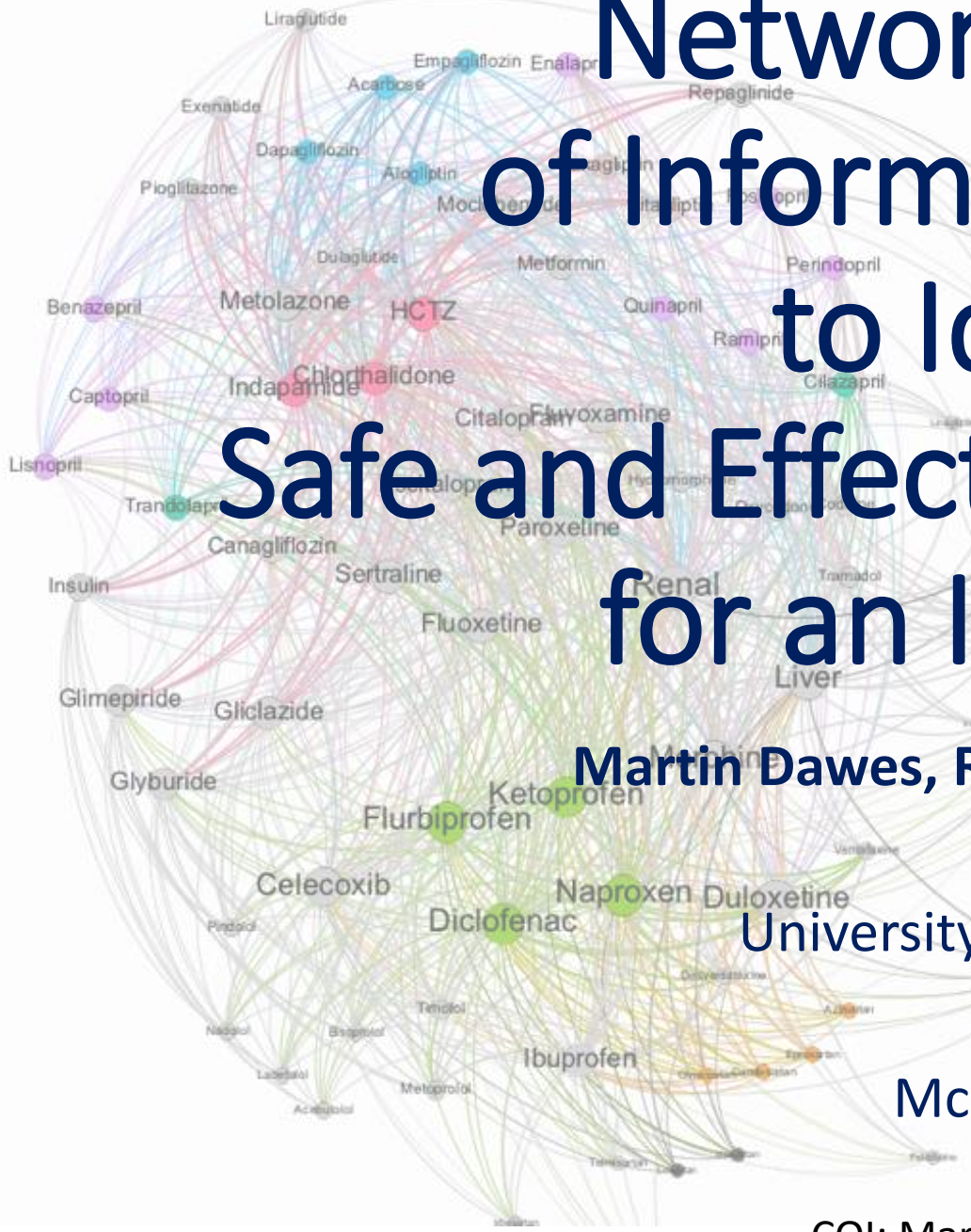


Network Analysis of Information Needs to Identify Safe and Effective prescriptions for an Individual.

Martin Dawes, Roland Grad, Pierre Pluye

University of British Columbia

&

McGill University

COI: Martin Dawes receives funds from GenXys, a UBC spin-out company.

The Problem (s)

- **53% of adults have MM2+**
- **33% of adults have MM3+**
- **If you are treating someone with diabetes, depression, and arthritis it is hard to follow the EB guidelines**

- **13% of patients have “high risk” prescriptions even with ”good” electronic medical records**
- **10% if taking 2-4 drugs**
- **80% if taking > 14 drugs**

- **Adverse Drug Events**
- **Within 4 weeks of receiving a primary care prescription, 25% of patients experience an adverse drug event**
- Up to 70% of ADRs leading to ED visits are preventable

Aim: Using Network Analysis explore the potential interactions for a hypothetical patient

- Hypothetical comorbid MM5 patient
  - Osteoarthritis (12 drug options)
  - Depression (12 drug options)
  - Hypertension (34 drug options)
  - Diabetes (18 drug options)
  - Hyperlipidemia (4 drug options)

