Off-label indications for antidepressants in primary care: descriptive study of prescriptions from an indication based electronic prescribing system

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ABSTRACT

OBJECTIVE

To examine off-label indications for antidepressants in primary care and determine the level of scientific support for off-label prescribing.

DESIGN

Descriptive study of antidepressant prescriptions written by primary care physicians using an indication based electronic prescribing system.

SETTING

Primary care practices in and around two major urban centres in Quebec, Canada.

PARTICIPANTS

Patients aged 18 years or older who visited a study physician between 1 January 2003 and 30 September 2015 and were prescribed an antidepressant through the electronic prescribing system.

MAIN OUTCOME MEASURES

Prevalence of off-label indications for antidepressant prescriptions by class and by individual drug. Among off-label antidepressant prescriptions, the proportion of prescriptions in each of the following categories was measured: strong evidence supporting use of the prescribed drug for the respective indication; no strong evidence for the prescribed drug but strong evidence supporting use of another drug in the same class for the indication; or no strong evidence supporting use of the prescribed drug and all other drugs in the same class for the indication.

RESULTS

106 850 antidepressant prescriptions were written by 174 physicians for 20 920 adults. By class, tricyclic antidepressants had the highest prevalence of off-label indications (81.4%, 95% confidence interval, 77.3% to 85.5%), largely due to a high off-label prescribing rate for amitriptyline (93%, 89.6% to 95.7%). Trazodone use for insomnia was the most common off-label use for antidepressants, accounting for 26.2% (21.9% to 30.4%) of all off-label prescriptions. For only 15.9% (13.0% to 19.3%) of all off-label prescriptions, the prescribed drug had strong scientific evidence for the respective indication. For 39.6% (35.7% to 43.2%) of off-label prescriptions, the prescribed drug did not have strong evidence but another antidepressant in the same class had strong evidence for the respective indication. For the remaining 44.6% (40.2% to 49.0%) of off-label prescriptions, neither the prescribed drug nor any other drugs in the class had strong evidence for the indication.

CONCLUSIONS

When primary care physicians prescribed antidepressants for off-label indications, these indications were usually not supported by strong scientific evidence, yet often another antidepressant in the same class existed that had strong evidence for the respective indication. There is an important need to generate and provide physicians with evidence on off-label antidepressant use to optimise prescribing decisions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Off-label drug use without strong scientific evidence is associated with an increased risk of adverse drug events

About a third of all antidepressants in primary care are prescribed for off-label indications

The degree to which off-label antidepressant prescriptions are supported by strong scientific evidence is unknown

WHAT THIS STUDY ADDS

Most off-label antidepressant prescriptions lack strong scientific evidence, but another evidence based antidepressant from the same class could often be considered as an alternative

There is an important need to produce more evidence evaluating the clinical outcomes associated with off-label antidepressant use

Indication based electronic prescribing systems represent an effective means to study off-label antidepressant use and communicate evidence back to physicians to optimise prescribing decisions

Introduction

Antidepressant use has increased substantially in the UK[1 2] and in other western countries such as Canada[3] and the USA.[4] In fact, the number of antidepressants dispensed in England increased by 3.9 million (6.8%) between 2014 and 2015—more than any other therapeutic class of prescription drugs.[2] One suspected factor underlying the widespread use of antidepressants is an expanding array of indications for these drugs, many of which are unapproved (off-label) for certain antidepressants.[5]

There is a lack of epidemiological evidence on the extent to which physicians prescribe antidepressants for off-label indications because treatment indications are not documented for most prescriptions.[6] With the advent of electronic prescribing (e-prescribing) systems, however, formal documentation of treatment indications linked to prescriptions (that is, indication based prescribing) is possible. Although indication based prescribing is not broadly used at the moment, it represents a valuable means for studying off-label prescribing.[7] We recently used data from a unique, indication based e-prescribing system to describe treatment

indications for antidepressants in primary care.[8] We found that over the past decade, primary care physicians commonly and increasingly prescribed antidepressants for non-depressive indications. Moreover, when antidepressants were not prescribed for depression, two of three prescriptions were for an off-label indication.

