Use of Natural Language Processing Text-Mining to Identify Differences in the OVERDOSAGE Section of Drug Labeling

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Abstract

Background: The OVERDOSAGE section of labeling of different drugs with the same active ingredient typically have similar language. However, sometimes there are differences in the content of the OVERDOSAGE section of labeling for drugs with the same active ingredient (e.g., due to differences in the conditions of use of the drugs). A manual review of the OVERDOSAGE section of labeling for a specific active ingredient to identify differences may be labor intensive. Natural Language Processing (NLP) text mining tools may facilitate the process of identifying similarities and differences in the OVERDOSAGE section of labeling with drugs with the same active ingredient. **Purpose:** Perform a test case to evaluate the ability of an automated NLP text mining tool to search a labeling database, identify and extract targeted information from the OVERDOSAGE section of labeling, generate structured output, and analyze for similarities and differences in the wording in the OVERDOSAGE section of labeling for a specific active ingredient. **Methodology:** A query was developed using the text-mining platform, Linguamatics. The query searched the OVERDOSAGE section of drug labeling with the same active ingredient (identified by its Unique Ingredient Identifier (UNII)) using structured product labeling files in DailyMed. Subsequently, the wording in the OVERDOSAGE section of the labeling for this active ingredient was searched and analyzed for similarities and differences. **Results:** The query retrieved 48 different labeling [Physician Labeling Rule (PLR) format and non-PLR format labeling] for drugs with the active ingredient including 38 fixed combination drug products (containing the active ingredient and at least one additional active ingredient) and 10 single ingredient products. Among 48 labeling, 17% were for prescription drugs approved under New Drug Applications (NDAs) and 83% were for prescription generic drugs approved under Abbreviated New Drug Applications (ANDAs). Of the 8 labeling under NDAs, 6 had different content in the OVERDOSAGE section. Of the 40 labeling under ANDAs (generic drug labeling), there were two sets of labeling with different content in the OVERDOSAGE section. **Conclusions:** Natural Language Processing text mining can be used to query labeling in DailyMed and identify the differences in the OVERDOSAGE section labeling for a specific active ingredient.

Introduction

- Drug overdosage is the leading cause of injury-related deaths in the United States, surpassing deaths from motor vehicle accidents and homicides over the past two decades.[1,2]
- According to Food and Drug Administration (FDA) regulations, the OVERDOSAGE section of labeling for human prescription drugs must include: signs, symptoms, laboratory findings, and complications of overdosage; drug concentration associated with toxicity; amount of drug associated with overdosage and the amount of drug that is likely to be life-threatening; dialyzable information; and recommended overdosage treatment.[3]
- FDA regulations require that the OVERDOSAGE section of labeling is updated when new information becomes available that causes the labeling to be inaccurate, false, or misleading.[4]
- CDER is working to update the OVERDOSAGE section of labeling for drug classes associated with the most fatalities according to National Poison Data System (NPDS) data[5] from the American Association of Poison Control Centers (Fig. 1).
- Natural Language Processing (NLP) text mining can be used to efficiently query labeling in DailyMed and identify the similarities and differences in the OVERDOSAGE section of labeling for a specific active ingredient.

