Exploration of Claims-Based Utilization Measures for Detecting Potential Nonmedical Use of Prescription Drugs

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ABSTRACT

BACKGROUND: Nonmedical use of prescription medication is a significant and growing public health concern in the United States. Drug utilization measures that can reliably quantify the extent of nonmedical use of a given medication or medication class would greatly facilitate efforts to identify, monitor, and constrain nonmedical prescription drug use. Measures making use of prescription claims data would be especially valuable given the ready availability of these data among health care plans and payers.

OBJECTIVE: To explore the extent to which claims-based utilization measures can provide information that aids in identifying and quantifying non-medical drug use.

METHODS: Prescription claims from a large employer-based administrative claims database (MarketScan) were used to evaluate drug utilization during the first year after an index prescription for 6 classes of drugs with a known abuse potential and 3 classes without. Traditional population-level measures of adherence (i.e., medication possession ratio [MPR] and proportion of days covered [PDC]) and a novel measure of overlapping days supply (MPR/PDC ratio) were calculated for all medications. Measures of asymmetrical use within a population were evaluated with the Lorenz curve, representing the total drug supply used by the heaviest 1%, 5%, and 50% of all users. All of the measures across compounds were compared with Spearman nonparametric rank correlations, and the Friedman's test was performed to determine whether the rankings were consistent in pairwise analysis. The ability of each measure to discriminate between abusable and nonabusable compounds was evaluated using the c-statistic.

RESULTS: The study cohort included 6,291,810 patients, mean age 52 years, 57.9% female. The mean MPR and mean PDC for drugs with known abuse potential were both lower than for drugs without known abuse potential. The MPR/PDC ratio (MPR:PDC) ranged from 1.02-1.09. Highest values for the Lorenz-1 curve were seen for acetaminophen with codeine, acetaminophen with oxycodone, oxycodone, and acetaminophen with hydrocodone. The individual MPR and PDC were strongly correlated to each other ($r=0.99$; $P<0.001$ for both), moderately correlated with the MPR:PDC ($r=0.62$ and 0.57 , respectively) and moderately inversely correlated with Lorenz 1 ($r=-0.83$ and -0.86 , respectively, $P<0.001$ for both). The MPR:PDC was inversely correlated with the Lorenz-1 ($r=-0.39$; $P=0.02$). After rank ordering individual drugs by each measure from highest to lowest value, the MPR:PDC resulted in consistent distributions with the individual MPR ($P=0.0097$) and PDC ($P=0.0018$), but not the Lorenz-1 ($P=0.0835$), nor Lorenz-50 ($P=0.1343$). The MPR, PDC, Lorenz-1, and Lorenz-50 were able to discriminate between the drugs with known abuse potential and those without (c-statistic 0.979 to 1), while the MPR:PDC was not (c-statistic 0.592).

CONCLUSIONS: When comparing classes of drugs with a known abuse potential with classes of drugs not prone to such use, using an array of drug utilization measures, significantly different patterns emerge, although the ability of these measures to serve as reliable indicators of the extent of nonmedical prescribing may be limited. There is a need for valid and reliable algorithms to detect the extent of nonmedical use at a population

level to help target public health interventions aimed at constraining illicit use. Further work is warranted on the development of novel measures that make use of individual patient-level use patterns.

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What is already known about this subject

- While there is no gold standard for identifying nonmedical drug use, the Lorenz percentiles have been used to show heavy use of opioid analgesics and carisoprodol.
- Commonly used measures to describe treatment compliance (i.e., medication possession ratio [MPR] or proportion of days covered [PDC]) may provide clues of nonmedical use such as irregular refill behavior.

What this study adds

- Based on the distribution of drugs ranked highest to lowest by each measure, the MPR, PDC, and MPR/PDC ratio resulted in consistent distributions, but different than that produced by the Lorenz percentiles. The MPR, PDC, and Lorenz percentiles were able to discriminate between abusable and nonabusable drugs, while the MPR/PDC ratio was not.
- When comparing traditional measures of treatment compliance, a novel method of excess drug supply (MPR/PDC ratio), and a measure of skewed utilization pattern, one can observe significantly different patterns, although the ability of these measures to serve as reliable indicators of the extent of nonmedical prescribing may be limited.

