



Recap On InfoMedEx



What is InfoMedEx?

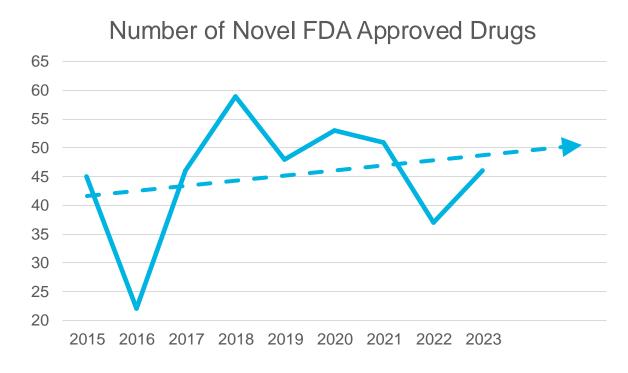
Al models to predict drug-drug interactions

- Deep learning models
- Given two drug (e.g. Aspirin and Warfarin) predict the interaction for reports or be provided by an API to other companies
 - Aspirin may increase the anticoagulant activities of Warfarin.



Why Develop InfoMedEx?

- Allows us to quickly add new drugs to our reports; onboard new assays
- Applications in drug development
- Develop IP and display technical expertise to investors





Interactions between your drugs

Moderate Applies t

Applies to: aprepitant, cariprazine

MONITOR: Coadministration with moderate inhibitors of CYP450 3A4 may increase the plasma concentrations of cariprazine and its major active metabolite, didesmethyl cariprazine (DDCAR), both of which are primarily metabolized by the isoenzyme. When cariprazine (0.5 mg/day) was coadministered with the potent CYP450 3A4 inhibitor, ketoconazole (400 mg/day), cariprazine peak plasma concentration (Cmax) and systemic exposure (AUC) increased by approximately 3.5- and 4-fold, respectively, while Cmax and AUC of DDCAR increased by approximately 1.5-fold each. The Cmax and AUC of another active metabolite, desmethyl cariprazine (DCAR), decreased by approximately one-third. The extent to which other, less potent inhibitors of CYP450 3A4 may interact with cariprazine and its metabolites is unknown.

MANAGEMENT: Caution is advised when cariprazine is prescribed with moderate CYP450 3A4 inhibitors. Patients should be monitored for adverse effects such as extrapyramidal symptoms, cognitive and motor impairment, hyperglycemia, dyslipidemia, weight gain, orthostatic hypotension, leukopenia, neutropenia, seizures and dysphagia, and the dosage of cariprazine adjusted as necessary in accordance with the product labeling.

References

1. "Product Information. Vraylar (cariprazine)." Actavis Pharma, Inc. (2015):

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VRAYLAR safely and effectively. See full prescribing information for VRAYLAR.

VRAYLAR™ (cariprazine) capsules, for oral use Initial U.S. Approval: XXXX

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.
- VRAYLAR is not approved for the treatment of patients with dementia-related psychosis. (5.1)

-----INDICATIONS AND USAGE--

VRAYLAR is an atypical antipsychotic indicated for the:

- Treatment of schizophrenia (1)
- Acute treatment of manic or mixed episodes associated with bipolar I disorder (1)

-- DOSAGE AND ADMINISTRATION-

Administer VRAYLAR once daily with or without food (2)

	Starting Dose	Recommended Dose
Schizophrenia (2.2)	1.5 mg/day	1.5 mg to 6 mg/day
Bipolar Mania (2.3)	1.5 mg/day	3 mg to 6 mg/day

 Doses above 6 mg daily do not confer significant benefit but increased the risk of dose-related adverse reactions.

-----DOSAGE FORMS AND STRENGTHS-----

Capsules: 1.5 mg, 3 mg, 4.5 mg, and 6 mg (3)

-----CONTRAINDICATIONS-----

Known hypersensitivity to VRAYLAR (4)

-- WARNINGS AND PRECAUTIONS--

- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack) (5.2)
- Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring (5.3)
- Tardive Dyskinesia: Discontinue if appropriate (5.4)
- Late-Occurring Adverse Reactions: Because of VRAYLAR's long halflife, monitor for adverse reactions and patient response for several weeks after starting VRAYLAR and with each dosage change (5.5)
- Metabolic Changes: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia and weight gain (5.6)
- Orthostatic Hypotension: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.8)

-----ADVERSE REACTIONS------

Most common adverse reactions (incidence \geq 5% and at least twice the rate of placebo) were (6.1):

- Schizophrenia: extrapyramidal symptoms and akathisia
- Bipolar mania: extrapyramidal symptoms, akathisia, dyspepsia, vomiting, somnolence, and restlessness

To report SUSPECTED ADVERSE REACTIONS, contact Actavis at 1-800-272-5525 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- Strong CYP3A4 inhibitors: reduce VRAYLAR dosage by half (2.4, 7.1)
- CYP3A4 inducers: do not recommend use with VRAYLAR (2.4, 7.1)

-----USE IN SPECIFIC POPULATIONS----

 Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2015

FULL PRESCRIBING INFORMATION: CONTENTS* WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

- 1. INDICATIONS AND USAGE
- 2. DOSAGE AND ADMINISTRATION
 - 2.1 GENERAL DOSING INFORMATION
 - 2.2 SCHIZOPHRENIA
 - 2.3 MANIC OR MIXED EPISODES ASSOCIATED WITH BIPOLAR I DISORDER
 - 2.4 DOSAGE ADJUSTMENTS FOR CYP3 A4 INHIBITORS AND INDUCERS
 - 2.5 TREATMENT DISCONTINUATION
- 3. DOSAGE FORMS AND STRENGTHS
- 4. CONTRAINDICATIONS
- 5. WARNINGS AND PRECAUTIONS
 - 5.1 INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
 - 5.2 CEREBROVASCULAR ADVERSE REACTIONS, INCLUDING STROKE, IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
 - 5.3 NEUROLEPTIC MALICMANT SYMPROME (NMS)

