Comparison of Linguamatics and FDALabel Natural Language Processing Text-Mining to Identify Information in the OVERDOSAGE Section of Tramadol Drug Labels

Ihechiluru Nzeako, MD[1,2]; Keith Burkhart, MD[1]

U.S. Food and Drug Administration/CDER/OTS/OCP/Division of Applied Regulatory Science, Silver Spring, MD; [2]Oak Ridge Institute for Science and Education, Oak Ridge, TN.

Abstract

Background: The OVERDOSAGE section of prescription drug labels require analysis for outdated information that may be inaccurate or misleading. Prescription drug labels containing the same active ingredient in the same formulation should be identical. Natural language processing (NLP) text-mining can be used to efficiently query labeling to identify differences. **Purpose:** Perform a comparison of results extracted through text-mining, using Linguamatics and FDALabel, to search DailyMed for targeted information in the OVERDOSAGE section of tramadol drug labeling. Identify differences among labeling versions. **Methodology:** The OVERDOSAGE sections of tramadol drug labeling was extracted using a custom query in Linguamatics, an NLP text-mining tool. Using the unique ingredient identifier (UNII) code, the query was able to identify drugs with the same active ingredient. The results were then compared to a search of the OVERDOSAGE sections of tramadol drug labeling performed on FDALabel. Labeling was then manually analyzed for differences. **Results:** The query in Linguamatics, retrieved 237 drug labeling, under 30 drug application numbers; seven (23%) drugs are New Drug Application(s) (NDA); 23 (77%) are generic drugs approved under an Abbreviated New Drug Application(s) (ANDA). Results retrieved using the FDALabel platform are identical. Depending on the link re-packagers use for labeling, a single drug application number may appear multiple times with different labeling versions (ex. ANDA201384), others may appear with the same labeling (ex. ANDA200503). Four different versions of the OVERDOSAGE section were identified for tramadol NDAs. Clinical manifestations were similar across versions. However, two (50%) versions did not mention seizures, one (25%) did not mention QT prolongation, and only three (75%) discussed increased risk of fatal overdose with co-ingestants. Management was also similar. However, one (25%) version mentioned the use of nalmefene, three (75%) discussed monitoring patients for spontaneous respiration, potential need of additional administration of antagonist, and management of opioid dependent individuals. **Conclusions:** Linguamatics and FDALabel natural language processing text-mining efficiently extracted identical information of the OVERDOSAGE sections of tramadol drug labeling. Depending on the product selected, a search on DailyMed may not provide the most up to date labeling. This is due to re-packagers not linking the most recent labeling version.

Introduction

- In the United States, drug overdose continues to be a leading cause of injury related deaths, with an increase of 31% in 2020, compared to the year prior. [1, 2]
- FDA regulations requires that CDER updates outdated information in the OVERDOSAGE section. [3] Prescription drug labeling that contain the same active ingredient in the same formulation should be identical.
- Linguamatics and FDALabels are two Natural Language Processing (NLP) text mining platforms that can be used to query labeling in DailyMed. Manual analysis identifies the similarities and differences.

Disclaimer: This poster reflects the views of the authors and should not be construed to represent the FDA's views or policies.

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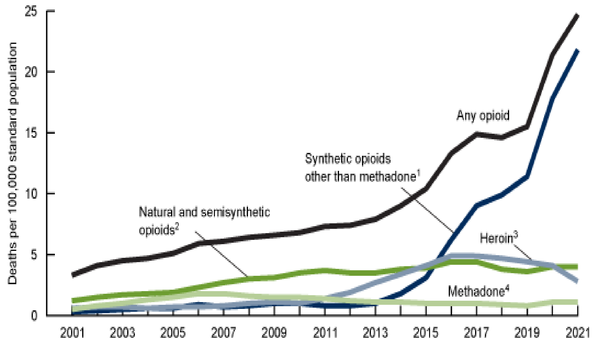

Figure 1. Rate of drug overdose deaths involving opioids, by type of opioid: United States, 2001–2021

Materials and Methods

- A custom query in Linguamatics, a machine learning based NLP text-mining platform, was used to extract the OVERDOSAGE section of tramadol drug labeling in the *National Institutes of Health's (NIH)* DailyMed labeling database (Fig. 2).
- Using the active ingredient's Unique Identifier (UNII) for the drug class, the query was able to extract all the labeling in the drug class, on December 1st 2022.
- The language of the labeling are then manually analyzed for their differences.
- FDALabel was used to extract the OVERDOSAGE section of tramadol.
- Results from FDALabel were then compared to results retrieved through Linguamatics.

