Ontology of Adverse Events (OAE) and its Applications

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Ontology of Adverse events (OAE)

- OAE: A biomedical ontology in the domain of adverse events.
- Align with Basic Formal Ontology (BFO) and Relation Ontology (RO)
- Follow OBO Foundry principles, e.g., openness, collaboration, and use of a common shared syntax

Reference: Smith et al. (2007). The OBO Foundry: coordinated evolution of ontologies to support biomedical data integration. *Nat Biotechnol* 25 (11): 1251-5.

http://www.oae-ontology.org/

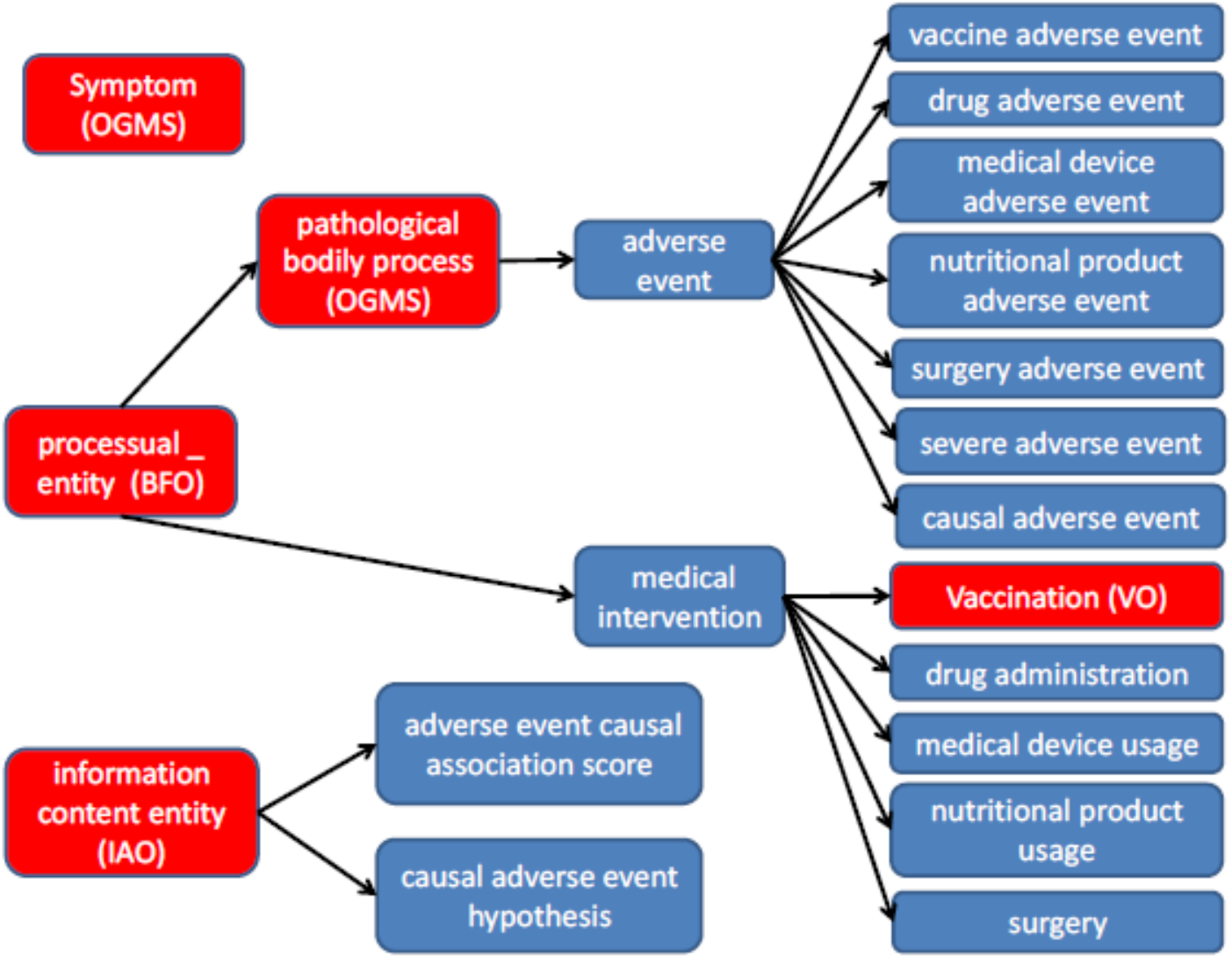
The Scope of OAE

- Defines adverse events (AE) and causal AE.
- Assesses causal associations between what is reported and a medical intervention, esp. vaccination and drug administration
- Generates hypotheses about vaccine and drug response mechanisms