- 8.1 PREGNANCY
- 8.2 LACTATION
- 8.4 PEDIATRIC USE
- 8.5 GERIATRIC USE
- 8.6 HEPATIC IMPAIRMENT
- 8.7 RENAL IMPAIRMENT
- 8.8 SMOKING
- 8.9 OTHER SPECIFIC POPULATIONS

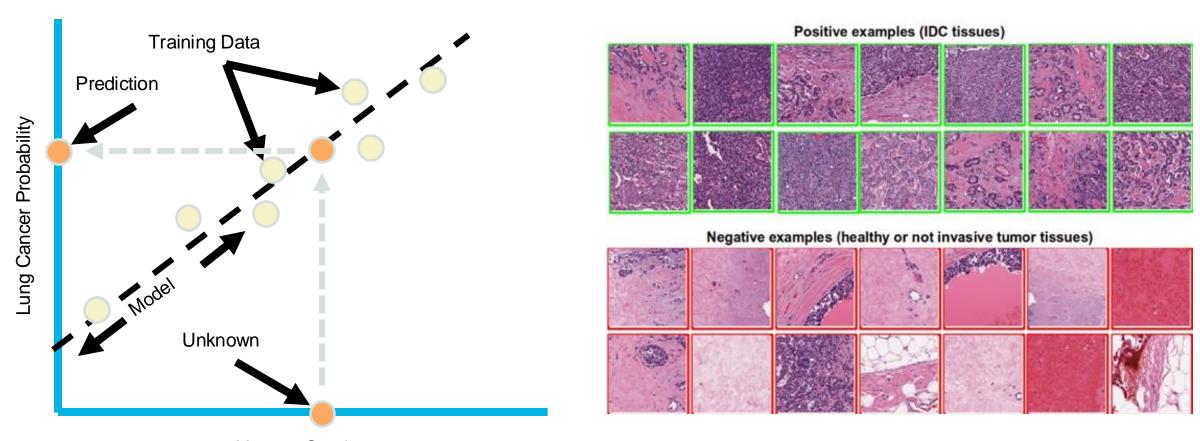
9. DRUG ABUSE AND DEPENDENCE

- 9.1 CONTROLLED SUBSTANCE
- 9.2 ABUSE
- 9.3 DEPENDENCE

10. OVERDOSAGE

- 10.1 HUMAN EXPERIENCE
- 10.2 MANAGEMENT OF OVERDOSAGE
- 11. DESCRIPTION
- 12. CLINICAL PHARMACOLOGY
 - 12.1 MECHANISM OF ACTION

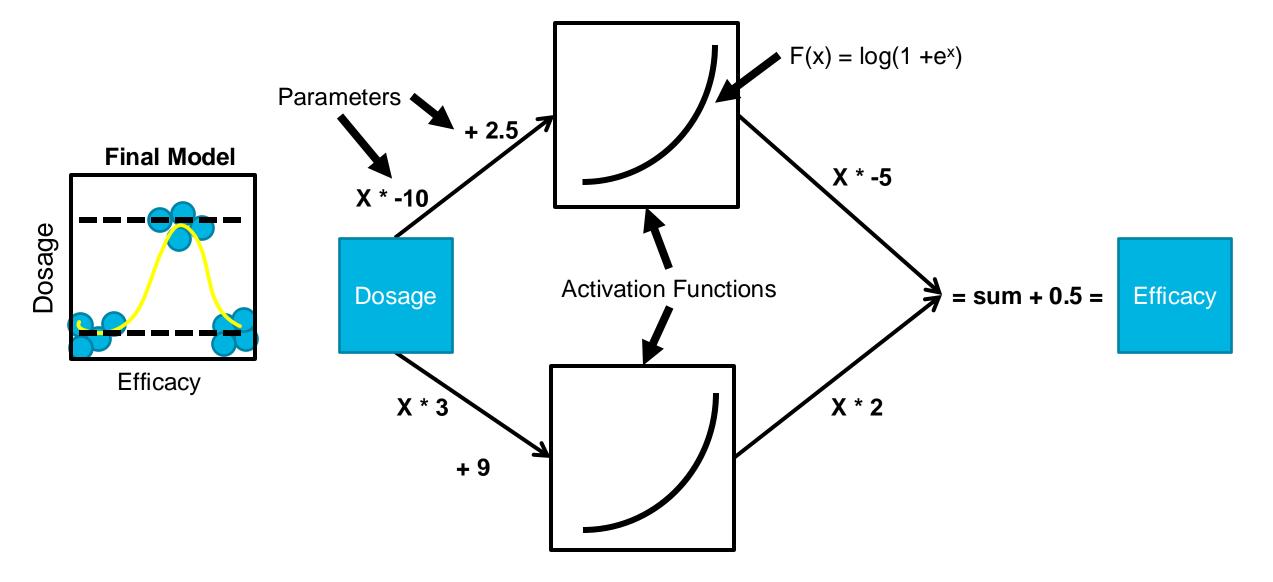
Modeling, Data, Learning







Simple Neural Network



Drug Chemical Structure (SMILES)