Off-label prescribing warrants particular attention and oversight when the drug use is not supported by scientific evidence showing greater benefits relative to risk.[9 10] Inefficacious antidepressant use is a concern because it creates unnecessary costs and puts patients at risk of experiencing burdensome side effects and serious adverse events that could be avoided. For example, even though newer generation antidepressants such as selective serotonin reuptake inhibitors (SSRIs) are considered safer and more tolerable than the older generation tricyclic antidepressants (TCAs), they are costly and have still been associated with notable side effects and safety concerns. These side effects include sexual dysfunction, drowsiness, insomnia, weight gain, and fatigue,[11-13] and safety concerns include an increased risk of fractures[14] and upper gastrointestinal bleeds.[15 16] Off-label antidepressant use could also expose patients to unknown health risks if their clinical characteristics differ from the patient populations studied in pre-market clinical trials.[17] Indeed, the risk of adverse drug events has been found to be 54% higher when drugs are used off-label without strong scientific evidence than when drugs are used on-label.[18]

Although an estimated 29% of antidepressants are prescribed for off-label indications,[8] it is unknown to what extent these off-label prescriptions are supported by scientific evidence. Thus, the objective of this study was to examine off-label indications for antidepressants in primary care and assess the level of scientific evidence supporting these off-label prescriptions.

Methods

Study design and setting

This descriptive study took place in the Canadian province of Quebec, where a universal health insurance programme covers the cost of essential medical care for all residents. By law, all residents must be covered for prescription drugs through either private plans (that is, group or employee benefit plans) or the public drug insurance plan. About 50% of residents are registered in the public drug insurance plan, including those older than 65, welfare recipients, and those not insured through an employer. At a minimum, all private plans must provide the same formulary for insured drugs as the public drug insurance plan.[19]

Data source and study population

The Medical Office of the XXIst Century (MOXXI) is an electronic prescription and drug management system used by consenting primary care physicians in community based, fee-for-service practices around two major urban centres in Quebec.[20] Since 2003, 207 physicians (25% of eligible physicians) and over 100 000 patients (26% of all who visited a MOXXI physician) have consented to participate in the MOXXI programme and have their information used for research purposes.

The e-prescribing tool in the MOXXI system requires physicians to explicitly record at least one treatment indication per prescription by either using a dropdown menu that lists on-label and off-label indications (without distinction) or typing the indication(s) into a free text field. In a validation study,[21] these physician documented indications had excellent sensitivity (98.5%) and high positive predictive value (97.0%) when compared with a blinded, post hoc, physician facilitated chart review. The MOXXI system also provides physicians with access to professional drug monographs that are maintained by a commercial vendor[22] and produces automated drug alerts about potential prescribing problems. Alerts are generated when potential dosing errors or drug-drug, drug-disease, drug-age, or drug-allergy contraindications are identified; however, alerts are not generated when drugs are prescribed for off-label indications. This study was approved by the McGill institutional review board.

Inclusion and exclusion criteria

This study included prescriptions of drugs approved for depression that were written by MOXXI physicians between 1 January 2003 and 30 September 2015 for patients aged 18 years or older. The antidepressant prescription was the unit of analysis. We excluded drugs with fewer than 150 prescriptions during the study period (roughly corresponding to a prescribing frequency of fewer than once per month). This resulted in the exclusion of all monoamine oxidase inhibitors (phenelzine, tranylcypromine, moclobemide, and isocarboxazid), nefazodone, maprotiline, and vortioxetine.

Measurements

On-label versus off-label indications

Treatment indications were first categorised by use of ICD-10 (international classification of diseases, 10th revision). Each prescription—representing a drug-indication pair—was then classified as on-label or off-label, depending on whether the drug had been approved for the indication by Health Canada or the US Food and Drug Administration as of September 2015 (the end of the study period). Approved indications were determined at the end of the study period rather than the year in which the prescription was written so that all prescriptions would be classified using the same benchmark. If a physician recorded multiple indications for the drug (n=1922, 1.8% of all antidepressant prescriptions), the prescription was classified as off-label only if all the indications were not approved.

Level of scientific evidence for off-label prescriptions

Off-label prescriptions were further analysed according to the level of scientific evidence supporting the drug's use for the off-label indication. Off-label prescriptions were assigned to one of three categories: strong evidence for the prescribed drug, no strong evidence for the prescribed drug but strong evidence for another drug in the same class, or no strong evidence for the

prescribed drug and all other drugs in the same class. To determine whether off-label prescriptions had strong evidence for the prescribed drug, we used the DRUGDEX compendium (Thomson Micromedex),[23] which is a reputable and authoritative reference used by the US Centers for Medicare and Medicaid Services to determine coverage for off-label drug uses.[24] The compendium contains evaluations of drug efficacy, strength of recommendation, and strength of evidence for off-label drug indication pairs.

