NUTRITIONAL AND HERBAL PRESCRIBING AND ORAL HYPOGLYCAEMIC MEDICINES IN TYPE 2 DIABETES:

For Pharmacists.

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Co-Prescribing & Safe Practice

- First principle of Naturopathy – Do No Harm, similarly
- Australia's National Health Policy - Quality use of medicines (QUM) requires everyone to
  - Using medicines safely and effectively
  - This includes: Monitoring prescribed and self selected medicines
  - Medicines include non-prescription and complementary medicine (CM) products[1]
- Increasing use of Professionally prescribed or self selected Herbal and Nutritional Medicines increases the risks associated with Polypharmacy
- Increased need for expert advice
- To ensure safe practice knowledge of potential drug-drug, drug-herb and drug-nutrient interactions is essential
- Naturopaths – qualified health science practitioners, trained in nutritional and herbal medicine

Adverse Drug Reactions and Adverse Drug Interactions

- Adverse drug interactions (ADI) - interaction between co-administered drugs that causes alteration in toxicity or effectiveness of any medications
- Adverse drug reactions (ADR) – injury caused by taking a medication[2,3]
- Increased risk is seen in those taking multiple drugs, having multiple prescribers and the elderly[4]
- Polypharmacy more frequent in diabetics as they require multiple pharmaceutical treatments and often have comorbidities[3]
- 58% of patients concerned about drug interactions of prescribed medicines[3]
- Diabetes educators rely heavily on pharmacists and prescribers to screen for drug interactions[3]
- Unfortunately avoiding ADI and ADR is hampered by a lack of clear, comprehensive and accessible resources of potential drug Represented in both CM and pharmaceutical medicine[3,5]
- Drug interactions may be pharmacodynamic or pharmacokinetic[3]
- This aspect of drug knowledge will indicate potential interactions

Pharmacodynamic ADI

- Pharmacodynamic interactions affect either the efficacy or the magnitude of side effects of a drug without affecting its plasma levels[2]
- Additive effects that increase wanted effect of the drug are beneficial[3]
- Those that increase unwanted or enhance harmful effects are not[3]
- Antagonistic effects are detrimental or useless - negating each other[3]

Pharmacokinetic ADI

- Absorption – changed drug effects from concurrently taken drugs, that slows absorption, changes amount of drug absorbed or its bioavailability
- Distribution - via bloodstream, extracellular and intracellular fluid.
- Metabolism - systemic drug concentration can be altered by liver degradation and drug transporter P-glycoprotein.[2] Cytochrome p540 isoenzymes may be induced, reducing circulating drug concentration or inhibited which increases drug amount present in the body. [3]
- CYP2C9 and CYP3A4 are clinically relevant for diabetic patients[2]
- Genetic differences that affect CYP enzymes are clinically important in drug interactions[2]

Overview:
Type 2 Diabetes Mellitus

- Common Chronic metabolic disorder
- Characterised by; Hyperglycaemia, insulin resistance and relative insulin deficiency[6]
- Hyperglycaemia damages small blood vessels and causes atherosclerotic damage leading to neuropathy blindness and mortality
- ADE and ADR occur in hypoglycaemic and hyperglycaemic situations
- Blood Glucose Levels (BGL) kept as stable as possible
- No Cure
- Treatment: lifestyle modifications, oral hyperglycaemic and insulin sensitising medications[6]

Oral Hypoglycaemic Medicines:

