NARxCHECK® Score as a Predictor of Unintentional Overdose Death

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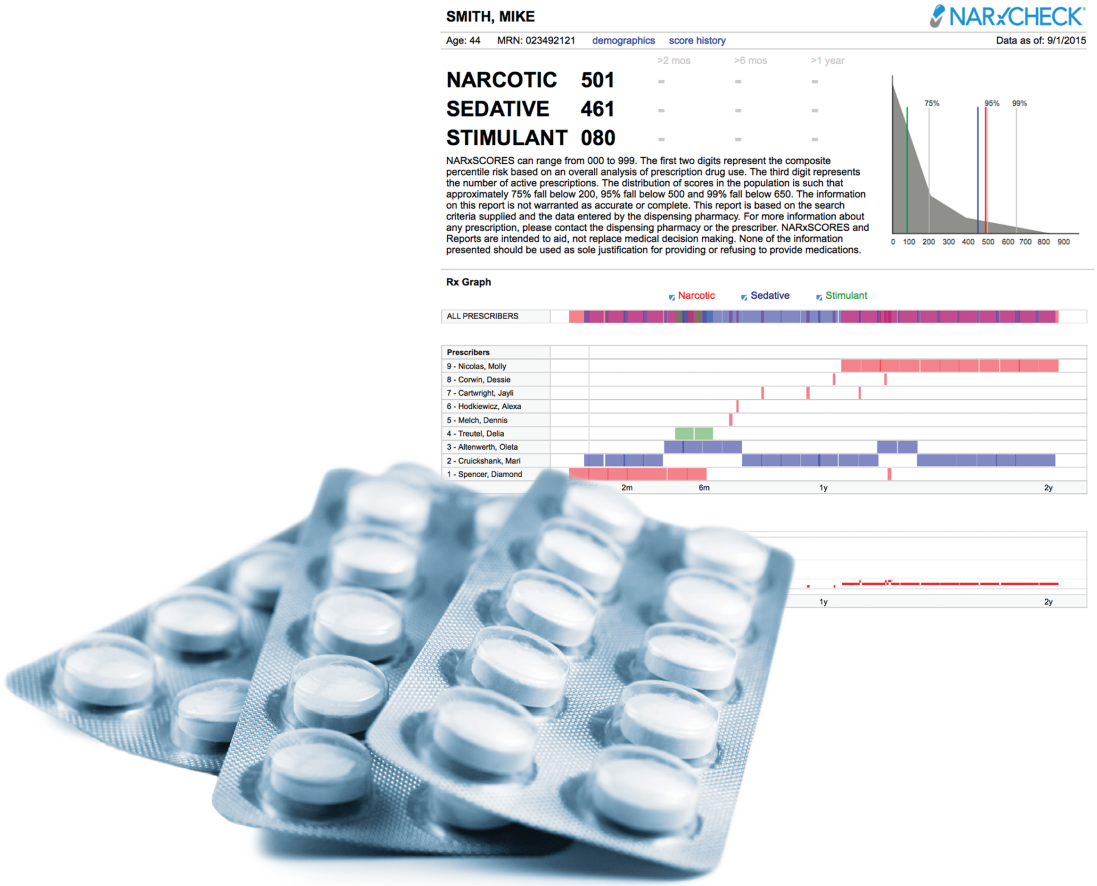
October 2016
Appriss, Inc.



NOTE: This paper was previously published with an unrecognized sampling error that has been corrected. Please disregard all previous versions.

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Abstract

Introduction

Prescription drug abuse is a growing public health problem. NARxCHECK analyzes and scores the patient risk factors found within Prescription Drug Monitoring Program (PDMP) data and creates a 3-digit score ranging from 000 – 999 that corresponds to overall risk. The NARxCHECK algorithm was retrospectively applied to a large population of known unintentional overdose deaths and compared to a traditional approach using published red flags as risk factor determinants.

Design

Retrospective case/control study

Data

A complete hashed dataset of Ohio PDMP data from 2009 to Q3 2015 with 1,687 hashed patient identities corresponding to coroner-declared unintentional overdose deaths.

Findings

NARxCHECK Narcotic Scores were found to be a statistically significant predictor of unintentional overdose deaths with increasing odds ratios (OR) as the scoring thresholds increased; ≥ 400 (OR 28.0, CI 22.3–35.2), ≥ 600 (64.3, CI 50.2–82.3), ≥ 800 (104.9, CI 69.4–158.6).

Summary

NARxCHECK is an effective measurement tool to assess risk of unintentional overdose death. It is equivalent to a multi-variable Red-Flag approach while offering automated analysis and significant ease-of-use for clinicians to assess a patient's risk at a glance.