Using the same criteria as in previous studies,[7 18 25] we classified off-label prescriptions as having strong evidence for the prescribed drug if evidence showed that the drug was effective or favoured efficacy for the indication, the drug was recommended for all or most patients with the indication, and at least one randomised clinical trial was included among the studies used to evaluate the drug's efficacy for the indication. If an off-label prescription did not have strong evidence for the prescribed drug, we then determined whether there was strong evidence for another drug in the same class. This condition was satisfied if another drug in the same class was either on-label or off-label with strong evidence for the indication. If an off-label prescription still did not have strong evidence for another drug in the class, then the prescription was classified as having no strong evidence for the prescribed drug and all other drugs in the same class.

Statistical analysis

Patient and physician characteristics were summarised by use of descriptive statistics. The prevalence of off-label indications was estimated as the number of off-label prescriptions divided by the total number of antidepressant prescriptions overall, in the class, or for the individual drug. We estimated the level of scientific evidence for off-label prescriptions as the number of off-label prescriptions in each evidence category divided by the total number of off-label antidepressant prescriptions overall or in the class. The prevalence of different treatment indications for each drug was estimated as a proportion, using the total number of prescriptions for the drug as the denominator. For all proportions, we calculated 95% confidence intervals using a cluster bootstrap approach[26] to account for within-cluster correlation among prescriptions for the same patient and from the same physician. The reported 95% confidence intervals correspond to the values of the 2.5th and 97.5th percentiles of the distribution of the respective estimates across 1000 bootstrap re-samples.[26] All analyses were conducted using SAS (SAS Institute) software, version 9.4.

Patient involvement

No patients were involved in setting the research question or the study measures, nor were they involved in developing plans for the design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. The study findings will be disseminated to study participants through physician newsletters and patient-friendly handouts.

Results

During the study period, 106 850 antidepressant prescriptions (5.8% of 1.83 million prescriptions for any drug) were written by 174 primary care physicians for 20 920 adults. There was roughly an equal number of male (n=90; 52%) and female (n=84; 48%) physicians, most of whom had been trained in North America (n=160; 92%) and practicing for at least 15 years (n=131; 75%). Two thirds of patients were female (n=13 990; 66.9%), most patients were middle aged at the time of their earliest antidepressant prescription (median 53 years, interquartile range 43-65), and patients were equally likely to have public (n=10 875; 52.0%) or private (n=10 045; 48.0%) drug insurance. Over the study period, patients had a median of three (interquartile range 1-7) antidepressant prescriptions and were prescribed a median of one (1-2) type of antidepressant drug.

Prevalence of off-label indications

Overall, 29.3% (95% confidence interval 26.6% to 32.3%) of all antidepressant prescriptions were written for an off-label indication (table 1). By class, TCAs had the highest prevalence of off-label indications (81.4%, 77.3% to 85.5%), followed by other antidepressants (trazodone, bupropion, and mirtazapine; 42.4%, 37.1% to 47.7%) and SSRIs (21.8%, 19.0% to 25.0%). By contrast, the prevalence of off-label indications was much lower for serotonin-norepinephrine (noradrenaline) reuptake inhibitors (SNRIs; 6.1%, 4.8% to 7.5%). The high prevalence of off-label indications for TCAs was mostly due to amitriptyline, which was only approved for depression but was almost exclusively prescribed for off-label indications (93.0%, 89.6% to 95.7%)—most commonly pain (48.4%, 39.7% to 57.8%), insomnia (22.5%, 13.6% to 31.3%), and migraine (16.7%, 12.2% to 21.9%; table 2). The high prevalence of off-label indications among other antidepressants (trazodone, bupropion, and mirtazapine) was largely due to trazodone, which was mostly prescribed for insomnia (82.5%, 74.5% to 88.1%) even though it was not approved for this indication. SSRIs and SNRIs had a lower prevalence of off-label indications because they were more frequently prescribed for depression than TCAs, which by definition was an approved indication for all antidepressants (table 2).

