JAMIA Open, 1(2), 2018, 233–245
doi: 10.1093/jamiaopen/ooy037
Advance Access Publication Date: 24 September 2018
Research and Applications

Research and Applications

Using electronic health records to characterize prescription patterns: focus on antidepressants in nonpsychiatric outpatient settings

Joseph J. Deferio,[1] Tomer T. Levin,[2] Judith Cukor,[3] Samprit Banerjee,[1] Rozan Abdulrahman,[1] Amit Sheth,[4] Neel Mehta,[5] and Jyotishman Pathak[1]

[1]Department of Healthcare Policy and Research, Weill Cornell Medicine, Cornell University, New York, New York, USA, [2]Beacon Health Options, New York, New York, USA, [3]Department of Psychiatry, Collaborative and Integrative Care, Weill Cornell Medicine, Cornell University, New York, New York, USA, [4]Kno.e.sis Center, Wright State University, Dayton, Ohio, USA and [5]Department of Anesthesiology, Pain Medicine/Management, Weill Cornell Medicine, Cornell University, New York, New York, USA

Corresponding Author: Jyotishman Pathak, PhD, Department of Healthcare Policy and Research, Weill Cornell Medicine, 425 E 61 ST, Suite 301, New York, NY 10065, USA (pathak@med.cornell.edu)

Received 12 April 2018; Revised 13 July 2018; Editorial Decision 10 August 2018; Accepted 30 August 2018

ABSTRACT

Objective: To characterize nonpsychiatric prescription patterns of antidepressants according to drug labels and evidence assessments (on-label, evidence-based, and off-label) using structured outpatient electronic health record (EHR) data.

Methods: A retrospective analysis was conducted using deidentified EHR data from an outpatient practice at a New York City-based academic medical center. Structured "medication–diagnosis" pairs for antidepressants from 35 325 patients between January 2010 and December 2015 were compared to the latest drug product labels and evidence assessments.

Results: Of 140 929 antidepressant prescriptions prescribed by primary care providers (PCPs) and nonpsychiatry specialists, 69% were characterized as "on-label/evidence-based uses." Depression diagnoses were associated with 67 233 (48%) prescriptions in this study, while pain diagnoses were slightly less common (35%). Manual chart review of "off-label use" prescriptions revealed that on-label/evidence-based diagnoses of depression (39%), anxiety (25%), insomnia (13%), mood disorders (7%), and neuropathic pain (5%) were frequently cited as prescription indication despite lacking ICD-9/10 documentation.

Conclusions: The results indicate that antidepressants may be prescribed for off-label uses, by PCPs and nonpsychiatry specialists, less frequently than believed. This study also points to the fact that there are a number of off-label uses that are efficacious and widely accepted by expert clinical opinion but have not been included in drug compendia. Despite the fact that diagnosis codes in the outpatient setting are notoriously inaccurate, our approach demonstrates that the correct codes are often documented in a patient's recent diagnosis history. Examining both structured and unstructured data will help to further validate findings. Routinely collected clinical data in EHRs can serve as an important resource for future studies in investigating prescribing behaviors in outpatient clinics.

Key words: antidepressants, prescription patterns, EHR, outpatient

INTRODUCTION

In the United States (US), treatment for depression is increasingly occurring outside of traditional contexts and predominantly in the primary care setting.[1–4] The collaborative and integrative care movement embraces the expansion of treatment across broader medical populations but also emphasizes a team-based approach, involving psychiatrists as consultants—thereby improving care and widening of the arc of nonpsychiatrists who prescribe antidepressants.[3,4] Despite its promise, collaborative care has yet to become standard practice—thus understanding the patterns of medication prescribing by primary care providers (PCPs) and nonpsychiatric specialists is important because it remains unclear as to how antidepressants are being prescribed in this setting.

The prescribing patterns of nonpsychiatrists are of particular importance because the prevalence of antidepressant medication use is rising in the US.[5–7] This increase is partly driven by a greater number of medications on the market,[8] improved public acceptance of psychiatric drugs,[9] and a broadening of the clinical indications. According to the Centers for Disease Control and Prevention, use of antidepressants has increased nearly 5-fold in the US since the 1980s, and roughly 12% of the adult population are now taking these medications.[10,11] Antidepressants are primarily designed to treat depression and anxiety, but they are commonly prescribed for related problems such as chronic pain,[12] neuropathies,[13,14] insomnia,[15,16] and eating disorders.[17] Prescriptions for indications other than those approved by the US Food and Drug Administration (FDA) are considered to be "off-label," and have been estimated to occur at nearly 30% or higher for antidepressant medications.[18–20] However, the drug label is not always a comprehensive indicator of a medication's use. In fact, drug labels and evidence assessments are frequently determined by pharmaceutical marketing strategies, incentives for research and development, and the cost of randomized controlled trials (RCTs).

Despite an increase in antidepressant prescriptions, there is limited knowledge on trends in prescribing by PCPs and nonpsychiatric specialists.[6,20] For instance, the risk/benefit ratios of most off-label uses are variable, thus there is added benefit to understanding "real-world" prescription patterns with respect to drug labels and evidence assessments. Electronic health records (EHRs) routinely collect data on prescription patterns across all care settings including outpatient and inpatient practices, and emergency departments, and may provide further insight into clinical use of medications. Additionally, EHRs provide a platform for longitudinal data collection covering a wide range of phenotypic expressions via both structured data and unstructured clinical text. Therefore, the primary goal of our study is to characterize nonpsychiatric outpatient prescriptions of antidepressants using structured diagnosis data from EHRs.

METHODS

Study design

This retrospective study was conducted using outpatient EHR data (Epic Systems®) at a large New York City-based academic medical center. The EHR data repository was queried to retrieve demographics, encounter, diagnosis, and associated medication data for outpatients who had received antidepressants.[21] As of July 2016, there were 123 702 unique patients who had been prescribed a total of 401 734 unique prescriptions of antidepressant medications.

This study, however, included only those antidepressant prescriptions actively written for individuals aged ≥18 between January 1, 2010 and December 31, 2015—to capture more than 5 full years of data during a period in which the EHR Computerized Provider Order Entry (CPOE) use was predominant. We queried prescriptions issued at the institution's outpatient practices (stored as a structured data element in the EHR data repository) and not those documented as historical medications because of potential recall biases and inaccurate association of indications for each prescription. Antidepressant medications were identified using national drug codes (NDC) located in the Healthcare Effectiveness Data and Information Set (HEDIS) 2016 final NDC lists.[22] The HEDIS lists are provided by the National Committee for Quality Assurance (NCQA) and represent unique codes for distinct combinations of drug ingredients, strength, and route. Structured diagnoses were coded according to the *International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification* (ICD-9-CM/ICD-10-CM). Both ICD-9 and ICD-10 codes are available for all diagnoses in the EHR system due to extensive code mapping completed at the institution during the code transition period surrounding October 2015. However, given that the transition occurred at the end of the study period, our syntax searched for relevant ICD-9 codes prior to ICD-10. We excluded all prescriptions that had been issued by physicians, certified nurse practitioners and other healthcare providers with prescribing privileges from the Department of Psychiatry, choosing instead to focus only on PCP and nonpsychiatric specialty prescribing. Lastly, to account for recent medical history, each prescription was matched to all structured diagnoses made for the corresponding patient during the previous 5 years (including data between 2005 and 2015). After applying our inclusion/exclusion criteria, we were left with 35 325 unique patients and 140 929 prescriptions between 2010 and 2015 (Figure 1).

