WG Evidence - Evidence Review Protocol

The Drugs to Review

- Antidepressants currently available in US with an FDA approved indication for treatment of depressive symptoms as April 1st 2014
- Antipsychotics currently available in the US with an FDA approved indication for treatment of schizophrenia as of April 1st 2014
- Sedative hypnotics currently available in the US with an FDA approved indication for the short-term treatment of insomnia as of April 1st 2014

- Statins currently available in the US with an FDA approved indication for treatment of hyperlipidemia as of April 1st 2014
- Warfarin and oral anticoagulants
- Regarding combination products:
    - Cases exist where DDIs involving combination products can be identified but the precipitant drug is not clear
        - e.g., possibly Lovastatin + niacin ER (Advicor), Ezetimibe + simvastatin (Vytorin) Niacin ER + simvastatin (Simcor)
    - For now, we will exclude these from the evidence review (i.e., we will not specifically search for these)

Source: Drug Facts & Comparisons. 2014. Wolters Kluwer Health, Inc. Accessed on April 3, 2014. Available with subscription at: http://online.factsandcomparisons.com/index.aspx

Antidepressants	Antipsychotics	Sedative Hypnotics	Statins	anticoagulants
MAOI Isocarboxazid Phenelzine Tranylcypromine Selegeline (patch) **SSRI** Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline Vilazodone (5HT1a receptor antagonist) **SNRI** Desvenlafaxine Duloxetine Levomilnacipran Milnacipran Venlafaxine **Tetracyclic** Maprotiline Mirtazapine **TCAs** Amitriptyline Amoxapine Clomipramine	Iloperidone Paliperidone Risperidone Ziprasidone Lurasidone Asenapine Clozapine Loxapine Olanzapine Quetiapine Chlorpromazine Fluphenazine Perphenazine Prochlorperazine Thioridazine Trifluoperazine Haloperidol Aripiprazole Thiothixene	**Nonbarbiturate** Eszopiclone Zaleplon Zolpidem **Benzodiazepine** Estazolam Flurazepam Quazepam Temazepam Triazolam	Atorvastatin Fluvastatin Lovastatin Pitavastatin Pravastatin Rosuvastatin Simvastatin	warfarin dabigatran apixaban rivaroxaban

Desipramine Doxepin Imipramine Nortriptyline Protriptyline Trimipramine **Other** Buproprion Nefazodone Vortioxetine				

Exclude:

Barbiturates - not typically used outside of the hospital setting and they are not typically used for anxiety

Melatonin receptor agonists - not a sedative hypnotic

Chloral hydrate - not typically used

The scope of evidence for drug-drug interactions

A detailed description of the scope of evidence and detailed inclusion criteria for the various evidence types is provided here:

http://dbmi-icode-01.dbmi.pitt.edu/dikb-evidence/just-inclusion-criteria/just-inclusion-criteria.html

Excluded study types

- Studies and experiments for drugs not available for prescription or OTC on the US market. For example, if a PK study includes a non-US drug as a precipitant or object, it would be excluded. NOTE: we may include drugs approved only in other countries if those drugs are probe substrates or inhibitors of the enzymes and transporters we follow. An example would be sparteine which is a probe substrate of CYP2D6
- Unpublished observational reports such as spontaneous adverse event reports in VigiBase, FDA Adverse Event Reporting system, or events linked to clinical trials in ClinicalTrials.gov.
- Metabolic and transporter induction interactions, both observed in studies and inferrable from reasonable extrapolation (see PK Study Considerations for situations like inhibition of transport that might present similarly to induction with respect to pharmacokinetic changes)
  - Although these kinds of interactions are important for some drugs (e.g., barbiturates and alprazolam), we will postpone including them in the evidence base because evaluation of the evidence will require much further discussion. The dose and duration of the precipitants affects the timing of induction interactions in ways that make evidence assessment more challenging than for inhibition interactions.
  - It is noted that some drugs, in particular rifampin and ritonavir, have inhibitory and induction properties depending on complicated factors.
- Pharmacodynamic interactions

- For now, this study is limited to PK interactions that occur by inhibition of a metabolic or transport enzyme
  - Rationale: Currently, assessment of PD interactions is judged by our team to be too subjective in nature and lack standards for evaluation, e.g., poor ability of authors to accurately diagnose serotonin toxicity and assess causation. Future work will aim to explore methods for extended the project to PD interactions

PK Study Considerations

- PK interactions include AUC, Clearance, and Cmax changes that are relevant for PDDIs that occur by inhibition of a metabolic or transport enzyme
  - NOTE: The focus on inhibition of a metabolic or transport enzymes means that, in general, the AUC, Clearance, and Cmax of the object drug will be increased as a result of the interaction. However, we do allow for the decrease of these parameters in a situation where the mechanism is not CYP induction. For example, inhibition of an influx transporter might lead to a decerase in AUC or Clearance (see http://www.ncbi.nlm.nih.gov/pubmed/22574741).
- Absorption interactions may be included but must include extent. Further discussion will be warranted once we find a case
- Efficacy criteria for some drugs is maintaining a concentration above a Cmin for a certain amount of time.
- For other drugs, toxicity is linked to Cmax. And for these drugs, the difference in Cmax or Cmin may be statistically significant while the change in AUC is not or vice versa. What do you do then?
- Arithmetic means vs. geometric means ?
  - The evidence entry process will capture both where they are available
    - Geometric mean preferred by FDA because it is useful for dealing with data that are nonlinear for example
    - BUT the arithmetic mean may be statistically significant while the geometric mean is not or vice versa.
    - Arithmetic mean preferred by Carol because it makes more sense clinically
    - BUT if you are looking at nonlinear data, the geometric means are more likely to be correct

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Some notes for collecting evidence of pharmacokinetic mechanisms

- The evidence types and inclusion criteria at the following URL will be used to determine the type of evidence, and if it meets the minimum quality criteria for acceptance:
  - http://bit.ly/1prFY0B

- A note on mass balance studies:
    - There are drugs where the main enzyme of metabolism was incorrectly assigned (example citalopram) or a significant route of metabolism is incorrectly assigned (example alprazolam) and these errors lead to incorrect predictions.
    - If you look at these drugs closely, the assignments were made by in vitro reaction phenotyping. What was not done was a correctly performed *mass balance study* (what you term a *clinical pharmacokinetic study* in your dissertation) to confirm the circulating and eliminating entities corresponding to the reaction phenotyping.
        - Scott Obach and Dennis Smith published a review on this topic (Roffey SJ, Obach RS, Gedge JI, Smith DA. What is the objective of the mass balance study? A retrospective analysis of data in animal and human excretion studies employing radiolabeled drugs. Drug Metab Rev. 2007;39(1):17-43. Review. PubMed PMID: 17364879.) .
            - The criteria gleaned from their article is that recovery of labeled entities should be equal or greater than 80%.
            - Apixaban is a good example of a drug where the mass balance study was inadequate and can lead to the incorrect assumption that CYP3A4 inhibition can lead to clinically significant drug interactions.

Review process

One informaticist (RB) and three drug-experts (LH/AG, CC, and JH) formed an evidence board that was responsible for collecting and entering all evidence into the DIKB. The evidence collection process was preceded by revision to the evidence types and inclusion criteria (http://bit.ly/1prFY0B) to reflect updated knowledge of in vitro metabolic and transporter inhibition experiments and additions to the pharmacokinetic parameters being collected.

The evidence collection process for DDIs from the indexed literature:
(1) The drug-experts on the evidence board chose a particular drug to review
(2) RB provided what had already been entered into the DIKB
(2) CC provided evidence collected by the DIDB
- covers NDAs and the DIDB team's accepted evidence from the scientific literature
- Consider as a complementary source to drugs@fda
(3) LH was in charge of updated the default evidence statements from the 2006 FDA Draft guidance to the more recent 2012 FDA Draft guidance
- Statements in the 2012 draft guidance and the FDA website will completely replace the 2006 statements

- ○ Cross reference with FDA Website tables & note differences http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm
- Include: Genetic polymorphism, time-dependent inhibition, induction, footnotes, statements in text where additional information provided beyond the table
- Exclude: Herbals, food, discontinued, investigational drugs, therapeutic proteins, Table 1 (transporter clinically significant DDI examples) because the table is is speculative in nature and meant to provide examples vs. the provision of scientific evidence. It does not meet our criteria for default statements.

(4) LH/AG was in charge of executing the literature search and RB supported with some tools where possible:

- for evidence in PubMed, see the search strategy below which maintains a list of articles to screen out because they have already been reviewed by the evidence board during prior searches
- Full text will be retrieved from U of A or Pitt depending on if there is a cost. If there is a cost, Pitt will pull the article. Also, we will discuss the process for batch full text downloads using SCOPUS or OVID

(5) A search was repeated in EMBASE removing all Pubmed results from our prior search

Screening selected papers in the literature

(1) AG will send out a paper for review as evidence for or against a specific assertion

(1.1) If the article clearly does not meet inclusion criteria then AG will note it as a possible rejection

(2) CC and JH will independently look at the article and vote for inclusion or rejection as indicated

(3) The evidence board would then meet and decide as a group whether each evidence item should enter the DIKB's evidence-base or be rejected as support or rebuttal for a specific assertion.

(4) NOTE: the evidence collection form is used for every evidence item screened to track the process and then prepare the evidence item for entry into the DIKB: https://docs.google.com/viewer?a=v&pid=sites&srcid=ZGVmYXVsdGRvbWFpbnxkZGlrcmFuZGlyfGd4OjE0ZGIwY2IwNzJhOWNjMjY

Screening selected papers in the product labeling

(1) A separate search for product labeling is done but using the same delegation of work

- Go to the actual application (NDA) if its available + product label
  - ○ things get added after marketing but the NDA has more detail
- most recent product label in dailymed or drugs@fda for a drug that is currently marketed according to drugs@fda
  - ○ NOTE: This spreadsheet tracks all of the work on FDA product label documents (backed up to Dropbox DDI-pipeline):

Evidence entry process into the DIKB

(1) The informaticist would then summarize all evidence items from each source, classify their evidence types, and check if they met inclusion criteria.
(2) The informaticist would enter accepted evidence items into the DIKB using the DIKB's Web interface. He also entered rejected evidence items into a simple database used by the DIKB during evidence validation tests.

Search Strategy

Phase I strategy -- used for all 65 drugs

From 2015 into the first quarter of 2017, the following review search strategies were executed periodically. Each strategy searches for new drug-interaction reviews since 2012. The results of the searches were screened by Amy and Rich to identify relevant review articles. The citation lists of the review articles were then screened for relevant primary studies and case reports.

