The use of a prescription drug monitoring program to develop algorithms to identify providers with unusual prescribing practices for controlled substances

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Abstract

The misuse, abuse and diversion of controlled substances have reached epidemic proportion in the United States. Contributing to this problem are providers who over-prescribe these substances. Using one state's prescription drug monitoring program, we describe a series of metrics we developed to identify providers manifesting unusual and uncustomary prescribing practices. We then present the results of a preliminary effort to assess the concurrent validity of these algorithms, using death records from the state's vital records database pertaining to providers who wrote prescriptions to patients who then died of a medication or drug overdose within 30 days. Metrics manifesting the strongest concurrent validity with providers identified from these records related to those who co-prescribed benzodiazepines (e.g., valium) and high levels of opioid analgesics (e.g., oxycodone), as well as those who wrote temporally overlapping prescriptions. We conclude with a discussion of a variety of uses to which these metrics may be put, as well as problems and opportunities related to their use.

Keywords: aberrant prescribing, unusual prescribing, controlled substances, opioids

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Introduction

Over the course of the last decade, a wide variety of strategies have been developed to stem the epidemic of the nonmedical use of controlled substances in general, and opioid analgesics in particular. While the rate of increase of this epidemic has attenuated (Chen, Hedegaard & Warner, 2014), the problem persists. In 2012, 5.3% of youth aged 12-17, 10.1% of young adults aged 18-25 and 3.8% of the adult population over 25 reported that they had used medical pain relievers for nonmedical purposes in the previous year (SAMHSA, 2013). Over the past ten years, the annual number of prescriptions for opioid analgesics increased from 76 to 210 million (Manchikanti, Fellows & Ailinani, 2010). In 2009 there were 1.2 million visits to emergency departments (EDs) attributable to the nonmedical use of prescription drugs (CDC, 2011), and in 2012 16,007 deaths were attributed to opioid analgesics (Rossen, Khan & Warner, 2014). It has been estimated that in 2007 the total cost to the United States of the nonmedical use of prescription opioids, including lost earnings, excess medical care costs, and correctional and police costs, was $55.4 billion (Birnbaum, White, Schiller, Waldman, Cleveland, & Roland, 2011).

Many of the strategies that have been implemented to address the epidemic have focused on prescribers' utilization of state-level prescription drug monitoring programs (PDMPs) to reduce access to controlled substances by patients at high risk of opioid misuse, abuse, and diversion. PDMPs, which, as of October of 2014, were operational in all states but Missouri (National Alliance of Model State Drug Laws, 2014), constitute databases that providers and dispensers can consult to learn their patients' histories of filled prescriptions for controlled substances. These registries typically comprise data submitted by pharmacies that include the date dispensed, type, strength, and duration of each prescription, and provide information pertinent to the patient, provider, and dispenser. Supported by the Harold Rogers Prescription Drug Monitoring Program (Paulozzi, Kilbourne & Desai, 2011), established

by Congress in 2002, the registries have been developed to promote appropriate prescribing practices and detect fraudulent behavior.

While the use of these registries has yielded promising effects in several states (Garrettson & Ringwalt, 2013), they have yet to demonstrate consistently positive outcomes, in part because of variations in the states' regulations concerning providers' registration with and utilization with their respective PDMPs[1]. A recent evaluation found that the implementation of state PDMPs from 1998 to 2008 was associated with a statistically non-significant 3% decrease in morphine milligram equivalents (MMEs) filled *per capita,* and reported a high level of variability by state in trajectories of prescribing (Brady, Wunsch, DiMaggio, Lang, Giglio, & Li, 2014). Another study that compared states with and without PDMPs found no differences in reductions of drug overdose mortality, at least through 2008 (Li, Brady, Lang, Giglio, Wunsch, & DiMaggio, 2014). Similar findings have been reported by at least one other national evaluation (Paulozzi, Kilbourne & Desai, 2011). A variety of prevention policies and strategies need to be considered if PDMPs are to live up to their full potential. Among these are increasing providers' ease of registration with their state's PDMP and allowing them to delegate to select office personnel the ability to access it; unsolicited reporting by their PDMP of patients who exceed a certain threshold of providers or pharmacies visited within a specified time period (i.e., doctor shoppers); required provider education concerning the appropriate use of PDMPs; and mandatory use of PDMPs to examine the records of patients to whom providers are considering prescribing certain classes or strengths of opioid analgesics.

