred) or psychotherapy.
Pharmacotherapy first-line treatment	Antidepressant selection should be based on the tolerability, safety and cost of the medication, as well as patient preference and history of prior medication treatment. SSRIs, SNRIs, mirtazapine and bupropion are optimal for most patients. MAOIs are limited to patients who do not respond to other treatments.	Prescribed antidepressant should normally be an SSRI in a generic form. When prescribing drugs other than SSRIs, the following should be considered: ▶ The increased likelihood of the person stopping treatment because of side effects (and the consequent need to decrease the dose gradually) with venlafaxine, duloxetine and TCAs. ▶ The specific cautions, contraindications and monitoring requirements for some drugs. ▶ Non-reversible MAOIs, such as phenelzine, should normally be prescribed only by specialist mental health professionals. ▶ Dosulepin should not be prescribed.	Choice of antidepressant should be based on patient factors (clinical features, patient preference, etc) and medication factors (drug–drug interactions, cost, availability, efficacy and tolerability). First-line treatments include SSRIs, SNRIs, agomelatine, bupropion, mirtazapine, mianserin and vortioxetine. Second-line treatments include TCAs, quetiapine and trazodone, moclobemide and selegiline, levomilnacipran and vilazodone. Third-line treatments include MAOIs and reboxetine.	SSRIs, SNRIs or any one of the newer antidepressive agents except MAOIs.

APA, American Psychological Association; CANMAT, Canadian Network for Mood and Anxiety Treatments; CBT, cognitive behavioural therapy; IPT, interpersonal therapy; MAOIs, monoamine oxidase inhibitors; MDD, major depressive disorder; NICE, National Institute for Health and Care Excellence; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

quantity, duration, number of refills) and data from discharge summaries of emergency department visits and hospital stays (date of admission and discharge, primary and secondary diagnoses and procedures).

USA

Boston, Massachusetts EMR cohort

Data were extracted from the Partners HealthCare Research Patient Data Registry (RPDR), which provides care for approximately 3 million of 5 million residents in Boston and surrounding areas. RPDR includes data from the longitudinal medical record (LMR), an internally developed, web-based, fully functional EMR that was in use during this period for the participating primary care clinics from Brigham and Women's Hospital (BWH) and Massachusetts General Hospital (MGH), the two founding members of Partners Healthcare in Boston, Massachusetts. Data were retrieved from the structured clinical encounter information from RPDR for all outpatient primary care visits. To ensure complete follow-up, patients were eligible if they were seen in one of 37 BWH-affiliated or MGH-affiliated primary care or diabetes clinics.

UK

EMR cohort

Data were extracted from the Clinical Practice Research Datalink (CPRD), an anonymised LMRs database for primary care. The primary care EHR includes information on all primary care interactions, including documented health problems, visit notes, prescriptions and records of specialty referrals, as well as information on lab results, hospitalisations and death. The CPRD includes more than 4 million active patients, 76% of whom are in England, representing 6.9% of the 64 million primary care population in the UK, and around 600 primary care practices.[29] Patients were included if their records met minimum quality standards and there were no gaps in registration. A 10% random sample of the 2 436 180 elderly patients in the database were extracted.

Taiwan

Administrative data cohort

Data were extracted from the Taiwanese National Health Insurance (NHI) system databases. The NHI provides health coverage to around 99% of Taiwan's population of 23 million, providing comprehensive coverage for all health services, including dental, preventive, Western medicine and traditional Chinese medicine services. A random sample of 103 400 of the 3.6 million residents who were ≥65 years in Taiwan between 2007 and 2014 was extracted for this study. The NHI's research databases include a registry for beneficiaries (eg, registrant's age, sex and residence), an outpatient visit database (date and time of visit, ICD-9-CM codes of existing health problems, service provided), an inpatient visit database (date of hospitalisation and discharge, ICD-9-CM codes of existing health problems, procedure codes and dates) and a pharmacy database (drug prescribed, date, duration, dosage, prescribing physician, dispensing pharmacy).

Measurement

Patient characteristics

Age and sex

Date of birth and sex were retrieved from the administrative data in Canada and Taiwan as these data are verified at the time of enrollment in the health plan. For the USA and UK, these data were retrieved from the EMR.