- Antidepressants:

("Antidepressive Agents"[All Fields] OR "monoamine oxidase inhibitors"[All Fields] OR "selective serotonin reuptake inhibitor"[All Fields] OR "5ht1a agonist"[All Fields] OR "5ht1a receptor agonist"[All Fields] OR "selective norepinephrine reuptake inhibitor"[All Fields] OR "tricyclic antidepressant"[All Fields] OR "tetracyclic antidepressant"[All Fields] OR "Isocarboxazid"[All Fields] OR "Phenelzine"[All Fields] OR "Tranylcypromine"[All Fields] OR "Selegeline"[All Fields] OR "Citalopram"[All Fields] OR "Escitalopram"[All Fields] OR "Fluoxetine"[All Fields] OR "Fluvoxamine"[All Fields] OR "Paroxetine"[All Fields] OR "Sertraline"[All Fields] OR "Vilazodone"[All Fields] OR "Desvenlafaxine"[All Fields] OR "Duloxetine"[All Fields] OR "Levomilnacipran"[All Fields] OR "Venlafaxine"[All Fields] OR "Tetracyclic"[All Fields] OR "Maprotiline"[All Fields] OR "Mirtazapine"[All Fields] OR "Amitriptyline"[All Fields] OR "Amoxapine"[All Fields] OR "Clomipramine"[All Fields] OR "Desipramine"[All Fields] OR "Doxepin"[All Fields] OR "Imipramine"[All Fields] OR "Nortriptyline"[All Fields] OR "Protriptyline"[All Fields] OR "Trimipramine"[All Fields] OR "Buproprion"[All Fields] OR "Nefazodone"[All Fields] OR "Vortioxetine"[All Fields]) AND "Drug Interactions"[All Fields] AND Review[Publication Type] AND ("2012"[PDAT] : "3000"[PDAT])

- Antipsychotics:

("Antipsychotic Agents"[All Fields] OR "first generation antipsychotic"[All Fields] OR "second generation antipsychotic"[All Fields] OR "third generation antipsychotics"[All Fields] OR "atypical antipsychotics"[All Fields] OR "Iloperidone"[All Fields] OR "Paliperidone"[All Fields] OR "Risperidone"[All Fields] OR "Ziprasidone"[All Fields] OR "Lurasidone"[All Fields] OR

"Asenapine"[All Fields] OR "Clozapine"[All Fields] OR "Loxapine"[All Fields] OR "Olanzapine"[All Fields] OR "Quetiapine"[All Fields] OR "Chlorpromazine"[All Fields] OR "Fluphenazine"[All Fields] OR "Perphenazine"[All Fields] OR "Prochlorperazine"[All Fields] OR "Thioridazine"[All Fields] OR "Trifluoperazine"[All Fields] OR "Haloperidol"[All Fields] OR "Aripiprazole"[All Fields] OR "Thiothixene"[All Fields]) AND "Drug Interactions"[All Fields] AND Review[Publication Type] AND ("2012"[PDAT] : "3000"[PDAT])

- Sedative hypnotics

("sedative"[All Fields] OR "hypnotic"[All Fields] OR "barbiturate"[All Fields] OR "benzodiazepine"[All Fields] OR "Eszopiclone"[All Fields] OR "Zaleplon"[All Fields] OR "Zolpidem"[All Fields] OR "Estazolam"[All Fields] OR "Flurazepam"[All Fields] OR "Quazepam"[All Fields] OR "Temazepam"[All Fields] OR "Triazolam"[All Fields]) AND "Drug Interactions"[All Fields] AND Review[Publication Type] AND ("2012"[PDAT] : "3000"[PDAT])

- Statins

("statin"[All Fields] OR "hmg co a reductase inhibitors"[All Fields] OR "Atorvastatin"[All Fields] OR "Fluvastatin"[All Fields] OR "Lovastatin"[All Fields] OR "Pitavastatin"[All Fields] OR "Pravastatin"[All Fields] OR "Rosuvastatin"[All Fields] OR "Simvastatin"[All Fields]) AND "Drug Interactions"[All Fields] AND Review[Publication Type] AND ("2012"[PDAT] : "3000"[PDAT])

- Anticoagulants

("anticoagulant"[All Fields] OR "warfarin"[All Fields] OR "dabigatran"[All Fields] OR "apixaban"[All Fields] OR "rivaroxaban"[All Fields]) AND "drug interactions"[All Fields] AND Review[Publication Type] AND ("2012"[PDAT] : "3000"[PDAT])

The final list of screened articles using the method as of January 2018 is included in this document which also tracks the inclusion/exclusion status of each article (backed up to Dropbox DDI-pipeline):
https://docs.google.com/spreadsheets/d/14FrV1MpNC6nermJfP0WZSUjAfNEqLbSJhVcFQVon394

As of January 2018, this PubMed query can be used to retrieve all articles screened during the NLM R01 project. It was taken from the above linked document by extracting the PMIDs from the identifiers in Column A in
https://docs.google.com/spreadsheets/d/14FrV1MpNC6nermJfP0WZSUjAfNEqLbSJhVcFQVon394/edit#gid=0 :

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OR 21555828[uid] OR 15921508[uid] OR 18281922[uid] OR 9536449[uid] OR 21515813[uid] OR 3779574[uid] OR 12410494[uid] OR 22348256[uid] OR 18443034[uid] OR 16595711[uid] OR 23100282[uid] OR 11709322[uid] OR 22850760[uid] OR 17426664[uid] OR 20966146[uid] OR 11550401[uid] OR 19046202[uid] OR 23314529[uid] OR 18363538[uid] OR 17323791[uid] OR 19552746[uid] OR 14748817[uid] OR 19196846[uid] OR 18665165[uid] OR 23388500[uid] OR 18650507[uid] OR 22504754[uid] OR 17145598[uid] OR 9167522[uid] OR 12445025[uid] OR 22398967[uid] OR 17724362[uid] OR 21822144[uid] OR 17595891[uid] OR 23305158[uid] OR 10435174[uid] OR 17708069[uid] OR 19286776[uid] OR 16097365[uid] OR 19228618[uid] OR 19667285[uid] OR 19857154[uid] OR 8617706[uid] OR 8617707[uid] OR 8617708[uid] OR 7427137[uid] OR 17659194[uid] OR 19151423[uid] OR 19067264[uid] OR 20721515[uid] OR 1988413[uid] OR 9839766[uid] OR 21993870[uid] OR 21177986[uid] OR 18227146[uid] OR 18521091[uid] OR 9926737[uid] OR 22242932[uid] OR 16401168[uid] OR 23469685[uid] OR 23556337[uid] OR 11259986[uid] OR 19552747[uid] OR 19252767[uid] OR 19549094[uid] OR 21635243[uid] OR 21876043[uid] OR 22464259[uid] OR 23155151[uid] OR 23210726[uid] OR 20738227[uid] OR 20739919[uid] OR 20703222[uid] OR 21434975[uid] OR 20519340[uid] OR 22348256[uid] OR 21414947[uid] OR 19667285[uid] OR 20565450[uid] OR 16514303[uid] OR 18477279[uid] OR 17911146[uid] OR 16050864[uid] OR 18443034[uid] OR 16595711[uid] OR 17484083[uid] OR 15949157[uid] OR 16095503[uid] OR 17470528[uid] OR 17708069[uid] OR 18420781[uid] OR 17615423[uid] OR 15477442[uid] OR 18520113[uid] OR 17585018[uid] OR 10064574[uid] OR 9627209[uid] OR 7742153[uid] OR 10982203[uid] OR 15025747[uid] OR 2020000[uid] OR 9497982[uid] OR 12715317[uid] OR 12485953[uid] OR 14503117[uid] OR 7654493[uid] OR 9248876[uid] OR 8027418[uid] OR 495610[uid] OR 11237079[uid] OR 9384461[uid] OR 15140859[uid] OR 6140941[uid] OR 14998424[uid] OR 2718223[uid] OR 14984623[uid] OR 10497145[uid] OR 9160078[uid] OR 882479[uid] OR 9114914[uid] OR 7714757[uid])

The list of PMIDs below includes all PubMed indexed articles loaded into the DIKB prior to the NLM project starting in 2014 (this was pulled from the pickle data https://github.com/dbmi-pitt/DIKB-Evidence-analytics/tree/master/Drive-Experiment/dikb-pickles commit Latest commit 39a19f2 on Apr 11, 2016):

(10048600[uid] OR 10073324[uid] OR 10073330[uid] OR 10192752[uid] OR 10192828[uid] OR 10234598[uid] OR 10445377[uid] OR 10460810[uid] OR 10492058[uid] OR 10494454[uid] OR 10548453[uid] OR 10579479[uid] OR 10634135[uid] OR 10640508[uid] OR 10741630[uid] OR 10771448[uid] OR 10771449[uid] OR 10771452[uid] OR 10771455[uid] OR 10771458[uid] OR 10890312[uid] OR 10907965[uid] OR 10950845[uid] OR 10952477[uid] OR 10997935[uid] OR 10997944[uid] OR 11009047[uid] OR 11038166[uid] OR 11061579[uid] OR 11075313[uid] OR 11084219[uid] OR 11136295[uid] OR 11147928[uid] OR 11180037[uid] OR 11213852[uid] OR 11240973[uid] OR 11270914[uid] OR 11304903[uid] OR 11372588[uid] OR 11422004[uid] OR 11452243[uid] OR 11454728[uid] OR 11563412[uid] OR 11583471[uid] OR 11673748[uid] OR 11719727[uid] OR 11872324[uid] OR 11907488[uid] OR 11910256[uid] OR 11910262[uid] OR 11910267[uid] OR 11936570[uid] OR 12102620[uid] OR 12102670[uid] OR 12124305[uid] OR 12173784[uid] OR 12235455[uid] OR 12397887[uid] OR 12404553[uid] OR 12451430[uid] OR