Another use for PDMPs is to identify providers manifesting unusual or uncustomary practices related to prescriptions for opioid or other controlled substances. To our knowledge this promising strategy has yet to be adopted by any state or to generate any research scrutiny (Brady et al., 2014). The reluctance

[1] For further information, see the National Alliance for Model State Drug Laws at http://www.namsdl.org/prescription-monitoring-programs.cfm

of states to embrace this approach to opioid overdose prevention may be partly attributable to the lack of clarity as to which indicators, in what combination, may suggest that a given provider's prescribing practices may be unusual or uncustomary. There is also reason for concern that any algorithms designed to screen for providers manifesting such prescribing patterns are likely to identify many false positives. That is, providers may have entirely legitimate reasons for these patterns, including the characteristics of their patient caseload, such as chronic severe pain attributable to cancer, sickle cell anemia, and end of life care (Bradford & Rodwell, 2011). Indeed, reviews of algorithms designed to identify inappropriate prescribing have reported that false positives generally constitute between 70% and 90% of cases later subjected to expert judgment, according to a now dated study (Bondy, Byrns, Steiner, et al., 1990). Further, concerns have been raised that providers who believe that their prescribing patterns may be subject to scrutiny may decline to accept patients with chronic pain in their practices, dismiss those they do have prematurely, or treat them sub-optimally by decreasing the strength or duration of their prescriptions (Ringwalt, Garrettson & Alexandridis, in press). However, several studies have suggested that it is time to consider developing algorithms of this nature (e.g., Deyo et al., 2013). This notion is hardly new; under the name of drug utilization reviews (DURs) they have been discussed in the literature for the last 50 years (Hoaken, 1963). Indeed, the genesis of such reviews may date to the late 60s, when the then Department of Health Education and Welfare stressed the importance of prescribing "the right drug for the right patient in the right amount" (US HEW, 1969). What was written about DURs 20 years ago is equally applicable to identifying inappropriate prescribing patterns for controlled substances today: the process lacks methodological rigor and uniformity, and varying approaches have yet to be compared, much less replicated, validated, and evaluated (Lipton & Bird, 1993).

Currently, providers with unusual patterns of prescribing behavior may be identified through a variety of idiosyncratic strategies, including complaints from patients or colleagues, audits of medical records, or investigations by coroners or chief medical examiners (Finucane, Bourgeois-Law, Ineson, & Kaigas,

2003). Further, suggestions are appearing in the literature that states develop processes to systematically review PDMPs to identify providers with inappropriate prescribing behaviors and then to refer them to appropriate licensing or law enforcement authorities (Foster, 2012). However, a study that appeared in 2005 (Hallas) reported that there is no standardized set of strategies available to search for providers with unusual prescribing patterns. This statement remains accurate, as does the paper's conclusion that policy makers have a vested interest in analyzing PDMPs to identify these providers.

There is little empirical data available concerning risk factors that are associated with unusual or uncustomary provider prescribing patterns related to controlled substances, although one study of pertinent criminal and administrative cases reported that they tended to lack Board certification and to be older and male (Goldenbaum et al., 2008). However, the literature does suggest several characteristics of individuals filling prescriptions at high risk for opioid misuse, abuse, and diversion. These include securing prescriptions from multiple providers and filling multiple prescriptions, filling them at multiple pharmacies, refilling prescriptions early, and filling prescriptions for multiple controlled substances (e.g., opioids, sedatives/hypnotics, and benzodiazepines) and *high* doses of opioids (Cochran et al., 2014; Rice, White, Birnbaum, Schiller, Brown, & Roland, 2012; White, Birnbaum, Schiller, Tang, & Katz, 2009).

In this manuscript we describe the process by which we developed a set of metrics based on North Carolina's PDMP to identify prescribers with unusual or uncustomary prescribing practices, and specify and define the metrics themselves. We also present the results of a preliminary effort to assess the concurrent validity of these metrics, by comparing the providers we identified in the extreme tail of each to data from contemporaneous resident death records in the State concerning providers who wrote prescriptions for controlled substances to individuals who then died of medication or drug overdoses. We conclude with a discussion as to how these metrics can be used to mitigate the misuse, abuse, and diversion of controlled substances.

Methods

Metric development: North Carolina enacted its PDMP, called the Controlled Substances Reporting System (CSRS), in 2005, and the system became operational in 2007. By statute, at the time the data pertinent to this study were collected, all dispensers (i.e., pharmacies) except those attached to hospitals, long term care facilities, and veterinary care facilities were required to report the following information for each controlled substance dispensed in Schedule II-V: the prescriber's and dispenser's Drug Enforcement Administration (DEA) numbers, the patient's identifying information and date of birth, the metric quantity of the drug dispensed and the estimated number of days of the supply, the dates the prescription was written and filled, and whether the prescription was either new or a refill. Note that the enacting legislation did not require that the method of payment be specified; and payer data was not authorized until the beginning of 2014. Nor does the PDMP contain any data concerning the provider's specialty; at present, this information is not even collected by the DEA as part of its license application process.

Among the provisions of the law was one that permits the State's Department of Health and Human Services (DHHS), which is charged with maintaining the PDMP, to "provide data to public or private entities for statistical, research, or educational purposes" (North Carolina Controlled Substances Reporting Act, 2005). Based on this law, and with approval from our institution's Institutional Review Board, the University of North Carolina secured a copy of the State's PDMP data for the years 2009-2013 inclusive, after all patient-level data were de-identified. Provider and dispenser names were also removed from the dataset. We were, however, able to link prescriptions across patients by means of a unique identification number provided to us by the vendor for the State's PDMP, and could also link patients' providers and dispensers over time by means of their respective DEA numbers.