Depression, other mental health comorbidities and chronic pain

We measured the existence of potential indications for antidepressant use[11 12] including depression, other mental health conditions and chronic pain. Depression included mild, moderate, major single or recurrent depressive disorder with or without psychotic symptoms, adjustment reaction and mixed anxiety and depression. Other mental health conditions included anxiety, alcohol abuse, illicit drug use, attempted suicide, psychosis, schizophrenia and bipolar disorder. Anxiety included dissociative and somatoform disorders. We used standard diagnostic codes (ICD 9, ICD 10 and Read codes) retrieved from the EMR, and/or medical services claims, and hospitalisations in the 2 years prior to the first antidepressant prescription to measure these conditions (see online supplementary appendix).

To measure chronic pain, we used a previously validated ICD9 and ICD10 code set for non-cancer pain.[30] The concepts and definitions used in the development and validation of this code set were used to map to Read codes (appendix available on request). Chronic non-cancer pain conditions included lumbar pain, back disorders that are often associated with pain (eg, degenerative disc disease), neck and back problems (eg, spondylosis), fibromyalgia, complex regional pain syndromes (eg, mononeuritis), painful neuropathic disorders (eg, postherpetic neuralgia), pain disorders with psychosocial dysfunction and unclassified chronic pain problems.

Characterising antidepressant use

The characteristics of antidepressant use were compared in the population of seniors with a new episode of antidepressant use in each country, overall and then within subgroups that had a diagnosis of (a) depression, (b) chronic pain or (c) other mental health problems.

Classification of starting therapy

The Anatomic Therapeutic Classification system[31] was used to map national drug names and identification numbers to a common nomenclature based on the antidepressants that were prescribed during the study time period. Therapeutic classes included tricyclic antidepressants (TCAs), SSRIs, SNRIs, serotonin antagonist and reuptake inhibitors (SARIs), norepinephrine–dopamine reuptake inhibitors (NDRIs), noradrenergic and specific serotonergic antidepressants, tetracyclic antidepressants, melatonergic agonists and NRIs. Monoamine oxidase inhibitors were excluded as they are rarely used and only

for bipolar disorder. Starting therapy was classified by therapeutic class and drug, and by the number of antidepressants prescribed at treatment initiation.

Starting antidepressant dose

To enable comparisons in the dose prescribed among antidepressants, we created a standardised dose for each drug by dividing the prescribed dose by the WHO recommended daily dose for adults. The resulting indicator represents the proportion of the recommended daily adult dose that was prescribed. When more than one antidepressant was prescribed concurrently, we summed the standardised dose for each drug.

Analysis

The cumulative incidence of older adults with new episodes of antidepressant use in the period 2009 to 2014 was measured by dividing the number of new users by the total population that was ≥65 years during this time period. Rates were standardised for age and sex using the direct method and the UK as the reference population. New episodes of use were defined as those who had no prior prescription of an antidepressant in the 2 years preceding their first prescription. Descriptive statistics were used to compare the proportion of new antidepressant users by the antidepressant prescribed, therapeutic class, country and potential treatment indication, as well as the characteristics of the first treatment episode. As the coexistence of other mental health conditions may modify treatment choices, we used the prevalence ratio to estimate the concurrence of other mental health problems, chronic pain and depression. The prevalence ratio allowed us to compare between countries even if the prevalence of these conditions is different.[32] It was calculated as the prevalence of the health problem of interest among individuals with depression, divided by the prevalence of the health problem among individuals without depression.

Patient and public involvement

Patients and members of the public were not involved in the development of research questions or outcome measures, design or implementation of this study. There are no plans to involve patients in dissemination of research results.

RESULTS

The age-standardised cumulative incidence of antidepressant use in persons aged ≥65 in the period 2009–2014 was highest in Taiwan (18.6%) and Ontario, Canada (15.3%), and lowest in Quebec-Montreal (4.7%) and England (6.6%) (table 2). Simlarly, the overall prevalence of antidepressant use in the same time period was lowest in England (10.3%), and highest in Ontario, Canada (26.8%) and Taiwan (23.4%). The distribution of age was similar in all jurisdications.

Frequency distribution of the first antidepressant prescription by therapeutic class

Overall, there were substantial differences between jurisdictions in the choice of starting therapy for new users (table 3). Tricyclic antidepressants were the most commonly used class of antidepressants in England (48.8%) and Taiwan (52.4%) compared with SSRIs in North American jurisdictions (42.3%–53.3%). Notably, in the UK, approximately one-quarter of antidepressant prescriptions were for newer classes of antidepressants: serotonin antagonist and reuptake inhibitors (trazodone), norepinephrine–dopamine reuptake inhibitors (bupropion) and noradrenergic serotonin-specific antidepressants (mirtazapine).