Nonmedical use of prescription medications, defined as use by someone other than he or she whom the prescriber intended or for the experience or feeling caused rather than for therapeutic reasons, is a significant and growing public health concern in the United States.¹ The 2007 National Survey on Drug Use and Health (NSDUH), an annual survey of Americans aged 12 years and older, estimated that 2.8% of the population had used prescription psychotherapeutic medications nonmedically in the month prior to being surveyed, including 5.2 million using pain relievers, 1.8 million using tranquilizers, and 1.1 million using stimulants.¹ Manchikanti et al. (2010) reported that retail sales of morphine and oxycodone increased by 222% and 866%, respectively, from 1997 to

FIGURE 1 Example Prescription Refill Patterns and Their Resulting MPRs, PDCs, and MPR:PDCs

MPR = medication possession ratio; MPR:PDC = MPR/PDC ratio; PDC = proportion of days covered.

2007, with a steady increase in opioid abuse during the same time period.² The economic burden of nonmedical prescription drug use is also substantial. Using data from the NSDUH, Hansen et al. (2011) estimated that the total cost of nonmedical prescription opioid use in 2006 in the United States was \$53.4 billion.³ Aldridge et al. (2011) estimated that 3.6% of the total costs paid by private insurers for attention deficit hyperactivity disorder (ADHD) medications were for diverted stimulant medications.⁴ This resulted in an estimated annual cost of between \$83 and \$204 million, while White et al. evaluated the direct health care costs paid by private insurers for a population with an opioid abuse diagnosis and found the excess annual cost burden of opioid abuse compared with nonabusers was \$14,054 per patient.⁵

Drug utilization measures that can reliably quantify the extent of nonmedical use of a given medication or medication class would greatly facilitate efforts to identify, monitor, and constrain nonmedical prescription drug use. Measures making use of prescription claims data would be especially valuable given the ready availability of these data among health care plans and payers. While there is no gold standard for identifying nonmedical drug use, patient prescription refill data may provide suggestive clues. For example, individuals abusing or diverting prescription medications could be expected to fill more prescriptions on average than those using medications as prescribed and may also demonstrate irregular and erratic refill behavior. A number of existing drug utilization measures reflect the total supply of a drug available to a patient over a given time period but are more limited in their ability to detect irregular patterns of use.

The medication possession ratio (MPR) and proportion of days covered (PDC) are commonly used to describe treatment adherence. The MPR reflects total drug supply available during

the time period of interest and can exceed 1, while the PDC reflects the proportion of days during which any drug supply is available and is capped at 1. Individuals abusing or diverting a given medication might be expected to have a relatively high MPR and/or PDC and thus skew population means for these measures. Martin et al. (2009) suggested that when identification of overuse is important, the PDC measure could be supplemented with traditional MPR calculations but did not suggest how this could be done or interpreted.⁶ One such approach could involve taking the ratio of the MPR to the PDC to reflect the “density” of medication availability, which might be more sensitive to irregular prescription fill behavior seen with nonmedical use. Figure 1 shows a hypothetical example of the MPRs, PDCs, and MPR to PDC ratios that result from different refill patterns over a 6-month period.

Another measure that uses prescription claims data to characterize population-level drug utilization is based on the Lorenz curve. The share of total drug volume purchased by the 1% most heavily consuming users of a drug is defined as the Lorenz 1-percentile, while the share of drug volume purchased by the 50% most heavily consuming users of a drug is defined as the Lorenz 50-percentile, and high values for either of these measures suggest a skewed utilization pattern.⁷ Measurement of the Lorenz curve has been used to demonstrate heavy use of opioid analgesics and carisprodol.^{7,8} Like MPR and PDC distributions, the Lorenz curve reflects differences in overall drug use within populations but not irregular use by individuals.