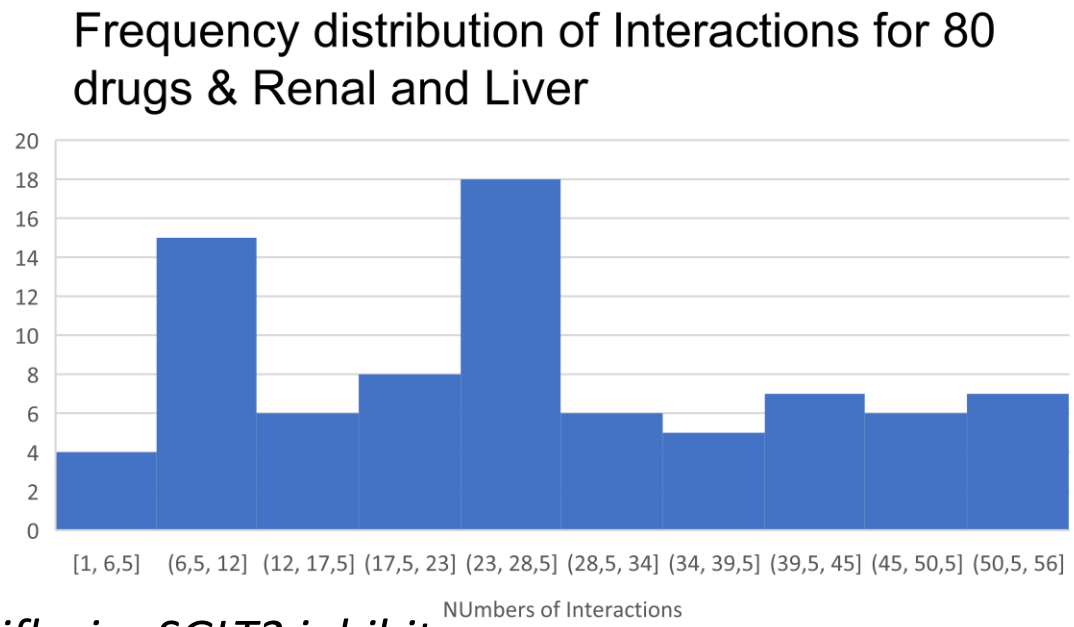
Total of 80 drugs used commonly in primary care available for this patient – no combinations included

- Liver & Renal
- Total of 82 nodes of a network
- That is 3,321 combinations to check for interactions (N*(N-1)/2)

Identify actual potential drug-drug, drug-liver, drug-renal interactions

- Drug Drug Interactions identified using a drug-drug interaction database (Lexicomp)
- Renal interactions identified using a renal drug interaction database and North American product monographs
- Liver Function interactions checked using North American product monographs
- Results: 1,113 described potential interactions

Results:
Types of Interaction



- Interactions were identified as
  - No Action Needed (n=189),
  - Monitor Therapy (n=777),
  - Consider therapy modification (n=144),
  - Avoid combination (n=3).
  - *No Action Needed example: Benazepril and Canagliflozin -SGLT2 inhibitor*
    - *Canagliflozin may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. Canagliflozin may enhance the hypotensive effect of Angiotensin II Receptor*
- The mean number of drug-drug, drug-liver, and drug-renal interactions was 27.1 (Range 1 to 56).
- The frequency of interactions was not normally distributed
- Renal dosing information was identified for 50 drugs,
- Liver dosing information was identified for 46 of the drugs.