- Records determined associations, such as those recorded on product labels, between vaccine/drug administration and medically relevant entities
- Not in OAE: how to report AEs

OAE Statistics

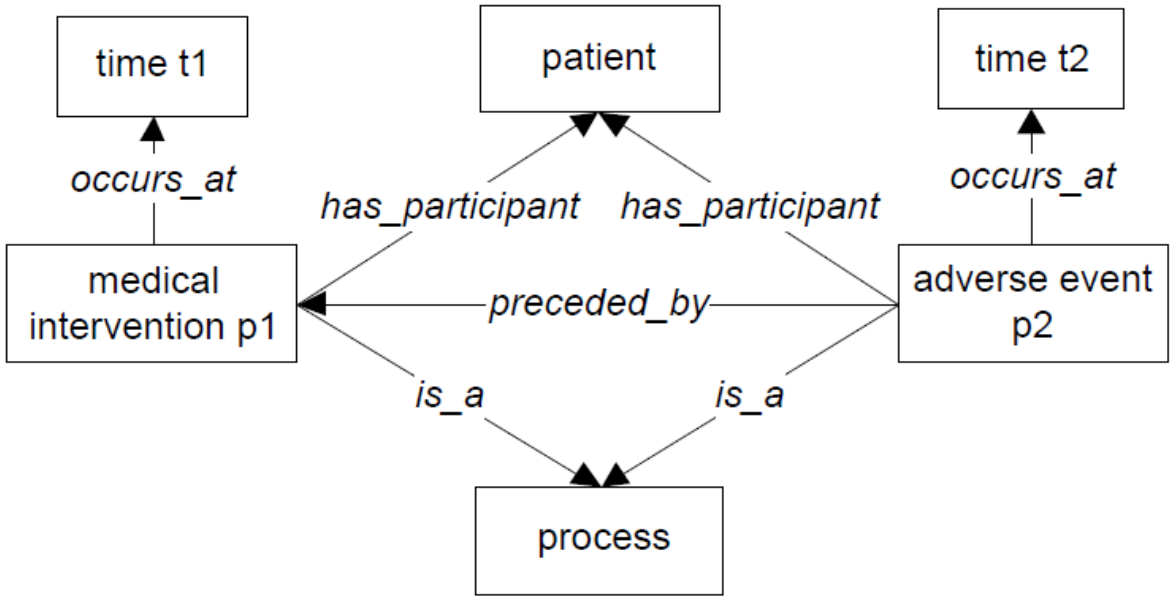
Ontology Names	Classes	Object properties	Total
OAE	991	3	994
BFO (Basic Formal Ontology)	22	38	60
RO (Relation Ontology)	0	24	24
IAO (Information Artifact Ontology)	3	0	3
OBI (Ontology for Biomedical Investigations)	10	7	17
OGMS (Ontology for General Medical Science)	4	0	4
VO (Vaccine Ontology)	7	0	7
GO (Gene Ontology)	759	0	759
PATO (Phenotypic Quality Ontology)	4	0	8
ChEBI (Chemical Entities of Biological Interest)	400	0	400
DOID (Disease Ontology)	1	0	1
RxNORM (Normalized Drugs)	186	0	186
Total	2387	72	2459

Key Top Level OAE Terms



Define ‘adverse event’ in OAE

AE Definition: a pathological bodily process in a patient that **occurs after (*preceded_by*)** a medical intervention.