Level of scientific evidence for off-label indications

Among all off-label antidepressant prescriptions, there were 143 unique drug indication pairs—the most common of which were trazodone for insomnia (representing 26.2%, 95% confidence interval 21.9% to 30.4%, of all off-label prescriptions), citalopram for anxiety (17.8%, 14.8% to 21.3%), amitriptyline for pain (13.8%, 11.0% to 16.9%), and amitriptyline for insomnia (6.4%, 3.9% to 9.5%; data not shown). Only three of these 143 off-label drug indication pairs met the predefined criteria[7 18 25] for having strong scientific evidence: amitriptyline (a TCA) for pain, escitalopram (an SSRI) for panic disorders, and venlafaxine (an SNRI) for obsessive compulsive disorder.

Table 1 | Proportion of antidepressants prescribed for off-label indications and level of evidence, by drug class

Drug class (No of prescriptions)	Off-label indication		Level of evidence for off-label indications					
			Strong evidence for prescribed drug‡		No strong evidence for prescribed drug but strong evidence for another drug in same class¶		No strong evidence for prescribed drug and all other drugs in same class	
	No	Percentage* (95% CI†)	No	Percentage§ (95% CI†)	No	Percentage§ (95% CI†)	No	Percentage§ (95% CI†)
SSRI (n=45 608)	9960	21.8 (19.0 to 25.0)	473	4.7 (2.7 to 7.2)	9160	92.0 (89.2 to 94.4)	327	3.3 (2.0 to 4.8)
SNRI (n=25 235)	1539	6.1 (4.8 to 7.5)	169	11.0 (4.6 to 18.4)	544	35.4 (25.0 to 46.7)	826	53.7 (40.6 to 66.6)
TCA (n=11 645)	9480	81.4 (77.3 to 85.5)	4335	45.7 (37.8 to 54.0)	2682	28.3 (20.5 to 36.6)	2463	26.0 (21.2 to 31.1)
Other** (n=24 362)	10 340	42.4 (37.1 to 47.7)	0	0.0 (0.0 to 0.0)	NA	NA	10 340	100.0 (100.0 to 100.0)
All classes (n=106 850)	31 319	29.3 (26.6 to 32.3)	4977	15.9 (13.0 to 19.3)	12 386	39.6 (35.7 to 43.2)	13 956	44.6 (40.2 to 49.0)

SSRI=selective serotonin reuptake inhibitors; SNRI=serotonin-norepinephrine reuptake inhibitors; TCA=tricyclic antidepressants; NA=not assessed for drugs in this category because they were not considered as part of the same class.
*Calculated using the total number of prescriptions in the class as the denominator.
†Calculated by a cluster bootstrap approach[26] to account for non-independence of prescriptions from the same physician and for the same patient. Reported 95% confidence intervals correspond to values at the 2.5th and 97.5th percentiles of the distribution of respective estimates across 1000 bootstrap re-samples.
‡Based on evaluations from DRUGDEX compendium in three dimensions: efficacy, strength of recommendation, and strength of evidence. Prescriptions for an off-label indication were classified as having strong evidence for a prescribed drug if evidence showed that the drug was effective or favoured efficacy for the indication, the drug was recommended for all or most patients with the indication, and at least one randomised controlled trial was included among the studies used to evaluate the drug's efficacy for the indication.
§Calculated using the number of prescriptions in the class that were written for an off-label indication as the denominator.
¶Off-label prescriptions where the prescribed drug did not have strong evidence for the indication, but another drug in the class was either on-label or off-label with strong evidence for the indication based on evaluations from the DRUGDEX compendium.
**Includes trazodone, bupropion, and mirtazapine.

These three pairs collectively comprised 15.9% (13.0% to 19.3%) of all off-label antidepressant prescriptions (table 1)—most which were amitriptyline prescriptions for pain (representing 87.1%, 80.9% to 92.1%, of all off-label prescriptions with strong evidence for the prescribed drug). As a result, the proportion of off-label antidepressant prescriptions with strong evidence for the prescribed drug was much higher for TCAs (45.7%, 37.8% to 54.0%) than for SNRIs (11.0%, 4.6% to 18.4%) and SSRIs (4.7%, 2.7% to 7.2%; table 1).