The objective of this study was to explore the extent to which claims-based utilization measures can provide information that aids in identifying and quantifying nonmedical drug use. Specifically, we compared values for the measures just described for medications prone to nonmedical use with those for medications that are not. Our hope is that our results will

TABLE 1 Methodology for Identifying Patient Cohort

Patient Selection	N	%
Patients with a prescription for a drug of interest during the index period ^a	10,538,553	100.0
With 12 months of continuous pharmaceutical and medical benefit enrollment from index date	7,444,967	70.6
Exclude patients with outliers as defined: metric quantity > 1,500; days supply < 1 or days supply > 365; dose strength equal missing	6,840,355	64.9
Exclude patients aged < 18 years	6,291,810	59.7

^aDrugs of interest are as follows: **hypnotics:** eszopiclone, hydroxyzine, zolpidem; **benzodiazepines:** alprazolam, clonazepam, diazepam, lorazepam, temazepam; **calcium channel blockers:** amlodipine, diltiazem, nifedipine, verapamil; **strong opioids:** acetaminophen with codeine, acetaminophen with hydrocodone, acetaminophen with oxycodone, morphine, oxycodone; **weak opioids:** acetaminophen with propoxyphene, tramadol; **statins:** atorvastatin, rosuvastatin, simvastatin; **short-acting stimulants:** amphetamine salt combination, dextmethylphenidate; Adderall, dextroamphetamine, Focalin, Methylin, methylphenidate, mixed amphetamine salt, Provigil; **long-acting stimulants:** Adderall XR, Concerta, Focalin XR, Metadate CD, Ritalin LA, Vyvanse; **thyroid:** levothyroxine.

motivate further research aimed at developing more discerning measures of nonmedical use that can be used for public health and quality improvement initiatives.

Methods

To facilitate the ability to distinguish potential patterns of drug abuse/diversion, we chose to evaluate the use of 7 classes of drugs, some with a known abuse potential (benzodiazepines, hypnotics, opioids, stimulants) and some without (calcium channel blockers, thyroid replacement therapy, statins). The opioids and stimulant classes were further divided into weak versus strong, and stimulants into short acting versus long acting. For the opioids, the World Health Organization's classification of analgesics for the management of cancer pain was used,⁹ while the stimulants were differentiated by their half-life, similar to what was done in a study by Pohl et al. (2009).¹⁰ Truven's MarketScan database, a large U.S.-based claims database was used to identify the study cohort. Patients were included if they were aged > 18 years, had 2 or more prescriptions for a benzodiazepine, hypnotic, opioid, calcium channel blocker, thyroid replacement therapy, statin, or stimulant (only solid, oral dosage forms were considered) during the index period between January 1, 2008, and December 31, 2008, and had 1 year of continuous pharmaceutical and medical benefit enrollment after the index period. An index date was defined as the date on which the first prescription for any of the medications of interest was filled by the patient. Although stimulants are often used in children, we chose to limit the patient population to aged > 18 years because, across all of the drug categories of interest, there was overall more drug use in adults versus children, and those aged < 18 years contributed disproportionately across all of the categories. Additionally, this was also the population reported by Aldridge et al. in their research on cost of diversion of ADHD medications.⁴ There was not a distinction between current and new users. The specific agents within each class that were included in the analysis were those that were the most frequently prescribed within each class. If an individual was taking medications from more than 1 class, all

prescriptions were included in the corresponding calculations for each individual medication taken (Table 1). Drug utilization was assessed during the first year after an index prescription using traditional adherence measures, a novel method of overlapping days supply (MPR/PDC ratio), and measures of asymmetrical use within a population.

Measures of Drug Utilization

Medication utilization was measured in terms of adherence to individual agents within a drug class, as well as compliance/hypercompliance within a drug class overall. We did not examine compliance/hypercompliance to agents across related medication classes (e.g., weak and strong opioids). The 5 compliance/hypercompliance measures compared are reported in Table 2.

Statistical Methods

The proportion of individuals falling into each MPR category (MPR ≤ 0.5; MPR = 0.5 to < 0.8; MPR = 0.8 to < 1.0; MPR > 1.0) was calculated for each compound and plotted as histograms. In addition, Lorenz curves were generated and illustrated at the drug-class level. MPR, PDC, MPR/PDC ratio, Lorenz-1, and Lorenz-50 values across the compounds were compared with Spearman nonparametric rank-correlations and tested to determine whether the correlation was significantly different from the null hypothesis of no correlation. Also, Friedman's test was performed to determine whether the rankings were consistent in pairwise analysis. The ability of each measure to discriminate between abusable and nonabusable compounds was evaluated using the c-statistic or area under the receiver-operator characteristic (ROC) curve. The area under the ROC curve ranged from 0.500 (inability to discriminate) to 1.00 (complete discrimination with no overlap in scores between the 2 groups).