Prescription classification

For the purposes of this study, prescriptions were then classified as "on-label" if an associated diagnosis matched those provided in the FDA list of approved indications, or "evidence-based" for diagnoses in which evidence favors efficacy as of August 2016. We applied methods previously reported,[20,23] in which product label information, class of recommendation, and the strength of scientific evidence or clinical effectiveness assessments were distinguished by the DrugDex system (Truven Health Analytics Micromedex Solutions, Greenwood Village, CO, USA).[24] DrugDex is considered to be an authoritative compendium, which is used by the Centers for Medicare and Medicaid Services (CMS) to determine coverage for off-label uses of medications, and has also been used for research in multiple prior studies.[23,25–32] Within the compendium, benefit classes range from I (strong, benefit $\ggg$ risk) to III (No benefit or benefit $\leq$ risk), and level of evidence ranges from Category A to C-EO. Only those medication–indication pairs in which the class of recommendation is listed as I, IIa (moderate, benefit $\gg$ risk), or IIb (weak, benefit $\geq$ risk), and evidence Category A (high quality evidence from >1 RCT) or B (moderate evidence from $\geq$ 1 RCT or well-designed nonrandomized study, observational study, etc.) were considered as medically accepted and rigorous enough for this study. The list of antidepressant classes found in the dataset and their on-label/evidence-based uses are included in Table 1. The full list of each individual antidepressant medication and their on-label/evidence-based uses can be found in Supplementary Table S1. Finally, all prescriptions associated with diagnoses that were not

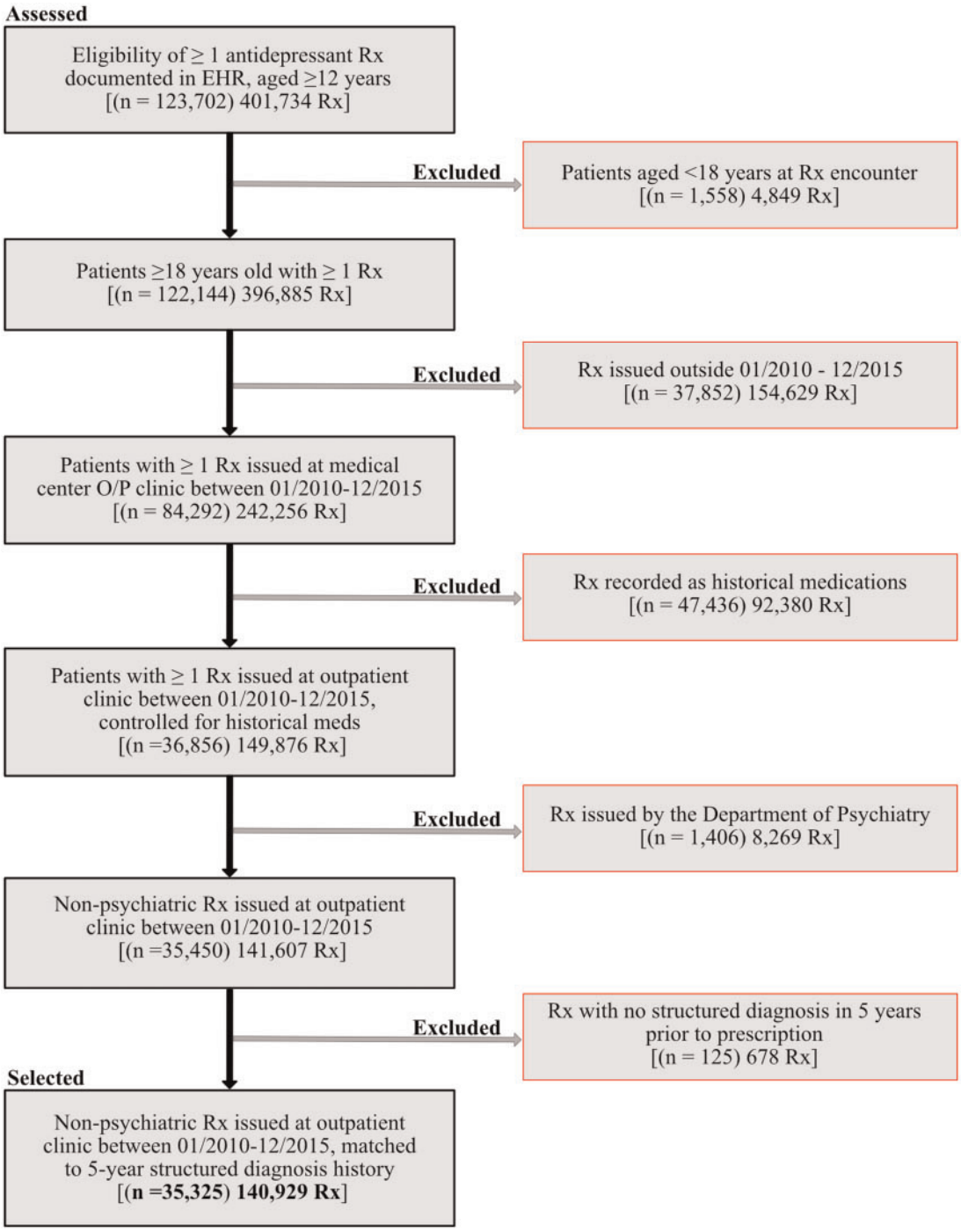

Figure 1. Prescription eligibility CONSORT diagram.

matched to drug labels or evidence assessments, were considered to be off-label use.

In order to determine the effect that medical history played on the classification of prescriptions, we then examined trends in on-label/evidence-based versus off-label use over periods of up to 5 years prior to each prescription date (Figure 2A and B). The 5-year time frame was selected because it represents a period of recent medical history in which an individual likely still suffers from the chronic ailments that are traditionally associated with antidepressant medications. In addition, past medical history is not always recaptured via diagnosis codes in subsequent clinical encounters. Five years is also close to the upper limit of mean data available in the outpatient EHRs. Medication–diagnosis pairs and on-label/evidence-based classifications using the 5-year time frame are characterized in Table 2.

For prescriptions classified as off-label use, only those diagnoses that were made during the most recent clinical encounter were included in the analysis. This was done based on the findings that no diagnoses during the selected medical history window could be matched to product labels or evidence assessments, yet a structured diagnosis was required for the analysis.

Table 1. DrugDex list of antidepressant classes by on-label and evidence-based uses

Therapeutic class	On-label use	Evidence-based use
SSRI	Abnormal vasomotor function—menopause	Alcoholism
	Bulimia	Binge-eating syndrome
	Depression	Bipolar disorder, depressed phase; adjunct
	Generalized anxiety disorder	Body dysmorphic disorder
	Obsessive–compulsive disorder	Cancer—depression
	Panic disorders	Cancer pain
	Post-traumatic stress disorder	Cerebrovascular accident—depression
	Premenstrual disorders	Coronary arteriosclerosis—depression
	Social phobia	Depression
		Depression—diabetes mellitus
		Depression—myocardial infarction; post
		Drug-induced depressive state
		Dysthymia
		Eating disorder
		Fibromyalgia
		Generalized anxiety disorder
		Hot sweats
		Mixed anxiety and depressive disorder
		Night eating syndrome
		Obsessive–compulsive disorder
		Panic disorder
		Postmenopausal flushing
		Post-traumatic stress disorder
		Premature ejaculation
		Premenstrual dysphoric disorder
		Raynaud's phenomenon
		Severe depression with psychotic features; adjunct
		Social phobia
		Vasovagal syncope
SNRIs	Chronic pain (musculoskeletal)	Attention-deficit/hyperactivity disorder
	Depression	Binging–eating disorder
	Diabetic neuropathy—pain	Bipolar disorder, depressed phase
	Fibromyalgia	Cerebrovascular accident—depression
	Generalized anxiety disorder	Depression—perimenopausal disorder
	Panic disorders	Diabetic neuropathy
	Social phobia	Dysthymia
		Hot sweats, breast cancer-related
		Menopausal flushing
		Migraine
		Obsessive–compulsive disorder
		Pain, chemotherapy-induced—peripheral nerve disease
		Post-traumatic stress disorder
		Premenstrual dysphoric disorder
		Recurrent major depressive episodes; prophylaxis
		Tension-type headache; prophylaxis
		Urinary incontinence
Tricyclic	Alcoholism	ADHD
	Anxiety	Binging
	Depression	Cataplexy
	Endogenous depression	Delusional disorder
	Insomnia	Depression
	Nocturnal enuresis (pediatric only)	Diabetic neuropathy
	Obsessive–compulsive disorder	Disorder of ejaculation (sex dysfunction)
	Pruritus	Fibromyalgia
	Psychotic depressive disorders	Headache
	Severe major depression with psychotic features	Irritable bowel syndrome
		Neurogenic bladder
		Nocturnal enuresis
		Obsessive–compulsive disorder; intravenous therapy
		Pain
		Pain, chronic
		Panic disorder
		Postherpetic neuralgia
		Smoking cessation assistance
		Subjective tinnitus
		Urinary incontinence
		Urticaria
Tetracyclic	Bipolar disorder	Anxiety
	Depression	Cancer, symptomatology
	Dysthymia	Dysthymia
	Mixed anxiety and depressive disorder	Obsessive–compulsive disorder
		Pain
		Panic disorder
		SSRI adverse reaction—sexual dysfunction
Phenylpiperazine	Depression	Insomnia
Misc.	Depression	Bipolar disorder
	Depression, associated with seasonal affective disorder; prophylaxis	Sexual dysfunction due to substance, SSRI
	Smoking cessation	
Others	Bipolar disorder	Agoraphobia