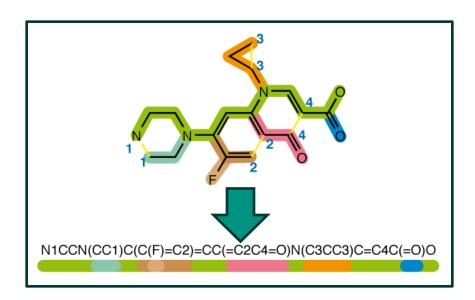
[CH3;!R;C], [C;!R;COO], (, =, [O;!R;C],), [O;!R;CC], [c;R;CCO], 1, [cH;R;CC], [cH;R;CC], [cH;R;CC], 1, [C;!R;COO], (, =, [O;!R;C],), [OH;!R;C]



ML Transformers

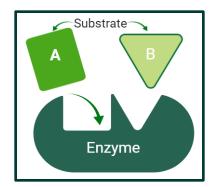
- Chemical structure has its order maintained through a transformer
- Can be trained to emphasize important features of a sentence

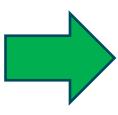


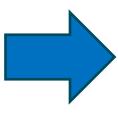




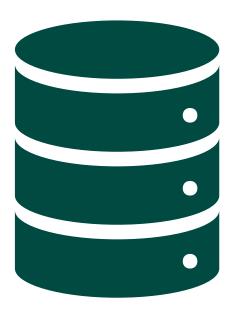
Or Minor/Moderate/Major









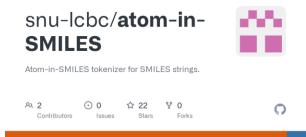


