Coexistence of depression, other mental health problems and chronic pain

The prevalence of a depression diagnosis among new antidepressant users was relatively low, varying from 9.1% (Taiwan) to 21.7% (USA). The exception was the EMR cohort in Quebec where the prevalence was 43.0% (table 4). Among new antidepressant users with a diagnosis of depression, there was a 30% (UK prevalence ratio: 1.3) to sevenfold (USA prevalence ratio: 7.3) increase in the likelihood of also having an alcohol or other substance abuse problem. Anxiety, which varied from being present in 12.1% of new antidepressant users in the UK to 47.8% of new users in Taiwan, was the most common mental health problem, and was also more likely to be present among persons with depression (Prevalence ratio: 1.3 [Ontario, Quebec] to 3.6 [USA]). Although less common in all jurisdictions, both major mental illness and suicide attempt were more likely to be present among antidepressant users with depression compared with those without depression. In contrast, chronic pain was the most prevalent problem among new antidepressant users (41.2% [UK] to 68.2% [Taiwan]), and was as likely to be present among those with or without depression (Prevalence ratio: 0.9–1.3) (table 4). For almost one-third of new antidepressant users, there was no documented diagnosis of depression, other mental health problems or chronic pain.

Choice of antidepresssant by potential treatment indication

Among new antidepressant users with a diagnosis of depression, SSRIs were selected as the starting therapy for 55.2% (Ontario) to 71.4% (UK), followed by SNRIs in Canadian jurisdictions and newer antidepressants in Boston, the UK and Taiwan (table 5). For antidepressant users with a diagnosis of chronic pain, starting therapy was predominantly with SSRIs in North American jurisdictions (33.5%–46.1%), and with TCAs in the UK and Taiwan (55.2%–60.4%). Selection of therapy for other mental health problems was a mixture of choices made for persons with a diagnosis of depression and chronic pain.

Characteristics of the first treatment episode by potential treatment indication

Among patients with a diagnosis of depression who were started on antidepressants, 54% (Ontario) to 68%

Table 2 Comparisons in the cumulative incidence and prevalence of episodes of antidepressant use in adults ≥65 years between regions and countries

Elderly population	Canada			USA	UK	Taiwan
	Ontario sample (Admin. data)*†	Montreal sample (Admin. data)*†	Quebec city and Montreal (EMR data)‡	Boston (EMR data)‡	CPRD sample (EMR data)†‡	NHIRDB (Admin. data)*
Total elderly population	**405 141**	**120 777**	**28 273**	**83 394**	**241 339**	**103 400**
All users of antidepressants§						
No of users	108 577	23 422	4450	17 359	24 858	24 239
Prevalence in elderly (%)	26.8	19.4	15.7	20.8	10.3	23.4
New episodes of antidepressant use¶						
Number of new users	60 366	13 303	1308	10 131	15 868	17 580
Incidence in elderly (%)	14.9	11.0	4.6	12.2	6.6	17.0
Age-standardised -incidence (%)	15.3	12.1	4.7	12.3	6.6 (reference)	18.6
Sex-standardised incidence (%)	14.9	11.0	4.6	12.1	6.6 (reference)	17.0
Demographics						
Between 65 and 74 years old	32 115 (53.2%)	5713 (42.9%)	699 (53.4%)	5826 (57.5%)	7129 (44.9%)	8811 (50.1%)
≥75 years	28 251 (46.8%)	7590 (57.1%)	609 (46.6%)	4305 (42.5%)	8739 (55.1%)	8769 (49.9%)
Female	36 884 (61.1%)	8986 (67.5%)	853 (65.2%)	6136 (60.6%)	10 045 (63.3%)	9539 (54.3%)

*Administrative data are retrieved from population-based health insurance claims for medical visits and prescriptions.
†Ontario represents a 20% random sample of elderly, Montreal represents a 25% annual random sample of Montreal residents and the UK represents a 10% random sample of elderly in the CPRD.
‡EMR data are extracted from primary care clinic electronic health records in the USA (Partners), Quebec (MOXXI) and the UK (Clinical Practice Research Database).
§All users include persons with an active prescription or dispensed supply of antidepressants between 2007 and 2008 as well as all new users between the period 2009 and 2014.
¶New episodes of use of antidepressants were defined as no prescription or dispensing of an antidepressant in the 2 years prior to the first antidepressant in the period N2009–2014.
CPRD, Clinical Practice Research Datalink; EMR, electronic medical record; MOXXI, Medical Office of the 21stst Century; NHIRDB, National Health Insurance Research Database.