(continued)

Table 1. continued

Therapeutic class	On-label use	Evidence-based use
	Depression	Bulimia nervosa
	Depression, atypical, nonendogenous, or neurotic	Social phobia
	Mixed anxiety and depressive disorder	
	Schizophrenia	

Notes: Selective Serotonin Reuptake Inhibitor (SSRI) includes citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. Serotonin-Norepinephrine Reuptake Inhibitor (SNRI) includes desvenlafaxine, duloxetine, levomilnacipran, and venlafaxine. Tricyclic antidepressants include amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, and protriptyline. Tetracyclic antidepressants include maprotiline and mirtazapine. Phenylpiperazine includes trazodone and nefazodone. Miscellaneous antidepressants include bupropion, vilazodone, and vortioxetine. Others include monoamine oxidase inhibitors (MAOIs): phenelzine and tranylcypromine; and psychotherapeutic combinations: fluoxetine-olanzapine, amitriptyline-chlordiazepine and amitriptyline-perphenazine.

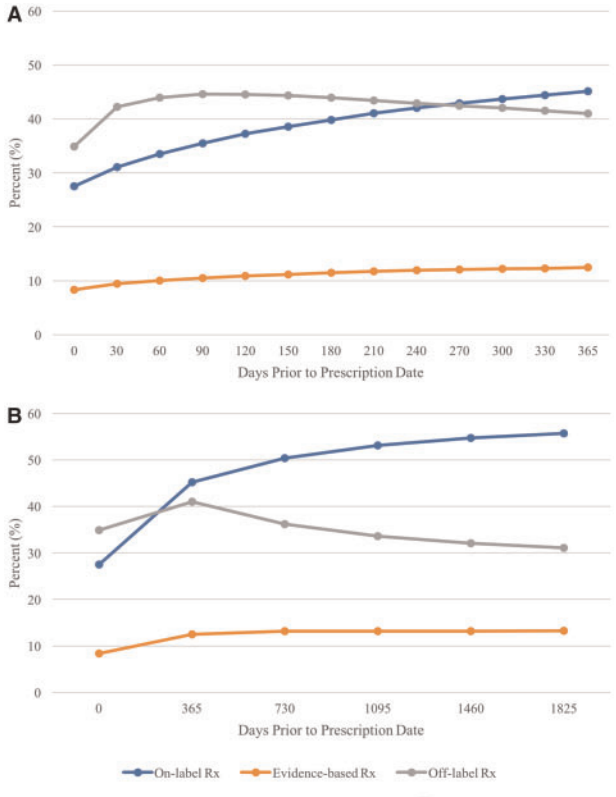

Figure 2. (A and B) Prescription classification adjusted by no. of days of medical history examined, 1 year (A) and 5 year (B).

We examined the distribution of prescriptions within the context of the medical specialty of the prescriber. For the clinical specialties in which the greatest number of off-label use prescriptions were issued, we tabulated major characteristics of the prescriptions. Such characteristics included prominent diagnosis classes, number of prescriptions on which the classes occur, the most common diagnoses within each class, and most frequently prescribed antidepressant drug classes (Table 3). Diagnosis classes and specific diagnoses were chosen based on their frequency within the specialty, severity, and potential relationship with depression.

Assessment and validation of indication identification

In order to assess the accuracy of our methodology, we then performed a sensitivity analysis via chart review on 1% of the patients that had received a prescription for an off-label use (n_{patients} = 259).[33] During this review, we randomly sampled patients and their prescriptions, then compared the encounter diagnoses that were listed in our dataset to the diagnoses that were specifically linked to each prescription within the EHR system. If a patient received two different antidepressant prescriptions in the same encounter, both were recorded ($n_{\text{prescriptions}}$ =270). In addition, we reviewed clinical notes to determine the physician-documented reason for ordering the antidepressant. A sample of the results are displayed in Table 4. As an added validation step, a chart review was performed on 1% of the patients (n_{patients} = 190) that had received an on-label/evidence-based use prescription, comparing the earliest approved structured diagnosis to the physician-documented indication within the clinical text.

All data management and analyses were performed using SAS software version 9.4 (SAS Institute). This study was reviewed and approved by the Institutional Review Board (No. 1510016639).

RESULTS

Study cohort characteristics

On average, we had 4.1 (±5.8) unique antidepressant prescriptions and 3.0 (±2.7) years of diagnosis data per patient. The mean age of the study population was 56.7 (±16.4) years. There were also twice as many females (67%) in the population as males.

Examination of treatment indications and prescriptions patterns

Frequencies of prescriptions stratified by treatment indication and on-label/evidence-based use classification are provided in Table 2. Using our matching method, the most commonly appearing diagnoses across all prescriptions were depressive disorders (48%), pain (35%), anxiety disorders (23%), symptoms (eg chronic fatigue and malaise) (17%), digestive system disorders (15%), insomnia (13%), weight problems (12%), and headache or migraine (11%). All prescriptions which included a diagnosis of depression in the previous 5 years were written for on-label/evidence-based uses, while prescriptions with histories of insomnia or anxiety disorders were supported by on-label/evidence-based uses 93% and 87% of the time, respectively.

Prescriptions classified as off-label uses were most frequently associated with diagnoses of Parkinson's disease (32%), headache/migraine (25%), bipolar disorder (20%), fibromyalgia (17%), weight problems, and pain (16%).

Characterization of off-label use prescription patterns by medical specialty

Prescriptions classified as off-label use were stratified by medical specialty and further analyzed in an attempt to further investigate the clinical reason for the prescription order. Table 3 also shows that specialty prescribing often includes diagnoses of chronic and/or debilitating conditions that have been associated with depression. Anxiety and pain seem to also be commonly diagnosed. Internal

Table 2. Treatment indication diagnoses and prescribing patterns for antidepressant medications, 2010–2015

Prescription diagnoses[a]	Number of prescriptions (%)[b] $n = 140\,929$ (100)	For on-label use (%)[c] $n = 78\,468$ (55.7)	Where evidence favors efficacy (%)[d] $n = 18\,613$ (13.2)	For off-label use (%) $n = 43\,848$ (31.1)
Depressive disorders	67 233 (47.7)	65 475 (97.4)	1758 (2.6)	0 (0)
Pain	48 680 (34.5)	33 591 (69.0)	7233 (14.9)	7856 (16.1)
Anxiety disorders	32 890 (23.3)	23 490 (71.4)	5049 (15.4)	4351 (13.2)
Symptoms	23 240 (16.5)	16 968 (73.0)	3506 (15.1)	2766 (11.9)
Digestive system disorders	21 596 (15.3)	16 051 (74.3)	2855 (13.2)	2690 (12.5)
Insomnia	18 377 (13.0)	12 610 (68.6)	4609 (25.1)	1158 (6.3)
Weight problems	16 612 (11.8)	12 342 (74.3)	1565 (9.4)	2705 (16.3)
Headache/migraine	15 109 (10.7)	8043 (53.2)	3354 (22.2)	3712 (24.6)
Urinary system disorders	14 604 (10.4)	11 248 (77.0)	1876 (12.8)	1480 (10.1)
Dermatological conditions	11 471 (8.1)	8404 (73.3)	1932 (16.8)	1135 (9.9)
Sleep disorders	10 456 (7.4)	7797 (74.6)	1301 (12.4)	1358 (13.0)
Nicotine dependence	8593 (6.1)	7504 (87.3)	791 (9.2)	298 (3.5)
Fibromyalgia	7702 (5.5)	4655 (60.4)	1716 (22.3)	1331 (17.3)
Sexual dysfunction	5174 (3.7)	3658 (70.7)	822 (15.9)	694 (13.4)
Drug abuse	4807 (3.4)	4313 (89.7)	347 (7.2)	147 (3.1)
Bipolar	4027 (2.9)	2275 (56.5)	947 (23.5)	805 (20.0)
Alcohol abuse	3554 (2.5)	2957 (83.2)	456 (12.8)	141 (4.0)
Nausea and vomiting	3266 (2.3)	2538 (77.7)	399 (12.2)	329 (10.1)
Panic disorder	2733 (1.9)	2118 (77.5)	572 (20.9)	43 (1.6)
Abnormal vasomotor function—menopause	2580 (1.8)	1243 (48.2)	1017 (39.4)	320 (12.4)
Pruritus	2550 (1.8)	2230 (87.5)	202 (7.9)	118 (4.6)
Eating disorders	1782 (1.3)	1491 (83.7)	118 (6.6)	173 (9.7)
Parkinson's disease	1732 (1.2)	1033 (59.6)	139 (8.0)	560 (32.3)
Attention-deficit/hyperactivity disorder	1395 (1.0)	898 (64.4)	317 (22.7)	180 (12.9)
Post-traumatic stress disorder	1189 (0.8)	992 (83.4)	147 (12.4)	50 (4.2)
Premenstrual dysphoric disorder	1186 (0.8)	940 (79.3)	210 (17.7)	36 (3.0)
Obsessive–compulsive disorder	950 (0.7)	805 (84.7)	131 (13.8)	14 (1.5)
Schizophrenia	849 (0.6)	620 (73.0)	99 (11.7)	130 (15.3)
Social phobia	187 (0.1)	178 (95.2)	2 (1.1)	7 (3.7)
Other	117 845 (83.6)	69 772 (59.2)	14 930 (12.7)	33 143 (28.1)