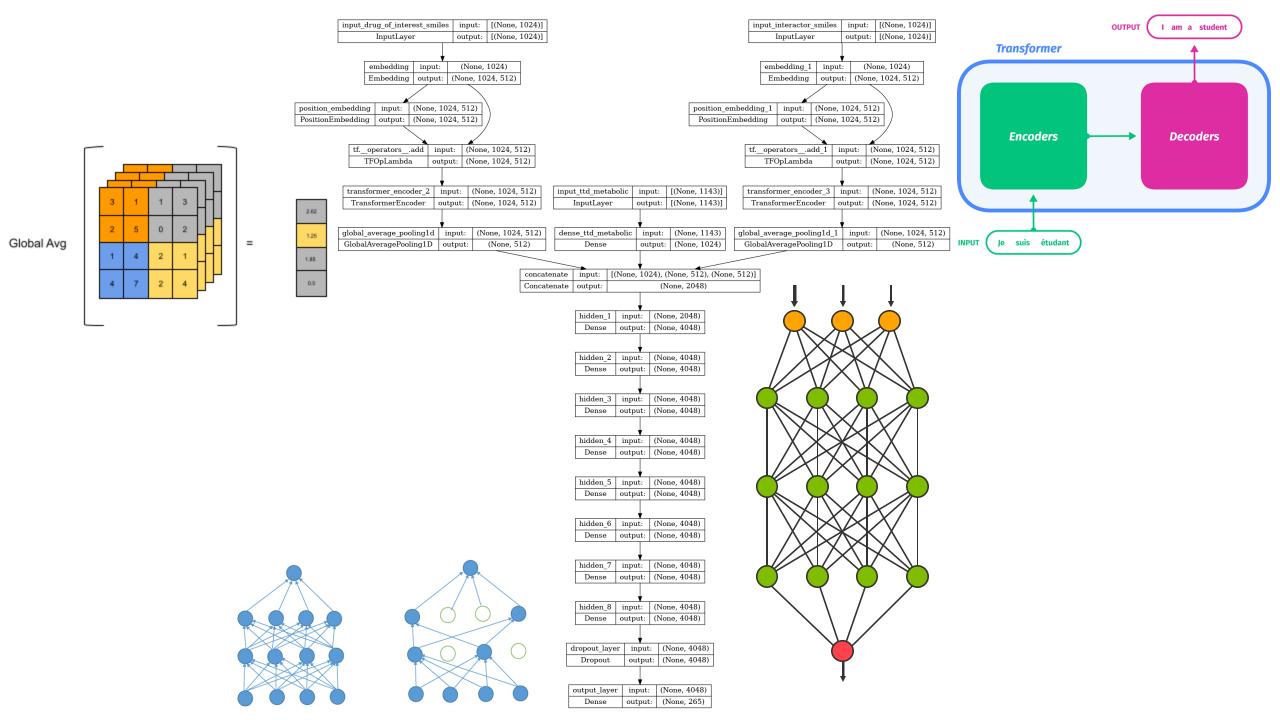
InfoMedEx Model Update

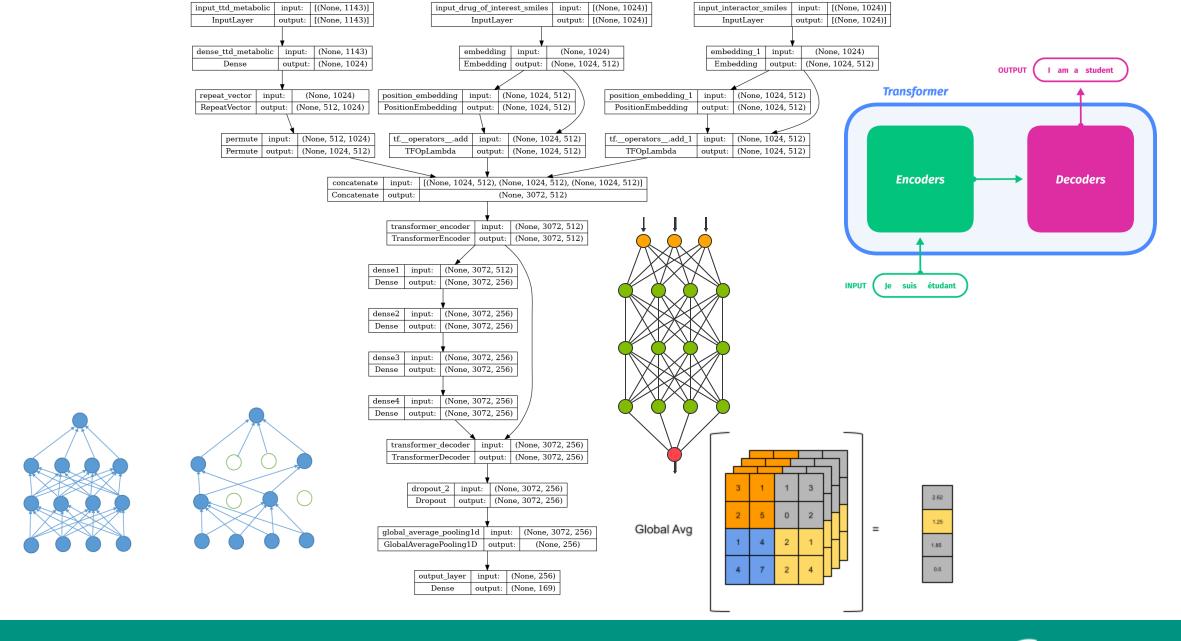


Interaction Type Prediction Model

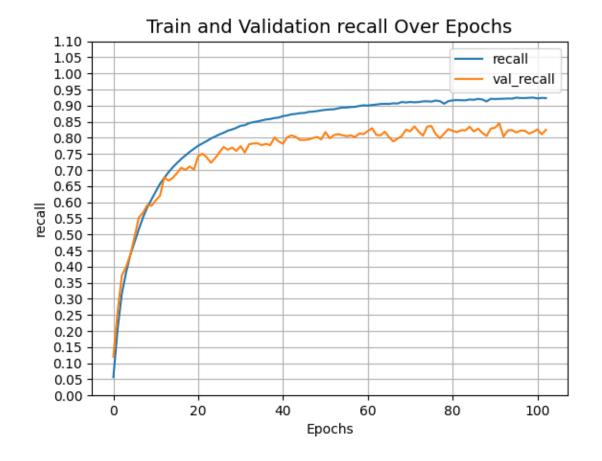
- More accurate, with clear room for improvement
- Includes drugs and interaction types that occur at least 50 times
 - Improved from 100; more types of interactions predicted >160
- Focal Loss
 - Handles class imbalance better, a major challenge we were encountering before
- Adding a dedicated decoder for the transformer encoder
- Trained using 198gb of ram, 48 CPUs, 4 GPUs over 150 hours