Under the terms of the legislation that enacted North Carolina's PDMP , the State's DHHS is charged with reporting providers manifesting "unusual patterns of prescribing medications" to the Attorney General's office which may, at its discretion, refer these providers to the State Bureau of Investigation (SBI) for appropriate action (Article 5E, § 90-113.74(e)). In 2013 the law was amended to allow the CSRS to alert prescribers' licensing boards of providers with unusual prescribing patterns (Bronson, 2013).

The dataset received from the PDMP vendor required extensive cleaning and variable creation. We began by deleting prescriptions for all non-controlled substances and eliminating records with incomplete data in the fields required for the metrics. We also deleted all DEA numbers for pharmacies that we found duplicated in the prescriber field. We made the decision to delete all Schedule V drugs, which comprise those with the least potential for abuse of the four categories (i.e., II-V) of legal controlled substances. We also excluded all records of prescriptions for all forms of buprenorphine/naloxone and buprenorphine, including transdermal, because they constitute drugs that are used in opioid addiction treatment. Tramadol, another candidate, was not included in the State's PDMP in 2012. We further deleted all prescriptions for controlled substances dispensed in vials, because injected medications have specialized uses in outpatient settings, so including these drugs would have been likely to increase the rate of false positives. Finally, we calculated a common metric for all opioid analgesics using a standard measure of milligrams of morphine equivalents (MMEs) (PDMP TTAC, 2013). Altogether, we deleted 0.4% of existing records of prescribed substances, and did not impute any data. The resulting dataset comprised records related to 16,837,380 unique prescriptions, 3,684,807 unique patients filling prescriptions, 33,635 unique providers, and 2383 unique dispensers.

We then initiated a series of discussions with PDMP and SBI personnel concerning the algorithms, or metrics, that they would like to see applied to the PDMP dataset to identify prescribers with unusual or

uncustomary prescriber practices. These discussions led to an invitation to join an advisory committee that focused on the utilization of the State's PDMP and included representatives from the SBI, the Division of Public Health, the State's Medical and Pharmacy Boards, and several other State organizations. This body evolved into our study's informal steering committee, and advised us on the potential utility of the algorithms we proposed to identify providers with unusual prescribing practices. We also initiated discussions with the State's Medical Board, after the law enacting the CSRS was amended to allow its program staff to alert the Board directly concerning providers manifesting questionable prescribing behaviors (Bronson, 2013).

Table 1 displays a list of the metrics we developed along with explanations pertaining to each. As the table indicates, we sought to identify providers writing high numbers of prescriptions for high doses of opioids greater than 100 MMEs daily, a definition which is emerging as the industry standard (Baumblatt, Wiedeman, Dunn, Schaffner, Paulozzi, & Jones, 2014; Logan, 2013). We also developed a metric to identify providers who consistently prescribe high levels of opioids that fall below this threshold, to identify those who may seek to avoid detection as a "pill mill" (Okie, 2010). In addition, we searched for providers who wrote multiple prescriptions for various classes of controlled substances, regardless of dose. In so doing, we paid particular attention to those who co-prescribed opioids and benzodiazepines, which are potentially hazardous when taken in combination (Dormuth, Miller, Huang, Mamdani, & Juurlink, 2012; Jones, Mack & Paulozzi, 2013; Jones, Mogali & Comer, 2012; Maxwell, 2011). We also developed a metric to identify providers who wrote high numbers of temporally overlapping prescriptions. As suggested by Logan, Liu, Paulozzi, Zhang, & Jones, 2013), we defined a temporally overlapping prescription as one written more than seven days before the expiration date of an earlier prescription for the same class of controlled substance. We also examined patients manifesting unusual behaviors in regards to filling prescriptions for controlled substances, reasoning that these patients might gravitate to providers whom they thought would prescribe these substances liberally. We thus examined the providers of multiple patients who traveled the furthest from their homes either to secure prescriptions from their providers or fill these prescriptions at distant

pharmacies (Betses & Brennan, 2013; Gourlay & Heit, 2009). We also identified providers of patients who visited multiple providers or pharmacies to secure or fill controlled substances, practices known as doctor shopping" (Pradel et. al, 2009; Worley, 2012) and "pharmacy hopping" (Fisher, Sanyal, Frail, & Sketris, 2012; Gilson, Fishman, Wilsey, Casamalhuapa, & Baxi, 2012), respectively.