Note: All variables are represented as counts (percentage).

[a]Five-year diagnosis history was accounted for, and 68% of all antidepressant prescriptions had multiple treatment indications and thus were assigned to more than one category. Therefore, the sum of prescriptions across the individual treatment indication categories exceeds the total number of prescriptions (first row).

[b]Percentages calculated using the total number of antidepressant prescriptions for any indication ($N = 140\,929$) as the denominator.

[c]Number of prescriptions that were considered on-label for the specified treatment indication, according to the US Food and Drug Administration (FDA).

[d]This column reflects the number of antidepressant prescriptions that were written in which the evidence favors efficacy for treatment of the associated diagnosis, as noted by the DrugDex System.

medicine specialists predominantly prescribed selective-serotonin reuptake inhibitors (SSRI's) and diagnosed pain [(back pain, chest pain, osteo-/rheumatoid arthritis, hip pain, and sciatica, etc.) 16%], anxiety (14%), and fatigue and malaise symptoms on 8% of the prescriptions. Neurologists frequently diagnosed chronic headache/migraine (34%), multiple sclerosis and Alzheimer's disease (18%), back, neck, and miscellaneous neuropathies [(diabetic peripheral neuropathy, etc.) 15%] and Parkinson's disease (6%), while prescribing largely SSRIs and tricyclic antidepressants (TCAs). Infectious disease specialists often diagnosed HIV and AIDS (63%) and bipolar disorder (14%) in patients with off-label use prescriptions. In terms of antidepressants, SSRIs and phenylpiperazine (eg trazodone, nefazodone) were the most commonly prescribed antidepressant classes. Pain specialists largely prescribed TCAs for neuropathic back and neck pain and myofascial pain 97% of the time. OB/GYN specialists most often diagnosed patients with urinary disorders (20%), such as urinary frequency, dysuria, urge incontinence, and urinary tract infections, while they prescribed TCAs and SSRI's. Gastroenterology and hepatology specialists often prescribed SSRIs or phenylpiperazine in the setting of cirrhosis, chronic hepatitis C, hepatic encephalopathy, irritable bowel syndrome (IBS), and diarrhea. Diagnoses related to weight, such as abnormal weight gain and obesity, were matched with the majority of prescriptions being issued by endocrinologists (66%), while miscellaneous antidepressants (eg bupropion) were issued in greatest proportion.

Sensitivity analysis

A sample of findings from the chart review of off-label use prescriptions is displayed in Table 4. Approximately 69% of the 270 prescriptions reviewed did not have a structured ICD-9/10 diagnosis specifically associated with the medication in EHR. Of those that did, the EHR-documented prescription diagnosis was often one or all of the encounter diagnoses. Upon examining the free-text clinical notes, however, it was found that 39% ($n = 105$) of the random sample of prescriptions included a physician-documented history of depression as the primary reason for antidepressant therapy. For prescriptions characterized as on-label, we found that our methodology using purely structured diagnosis data was 83% accurate in identifying the physician-documented indication in free-text clinical

Table 3. Prescribing trends of antidepressant prescriptions for off-label uses by top 8 department specialties and diagnosis classes, 2010–2015

Specialty no. of off-label Rx (%)[a]	Prominent diagnosis class	No. of off-label Rx with Dx class (%)[b]	Prominent diagnoses[c]	Drug class (%)[c]
Internal Medicine $n = 20834$ (26.7)	Hypertension	3296 (15.8)	Hypertension, essential hypertension, benign hypertension, elevated BP, hypertensive retinopathy	SSRI (60), Phenyl, Misc, Tricyclic
	Pain	3231 (15.5)	Back pain, knee pain, chest pain, neck pain, osteoarthritis, rheumatoid arthritis, shoulder pain, abdominal pain, neuropathic pain, chronic pain, limb pain, sciatica, arthralgia, cervicalgia, etc.	SSRI (57), Phenyl, Tricyclic, Misc
	Hyperlipidemia	3002 (14.4)	Hyperlipidemia, hypercholesterolemia, mixed hyperlipidemia, familial hyperlipidemia, other and unspecified hyperlipidemia, etc.	SSRI (64), Phenyl, Misc, SNRI
	Anxiety	2962 (14.2)	Anxiety, generalized anxiety disorder, chronic anxiety, adjustment disorder, etc.	SSRI (80), Misc, SNRI
	Diabetes	1792 (8.6)	DM, T2DM, T2 or unspecified DM, diabetes uncomplicated adult-type II, T2DM controlled, etc.	SSRI (55), Phenyl, Tricyclic, Misc, SNRI
	Symptoms	1749 (8.4)	Fatigue, cough, other malaise and fatigue, memory loss, shortness of breath, dizziness, etc.	SSRI (70), Phenyl, SNRI, Misc
	Digestive disorder	1150 (5.5)	Diarrhea, constipation, IBS, dysphagia, abdominal bloating, chronic constipation, nausea, rectal bleeding, gastritis, vomiting, Crohn's disease, etc.	SSRI (62), Phenyl, Tricyclic, Misc
	Cardiac conditions	923 (4.4)	Coronary artery disease, atrial fibrillation, coronary atherosclerosis, CHF, mitral valve disorders, chronic ischemic heart disease, aortic valve disorders, chronic diastolic heart failure, etc.	SSRI (54), Phenyl, Tricyclic, Misc
Neurology $n = 8158$ (42.3)	Headache/migraine	2787 (34.2)	Headache, chronic migraine w/o aura, migraine w/o aura, migraine, chronic daily headache, tension headache, migraine w/ aura, daily persistent headaches, etc.	Tricyclic (76), SNRI, SSRI
	Cerebral degeneration	1459 (17.9)	Multiple sclerosis, Alzheimer's, dementia, other degenerative diseases of basal ganglia, frontotemporal lobar degeneration, etc.	SSRI (56), SNRI, Tricyclic, Misc, Phenyl
	Pain	1193 (14.6)	Cervical radiculopathy, lumbar radiculopathy, neck pain, cervicalgia, neuropathic pain, neuralgias, back pain, brachial neuritis or radiculitis, diabetic neuropathy, etc.	Tricyclic (55), SNRI, SSRI
	Sleep disorders	524 (6.4)	Sleep disturbance unspecified, OSA, hypersomnia, RLS/PLM, narcolepsy, sleep apnea, delayed sleep phase syndrome, REM sleep behavior disorder, etc.	SSRI (25), Tricyclic, Phenyl, Tetracyclic, SNRI
	Parkinson's Disease	505 (6.2)	Parkinson's disease (paralysis agitans), secondary parkinsonism	SSRI (48), Tetracyclic, SNRI, Tricyclic
Infectious Disease $n = 1300$ (8.6)	HIV	823 (63.3)	HIV/AIDS	SSRI (48), Phenyl, Tricyclic, Tetracyclic
	Bipolar	187 (14.4)	Mood disorder, bipolar II disorder, bipolar mixed, bipolar depression, bipolar I, unspecified episodic mood disorder	SSRI (66), Phenyl, Tetracyclic
	Pain	148 (11.4)	Back pain, neuropathies, trigeminal neuralgia, osteoarthritis, limb pain, abdominal pain, joint pains, etc.	SSRI (43), Phenyl, Tricyclic, Tetracyclic
Pain medicine/management $n = 2719$ (52.5)	Pain	2510 (92.3)	Disc disorder, lumbar radiculopathy, low back pain, neck pain, neuropathic pain, cervical radiculopathy, thoracic or lumbosacral neuritis or radiculitis, facet arthropathy, postlaminectomy syndrome, joint pain, cancer-related pain, limb pain, osteoarthritis, etc.	Tricyclic (97)
OB/GYN $n = 1923$ (51.7)	Urinary conditions	391 (20.3)	Urinary frequency, dysuria, urgency of urination, urge incontinence, nocturia, UTI, mixed incontinence, etc.	Tricyclic (90), SSRI
	Abnormal vasomotor function—menopause	170 (8.8)	Menopause syndrome, symptomatic menopausal or female climacteric states, menopause, hot flushes, menopausal symptoms, perimenopause, etc.	SSRI (63), Tricyclic
	Anxiety	102 (5.3)	Anxiety, agoraphobia w/panic	SSRI (87), Tricyclic