Drug Class[10]	Drug[10]	Brand/ Trade name[10]	Pharmacodynamics[10]
Sulfonylureas (First Generation)	Glicazide Glibenclamide Glipizide Glimepiride Glyburide Chlorpropramide Tolazamide Tolbutamide	Diamicron Glyade Mellihexal Nidem Oziclide Daonil Glimel Glucatrol Amaryl Aylide Diapride Dimirel Glimepirdie Micronase, Diabeta Melizide Minidiab, Diabanese	↑ glucose uptake via increased insulin receptor sensitivity in peripheral target tissues ↑ pancreatic ß cell insulin secretion ↓ liver production of glucose
Biguanides	Metformin	Glucophage	↑ insulin sensitivity in target cells ↓ liver production of glucose ↓ GIT absorption of glucose
Thiazolidinediones (glitazones)	Rosiglitazone Pioglitazone	Avandia Actos	↑ Insulin receptor sensitivity Alteration of gene products involved in glucose and lipid metabolism
Alpha glucosidase inhibitors	Acarbose Miglitol	Glucobay Glyset	Inhibit upper GIT enzymes that convert dietary carbohydrates to simple sugars for absorption
Meglitinides (Short-acting secretagogues)	Repaglinide Nataglinide	Novonorm Trippid	Stimulate pancreas to release more insulin [9]
Dipeptidyl peptidase-4 (DPP-4) inhibitors[9]	Sitagliptin Vildagliptin	Januvia Galvus (Janumet contains this and metformin)	Enhance body's ability to lower elevated blood glucose by inhibiting enzyme DPP-4 which enhances levels of active incretin hormone that lowers blood glucose by increasing insulin secretion and decreasing glucagon secretion[9]

Oral Hypoglycaemic Medicines: Drug-Drug Interactions

- Oral hypoglycaemics are recommended to be used in combination which increases potential for hypoglycaemia due to additive pharmacodynamics[9,11]
- Antacids containing magnesium hydroxide affect absorption of oral hypoqlycaemics. [2] Separate administration 6 hours before or 2 hours after[12]
- Systemic glucocorticoids increase BGL[2]
- Various antipsychotics associated with weight gain negatively affect insulin sensitivity[2]
- As do OCP, protease inhibitors and calcineurin inhibitors.
- Sympathomimetic agents alter glycaemic control[2] Also calcium –Channel Blockers, Diuretic – Thiazide, Estrogens, Isoniazid, Phenothiazines, Phenytoin, Rifampin, and Thryoid agents[10]

Sulfonylureas Class: Drug-Drug Interactions

- First generation [3] effects are influenced by many drugs[13]
- Co-administration of phenylbutazone, sulphaphenazole may lead to severe hypoglycaemic collapse [13]
- Oral anticoagulants,, Hydantoins, NSAIDs , sulfonamides. Dicumarol, Indoprofen, Salicylate, will take precedence in protein binding
- Pharmacokinetic interaction with protein-bound drugs – alters serum levels of both drugs. Potential for hyperglycaemia or hypoglycaemic adverse drug interactions.[10] Increase active drug available[3]
- Previously in vitro studies represented high interaction although in more recent research in vivo, these reactions are seen to be and have been since designated CYP isoenzyme system related[3]
- First generation sulfonylureas, particularly chloropropramide with alcohol causes facial flushing possibly due to aldehyde dehydrogenase blocking, increasing levels of acetylaldehyde[3]

Sulfonylureas Class: Drug-Drug Interactions

- Gastric pH changes alter bioavailability[2]
- NSAIDS, Beta blockers or salicylates increase hypoglycaemic action[2]
- CYP2c9 interactions with antibiotic drugs[2] metronidazole trimethorprim
- Other substrates that use CYP2c9 are natelinide, losartan, irbersartan, warfarin and zafirlukast[3]
- Inhibitors that will increase sulfronyleaas are amiodarone zarifirlukast and antifungals fluconazole [13], ketoconazole, voriconazole also cimetidine, ranitidine, bonestan, fluoxetine, fluvoxamine, fluvastatin, leflunomide, and noscapine[2]
- Inducers rifampicin, phenobarbital[3], carbamazepine and ritonavir[2]will reduce drug levels
- And potentially with strong CYP3A4 inhibitors[11]
- Secondary infections are common in patients with Type 2 Diabetes. Antifungals increase hypoglycaemic effects of sylfonylureas class drug glipizide by increasing drug levels [10,15]