Basic Network with node size adjusted according to number of interactions

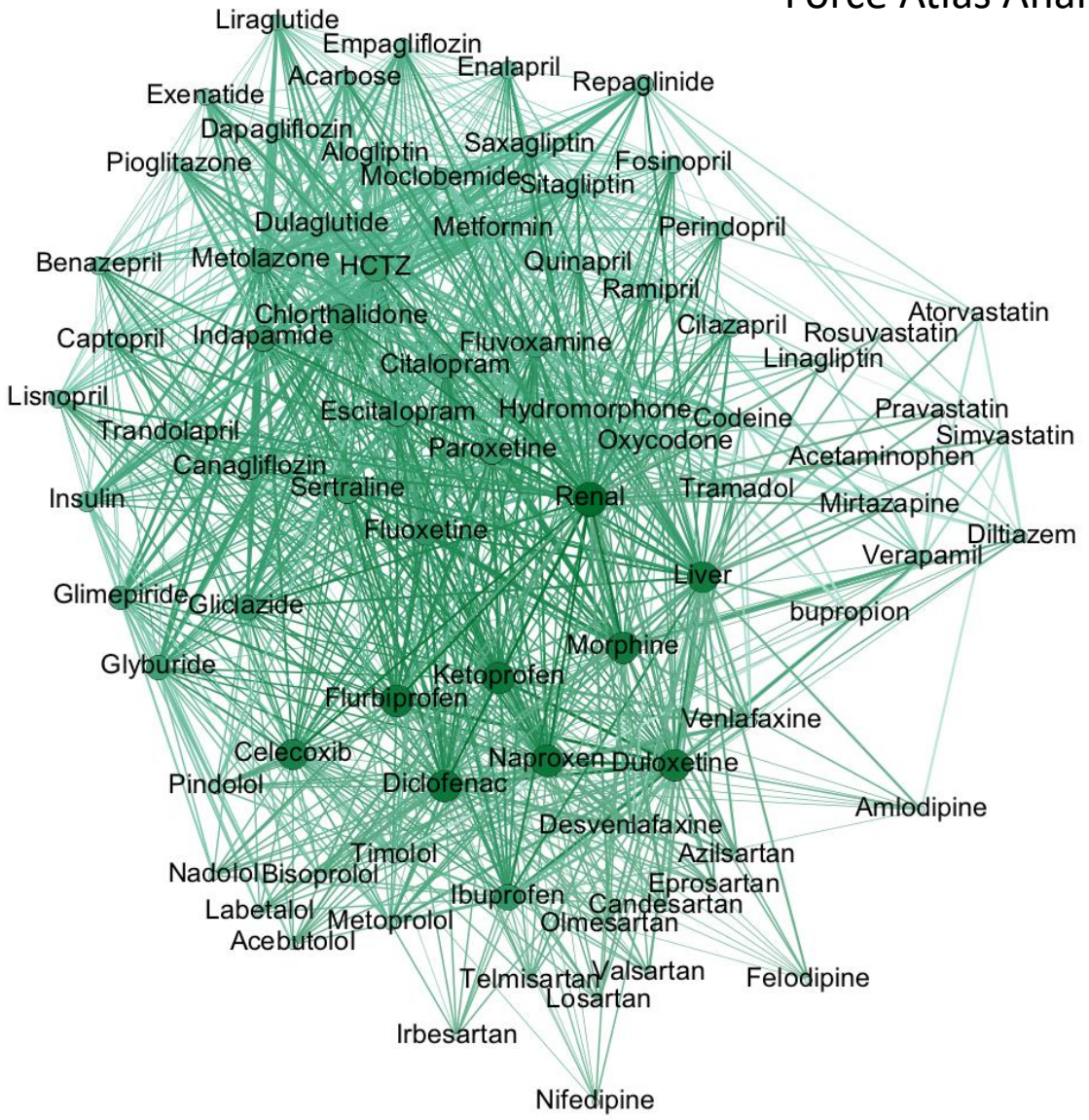
470	Irbesartan	Flurbiprofen	2	C: Monitor therapy	**Summary** Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Specifically, t
471	Labetalol	Flurbiprofen	2	C: Monitor therapy	Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Severity**Moderate **Reliability Rating** Fa
472	Lisnopril	Flurbiprofen	2	C: Monitor therapy	**Summary** Angiotensin-Converting Enzyme Inhibitors may enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Sp
473	Losartan	Flurbiprofen	2	C: Monitor therapy	**Summary** Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Specifically, t
474	Metolazone	Flurbiprofen	2	C: Monitor therapy	Thiazide and Thiazide-Like Diuretics may enhance the nephrotoxic effect of Nonsteroidal Anti-Inflammatory Agents. Nonsteroidal Anti-Infla
475	Metoprolol	Flurbiprofen	2	C: Monitor therapy	Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Severity**Moderate **Reliability Rating** Fa
476	Nadolol	Flurbiprofen	2	C: Monitor therapy	Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Severity**Moderate **Reliability Rating** Fa
477	Olmesartan	Flurbiprofen	2	C: Monitor therapy	**Summary** Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Specifically, t
478	Perindopril	Flurbiprofen	2	C: Monitor therapy	**Summary** Angiotensin-Converting Enzyme Inhibitors may enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Sp
479	Pindolol	Flurbiprofen	2	C: Monitor therapy	Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Severity**Moderate **Reliability Rating** Fa
480	Quinapril	Flurbiprofen	2	C: Monitor therapy	**Summary** Angiotensin-Converting Enzyme Inhibitors may enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Sp
481	Ramipril	Flurbiprofen	2	C: Monitor therapy	**Summary** Angiotensin-Converting Enzyme Inhibitors may enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Sp
482	Telmisartan	Flurbiprofen	2	C: Monitor therapy	**Summary** Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Specifically, t
483	Timolol	Flurbiprofen	2	C: Monitor therapy	Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Severity**Moderate **Reliability Rating** Fa
484	Trandolapril	Flurbiprofen	2	C: Monitor therapy	**Summary** Angiotensin-Converting Enzyme Inhibitors may enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Sp
485	Valsartan	Flurbiprofen	2	C: Monitor therapy	**Summary** Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Specifically, t
486	Venlafaxine	Flurbiprofen	2	C: Monitor therapy	Agents with Antiplatelet Properties may enhance the antiplatelet effect of other Agents with Antiplatelet Properties. **Severity** Moderate **Re**
487	Venlafaxine	Flurbiprofen	2	C: Monitor therapy	Serotonin/Norepinephrine Reuptake Inhibitors may enhance the antiplatelet effect of Nonsteroidal Anti-Inflammatory Agents (Nonselectiv
488	Chlorthalidone	Fluvoxamine	2	C: Monitor therapy	**Summary** Selective Serotonin Reuptake Inhibitors may enhance the hyponatremic effect of Thiazide and Thiazide-Like Diuretics. **Severity**
489	Dulaglutide	Fluvoxamine	2	C: Monitor therapy	Selective Serotonin Reuptake Inhibitors may enhance the hypoglycemic effect of Blood Glucose Lowering Agents. **Severity** Moderate **Relia**
490	Hydrochlorthiazide	Fluvoxamine	2	C: Monitor therapy	**Summary** Selective Serotonin Reuptake Inhibitors may enhance the hyponatremic effect of Thiazide and Thiazide-Like Diuretics. **Severity**
491	Indapamide	Fluvoxamine	2	C: Monitor therapy	**Summary** Selective Serotonin Reuptake Inhibitors may enhance the hyponatremic effect of Thiazide and Thiazide-Like Diuretics. **Severity**
492	Metolazone	Fluvoxamine	2	C: Monitor therapy	**Summary** Selective Serotonin Reuptake Inhibitors may enhance the hyponatremic effect of Thiazide and Thiazide-Like Diuretics. **Severity**