(continued)

Table 3. continued

Specialty no. of off-label Rx (%)[a]	Prominent diagnosis class	No. of off-label Rx with Dx class (%)[b]	Prominent diagnoses[c]	Drug class (%)[c]
Oncology $n = 1791$ (50.3)	Cancer[d]	1205 (67.3)	malignant neoplasm of breast (female), breast cancer, prostate cancer, malignant neoplasm of colon, colon cancer, lung cancer, malignant neoplasm of prostate, etc.	SSRI (46), SNRI, Misc
	Nausea/vomiting	105 (5.9)	Nausea and vomiting, nausea alone, nonintractable vomiting w/nausea	SSRI (54), SNRI
	Symptoms	90 (5)	Fatigue, cough, shortness of breath, weakness, debility	SSRI (70), Tricyclic, SNRI
	Pain	80 (4.5)	Neuropathies, abdominal pain, back pain, chest pain, cancer associated pain, trigeminal neuralgia, joint pains etc.	SSRI (46), SNRI, Tricyclic, Tetra
Gastroenterology & Hepatology $n =$ 1822 (57.9)	Digestive disorder	1032 (56.6)	Diarrhea, IBS, constipation, abdominal bloating, colitis, regional enteritis, etc.	SSRI (60), Tricyclic, Misc
	Hepatitis	403 (22.1)	Chronic hepatitis C, hepatitis C w/o hepatic coma, hepatitis B	SSRI (70), Phenyl
	Pain	270 (14.8)	Abdominal pain, abdominal cramping, epigastric pain, leg pain, back pain, noncardiac chest pain, chest pain, etc.	SSRI (66), Tricyclic, Misc, Tetracyclic
	Anxiety	197 (10.8)	Anxiety, insomnia due to anxiety, acute reaction to stress, hypochondriasis	SSRI (89), Tricyclic
	Liver damage	180 (9.9)	Cirrhosis w/o mention of EtOH, NASH, biliary cirrhosis, liver fibrosis, EtOH cirrhosis of liver, hepatic encephalopathy, etc.	Phenyl (63), SSRI, Tetracyclic
Endocrinology $n =$ 2189 (71.9)	Weight problems	1438 (65.7)	Abnormal weight gain, obesity unspecified, morbid obesity, overweight, excessive weight gain, etc.	Misc (89), SSRI

Notes: Selective Serotonin Reuptake Inhibitor (SSRI) includes citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. Serotonin-Norepinephrine Reuptake Inhibitor (SNRI) includes desvenlafaxine, duloxetine, levomilnacipran, and venlafaxine. Tricyclic antidepressants include amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, and protriptyline. Tetracyclic antidepressants include maprotiline and mirtazapine. Phenylpiperazine includes trazodone and nefazodone. Miscellaneous antidepressants include bupropion, vilazodone, and vortioxetine. Others include monoamine oxidase inhibitors (MAOIs): phenelzine, tranylcypromine; Phenylpiperazine antidepressants: nefazodone, trazodone; and psychotherapeutic combinations: fluoxetine-olanzapine, amitriptyline-chlordiazepine, amitriptyline-perphenazine.

Abbreviations: Rx: prescription; Dx: diagnosis; Phenyl: phenylpiperazine; Misc.: miscellaneous; UTI: urinary tract infection; IBS: irritable bowel syndrome; EtOH: alcohol; NASH: nonalcoholic steatohepatitis; OSA: obstructive sleep apnea; RLS/PLM: restless legs syndrome/periodic limb movement; REM: rapid eye movement; BP: blood pressure; DM: diabetes mellitus; T2DM: type 2 diabetes mellitus; CHF: congestive heart failure.

aValues represent fraction of prescription totals by department: Internal Medicine, $n = 110721$; Infectious Disease, $n = 20124$; Neurology, $n = 19242$; Pain Medicine/Management, $n = 6465$; Gastroenterology & Hepatology, $n = 4333$; OB/GYN, $n = 4452$; Oncology, $n = 3807$; Endocrinology, $n = 2583$.

bNo. of prescriptions associated with each prominent diagnosis class are not mutually exclusive and will not necessarily sum to 100%.

cValues are listed in descending order, left to right, from most frequent to least frequent (Drug classes cover approximately 90% of drugs within the diagnosis class), while the % represent the most frequent drug class.

dOnly those cancers listed amongst the CMS Chronic Conditions Warehouse (CCW) were selected: breast, prostate, endometrial, lung, and colorectal.

Table 4. Sample of results from chart review of EHR-documented prescriptions for off-label uses ($n = 270$)

Specialty	Prescription	Encounter diagnosis	Prescription diagnosis	Indication for prescription in clinical text	Excerpt from clinical text
Internal Medicine	Trazodone HCl 50 mg	Hypercholesterolemia, HTN, spina BIFIDA, T2DM, peripheral edema		Insomnia	"Insomnia—c/w trazodone at night"
	Paroxetine 20 mg	Hypertension, smoking	Hypertension	Depression	"Depression: stable: continue Paxil and trazodone for sleep"
Neurology	Bupropion 75 mg	Headache, vertigo	Headache	Depression and/or migraines	"history of migraines and depression, both well controlled on bupropion and amitriptyline"
	Escitalopram Oxalate 5 mg	Parkinson's disease, localization-related epilepsy and epileptic syndromes, memory loss	Parkinson's disease, localization-related epilepsy and epileptic syndromes, memory loss	Depression	"Will try an antidepressant to see if it helps to improve interest in activities. The history is suggestive of depression"
Infectious Disease	Nortriptyline HCl 25 mg	HIV, systolic murmur	HIV	Chronic foot pain (not neuropathic)	"foot pain—chronic, not neuropathy apparently, will give trial of nortrip in case"
	Mirtazapine 7.5 mg	HIV, insomnia, PPD screen	Insomnia	OCD/insomnia, past Rx also associated with HIV, OCD	"still not entirely clear how pt is taking mirtazapine or how frequently. Advised that pt try to take it every night, which may reduce overall anxiety"
Pain Medicine/ Management	Nortriptyline HCl 25 mg	Lumbar radiculopathy, disc disorder of lumbar region, sacroiliitis, spondylolisthesis grade 1, spinal stenosis		Neuropathic pain, Pt listed as being depressed 4 months prior	"Back pain improved with addition of nortriptyline"
	Nortriptyline HCl 10 mg	Low back pain, disc disorder of lumbar region, lumbar radiculopathy, knee pain, myofascial muscle pain, foraminal stenosis of lumbar region		Neuropathic pain	"Has been taking increased dose of nortriptyline since last visit and notes much less pain radiating to leg"
OB/GYN	Nortriptyline HCl 10 mg	Vulvar pain, vulvitis	Vulvar pain, vulvitis	HSV-associated pain	"Pt is really bothered by the diagnosis (culture + HSV1), told unlikely to recur. Start nortriptyline and a local steroid"
	Fluoxetine HCl 10 mg	Menopausal syndrome, nicotine addiction		Menopausal syndrome	"Menopausal syndrome—given smoking and hyperlipidemia, we will try nonhormonal options. Rx prozac"
Oncology	Escitalopram Oxalate 10 mg	Lung cancer, secondary malignant neoplasm of retroperitoneum and peritoneum, rash, malignant neoplasm of bronchus and lung	Lung cancer	Symptoms of depression	"Pt given for lexapro 10 mg daily × 1 week to be increased to 2 tabs (20 mg) daily for sx's of depression"
	Citalopram HBr 20 mg	Breast cancer, malignant neoplasm of breast		Mood	"Citalopram for depressed mood"
Gastroenterology & Hepatology	Escitalopram Oxalate 5 mg	Dyssynergia, Gastroesophageal reflux disease, chronic constipation, anxiety, and IBS		Constipation (intermittent, increased with anxiety)/ anxiety, worry	"Pt was told to continue Lexapro. RX options for her constipation were reviewed"
	Citalopram HBr 20 mg	Insect bite, hepatitis C			"Very anxious about becoming depressed on therapy. Extensive discussion. Given rx