Off-label antidepressant prescriptions had strong evidence for another drug in the same class—but not the prescribed drug—in 39.6% (95% confidence interval 35.7% to 43.2%) of all cases (table 1). This proportion was highest among off-label SSRI prescriptions (92.0%, 89.2% to 94.4%), and lower among off-label prescriptions for SNRIs (35.4%, 25.0% to 46.7%) and TCAs (28.3%, 20.5% to 36.6%). This proportion was not assessed for other antidepressants because trazodone, bupropion, and mirtazapine were not considered as part of the same class.

For the remaining 44.6% (95% confidence interval 40.2% to 49.0%) of off-label antidepressant prescriptions, neither the prescribed drug nor any other drug in the same class had strong evidence for the indication (table 1). All off-label prescriptions for other antidepressants (trazodone, bupropion, and mirtazapine) were classified in this evidence category. The proportion of off-label prescriptions with no scientific support for any drug in the class was also quite high for SNRIs (53.7%, 40.6% to 66.6%) and TCAs (26.0%, 21.2% to 31.1%), but was much lower for SSRIs (3.3%, 2.0% to 4.8%).

Discussion

This study provides evidence on the level of scientific support for off-label antidepressants prescriptions, the prevalence of off-label indications for individual antidepressants, and the most common off-label uses for antidepressants. Nearly a third (29%) of all antidepressants in this study were prescribed for an off-label indication, as found previously.[8] Among all off-label antidepressant prescriptions, only one in six prescriptions was supported by strong scientific evidence, but there was often another antidepressant in the same class with strong evidence that could have been considered instead, especially among off-label SSRI prescriptions. Still, nearly half of all off-label antidepressant prescriptions did not have strong evidence for the prescribed drug and all other antidepressants in the same class. Among the many off-label uses for antidepressants, physicians most frequently prescribed trazodone for insomnia even though this use was not evidence based.

Comparison with other studies

Few published studies exist on off-label prescribing, owing to challenges associated with measuring diagnoses (indications) for prescriptions. Compared with our findings where 29% of antidepressant prescriptions were off-label, Chen and colleagues[27] found that 75% of people enrolled to Georgia Medicaid who were being treated with antidepressants received at least one antidepressant off-label. The rate of off-label antidepressant use was notably higher in this study because the authors classified prescriptions as off-label if the patient did not have a diagnostic code for an approved indication recorded in administrative claims data during the same year. This methodology most likely overestimated the off-label prescribing rate because diagnostic codes in administrative data are often incomplete or inaccurate, especially for psychiatric conditions.[28]

Only three studies—one Canadian[7] and two US[25 29]—have used documented treatment indications to study off-label prescribing, none of which focused specifically on antidepressants. Eguale and colleagues[7] combined antidepressants with other central nervous system drugs but reported fairly comparable results, with 26% of prescriptions for off-label indications—18% of which

Table 2 | Off-label indications and most common indications for antidepressant treatment, by drug