12544511[uid] OR 12584155[uid] OR 12621382[uid] OR 12682802[uid] OR 12709722[uid] OR 12723462[uid] OR 12891223[uid] OR 12911366[uid] OR 12920410[uid] OR 1387301[uid] OR 1412613[uid] OR 1438031[uid] OR 14551182[uid] OR 14610241[uid] OR 14667956[uid] OR 14709940[uid] OR 1474166[uid] OR 14747427[uid] OR 1487561[uid] OR 15114429[uid] OR 15258107[uid] OR 1531484[uid] OR 1544284[uid] OR 15496643[uid] OR 15518608[uid] OR 15599502[uid] OR 15601809[uid] OR 15743977[uid] OR 15770075[uid] OR 15834460[uid] OR 15876900[uid] OR 15961986[uid] OR 15963095[uid] OR 15998357[uid] OR 16003291[uid] OR 16120067[uid] OR 1613128[uid] OR 16172184[uid] OR 16390352[uid] OR 16416302[uid] OR 16432272[uid] OR 16580903[uid] OR 16638740[uid] OR 16679385[uid] OR 16680561[uid] OR 16684709[uid] OR 16765141[uid] OR 16765147[uid] OR 16778714[uid] OR 1680649[uid] OR 17124578[uid] OR 17244765[uid] OR 17429316[uid] OR 17571477[uid] OR 17652181[uid] OR 17687273[uid] OR 18094219[uid] OR 18307373[uid] OR 18809731[uid] OR 18832427[uid] OR 19001559[uid] OR 19142106[uid] OR 19242403[uid] OR 19444001[uid] OR 19585395[uid] OR 2007317[uid] OR 20484617[uid] OR 2124217[uid] OR 2530759[uid] OR 2567646[uid] OR 3323671[uid] OR 3428348[uid] OR 3508549[uid] OR 3608351[uid] OR 3771812[uid] OR 3788228[uid] OR 3792426[uid] OR 3912187[uid] OR 3932079[uid] OR 3950073[uid] OR 6152055[uid] OR 6684932[uid] OR 6692646[uid] OR 6726654[uid] OR 6861848[uid] OR 7690693[uid] OR 7891353[uid] OR 7923194[uid] OR 7946933[uid] OR 7995001[uid] OR 8157044[uid] OR 8181191[uid] OR 8195463[uid] OR 8198928[uid] OR 8243504[uid] OR 8331208[uid] OR 8408732[uid] OR 8451775[uid] OR 8453848[uid] OR 8466541[uid] OR 8513845[uid] OR 8562300[uid] OR 8612379[uid] OR 8623953[uid] OR 8632299[uid] OR 8646822[uid] OR 8689810[uid] OR 8689812[uid] OR 8720318[uid] OR 8730978[uid] OR 8748428[uid] OR 8801057[uid] OR 8823236[uid] OR 8830062[uid] OR 8830063[uid] OR 8841155[uid] OR 8866916[uid] OR 8880291[uid] OR 8889898[uid] OR 8904618[uid] OR 8911886[uid] OR 8930024[uid] OR 8941024[uid] OR 8988072[uid] OR 9010634[uid] OR 9029748[uid] OR 9049584[uid] OR 9088587[uid] OR 9146848[uid] OR 9152603[uid] OR 9205822[uid] OR 9241008[uid] OR 9278211[uid] OR 9284850[uid] OR 9321523[uid] OR 9331518[uid] OR 9333110[uid] OR 9366029[uid] OR 9378846[uid] OR 9384460[uid] OR 9431831[uid] OR 9542477[uid] OR 9549635[uid] OR 9602962[uid] OR 9626922[uid] OR 9690949[uid] OR 9695720[uid] OR 9728893[uid] OR 9728898[uid] OR 9757147[uid] OR 9757151[uid] OR 9784084[uid] OR 9797793[uid] OR 9825830[uid] OR 9855322[uid] OR 9871431[uid] OR 9929499[uid])

And this list is the PMIDS of all rejected evidence for the DIKB prior to the NLM project start in 2014 (this was extracted from the rejected_evidence file in https://github.com/dbmi-pitt/DIKB-Evidence-analytics/tree/master/data dated 2015) :

(10048600[uid] OR 10192828[uid] OR 10211917[uid] OR 10361775[uid] OR 10379638[uid] OR 10454485[uid] OR 10460810[uid] OR 10466919[uid] OR 10490896[uid] OR 10494454[uid] OR 10516882[uid] OR 10579150[uid] OR 10600094[uid] OR 10771452[uid] OR 10771453[uid] OR 10971313[uid] OR 1101843[uid] OR 11038161[uid] OR 11038166[uid] OR 11084219[uid] OR 11136295[uid] OR 11147928[uid] OR 11181496[uid] OR 11197581[uid] OR 11213852[uid] OR 11233461[uid] OR 11292004[uid] OR 11422004[uid] OR 11454728[uid] OR 11528245[uid] OR

11675851[uid] OR 11719727[uid] OR 11744603[uid] OR 11852294[uid] OR 11854151[uid] OR 11910263[uid] OR 11926715[uid] OR 12023534[uid] OR 12102670[uid] OR 12172337[uid] OR 12173784[uid] OR 12202291[uid] OR 12243603[uid] OR 12380704[uid] OR 12397859[uid] OR 12451428[uid] OR 12544321[uid] OR 12773066[uid] OR 12809966[uid] OR 12816614[uid] OR 12841814[uid] OR 136668[uid] OR 1412613[uid] OR 14570351[uid] OR 14966253[uid] OR 15048613[uid] OR 15096363[uid] OR 15199083[uid] OR 15342470[uid] OR 15531380[uid] OR 15545309[uid] OR 15545884[uid] OR 15618724[uid] OR 15625612[uid] OR 15735612[uid] OR 15801939[uid] OR 15834460[uid] OR 16141567[uid] OR 16159992[uid] OR 16288136[uid] OR 16390352[uid] OR 16473984[uid] OR 16684709[uid] OR 17216557[uid] OR 17353373[uid] OR 17368833[uid] OR 17381388[uid] OR 17687273[uid] OR 1815969[uid] OR 18648229[uid] OR 18832427[uid] OR 19001559[uid] OR 1914376[uid] OR 19242403[uid] OR 1976071[uid] OR 2006579[uid] OR 2007317[uid] OR 20631572[uid] OR 2265054[uid] OR 3069477[uid] OR 3146770[uid] OR 3381243[uid] OR 3421582[uid] OR 4061700[uid] OR 4571186[uid] OR 6255531[uid] OR 6282204[uid] OR 6643704[uid] OR 6707884[uid] OR 6734030[uid] OR 6737261[uid] OR 7586933[uid] OR 7637734[uid] OR 7690693[uid] OR 7741408[uid] OR 7891353[uid] OR 7972311[uid] OR 8148222[uid] OR 8225700[uid] OR 8267647[uid] OR 8333005[uid] OR 8466541[uid] OR 849674[uid] OR 8764380[uid] OR 8823236[uid] OR 8834415[uid] OR 8861737[uid] OR 8918636[uid] OR 8941024[uid] OR 8986013[uid] OR 9002485[uid] OR 9023308[uid] OR 9024962[uid] OR 9205822[uid] OR 9220046[uid] OR 9223567[uid] OR 9378846[uid] OR 9394027[uid] OR 9431831[uid] OR 9447478[uid] OR 9455717[uid] OR 9496876[uid] OR 9574817[uid] OR 9681669[uid] OR 9825830[uid] OR 9855322[uid])

Phase II search strategy -- used for a subset of the 65 drugs based on the need to support specific research studies:

The above strategy for Phase I was useful for conveniently acquiring relevant articles for screening, annotation, and data entry. However, it is not a comprehensive strategy. The following strategy, shown with an example, is much more comprehensive. Also, it uses all of the reported search strategy elements for evidence that a drug interaction exists reported by participants in our 2017 survey study (Grizzle, AJ., Horn, J., Collins, C., Malone, DC., Stottlemyer, B., Boyce, RD. A survey of strategies used by drug information experts to search for evidence about potential drug-drug interactions. AMIA Informatics Summit. March 12-15th 2018. San Francisco, CA. USA.):
using anticoagulants as an example

Case reports (using anticoagulants as an example):

Step 1) Log into My NCBI and go to Pubmed: https://www.ncbi.nlm.nih.gov/pubmed/

Step 2) In the advanced search form, clear the search history

Step 3) Paste in the query [As of January 2018, this PubMed query can be used to...](#) into builder (using 'edit') and click "add to history" - this is referred to as '#1' in the rest of this Case report search strategy

Step 4) Paste in the query [The list of PMIDs below includes all PubMed indexed articles loaded into...](#) into builder (using 'edit') and click "add to history" - this is referred to as '#2' in the rest of this Case report search strategy

Step 5) Paste in the query [And this list is the PMIDS of all rejected evidence for the...](#) into builder (using 'edit') and click "add to history" - this is referred to as '#3' in the rest of this Case report search strategy

Step 6) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#4' in the rest of this Case report search strategy:

Case Reports [PT] AND (Anticoagulants[MeSH Terms] OR "anticoagulant"[All Fields] OR "warfarin"[All Fields] OR "dabigatran"[All Fields] OR "apixaban"[All Fields] OR "rivaroxaban"[All Fields]) AND "drug interactions"[All Fields]

Step 7) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#5' in the rest of this Case report search strategy:

#1 OR #2 OR #3

Step 8) Paste in this query - this is referred to as '#6' in the rest of this Case report search strategy:

#4 NOT #5

Step 9) Check that the 'items found" counts shown in the history table make sense given the queries and double check that the queries were correctly entered

Step 10) Download history and save it to a text file e.g., "Search history for Final R01 Case Report search for anticoagulants 1/2018.txt"

Step 11) Click on the "items found" count for #6. Use the PubMed "Send To" interface to save all of the results to a new named collection in My NCBI e.g., "Final R01 Case Report search for anticoagulants 1/2018". After the collection is created, make the collection public. Also, download as CSV.

Clinical drug-interaction studies (using anticoagulants as an example):

Step 1) Follow the same steps as for Case reports to build the history.

Step 2) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#7' in the rest of this search strategy:

(Clinical Trial [PT] AND (Anticoagulants[MeSH Terms] OR "anticoagulant"[All Fields] OR "warfarin"[All Fields] OR "dabigatran"[All Fields] OR "apixaban"[All Fields] OR "rivaroxaban"[All Fields]) AND "drug interactions"[All Fields]) NOT Review [PT]

Step 3) Paste in this query - this is referred to as '#8' in the rest of the search strategy:
#7 NOT #5

Step 4) Check that the 'items found" counts shown in the history table make sense given the queries and double check that the queries were correctly entered

Step 5) Download history and save it to a text file e.g., "Search history for Final R01 DDI Clinical Trial search for anticoagulants 1/2018.txt"

Step 6) Click on the "items found" count for #6. Use the PubMed "Send To" interface to save all of the results to a new named collection in My NCBI e.g., "Final R01 DDI Clinical Trial search for anticoagulants 1/2018". After the collection is created, make the collection public. Also, download as CSV.