(continued)

Table 4. continued

Specialty	Prescription	Encounter diagnosis	Prescription diagnosis	Indication for prescription in clinical text	Excerpt from clinical text
				Depression/anxiety associated with PEG-Intron medication (Hep C)	for celexa, aware not to initiate antidepressant treatment until we discuss first"
Endocrinology	Bupropion HCl ER 100 mg	Abnormal weight gain, essential hypertension, sleep disorder, proteinuria, impaired fasting glucose, and mixed hyperlipidemia	Abnormal weight gain	Smoking cessation and excessive eating, and mood	"Discussed the use of bupropion for smoking and eating. Add bupropion 100 mg SR in the morning/wellbutrin is helping mood"
	Clomipramine HCl 25 mg	Benign prostatic hyperplasia, DM w/ renal complications, HTN, lipids abnormal, microalbuminuria, Gastroesophageal reflux disease, vitamin D deficiency, and Gout	Diabetes mellitus w/renal complications	Weight loss, excessive weight gain	"bmi 37.5, discussed wt loss surgery and drugs, on anafranil (Clomipramine)"

Abbreviations: Rx: prescription; HTN: hypertension; T2DM: type 2 diabetes mellitus; HIV: human immunodeficiency virus; PPD: postpartum depression; OCD: obsessive–compulsive disorder; HSV: herpes simplex virus; Pt: patient.

notes. However, if we adjust for the patients with a reference to active depression in their notes—or multiple on-label indications during the same encounter—then our accuracy increased to 93%. On average, the earliest diagnosis that could be considered on-label was made 636 days (1.74 years) prior to the prescription date.

DISCUSSION

As the use of antidepressants rises in the US, partly due to a large number of PCPs and nonpsychiatric specialists ordering these medications[2,4]—it has become increasingly important to understand the prescribing patterns of nonpsychiatric specialties. The data mining method employed in this study provided a unique probe to assess "real-world" clinical data across a large number of prescriptions in an outpatient setting. Further, it allowed us to examine the nuances of provider documentation when interacting with the EHR's CPOE system, comparing structured diagnosis data to unstructured clinical notes.

By applying our method of matching antidepressant prescriptions to prior diagnosis history, we were able to characterize antidepressant prescriptions in the context of drug labels and evidence assessments within the EHRs and CPOE at the institution. Our results suggest that approximately 69% of the antidepressants issued through the institution's outpatient CPOE between 2010 and 2015 can be classified as an "on-label/evidence-based use." Further, our methodology allowed us to estimate the disease burden under which patients had received antidepressants. Relying solely on coded (and structured) diagnosis data to infer prescription indications can be challenging, and even inaccurate, as diagnosis codes are not always carried over to subsequent clinical encounters. Even though it may appear as though prescriptions are issued for off-label uses, there is often additional, pertinent information that is captured throughout the EHR in unstructured clinical notes.[34] Therefore, using only structured diagnosis data to characterize prescription patterns could have led to false conclusions, and thus attempts to mine unstructured data throughout the EHR should be considered for future studies. Additionally, nonpsychiatric clinicians have been shown to misdiagnose depression based on uncertainty about the diagnosis and potential implications based on the presence of the diagnosis code in EHRs.[35–38] In accordance with this finding, recent studies have shown that clinical decision support mechanisms can be implemented directly into EHR systems, which improve recognition and screening for conditions such as postpartum depression and bipolar disorder.[39,40] We attempted to adjust for such complications by incorporating increasing medical history time frames—thereby accounting for physician changes and their associated practice patterns, as well as collaborative and integrative care. This analysis demonstrated that applying a 5-year time frame allowed us to capture the correct indication with a relatively high degree of accuracy, although as discussed above, an on-label diagnosis was identified, on average, 1.74 years prior to the prescription.

For prescriptions characterized as off-label use, structured diagnosis data alone were not enough to determine prescriptions indications. A sensitivity analysis revealed that a large proportion of the patients had a physician-documented history of depression or clinical note citing depression as the indication in unstructured clinical notes (39%), despite no formal ICD-9/10 code registered. This finding may be partially explained by the fact that over half of the off-label prescriptions lacked a formal association with a diagnosis. Together, these results highlight a significant gap in recording diagnoses of depression in the EHR using structured data and appear to give credence to claims that nonpsychiatric specialists may

be hesitant to formally diagnose depression.[35–38] We see this trend within neurology and internal medicine specialty notes, as nearly half of all prescriptions examined showed either active or history of depression that was not documented in the form of a structured data entry using ICD-9/10 diagnosis codes. This study however was not limited to depression, as anxiety (25%), insomnia (13%), mood disorder (7%), and neuropathic pain (5%) were all cited as a reason for antidepressant therapy in progress notes but lacked ICD-9/10 codes in diagnosis history. These findings also suggest that secondary use of EHR data could be improved by requiring physicians to document a diagnosis code when issuing prescriptions through the CPOE, particularly in the absence of advanced natural language processing (NLP) techniques.

The chart review further revealed that the number of prescriptions without sufficient evidence to support their efficacy may be even lower. We found that 92% of the off-label use prescriptions examined within pain medicine/management specialty notes were, in fact, nortriptyline or duloxetine for the treatment of neuropathic pain. Despite exclusion from the drug reference compendium, there have been a number of well-discussed and rigorous studies that support the use of TCAs and serotonin-norepinephrine reuptake inhibitors (SNRIs) when treating neuropathic pain.[41–46] These drugs may have a weaker evidence base, but they display some potential to alleviate suffering and pose less severe risks than alternatives. The American College of Physicians, for example, recently published new guidelines for the treatment of low back pain—often characterized by neuropathies—which emphasize nondrug therapies, but suggest that an antidepressant such as duloxetine (SNRI) may be appropriate if pain persists.[47,48] These results imply that prescribing for off-label uses—or prescribing without sufficient evidence of efficacy, may occur less frequently than believed.[23,30]

Significance and relation to current literature

To date, only a few studies have estimated disease burden and examined diagnosis-based prescribing patterns within the context of drug labels and evidence assessments. To our knowledge, this is the first study to have examined these patterns specifically for antidepressants prescribed to adults by nonpsychiatrists, through leveraging outpatient EHR data from a large U.S. academic medical center. In addition, we tried to control for potential overestimates of "off-label uses" experienced by a previous study that used a short medical history window.[19] Using a 5-year time frame revealed that the first on-label diagnosis was made, on average, nearly 2 years prior to the prescription in this population.

Our work followed a 2016 study from Wong *et al.*,[20] which examined treatment indications in primary care practices for antidepressant prescriptions in Quebec, Canada, and used approved product labels dictated by the FDA and Health Canada as references.[20] Wong *et al.*[30] subsequently published a detailed study in 2017 in which they report 29% of approximately 106 000 prescriptions to be "off-label," with 40% of those prescriptions having strong evidence of efficacy for another drug in the same class, but not the one prescribed. Their study describes methods that are similar to those that we have used; however, their data was collected via the Medical Office of the XXIst Century (MOXXI), which is an EHR-based drug management and e-prescribe system focused solely on PCPs in Canada, and required the documentation of specific indications when ordering medications.