493	Acebutolol	Gliclazide	2	C: Monitor therapy	Beta-Blockers may enhance the hypoglycemic effect of Sulfonylureas. Cardioselective beta-blockers (eg, acebutolol, atenolol, metoprolol,
494	Bisoprolol	Gliclazide	2	C: Monitor therapy	Beta-Blockers may enhance the hypoglycemic effect of Sulfonylureas. Cardioselective beta-blockers (eg, acebutolol, atenolol, metoprolol,
495	Celecoxib	Gliclazide	2	C: Monitor therapy	Nonsteroidal Anti-Inflammatory Agents may diminish the hypoglycemic effect of Sulfonylureas. Nonsteroidal Anti-Inflammatory Agents m
496	Chlorthalidone	Gliclazide	2	C: Monitor therapy	Hyperglycemia-Associated Agents may diminish the therapeutic effect of Antidiabetic Agents. **Severity** Moderate **Reliability Rating** Fair
497	Chlorthalidone	Gliclazide	2	C: Monitor therapy	Thiazide and Thiazide-Like Diuretics may diminish the therapeutic effect of Antidiabetic Agents. **Severity** Moderate **Reliability Rating** Good
498	Citalopram	Gliclazide	2	C: Monitor therapy	Selective Serotonin Reuptake Inhibitors may enhance the hypoglycemic effect of Blood Glucose Lowering Agents. **Severity** Moderate **Relia**
499	Diclofenac	Gliclazide	2	C: Monitor therapy	Nonsteroidal Anti-Inflammatory Agents may diminish the hypoglycemic effect of Sulfonylureas. Nonsteroidal Anti-Inflammatory Agents m
500	Escitalopram	Gliclazide	2	C: Monitor therapy	Selective Serotonin Reuptake Inhibitors may enhance the hypoglycemic effect of Blood Glucose Lowering Agents. **Severity** Moderate **Relia**
501	Fluoxetine	Gliclazide	2	C: Monitor therapy	Selective Serotonin Reuptake Inhibitors may enhance the hypoglycemic effect of Blood Glucose Lowering Agents. **Severity** Moderate **Relia**
502	Flurbiprofen	Gliclazide	2	C: Monitor therapy	Nonsteroidal Anti-Inflammatory Agents may diminish the hypoglycemic effect of Sulfonylureas. Nonsteroidal Anti-Inflammatory Agents m
503	Fluvoxamine	Gliclazide	2	C: Monitor therapy	Selective Serotonin Reuptake Inhibitors may enhance the hypoglycemic effect of Blood Glucose Lowering Agents. **Severity** Moderate **Relia**
504	Hydrochlorthiazide	Gliclazide	2	C: Monitor therapy	Hyperglycemia-Associated Agents may diminish the therapeutic effect of Antidiabetic Agents. **Severity** Moderate **Reliability Rating** Fair
505	Hydrochlorthiazide	Gliclazide	2	C: Monitor therapy	Thiazide and Thiazide-Like Diuretics may diminish the therapeutic effect of Antidiabetic Agents. **Severity** Moderate **Reliability Rating** Good
506	Ibuprofen	Gliclazide	2	C: Monitor therapy	Nonsteroidal Anti-Inflammatory Agents may diminish the hypoglycemic effect of Sulfonylureas. Nonsteroidal Anti-Inflammatory Agents m
507	Indapamide	Gliclazide	2	C: Monitor therapy	Hyperglycemia-Associated Agents may diminish the therapeutic effect of Antidiabetic Agents. **Severity** Moderate **Reliability Rating** Fair
508	Indapamide	Gliclazide	2	C: Monitor therapy	Thiazide and Thiazide-Like Diuretics may diminish the therapeutic effect of Antidiabetic Agents. **Severity** Moderate **Reliability Rating** Good
509	Ketoprofen	Gliclazide	2	C: Monitor therapy	Nonsteroidal Anti-Inflammatory Agents may diminish the hypoglycemic effect of Sulfonylureas. Nonsteroidal Anti-Inflammatory Agents m
510	Labetalol	Gliclazide	2	C: Monitor therapy	Beta-Blockers may enhance the hypoglycemic effect of Sulfonylureas. Cardioselective beta-blockers (eg, acebutolol, atenolol, metoprolol,
511	Metolazone	Gliclazide	2	C: Monitor therapy	Hyperglycemia-Associated Agents may diminish the therapeutic effect of Antidiabetic Agents. **Severity** Moderate **Reliability Rating** Fair
512	Metolazone	Gliclazide	2	C: Monitor therapy	Thiazide and Thiazide-Like Diuretics may diminish the therapeutic effect of Antidiabetic Agents. **Severity** Moderate **Reliability Rating** Good