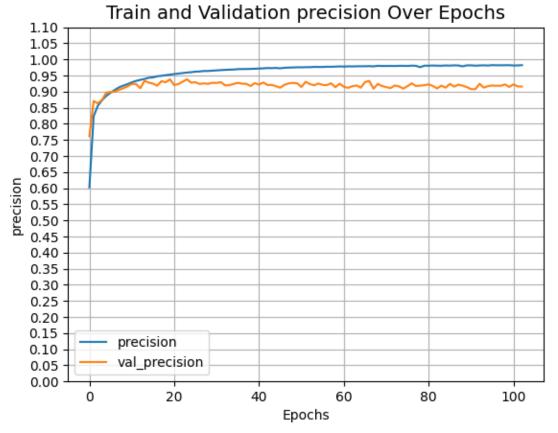




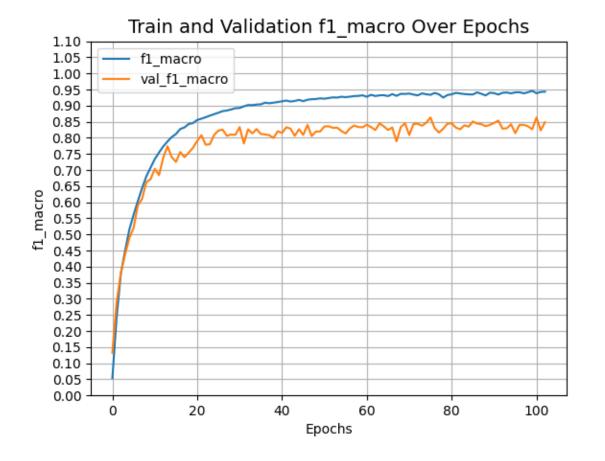


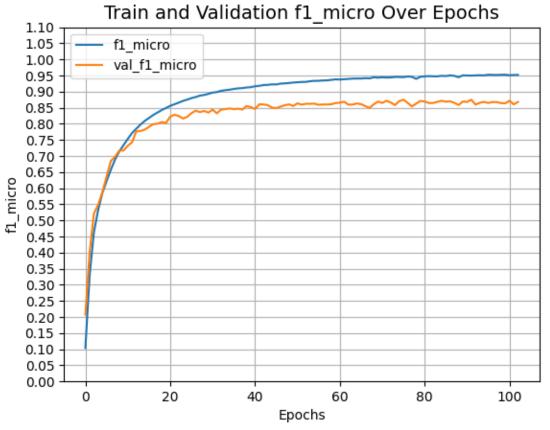




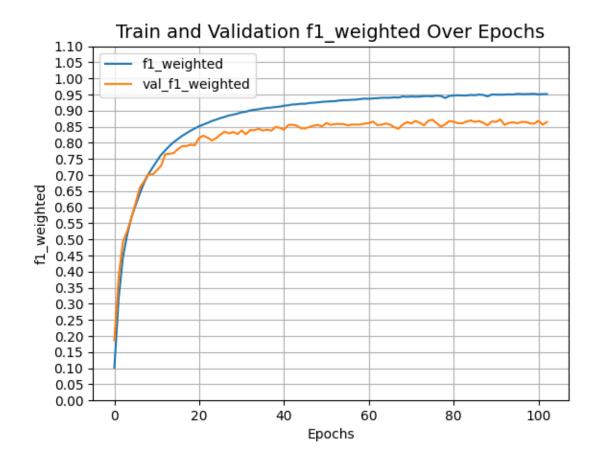


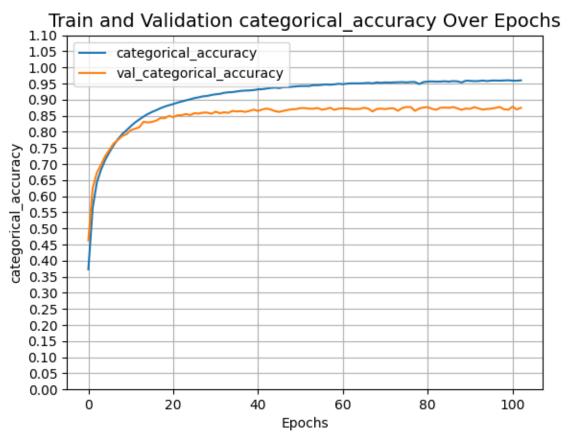














InfoMedEx Databases

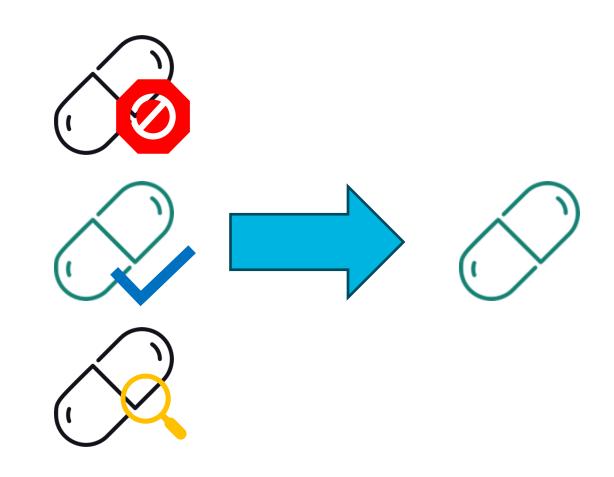


Drug Alternatives Database



Recommending Drug Alternatives

- Database of drugs organized by condition treated, drug type, etc.
 - Antimanic Agents, Antineoplastic Topoisomerase Inhibitors
- If a drug combination has adverse interactions, we can offer an alternative without an interaction from the same class





Drug Alternatives Database

- Pulled from RxList
- 3,605 drugs
- 738 Categories



Condition	Drug
Anxiolytics, Benzodiazepines	Seizalam
Anxiolytics, Benzodiazepines	Tranxene
Anxiolytics, Benzodiazepines	Valium
Anxiolytics, Benzodiazepines	Xanax XR
Anxiolytics, Nonbenzodiazepines	Buspirone
Anxiolytics, Nonbenzodiazepines	dopamine
Anxiolytics, Nonbenzodiazepines	Meprobamate
Anxiolytics, Nonbenzodiazepines	granulocytes
Appetite Stimulants	oxandrolone
Appetite Stimulants	dronabinol
Appetite Stimulants	Megace ES
Appetite Stimulants	Oxandrin
Appetite Stimulants	Marinol
Appetite Stimulants	mirtazapine
Appetite Stimulants	Remeron
Appetite Stimulants	cyproheptadine
augmentin antimicrobial for infections	Amoxicillin
augmentin antimicrobial for infections	Augmentin
B Vitamins	thiamine
B Vitamins	niacin
B Vitamins	pantothenic acid
B Vitamins	biotin



DDI References Database



DDI References Web Scraper

- Code pulls from Google Scholar the 3 most prominent references for a DDI
- Example for Levothyroxine and Ritonavir:
 - Title: Probable interaction between levothyroxine and ritonavir: Case report and literature review
 - Authors: R Sahajpal, RA Ahmed, CA Hughes American Journal of, 2012 - academic.oup.com
 - URL: https://academic.oup.com/ajhp/articleabstract/74/8/587/5103380