There are three major differences between this study by Wong *et al.* and our study. First, prescriptions were classified differently according to evidence assessments. Second, our study examined the prescribing trends across medical specialties, reaching beyond primary care. Third, we did not seek to determine within-class efficacy.

For our purposes, if the compendium registered a sufficient level of evidence towards efficacy (benefit category I or IIa/b; evidence category A or B), then we considered the medication as an "on-label/evidence-based use," instead of "off-label." While "on-label" and "evidence-based" are distinct categories, they were conceptually merged for most of the analyses because this clinical assumption represents a reasonable standard of care. Given this difference in prescription classification, we found a similar ratio of off-label prescriptions (31%) as compared with Wong *et al.* (29%) amongst a significantly larger sample size. Our analysis also extends beyond primary care. We also examined patterns by the clinical department of the prescriber—which had not been previously characterized. In contrast to the strategies used by Wong *et al.* to assess within-class efficacy, we attempted to estimate the conditions in which patients were receiving these antidepressants (Table 3) and reviewed clinical text to determine prescription indications (Table 4). This yielded a significant number of prescriptions that should be reclassified as "on-label/evidence-based use," thus giving strength to current medical practice, and also demonstrated how nonpsychiatric specialists may interact with the EHR/CPOE systems.

Study limitations

Our study has several limitations. Principally, our analysis is restricted by the structured data that is documented within the outpatient EHR. The EHR/CPOE allows prescribing clinicians the opportunity to associate specific encounter diagnoses, all diagnoses, or bypass associations entirely when ordering medications. Thus, documenting an associated indication is not a necessary step for ordering prescriptions. The only method of retrospectively assessing a physician's order would be to examine all EHR-documented prescriptions individually or work with hospital information technology services to tailor data retrieval. Since the study relied on examining medication–diagnosis pairs, some prescriptions were lost due to lack of a documented diagnosis. In addition, the subjective nature of clinical diagnostics influences prescribing patterns, thus studying the ICD-9/10 diagnosis data alone does not provide sufficient insight into the rationale behind practice patterns. While a sensitivity analysis was conducted on 1% random samples of patients receiving on-label and off-label use prescriptions, review of all 35 325 charts would have required automated NLP—which is out of scope for this article. For on-label use prescriptions, these were estimated based on prior medical history and subsequent verification, whereas off-label use prescriptions required a manual chart review and extrapolation of results. Therefore, we do not have a comprehensive view of diagnosis and antidepressant prescribing trends, and definitive conclusions about the overall percentage of prescriptions written for off-label uses cannot be drawn from the existing data.

Our results are also based on the DrugDex System reports as of August 2016. Any updates to drug evidence, or the addition of newer drugs to the market during the study period, almost certainly will have had an influence on prescription patterns. However, attempting to analyze these temporal factors in the study would have complicated interpretation of results, therefore we applied the latest product labels and strength of evidence to each of the antidepressants represented. Using this approach, Figure 3 demonstrates that the number of prescriptions classified as "evidence-based use" nearly plateaus after 1 year of medical history inclusion, while the number of on-label and off-label use prescriptions continue to increase

and decrease, respectively. Due to the relative stability of drug labels, we believe that our methodology does not significantly weaken interpretability, yet it remains a limitation nonetheless. Further, we did not compare DrugDex reports to other drug reference compendia, such as the American Hospital Formulary Service-Drug Information (AHFS-DI) or the United States Pharmacopeia-National Formulary (USP-NF).

We are also limited by the differing definitions of labeled uses between researchers and clinicians. Our study strictly followed the labels and evidence assessments as dictated by the DrugDex compendium; however, this approach is likely to be narrower than a clinician's definition. As such, bipolar disorder and schizophrenia were treated as any other condition, for which they were categorized as "on-label/evidence-based uses" if they matched their associated drug labels and evidence assessments. Similarly, combination-therapy (antidepressant + another drug class) was assessed based on the indications listed within the compendium, and not strictly for the antidepressant properties.

Lastly, we are limited to the available data within the EHR system of a single institution. As such, we could not determine the true extent of a patient's medical history, since we were limited to their testimonials and encounters with the outpatient services, and are unable to capture data from outside of the provider network. Further, the EHR/CPOE use patterns found here are likely to differ between institutions, and therefore our results may not translate to other health systems.

CONCLUSIONS

The results indicate that antidepressants may be prescribed for off-label uses, by PCPs and nonpsychiatry specialists, less frequently than believed. This study also points to the fact that there are a number of off-label uses that are efficacious and widely accepted by expert clinical opinion, but have not been included in drug compendia. Despite the fact that diagnosis codes in the outpatient setting are notoriously inaccurate, our approach demonstrates that the correct codes are often documented at some point in a patient's recent diagnosis history. Because such a wide range of medical specialties are using antidepressants, there is benefit in studying routinely collected data in EHRs. That is, to better understand the prescribing patterns of providers outside of controlled research settings, in which study participants tend to be homogeneous.

However, depending on the EHR system, structured diagnosis/billing data alone may be insufficient to track indications and carry out prescription classification. Instead, a more robust methodology for future EHR-based studies should include an analysis of unstructured clinical text using NLP, in addition to structured diagnosis data. Examining these data elements in conjunction will help to triangulate and validate findings, thereby producing more accurate and meaningful results. While our results confirm several patterns reported by previous studies, the data are not comprehensive and larger studies across several health systems will be required to draw significant conclusions. Finally, the results also highlight some of the challenges of secondary use of EHR data.

FUNDING

This work was supported by the National Institutes of Health Grant Number R01MH105384, and the National Institute of General Medical Sciences Grant Number R01GM105688.

Conflict of interest statement. None declared.

CONTRIBUTORS

Study concept and design: JJD, JP, SB, TTL, JC, RA, and AS. Analysis and interpretation of data: JJD, JP, SB, TTL, JC, NM, and RA. Drafting of manuscript: JJD, JC, TTL, NM, and JP. Critical revision of the manuscript for important intellectual content: JJD, JP, NM, TTL, JC, SB, and AS. Obtained funding: JP. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Journal of the American Medical Informatics Association* online.

ACKNOWLEDGMENTS

This study also received support from New York-Presbyterian Hospital (NYPH) and Weill Cornel Medical College (WCMC), including the Clinical and Translational Science Center (CTSC) (UL1 TR000457) and Joint Clinical Trials Office (JCTO).

REFERENCES

1. Frank RG, Huskamp HA, Pincus HA. Aligning incentives in the treatment of depression in primary care with evidence-based practice. *Psychiatr Serv* 2003; 54 (5): 682–7.
2. Wang PS, Demler O, Olfson M, Pincus HA, Wells KB, Kessler RC. Changing profiles of service sectors used for mental health care in the United States. *Am J Psychiatry* 2006; 163 (7): 1187–98.
3. Barkil-Oteo A. Collaborative care for depression in primary care: how psychiatry could "troubleshoot" current treatments and practices. *Yale J Biol Med* 2013; 86 (2): 139–46.
4. Kroenke K, Unutzer J. Closing the false divide: sustainable approaches to integrating mental health services into primary care. *J Gen Intern Med* 2017; 32 (4): 404–10.
5. Milea D, Verpillat P, Guelfucci F, Toumi M, Lamure M. Prescription patterns of antidepressants: findings from a US claims database. *Curr Med Res Opin* 2010; 26 (6): 1343–53.
6. Mojtabai R, Olfson M. National trends in long-term use of antidepressant medications: results from the U.S. National Health and Nutrition Examination Survey. *J Clin Psychiatry* 2014; 75 (2): 169–77.
7. Olfson M, Marcus SC. National patterns in antidepressant medication treatment. *Arch Gen Psychiatry* 2009; 66 (8): 848–56.
8. Nielsen M, Gotzsche P. An analysis of psychotropic drug sales. Increasing sales of selective serotonin reuptake inhibitors are closely related to number of products. *Int J Risk Saf Med* 2011; 23 (2): 125–32.
9. Mojtabai R. Americans' attitudes toward psychiatric medications: 1998-2006. *Psychiatr Serv* 2009; 60 (8): 1015–23.
10. National Center for Health Statistics (US). *Health, United States: 2010 With Special Feature on Death and Dying*. Hyattsville (MD): National Center for Health Statistics; 2011 February Report No.: 2011-1232.
11. Pratt LA, Brody, DJ, Gu, Q. *Antidepressant Use Among Persons Aged 12 and Over: United States, 2011-2014*. Hyattsville, MD: National Center for Health Statistics; 2017. Contract No.: No. 283.
12. Abou-Raya S, Abou-Raya A, Helmii M. Duloxetine for the management of pain in older adults with knee osteoarthritis: randomised placebo-controlled trial. *Age Ageing* 2012; 41 (5): 646–52.
13. Lunn MPT, Hughes RAC, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database Syst Rev* 2014; (1): Cd007115.
14. Max MB, Kishore-Kumar R, Schafer SC, *et al*. Efficacy of desipramine in painful diabetic neuropathy: a placebo-controlled trial. *Pain* 1991; 45 (1): 3–9. discussion 1-2.