Introduction

Prescription drug abuse (PDA) and overdose is a persistent, growing public health problem in the United States. The CDC has published data for 2014 that indicates 47,055 overdose deaths occurred, and of that total, 18,893 were related to opioid analgesics[1]. To help combat the problem of PDA, 49 states have established a Prescription Drug Monitoring Program (PDMP). These programs require pharmacies and other dispensers of controlled substance medications to report the details of the dispensation to a centralized, state-run database. Most PDMP programs use the reported controlled substance data to create detailed reports of a patient's aggregate controlled substance history at the request of providers who are treating or dispensing medications to the patient. The expectation is that providers will use the PDMP data to make a determination of the risk/benefit ratio when prescribing (or dispensing) a controlled substance.

A literature search reveals many published research articles that retrospectively evaluate the risk factors that can be found in a PDMP report in the context of unintentional drug overdose. Much of the research has focused on assessing relatively easy to quantify metrics such as morphine milligram equivalents per day (MME/day), total number of providers, and total number of pharmacies[2-5]. Counting overlapping prescription days has also been studied[6] and found to be a determinant of risk.

Numerous "Red Flags" have been promoted to guide clinicians in making risk/benefit decisions. For the purposes of this paper, we've chosen the following to represent a cross section of the red-flag proposals that are found in the literature and based on PDMP data:

- Paulozzi, et al. published **40 MME/day average** as a risk factor[5]
- Yang, et al. published **4 or more pharmacies in a 90-day interval** as a risk factor[6]
- Hall, et al. published **5 or more clinicians** in the preceding year as a risk factor[4]

With careful examination, these red flags can be derived from a PDMP report that publishes morphine equivalent dose values along with the core components of the prescription data. Each of these studies evaluated a single red flag variable to assess overdose risk. However, combining multiple variables into a composite risk index can better assess a continuum of risk.

NARxCHECK

NARxCHECK is a patented algorithm that analyzes controlled substance data from PDMPs and provides easy-to-use insights into a patient's controlled substance use. NARxCHECK quantifies risk with a 3-digit score, termed a "Narx Score," which ranges from 000-999. A detailed mathematical explanation of a Narx Score is beyond the scope of this paper, but in general, it is a weighted combination of multiple variables (drug equivalents, number of providers, potentiating drugs, number of pharmacies, and number of overlapping prescription days). The score is intended to create a composite risk index, which increases as the value of one or more of the risk factors in a PDMP report increases. Narx Scores have been computed for 3 different drug types; specifically, narcotics, sedatives, and stimulants. The distribution of the scores are such that in any given population, about 75% of scores will fall below 200, about 5% will be above 500, and only 1% will be above 650. One additional nuance of the Narx Score is that the last digit represents the number of active prescriptions that a patient will have if medications are taken as directed.

This paper investigates the predictive capability of the NARxCHECK Narcotic Score for unintentional overdose death using a 2014 sampling of overdose death data from the State of Ohio. The NARxCHECK Narcotic Score is also compared with a reference Red-Flag strategy containing risk factor thresholds supported in the literature.

Data Overview

The Ohio Automated Rx Reporting System, also known as OARRS, is one of the country's leading PDMP programs. On average, 23 million controlled substance prescriptions are reported annually. These account for the prescription history of approximately 5.6 million patients. The Ohio Department of Health (ODOH) recently released to OARRS the identities of almost 2,500 unintentional overdose deaths from the calendar year 2014. 1,687 of the ODOH identities were matched to OARRS patient identities. In support of this study, a research set of hashed (de-identified) OARRS data, representing Q1 2009 to Q3 2015 was made available along with the hashed identities and the date of death for the 1,687 unintentional overdose decedents.

Sampling Method

The OARRS prescription records for the 3 years preceding the date of death were isolated for the 1,687 decedents. For each decedent, a cohort of 100 living patients was randomly selected and the corresponding 3 years of prescription records were isolated from the OARRS dataset. The control patients were required to be found in OARRS in 2014 and also have a dispensation in the third quarter of 2015 to insure that they were alive at the associated case's date of death. This method resulted in a case/control study set of 1,687 decedents and 168,700 living patients.

Study Method & Results

NARxCHECK Narcotic Score Methods and Results

For each case and 100 matching control subjects, we calculated the highest NARxCHECK Narcotic Score for every day in the year preceding the date of death. In Table 1, the Odds Ratio (OR) was calculated for different NARxCHECK Narcotic Score ranges using the range 000 – 099 as the reference group.