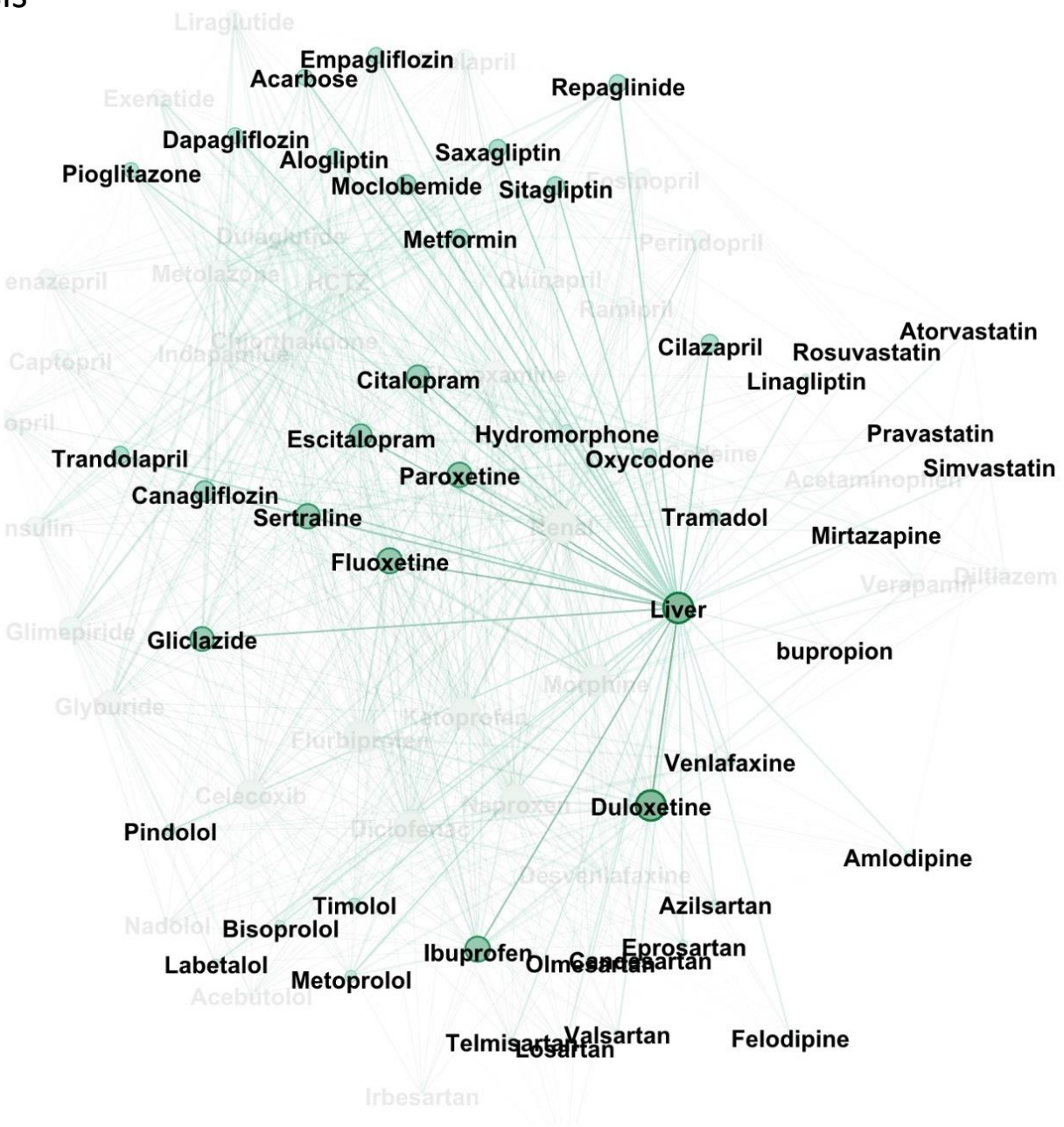
Renal

cocoon of a Cyna moth pupa

on-steroidal anti-inflammatory drugs,
uretics, morphine and duloxetine,
ere the drugs with most interactions.