INSERT TABLE 1 HERE

Metric validation. Our next step in the development of these algorithms comprised an exploratory effort to validate their utility as a screening mechanism by comparing the DEA numbers of providers identified in the tail of each distribution with a list of providers who were associated with decedents whose deaths were attributed to unintentional or undetermined drug-related poisoning. To that end, we examined the records of 1,140 decedents for the 12 month period beginning in January 2012 that were archived in North Carolina's Vital Records Death Certificate data file, using ICD10 codes representing drug-related poisonings:[2]. We identified those who had received at least one prescription for a controlled substance within 30 days of their death (N=520), a referent period that we believed was reasonable to implicate the prescription in the overdose noted. We then selected all records with t-codes for a medication or drug death (N=465). Finally, we identified the DEA numbers of all providers (N=651) who had prescribed at least one controlled substance to these decedents. Note that decedents could have received prescriptions for controlled substances from multiple providers within 30 days prior to their death.

Results

Metric development. The distributions of the various metrics we examined all assumed the same general shape. The example displayed in Figure 1 pertains to the average daily rate at which providers in North Carolina wrote prescriptions for high levels (>100 MMEs) of opioid analgesics over the period

[2] 391, 402, 403, 404, 406, 424, 426, 428, 430, 432, 435, 436, 455, 450, 461, 462, 465, 476, and 509

2009 through 2011, on the days they wrote any prescriptions for controlled substances. Note that the vast majority of all providers wrote, on average, fewer than one prescription for a controlled substance a day. We selected this criterion to control for providers who see patients, and thus write prescriptions for them, only on a part-time or infrequent basis. For example, this metric would be as likely to identify physicians who wrote prescriptions for controlled substances to patients on a daily basis for 20 days as those who only wrote prescriptions on five days over the course of a given month. This metric reveals a precipitous decline after two prescriptions per day and a long tail that stretches to almost 30 per day; Figure 2, its companion, displays the distribution of this tail over the period 2009 through 2011. In this particular case, only 44 providers wrote at least five prescriptions for opioids daily that exceeded 100 MMEs. Of these, eight wrote between 10 and 20 prescriptions, inclusive, and one clear outlier wrote an average of 28 per day. We have provided the State's CSRS with graphics of this nature that depict the distributions of each of the metrics specified in Table 1. We have also provided, in descending order for each metric, the top 1% of providers in the tail of its distribution, including their rank (i.e., 1-100), metric score (e.g., 28), and DEA number. By this mechanism, the SBI or State Medical Board will be able to show all providers on whom they may choose to open an investigation the shape of the entire distribution and their precise place along the curve. Graphics displaying the exact shape and distribution of the curve related to each metric are available from the first author upon request.

INSERT FIGURES 1 AND 2 HERE

Metric validation. The results of our exploratory effort to assess the concurrent validity of our metrics are displayed in Table 2, which indicate the percent in the top 0.1% of each tail in 2012 who also prescribed an opioid analgesic within 30 days to a decedent whose death in the same year was attributed to a medication or drug overdose. At the suggestion of staff in the State's PDMP office, we further restricted the providers in each tail whom we examined by constraining the list to those who were also in the top 1% of prescribers for all controlled substances.

INSERT TABLE 2 HERE

As indicated in Table 2, we found that the metrics most closely associated with records of decedents whose deaths were attributable to medication or drug overdoses were providers who prescribed high numbers of prescriptions for: (1) benzodiazepines in conjunction with high levels (>100 MMEs) of opioids, (2) opioids regardless of dose, (3) high level opioids, and (4) benzodiazepines. Among providers who appeared in the top 1% of each metric, between 30% and 46% had also prescribed an opioid analgesic to a patient within 30 days of his or her death. When we constrained the providers in the tail of the distribution of each metric to those who were also among the top 1% of all prescribers of controlled substances, the range varied between 32% and 77%. In addition, providers in the metric representing overlapping prescriptions, which performed poorly in this validation effort among all providers in the top 1% of the metric, were associated with prescriptions for 61% of decedents when we limited the list to those who were also in the top 1% of all prescribers.

In sharp contrast, the tails of metrics associated with patients who traveled the furthest from their homes to their providers and pharmacies, and who visited multiple providers and pharmacies, yielded very few (<3) providers who were associated with individuals whose deaths related to a medication or drug overdose.

Discussion

Our study is the first in the academic literature to describe what we believe to be a practical approach to conducting an initial screen of providers with manifesting “unusual or uncustomary” prescribing practices. We generally prefer this phrase to the use of the simpler word “aberrant,” because the former is more suggestive of statistical outliers, for which there are often readily defensible explanations, whereas the latter has a more judgmental and potentially stigmatizing connotation. The particular advantage to our process, we believe, is that it provides state-level institutions that have the statutory authority and responsibility to investigate these providers – in North Carolina, these comprise the

State's Bureau of Investigation and Medical Board – the opportunity to select for themselves the metric that they believe is most likely to yield providers that warrant investigation. If a given institution discovers that some metrics yield fewer providers manifesting questionable prescribing practices than others, it can then turn quickly to another. Further, once an investigation is opened, the institution can, at its discretion, reveal to the provider the shape of the tail of the distribution in which the provider has appeared, along with both the provider's particular ranking and score on that metric. Thus initial questions from the provider concerning the equity of the process that led to the investigation can be at least partially forestalled.