15. Nierenberg AA, Adler LA, Peselow E, Zornberg G, Rosenthal M. Trazodone for antidepressant-associated insomnia. *Am J Psychiatry* 1994; 151 (7): 1069–72.
16. Kaynak H, Kaynak D, Gozukirmizi E, Guilleminault C. The effects of trazodone on sleep in patients treated with stimulant antidepressants. *Sleep Med* 2004; 5 (1): 15–20.
17. O'Reardon JP, Allison KC, Martino NS, Lundgren JD, Heo M, Stunkard AJ. A randomized, placebo-controlled trial of sertraline in the treatment of night eating syndrome. *Am J Psychiatry* 2006; 163 (5): 893–8.
18. Eguale T, Buckeridge DL, Winslade NE, Benedetti A, Hanley JA, Tamblyn R. Drug, patient, and physician characteristics associated with off-label prescribing in primary care. *Arch Intern Med* 2012; 172 (10): 781–8.
19. Chen H, Reeves JH, Fincham JE, Kennedy WK, Dorfman JH, Martin BC. Off-label use of antidepressant, anticonvulsant, and antipsychotic medications among Georgia medicaid enrollees in 2001. *J Clin Psychiatry* 2006; 67 (06): 972–82.
20. Wong J, Motulsky A, Eguale T, Buckeridge DL, Abrahamowicz M, Tamblyn R. Treatment indications for antidepressants prescribed in primary care in Quebec, Canada, 2006-2015. *JAMA* 2016; 315 (20): 2230–2.
21. Sholle ET, Kabariti J, Johnson SB, *et al*. Secondary use of patients' electronic records (super): an approach for meeting specific data needs of clinical and translational researchers. *AMIA Annu Symp Proc* 2017; 2017: 1581–8.
22. Healthcare Effectiveness Data and Information Set (HEDIS). Hedis 2016 final NDC lists National Committee for Quality Assurance (NCQA) 2016. http://www.ncqa.org/hedis-quality-measurement/hedis-measures/hedis-2016/hedis-2016-ndc-license/hedis-2016-final-ndc-lists. Accessed June 05, 2016.
23. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. *Arch Intern Med* 2006; 166 (9): 1021–6.
24. Drugdex system® (internet database) [Internet]. Truven Health Analytics Micromedex Solutions. 2016. http://www.micromedexsolutions.com/micromedex2/librarian/. Accessed July 12, 2016.
25. Chen DT, Wynia MK, Moloney RM, Alexander GC. U.S. Physician knowledge of the FDA-approved indications and evidence base for commonly prescribed drugs: results of a national survey. *Pharmacoepidem Drug Saf* 2009; 18 (11): 1094–100.
26. Dos Santos L, Heineck I. Drug utilization study in pediatric prescriptions of a university hospital in Southern Brazil: off-label, unlicensed and high-alert medications. *Farm Hosp* 2012; 36 (4): 180–6.
27. Pelaez-Ballestasa I, Melendez-Mercado C, Hernandez-Garduno A, Viramontes-Madrid JL, Burgos-Vargas R. Drug-drug interactions of non-steroidal anti-inflammatory drugs with other drugs in patients with rheumatic diseases. *Reumatol Clin* 2005; 1 (2): 116–20.
28. Trifiro G, Corrao S, Alacqua M, *et al*. Interaction risk with proton pump inhibitors in general practice: significant disagreement between different drug-related information sources. *Br J Clin Pharmacol* 2006; 62 (5): 582–90.
29. Walton SM, Schumock GT, Lee KV, Alexander GC, Meltzer D, Stafford RS. Prioritizing future research on off-label prescribing: results of a quantitative evaluation. *Pharmacotherapy* 2008; 28 (12): 1443–52.
30. Wong J, Motulsky A, Abrahamowicz M, Eguale T, Buckeridge DL, Tamblyn R. Off-label indications for antidepressants in primary care: descriptive study of prescriptions from an indication based electronic prescribing system. *BMJ* 2017; 356: j603.
31. Centers for Medicare and Medicaid Services. Medicare prescription drug benefit manual, Chapter 6—Part D Drugs and formulary requirements, section 10.6, 2010. https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/downloads/Chapter6.pdf. Accessed December 7, 2017.
32. Center for Medicare Advocacy. CMA report: medicare coverage for off-label drug use: Center for Medicare Advocacy; 2010. http://www.medicareadvocacy.org/cma-report-medicare-coverage-for-off-label-drug-use/. Accessed December 7, 2017.
33. Eguale T, Winslade N, Hanley JA, Buckeridge DL, Tamblyn R. Enhancing pharmacosurveillance with systematic collection of treatment indication in electronic prescribing. *Drug Saf* 2010; 33 (7): 559–67.
34. Perlis RH, Iosifescu DV, Castro VM, *et al*. Using electronic medical records to enable large-scale studies in psychiatry: treatment resistant depression as a model. *Psychol Med* 2012; 42 (01): 41–50.
35. Rost K, Smith R, Matthews DB, Guise B. The deliberate misdiagnosis of major depression in primary care. *Arch Fam Med* 1994; 3 (4): 333–7.
36. Gerrits MM, van Marwijk HW, van Oppen P, van der Horst H, Penninx BW. The role of somatic health problems in the recognition of depressive and anxiety disorders by general practitioners. *J Affect Disord* 2013; 151 (3): 1025–32.
37. Mitchell AJ, Rao S, Vaze A. Can general practitioners identify people with distress and mild depression? A meta-analysis of clinical accuracy. *J Affect Disord* 2011; 130 (1-2): 26–36.
38. Mogi T, Toda H, Yoshino A. Clinical characteristics of patients with diagnostic uncertainty of major depressive disorder. *Asian J Psychiatr* 2017; 30: 159–62.
39. Gill JM, Chen YX, Grimes A, Klinkman MS. Using electronic health record-based tools to screen for bipolar disorder in primary care patients with depression. *J Am Board Fam Med* 2012; 25 (3): 283–90.
40. Loudon H, Nentin F, Silverman ME. Using clinical decision support as a means of implementing a universal postpartum depression screening program. *Arch Womens Ment Health* 2016; 19 (3): 501–5.
41. Dworkin RH, O'Connor AB, Backonja M, *et al*. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 2007; 132 (3): 237–51.
42. Finnerup NB, Attal N, Haroutounian S, *et al*. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* 2015; 14 (2): 162–73.
43. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. *Cochrane Database Syst Rev* 2007; (4): Cd005454.
44. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain: a cochrane review. *J Neurol Neurosurg Psychiatry* 2010; 81 (12): 1372–3.
45. Jackson KC 2nd, St Onge EL. Antidepressant pharmacotherapy: considerations for the pain clinician. *Pain Pract* 2003; 3 (2): 135–43.
46. Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. *Pain* 2004; 110 (3): 697–706.
47. Chou R, Deyo R, Friedly J, *et al*. Systemic pharmacologic therapies for low back pain: A systematic review for an American College of Physicians clinical practice guideline. *Ann Intern Med* 2017; 166 (7): 480–92.
48. Qaseem A, Wilt TJ, McLean RM, Forciea MA. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2017; 166 (7): 514–30.