Drug name, by class	Total No of prescriptions	Off-label indication		Treatment indications and No (%) of prescriptions								
				Most common			Second most common			Third most common		
		No	Percentage* (95% CI†)	Indication	No	Percentage* (95% CI†)	Indication	No	Percentage* (95% CI†)	Indication	No	Percentage* (95% CI†)
Selective serotonin reuptake inhibitors												
Citalopram	19480	6988	35.9 (31.5 to 40.9)	Depression‡	12492	64.1 (59.1 to 68.5)	Anxiety disorder§	5745	29.5 (25.0 to 34.6)	Panic disorder	882	4.5 (2.7 to 7.2)
Paroxetine	9212	94	1.0 (0.4 to 1.9)	Depression‡	4476	48.6 (40.2 to 57.3)	Anxiety disorder‡§	2719	29.5 (23.6 to 36.0)	Panic disorder‡	1563	17.0 (10.6 to 23.8)
Escitalopram	7108	601	8.5 (5.7 to 11.4)	Depression‡	4354	61.3 (55.2 to 67.0)	Anxiety disorder‡§	2075	29.2 (23.2 to 35.3)	Panic disorder	503	7.1 (4.6 to 9.9)
Sertraline	6805	1680	24.7 (18.6 to 31.8)	Depression‡	4383	64.4 (55.4 to 71.8)	Anxiety disorder§	1847	27.1 (20.6 to 34.1)	Panic disorder‡	398	5.8 (2.4 to 10.0)
Fluoxetine	2079	322	16.0 (10.0 to 24.5)	Depression‡	1566	75.3 (65.1 to 83.2)	Anxiety disorder§	249	12.0(7.1 to 18.2)	Panic disorder‡	64	3.1 (0.2 to 7.4)
Fluvoxamine	924	265	28.7 (15.6 to 45.3)	Depression‡	592	64.1 (47.5 to 76.5)	Anxiety disorder§	233	25.2 (13.8 to 41.9)	OCD‡	71	7.7 (2.9 to 15.5)
Serotonin-norepinephrine reuptake inhibitors												
Venlafaxine	21369	1501	7.0 (5.5 to 8.7)	Depression‡	14282	66.8 (62.3 to 71.2)	Anxiety disorder‡§	5053	23.6 (19.4 to 27.9)	Panic disorder‡	782	3.7 (2.6 to 4.9)
Duloxetine	2969	9	0.3 (0.0 to 1.0)	Depression‡	1139	38.4 (31.4 to 45.4)	Pain‡	1053	35.5 (27.8 to 43.1)	Fibromyalgia‡	604	20.3 (14.5 to 27.1)
Desvenlafaxine	897	29	3.2 (0.7 to8.0)	Depression‡	868	96.8 (91.9 to 99.3)	Anxiety disorder§	16	1.8 (0.0 to 5.5)	Menopausal hot flashes	6	0.7 (0.0 to 1.8)
Tricyclic antidepressants												
Amitriptyline	8993	8361	93.0 (89.6 to 95.7)	Pain	4349	48.4 (39.7 to 57.8)	Insomnia	2023	22.5 (13.6 to 31.3)	Migraine	1501	16.7 (12.2 to 21.9)
Doxepin	782	92	11.8 (3.2 to 21.3)	Insomnia‡	285	36.4 (24.1 to 49.3)	Depression‡	171	21.9 (9.7 to 35.9)	Anxiety disorder‡§	150	19.2 (9.0 to 32.0)
Nortriptyline	592	458	77.4 (59.9 to 89.5)	Pain	340	57.4 (35.0 to 74.1)	Depression‡	126	21.3 (9.5 to 38.5)	Anxiety disorder§	49	8.3 (2.4 to 20.0)
Trimipramine	562	165	29.4 (15.9 to 43.9)	Depression‡	397	70.6 (55.9 to 84.0)	Pain	93	16.5(5.2 to 29.9)	Insomnia	22	3.9 (0.2 to 11.3)
Imipramine	285	218	76.5 (55.4 to 90.6)	Panic disorder	69	24.2 (1.6 to 42.5)	Depression‡	67	23.5 (9.4 to 44.5)	Urinary disorders	64	22.5 (4.7 to 54.6)
Desipramine	216	127	58.8 (30.5 to 80.7)	Depression‡	89	41.2 (19.2 to 69.1)	Pain	81	37.5 (12.0 to 61.4)	Anxiety disorder§	16	7.4 (1.1 to 21.3)
Clomipramine	215	59	27.4 (8.9 to 51.1)	Depression‡	107	49.8 (25.8 to 72.3)	OCD‡	49	22.8 (7.2 to 42.0)	Anxiety disorder§	36	16.7 (2.6 to 37.9)
Other												
Trazodone	10070	8938	88.8 (81.5 to 93.7)	Insomnia	8303	82.5 (74.5 to 88.1)	Depression‡	1132	11.2 (6.3 to 18.4)	Anxiety disorder§	574	5.7 (3.8 to 8.2)
Bupropion	8384	780	9.3 (6.3 to 12.7)	Depression‡	7052	84.1 (79.9 to 87.9)	Nicotine dependence‡	565	6.7 (4.4 to 9.6)	ADHD	372	4.4 (2.5 to 6.9)
Mirtazapine	5908	622	10.5 (6.7 to 14.9)	Depression‡	5286	89.5 (85.1 to 93.7)	Anxiety disorder§	473	8.0 (4.3 to 13.2)	Insomnia	157	2.7 (0.8 to 4.8)