Table1 – NARxCHECK Narcotic Score Odds Ratio (OR) w/ Confidence Intervals (CI) - 100 Point Bin Results

Narcotic Score	Living	Deceased	OR	95% Lower CI	95% Upper CI	P-Value
000 – 099	71,701	80	1			
100 – 199	27,153	238	7.9	6.1	10.1	P < 0.0001
200 – 299	19,546	220	10.1	7.8	13	P < 0.0001
300 – 399	21,002	234	10.0	7.7	12.9	P < 0.0001
400 – 499	16,303	297	16.3	12.7	20.9	P < 0.0001
500 – 599	8,629	305	31.7	24.7	40.6	P < 0.0001
600 – 699	3,005	188	56.1	43.1	73	P < 0.0001
700 – 799	1,062	90	76.0	55.9	103.3	P < 0.0001
800 – 899	283	32	101.3	66.2	155.2	P < 0.0001
900 – 999	16	3	168.1	48	588	P < 0.0001
Total	**168,700**	**1,687**				

Table 1 shows the results of the OR analysis for NARxCHECK Narcotic Scores using 100 point bins. Each successive score bin shows an increasing odds ratio with a statistically significant difference from the reference group. While data in the 900 – 999 bin is sparse, the 800 – 899 bin shows an odds of death 101.3 times that of the reference group.

In Table 2, we calculated the OR comparing NARxCHECK Narcotic Scores at or above each 100 points of score using 000 – 099 as the reference group. A Narcotic Score of 650 is also highlighted as that value is often referenced as a threshold equivalent to the 99th scoring percentile in NARxCHECK.

Table 2 – NARxCHECK Narcotic Score Odds Ratio (OR) w/ Confidence Intervals (CI) Using "At Or Above" Threshold Results

Narcotic Score	Living	Deceased	OR	95% Lower CI	95% Upper CI	P-Value
000 – 099	71,701	80	1			
≥ 100	96,999	1,607	14.9	11.9	18.6	P < 0.0001
≥ 200	69,846	1,369	17.6	14	22	P < 0.0001
≥ 300	50,300	1,149	20.5	16.3	25.7	P < 0.0001
≥ 400	29,298	915	28.0	22.3	35.2	P < 0.0001
≥ 500	12,995	618	42.6	33.7	53.8	P < 0.0001
≥ 600	4,366	313	64.3	50.2	82.3	P < 0.0001
≥ 650	2,503	208	74.5	57.4	96.7	P < 0.0001
≥ 700	1,361	125	82.3	61.9	109.5	P < 0.0001
≥ 800	299	35	104.9	69.4	158.6	P < 0.0001
≥ 900	16	3	168.1	48	588	P < 0.0001

Similar to the results in Table 1, Table 2 shows that each successive score threshold has an increasing odds ratio with a statistically significant difference.

Red-Flag Methods and Results

For every day in the year preceding death for each case and the matching control subjects, we looked back 2 years and determined if the PDMP record would have revealed a red flag as measured by any, or a combination of the following criteria. Given the NARxCHECK Narcotic Score evaluates two years of data incorporating both opioid and sedative medications, these criteria, although based on the literature references above, were slightly modified for similar drug type and timeframe.

- ≥ 5 opioid or sedative providers in any year in the last 2 years
- ≥ 4 opioid or sedative dispensing pharmacies in any 90 day period in the last 2 years
- > 100 MME total and 40 MME/day average

In Table 3, we calculated the OR for each individual red flag and for combinations of red flags using the following as reference values:

- 0 – 100 MME total in the last 2 years (reference 1)
- Maximum of 1 pharmacy in the last 2 years (reference 2)
- Maximum of 1 prescriber in the last 2 years (reference 3)

Additionally, in Table 4, we compare to the NARxCHECK Narcotic Score for equivalent numbers of records both in the reference group and in the Red-Flag group.

Table 3 – "Red Flag" Odds Ratio (OR)

Risk Indicator	Living	Deceased	OR
Reference 1	82,434	148	
≥ 40 MME/day avg (A)	29,949	845	15.7
Reference 2	107,176	289	
≥ 4 Pharmacies in 90d (B)	6,434	477	27.5
Reference 3	87,202	182	
≥ 5 Providers in 1yr (C)	19,680	771	18.8
Reference 1, 2	75,763	99	
A and B	3,335	280	64.3
Reference 1, 2, 3	71,576	86	
A, B, and C	2,282	225	82.1

Table 4 – "Red Flag" OR Compared to NARxCHECK Narcotic Score Using Equivalent Populations

	Red-Flag Results			NARxCHECK Narcotic Score ≥ 650			
	Living	Deceased	OR	Living	Deceased	OR	P Value
Reference 1, 2, 3	71,576	86		71,591	77		Not Statistically Different
A, B, and C	2,282	225	82.1	2,308	199	80.2	

Table 4 shows that when the multivariable Red-Flag results are compared with NARxCHECK Narcotic Scores for equivalent population sizes, there is no statistically significant difference between the two approaches. Equivalent population methodology dictates that in this case, the 71,662 patients with the lowest Narx Scores are used for the reference population and the 2,507 patients with the highest Narx Scores are used for the exposed population.