That said, we fully recognize that the process we have described constitutes only an initial screen, and that a substantial amount of work must be conducted by a given state's responsible authorities to identify providers worthy of further attention. The development of our algorithms thus begged the question as to how the results they present may best be validated. We initially considered two different approaches to this task. The first comprised a comparison of the providers whose DEA numbers our algorithms identified with providers who had been sanctioned by the North Carolina Medical Board and State Bureau of Investigation. However, each of these two sources presented problems. In regards to the Medical Board, which is charged by statute in North Carolina with regulating the practice of medicine in the State, the names of disciplined providers are publicly available, as is the nature of their offenses. However, in North Carolina it is unclear when many of these offenses were committed, so that they may have occurred prior to the year that a given provider's behavior was identified by one of our algorithms. State Bureau of Investigation data are similarly problematic in that regard. Further, a perusal of the Medical Board's list of prescribers who were disciplined for behavior related to controlled substances suggests that they were sanctioned for a variety of reasons, only some of which are pertinent to a validation process. That is, some wrote scripts to themselves or family members; some prescribed without first conducting a proper, in-office examination, did not check the medical history of

their patient, or did not maintain adequate medical records; and some wrote prescriptions when they lacked the authority to do so.

Further, the processes by which cases come to the attention of either the SBI or the Medical Board are unclear, and may depend largely on the vagaries of nominations from the field. In that regard, we are considerably more comfortable with the systematic process by which our State's Division of Public Health utilized mortality records to identify providers who were temporally linked by their prescribing records to individuals who died from an overdose. However, the level of detail present in these records is inconsistent, and there may be regional variation in the accessibility of emergency services available to reverse overdoses, which may affect mortality rates in rural areas. Thus none of these sources of data should be considered a gold standard against which the sensitivity and specificity of our algorithms may be judged, although there is certainly value in assessing their concurrent validity.

We found a relatively high level of concordance between providers whose DEA numbers were present in the tails of several of the key metrics we examined, and those who prescribed controlled substances that were filled by patients who then died within 30 days of a medication or drug overdose. The most salient of these metrics pertained to providers in the tail of the distribution, and who were also in the top 1% of all prescribers of controlled substances, who co-prescribed benzodiazepines and high levels of opioid analgesics to their patients. Over three-quarters of these providers were linked to the decedents. The other metrics that we identified as most closely associated with deaths attributable to a medication or drug overdose were providers who wrote high numbers of prescriptions that contained a daily dose of greater than or equal to 100 MMEs, and those who wrote high numbers of prescriptions for benzodiazepines and opioids (considered separately). Also of significance were providers in the top 1% of all prescribers who wrote a high number of temporally overlapping prescriptions, which we defined as a prescription for an opioid analgesic filled within seven days of the expiration of a previous one. While our validation effort was more successful for providers who appeared in the top 1% of both the key

metrics specified above *and* the top 1% of all prescribers of controlled substances, we can attribute this to the fact that their larger patient load increased their likelihood of prescribing to a patient who then died of an overdose.

Of much less potential utility in this exploratory validation procedure were several metrics we developed to identify providers serving patients who traveled the furthest, and who visited multiple providers and pharmacists, to secure or fill prescriptions. We are unsure as to why these indicators proved so unsatisfactory in this particular validation effort, but suggest that metrics assessing doctor shopping and pharmacy hopping be considered in future efforts of this nature. In the meantime, it seems reasonable to suggest that regulatory authorities seeking a mechanism to conduct an initial screening for high risk prescribers focus first on those metrics that have yielded the greatest evidence of validity, however preliminary.

Ultimately, we believe that the collective and relative value of our algorithms can only be determined in a prospective, longitudinal context by comparing the costs associated with weeding out false positives to the benefits to society of identifying and curtailing true positives. Unfortunately, even the most refined of algorithms are likely to yield both false positives and false negatives, given the ambiguous nature of what constitutes legitimate medical practice in prescribing behaviors related to controlled substances (Robinson, 2009).

We also note that prescribers of controlled substances – and particularly those who have either neglected to register with the PDMP or consult it only irregularly when they write prescriptions - could be notified of their position on some of these metrics. This private presentation might motivate providers to utilize the PDMP more frequently and review their own prescribing pattern. In this regard there has been considerable discussion concerning how best to address providers whose long term behavior or patient load indicates a cause for concern. One strategy is to issue an automated alert to providers

whose practices include a specified number of questionable prescribing practices to strongly encourage them to register with and routinely query their state's PDMP. Eligible providers who fail to heed this advice could then be automatically flagged by the PDMP and reported to their appropriate licensing board (Clark, Eadie, Kreiner, Strickler, Brandeis University, Florence Heller Graduate School of Social Welfare, & United States of America, 2012).