Mechanistic drug studies useful for inferring drug interactions (using anticoagulants as an example):

Step 1) Log into My NCBI and go to Pubmed: https://www.ncbi.nlm.nih.gov/pubmed/

Step 2) In the advanced search form, clear the search history

Step 3) Paste in the query As of January 2018, this PubMed query can be used to...... into builder (using 'edit') and click "add to history" - this is referred to as '#1' in the rest of this search strategy

Step 4) Paste in the query The list of PMIDs below includes all PubMed indexed articles loaded into... into builder (using 'edit') and click "add to history" - this is referred to as '#2' in the rest of this search strategy

Step 5) Paste in the query [And this list is the PMIDS of all rejected evidence for the...](#) into builder (using 'edit') and click "add to history" - this is referred to as '#3' in the rest of this search strategy

Step 6) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#4' in the rest of this search strategy:

"Cytochrome P-450 Enzyme System"[MeSH Terms] OR "Cytochrome P450 Family 1"[MeSH Terms] OR "Cytochrome P450 Family 2"[MeSH Terms] OR "Cytochrome P450 Family 3"[MeSH Terms] OR CYP1A1[All Fields] OR CYP1A2[All Fields] OR CYP1A3[All Fields] OR CYP1A4[All Fields] OR CYP1A5[All Fields] OR CYP2D6[All Fields] OR CYP2C9[All Fields] OR CYP2A6[All Fields] OR CYP2C8[All Fields] OR CYP2C19[All Fields] OR CYP2B6[All Fields] OR CYP2B1[All Fields] OR CYP2E1[All Fields] OR CYP3A4[All Fields] OR CYP3A5[All Fields] OR UGT1[All Fields] OR UGT1A1[All Fields] OR UGT1A3[All Fields] OR UGT1A4[All Fields] OR UGT1A5[All Fields] OR UGT1A6[All Fields] OR UGT1A7[All Fields] OR UGT1A8[All Fields] OR UGT1A9[All Fields] OR UGT1A10[All Fields] OR UGT2[All Fields] OR UGT2A1[All Fields] OR UGT2A2[All Fields] OR UGT2A3[All Fields] OR UGT2B4[All Fields] OR UGT2B7[All Fields] OR UGT2B10[All Fields] OR UGT2B11[All Fields] OR UGT2B15[All Fields] OR UGT2B17[All Fields] OR UGT2B28[All Fields] OR B3GAT1[All Fields] OR B3GAT2[All Fields] OR B3GAT3[All Fields]

Step 7) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#5' in the rest of this search strategy

"Solute Carrier Proteins"[MeSH Terms] OR "Membrane Transport Proteins"[MeSH Terms] OR "P-gp"[All Fields] OR "p-glycoprotein"[All Fields] OR BCRP[All Fields] OR OCT2[All Fields] OR "Organic Cation Transporter 2"[MeSH Terms] OR "Organic Cation Transport Proteins"[MeSH Terms] OR MATE1[All Fields] OR "SLC4A Proteins"[MeSH Terms] OR MATE-2K[All Fields] OR "SLC4A Proteins"[MeSH Terms] OR OATP[All Fields] OR OAT1[All Fields] OR "Organic Anion Transport Protein 1"[MeSH Terms] OR OAT3[All Fields] OR UGT1[All Fields] OR "Glucuronosyltransferase"[MeSH Terms] OR ABC[All Fields] OR "ATP-Binding Cassette Transporters"[MeSH Terms]

Step 8) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#6' in the rest of this search strategy

((((Anticoagulants[MeSH Terms] OR "anticoagulant"[All Fields] OR "warfarin"[All Fields] OR "dabigatran"[All Fields] OR "apixaban"[All Fields] OR "rivaroxaban"[All Fields]) NOT Review [PT]) NOT Clinical Trial [PT]) NOT Case Reports [PT])

Step 9) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#7' in the rest of this search strategy

(Pharmacokinetics[MeSH Terms] OR pharmacokinetic[All Fields]) or (inhibit[All Fields] or inhibition[All Fields]) OR substrate[All Fields]

Step 10) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#8' in the rest of this search strategy

#6 AND #7 AND (#4 OR #5)

Step 11) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#9' in the rest of this search strategy

#1 OR #2 OR #3

Step 12) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#10' in the rest of this search strategy

#8 NOT #9

Step 13) Check that the 'items found" counts shown in the history table make sense given the queries and double check that the queries were correctly entered

Step 14) Download history and save it to a text file e.g., "Search history for Final R01 PK Mechanism search for anticoagulants 1/2018.txt"

Step 15) Click on the "items found" count for #6. Use the PubMed "Send To" interface to save all of the results to a new named collection in My NCBI e.g., "Final R01 PK Mechanism search for anticoagulants 1/2018". After the collection is created, make the collection public. Also, download as CSV.

Other notes on search strategy
- For both new drugs, and those we have previously examined, we will complement the above MEDLINE search strategies using EMBASE with MeSH Mappings to EMTREE terms wherever relevant
- Product Labeling and other FDA Documents
  - We will also review the most recent product labeling or other FDA information available from NML DailyMed, and secondarily at drugs@fda for each included drug.
    - The United States Code of Federal Regulations specifies that the most up-to-date product labeling is to be posted at the NLM's DailyMed website; however, 2006 CFR did not specify any penalties for

pharmaceutical companies that do not send their labels to Daily Med). Therefore, also use Drugs@FDA

- ○ We will preferentially use the information from the drug's review (Clinical Pharmacology Biopharmaceutics Review at Drugs@fda) over the product label unless the information in the label is not in the CPB review (for example more recent drug interaction info).
    - Rationale: The CPB review is written by the FDA reviewers while the Product Label is written by the company; and The CPB review usually contains far more details regarding the study.
    - Review of evidence in FDA documents can provide important unpublished evidence.[McDonagh2013] However, publicly available FDA reviews are challenging to find and improved access to is needed.[O'Connor2009] Turner et al provide a process for accesses FDA drug approval packages.[Turner]
- We will search the FDA-USC Transportal database for studies focused on transport proteins: http://bts.ucsf.edu/fdatransportal/ (see also: Morrissey KM, Wen CC, Johns SJ, Zhang L, Huang SM, Giacomini KM, "The UCSF-FDA TransPortal: A Public Drug Transporter Database", *Clinical Pharmacology and Therapeutics* (2012) 92(5):545-6.)
- We will also search updated versions of FDA Guidance documents, standard drug interaction references, and papers identified from the reference lists of relevant book chapters. [Flockhart, Hansten Top 100, FDA Guidance]
    - ○ http://www.ncbi.nlm.nih.gov/pubmed/22414078,22171584,22866966,22416996,21682551,23129335,22311403
    - ○ Bellosta S, Corsini A. Statin drug interactions and related adverse reactions. Expert Opin Drug Saf. 2012 Nov;11(6):933-46. doi: 10.1517/14740338.2012.712959. Epub 2012 Aug 7. Review. PubMed PMID: 22866966. (requested from AHSL)
    - ○ Corsini A, Ceska R. Drug-drug interactions with statins: will pitavastatin overcome the statins' Achilles' heel? Curr Med Res Opin. 2011 Aug;27(8):1551-62. doi: 10.1185/03007995.2011.589433. Epub 2011 Jun 17. Review. PubMed PMID: 21682551.
    - ○ Florentin M, Elisaf MS. Simvastatin interactions with other drugs. Expert Opin Drug Saf. 2012 May;11(3):439-44. doi: 10.1517/14740338.2012.670633. Epub 2012 Mar 15. Review. PubMed PMID: 22416996. (requested from AHSL)
    - ○ Hiemke C, Pfuhlmann B. Interactions and monitoring of antipsychotic drugs. Handb Exp Pharmacol. 2012;(212):241-65. doi: 10.1007/978-3-642-25761-2_10. Review. PubMed PMID: 23129335. (have)
    - ○ Mandrioli R, Mercolini L, Saracino MA, Raggi MA. Selective serotonin reuptake inhibitors (SSRIs): therapeutic drug monitoring and pharmacological interactions. Curr Med Chem. 2012;19(12):1846-63. Review. PubMed PMID: 22414078. (requested from AHSL)
    - ○ Muscatello MR, Spina E, Bandelow B, Baldwin DS. Clinically relevant drug interactions in anxiety disorders. Hum Psychopharmacol. 2012

May;27(3):239-53. doi: 10.1002/hup.2217. Epub 2012 Feb 7. Review. PubMed PMID: 22311403.

- Spina E, Trifirò G, Caraci F. Clinically significant drug interactions with newer antidepressants. CNS Drugs. 2012 Jan 1;26(1):39-67. doi: 10.2165/11594710-000000000-00000. Review. PubMed PMID: 22171584.
- Seidling et al Eur J Clin Pcol has a nice list of statin DIs but is not up to date.

· Boyce R, Collins C, Horn J, Kalet I. Computing with evidence Part II: An evidential approach to predicting metabolic drug-drug interactions. J Biomed Inform. 2009 Dec;42(6):990-1003. doi: 10.1016/j.jbi.2009.05.010. Epub 2009 Jun 16. PubMed PMID: 19539050; PubMed Central PMCID: PMC2783683.

· Boyce R, Collins C, Horn J, Kalet I. Computing with evidence Part I: A drug-mechanism evidence taxonomy oriented toward confidence assignment. J Biomed Inform. 2009 Dec;42(6):979-89. doi: 10.1016/j.jbi.2009.05.001. Epub 2009 May 10. PubMed PMID: 19435613; PubMed Central PMCID: PMC2783801.

· Boyce RD, Collins C, Clayton M, Kloke J, Horn JR. Inhibitory metabolic drug interactions with newer psychotropic drugs: inclusion in package inserts and influences of concurrence in drug interaction screening software. Ann Pharmacother. 2012 Oct;46(10):1287-98. doi: 10.1345/aph.1R150. Epub 2012 Oct 2. PubMed PMID: 23032655.

· Boyce RD, Handler SM, Karp JF, Hanlon JT. Age-related changes in antidepressant pharmacokinetics and potential drug-drug interactions: a comparison of evidence-based literature and package insert information. Am J Geriatr Pharmacother. 2012 Apr;10(2):139-50. doi: 10.1016/j.amjopharm.2012.01.001. Epub 2012 Jan 27. Review. PubMed PMID: 22285509; PubMed Central PMCID: PMC3384538.

· Drug Facts & Comparisons. 2014. Wolters Kluwer Health, Inc. Accessed on April 3, 2014. Available with subscription at: http://online.factsandcomparisons.com/index.aspx?

· FDA. Drugs@FDA. 2014. Accessed on: April 3, 2014. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

· McDonagh MS, Peterson K, Balshem H, Helfand M. US Food and Drug Administration documents can provide unpublished evidence relevant to systematic reviews. *J Clin Epidemiol.* 2013;66(10):1071-108180.

· O'Connor AB. The need for improved access to FDA reviews. *JAMA.* 2009;302(2):191-193.

· Turner EH. How to access and process FDA drug approval packages for use in research. *BMJ.* 2013;347:f5992.

Februrary 2020 search to support Linh Hoang's study

Clinical drug-interaction studies (removing any studies that involved the 65 drugs in our prior work):

Step 1) Initiate search history in https://www.ncbi.nlm.nih.gov/pubmed/advanced.