Biguanides Class (Metformin): Drug-Drug Interactions

- Metformin hydrochloride has low plasma binding and is excreted renally with no hepatic metabolism[2]
- Cationic positive charge competition with other cationic drugs in renal secretion such as procainamide, digoxin, quinidine, trimethoprim and vancomycin [3] , amiloride, quinine, ranitidine, vancomycin, cephalexin or pyrimethamine. [2]
- Therefore contraindicated with renal impairing drugs although low interaction potential [2]
- Cimetidine common in otc heartburn medicines only one implicated in one case of metformin associated lactic acidosis. [3]
- Metformin can cause lactic acidosis must monitor kidney function before and after contrast radiologic studies Drug is withheld the day of procedure to 2-3 days later. [3]
- Anticholinergics alter GIT motility and increase bioavailability of drug[2]
- Hypoglycaemia when combined with sulfonylureas or repaflinide or insulin. Hypertension and heart meds beta blockers calcium channel blockers and ACE inhibitors including metoprolol, nifedipine and enalapril. Warfarin. Diuretics thyroxine cimetidine (reflux ulcer med). Glucocorticoids Asthma meds salbutamol terbutaline. change dose or medication. [13]

Meglitinides Class: Drug-Drug Interactions

- Cyclosporine and gemfibrozil contraindicated with repaglinide due to CYP, UDP, UGT and OA1B1 elimination interactions[2]
- Enhance hypoglycaemic effect with azole antifungal agents and erythromycin derivatives as they are strong inhibitors of CYP 3A4. [3]
- Inducers of cyp2c8 or 3A4 reduce efficacy and may need increased dose. [3]
- Nateglinide metab 70% cyp2C9 and 30% cyp 3A4 could be affected by cypc9 inhibitors inducers no Significant drug drug interactions reported. [3]
- Repaglinide metab by cyp3A4 and Cyp2C8 and extensively glucuronidated in phase 2 liver. D-d interaction serious with gemfibrozil triglyceride loweing med likely d2 its inhibition of cyp2c8 and glucoronidation. In vivo 8 fold increase total exposure to repaglinide. Severe prolonged hypoglycaemia events documented. [3]

Thiazolidinediones: Drug-Drug Interactions

- NSAIDS may increase fluid retention, heart failure and hypoglycaemic potential[2]
- Rosiglitazone and nitrates contraindicated[2]
- No significant elimination or metabolism ADIs reported[3]
- Rosiglitazone Substrate for CYP2c8 and lesser extent CYP2c9[3]
- Pioglitazone substrate for CYP2c8 9% 3a4 17% and other CYP 450 pathways. Affected in vivo by CYP2c8 inhibitors or inducers[3]

DPP-4 Inhibitors: Drug-Drug Interactions

- Dipeptidyl peptidase-4 [9]
- DPP-4 inhibitors except saxgliptin low interaction potential. Any drug that affects drug transporter P-glycoprotein used with caution [2]
- As substrates of P-glycoprotein they may increase serum digoxin levels when coadministered [2]
- May increase angioedema with ACE inhibitors [2]
- Saxgliptin metabolised via CYP3a4, therefore interacts with inhibitors ketoconazole, diltiazem, atazanavir, ritonavir and clarithromycin and inducers eg rifampicin [2]
- Organic anion transporting polypeptides found in human pancreas to facilitate glibenclamide cellular entry may be a source of drug-drug reactions in those with genetic variants for these and sulfonylureas class [2]

α-Glucosidase inhibitors: Drug-Drug Interactions

- Not extensively metabolized
- no significant metabolism interactions
- several case reports of a reduction in absorption of digoxin and an increase in absorption of warfarin.
- It is recommended that any drug with a very small dose and a narrow safety margin (Therapeutic index) be administered apart from acarbose or miglitol [3]
- As with the DPP-4 inhibitors, concurrent sulfonylureas therapy may induce hypoglycaemia via adjuvant effect [2]

Oral Hypoglycaemic medicines and Drug-Drug Interactions

- Revision for Pharmacists
- Knowledge for Dispensary Technicians, Pharmacy Assistants and Vitamin Consultants
- May notice patients presenting prescriptions for both medications
- Or patients displaying or describing symptoms of adverse drug interactions
- Speak with your pharmacist if concerned
- Refer patient to Pharmacist for clarification or a Medications Review (Meds. Check), consultation.