Of greater concern are providers who cannot adequately defend their prescribing practices to investigating authorities. Except in clear cases of fraud – where provider behaviors can be readily attributed to malfeasance for monetary gain – the literature generally recommends any of a variety of remedial measures. These include referral of the provider to treatment if impairment is discovered, as well as tailored (or "detailed") education programs designed to improve prescribing practices. There are clear guidelines governing prescribing practices related to controlled substances. Where a remedial approach is adopted, continued monitoring is recommended to determine compliance. With the growing use of PDMPs such monitoring can be conducted unobtrusively and, given the brevity in an increasing number of states of pharmacies' required reporting periods to their PDMPs, almost in real time (Clark et al., 2012; Lipton & Bird, 1993).

The above strategies of motivation, enforcement and remediation serve to minimize the risk of taking false positives to the level of prosecution. Privately providing physicians with information regarding their ranking among their peers will give those who are false positives the opportunity to improve their behavior in a way that removes them from suspicion. Of course, this information may also allow those who are true positives to modify their behavior to remove themselves from suspicion, but if the goal to be achieved is better prescribing patterns this unintended consequence may be acceptable.

Limitations. The North Carolina CSRS dataset that we analyzed lacked several variables that would have greatly facilitated the initial screening process. The first related to providers' specialty; for

example, it seems safe to assume that oncologists and providers serving patients in hospice settings could be expected to have prescribing patterns that are very different from those of dentists or general practitioners. Second, we believe that we were only partially successful in removing from the dataset DEA numbers that are affiliated with teaching hospitals as opposed to a specific provider. These institutional DEA numbers are used by many medical residents on prescriptions. Third, we lacked information concerning the payer for these prescriptions. It seems reasonable to assume that patients paying cash when filling prescriptions for controlled substances might be more likely to intend to sell or otherwise divert them. Of particular note are patients who charge one of several prescriptions for controlled substances to their insurance carrier and then pay cash for the remainder. Fourth, it would be very helpful if our State's CSRS were electronically linked to those of its neighbors, which would greatly increase the reach and sensitivity of our various metrics; for example, we would be able to detect out-of-state patients who traveled the furthest to visit NC providers (Deyo et al., 2013). It would also be helpful if data concerning providers' specialty, disciplinary status, retirement, or death were linked to their DEA numbers and then integrated into the State's CSRS, which would facilitate the immediate identification of prescriptions that individuals secure from ineligible prescribers (Clark et al., 2012). Fifth, our decision rules concerning various cut points related to the definitions of our metrics may be considered somewhat arbitrary, as were the numbers of providers at the extreme end of the tails of each metric whom we compared to providers whose prescriptions were temporally linked to medication or drug overdose-related deaths. A sensitivity analysis of these various cut points, which was beyond the scope of this project, may yield insights into more empirically valid definitions or more sensitive cut points. Sixth, future studies should pay particular attention to providers who appear in the tails of multiple distributions, even if they are not identified at the top of any. Seventh, some of our metrics may appear arbitrary, and there are certainly others that should be considered by future investigators. In developing the study's metrics, however, we paid particular attention to recommendations by key stakeholders in the State as to which metrics they thought would prove most fruitful. Finally, our validation effort was exploratory, insofar as we could only assess the concurrent

validity of the results of our algorithms relative to a dataset of providers implicated in – but not necessarily responsible for – the medication or drug overdose deaths noted. Indeed, the mortality records we examined probably under-counted the number of deaths that could be attributed to unintentional or undetermined drug-related poisonings, at least in part because medical examiners may have chosen to spare the decedents' families from public exposure. A true gold standard against which to compare the results of our algorithms would require records of providers sanctioned, following an investigation, either by the State's Bureau of Investigation or by its Medical Board. Unfortunately, the time required for a prospective study of this nature was well beyond the scope of this investigation.

That said, our study is the first to report the results of a series of algorithms designed to mine a PDMP to indicate providers manifesting unusual or uncustomary prescribing practices. It is also the first to report the results of an exploratory effort to validate these algorithms. As such, it adds to the already considerable literature on the use of PDMPs to identify patients who are doctor shopping and pharmacy hopping (Pradel et. al, 2009; Worley, 2012). We believe that there are clear opportunities to reduce the nonmedical use of controlled substances by a dual approach to addressing the epidemic.

Conclusions. The development of accurate and efficient algorithms that yield lists of prescribers manifesting unusual prescribing patterns that maximize true positives and minimize false positives presents multiple challenges. But the results, if obtainable, should be well worth the effort, particularly if they are utilized in conjunction with other strategies, such as clear guidelines governing prescribing practices related to controlled substances, and automated warning letters or email messages to providers whose prescribing patterns have been identified as unusual and potentially uncustomary (Simoni-Wastila & Tompkins, 2001;Clark et al., 2012). As has been compellingly stated, "One renegade physician can illegally prescribe enough narcotic drugs to cripple an entire county with addiction" (Robinson, 2009).

