Emperator Enally Enally Enally Size Liradutide Exenatide of Information Needs **to Identify** Quinapril Metolazone Benazepri Indapaminghalidone Captopril Safe and Effective prescriptions Lisnopri for an Individual. Sertraline Insuli Fluoxetine Glimepiride Gliclazide Martin Dawes, Roland Grad, Pierre Pluye Glyburide Flurbiprofer Celecoxib Naproxen Duloxetine Diclofenac University of British Columbia & McGill Ibuprofen 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 <u>commonly</u> 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.

Frequency distribution of Interactions for 80 drugs & Renal and Liver



[1, 6,5] (6,5, 12] (12, 17,5] (17,5, 23] (23, 28,5] (28,5, 34] (34, 39,5] (39,5, 45] (45, 50,5] (50,5, 56]

NUmbers of Interactions

Basic Network with node size adjusted according to number of interactions

4/U Irbesartan 2 C: Nonitor therapy Elurbiproten 471 Labetalol Flurbiprofen 2 C: Monitor therapy 472 Lisnopril Flurbiprofen 2 C: Monitor therapy 473 Losartan Flurbiprofen 2 C: Monitor therapy 474 Metolazone Flurbiprofen 2 C: Monitor therapy 475 Metoprolo Flurbiprofen 2 C: Monitor therapy 476 Nadolol Flurbiprofen 2 C: Monitor therapy 477 Olmesartan Flurbiprofen 2 C: Monitor therapy 478 Perindopril Flurbiprofen 2 C: Monitor therapy 479 Pindolol Flurbiprofen 2 C: Monitor therapy 480 Quinapril Flurbiprofen 2 C: Monitor therapy 481 Ramipril Flurbiprofen 2 C: Monitor therapy 482 Telmisartan Flurbiprofen 2 C: Monitor therapy 483 Timolo Flurbiprofen 2 C: Monitor therapy 484 Trandolapril Flurbiprofen 2 C: Monitor therapy 485 Valsartan Flurbiprofen 2 C: Monitor therapy 486 Venlafaxine Flurbiprofen 2 C: Monitor therapy 487 Venlafaxine Flurbiprofen 2 C: Monitor therapy 488 Chlorthalidone Fluvoxamine 2 C: Monitor therapy 489 Dulaglutide 2 C: Monitor therapy Fluvoxamine 490 Hydrochlorthiazide Fluvoxamine 2 C: Monitor therapy 491 Indapamide 2 C: Monitor therapy Fluvoxamine 492 Metolazone Fluvoxamine 2 C: Monitor therapy 493 Acebutolol 2 C: Monitor therapy Gliclazide 494 Bisoprolol Gliclazide 2 C: Monitor therapy 495 Celecoxib Gliclazide 2 C: Monitor therapy 496 Chlorthalidone Gliclazide 2 C: Monitor therapy 497 Chlorthalidone Gliclazide 2 C: Monitor therapy 498 Citalopram Gliclazide 2 C: Monitor therapy 499 Diclofenac Gliclazide 2 C: Monitor therapy 500 Escitalopram Gliclazide 2 C: Monitor therapy 501 Fluoxetine Gliclazide 2 C: Monitor therapy 502 Flurbiprofen Gliclazide 2 C: Monitor therapy 503 Fluvoxamine Gliclazide 2 C: Monitor therapy 504 Hydrochlorthiazide Gliclazide 2 C: Monitor therapy 505 Hydrochlorthiazide Gliclazide 2 C: Monitor therapy 506 Ibuprofen Gliclazide 2 C: Monitor therapy 507 Indapamide 2 C: Monitor therapy Gliclazide 508 Indapamide Gliclazide 2 C: Monitor therapy 509 Ketoprofen Gliclazide 2 C: Monitor therapy 510 Labetalol Gliclazide 2 C: Monitor therapy 511 Metolazone Gliclazide 2 C: Monitor therapy 512 Metolazone Gliclazide 2 C: Monitor therapy F43 a C. Maultauthouse

Summary Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents, Specifically, t Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. SeverityModerate Reliability Rating Fa Summary Angiotensin-Converting Enzyme Inhibitors may enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Sp. Summary Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents, Specifically, t Thiazide and Thiazide-Like Diuretics may enhance the nephrotoxic effect of Nonsteroidal Anti-Inflammatory Agents. Nonsteroidal Anti-Infla Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. SeverityModerate Reliability Rating Fa Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. 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Renal



cocoon of a Cyna moth pupa

Thiazide and Thiazide-Like Diuretics may diminish the therapeutic effect of Antidiabetic Agents. Severity Moderate Reliability Rating Good



Weighting appears to highlight diuretics

Metolazone

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



Clustering Coefficient 0.243

Liraglutide Empagliflozin Enatapril Repaglinide Acarbose Exenatide Dapagliflozin Alogliptin Saxagliptin Fosinopril Pioglitazone MoclobemideSitagliptin Dulaglutide Metformin Perindopril Benazepril Metolazone HCTZ Quinapril Ramipril Atorvastatin Chlorthalidone Cilazapril Rosuvastatin Captopril Indapamide Fluvoxamine Linagliptin Citalopram Lisnopril Escitalopram HydromorphoneCodeine Pravastatin Trandolapril Simvastatin Oxycodone Paroxetine Acetaminophen Canagliflozin Sertraline Tramadol Renal Mirtazapine Insulin Fluoxetine Diltiazem Verapami Liver GlimepirideGliclazide bupropion Morphine Glyburide Ketoprofen Flurbiprofen Venlafaxine Celecoxib Naproxen Duloxetine Diclofenac Pindolol Amlodipine Desvenlafaxine Azilsartan Timolol Nadolol Bisoprolol Eprosartan Ibuprofen Candesartan Olmesartan Labetalol Metoprolol Acebutolo Telmisartan alsartan Felodipine osartan Irbesartan Nifedipine

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

Liraglutide Empagliflozin Enalapril Repaglinide Acarbose Exenatide Dapagliflozin Alogliptin Saxagliptin Fosinopril Pioglitazone MoclobemideSitagliptin Dulaglutide Metformin Perindopril Benazepril Metolazone HCTZ Quinapril Ramipril Atorvastatin Chlorthalidone Cilazapril Rosuvastatin Captopril Indapamide Fluvoxamine Linagliptin Lisnopril Escitalopram HydromorphoneCodeine Pravastatin Trandolapril Oxycodone Simvastatin Paroxetine Acetaminophen Canagliflozin Sertraline Tramadol Renal Mirtazapine Insulin Fluoxetine Diltiazem Verapami Liver GlimepirideGliclazide bupropion Morphine Glyburide Ketoprofen Flurbiprofen Venlafaxine Celecoxib Naproxen Duloxetine Diclofenac Pindolol Amlodipine Desvenlafaxine Timolol Azilsartan Nadolol Bisoprolol Eprosartan Ibuprofen Candesartan Labetalol Metoprolol Olmesartan Acebutolo Telmisartan alsartan Felodipine osartan Irbesartan Nifedipine

Weighted Force Atlas Clustering Coefficient

Weighted Force Atlas

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?"

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Medication Decision Support

Medication Options