Table 3 Frequency distribution of the first antidepressant prescribed for new antidepressant users by therapeutic class by country and jurisdiction

	Canada			USA	UK	Taiwan
	Ontario sample (n=60 366 patients n=61 696 Rx)	Montreal sample (n=13 303 patients n=14 217 Rx)	Quebec city and Mtl (n=1308 patients n=1324 Rx)	Boston (n=10 131 patients n=10 586 Rx)	CPRD (n=15 868 patients n=15 970 Rx)	NHIRDB (n=17 580 patients n=17 790 Rx)
Antidepressant	**n Rx (%)**	**n Rx (%)**	**n Rx (%)**	**n Rx (%)**	**n Rx (%)**	**n Rx (%)**
Selective serotonin reuptake inhibitors						
Citalopram	8760 (14.2)	4708 (33.1)	410 (30.9)	2117 (19.9)	4232 (26.4)	335 (1.8)
Escitalopram	9000 (14.6)	1 (0.0)	73 (5.5)	438 (4.1)	145 (0.9)	825 (4.6)
Fluoxetine	697 (1.1)	114 (0.8)	8 (0.6)	1156 (10.9)	876 (5.4)	773 (4.3)
Fluvoxamine	172 (0.3)	44 (0.3)	6 (0.4)	29 (0.2)	1 (0.0)	101 (0.5)
Paroxetine	1924 (3.1)	515 (3.6)	23 (1.7)	432 (4.0)	92 (0.5)	435 (2.4)
Sertraline	2561 (4.2)	640 (4.5)	132 (20.2)	1481 (13.9)	990 (6.1)	1174 (32.2)
Subtotal	23 114 (37.4)	6022 (42.3)	652 (49.2)	5653 (53.3)	6336 (39.6)	3643 (20.4)
Selective norepinephrine reuptake inhibitors						
Desvenlafaxine	0 (0.0)	1 (0.0)	4 (0.3)	28 (0.2)	–	–
Duloxetine	3190 (5.2)	161 (1.1)	57 (4.3)	267 (2.5)	156 (0.9)	241 (1.3)
Milnacipran	0 (0.0)	–	–	2 (0.0)	–	18 (0.1)
Venlafaxine	3323 (5.4)	1514 (10.6)	105 (7.9)	434 (4.0)	144 (0.8)	206 (1.1)
Subtotal	6513 (10.5)	1676 (11.7)	166 (12.5)	731 (6.9)	290 (1.8)	465 (2.6)
Tricyclic antidepressants						
Amitriptyline	10 448 (16.9)	2629 (18.4)	120 (9.0)	796 (7.5)	7255 (45.4)	1181 (6.6)
Dosulepin	–	–	–	–	177 (1.1)	25 (0.2)
Imipramine	–	–	–	32 (0.3)	54 (0.3)	7340 (41.2)
Nortriptyline	3158 (5.1)	95 (0.6)	18 (1.3)	566 (5.3)	208 (1.3)	–
Other TCAs*	1860 (12.0)	263 (1.8)	24 (1.8)	117 (1.1)	113 (0.%)	778 (4.4)
Subtotal	15 466 (25.0)	2987 (21.0)	162 (12.2)	1511 (14.2)	7807 (48.8)	9324 (52.4)
Serotonin antagonist and reuptake inhibitors						
Trazodone	12 373 (20.1)	2362 (16.6)	192 (14.5)	1279 (12.0)	360 (2.2)	3574 (20.0)
Norepinephrine–dopamine reuptake inhibitors						
Bupropion	1406 (2.3)	278 (1.9)	49 (3.7)	1056 (9.9)	34 (0.2)	215 (1.2)
Noradrenergic serotonin-specific antidepressants						
Mirtazapine	2819 (4.6)	892 (6.2)	103 (7.7)	354 (3.3)	1141 (7.1)	535 (3.0)
Subtotal	16 598 (26.9)	3532 (24.8)	344 (26.0)	2689 (25.%)	1535 (9.6)	4324 (24.3)
Other antidepressants†	5 (0.0%	0 (0.0)	0 (0.0)	2 (0.0)	2 (0.%)	34 (0.2)

*Other TCAs include Amoxapine, Clomipramine, Desipramine, Doxepin, Lofepramine and Trimipramine.
†Other antidepressants include Nefazodone, Maprotiline, Agomelatine and Roboxetine.
CPRD, Clinical Practice Research Datalink; NHIRDB, National Health Insurance Research Database; TCAs, tricyclic antidepressants.