Step 2) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#1' in the rest of this search strategy:

Clinical Trial [PT] AND "drug interactions"[All Fields]

Step 3) Paste in this query - this is #2 in the search strategy

Antidepressants[All Fields] OR MAOI[All Fields] OR Isocarboxazid[All Fields] OR Phenelzine[All Fields] OR Tranylcypromine[All Fields] OR Selegeline[All Fields] OR SSRI[All Fields] OR Citalopram[All Fields] OR Escitalopram[All Fields] OR Fluoxetine[All Fields] OR Fluvoxamine[All Fields] OR Paroxetine[All Fields] OR Sertraline[All Fields] OR Vilazodone[All Fields] OR SNRI[All Fields] OR Desvenlafaxine[All Fields] OR Duloxetine[All Fields] OR Levomilnacipran[All Fields] OR Milnacipran[All Fields] OR Venlafaxine[All Fields] OR Tetracyclic[All Fields] OR Maprotiline[All Fields] OR Mirtazapine[All Fields] OR TCAs[All Fields] OR Amitriptyline[All Fields] OR Amoxapine[All Fields] OR Clomipramine[All Fields] OR Desipramine[All Fields] OR Doxepin[All Fields] OR Imipramine[All Fields] OR Nortriptyline[All Fields] OR Protriptyline[All Fields] OR Trimipramine[All Fields] OR Buproprion[All Fields] OR Nefazodone[All Fields] OR Vortioxetine[All Fields] OR Iloperidone[All Fields] OR Paliperidone[All Fields] OR Risperidone[All Fields] OR Ziprasidone[All Fields] OR Lurasidone[All Fields] OR Asenapine[All Fields] OR Clozapine[All Fields] OR Loxapine[All Fields] OR Olanzapine[All Fields] OR Quetiapine[All Fields] OR Chlorpromazine[All Fields] OR Fluphenazine[All Fields] OR Perphenazine[All Fields] OR Prochlorperazine[All Fields] OR Thioridazine[All Fields] OR Trifluoperazine[All Fields] OR Haloperidol[All Fields] OR Aripiprazole[All Fields] OR Thiothixene[All Fields] OR Eszopiclone[All Fields] OR Zaleplon[All Fields] OR Zolpidem[All Fields] OR Benzodiazepine[All Fields] OR Estazolam[All Fields] OR Flurazepam[All Fields] OR Quazepam[All Fields] OR Temazepam[All Fields] OR Triazolam[All Fields] OR Atorvastatin[All Fields] OR Fluvastatin[All Fields] OR Lovastatin[All Fields] OR Pitavastatin[All Fields] OR Pravastatin[All Fields] OR Rosuvastatin[All Fields] OR Simvastatin[All Fields] OR warfarin[All Fields] OR dabigatran[All Fields] OR apixaban[All Fields] OR rivaroxaban[All Fields]

Step 4) Check that the 'items found" counts shown in the history table make sense given the queries and double check that the queries were correctly entered

Step 5) paste in the following query to remove all studies that mention the 65 drugs - this is #3

#1 NOT #2

Step 6) paste in the queries for prior DIKB studies examined (see As of January 2018, this PubMed query can be used to… , The list of PMIDs below includes all PubMed indexed articles loaded into…, And this list is the PMIDS of all rejected evidence for the… - these are #4, #5, and #6 -- and then run this query which will be #7

#3 NOT (#4 AND #5 AND #6)

Step 7) Since there were >6K results, we narrowed down the search by picking a few different classes

ATC: urologicals (G04B); INSULINS AND ANALOGUES (A10A), PPIs (A02B), Adrenergic and dopaminergic agents (C01CA), Corticosteroids (A01AC)

-- Used this query in CEM staging_vocabulary to get the ingredient and class names:
```
cem=> with anc_ids as (select concept_id from concept where
concept_code in ('G04B','A10A','A02B','C01CA','A01AC')) select * from
concept_ancestor inner join concept c2 on c2.concept_id =
concept_ancestor.descendant_concept_id where c2.vocabulary_id = 'ATC'
and c2.concept_class_id in ('ATC 4th','ATC 5th') and
ancestor_concept_id in (select anc_ids.concept_id from anc_ids);
cem=> with anc_ids as (select concept_id from concept where
concept_code in ('G04B','A10A','A02B','C01CA','A01AC')) select
distinct c2.concept_name from concept_ancestor inner join concept c2
on c2.concept_id = concept_ancestor.descendant_concept_id where
c2.vocabulary_id = 'ATC' and c2.concept_class_id in ('ATC 4th','ATC
5th') and ancestor_concept_id in (select anc_ids.concept_id from
anc_ids);
```

Here is the query -- #8

"Acidifiers"[All Fields] OR "Adrenergic agents"[All Fields] OR "Corticosteroids"[All Fields] OR "H2-receptor antagonists"[All Fields] OR "Prostaglandins"[All Fields] OR "Proton pump inhibitors"[All Fields] OR "Urinary concrement solvents"[All Fields] OR "acetohydroxamic acid"[All Fields] OR "acetoxolone"[All Fields] OR "alginic acid"[All Fields] OR "alprostadil"[All Fields] OR "amezinium metilsulfate"[All Fields] OR "ammonium chloride"[All Fields] OR "amoxicillin"[All Fields] OR "apomorphine"[All Fields] OR "arbutamine"[All Fields] OR "avanafil"[All Fields] OR "bismuth subcitrate"[All Fields] OR "bismuth subcitrate"[All Fields] OR "bismuth subnitrate"[All Fields] OR "cafedrine"[All Fields] OR "calcium chloride"[All Fields] OR "carbenoxolone"[All Fields] OR "carbenoxolone"[All Fields] OR "cimetidine"[All Fields] OR "clarithromycin"[All Fields] OR "collagen"[All Fields] OR "dapoxetine"[All Fields] OR

"darifenacin"[All Fields] OR "desfesoterodine"[All Fields] OR "dexamethasone"[All Fields] OR "dexlansoprazole"[All Fields] OR "dexrabeprazole"[All Fields] OR "dimethyl sulfoxide"[All Fields] OR "dimetofrine"[All Fields] OR "dobutamine"[All Fields] OR "dopamine"[All Fields] OR "dopaminergic agents"[All Fields] OR "dopexamine"[All Fields] OR "droxidopa"[All Fields] OR "emepronium"[All Fields] OR "enprostil"[All Fields] OR "ephedrine"[All Fields] OR "epinephrine"[All Fields] OR "esomeprazole"[All Fields] OR "etilefrine"[All Fields] OR "famotidine"[All Fields] OR "fenoldopam"[All Fields] OR "fesoterodine"[All Fields] OR "flavoxate"[All Fields] OR "gefarnate"[All Fields] OR "gepefrine"[All Fields] OR "hydrocortisone"[All Fields] OR "ibopamine"[All Fields] OR "insulin"[All Fields] OR "isoprenaline"[All Fields] OR "lafutidine"[All Fields] OR "lansoprazole"[All Fields] OR "magnesium hydroxide"[All Fields] OR "meladrazine"[All Fields] OR "mephentermine"[All Fields] OR "metaraminol"[All Fields] OR "methiosulfonium chloride"[All Fields] OR "methoxamine"[All Fields] OR "metronidazole"[All Fields] OR "midodrine"[All Fields] OR "mirabegron"[All Fields] OR "misoprostol"[All Fields] OR "moxisylyte"[All Fields] OR "niperotidine"[All Fields] OR "nizatidine"[All Fields] OR "norepinephrine"[All Fields] OR "norfenefrine"[All Fields] OR "octopamine"[All Fields] OR "omeprazole"[All Fields] OR "oxedrine"[All Fields] OR "oxybutynin"[All Fields] OR "pantoprazole"[All Fields] OR "pantoprazole"[All Fields] OR "papaverine"[All Fields] OR "pentosan polysulfate sodium"[All Fields] OR "phenazopyridine"[All Fields] OR "phenyl salicylate"[All Fields] OR "phenylephrine"[All Fields] OR "pirenzepine"[All Fields] OR "prednisolone"[All Fields] OR "prenalterol"[All Fields] OR "proglumide"[All Fields] OR "propiverine"[All Fields] OR "rabeprazole"[All Fields] OR "ranitidine"[All Fields] OR "ranitidine bismuth citrate"[All Fields] OR "rebamipide"[All Fields] OR "roxatidine"[All Fields] OR "sildenafil"[All Fields] OR "solifenacin"[All Fields] OR "succinimide"[All Fields] OR "sucralfate"[All Fields] OR "sulglicotide"[All Fields] OR "tadalafil"[All Fields] OR "terodiline"[All Fields] OR "tetracycline"[All Fields] OR "theodrenaline"[All Fields] OR "tiopronin"[All Fields] OR "tolterodine"[All Fields] OR "triamcinolone"[All Fields] OR "trospium"[All Fields] OR "troxipide"[All Fields] OR "udenafil"[All Fields] OR "urologicals"[All Fields] OR "vardenafil"[All Fields] OR "yohimbine"[All Fields] OR "zolimidine"[All Fields]

Step 7) paste in this query which should be clinical drug interaction trials for involving the drugs in the set of drugs, excluding the previously screened studies and the drugs chosen for the prior work - #9

(#1 AND #8) NOT (#2 AND #4 AND #5 AND #6)

Step 8)

#9 AND ("loattrfree full text"[sb] AND "humans"[MeSH Terms])

Step 8) Download history and save it to a text file e.g., "Search history for update for Linh Hoang 2.2020.txt"

Step 9) Click on the "items found" count for #9. Use the PubMed "Send To" interface to save all of the results to a new named collection in My NCBI e.g., "Clinical study update update for Linh Hoang 2.2020". After the collection is created, make the collection public. Also, download as CSV.