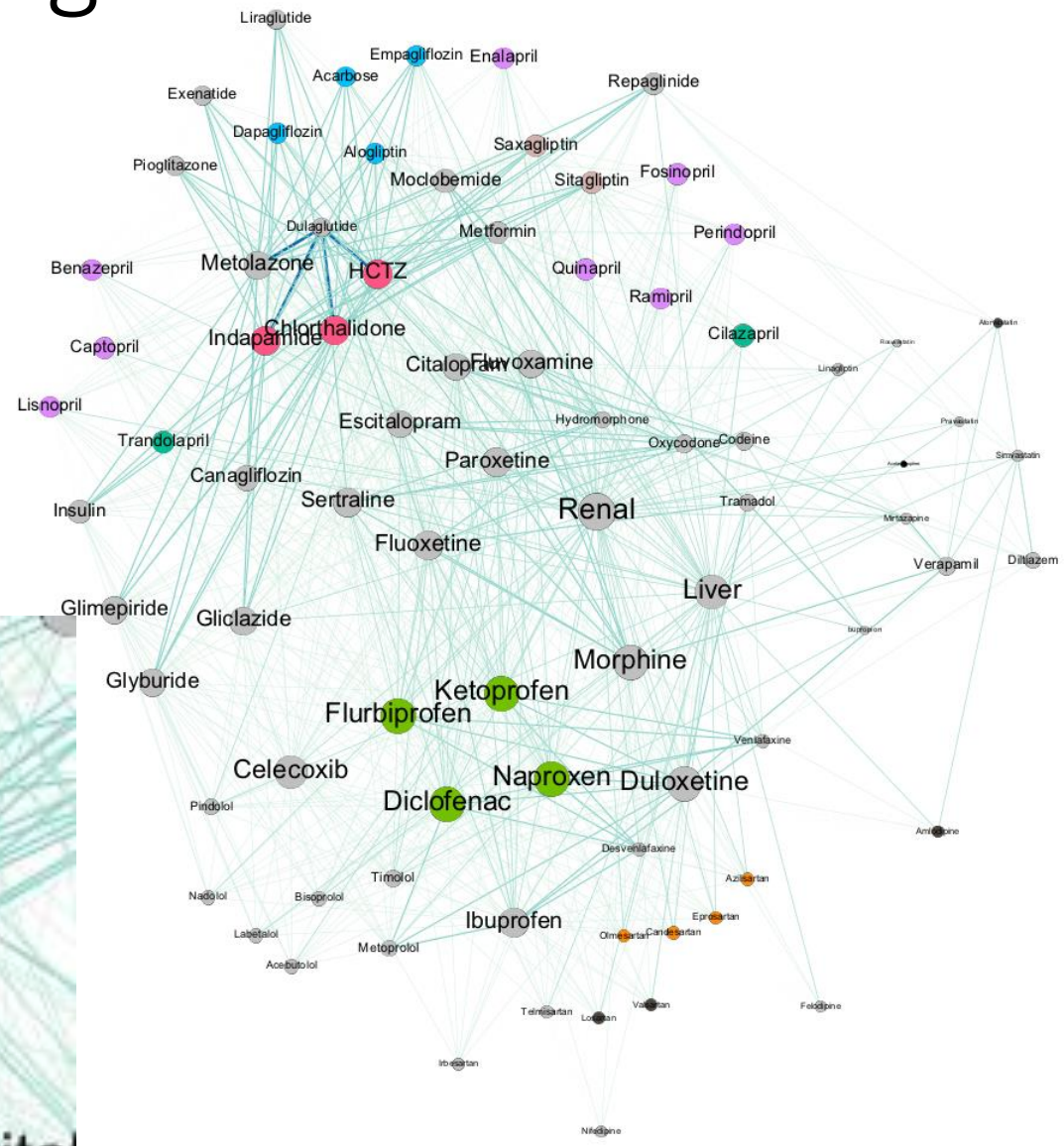
Force Atlas Analysis

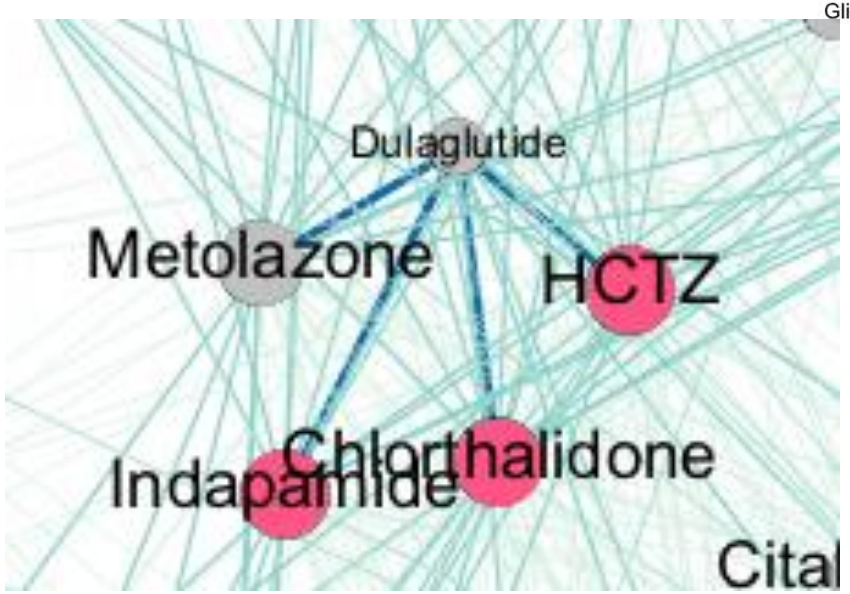




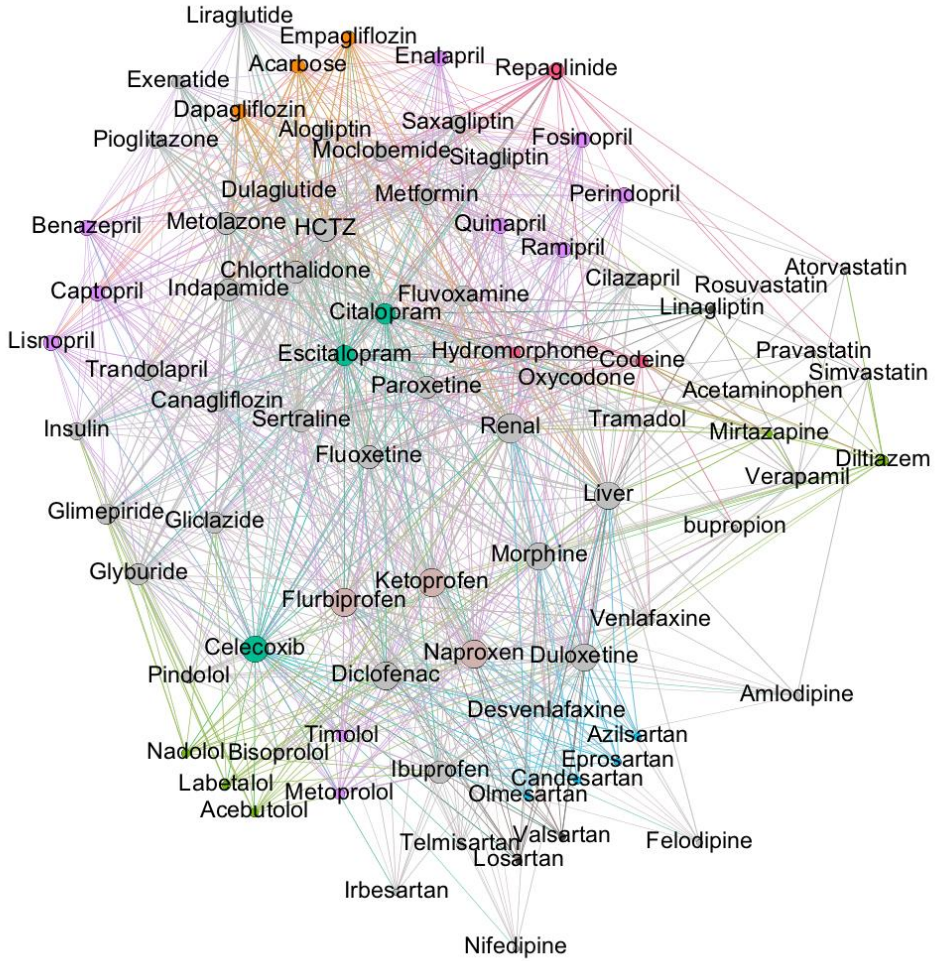
Weighting appears to highlight diuretics

Drug Interaction	Weighting
B: No action needed	0
C: Monitor therapy	1
D: Consider therapy modification	2
X: Avoid combination	3
Liver Dosing	2
Renal Dosing	2