Table 4 Prevalence of potential therapeutic indications: depression, other mental health problems and chronic pain among new antidepressant users, and the proportion of persons with depression who had other concurrent mental health problems or pain by jurisdiction

	Canada			USA	UK	Taiwan
	Ontario sample (n=60 366 patients)	Montreal sample (n=13 303 patients)	Quebec City and Montreal (n=1308 patients)	Boston (n=10 131 patients)	CPRD (n=15 868 patients)	NHIRDB (n=17 580 patients)
Depression						
Prevalence, N (%)	7484 (12.4)	2333 (17.5)	563 (43.0)	2203 (21.7)	2478 (15.6)	1603 (9.1)
Alcohol/Drug abuse						
Prevalence, N (%)	1989 (3.3)	326 (2.5)	23 (1.8)	290 (2.9)	4188 (26.4)	224 (1.3)
Abuse in depressed, N (%)	450 (6.0)	97 (4.2)	12 (2.1)	194 (8.8)	795 (32.1)	25 (1.6)
Prevalence ratio	2.1	2.0	1.4	7.3	1.3	1.3
Anxiety						
Prevalence, N (%)	23 374 (38.7)	3641 (27.4)	465 (35.6)	1798 (17.7)	1914 (12.1)	6277 (35.7)
Anxiety in depressed, N (%)	3684 (49.2)	807 (34.6)	218 (38.7)	905 (41.1)	588 (23.7)	767 (47.8)
Prevalence ratio	1.3	1.3	1.2	3.6	2.4	1.4
Major mental illness						
Prevalence, N (%)	2627 (4.4)	692 (5.2)	50 (3.8)	502 (5.0)	253 (1.6)	570 (3.2)
Mental illness in depressed, N (%)	1473 (19.7)	225 (9.6)	23 (4.1)	323 (14.7)	79 (3.2)	95 (5.9)
Prevalence ratio	9.0	2.3	1.1	6.5	2.5	2.0
Suicide attempt						
Prevalence, N (%)	101 (0.2)	30 (0.2)	–	72 (0.7)	129 (0.8)	6 (0.0)
Suicide attempt in depressed, N (%)	80 (1.1)	8 (0.3)	–	67 (3.0)	67 (2.7)	2 (0.1)
Prevalence ratio	26.9	1.7	–	48.2	5.8	5.0
Chronic pain						
Prevalence, N (%)	28 687 (47.5)	6379 (48.0)	571 (43.7)	5200 (51.3)	6539 (41.2)	11 994 (68.2)
Pain in depressed, N (%)	3591 (48.0)	1105 (47.4)	235 (41.7)	1365 (62.0)	1021 (41.2)	994 (62.0)
Prevalence ratio	1.0	1.0	0.9	1.3	1.0	0.9

CPRD, Clinical Practice Research Datalink; NHIRDB, National Health Insurance Research Database.

Table 5 Starting therapy for new users of antidepressants by potential therapeutic indication by therapeutic class and country

	Canada			USA	UK	Taiwan
	Ontario sample (n=60 366 patients)	Montreal sample (n=13 303 patients)	Quebec city and Montreal (n=1308 patients)	Boston (n=10 131 patients)	CPRD (n=15 868 patients)	NHIRDB (n=17 580 patients)
Therapeutic class	**n Rx (%)**	**n Rx (%)**	**n Rx (%)**	**n Rx (%)**	**n Rx (%)**	**n Rx (%)**
Starting therapy for persons with a diagnosis of depression						
SSRIs	4357 (55.2)	1548 (59.5)	386 (67.5)	1388 (59.0)	1797 (71.4)	930 (55.8)
SNRIs	1039 (13.2)	408 (15.7)	72 (12.6)	162 (6.9)	67 (2.7)	104 (6.2)
TCAs	647 (8.2)	129 (5.0)	20 (3.5)	179 (7.6)	319 (12.7)	138 (8.3)
SARIs	940 (11.9)	212 (8.2)	32 (5.6)	269 (11.4)	56 (2.2)	263 (15.8)
NDRIs	321 (4.1)	81 (3.1)	30 (5.2)	233 (9.9)	1 (0.0)	43 (2.6)
Noradrenergic serotonin specific	590 (7.5)	224 (8.6)	32 (5.6)	120 (5.1)	277 (11.0)	184 (11.0)
Other	1 (0.0)	–	–	1 (0.0)	–	4 (0.2)
Starting therapy for persons with a diagnosis of chronic pain						
SSRIs	9823 (33.5)	2643 (39.0)	268 (46.4)	2481 (46.1)	2085 (31.8)	2291 (18.9)
SNRIs	3516 (12.0)	762 (11.2)	83 (14.4)	395 (7.3)	95 (1.5)	315 (2.6)
TCAs	8771 (29.9)	1863 (27.5)	100 (17.3)	1176 (21.8)	3963 (60.4)	6703 (55.2)
SARIs	5410 (18.5)	1020 (15.0)	65 (11.3)	703 (13.0)	89 (1.4)	2353 (19.4)
NDRIs	551 (1.9)	108 (1.6)	24 (4.2)	424 (7.9)	17 (0.3)	126 (1.0)
Noradrenergic serotonin specific	1221 (4.2)	386 (5.7)	38 (6.6)	211 (3.9)	315 (4.8)	330 (2.7)
Other	3 (0.0)	–	–	2 (0.0)	1 (0.02)	27 (0.2)
Starting therapy for persons with a diagnosis of other mental health problems						
SSRIs	13 018 (49.5)	2459 (53.3)	309 (61.1)	1384 (61.4)	2565 (45.1)	2212 (32.3)
SNRIs	3099 (11.8)	550 (11.9)	61 (12.1)	147 (6.5)	105 (1.9)	254 (3.7)
TCAs	3823 (14.5)	563 (12.2)	28 (5.5)	186 (8.2)	2518 (44.3)	2250 (32.8)
SARIs	4107 (15.6)	591 (12.8)	53 (10.5)	280 (12.4)	102 (1.8)	1684 (24.6)
NDRIs	773 (2.9)	98 (2.1)	18 (3.6)	163 (7.2)	20 (0.4)	126 (1.8)
Noradrenergic serotonin specific	1480 (5.6)	357 (7.7)	37 (7.3)	94 (4.2)	374 (6.6)	318 (4.6)
Other	3 (0.0)	–	–	2 (0.1)	1 (0.0)	15 (0.2)