Previous AE Definition: a pathological bodily process in a patient that ***is induced by*** a medical intervention.

Why not assume causal association in current OAE term ‘adverse event’?

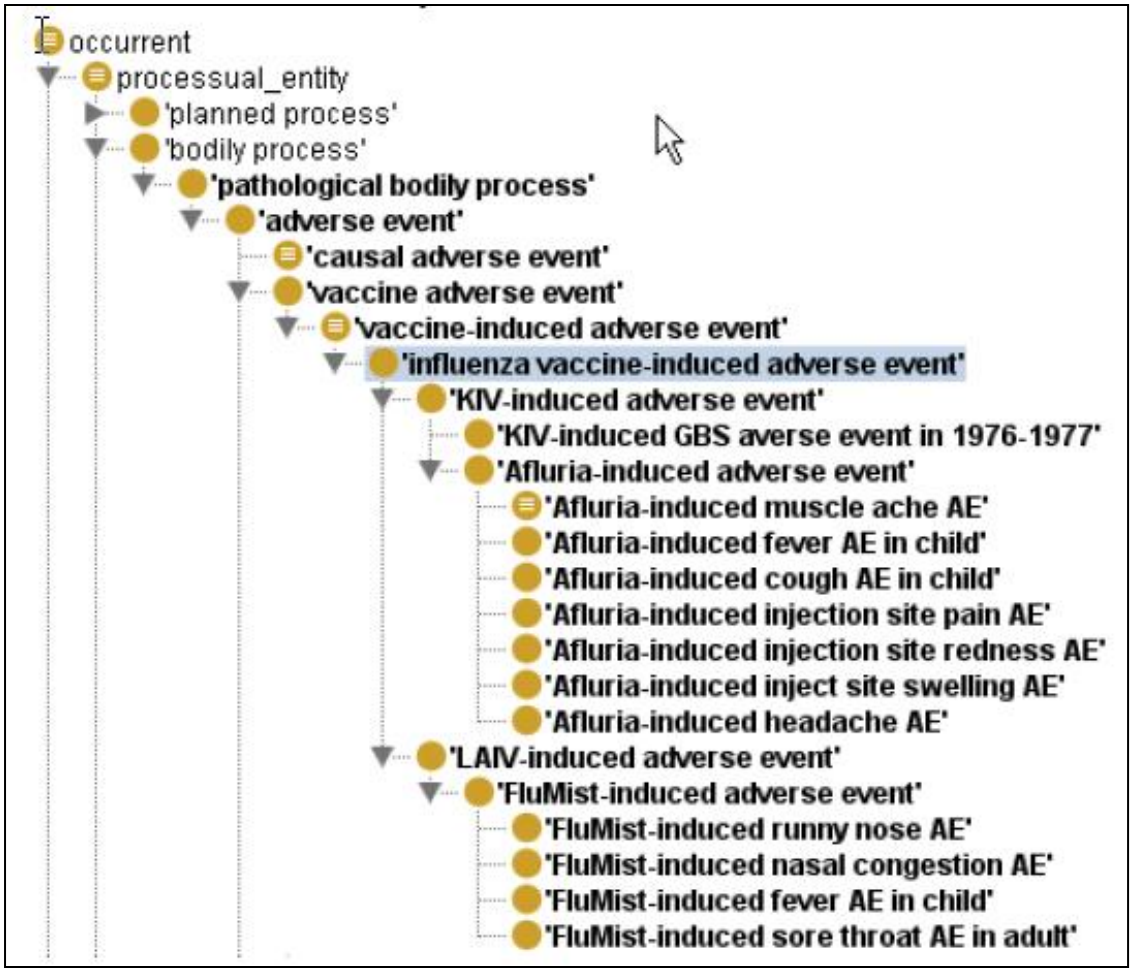
- Generally impossible to distinguish causal or non-causal adverse events following an intervention
- The USA Adverse Events Reporting System (AERS) and the Vaccine Adverse Events Reporting System (VAERS) clearly state no assumption
- The causality assumption would make it difficult to use the term ‘adverse event’ to represent individual cases.
- The inclusion of ‘causal adverse event’ allows us to examine ways to assess the causality

How assess causality of adverse events?