OCD=obsessive compulsive disorder; ADHD=attention deficit/hyperactivity disorder.
*Calculated using total number of prescriptions for the drug as the denominator.
†Calculated by a cluster bootstrap approach[26] to account for non-independence of prescriptions from the same physician and for the same patient. Reported 95% confidence intervals correspond to values at the 2.5th and 97.5th percentiles of the distribution of respective estimates across 1000 bootstrap re-samples.[26]
‡Indications approved for drug by Health Canada or the US Food and Drug Administration as of September 2015 (end of study period).
§Includes anxiety, generalised anxiety disorder, and other anxiety disorders. Excludes panic disorder, phobias, OCD, and post-traumatic stress disorder.

were supported by strong evidence. Radley and colleagues[29] combined antidepressants with anxiolytic and antipsychotic drugs, but again reported a similar off-label prescribing rate of 31%. However, the proportion of off-label prescriptions with strong scientific support in this study was notably lower than ours at only 6%, possibly due to the inclusion of other psychiatric drugs or because evidence to support some off-label antidepressant uses had not been generated at the time of the analysis. Finally, Walton and colleagues[25] presented results for only five antidepressants but similarly found that amitriptyline and trazodone were the antidepressants most frequently prescribed for off-label indications. However, their off-label prescribing rate was notably lower for amitriptyline (69%) and trazodone (43%) than our rates, possibly reflecting inter-country differences in the use of antidepressants versus other drugs to treat pain and insomnia.

In all of these studies, none of the authors assessed the proportion of off-label antidepressant prescriptions where the prescribed drug did not have strong evidence but another antidepressant from the same class existed that had strong evidence for the respective indication.

Potential explanations for off-label prescribing

Several contextual factors could contribute to physicians prescribing antidepressants for off-label indications. Firstly, the vast and increasing number of drugs on the market makes it challenging for physicians to keep track of which indications are approved for specific products,[30] especially when pharmaceutical companies have been known to promote drug use for off-label indications.[31] Secondly, constraints such as the list of drugs included on patients' health plan formularies could influence which drugs physicians prescribe, especially if physicians presume that drugs in the same class are interchangeable.[32 33] For example, in our setting, escitalopram was not covered for patients enrolled in the public drug insurance plan. We found that when study physicians prescribed SSRIs to patients with public drug insurance, they infrequently prescribed escitalopram (4.7% of all SSRI prescriptions for patients with public drug insurance) but frequently prescribed citalopram (51.4%). However, for patients with private drug insurance, study physicians equally prescribed escitalopram and citalopram (29.3% and 31.7% of all SSRI prescriptions for patients with private drug insurance, respectively).

Thirdly, primary care physicians might prescribe antidepressants off-label because alternative treatments for a given indication are contraindicated or perceived as higher risk medications. For example, benzodiazepines and Z drugs such as zolpidem and zaleplon have been shown to be efficacious for treating insomnia.[34] However, these drugs have been labelled as potentially inappropriate treatments for older adults, and if prescribed, could even negatively affect providers' quality and performance measures.[35] Many physicians who are concerned about the health of their older patients might consequently prescribe trazodone instead because they believe it is a safer treatment.

Finally, many off-label indications for antidepressants are symptom based conditions for which few approved drug treatments exist. Primary care physicians could be struggling to find effective treatments for these conditions and thus prescribe antidepressants as a last resort, indicating a gap in needed pharmacotherapy.

Implications of findings

For both primary care physicians and specialists (since specialists could initiate antidepressant treatment that is then continued by a primary care physician), our findings emphasise the importance of considering the level of evidence supporting risk-benefit when prescribing an antidepressant, especially if the drug is known to have important adverse side effects.[36] When evidence to support efficacy is lacking, physicians should exercise caution, prescribe conservatively, and inform patients of this information via a shared decision making process.[36] This ideal, however, is challenging to achieve because physicians face time constraints, the drug market and scientific literature are vast and ever-evolving, and many physicians find it challenging to critically appraise and interpret the results of epidemiological studies.[37] Indication based e-prescribing systems that are integrated with clinical decision support tools could help overcome these obstacles by notifying physicians when drugs are being prescribed off-label without supporting evidence and providing them with access to concise, up-to-date summaries of the available evidence. Providing the public with access to patient friendly resources about the level of scientific evidence supporting different treatment options for a given indication could further facilitate the decision making process between physicians and patients.