CPRD, Clinical Practice Research Datalink; NDRIs, norepinephrine- dopamine reuptake inhibitors; NHIRDB, National Health Insurance Research Database; SARIs, serotonin antagonist and reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

(Taiwan) remained on their initial course of antidepressant treatment (table 6A). For this group, the mean duration of treatment varied from 104.7 (Taiwan) to 340.9 (Quebec) days, and the mean dose varied from 0.6 of the recommended adult dose (Taiwan), to the recommended adult dose in the USA site (mean dose: 1.0). Among the 32% (Taiwan) to 46% (Ontario) with a change in treatment, the most common change in all jurisdictions was an increase in dose occurring in 20% (Taiwan) to 33% (Ontario) of patients, followed by a decrease in dose (13% [Taiwan] to 21% [Ontario]) and the addition of a drug from a different therapeutic class (6% [UK] to 18% [Ontario]). Among patients with a change in therapy in their initial treatment episode, the mean duration of treatment was almost double (mean duration 312.6 to 616.9 days) than for patients with no change, and the mean dose during treatment was substantially higher (mean standardised proportion of the adult dose: 0.8 to 1.4).

The first treatment episode for new antidepressant users with a diagnosis of chronic pain was substantially different from patients with a diagnosis of depression (table 6B). Overall, 66% (Ontario) to 79% (Taiwan) were kept on the inititial treatment regimen, for a much shorter duration than for new users with a diagnosis of depression (mean duration: 83.6 days [Taiwan] to 300.9 days [Quebec]), and at lower mean doses (mean standardised proportion of the adult dose: 0.4 [Taiwan, UK, Montreal] to 0.8 [USA]). For the 21%–34% of patients who had a change in treatment, the most common changes in all jurisdictions were an increase in dose (13% to 25%), a decrease in dose (9% to 14%) and the addition of another drug from a different therapeutic class (3% to 11%). For those with a change in treatment, the duration of the treatment episode was considerably longer in all jurisdictions (264.4–590.0 days), and the mean dose during the treatment episode was higher (0.5–1.1).

INTERPRETATION

This multinational study is the first to compare the use of antidepressants among comparable cohorts of new users in different countries. We found wide variation in the incidence and prevalence of antidepressant use; the lowest rates included the UK, where guidelines for pharmacotherapy use for depression were the most conservative. Choice of starting therapy also varied widely by country and condition, with the UK and Taiwan more likely to use TCAs for persons with a diagnosis of chronic pain, whereas SSRIs were the most common choice for both depression and pain in North American settings. Overall treatment duration was longer for patients with depression than chronic pain, mean treatment doses were higher and there were more likely to be changes in therapy.