Mechanistic drug studies useful for inferring drug interactions (using anticoagulants as an example):

Step 1) Log into My NCBI and go to Pubmed: https://www.ncbi.nlm.nih.gov/pubmed/

Step 2) In the advanced search form, clear the search history - search #1

Antidepressants[All Fields] OR MAOI[All Fields] OR Isocarboxazid[All Fields] OR Phenelzine[All Fields] OR Tranylcypromine[All Fields] OR Selegeline[All Fields] OR SSRI[All Fields] OR Citalopram[All Fields] OR Escitalopram[All Fields] OR Fluoxetine[All Fields] OR Fluvoxamine[All Fields] OR Paroxetine[All Fields] OR Sertraline[All Fields] OR Vilazodone[All Fields] OR SNRI[All Fields] OR Desvenlafaxine[All Fields] OR Duloxetine[All Fields] OR Levomilnacipran[All Fields] OR Milnacipran[All Fields] OR Venlafaxine[All Fields] OR Tetracyclic[All Fields] OR Maprotiline[All Fields] OR Mirtazapine[All Fields] OR TCAs[All Fields] OR Amitriptyline[All Fields] OR Amoxapine[All Fields] OR Clomipramine[All Fields] OR Desipramine[All Fields] OR Doxepin[All Fields] OR Imipramine[All Fields] OR Nortriptyline[All Fields] OR Protriptyline[All Fields] OR Trimipramine[All Fields] OR Buproprion[All Fields] OR Nefazodone[All Fields] OR Vortioxetine[All Fields] OR Iloperidone[All Fields] OR Paliperidone[All Fields] OR Risperidone[All Fields] OR Ziprasidone[All Fields] OR Lurasidone[All Fields] OR Asenapine[All Fields] OR Clozapine[All Fields] OR Loxapine[All Fields] OR Olanzapine[All Fields] OR Quetiapine[All Fields] OR Chlorpromazine[All Fields] OR Fluphenazine[All Fields] OR Perphenazine[All Fields] OR Prochlorperazine[All Fields] OR Thioridazine[All Fields] OR Trifluoperazine[All Fields] OR Haloperidol[All Fields] OR Aripiprazole[All Fields] OR Thiothixene[All Fields] OR Eszopiclone[All Fields] OR Zaleplon[All Fields] OR Zolpidem[All Fields] OR Benzodiazepine[All Fields] OR Estazolam[All Fields] OR Flurazepam[All Fields] OR Quazepam[All Fields] OR Temazepam[All Fields] OR Triazolam[All Fields] OR Atorvastatin[All Fields] OR Fluvastatin[All Fields] OR Lovastatin[All Fields] OR Pitavastatin[All Fields] OR Pravastatin[All Fields] OR Rosuvastatin[All Fields] OR Simvastatin[All Fields] OR warfarin[All Fields] OR dabigatran[All Fields] OR apixaban[All Fields] OR rivaroxaban[All Fields]

Step 3) Check that the 'items found" counts shown in the history table make sense given the queries and double check that the queries were correctly entered

Step 4) Paste in the query [As of January 2018, this PubMed query can be used to...](#).... into builder (using 'edit') and click "add to history" - this is referred to as '#2' in the rest of this search strategy

Step 4) Paste in the query [The list of PMIDs below includes all PubMed indexed articles loaded into...](#) into builder (using 'edit') and click "add to history" - this is referred to as '#3' in the rest of this search strategy

Step 5) Paste in the query [And this list is the PMIDS of all rejected evidence for the...](#) into builder (using 'edit') and click "add to history" - this is referred to as '#4' in the rest of this search strategy

Step 6) Paste in this query - #5

"Acidifiers"[All Fields] OR "Adrenergic agents"[All Fields] OR "Corticosteroids"[All Fields] OR "H2-receptor antagonists"[All Fields] OR "Prostaglandins"[All Fields] OR "Proton pump inhibitors"[All Fields] OR "Urinary concrement solvents"[All Fields] OR "acetohydroxamic acid"[All Fields] OR "acetoxolone"[All Fields] OR "alginic acid"[All Fields] OR "alprostadil"[All Fields] OR "amezinium metilsulfate"[All Fields] OR "ammonium chloride"[All Fields] OR "amoxicillin"[All Fields] OR "apomorphine"[All Fields] OR "arbutamine"[All Fields] OR "avanafil"[All Fields] OR "bismuth subcitrate"[All Fields] OR "bismuth subcitrate"[All Fields] OR "bismuth subnitrate"[All Fields] OR "cafedrine"[All Fields] OR "calcium chloride"[All Fields] OR "carbenoxolone"[All Fields] OR "carbenoxolone"[All Fields] OR "cimetidine"[All Fields] OR "clarithromycin"[All Fields] OR "collagen"[All Fields] OR "dapoxetine"[All Fields] OR "darifenacin"[All Fields] OR "desfesoterodine"[All Fields] OR "dexamethasone"[All Fields] OR "dexlansoprazole"[All Fields] OR "dexrabeprazole"[All Fields] OR "dimethyl sulfoxide"[All Fields] OR "dimetofrine"[All Fields] OR "dobutamine"[All Fields] OR "dopamine"[All Fields] OR "dopaminergic agents"[All Fields] OR "dopexamine"[All Fields] OR "droxidopa"[All Fields] OR "emepronium"[All Fields] OR "enprostil"[All Fields] OR "ephedrine"[All Fields] OR "epinephrine"[All Fields] OR "esomeprazole"[All Fields] OR "etilefrine"[All Fields] OR "famotidine"[All Fields] OR "fenoldopam"[All Fields] OR "fesoterodine"[All Fields] OR "flavoxate"[All Fields] OR "gefarnate"[All Fields] OR "gepefrine"[All Fields] OR "hydrocortisone"[All Fields] OR "ibopamine"[All Fields] OR "insulin"[All Fields] OR "isoprenaline"[All Fields] OR "lafutidine"[All Fields] OR "lansoprazole"[All Fields] OR "magnesium hydroxide"[All Fields] OR "meladrazine"[All Fields] OR "mephentermine"[All Fields] OR "metaraminol"[All Fields] OR "methiosulfonium chloride"[All Fields] OR "methoxamine"[All Fields] OR "metronidazole"[All Fields] OR "midodrine"[All Fields] OR "mirabegron"[All Fields] OR "misoprostol"[All Fields] OR "moxisylyte"[All Fields] OR "niperotidine"[All Fields] OR "nizatidine"[All Fields] OR "norepinephrine"[All Fields] OR "norfenefrine"[All Fields] OR "octopamine"[All Fields] OR "omeprazole"[All Fields] OR "oxedrine"[All Fields] OR "oxybutynin"[All Fields] OR "pantoprazole"[All Fields] OR "pantoprazole"[All Fields] OR "papaverine"[All Fields] OR "pentosan polysulfate sodium"[All Fields] OR "phenazopyridine"[All Fields] OR "phenyl salicylate"[All Fields] OR "phenylephrine"[All Fields] OR "pirenzepine"[All

Fields] OR "prednisolone"[All Fields] OR "prenalterol"[All Fields] OR "proglumide"[All Fields] OR "propiverine"[All Fields] OR "rabeprazole"[All Fields] OR "ranitidine"[All Fields] OR "ranitidine bismuth citrate"[All Fields] OR "rebamipide"[All Fields] OR "roxatidine"[All Fields] OR "sildenafil"[All Fields] OR "solifenacin"[All Fields] OR "succinimide"[All Fields] OR "sucralfate"[All Fields] OR "sulglicotide"[All Fields] OR "tadalafil"[All Fields] OR "terodiline"[All Fields] OR "tetracycline"[All Fields] OR "theodrenaline"[All Fields] OR "tiopronin"[All Fields] OR "tolterodine"[All Fields] OR "triamcinolone"[All Fields] OR "trospium"[All Fields] OR "troxipide"[All Fields] OR "udenafil"[All Fields] OR "urologicals"[All Fields] OR "vardenafil"[All Fields] OR "yohimbine"[All Fields] OR "zolimidine"[All Fields]

Step 7) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#6' in the rest of this search strategy:

"Cytochrome P-450 Enzyme System"[MeSH Terms] OR "Cytochrome P450 Family 1"[MeSH Terms] OR "Cytochrome P450 Family 2"[MeSH Terms] OR "Cytochrome P450 Family 3"[MeSH Terms] OR CYP1A1[All Fields] OR CYP1A2[All Fields] OR CYP1A3[All Fields] OR CYP1A4[All Fields] OR CYP1A5[All Fields] OR CYP2D6[All Fields] OR CYP2C9[All Fields] OR CYP2A6[All Fields] OR CYP2C8[All Fields] OR CYP2C19[All Fields] OR CYP2B6[All Fields] OR CYP2B1[All Fields] OR CYP2E1[All Fields] OR CYP3A4[All Fields] OR CYP3A5[All Fields] OR UGT1[All Fields] OR UGT1A1[All Fields] OR UGT1A3[All Fields] OR UGT1A4[All Fields] OR UGT1A5[All Fields] OR UGT1A6[All Fields] OR UGT1A7[All Fields] OR UGT1A8[All Fields] OR UGT1A9[All Fields] OR UGT1A10[All Fields] OR UGT2[All Fields] OR UGT2A1[All Fields] OR UGT2A2[All Fields] OR UGT2A3[All Fields] OR UGT2B4[All Fields] OR UGT2B7[All Fields] OR UGT2B10[All Fields] OR UGT2B11[All Fields] OR UGT2B15[All Fields] OR UGT2B17[All Fields] OR UGT2B28[All Fields] OR B3GAT1[All Fields] OR B3GAT2[All Fields] OR B3GAT3[All Fields]

Step 8) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#7' in the rest of this search strategy

"Solute Carrier Proteins"[MeSH Terms] OR "Membrane Transport Proteins"[MeSH Terms] OR "P-gp"[All Fields] OR "p-glycoprotein"[All Fields] OR BCRP[All Fields] OR OCT2[All Fields] OR "Organic Cation Transporter 2"[MeSH Terms] OR "Organic Cation Transport Proteins"[MeSH Terms] OR MATE1[All Fields] OR "SLC4A Proteins"[MeSH Terms] OR MATE-2K[All Fields] OR "SLC4A Proteins"[MeSH Terms] OR OATP[All Fields] OR OAT1[All Fields] OR "Organic Anion Transport Protein 1"[MeSH Terms] OR OAT3[All Fields] OR UGT1[All Fields] OR "Glucuronosyltransferase"[MeSH Terms] OR ABC[All Fields] OR "ATP-Binding Cassette Transporters"[MeSH Terms]

Step 9) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#8' in the rest of this search strategy

(((Pharmacokinetics[MeSH Terms] OR pharmacokinetic[All Fields]) or (inhibit[All Fields] or inhibition[All Fields]) OR substrate[All Fields]) NOT Clinical Trial [PT]) NOT Case Reports [PT]))

Step 10) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#9' in the rest of this search strategy

#5 AND #8

Step 11) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#10' in the rest of this search strategy

(#9 AND (#6 OR #7)) NOT (#1 AND #2 AND #3 AND #4)

Step 12) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#11' in the rest of this search strategy

#10 AND ("loattrfree full text"[sb] AND "humans"[MeSH Terms])

Step 13) Check that the 'items found" counts shown in the history table make sense given the queries and double check that the queries were correctly entered

Step 14) Download history and save it to a text file e.g., "Search history for Feb 2020 Mechanism search Linh Hoang.txt"

Step 15) Click on the "items found" count for #11. Use the PubMed "Send To" interface to save all of the results to a new named collection in My NCBI e.g., "Final Feb 2020 mechanism search for Linh Hoang". After the collection is created, make the collection public. Also, download as CSV.