- Analysis of adverse event causality using ‘adverse event causal association score’
  - In OAE, we generated a probability named ‘causal adverse event probability’ or ‘CAE probability’ → Bayesian analysis method can be used for calculation
  - Naranjo ADR Scale → questionnaire → assigned as definite, probable, possible or doubtful.
  - Drug Interaction Probability Scale (DIPS)
- Analysis of adverse event causality using the causal adverse event hypothesis
  - Null hypothesis: a causal association does not exist.
  - Statistical study: test this hypothesis.

Use case: Comparison between Afluria and FluMist-induced vaccine AEs using OAE

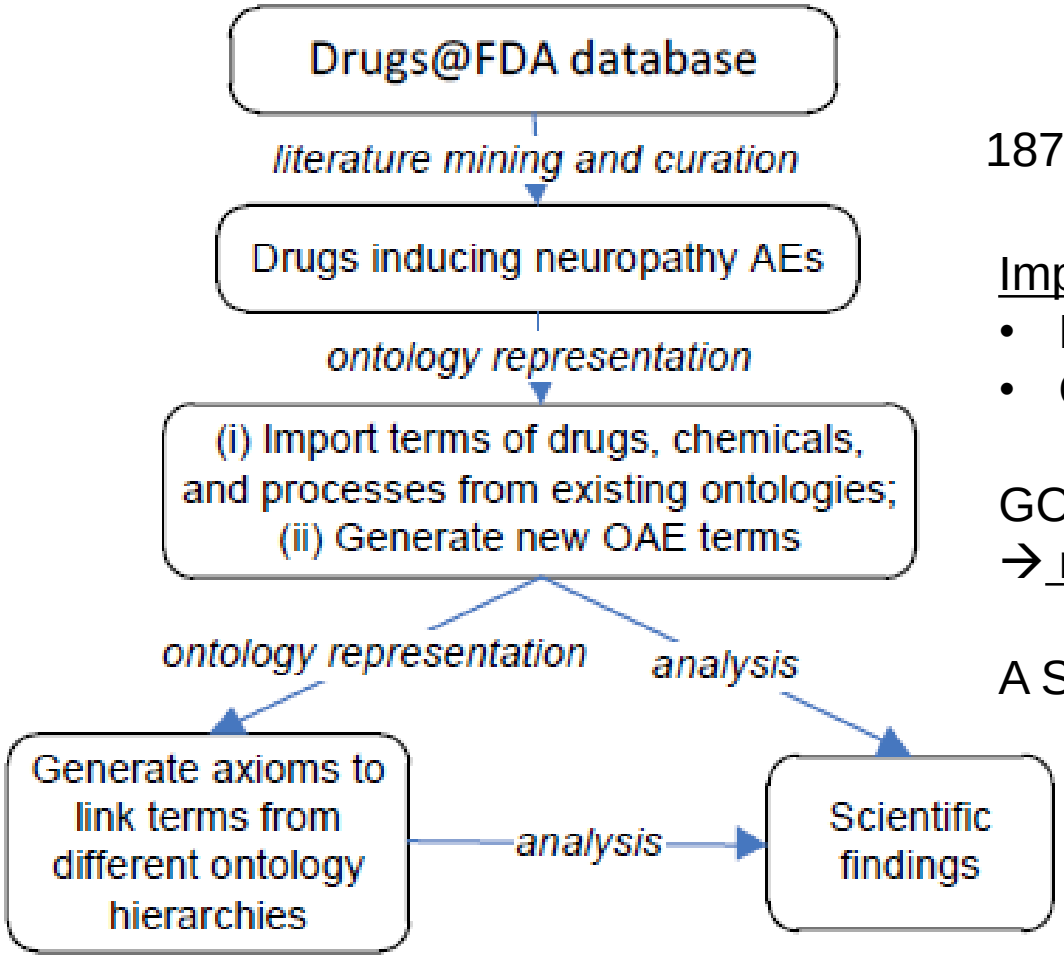
- Two types of influenza vaccines:
  - Killed influenza vaccine (KIV), like Afluria
  - Live attenuated influenza vaccine (LAIV) → FluMist
- Distinct AEs can be found from package inserts
- Collection in OAE helps analysis