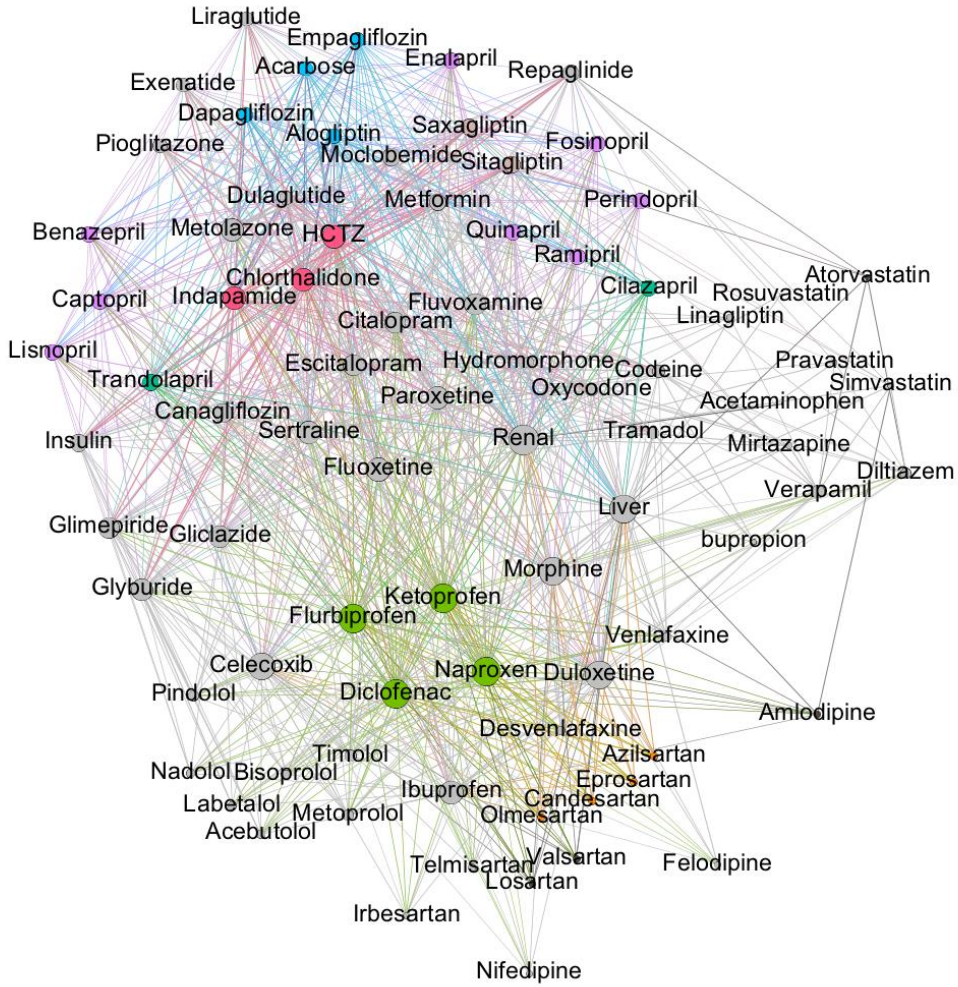


Clustering Coefficient 0.243



Weighted Force Atlas

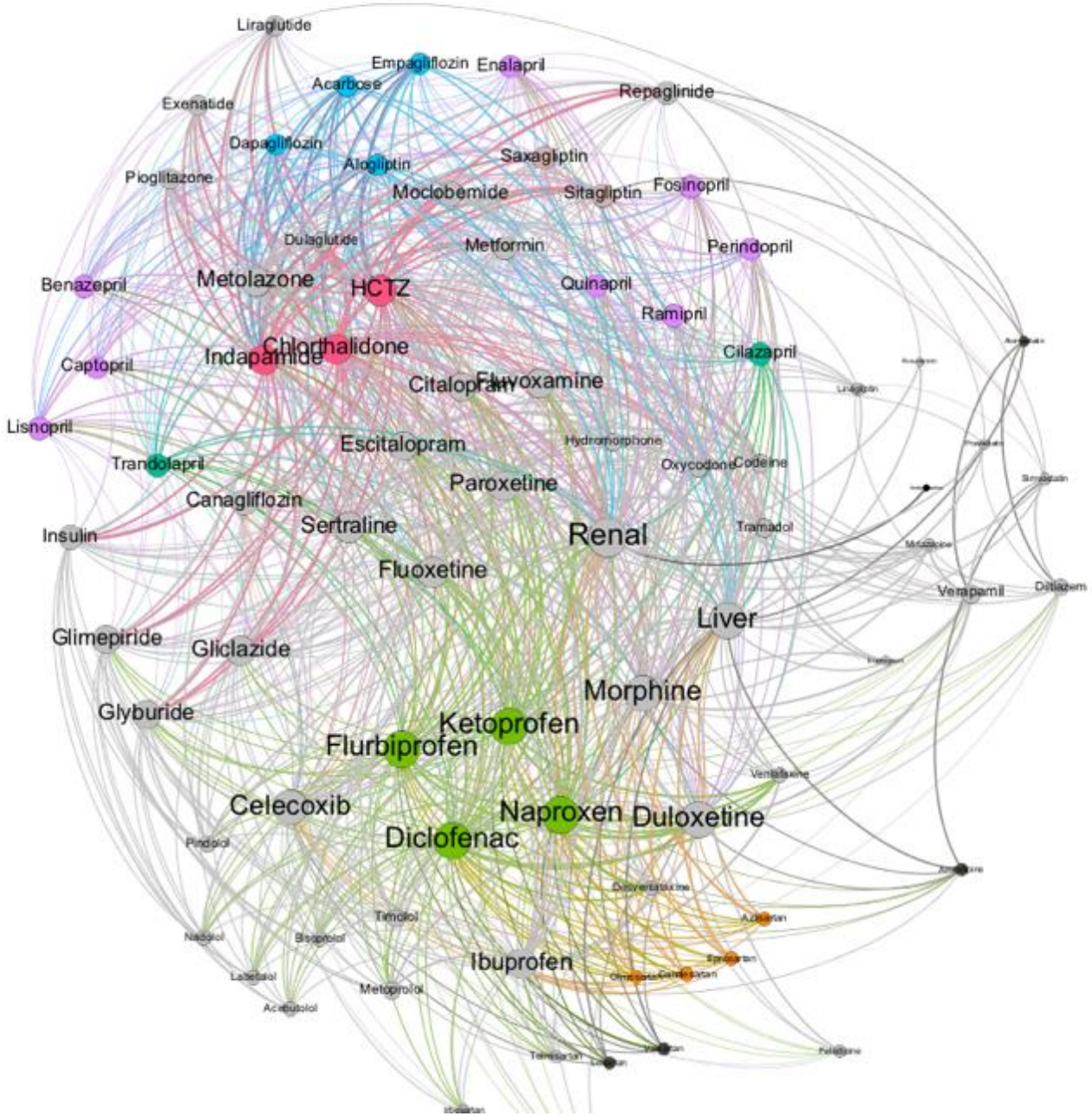
- Size and colors of nodes is clustering coefficient
- Clear groupings of drugs by mechanism of action, and interaction