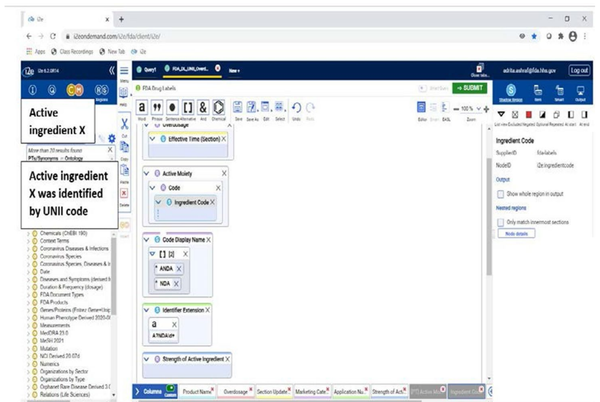

Figure 2. Linguamatics Query Used to Extract Wording in the OVERDOSAGE Section for Labeling with Active Ingredient tramadol.

Results and Discussion

- The query retrieved 237 labels on both the Linguamatics and FDALabel platforms under 30 drug application numbers; seven (23%) drugs are New Drug Application(s) (NDA); 23 (77%) are generic drugs approved under an Abbreviated New Drug Application(s) (ANDA) (Fig. 3).
- Among Tramadol NDAs four versions of the OVERDOSAGE section were identified.
  1. Clinical manifestations were similar across versions. However, two (50%) did not mention seizures, one (25%) did not mention QT prolongation, and only three (75%) discussed increased risk of fatal overdose with co-ingestants.
  2. Management was also similar. However, one (25%) version mentioned the use of nalmefene, three (75%) discussed monitoring patients for spontaneous respiration, potential need of additional administration of antagonist, and management of opioid dependent individuals.
- Preliminary analysis suggests that some re-packagers may not be referencing the latest labeling versions.[5]
- Depending on the link re-packagers use for labeling, a single drug application number may appear multiple times with different labeling versions (ex. ANDA201384), others may appear with the same labeling (ex. ANDA200503).
- Results from Linguamatics and FDALabel were identical.

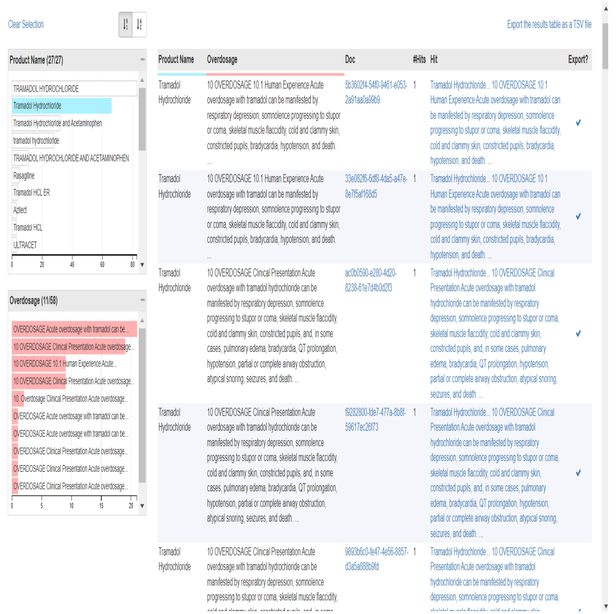

Figure 3. Linguamatics Output – List of Labeling with Different Wording in the OVERDOSAGE Section of Active Ingredient X

Table 1. Representative Example of the Similarities and Differences (Color-coordinated) Between Two OVERDOSAGE Sections of Labeling for Amphetamine.

39	1
Clinical Presentation paragraph ID (.id0343) Acute overdosage with tramadol hydrochloride extended-release tablets can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, QT prolongation, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations [see Clinical Pharmacology (12.2)] . Treatment of Overdose In case of overdose, priorities are the reestablishment 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 arrhythmias will require advanced life-support techniques. Opioid antagonists, such as naloxone,, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to opioid overdose, administer an opioid antagonist. While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. In animals, convulsions following the administration of toxic doses of tramadol hydrochloride extended-release tablets could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone 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 opioid reversal is expected to be less than the duration of action of tramadol in tramadol hydrochloride extended-release tablets, carefully monitor the patient until spontaneous respiration is reliably reestablished. Tramadol hydrochloride extended-release tablets will continue to release tramadol and add to the tramadol load for 24 to 48 hours or longer following ingestion, necessitating prolonged monitoring. If the response to an opioid 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 opioids, 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 physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.	Acute overdosage with tramadol can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension and death. Death due to overdose have been reported with abuse and misuse of tramadol, by ingesting, inhaling, or injecting the crushed tablets. The risk of fatal overdose is further increased when tramadol is abused concurrently with alcohol and other CNS depressants, including other opioids. In the treatment of tramadol overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. While naloxone will reverse some (but not all) symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. In animals, convulsions following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone 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.

Conclusion

- Linguamatics and FDALabel NLP text-mining was able to efficiently extract identical content from the OVERDOSAGE section of tramadol drug labeling for manual analysis.
- Manual review identified differences across tramadol labeling, which provided opportunities for harmonization.
- Re-packagers may not always contain the most up to date label version.

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