Use case: Drug-induced Neuropathy Adverse Events using OAE

- Chemotherapy-induced neuropathy can be as prevalent as 40% or more depending on the drugs, e.g., Bortezomib causes >40% neuropathy.
- It is crucial to identify internal mechanism why a drug administration causes neuropathy AE.
- Intervention can then be designed for significant improvement or symptom resolution
- Project Goal: Ontology representation and analysis of drug-induced neuropathy AEs.

Workflow



187 US FDA-licensed drugs identified

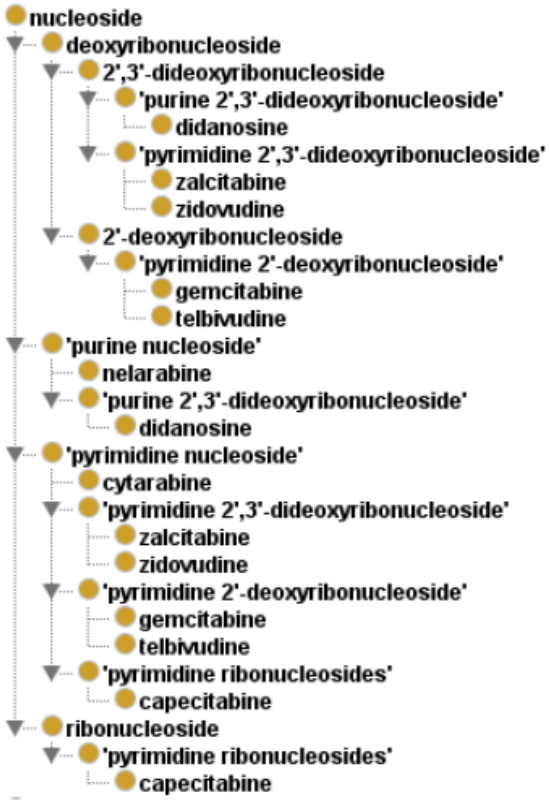
Imported to OAE:

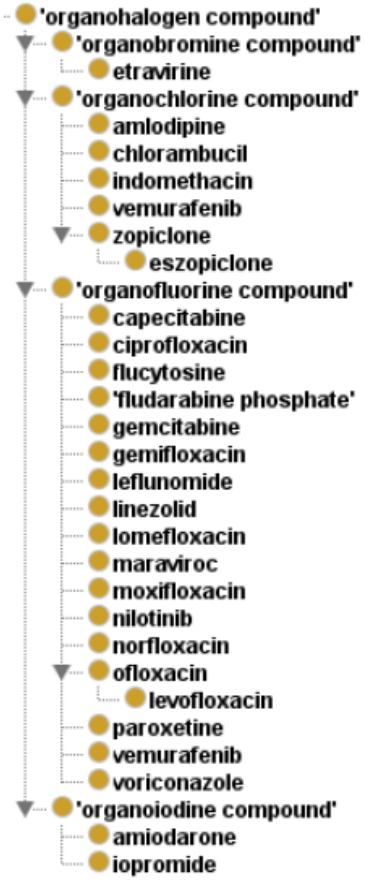
- Drug information stored in RxNorm
- Chemical annotation in CheEBI