All statistical tests were assessed with two-tailed tests and type 1 error rates of 5%, and all calculations were computed with SAS version 9.2 for Windows (SAS Institute, Cary, NC).

TABLE 2 Compliance/Hypercompliance Measures Evaluated

	Formula	Measures
MPR	The sum of days supply divided by the number of days in the study period	Mean ± standard deviation MPR ≤ 0.5 MPR = 0.5 to < 0.8 MPR = 0.8 to < 1.0 MPR > 1.0
PDC	The proportion of days within the study period that the patient had an available supply of medication.	Mean ± standard deviation PDC ≤ 0.5 PDC = 0.5 to < 0.8 PDC = 0.8 to < 1.0
MPR/PDC ratio	MPR divided by the PDC	Mean ± standard deviation
Lorenz-1 percentile	The share of the total drug volume purchased by the 1% most heavily consuming users of the drug	Percentage
Lorenz-50 percentile	The share of drug volume purchased by the 50% most heavily consuming users of the drug	Percentage

MPR = medication possession ratio; PDC = proportion of days covered.

TABLE 3 Number of Patients in Each Medication Cohort

	N	%
Drugs with known abuse potential		
Benzodiazepines	1,374,522	21.9
Hypnotics	868,560	13.8
Short-acting stimulants	137,428	2.2
Long-acting stimulants	109,420	1.7
Strong opioids	3,025,403	48.1
Weak opioids	1,042,179	16.6
Drugs without known abuse potential		
Calcium channel blockers	907,165	14.4
Statins	2,039,266	32.4
Thyroid replacement	1,054,667	16.8

Results

The study cohort consisted of 6,291,810 adult patients with a mean age of 52.1 years of which 57.9% (n=3,645,466) were female. The most commonly prescribed classes were strong opioids, followed by statins, then benzodiazepines (Table 3).

The MPR, PDC, and MPR/PDC Ratio

The individual MPR and PDC measures were evaluated individually for each drug and at the class level. For the medication classes without a known abuse potential (calcium channel blockers, statins, and thyroid replacement), the mean MPR for individual drugs ranged from 0.62 to 0.84, and the trend across the MPR categories were generally consistent with the highest percentage of values falling in the <0.5 and 0.8 up to <1 MPR categories. For the remaining drug classes (hypnotics, benzodiazepines, strong and weak opioids,⁹ short- and long-acting stimulants), the mean MPR for individual drugs was lower, ranging from 0.05 to 0.54. The pattern across MPR categories generally reflected the largest percentage of values falling in the MPR < 0.5 category with much smaller percentages falling in the MPR > 1.0 category. The MPR patterns for all of the agents evaluated are shown in Figure 2.

The PDC measure generally showed similar patterns to the MPR with the nonabusable medication classes having higher overall mean values (range of 0.59 to 0.77) compared with the other drug classes (range of 0.04 to 0.49). In general, the long-acting stimulant class overall had higher mean PDC values compared with the other nonchronic medications (range 0.38 to 0.47). Patterns of individual drugs within classes also tended to vary similarly to what was seen with the MPR measures (data not shown).

The class-level MPR/PDC ratio (MPR:PDC) ranged from 1.02-1.09. Across classes, weak opioids had the lowest MPR:PDC (1.02), while thyroid replacement and long-acting stimulants had the highest MPR:PDC (both 1.09). For individual drugs within classes, there did appear to be some outliers: morphine (1.14), oxycodone (1.13), and dextroamphetamine (1.12).

Lorenz-1 and Lorenz-50 Curves

Graphs of the Lorenz curves also show a different pattern across drug classes (5 classes illustrated in Figure 3). High values of the Lorenz-1 percentile describes heavy users of a particular drug and were seen for the overall classes of strong opioids, benzodiazepines, and weak opioids. Highest values for the Lorenz-1 were seen for acetaminophen with codeine (29.1%), acetaminophen with oxycodone (21.5%), oxycodone (18.4%), and acetaminophen with hydrocodone (18.3%). High values of the Lorenz-50 percentile implies widespread occurrence of occasional sporadic use. Highest values of the Lorenz-50 were seen for the overall classes of strong opioids (96.1%), benzodiazepines (95.3%), and weak opioids (92.8%).