Table 1: Description of study metrics

Label	Description and notes
Providers who write the highest:	
Rate of prescriptions for daily doses of opioids with ≥ 100 MMEs	Providers who write high rates of prescriptions for what is generally recognized as a high dose of opioids. The denominator for this metric is limited to the number of days on which the provider prescribed a controlled substance in a given period, to control for those who only occasionally write such prescriptions.
Average daily dose of MMEs	Providers who prescribe their patients a high level of MMEs *for each day* of the period their prescription encompasses, irrespective of the *duration* of the prescription; i.e., the strength of their daily dose *only.* The number of days that their prescription encompasses constitutes the denominator. Thus the metric specifies providers who write prescriptions for high levels of MMEs that may not meet the threshold of the 100 MMEs specified above.
Total MMEs for each prescription they write	Providers who write a high total number of MMEs *for the entire period* that the prescription encompasses: i.e., the strength of patients' daily dose multiplied by the number of days' supply.
Rate of prescriptions for benzodiazepines	Providers who write a high rate of prescriptions for benzodiazepines, *irrespective of their dose.* The denominator reflects the number of days on which a provider prescribes controlled substances.
Rate of prescriptions for opioids	Providers who write a high rate of prescriptions for opioids, *irrespective of their dose.* The denominator reflects the number of days on which a provider prescribes controlled substances.

Rate of prescriptions for stimulants	Providers who write a high rate of prescriptions for stimulants, *irrespective of their dose.* The denominator reflects the number of days on which a provider prescribes controlled substances.
Rate of co-prescribed benzodiazepines and high doses of opioids	Providers who write a high rate of prescriptions, on the same day and for the same patient, for benzodiazepines and high doses of opioids (≥ 100 MME).
Number of temporally overlapping prescriptions for controlled substances	Providers who write a second prescription for a controlled substance at least seven days before the initial prescription for a drug of the same class expires. As used here, "class" indicates an opioid, benzodiazepine, or stimulant.
Providers with patients who:	
Travel the furthest from their homes to their pharmacies	Providers whose patients travel the furthest from their home addresses to their pharmacies. Because this analysis is at the prescription level, individual patients may be counted multiple times, though a patient is counted only once for each pharmacy per day, regardless of the number of prescriptions filled on that visit. We eliminated from the dataset DEA numbers for two mail-order pharmacies, Medco and ExpressScripts.
Travel the furthest to their providers	Providers whose patients travel the furthest to see their providers. As above, the analysis is at the prescription level, so patients may be counted multiple times. In addition, we deleted outliers that suggest that some of the patients involved may be armed forces personnel who specify a home address at a military base in North Carolina and who may have visited oversees providers, but filled the prescription in the State.

Fill prescriptions for any controlled substance received from the highest number of providers.	Providers whose patients fill prescriptions for any controlled substance from the greatest number of providers within 12 months.
Fill prescriptions for benzodiazepines from the highest number of providers	Providers whose patients fill prescriptions for benzodiazepines from the greatest number of providers within 12 months.
Fill prescriptions for stimulants from the highest number of providers	Providers whose patients fill prescriptions for stimulants from the greatest number of providers within 12 months.
Fill prescriptions for opioids from the highest number of providers	Providers whose patients fill prescriptions for opioids from the greatest number of providers within 12 months.
Visit the highest number of pharmacies to fill prescriptions for any controlled substance	Providers whose patients visit the greatest number of pharmacies (i.e., “pharmacy hopping”) within 12 months. Note that patients can be counted more than once if they visit multiple providers.

Table 2: Providers identified in each metric tail who also wrote a prescription to a patient who died in 2012 within 30 days of a medication or drug overdose (N=465)

Metric label	Highest 1% of metric (N)	Highest 1% of metric: N,% of providers linked to the decedent	Highest 1% of metric who are also in top 1% of prescribers (N)	Highest 1% of metric w also in top 1% of presc N,% of providers linked decedent
Providers who write the highest:				
Rate of prescriptions for daily doses of opioids with ≥ 100 MMEs	157	54 (34.3%)	96	41 (42.7%)
Average daily dose of MMEs	290	5 (1.7%)	6	1 (16.7%)
Total MMEs for each prescription they write	289	15 (5.2%)	24	5 (20.8%)
Rate of prescriptions for benzodiazepines	271	80 (29.5%)	167	54 (32.3%)
Rate of prescriptions for opioids	290	105 (36.2%)	176	74 (42.0%)
Rate of prescriptions for stimulants	143	14 (9.8%)	39	10 (25.6%)
Rate of co-prescribed benzodiazepines and high (≥ 100 MMEs) doses of opioids	57	26 (45.6%)	31	24 (77.4%)

Number of temporally overlapping prescriptions for controlled substances	165	16 (9.7%)	18	11 (61.1%)
Providers with patients who:				
Travel the furthest from their homes to their pharmacies	336	1 (0.3%)	0	0 (0%)
Travel the furthest from their homes to their providers	335	1 (0.3%)	0	0 (0%)
Fill prescriptions for *any* controlled substance from the highest number of providers	336	0 (0%)	0	0 (0%)
Fill prescriptions for benzodiazepines from the highest number of providers	271	0 (0%)	0	0 (0%)
Fill prescriptions for stimulants from the highest number of providers	143	2 (1.4%)	0	0 (0%)