GO biological processes
→ manually assigned

A SPARQL server generated for query

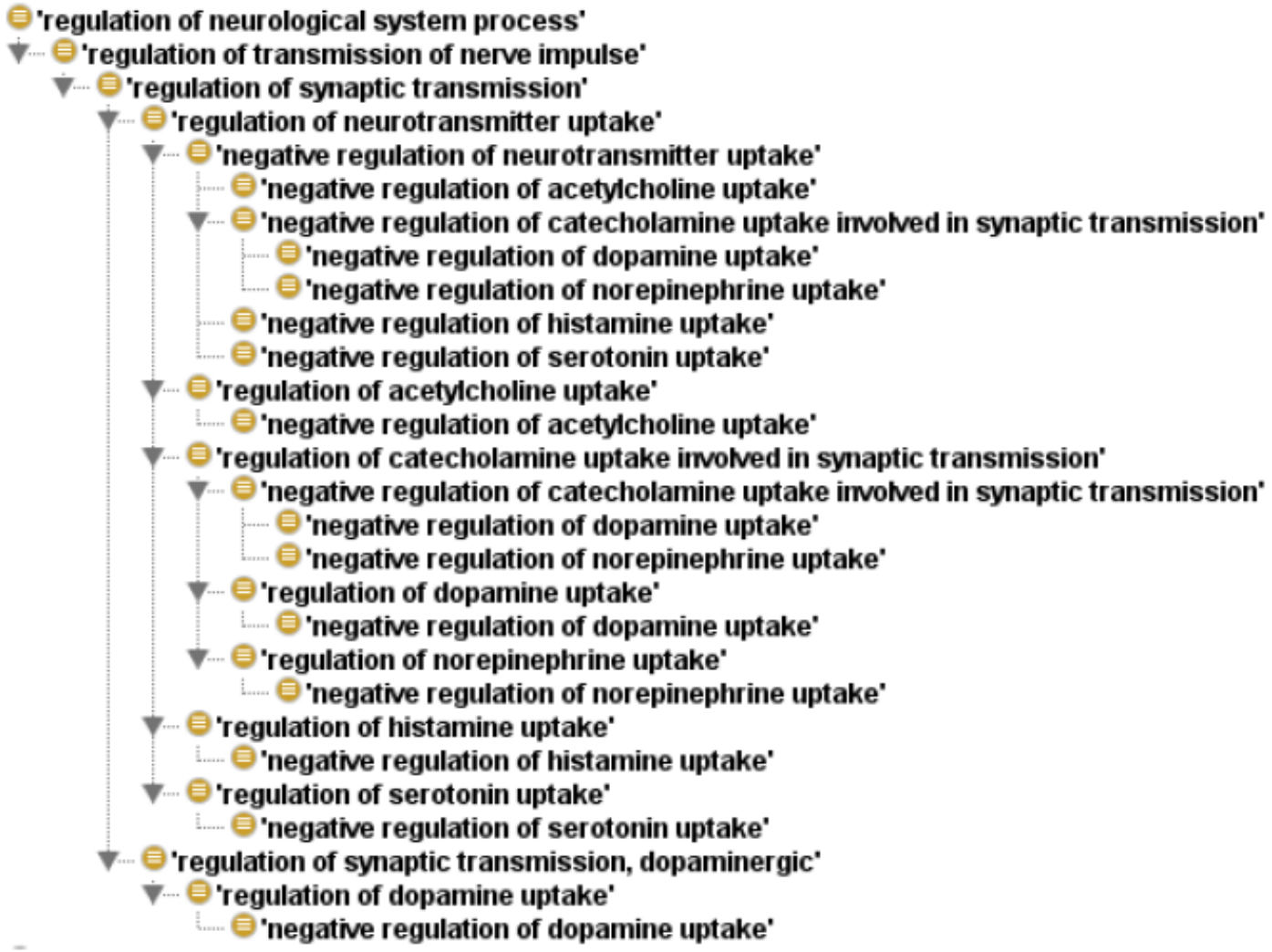
Example ChEBI classifications of drug chemicals inducing neuropathy AEs