Correlation Across Measures

Assessment of the correlation of the various measures across all compounds is shown in Table 4. The individual MPR and PDC were strongly correlated to each other, moderately correlated with the MPR:PDC, and were moderately inversely cor-

FIGURE 2 Categorical Patterns Across MPR Categories by Compound**A. Abusable Drugs** **B. Nonabusable Drugs**

Acet = acetaminophen; amph = amphetamine; MPR = medication possession ratio.

related with the Lorenz-1 for all compounds, but this was only statistically significant for the abusable class when evaluated separately from the nonabusable class. The individual MPR and PDC were inversely correlated with the Lorenz-50, with a higher correlation seen for the nonabusable compounds. The MPR:PDC was also inversely correlated with the Lorenz-1, although to a higher degree in the nonabusable class. The correlation with the Lorenz-50, however, was not statistically significant for either class.

Distribution of Drugs by MPR, PDC, MPR:PDC, and Lorenz Percentiles

The individual drugs were rank ordered highest to lowest by each of the measures to explore whether the distributions were similar or different across measures and to determine the ability of each measure to discriminate between abusable and nonabusable drugs (Table 5). Table 5 is a measure of discrimination and allows comparison of the the ability of the various measures to separate the drugs in these 2 categories. A strong

correlation between 2 measures indicates that they tend to have similar values across medications, while a high c-statistic for a given measure indicates that values for abusable drugs are systematically higher (or lower) than those for nonabusable drugs. The individual MPR and PDC values resulted in consistent distributions. The MPR:PDC resulted in consistent distributions with the individual MPR and PDC but not the Lorenz-1 nor Lorenz-50 ($P > 0.05$). The individual MPR, PDC, Lorenz-1, and Lorenz-50 were able to discriminate between abusable and nonabusable drugs (c-statistic range 0.979 to 1), while the MPR:PDC was not (c-statistic 0.592).

To illustrate the similarities and differences among the 5 measures, Table 6 examines 20 compounds with representatives from each class. Due to the negative correlation of Lorenz values with both MPR and PDC, rankings indicate the 5 smallest values of MPR, PDC, and the MPR:PDC, and the 5 largest values of Lorenz-1 and Lorenz-50, and vice versa.

FIGURE 3 Lorenz Percentiles 1-50 for 5 of the Drug Classes

Discussion

In this analysis of a large database of patient-level prescription drug claims, we calculated and qualitatively examined an array of drug utilization measures for 1 set of medications known to be subject to abuse and diversion and another set not prone to such use. The most commonly prescribed of the former were strong opioids (48.1% of all prescriptions), while the most commonly prescribed of the latter were statins (32.4% of all prescriptions). While medications in these 2 categories demonstrated significantly different patterns across the utilization measures examined, the ability of these measures to serve as reliable indicators of the extent of nonmedical prescribing may be limited for reasons we shall discuss.

The MPR and PDC are routinely used to assess levels of patient adherence and compliance to prescribed therapy, important targets in drug utilization review, and quality improvement efforts. While mean MPR and PDC values that we observed for medications with known abuse potential were in all cases lower than for those without, this may simply reflect the fact that these agents are often used on an acute, short-term basis, while the nonabusable medications we selected are more often used chronically. Furthermore, the population mean MPR and PDC may be more subject to overall variability in therapeutic use than to heavy use by the small number of individuals using these agents nonmedically, making them less useful for quantifying nonmedical use.

The MPR:PDC, while intuitively appealing, in fact proved inferior to MPR or PDC alone in its ability to discriminate between the categories of abusable and nonabusable medica-

TABLE 4 Correlation of Measures Across All Compounds (Abusable and Nonabusable)

	MPR	PDC	MPR:PDC	Lorenz-1	Lorenz-50
MPR	1.0	0.99 <0.0001	0.62 <0.0001	-0.83 ^a <0.0001	-0.72 <0.0001
PDC	0.99 <0.0001	1.0	0.57 0.0002	-0.86 ^a <0.0001	-0.75 <0.0001
MPR:PDC	0.62 <0.0001	0.57 0.0002	1.0	-0.39 ^b 0.02	-0.31 ^c 0.07
Lorenz-1	-0.83 <0.0001	-0.86 <0.0001	-0.39 0.02	1.0	0.87 <0.0001
Lorenz-50	-0.72 <0.0001	-0.75 <0.0001	-0.31 0.07	0.87 <0.0001	1.0

^aStatistically significant for abusable class only.