Fill prescriptions for opioids from the highest number of providers	290	2 (0.7%)	0	0 (0%)
Visit the highest number of pharmacies to fill prescriptions for any controlled substance	336	0 (0%)	2	0 (0%)

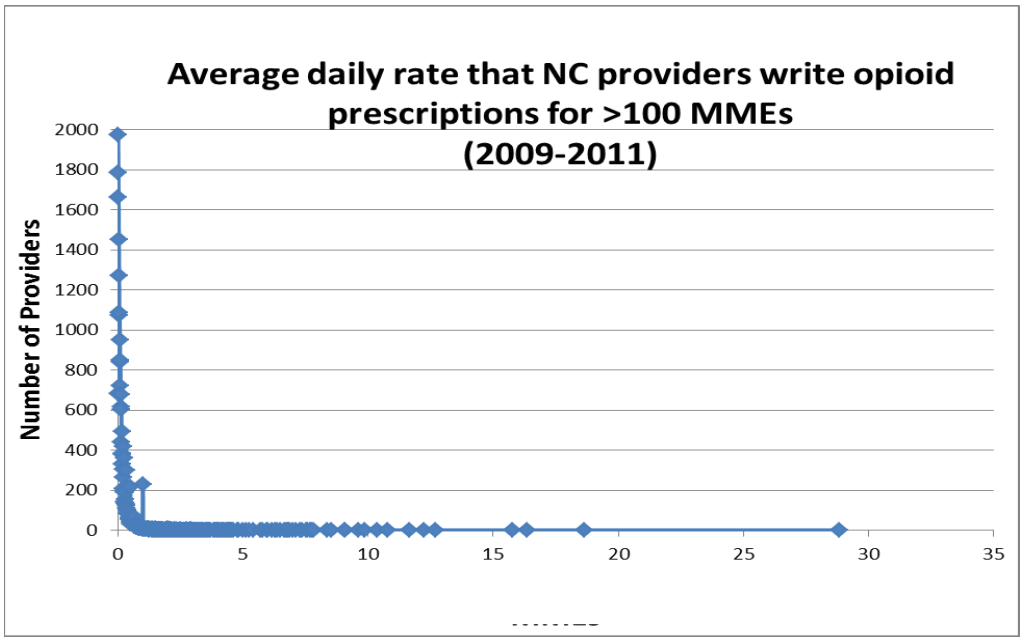

Figure 1: Full distribution of example metric

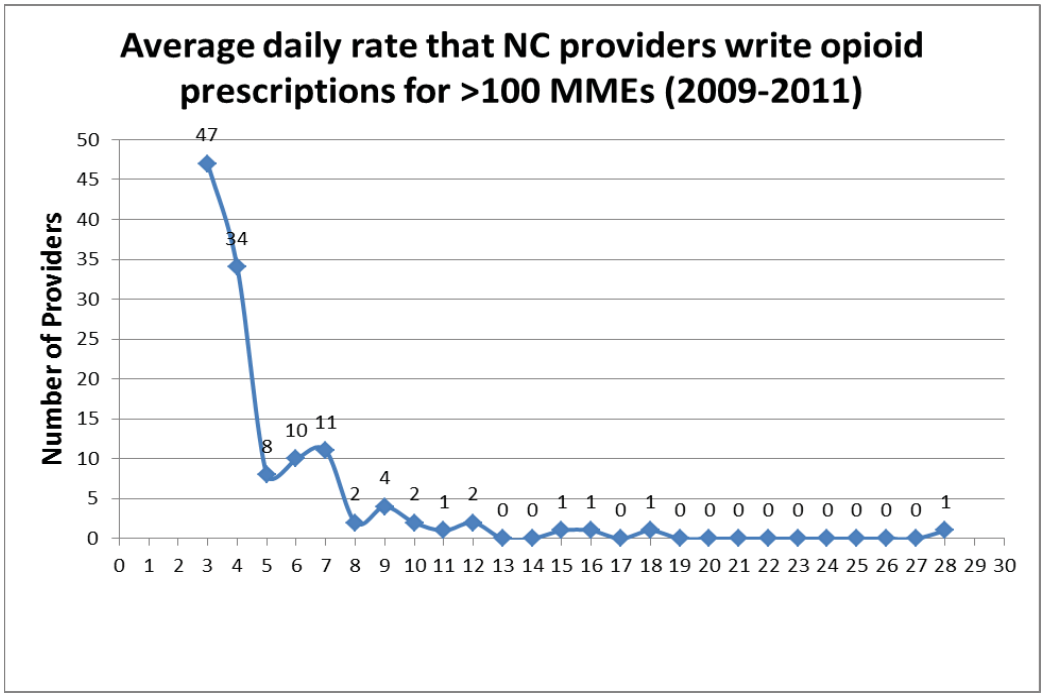

Figure 2: Tail of distribution of example metric, limited to providers who wrote at least 3 prescriptions daily

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