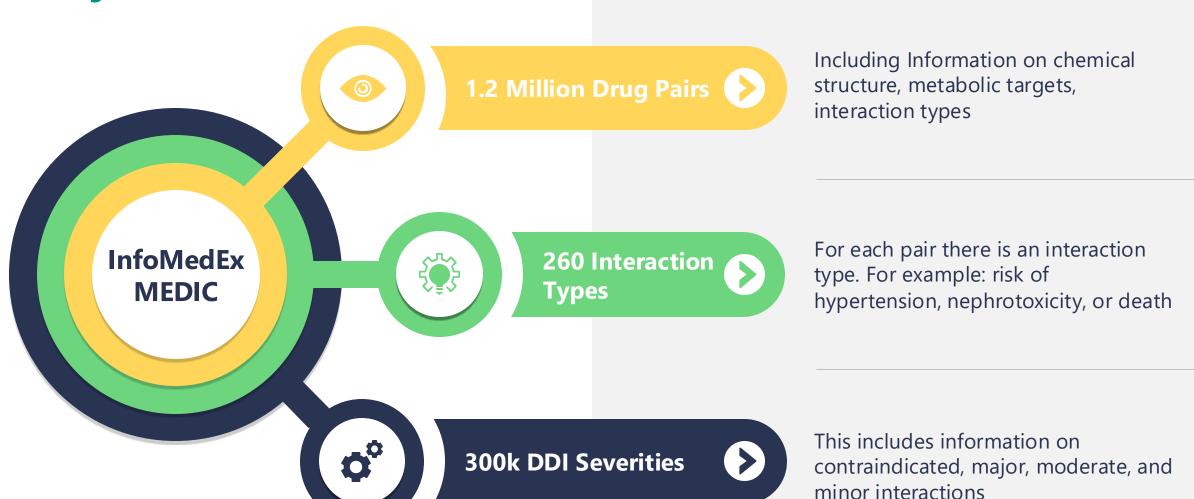


InfoMedEx MEDIC Database

Medical Drug Interaction Compendium



Key Points



Elements In The MEDIC Database

- Drug Of Interest & Interactor
- Interaction Severity Level Number
- Interaction Severity Level Letter
- Severity Based Warning
- DDI Interaction
- DDI Interaction Effect Warning
- DDI References





Severity Warnings

- A: No Interaction. (Not displayed on DDI reports)
- B: Coadministration of Drug 1 and Drug 2 has a low risk of adverse effects in some patients. Consider alternative medications if these effects are unacceptable to the patient.
- C: Coadministration of Drug 1 and Drug 2 has a moderate risk of adverse effects in some patients. Monitor the patient for potential adverse effects and dosage adjustments may be needed.
- D: Coadministration of Drug 1 and Drug 2 has an elevated risk of adverse side effects in some patients. Consider alternative medications or treatment options. If the benefits outweigh the risks steps should be taken to minimize the risks such as close monitoring or empirical dosage adjustments.
- X: Coadministration of Drug 1 and Drug 2 is contraindicated due to the potential for severe health risks. Find alternative medication or treatment options.



Interaction Warnings Language Example

Interaction

 Drug 1 can cause a decrease in the absorption of Drug 2 resulting in a reduced serum concentration and potentially a decrease in efficacy.

Warning

If Drug 1 and Drug 2 are given concomitantly monitor patient for decreased Drug 2 efficacy and adjust dosage according to the drug label or discontinue based on patient response.



Example Implementation Of MEDIC





Precision Genetics

430 Roper Mountain Rd Greenville, SC 29615

PATIENT INFORMATION

SPECIMEN DETAILS

PROVIDER INFORMATION

NAME:

PGXA PGXA-02

DOB:

01/01/2024

SEX:

SAMPLE ID:

PGXA-02

buccal Swab

FACILITY:

PROVIDER:

COLLECTION DATE:

SPECIMEN TYPE:

RECEIVED DATE:

01/26/2024 01/26/2024

REPORT DATE:

02/13/2024

PGx Primary

Current Medication	Selected Medication	Interaction Severity	Interaction	InfoMedEx
Warfarin	Aspirin		Bleeding Risk	
Amlodipine	Aspirin	Q	Hypertension Risk	1

Unrecognized Medications: None

Defined as medications that are not included in the testing database, medications that were misspelled on the Sonic PGx request form, medications that were listed as drug classes instead of individual medications, and/or medications not available in Australia. Some medications use US spelling.

Outside of Scope Medications: None

Defined as those that do not have PGx currently have pharmacogenetic guidance available to report.



Precision Genetics

430 Roper Mountain Rd Greenville, SC 29615

NAME:

PGXA PGXA-02

DOB:

01/01/2024

SEX:

SAMPLE ID:

PGXA-02

PROVIDER:

SPECIMEN TYPE:

buccal Swab

FACILITY:

COLLECTION DATE:

01/26/2024

RECEIVED DATE:

01/26/2024

REPORT DATE:

02/13/2024

PGx Primary			
Med	dication	Interaction Risk Level	Interaction
Current	Aliskiren	X	 Coadministration of Aliskiren and Lisinopril is contraindicated due to the potential for severe health risks. Find alternative medication or treatment options.
		Contraindicated (X)	The risk or severity of hypotension hyperkalemia and nephrotoxicity can be increased when Lisinopril is combined with Aliskiren.
Selected	Lisinopril		 If Aliskiren and Lisinopril are used concomitantly monitor patient for excessive tiredness and fatigue, lightheadedness, syncope, chest pain, heart palpitations, muscle weakness, decreased urination, swelling from fluid retention and high blood pressure.

References:

- Aliskiren FDA Label Information
- · Lisinopril FDA Label Information
- Daugherty, K. K. (2008). Aliskiren. American Journal of
- Health-System Pharmacy, 65(14), 1323-1332.
- Sanoski, C. A. (2009). Aliskiren: an oral direct renin inhibitor for the treatment of hypertension.
 Pharmacotherapy: The Journal of Human
- Pharmacology and Drug Therapy, 29(2), 193-212.
- Pool, J. L. (2007). Direct renin inhibition: focus on aliskiren. *Journal of Managed Care Pharmacy*, *13*(8 Supp B), 21-33.



Precision Genetics

430 Roper Mountain Rd Greenville, SC 29615

NAME:

PGXA PGXA-02

01/01/2024

DOB: SEX: SAMPLE ID:

PGXA-02

PROVIDER:

SPECIMEN TYPE:

buccal Swab

FACILITY:

COLLECTION DATE:

01/26/2024

RECEIVED DATE:

01/26/2024

REPORT DATE:

02/13/2024

PGx Primary			
Medication		Interaction Risk Level	Interaction
Current	Ziprasidone		 Coadministration of Ziprasidone and Lisinopril has a moderate risk of adverse effects in some patients. Monitor the patient for potential adverse effects and dosage adjustments may be needed.
Selected	Lisinopril	Moderate (C)	 Ziprasidone may increase the antihypertensive activities of Lisinopril. If Ziprasidone and Lisinopril are given concomitantly monitor patient for decreased blood pressure and blurry vision, confusion, syncope, dizziness, or trouble concentrating.