^bStatistically significant for both abusable and nonabusable classes.

^cStatistically significant for nonabusable only.

MPR = medication possession ratio; MPR:PDC = MPR/PDC ratio; PDC = proportion of days covered.

TABLE 5 Pairwise *P* Values from Friedman's Test of the Consistency of the Rankings^a and the C-Statistics to Evaluate Discrimination of Abusable and Nonabusable Drugs

Variable	MPR	PDC	MPR:PDC	Lorenz-1	Lorenz-50
MPR		0.0003	0.0097	0.0029	0.0079
PDC	0.0003		0.0018	0.0023	0.0063
MPR:PDC	0.0097	0.0018		0.0835	0.1343
Lorenz-1	0.0029	0.0023	0.0835		<0.0001
Lorenz-50	0.0079	0.0063	0.1343	<0.0001	

Abusable vs. nonabusable

c-statistic	1.000	1.000	0.592	0.979	1.000
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^a*P* < 0.05 indicated nonrandom association, i.e., consistent rankings.

MPR = medication possession ratio; MPR:PDC = MPR/PDC ratio; PDC = proportion of days covered.

tions. While some abusable drugs had relatively high MPR:PDCs (e.g., 1.14 for morphine and 1.13 for oxycodone), certain control medications also had high ratios (e.g., 1.09 for levothyroxine), and other agents with known abuse potential had some of the lowest ratios (e.g., 1.01 for weak opioids). We speculate that using the percentage of individuals with an MPR:PDC greater than a given threshold might be a more sensitive approach than using only the population-level mean value.

Our findings suggest that measures derived from the Lorenz curve might be somewhat better suited to quantifying non-medical use. For example, the Lorenz-1 would by definition be expected to be greatly influenced by a small group of very heavy drug users, in which individuals abusing or diverting a medication might be overrepresented. It has been suggested that a Lorenz-1 greater than 15% is considered a strong indicator that

TABLE 6 Rankings Within Each Measure of the 20 Most Commonly Prescribed Compounds in Each Class^a

		MPR		PDC		MPR:PDC		Lorenz-1		Lorenz-50	
		Mean	Rank	Mean	Rank	Mean	Rank	%	Rank	%	Rank
Hypnotics	Zolpidem tartrate	0.37	12	0.34	12	1.04	14	5.7	8	89.2	10
Benzodiazepines	Alprazolam	0.33	14	0.31	13	1.03	15	12.6	16	95.1	19
	Clonazepam	0.45	9	0.42	9	1.05	13	9.2	12	91.3	14
	Lorazepam	0.28	16	0.27	16	1.03	16	12.1	15	93.3	16
Strong opioids	Acetaminophen/hydrocodone bitartrate	0.1	18	0.09	18	1.02	18	19.5	19	94.8	18
	Acetaminophen/oxycodone hydrochloride	0.07	20	0.07	20	1.02	19	22.0	20	92.3	15
	Oxycodone hydrochloride	0.36	13	0.28	15	1.13	1	18.6	18	98.7	20
Weak opioids	Acetaminophen/propoxyphene napsylate	0.08	19	0.08	19	1.01	20	15.0	17	90.6	11
	Tramadol hydrochloride	0.17	17	0.16	17	1.02	17	11.3	14	93.5	17
Short-acting stimulants	Amphetamine salt combo	0.4	11	0.37	11	1.06	8	8.3	11	90.8	13
	Methylphenidate hydrochloride	0.32	15	0.29	14	1.07	6	10.9	13	90.8	12
	Provigil	0.47	8	0.44	8	1.05	12	5.3	7	86.3	9
Long-acting stimulants	Adderall XR	0.51	7	0.47	7	1.07	4	6.5	10	85.8	7
	Concerta	0.54	6	0.49	6	1.09	3	5.1	5	85.2	6
	Vyvanse	0.41	10	0.38	10	1.07	5	5.8	9	86.2	8
Thyroid replacement	Levothyroxine sodium	0.84	1	0.77	1	1.09	2	3.8	2	74.7	1
Statins	Atorvastatin calcium	0.72	2	0.68	2	1.05	9	5.3	6	80.6	2
	Rosuvastatin calcium	0.62	5	0.59	5	1.05	11	5.0	4	82.0	3
	Simvastatin	0.67	4	0.63	4	1.05	10	4.7	3	83.9	5
Calcium channel blockers	Amlodipine besylate	0.68	3	0.64	3	1.06	7	3.4	1	82.0	4

