Overview of the DMI2EpiTool and Polydrug Poisoning Classification Framework

In 2016, Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS), in collaboration with the U.S. Food and Drug Administration (FDA), developed a methodology for analysis of literal text on U.S. electronic death certificates to identify specific drugs mentioned with involvement (DMI) in drug poisoning (overdose) deaths.[1] The DMI methodology uses a drug search term list (including drug names, metabolites, and misspellings cross-walked to generic drug names) and contextual phrases to capture specific drugs identified by medical examiners/coroners as contributing to drug poisoning deaths. Building on the DMI methodology, we developed the DMI2EpiTool: an analytical tool that can be used by surveillance epidemiologists and researchers to identify drugs contributing to drug poisoning deaths and classify drug poisoning deaths as single- versus polydrug poisoning deaths using the literal text on the death certificate.

Herein we describe the updates made to the original NCHS search term list[2] used to identify drugs involved in drug poisoning deaths and the framework developed to classify deaths as single versus polydrug-involved.

I. Search Term Updates

The original NCHS search term list and DMI methodology did not recognize dashes and digits in search terms. Updated programming in the DMI2EpiTool allows for identification of terms that include these characters. Additionally, new search terms were identified for inclusion in the search term list using natural language processing.[3]

II. Search Term Mapping

Individual search terms were mapped to common drug/substance/class name (i.e., *Principal Variant* as originally described by Trinidad)[1]. In general, the principal variant represents the generic drug name or recognized chemical name. Search terms for combination products are mapped to principal variants for each component in the product (e.g., PERCOCET maps to both OXYCODONE and ACETAMINOPHEN principal variants). In some cases, the literal text search term is so fragmented or misspelled that it is impossible to accurately determine which drug/substance principal variant it represents (e.g., TETRAHYDRO, OXYM). In these cases, search terms are mapped to 'UNKNOWN' principal variant. In

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[1] Trinidad JP, Warner M, Bastian BA, Minino AM, Hedegaard H. Using Literal Text From the Death Certificate to Enhance Mortality Statistics: Characterizing Drug Involvement in Deaths. *Natl Vital Stat Rep*. Dec 2016;65(9):1-15.

[2] https://github.com/CDCgov/National-Vital-Statistics-Mortality-Data

[3] Ward, P.J., Young, A.M., Slavova, S., Liford, M., Daniels, L., Lucas, R., Kavuluru, R., 2023. Deep Neural Networks for Fine-Grained Surveillance of Overdose Mortality. *American journal of epidemiology* 192(2), 257-266.

other cases, the search term might be mapped to two or more drug/substance principal variants (e.g.,CLOZOPAM could map to CLONAZEPAM or CLONAZOLAM). In the cases where the potential drug/substance principal variants are within the same class (as with the previous example) then the search term is mapped at the class level (e.g., BENZODIAZEPINE). In the cases where the search term could map to a drug/substance in different class, the term is flagged as 'AMBIGUOUS' and prompts for manual review after running the DMI2EpiTool program.

III. Non-drug Search Terms Flagged

The original NCHS search term list includes terms and principal variants for many substances that are not considered drugs (i.e., are not active pharmaceutical ingredients; tobacco, pesticides, refrigerants, etc.). For the purposes of polydrug poisoning classification, these terms are flagged for exclusion.

IV. Referent Drugs Assigned

The Global Substance Registration System[4] (GSRS) was used to assign referent drug names. Principal variants that are listed as an 'active moiety' in GSRS are assigned as referent drug. Principal variants that are not active moieties (i.e., prodrugs, precursors, contaminants, or metabolites) are assigned to the related active moiety (e.g., NORBUPRENORPHINE is mapped to BUPRENORPHINE).

Drug naming nomenclature is complex, resulting in many different names and synonyms for an individual referent drug. For the purposes of the DMI2EpiTool and polydrug classification framework, we assigned the referent drug name that was the listed name in GSRS (e.g., the referent drug name assigned to 4-ANPP is DESPROPIONYLFENTANYL.)

Some newly identified psychoactive compounds (e.g., synthetic cannabinoids) are listed in the GSRS without an active moiety designation. These compounds have been mapped to their respective pharmacologic class until they are updated as active moieties or as having another relationship to an active moiety (i.e, precursor, metabolite, etc. as described above). In rare cases, drug principal variants were not yet listed in GSRS and classification of the drug/substance was unclear; in these cases, the principal variants were assigned as their own referent drugs.

[4] Tyler Peryea, Noel Southall, Mitch Miller, Daniel Katzel, Niko Anderson, Jorge Neyra, Sarah Stemann, Đắc-Trung Nguyễn, Dammika Amugoda, Archana Newatia, Ramez Ghazzaoui, Elaine Johanson, Herman Diederik, Larry Callahan, Frank Switzer, Global Substance Registration System: consistent scientific descriptions for substances related to health, *Nucleic Acids Research*, Volume 49, Issue D1, 8 January 2021, Pages D1179–D1185, https://doi.org/10.1093/nar/gkaa962

Finally, in some cases, search terms are not specific to an individual drug, but rather the literal text on the death certificate refers to a drug class (e.g., opioid) or is non-specific (drug intoxication, polydrug intoxication). In these situations, for the purposes of polydrug poisoning classification, the referent drug is the drug class, or non-specific term.

V. Classification of Single vs. Polydrug Poisoning

Single-substance drug poisoning
Death caused by drug poisoning with exactly one referent drug.

Poly-substance drug poisoning
Death caused by drug poisoning with more than one referent drug.

VI. Future Programming

For the purposes of drug poisoning surveillance, it's important to understand the complex relationships between referent drugs. In some cases, an active moiety referent drug is also a metabolite or precursor of another referent drug (e.g., NORFENTANYL is a metabolite of FENTANYL; AMPHETAMINE is a metabolite of METHAMPHETAMINE). As these are all considered individual referent drugs by our classification framework, deaths involving AMPHETAMINE and METHAMPHETAMINE will be classified as polydrug poisoning deaths. Future programming will flag these and numerous other referent drug characteristics (e.g., drug classification, associated ICD-10 drug poisoning codes) to assist epidemiologists and researchers in identifying these nuances and allowing analyses to be conducted at varying levels (drug class vs. individual referent drug).

Questions can be sent to DMI2EpiTool@uky.edu