Differences in the incidence of antidepressant use in different countries as well as the choice of antidepressant therapy may also be influenced by a variety of system-related factors. For example, direct to consumer advertising of prescription drugs is permitted in the USA but banned in Canada, Europe and the UK because these ads drive demand for specific treatments.[33] Also, drugs available and covered by public insurance plans in the UK, Taiwan and Canada are influenced by rigorous reviews and guidelines for the use of new drugs and technologies by national agencies such as the National Institute for Health and Care Excellence in the UK.[34–36]

A surprisingly large percentage of older adults were prescribed antidepressants for conditions other than depression. We found that chronic pain was the most common problem documented, and it appeared to be the most likely reason for antidepressant use. Chronic pain has an estimated prevalence of 11.8%[37]–43.5%[38] in adults, and increases with age, with an estimated 62% of those ≥75 years of age experiencing this problem.[38] While use of antidepressants for chronic pain has been shown to be effective, particularly TCAs (amitriptyline) and SNRIs (duloxetine) for neurogenic pain,[39 40] TCAs have been on the lists of potentially contraindicated medications for the elderly for over a decade because of their potent anticholinergic effects that can lead to cognitive impairment, and other avoidable morbidity.[41 42] Moreover, only one antidepressant, duloxetine, has been approved for treatment of chronic pain in North America and Europe.[11] Although the anticholinergic effects of TCAs have been well documented,[43–45] the actual 'real-world' evidence of harm is limited,[46] and should be addressed in future studies given the high rates of use.

Notably, in this study of older adults, depression was documented in only 2 in 10 users; the exception being in Quebec City/Montreal where 4 out of 10 patients were prescribed antidepressants for depression. There are known problems in underreporting, diagnosis and documentation of depression,[47–49] which may account for some or all of these differences between sites. The MOXXI system used in the Quebec cohort likely provides an approximate estimate of the extent to which depression is undocumented. In this cohort, physicians are required to document the treatment indication for each drug prescribed,[50] data that have been validated in prior studies.[51] Results from this setting suggest that twice as many patients receive antidepressants for depression, whereas a similar proportion of new antidepressant users had a diagnosis of chronic pain as in other sites.

Also, of interest, among patients with documented depression, antidepressant use in all countries followed current guidelines for depression management.[21 24 52 53] Choice of first-line therapy was predominantly SSRIs and SNRIs. Starting doses were lower than the recommended adult doses, mean duration of treatment was 251–525 days and the main changes in treatment were increases in doses and the addition of an antidepressant from a different therapeutic class. Not surprisingly, among patients where there was a change in treatment, both the average antidepressant dose was higher and treatment duration was longer, suggesting a lack of treatment effectiveness. The

Table 6A Characteristics of the first antidepressant treatment episode among persons with a diagnosis of depression

	Canada						USA		UK		Taiwan	
	Ontario		Montreal sample		Quebec city and Mtl		Boston		CPRD		NHIRDB	
Characteristics	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
All patients	4407	100	1221	100	324	100	1259	100	2152	100	835	100
No treatment change	2383	54	680	56	220	68	757	60	1317	61	566	68
Treatment change	2024	46	541	44	104	32	502	40	835	39	269	32
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
All patients												
Dose*	1.3	1.0	0.9	0.6	0.9	0.5	1.3	0.8	1.0	0.5	0.7	0.4
Duration (days)	519.5	285.1	462.5	298.9	467.7	255.0	395.6	266.2	356.2	278.7	217.0	248.0
No treatment change†												
Dose	0.9	0.7	0.7	0.4	0.8	0.4	1.0	0.9	0.8	0.4	0.6	0.4
Duration (days)	289.1	309.6	246.3	290.4	340.9	243.2	225.7	212.3	192.8	239.9	104.7	179.7
Treatment change†												
Dose	1.5	1.0	1.0	0.6	1.1	0.6	1.4	0.8	1.2	0.6	0.8	0.4
Duration (days)	616.9	209.8	569.0	240.8	574.7	213.9	507.7	239.4	469.5	247.6	312.6	260.2
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Type of changes‡												
Added molecule (different class)	796	18	139	11	31	10	125	10	125	6	72	9
Added molecule (same class)	174	4	22	2	6	2	42	3	54	3	26	3
Dose decrease	921	21	246	20	38	12	151	12	407	19	105	13
Dose increase	1464	33	387	32	64	20	348	28	611	28	171	20
Removed molecule (different class)	710	16	132	11	26	8	34	3	19	1	75	9
Removed molecule (same class)	178	4	23	2	5	2	6	0	6	0	28	3
Switch class	10	0	48	4	–	–	56	4	70	3	1	0
Switch molecule (same class)	5	0	11	1	–	–	19	2	24	1	–	–

*Dose is the proportion of the WHO recommended daily dose (dose prescribed/recommended daily dose).
†Treatment change in the first antidepressant episode, defined as continuous therapy with gaps of no greater than 90 days.
‡Patients can have more than one type of change in the episode of antidepressant use.
CPRD, Clinical Practice Research Datalink; NHIRDB, National Health Insurance Research Database.