References:

- Ziprasidone FDA Label Information
- Lisinopril FDA Label Information
- Buzea, C. A., Dima, L., Correll, C. U., & Manu, P.
 (2022). Drug-drug interactions involving antipsychotics
- and antihypertensives. Expert opinion on drug metabolism & toxicology, 18(4), 285-298.
- Monteith, S., & Glenn, T. (2019). A comparison of potential psychiatric drug interactions from six drug interaction database programs. Psychiatry research,
- 275, 366-372.
- Alpert, J. E. (2015). Drug-drug interactions in psychopharmacology. Massachusetts General Hospital Psychopharmacology and Neurotherapeutics, 113-127.

Balancing Factors In Drug Recommendations



Genotyp	e Risk
Consider Alternatives	3
Use with Caution	2
Standard Precautions	0



DDI Risl	(
Contraindicated	5
Major	3
Moderate	2
Minor	1
No Interaction	0



	<u> </u>	
Previous	Response	
Negative Response	5	
Unknown	0.5	
Positive Response	0	

Best Medication = Minimum(Genotype Risk+ DDI Risk + Previous Response)



Future Work



Future Work

- Collaboration with Clemson-MUSC AI hub
 - Publication field-area expertise
 - Computation resources to continue training
 - Publication
- Model Optimization
- Train severity model using new methods

- Integrate MEDIC database into reports
- Integrate drug alternatives into report workflows
- Resolve ambiguous interactions
 - "Risk of Adverse Side Effects" is most common type of interaction, but is not specific



MEDIC Refinement

- Due to the composite nature of the database, there is some missing information across the 1.2 million DDI pairs
- Resolving this missing information is not only a continuing project, but also a common issue in the field

A comparison of potential psychiatric drug interactions from six drug interaction database programs

```
Scott Monteith <sup>a</sup> A Monteith <sup>a</sup> A Monteith <sup>a</sup> Add to Mendeley A Share Monte Cite

https://doi.org/10.1016/j.psychres.2019.03.041
```

Highlights

- Compared category of potential DDI from 6 drug interaction database programs.
- Searched 100 drug interaction pairs containing psychiatric drugs.
- Overall percent agreement was 66%; overall Fleiss kappa interrater reliability was fair.
- Potential DDI categories from drug interaction database programs often differ.



MEDIC Refinement

- Resolve missing severity information
- Use new versions of databases to improve training
 - Less gaps, more information
- Can be helped by applying the next project

JOURNAL ARTICLE

DrugBank 6.0: the DrugBank Knowledgebase for 2024 8

Craig Knox, Mike Wilson, Christen M Klinger, Mark Franklin, Eponine Oler, Alex Wilson, Allison Pon, Jordan Cox, Na Eun (Lucy) Chin, Seth A Strawbridge ... Show more

Nucleic Acids Research, Volume 52, Issue D1, 5 January 2024, Pages D1265–D1275, https://doi.org/10.1093/nar/gkad976

Published: 11 November 2023 Article history ▼





DrSyn



DrSyn Overview

- Software that identifies drugs based on their name, including all the synonyms
 - Aspirin, acetylsalicylic acid, Bayer aspirin, etc.
- Similar software is sold by DrugBank, GoodRx, etc.

Premium Modules (each licensed separately)	US	Canada (English Language)	Canada (French Language)
CPOE and Order Entry			
-FDB OrderKnowledge®	✓	✓	
Interoperability			
Interoperability Module [™] Core Package	✓	Not applicable	Not applicable
Interoperability Module [®] Enhanced Package ^{**}	* 1	Not applicable	Not applicable
SNOMED CT (Canada)		✓	
Canadian Clinical Drug Interoperability Module [™]		✓	✓



DrSyn Updates

- Rebuild of Drug Library
 - NLM, NIH, PubChem, MeSH
- Added Precision Genetics Drug ID (PGDID) Generation and Mapping
 - Allows for unique IDs for each drug in the library
 - Ability to be updated without affecting current identification mapping
 - Reads library, finds new drugs present, creates new PGDID's, updates ID list
- Improved matching algorithm
- Implemented drug recognition module



DrSyn Updates

- Side by side performance testing with another similar utility
 - Fast Data Science Named Drug Entity Recognition
- Major improvements within source code optimization and documentation
- Creation of Jupytr Notebook for guiding users on proper usage
- Packaging the program and a public beta pre-release on GitHub





DrSyn: A Python Package for Drug Name Identification and Standardization

DrSyn is a powerful Python package designed to identify drug names within medical texts, extract them, and convert them to their common names based on MeSH standards. This tool is essential for standardizing drug names across various textual sources, making it invaluable for both healthcare and research purposes.