Weighted Force Atlas Clustering Coefficient

Network Analysis

- Takes highly complex data sets Combine all these features into one picture
- Clear groupings of drugs



Summary

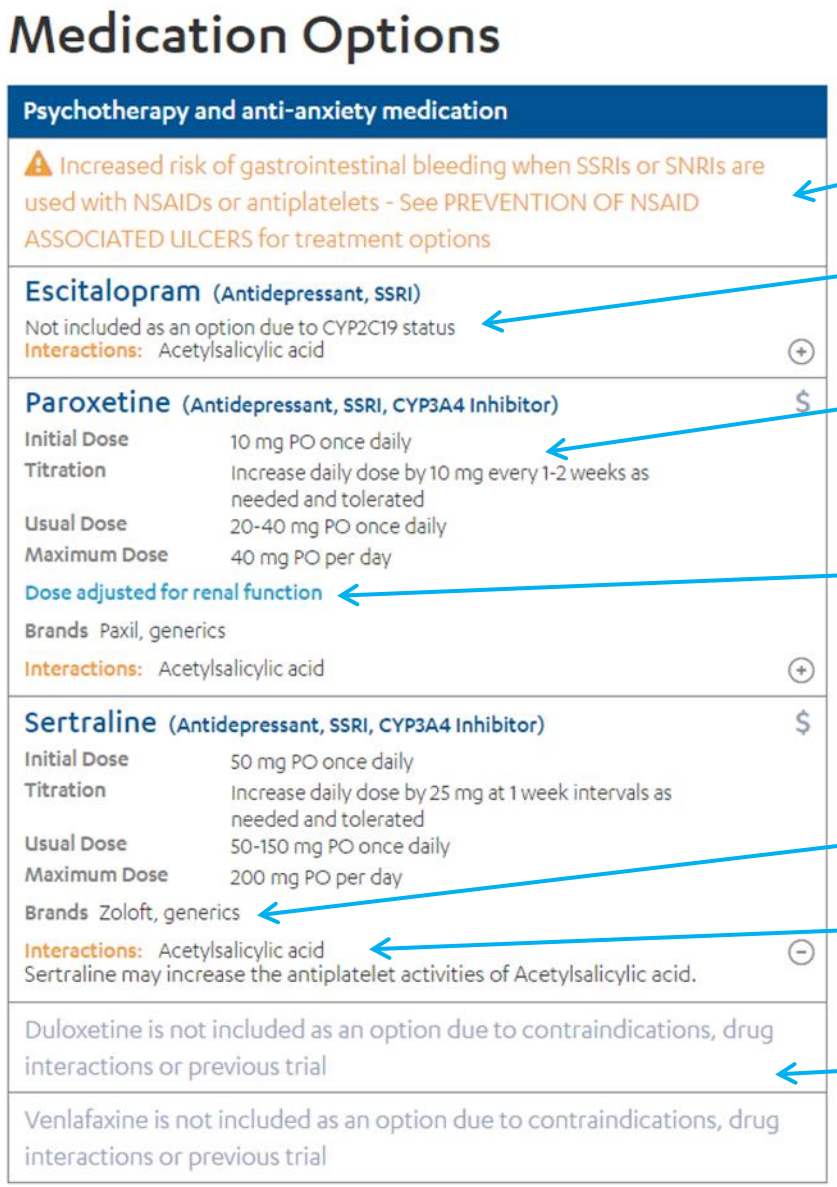
- Findings
  - There are clearly identified groups of drugs that are potentially more harmful than others (Diuretics, NSAIDs, Hypoglycemics)
  - The size these effects and their relationships can be identified and described using network analysis
- Limitations
  - Only commonly used drugs in primary are included
  - Only Drug-Drug, Liver and Renal interactions included
  - Only Lexicomp used
  - Does not take into account what the patient may be taking already – that reduces the network
- Next Steps
  - Start adding more information from the examples above
  - Explore whether and how guidelines/protocols can manage MM2+ to MM5+
  - Can Network Analysis help clinicians manage prescribing for patients with MM

Conclusions for EBHC guidance about medications

- For a patient with multimorbidity the complexity and volume of potential interactions identified using Network Analysis approach is staggering
- Class effects are significant but not universal
- Rational Prescribing approaches such as Deprescribing systems and Choosing Wisely need to take into account MM, perhaps using Network Analysis.
- “can I just click on the disease for my patient and see the Network Analysis?”

martin.dawes@ubc.ca

Medication Decision Support



Management of Drug-Drug Interactions

Drug-Gene Interactions

Specific Dosing
(initial, titration, maximum, target)

Dose Adjustment for Renal
& Hepatic Impairment

Price Comparison

Brand Names

Drug-Drug Interactions

Excluded Medications