Image 1. credit: Bundaberg Coral Coast Pharmacy. JBM Projects. (2014)

Naturopathic Care of Type 2 Diabetics

- Naturopathic treatment includes (as does pharmacy client care), Assistance with supportive lifestyle, and weight management strategies and recommend regular BGL monitoring and information about the signs and symptoms of hyperglycaemia and hypoglycaemia
- We also offer Dietary advice and planning and
- Prescription of Herbal Medicines/Nutrients as single or combination supplements
- Safe Practice includes knowledge of potential ADI & ADR. Resources with rating system of drug-CM interactions exist
- Practitioner Only Products (POPs)
  - Prescribed by Naturopaths, sometimes Pharmacists, Chiropractors Physiotherapists
  - Bioactive materials tested post sourcing, extracting and manufacturing to ensure correct material used and Standardised active component levels. High performance liquid chromatography best method for herbal constituent analysis [18]
  - Research and Evidence Based
  - Ongoing Practitioner monitoring and support
- Self selected products available off the shelf or over the counter (OTC)
- You can offer advice and recommend CM, if you are confident in your knowledge of potential ADI and ADR
- An Ideal way to integrate the wide variety of natural health products stocked in your pharmacy.

Oral Hypoglycaemic medicines: Drug-Herb Interactions

Image 2: Stepin2. (2016). Best herbs for diabetes. Retrieved from http://www.stepin2mygreenworld.com/healthyliving/greenfoods/best-herbs-for-diabetes/

Oral Hypoglycaemic medicines: Drug-Herb Interactions

- Anti-diabetic drugs from medicinal plants contain a complex mixture of bioactive substances
- The PK and PD not as clear as pharmaceuticals, due to multiple constituents and their synergistic effects
- Interact with pharmacological agents different and unpredictable ways [2]
- Whilst usually low risk these clinically important potential ADI are serious[2]
- Research is continuing and data is available for commonly used HM
- Again we see hypoglycaemia as the main ADI and ADR due to adjuvant or additive effects on patient's glucose control.
- Advise patient to monitor BGL and of the warning signs and symptoms of hypoglycaemia
- Products that have substituted an incorrect plant material are often represented in reported drug-herb adverse reactions.
- Absorption of drugs is reduced by soluble fibres such as Psyllium Husks, Guar Gum [17] and Slippery elm (*Ulmus rubra, Plantago ovata*) [18]

Oral Hypoglycaemic medicines: Drug-Herb Interactions

- St Johns wort (*Hypericum perforatum*) induces CYP3a4 CYP1a2 CYP2d6 CYP2e1 and P-glycoprotein[19]
- This affects pharmacokinetics of sulfonylureas and possibly thiazolidinediones meglitinides and DPP-4 inhibitors [2]
- St Johns wort with tolbutamide increased hypoglycaemia without pharmacokinetic interaction - low risk [18]
- Aloe vera, ginseng, andrographis, karela, lyceum and herbs with isoflavoines or levocarnitine may effect antidiabetic drug metabolism [2]
- Salicylate protein binding with glipizide [10]
- Bearberry and Phellodendron - berberine constituent theoretically potentiates drug effect via displacing bilirubin binding [18]