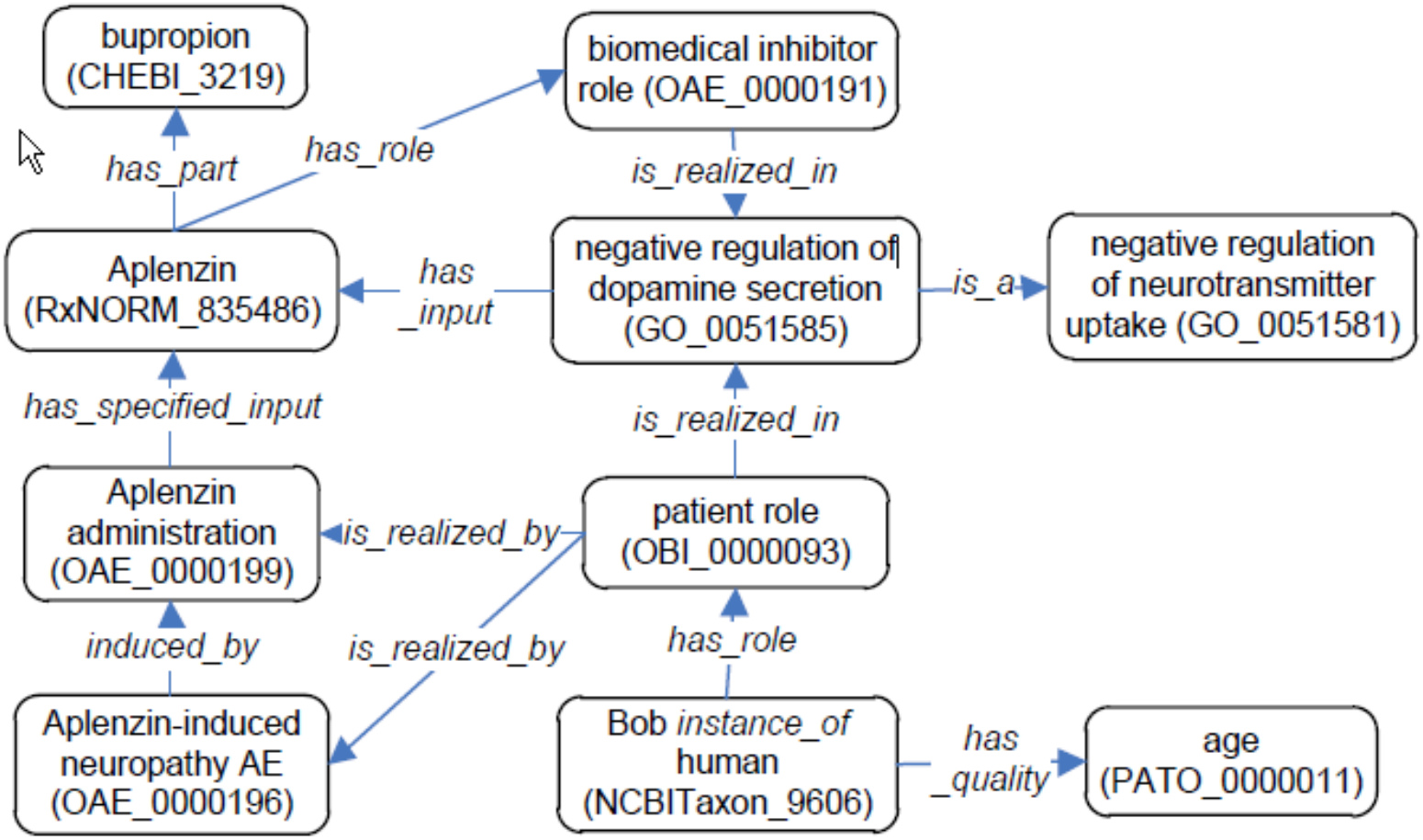


Many nucleoside (A) and organohalogen (B) compounds are able to induce neuropathy AEs

Many neurological processes negatively regulated based on GO analysis



OAE Modeling of Aplenzin-induced Neuropathy AE



Room for Improvements

- Many comments from reviewers:
  - Why not using DrugBank for drug targets?
  - Why not using NDF-RT for mechanisms of actions and physiological effects?
  - Why not using the Structured Product Labels in XML available in DailyMed (instead of extracting the same information from PDF files)?
- Efforts are undertaken to examine and compare these alternative methods

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