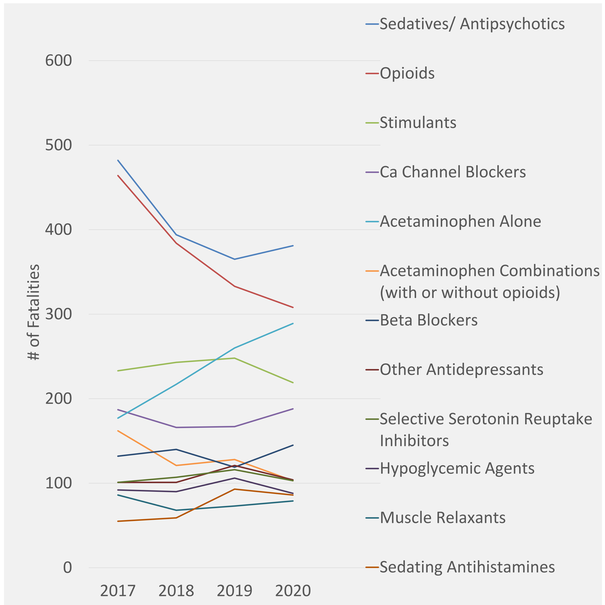

Figure 1. Drug Classes Associated with the Highest Number of Overdosage Fatalities (reported by the NPDS)

Materials and Methods

- A machine learning based NLP text-mining platform, Linguamatics, was used to query structured product labeling files in the *National Institutes of Health's* (*NIH*) DailyMed labeling database.
- For one active ingredient (i.e., active ingredient X) within the drug class listed above, the query extracted all the labeling in the drug class by using active ingredient X's Unique Ingredient Identifier (UNII).
- For each identified labeling, the wording in the OVERDOSAGE section of the labeling was extracted (Fig. 2) and then reviewed manually for similarities and differences.

Results and Discussion

- The query generated a structured output tabulating the drug name(s), dosage form(s), strength(s), marketing category (e.g., NDA, ANDA), application number(s), and date that the OVERDOSAGE section was updated. (Fig. 3)
- The query retrieved 48 different labeling [Physician Labeling Rule (PLR) format and non-PLR format labeling] containing active ingredient X (associated with 86 application numbers); of the 48 labeling, 38 were fixed combination drug products (active ingredient X and Y) and 10 were single ingredient products (active ingredient X).

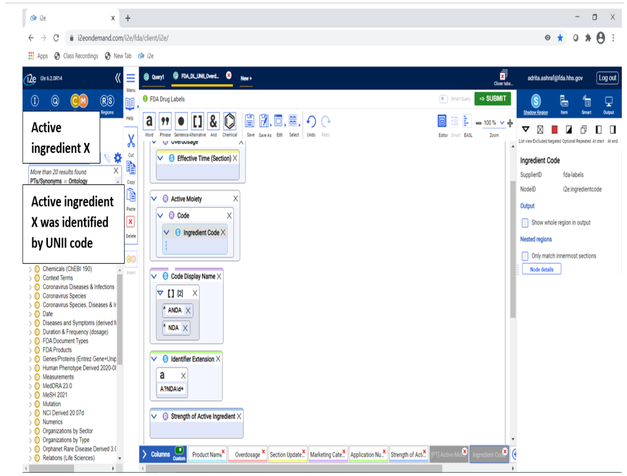

Figure 2. Linguamatics Query to Extract Wording in the OVERDOSAGE Section for Labeling with Active Ingredient X.

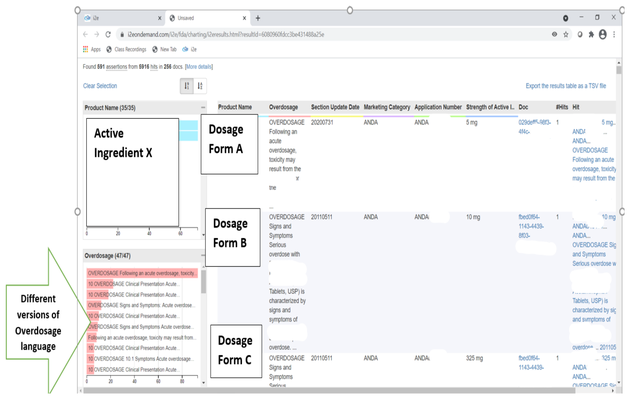

Figure 3. Linguamatics Output – List of Labeling with Different Wording in the OVERDOSAGE Section for Active Ingredient X.