^aItalicized values indicate the 5 smallest values of MPR, PDC, and the MPR:PDC and the 5 largest values of Lorenz-1 and Lorenz-50. Bold type indicates the 5 largest values of MPR, PDC, and the MPR:PDC and the 5 smallest values of Lorenz-1 and Lorenz-50.

MPR = medication possession ratio; MPR:PDC = MPR/PDC ratio; PDC = proportion of days covered.

a drug is being abused.^{7,11} In our study, the strong opioids had the highest Lorenz-1 values, ranging from 15.5% to 30.2%, consistent with the finding of a Lorenz-1 of 19.3% for opioid analgesics observed in studies by Hallas and Nissen (1994)⁷ and Hallas and Stovring (2006).¹¹ In contrast, Lorenz-1 values for our nonabusable control medications were generally less than 5%. It should be noted, however, that among the strong opioids, oxycodone—which is known to be widely abused and diverted and for which prescribing has increased dramatically in recent years¹²—had the next-to-lowest Lorenz-1 value (18.6%). Picking the optimal Lorenz threshold for use would require a greater understanding of the distribution of total drug supply obtained by nonmedical users, as well as the number of nonmedical users as a percentage of all users.

Limitations

By far, the greatest barrier to characterizing nonmedical use at the population level is the inability to definitively ascertain nonmedical use at the individual patient level. Our approach was limited to comparing utilization patterns between abusable and nonabusable drugs. Future studies linking claims to other data sources that permit direct assessment of nonmedical use (e.g., patient survey data) would permit development of algorithms with greater criterion validity that could then be used with greater confidence. Second, as previously stated, we explored

only population-level measures (e.g., mean MPR) rather than measures based on the percentage of patients meeting various criteria (e.g., an MPR:PDC greater than 1). Third, we treated the data as a single, static cross-sectional snapshot rather than leveraging the longitudinal nature of the data source. Making use of trends in the prescription data could enable the development of algorithms optimized for the monitoring of nonmedical use patterns over time, just as knowledge of temporal trends in nonmedical use could serve as an external standard against which to validate. Fourth, as the prescribed directions for use were not available through the MarketScan database, we were not able to proactively distinguish between patients taking drugs when needed versus regularly. Fifth, we included all diagnoses, thus, not excluding patients who may have a diagnosis where overuse of medications may be appropriate/necessary (e.g., cancer). Finally, only prescriptions reimbursed by commercial payers were captured, and it is not clear how much of the overall problem of prescription drug abuse and diversion are captured in this way, as many patients abusing medications may be paying cash.

Conclusions

There is a need for valid and reliable algorithms to detect the extent of nonmedical use at a population level for surveillance purposes and to help target public health interventions aimed

at constraining illicit use. Existing drug utilization measures were not designed for this purpose and are of limited utility. Future work should be focused on developing novel measures that make use of individual patient-level use patterns, including not only heavy use but also overlapping prescription availability and irregular refill behavior.

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DISCLOSURES

All authors are employees and stockholders of Eli Lilly and Company.

Study concept and design were contributed by Birt, Johnston, and Nelson, with assistance from Peter Classi. Data were collected by Birt, Johnston, and Nelson, with assistance from Jin Xie. Interpretation of data was primarily the responsibility of Johnston and Nelson, with assistance from Birt. The manuscript was written by Birt and Johnston, with assistance from Nelson, and revised by Johnston and Birt, assisted by Nelson.

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