Focused attempt to find DDI PK Clinical Non-Randomized parallel groups

Step 1) Initiate search history in https://www.ncbi.nlm.nih.gov/pubmed/advanced.

Step 2) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#1' in the rest of this search strategy:

Clinical Trial [PT] AND "drug interactions"[All Fields] AND ("Non-randomized"[All Fields] OR "Parallel"[All Fields])

Step 3) Paste in this query - this is #2 in the search strategy

Antidepressants[All Fields] OR MAOI[All Fields] OR Isocarboxazid[All Fields] OR Phenelzine[All Fields] OR Tranylcypromine[All Fields] OR Selegeline[All Fields] OR SSRI[All Fields] OR Citalopram[All Fields] OR Escitalopram[All Fields] OR Fluoxetine[All Fields] OR Fluvoxamine[All Fields] OR Paroxetine[All Fields] OR Sertraline[All Fields] OR Vilazodone[All Fields] OR SNRI[All Fields] OR Desvenlafaxine[All Fields] OR Duloxetine[All Fields] OR Levomilnacipran[All Fields] OR Milnacipran[All Fields] OR Venlafaxine[All Fields] OR Tetracyclic[All Fields] OR Maprotiline[All Fields] OR Mirtazapine[All Fields] OR TCAs[All Fields] OR Amitriptyline[All Fields] OR Amoxapine[All Fields] OR Clomipramine[All Fields] OR Desipramine[All Fields] OR Doxepin[All Fields] OR Imipramine[All Fields] OR Nortriptyline[All Fields] OR Protriptyline[All Fields] OR Trimipramine[All Fields] OR Buproprion[All Fields] OR Nefazodone[All Fields] OR Vortioxetine[All Fields] OR Iloperidone[All Fields] OR Paliperidone[All Fields] OR Risperidone[All Fields] OR Ziprasidone[All Fields] OR Lurasidone[All Fields] OR Asenapine[All Fields] OR Clozapine[All Fields] OR Loxapine[All Fields] OR Olanzapine[All Fields] OR Quetiapine[All Fields] OR Chlorpromazine[All Fields] OR Fluphenazine[All Fields] OR Perphenazine[All Fields] OR Prochlorperazine[All Fields] OR Thioridazine[All Fields] OR Trifluoperazine[All Fields] OR Haloperidol[All Fields] OR Aripiprazole[All Fields] OR Thiothixene[All Fields] OR Eszopiclone[All Fields] OR Zaleplon[All Fields] OR Zolpidem[All Fields] OR Benzodiazepine[All Fields] OR Estazolam[All Fields] OR Flurazepam[All Fields] OR Quazepam[All Fields] OR Temazepam[All Fields] OR Triazolam[All Fields] OR Atorvastatin[All Fields] OR Fluvastatin[All Fields] OR Lovastatin[All Fields] OR Pitavastatin[All Fields] OR Pravastatin[All Fields] OR Rosuvastatin[All Fields] OR Simvastatin[All Fields] OR warfarin[All Fields] OR dabigatran[All Fields] OR apixaban[All Fields] OR rivaroxaban[All Fields]

Step 4) Check that the 'items found" counts shown in the history table make sense given the queries and double check that the queries were correctly entered

Step 5) paste in the following query to remove all studies that mention the 65 drugs - this is #3

#1 NOT #2

Step 6) paste in the queries for prior DIKB studies examined (see As of January 2018, this PubMed query can be used to… , The list of PMIDs below includes all PubMed indexed articles loaded into…, And this list is the PMIDS of all rejected evidence for the… - these are #4, #5, and #6 -- then add these PMIDs which were screened in the 2020 clinical and mechanistic studies above as #7:

(31261930[uid] OR 30911906[uid] OR 30538075[uid] OR 30536154[uid] OR 30084103[uid] OR 30016552[uid] OR 29926968[uid] OR 29920736[uid] OR 29846770[uid] OR 29768713[uid] OR 29752643[uid] OR 29635061[uid] OR 29544728[uid] OR 29507283[uid] OR 29498038[uid] OR 29439084[uid] OR 29432286[uid] OR 29411268[uid] OR 29392574[uid] OR 29178272[uid] OR 29134635[uid] OR 29125715[uid] OR 29105855[uid] OR 28865153[uid] OR 28852909[uid] OR 28800141[uid] OR 28625018[uid] OR 28599060[uid] OR 28474741[uid] OR 28466366[uid] OR 28408803[uid] OR 28395507[uid] OR 28347654[uid] OR 28327932[uid] OR 28155129[uid] OR 28044450[uid] OR 28006886[uid] OR 27893182[uid] OR 27552251[uid] OR 27737436[uid] OR 27628584[uid] OR 27581248[uid] OR 27518170[uid] OR 27460746[uid] OR 27457818[uid] OR 27397444[uid] OR 27363313[uid] OR 27277189[uid] OR 27273343[uid] OR 27253174[uid] OR 27245553[uid] OR 27209586[uid] OR 27154174[uid] OR 27009433[uid] OR 26991517[uid] OR 26874330[uid] OR 26855561[uid] OR 26683949[uid] OR 26681081[uid] OR 26597253[uid] OR 26459906[uid] OR 26309401[uid] OR 25929560[uid] OR 25913040[uid] OR 25862215[uid] OR 25853370[uid] OR 25833022[uid] OR 25759565[uid] OR 25652672[uid] OR 25646891[uid] OR 25581063[uid] OR 25529192[uid] OR 25492571[uid] OR 25421879[uid] OR 25328082[uid] OR 25327812[uid] OR 25274610[uid] OR 25231186[uid] OR 25223504[uid] OR 25216597[uid] OR 25160589[uid] OR 24973042[uid] OR 24962473[uid] OR 24928479[uid] OR 24868146[uid] OR 24839948[uid] OR 24699894[uid] OR 24602137[uid] OR 24557425[uid] OR 24504700[uid] OR 24386300[uid] OR 24316175[uid] OR 24315907[uid] OR 24292052[uid] OR 24246616[uid] OR 24239201[uid] OR 24100471[uid] OR 24036846[uid] OR 23985411[uid] OR 23975654[uid] OR 23921573[uid] OR 23738582[uid] OR 23630016[uid] OR 23615868[uid] OR 23520311[uid] OR 23519656[uid] OR 23333143[uid] OR 23325481[uid] OR 23305158[uid] OR 23210726[uid] OR 23043164[uid] OR 23027198[uid] OR 22990092[uid] OR 22987022[uid] OR 22954754[uid] OR 22900583[uid] OR 22820908[uid] OR 22777148[uid] OR 22703532[uid] OR 22661187[uid] OR 22574741[uid] OR 22486858[uid] OR 22464259[uid] OR 22404145[uid] OR 22374642[uid] OR 22318618[uid] OR 22240839[uid] OR 22189672[uid] OR 22168398[uid] OR 21972820[uid] OR 21950641[uid] OR 21883386[uid] OR 21870106[uid] OR 21825263[uid] OR 21770762[uid] OR 21726302[uid] OR 21696537[uid] OR 21631929[uid] OR 21548660[uid] OR 21545485[uid] OR 21512411[uid] OR 21496065[uid] OR 21496064[uid] OR 21480191[uid] OR 21360514[uid] OR 21330636[uid] OR 21277984[uid] OR 21223356[uid] OR 21219403[uid] OR 21216137[uid] OR 21175437[uid] OR 21171670[uid] OR 21084246[uid] OR 20925534[uid] OR 20924751[uid] OR 20838775[uid] OR 20736505[uid] OR 20705902[uid] OR 20679179[uid] OR 20642546[uid] OR 20590587[uid] OR 20554869[uid] OR 20400652[uid] OR 20378736[uid] OR 20237299[uid] OR 20233203[uid] OR 20233197[uid] OR 20220040[uid] OR 20164296[uid] OR 20160047[uid] OR 20150302[uid] OR 20147896[uid] OR 20145345[uid] OR 20078609[uid] OR 20075384[uid] OR 20040040[uid] OR 20014909[uid] OR 20002088[uid] OR 19877981[uid] OR 19864219[uid] OR 19761935[uid] OR 19740396[uid] OR 19660002[uid] OR 19646280[uid] OR 19444001[uid] OR

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Step 7) Query #8:

#3 NOT (#4 AND #5 AND #6 AND #7)

Step 8) Query #9

#8 AND ("loattrfree full text"[sb] AND "humans"[MeSH Terms])

Focused attempt to find DDI PK Phenotype and Genotype

Step 1) Initiate search history in https://www.ncbi.nlm.nih.gov/pubmed/advanced.

Step 2) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#1' in the rest of this search strategy:

Clinical Trial [PT] AND "pharmacokinetic"[All Fields] AND ("phenotype"[All Fields] OR "genotype"[All Fields])) AND "drug"[All Fields]

Step 3) Paste in this query - this is #2 in the search strategy

Antidepressants[All Fields] OR MAOI[All Fields] OR Isocarboxazid[All Fields] OR Phenelzine[All Fields] OR Tranylcypromine[All Fields] OR Selegeline[All Fields] OR SSRI[All Fields] OR Citalopram[All Fields] OR Escitalopram[All Fields] OR Fluoxetine[All Fields] OR Fluvoxamine[All Fields] OR Paroxetine[All Fields] OR Sertraline[All Fields] OR Vilazodone[All Fields] OR SNRI[All Fields] OR Desvenlafaxine[All Fields] OR Duloxetine[All Fields] OR Levomilnacipran[All Fields] OR Milnacipran[All Fields] OR Venlafaxine[All Fields] OR Tetracyclic[All Fields] OR Maprotiline[All Fields] OR Mirtazapine[All Fields] OR TCAs[All Fields] OR Amitriptyline[All Fields] OR Amoxapine[All Fields] OR Clomipramine[All Fields] OR Desipramine[All Fields] OR Doxepin[All Fields] OR Imipramine[All Fields] OR Nortriptyline[All Fields] OR Protriptyline[All Fields] OR Trimipramine[All Fields] OR Buproprion[All Fields] OR Nefazodone[All Fields] OR Vortioxetine[All Fields] OR Iloperidone[All Fields] OR Paliperidone[All Fields] OR Risperidone[All Fields] OR Ziprasidone[All Fields] OR Lurasidone[All Fields] OR Asenapine[All Fields] OR Clozapine[All Fields] OR Loxapine[All Fields] OR Olanzapine[All Fields] OR Quetiapine[All Fields] OR Chlorpromazine[All Fields] OR Fluphenazine[All Fields] OR Perphenazine[All Fields] OR Prochlorperazine[All Fields] OR Thioridazine[All Fields] OR Trifluoperazine[All Fields] OR Haloperidol[All Fields] OR Aripiprazole[All Fields] OR Thiothixene[All Fields] OR Eszopiclone[All Fields] OR Zaleplon[All Fields] OR Zolpidem[All Fields] OR Benzodiazepine[All Fields] OR Estazolam[All Fields] OR Flurazepam[All Fields] OR Quazepam[All Fields] OR Temazepam[All Fields] OR Triazolam[All Fields] OR Atorvastatin[All Fields] OR Fluvastatin[All Fields] OR Lovastatin[All Fields] OR Pitavastatin[All Fields] OR Pravastatin[All Fields] OR Rosuvastatin[All Fields] OR Simvastatin[All Fields] OR warfarin[All Fields] OR dabigatran[All Fields] OR apixaban[All Fields] OR rivaroxaban[All Fields]