- Among these 48 labeling, 17% were for prescription drugs approved under New Drug Applications (NDAs) and 83% were for prescription generic drugs approved under Abbreviated New Drug Applications (ANDAs).
- Of the 8 labeling under NDAs, 6 had some differences in content in the OVERDOSAGE section due to different conditions of use of the drugs.
- Of the 40 labeling under ANDAs (generic drug labeling) one set of labeling (n=31 labeling) had some differences in content in the OVERDOSAGE section than another set of labeling (n=9 labeling) (the two sets of labeling were for two different dosage forms).
- Additional query and algorithm development may further reduce the manual component of these analyses.

Table 1. Representative Example of the Similarities and Differences (highlighted in yellow) Between Two OVERDOSAGE Sections of Labeling for Drugs with Active Ingredient X (drug names were redacted).

10 OVERDOSAGE	10 OVERDOSAGE
Clinical Presentation Acute overdosage with can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and, in some cases, pulmonary edema, bradycardia, QT prolongation, hypotension, partial or complete airway obstruction, atypical snoring, seizures, and death. Marked rather than may be seen with hypoxia in overdose situations. Deaths due to overdose have been reported with abuse and misuse of *[see WARNINGS AND PRECAUTIONS (5.1), DRUG ABUSE AND DEPENDENCE (9.2)]*. Review of case reports has indicated that the risk of fatal overdose is further increased when is abused concurrently with alcohol or other , including other . Treatment of Overdose In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or serious arrhythmias will require advanced life support measures. The antagonists, are specific antidotes to respiratory depression resulting from For clinically significant respiratory or circulatory depression secondary to overdose, administer . should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to overdose. While will reverse some, but not all, symptoms caused by overdosage with , the risk of seizures is also increased with administration. In animals, convulsions following the administration of toxic doses of could be suppressed with but were increased with . administration did not change the lethality of an overdose in mice. Hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period. Because the duration of reversal is expected to be less than the duration of action of in , carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information. In an individual physically dependent on , administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.	Clinical Presentation Acute overdose with can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, , and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked rather than may be seen with hypoxia in overdose situations *[see CLINICAL PHARMACOLOGY (12.2)]*. Treatment of Overdose Give primary attention to the reestablishment of a patent airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques. Once stable, examine the patient and ensure that all have been removed. The antagonists, such as , are specific antidotes to respiratory depression resulting from For clinically significant respiratory or circulatory depression secondary to overdose, administer . should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to overdose. Because the duration of reversal is expected to be less than the duration of action of carefully monitor the patient until spontaneous respiration is reliably reestablished. After system removal, serum concentrations decline gradually, falling about 50% in approximately 20–27 hours. Therefore, management of an overdose must be monitored accordingly, at least 72 to 96 hours beyond the overdose. In an individual physically dependent on administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

Conclusion

Natural Language Processing text mining can be used to efficiently query labeling in DailyMed and identify the similarities and differences in the content of the OVERDOSAGE section labeling for a specific active ingredient.

References

1. Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). Compressed mortality file 1979–1998. CDC WONDER on-line database, compiled from compressed mortality file CMF 1968–1988, Series 20, No. 2A, 2000 and CMF 1989–1998, Series 20, No. 2E, 2003.

2. Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). Underlying cause of death 1999–2016 on CDC WONDER online database, released December, 2017. Data are from the Multiple Cause of Death Files, 1999–2016, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program.

3. Code of Federal Regulations - 21 CFR 201.57(c)(11): https://www.ecfr.gov/cgi-bin/text-idx?SID=50438b5cc7161b2bd5102ff1abb9fb4f&mc=true&node=se21.4.201_157&rgn=div8

4. Code of Federal Regulations - 21 CFR 201.56(a)(2): https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=f06bb31d261a75f91e9fb5264da0e2fe&mc=true&n=sp21.4.201.b&r=SUBPART&ty=HTML#se21.4.201_156

5. National Poison Data System Annual Reports - Table 18. Categories Associated with Largest Number of Fatalities: https://www.npds.us/Reports

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