Discussion

Prescribers and pharmacists are increasing their use of PDMP data as a tool for clinical decision support. In some cases, the driver is self-motivation and in other cases, regulatory compliance. Regardless of the reason, the assumption is that PDMP data will better inform users of the risks and benefits of beginning, modifying, or stopping the use of controlled substances. However, the use of PDMP data is not straightforward. Paulozzi, et al., perhaps said it best:

> *"Providers are now increasingly being warned about the hazards of prescribing controlled substances, especially opioid analgesics, and are cautioned about overestimating their benefits. Without better risk information, however, providers have difficulty identifying the highest-risk patients and making risk–benefit calculations when prescribing such drugs.Similarly, health plan managers, prescription drug monitoring programs, and insurers do not have validated "flags" to identify patients who are at high risk of serious outcomes such as overdoses and therefore might benefit from special interventions such as management by a pain specialist, restriction to single providers, and/or referral to substance abuse treatment."*

For this study, we obtained a large collection of overdose death data on patients who had a PDMP record at some point in time prior to their death and then retrospectively evaluated two different approaches to assessing risk. Although somewhat artificial in practice, our study assumes that a provider could evaluate a PDMP report or a NARxCHECK Report every day for one year for a patient of interest.

When using a NARxCHECK Report with an automatically calculated NARxCHECK Narcotic Score, the 3-digit score itself acts as the risk indicator. When using a generic PDMP report, the provider is required to find, compute, and assess the average morphine equivalent dose, prescriber, and pharmacy red flag variables from the raw prescription data.

We found Narcotic Scores at a level of 650 and above are similar at grading risk to a red-flag approach that uses all three studied risk factors. However, the red-flag approach does not provide the granularity of a multi-dimensional index, and both above and below a narcotic score of 650, the NARxCHECK Narcotic Score continues to predict risk with a continuously higher OR. At the same time, it seems intuitive to declare that an automatically provided NARxCHECK Narcotic Score is much easier to evaluate as compared with the determination of multiple red flags.

We also found that as NARxCHECK Narcotic Scores increased, so did risk. Stated differently, there is a statistically significant continuum of risk represented within the range of NARxCHECK Narcotic Scores. We did find that the risk temporarily plateaued in the range of 200 – 400 but in general, as a patient's NARxCHECK Narcotic Score increased, so did their risk, especially in the upper ranges.

This differs significantly from a red-flag approach wherein patients accumulate a red flag when they pass a threshold and then do not get further refined. This is a substantial limitation of all red-flag approaches. For instance, taking the red flag of 40 MME/day average, if we have two patients above that threshold we have little ability to determine how much extra risk someone with 80 MME/day average has beyond that of a patient with 40 MME/day average.

Limitations

There are several important limitations of this study. The overdose death data doesn't represent all overdose deaths in the State of Ohio in 2014. The data used for this study was therefore a sampling, albeit a large sampling, and we did not have any control over the determination of overdose death as it was provided by the ODOH. It is possible that sampling errors upstream skewed our results.

Another limitation is that we chose one red-flag strategy amongst many that are recommended. Alternative red-flag strategies may have resulted in better OR calculations. Notably, even in that setting it seems obvious that any strategy that is more complicated than looking at an automatically provided 3 digit score will be more time consuming to execute or apply.

Conflict of Interest Statement

This research was accomplished in collaboration with the Ohio Automated Rx Reporting System (OARRS), who independently provided the PMP data and the hashed patient ID overdose death data. Authors Huizenga and Breneman are paid consultants to Appriss and are previous owners of NARxCHECK with a vested interest in the product. Authors Speights, Raz, and Patel provided statistical support and are employees of The Retail Equation, a company acquired by Appriss. This research was conducted using rigorous methods and protocols consistent with other published research in the field of prescription drug abuse. The raw data used to generate the calculations can be made available for independent verification of the results. Requests for the raw data can be submitted to Carl Flansbaum, RPh. at cflansbaum@appriss.com.

Summary

This study found that NARxCHECK Narcotic Scores are an effective determinant of risk of unintentional overdose death. The NARxCHECK Narcotic Score provides a granular continuum of risk with increasing odds ratios as the score increases, and is statistically as effective as a multi-variable red-flag approach. At the same time, the NARxCHECK Narcotic Score is intuitively much quicker and easier to use for clinical decision support.

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