Step 4) Check that the 'items found" counts shown in the history table make sense given the queries and double check that the queries were correctly entered

Step 5) paste in the following query to remove all studies that mention the 65 drugs - this is #3

#1 NOT #2

Step 6) paste in the queries for prior DIKB studies examined (see As of January 2018, this PubMed query can be used to… , The list of PMIDs below includes all PubMed indexed articles loaded into…, And this list is the PMIDS of all rejected evidence for the… - these are #4, #5, and #6 -- then add these PMIDs which were screened in the 2020 clinical and mechanistic studies above as #7:

(31261930[uid] OR 30911906[uid] OR 30538075[uid] OR 30536154[uid] OR 30084103[uid] OR 30016552[uid] OR 29926968[uid] OR 29920736[uid] OR 29846770[uid] OR 29768713[uid] OR 29752643[uid] OR 29635061[uid] OR 29544728[uid] OR 29507283[uid] OR 29498038[uid] OR 29439084[uid] OR 29432286[uid] OR 29411268[uid] OR 29392574[uid] OR 29178272[uid] OR 29134635[uid] OR 29125715[uid] OR 29105855[uid] OR 28865153[uid] OR 28852909[uid] OR 28800141[uid] OR 28625018[uid] OR 28599060[uid] OR 28474741[uid] OR 28466366[uid] OR 28408803[uid] OR 28395507[uid] OR 28347654[uid] OR 28327932[uid] OR 28155129[uid] OR 28044450[uid] OR 28006886[uid] OR 27893182[uid] OR 27552251[uid] OR 27737436[uid] OR 27628584[uid] OR 27581248[uid] OR 27518170[uid] OR 27460746[uid] OR 27457818[uid] OR 27397444[uid] OR 27363313[uid] OR 27277189[uid] OR 27273343[uid] OR 27253174[uid] OR 27245553[uid] OR 27209586[uid] OR 27154174[uid] OR 27009433[uid] OR 26991517[uid] OR 26874330[uid] OR 26855561[uid] OR 26683949[uid] OR 26681081[uid] OR 26597253[uid] OR 26459906[uid] OR 26309401[uid] OR 25929560[uid] OR 25913040[uid] OR 25862215[uid] OR 25853370[uid] OR 25833022[uid] OR 25759565[uid] OR 25652672[uid] OR 25646891[uid] OR 25581063[uid] OR 25529192[uid] OR 25492571[uid] OR 25421879[uid] OR 25328082[uid] OR 25327812[uid] OR 25274610[uid] OR 25231186[uid] OR 25223504[uid] OR 25216597[uid] OR 25160589[uid] OR 24973042[uid] OR 24962473[uid] OR 24928479[uid] OR 24868146[uid] OR 24839948[uid] OR 24699894[uid] OR 24602137[uid] OR 24557425[uid] OR 24504700[uid] OR 24386300[uid] OR 24316175[uid] OR 24315907[uid] OR 24292052[uid] OR 24246616[uid] OR 24239201[uid] OR 24100471[uid] OR 24036846[uid] OR 23985411[uid] OR 23975654[uid] OR 23921573[uid] OR 23738582[uid] OR 23630016[uid] OR 23615868[uid] OR 23520311[uid] OR 23519656[uid] OR 23333143[uid] OR 23325481[uid] OR 23305158[uid] OR 23210726[uid] OR 23043164[uid] OR 23027198[uid] OR 22990092[uid] OR 22987022[uid] OR 22954754[uid] OR 22900583[uid] OR 22820908[uid] OR 22777148[uid] OR 22703532[uid] OR 22661187[uid] OR 22574741[uid] OR 22486858[uid] OR 22464259[uid] OR 22404145[uid] OR 22374642[uid] OR 22318618[uid] OR 22240839[uid] OR 22189672[uid] OR 22168398[uid] OR 21972820[uid] OR 21950641[uid] OR 21883386[uid] OR 21870106[uid] OR 21825263[uid] OR 21770762[uid] OR 21726302[uid] OR 21696537[uid] OR 21631929[uid] OR 21548660[uid] OR 21545485[uid] OR 21512411[uid] OR 21496065[uid] OR 21496064[uid] OR 21480191[uid] OR 21360514[uid] OR 21330636[uid] OR 21277984[uid] OR 21223356[uid] OR 21219403[uid] OR 21216137[uid] OR 21175437[uid] OR 21171670[uid] OR 21084246[uid] OR 20925534[uid] OR 20924751[uid] OR 20838775[uid] OR 20736505[uid] OR 20705902[uid] OR 20679179[uid] OR 20642546[uid] OR 20590587[uid] OR 20554869[uid] OR 20400652[uid] OR 20378736[uid] OR 20237299[uid] OR 20233203[uid] OR 20233197[uid] OR 20220040[uid] OR 20164296[uid] OR 20160047[uid] OR 20150302[uid] OR 20147896[uid] OR 20145345[uid] OR 20078609[uid] OR 20075384[uid] OR 20040040[uid] OR 20014909[uid] OR 20002088[uid] OR 19877981[uid] OR 19864219[uid] OR 19761935[uid] OR 19740396[uid] OR 19660002[uid] OR 19646280[uid] OR 19444001[uid] OR

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6319541[uid] OR 6128999[uid] OR 6286112[uid] OR 7037029[uid] OR 6262771[uid] OR
6967506[uid] OR 110586[uid] OR 689037[uid] OR 4799079[uid])

Step 7) Query #8:

#3 NOT (#4 AND #5 AND #6 AND #7)

Step 8) Query #9

#8 AND ("loattrfree full text"[sb] AND "humans"[MeSH Terms])

Focused attempt to find DDI PK Clinical Non-Randomized parallel groups
Step 1) Initiate search history in https://www.ncbi.nlm.nih.gov/pubmed/advanced.

Step 2) Paste in this query into builder (using 'edit') and click "add to history" - this is referred to as '#1' in the rest of this search strategy:

Clinical Trial [PT] AND "drug interactions"[All Fields] AND ("Non-randomized"[All Fields] OR "Parallel"[All Fields])

Step 3) Paste in this query - this is #2 in the search strategy

Antidepressants[All Fields] OR MAOI[All Fields] OR Isocarboxazid[All Fields] OR Phenelzine[All Fields] OR Tranylcypromine[All Fields] OR Selegeline[All Fields] OR SSRI[All Fields] OR Citalopram[All Fields] OR Escitalopram[All Fields] OR Fluoxetine[All Fields] OR Fluvoxamine[All Fields] OR Paroxetine[All Fields] OR Sertraline[All Fields] OR Vilazodone[All Fields] OR SNRI[All Fields] OR Desvenlafaxine[All Fields] OR Duloxetine[All Fields] OR Levomilnacipran[All Fields] OR Milnacipran[All Fields] OR Venlafaxine[All Fields] OR Tetracyclic[All Fields] OR Maprotiline[All Fields] OR Mirtazapine[All Fields] OR TCAs[All Fields] OR Amitriptyline[All Fields] OR Amoxapine[All Fields] OR Clomipramine[All Fields] OR Desipramine[All Fields] OR Doxepin[All Fields] OR Imipramine[All Fields] OR Nortriptyline[All Fields] OR Protriptyline[All Fields] OR Trimipramine[All Fields] OR Buproprion[All Fields] OR Nefazodone[All Fields] OR Vortioxetine[All Fields] OR Iloperidone[All Fields] OR Paliperidone[All Fields] OR Risperidone[All Fields] OR Ziprasidone[All Fields] OR Lurasidone[All Fields] OR Asenapine[All Fields] OR Clozapine[All Fields] OR Loxapine[All Fields] OR Olanzapine[All Fields] OR Quetiapine[All Fields] OR Chlorpromazine[All Fields] OR Fluphenazine[All Fields] OR Perphenazine[All Fields] OR Prochlorperazine[All Fields] OR Thioridazine[All Fields] OR Trifluoperazine[All Fields] OR Haloperidol[All Fields] OR Aripiprazole[All Fields] OR Thiothixene[All Fields] OR Eszopiclone[All Fields] OR Zaleplon[All Fields] OR Zolpidem[All Fields] OR Benzodiazepine[All Fields] OR Estazolam[All Fields] OR Flurazepam[All Fields] OR Quazepam[All Fields] OR Temazepam[All Fields] OR Triazolam[All Fields] OR Atorvastatin[All Fields] OR Fluvastatin[All Fields] OR Lovastatin[All Fields] OR Pitavastatin[All Fields] OR Pravastatin[All Fields] OR Rosuvastatin[All Fields] OR Simvastatin[All Fields] OR warfarin[All Fields] OR dabigatran[All Fields] OR apixaban[All Fields] OR rivaroxaban[All Fields]

Step 4) Check that the 'items found" counts shown in the history table make sense given the queries and double check that the queries were correctly entered

Step 5) paste in the following query to remove all studies that mention the 65 drugs - this is #3

#1 NOT #2

Step 6) paste in the queries for prior DIKB studies examined (see As of January 2018, this PubMed query can be used to… , The list of PMIDs below includes all PubMed indexed articles loaded into…, And this list is the PMIDS of all rejected evidence for the… - these are #4, #5, and #6 -- then add these PMIDs which were screened in the 2020 clinical and mechanistic studies above as #7:

(31261930[uid] OR 30911906[uid] OR 30538075[uid] OR 30536154[uid] OR 30084103[uid] OR 30016552[uid] OR 29926968[uid] OR 29920736[uid] OR 29846770[uid] OR 29768713[uid] OR 29752643[uid] OR 29635061[uid] OR 29544728[uid] OR 29507283[uid] OR 29498038[uid] OR

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6967506[uid] OR 110586[uid] OR 689037[uid] OR 4799079[uid])

Step 7) Query #8:

#3 NOT (#4 AND #5 AND #6 AND #7)

Step 8) Query #9

#8 AND ("loattrfree full text"[sb] AND "humans"[MeSH Terms])