Key Features:

- Robust Drug Name Recognition: Accurately identifies drug names in medical texts, ensuring comprehensive extraction.
- MeSH Standard Conversion: Converts extracted drug names to their common or generic names, adhering to MeSH standards.
- Extensive Synonym Library: Utilizes a robust and accurate synonym library with data sourced from PubChem, maintained by NCBI.
- Versatile Text Processing: Capable of processing individual sentences or multiple documents to extract and standardize drug names.
- Enhanced Search Capability: Includes a pg_lookup feature for searching specific drug names or Precision

Easy To Use and Fast

Recognizing drugs within sentences, paragraphs, or the text of a single document

```
In [4]:
             # Test recognize drugs in text
             print("Testing recognize_drugs_in_text...")
             recognized drugs = DrSyn.recognize drugs in text(sample text)
             print("Recognized drugs in text:")
             for common name, pgid in recognized drugs:
                 print(f"Drug: {common name}, PGID: {pgid}")
       Testing recognize_drugs_in_text...
       Recognized drugs in text:
       Drug: aspirin, PGID: PGDID1906452
       Drug: acetaminophen, PGID: PGDID84099
       Drug: naproxen, PGID: PGDID1001887
       Drug: desvenlafaxine, PGID: PGDID1607287
       Drug: ibuprofen, PGID: PGDID217514
       Drug: amphetamine, PGID: PGDID2062818
       Drug: duloxetine, PGID: PGDID698212
       Drug: sertraline, PGID: PGDID734610
```



A Note About The Metrics

- Sentence
 - He uses Singulair and Advair for his allergies.
- Expected Drugs
 - Montelukast & Fluticasone
- Found Drugs
 - Montelukast & Fluticasone-Salmeterol
- Advair is Fluticasone-Salmeterol
 - We are performing better than the metrics will show and Fast Data Science is performing worse due







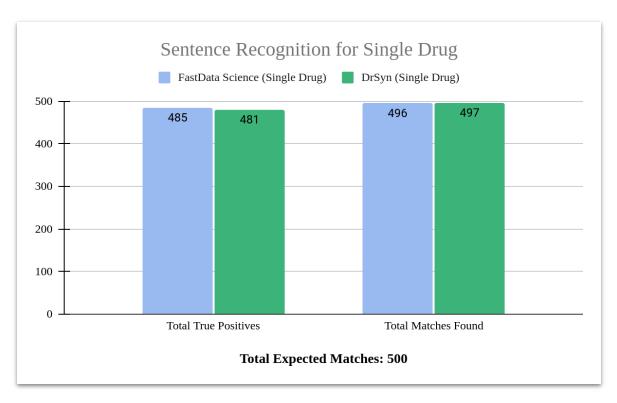
You can run the walkthrough Python notebook in Google Colab with a single click: Open in Colab

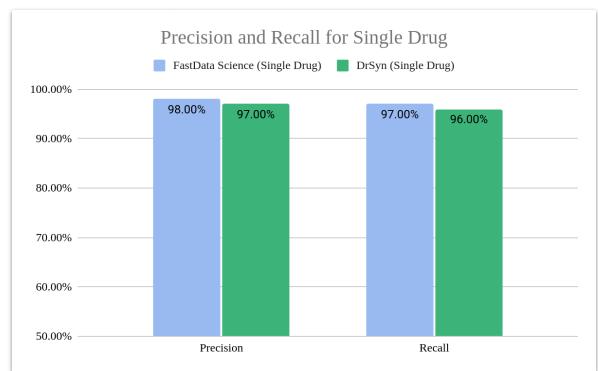
Drug named entity recognition Python library by Fast Data Science

Status In Development pip install drug named entity recognition version v1.0.3 license MIT pypi v1.0.3 version v1.0.3 pip downloads 72k Forks 6

Comparative Performance: DrSyn vs. FastData Science

-Single Drug Recognition Results-

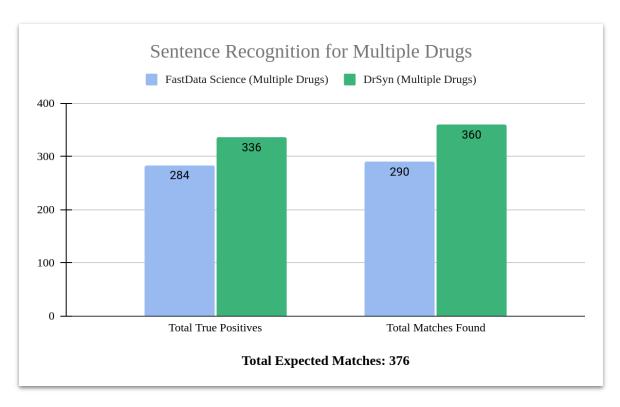


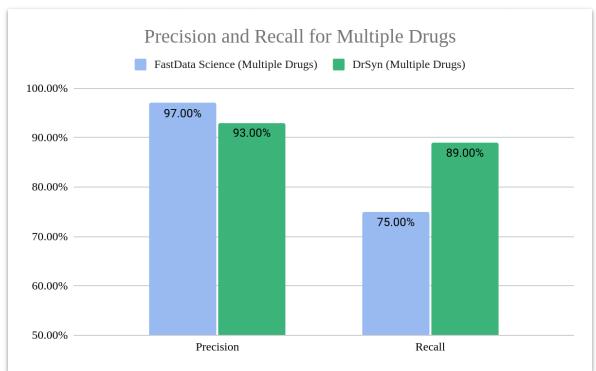




Comparative Performance: DrSyn vs. FastData Science

-Multiple Drug Recognition Results-







Highlights

- Massive drug-synonym library
- Outperforms competition in general recognition
- DrSyn recognizes multiple drugs in texts
- Fast Data Science struggles with drugs in a sentence adjacent to special characters (, | . | :)
- FastData Science maps various drugs incorrectly
 - Vicodin mapped to Acetaminophen



Future Work

- Apply to InfoMedEx MEDIC Database to help resolve missing data
- Promotion of the DrSyn tool package
- Bug testing and improvement based off feedback
- Full production release for professional implementation



Informed is InfoMedEx