Our finding that among off-label prescriptions, 40% were for indications where the prescribed drug did not have strong evidence but another drug in the same class was approved or supported by strong evidence is clinically important. Many physicians might view this type of off-label prescribing as different from off-label prescribing without scientific evidence for the entire class because they assume that drugs within the same class are interchangeable.[38 39] However, class effects cannot be assumed because even slight differences in chemical structure between drugs can alter their pharmacodynamic and pharmacokinetic properties, leading to clinically relevant differences in efficacy and risk.[39] For example, statins have been shown to differ not only in efficacy[40] but also in safety, as demonstrated by the withdrawal of cerivastatin from the market in 2001 because the risk of rhabdomyolysis was 10 times higher for cerivastatin than other statins.[41] Clinical guidelines recommend that when physicians select a particular drug to prescribe, they should consider the level of scientific evidence supporting the specific drug.[42] It should not be assumed that all drugs within a class are likely to be efficacious for treating an indication when one member of the class has proven efficacy.

Finally, more evidence is needed on the clinical outcomes associated with antidepressant use for off-label indications. However, within a context of limited

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resources, it is unlikely that randomised clinical trials will be conducted for each off-label drug-indication pair, especially for older drugs that are no longer owned by an innovator company.[9] Thus, in addition to randomised clinical trials, post-market drug surveillance systems represent valuable resources for assessing off-label antidepressant use. Such systems face challenges associated with measuring treatment indications and patient reported outcomes, but these challenges could be overcome by increasing the use of indication based e-prescribing systems and electronic health records that track patient outcomes. Indeed, this study demonstrates the benefits that indication based prescribing can have towards addressing knowledge gaps around off-label antidepressant prescribing.

Strengths and limitations

The key strength of this study is that it included more than 12 years of antidepressant prescriptions from an e-prescribing system where physicians systematically documented treatment indications at the point of prescribing. However, study participants were from one Canadian province where prescribers were generally younger and patients were generally older with more health complexities.[43] These characteristics could influence the generalisability of our findings, because younger physicians are more likely to prescribe drugs off-label without scientific evidence, and patients with more health complexities are less likely to receive off-label prescriptions.[7]

Another study strength is that physicians were unlikely to have altered their true responses when recording indications in the e-prescribing system because the dropdown menu did not distinguish between on-label and off-label indications for a drug. On the other hand, we could not identify when physicians consciously prescribed antidepressants off-label. Indeed, a portion of antidepressants in this study might have been prescribed off-label for a specific reason (eg, patient experienced side effects to another drug in the same class, or formulary restrictions).

Study considerations

Firstly, our estimates of off-label antidepressant prescribing were conservative because we did not consider other aspects of off-label drug use (eg, dose, frequency, duration of treatment), and we used the approved indications and available evidence at the end of the study period. Secondly, we presumed that approved indications for drugs were backed by strong scientific evidence, which might not have been true in some cases given that the quality of clinical trial evidence used by regulatory agencies as the basis for approving new therapeutics and supplemental indications has been shown to vary widely.[44 45]

Thirdly, to identify evidence based off-label uses for antidepressants, we used pre-established criteria that has been used in other studies.[7 18 25] However, our list of evidence based antidepressants for each indication might not always be identical to the recommendations from clinical guidelines. For example, recommendations from two national guidelines for managing anxiety related disorders[42 46] are similar but slightly more inclusive than ours. Finally, because regulatory bodies in North America and Europe are not entirely harmonised in their list of approved indications for drugs, slight discrepancies in the rate of off-label antidepressant use could exist between North America and Europe.

Conclusions

By using information from an indication based e-prescribing system, we found that when primary care physicians prescribed antidepressants for off-label indications, the prescribed drug was usually not supported by strong evidence for the respective indication. However, there was often another drug in the same class with strong evidence that could have been considered. These findings highlight an urgent need to produce more evidence on the risks and benefits of off-label antidepressant use and to provide physicians with this evidence at the point of prescribing. Technologies such as indication based e-prescribing systems and electronic health records have the potential to become essential components of effective post-market drug surveillance systems for monitoring and evaluating off-label antidepressant use. By integrating these technologies with knowledge databases and clinical decision support tools, they could also provide an effective means for communicating evidence back to physicians to optimise prescribing decisions.

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