Table 6B Characteristics of the first antidepressant treatment episode among persons with a diagnosis of chronic pain

	Canada						USA		UK		Taiwan	
	Ontario		Montreal sample		Quebec city and Montreal		Boston		CPRD		NHIRDB	
Characteristics	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
All patients, all changes	16 045	100	3276	100	349	100	2657	100	5360	100	6029	100
No treatment change	10 650	66	2220	68	261	75	1793	67	4017	75	4761	79
Treatment change	5395	34	1056	32	88	25	864	33	1343	25	1268	21
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
All patients, all changes												
Dose*	0.9	0.7	0.7	0.5	0.8	0.6	1.0	0.8	0.6	0.5	0.5	0.4
Duration (days)	416.3	312.8	407.8	313.7	437.0	263.6	384.6	261.7	257.6	270.8	168.9	227.3
No treatment change†												
Dose	0.6	0.5	0.4	0.3	0.6	0.5	0.8	0.7	0.40	0.4	0.4	0.3
Duration (days)	198.7	271.4	202.1	270.2	300.9	238.6	247.4	223.3	122.3	192	83.6	154.6
Treatment change†												
Dose	1	0.7	0.8	0.5	1.0	0.6	1.1	0.7	0.7	0.5	0.5	0.4
Duration (days)	534.6	260.5	534.7	265.1	590.0	201.5	482.2	239.6	398.0	266.9	264.4	252.8
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Type of changes‡												
Added molecule (different class)	1776	11	267	8	30	9	189	7	159	3	245	4
Added molecule (same class)	375	2	31	1	5	1	69	3	68	1	90	1
Dose decrease	2291	14	455	14	32	9	243	9	629	12	569	9
Dose increase	3980	25	818	25	58	17	611	23	1032	19	809	13
Removed molecule (different class)	1547	10	245	7	26	7	47	2	14	0	262	4
Removed molecule (same class)	372	2	32	1	4	1	6	0	7	0	95	2
Switch class	30	0	120	4	–	–	92	3	77	1	15	0
Switch molecule (same class)	22	0	30	1	–	–	27	1	29	1	4	0

*Dose is the proportion of the WHO recommended daily dose (dose prescribed/recommended daily dose).
†Treatment change in the first antidepressant episode, defined as continuous therapy with gaps of no greater than 90 days.
‡Patients can have more than one type of change in the episode of antidepressant use.
CPRD, Clinical Practice Research Datalink; NHIRDB, National Health Insurance Research Database.

cohort in Taiwan was different in a number of respects including lower antidepressant doses, shorter treatment duration and fewer changes in therapy once started. The reason for these differences in approach is not clear. They may represent an innate conservatism in the use of antidepressants in the Taiwanese population where there is an acknowledged absence of evidence to support clinical guidelines,[53] or known differences in genetic determinants of drug metabolism that have been established in population-based genomic studies of drug metabolism.[54]

This study has several limitations to consider in the interpretation of results. Efforts were made to harmonise data from different sources and countries; however, both measurement and reporting issues may lead to arbitrary differences between regions and countries. With the exception of the Quebec cohort, treatment indication is unknown. Documentation of health problems in medical services billing data and EMRs was used as a proxy for treatment indication, which based on past studies has a predictive value of 7.8%–80.3%.[55] The resulting misclassification will attenuate differences observed in treatment approach between conditions. Moreover, diagnoses of health problems tend to be underreported in adminsitrative data. Prescription data were used in the three jurisdictions and may overestimate the incidence and prevalence of antidepressant use as approximately 37% of antidepressant prescriptions are not filled.[56] The Ontario, Montreal and Taiwan cohorts represented total populations or representative samples, whereas the UK, Quebec and USA cohorts were assembled on the basis of practices supported by specific information technology systems. The trends observed in these more selected populations, however, are similar to those reported for antidepressant use in older adults in these countries.[6 57–62]

In conclusion, antidepressant use in older adults varies up to 24-fold by country (cumulative incidence from 0.7% to 17.0%), and chronic pain appears to be the most common treatment indication in all jurisdictions, even more so than depression. Evaluation of real-world risks and benefits of antidepressants by treatment indication should be a priority for future research. The relative contraindication of TCAs in older adults because of their potent anticholinergic effects needs to be assessed given their high rate of use and proven efficacy in pain management.[39–42]

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