Oral Hypoglycaemic medicines: Drug-Herb Interactions

- Ginkgo (ginkgo Biloba) 6g dried leaf with Glipizide, Metfomin or Pioglitazone may increase drug effect. > 1g/day Metformin increases this to moderate risk ADI[18]
  - –Tolbutamide – may decrease effectiveness of drug. 18g dried leaf day monitor low level risk. [18]
- Other HM that affect glucose stability
  - *Coccinia indica*, agrimony, alfalfa, cocoa, coffee, elder, holy basil, and herbs with glucosamines as ingredients [2]
  - Coriander (*Coriandrum sativum)*, Cumin (*Cuminum cyminum)*, Flaxseed (*Linum usitatissimum*) and Turmeric (*Curcuma longa) due to* curcuminoids and sesquiterpene components [20]

Oral Hypoglycaemic medicines: Drug-Herb Interactions

- Herbal Medicines with evidence based hypoglycaemic action and as adjuvants have potential ADI and ADR
  - Garlic (*Allium sativum*) supplementation increases hypoglycaemia when taken with chlorpropamide. [18,20,21,22]
  - Fenugreek (*Trigonella foenumgraecum*) [8,18,20]
  - Goat's Rue (*Galenga officinalis*) [18] and Olive leaf [8]
  - Ginseng [8] Korean ginseng (*Panax ginseng*) [18] Siberian ginseng and American ginseng [23]
  - St marys thistle (*Silybum marianum*) and polyphenol containing herbs, may improve insulin sensitivity at doses of 200-600mg/day [18]
  - Gymnemma (Gymnema sylvestre), "The pancreas support herb" reduced hypoglycaemic drug requirements in an uncontrolled trial [18]
  - These ADI are listed as moderate in regard to the likelihood of occurrence and the quality of the evidence [8]

CYP 450 enzymes in common with Oral hypoglycaemic medicines

- Inducers of CYP2C9
  - *Eleutherococcus senticoccus* – Siberian ginseng
    Hypericum perforatum – *St John's Wort*
    Panax ginseng - Korean ginseng
    Panax quinquefolius – American ginseng [23]
- Inducers of CYP3A4
  - *Eleutherococcus senticoccus* – Siberian ginseng
    Hypericum perforatum – *St John's Wort*
    Panax ginseng - Korean ginseng
    Panax quinquefolius – American ginseng [23]

CYP 450 enzymes in common with Oral hypoglycaemic medicines

Inhibitors of CYP3A4

- *Allium sativum* - Garlic
  Ammi visnaga - Khellin
  Azadirachta indica - Neem
  Cimicifuga racemose – Black Cohosh
  Harpagphytum procumbens – Devil's Claw
  Hydrastis Canadensis – Golden Seal
  Naringenin compounds – Grapefruit *flavones and flavinoids*
  Panax ginseng – Korean ginseng
  Panax quinquefolius – American ginseng
  Strychnos ligustrina – Nux vomica
  Uncaria tomentose – Cat's Claw [24]

Inhibitors of CYP2C9

- *Allium sativum* - Garlic
  Bergamottin
  Harpagophytum Procumbens - Devil's Claw
  Lycium barbarum – relative of *Lycium chinensis* - Chinese wolf berry, goji berries and boxthorn [24]

Oral Hypoglycaemic medicines: Drug-Nutrient Interactions

Image 3: Hendel, C. & Cooper L. (2016). What You Need to Know About Supplements and Drug Interactions. Retrieved from http://www.consumerreports.org/vitamins-supplements/supplement-and-drug-interactions/

Oral Hypoglycaemic medicines: Drug-Nutrient Interactions

- Nut supplements pharmacokinetic interactions via altered gastric pH or formation of insoluble complexes inside GIT. Can cause significant plasma concentration changes for several drugs. [2]
- Additive hypoglycaemic effects with biguanides and sulfonylureas class drugs:
  - Alpha-lipoic acid – low risk
  - CoQ10 – NADH oxidase is inhibited. CoQ10 interferes with P-glycoprotein [24]
  - Omega 3 – uncertain interaction, AE unlikely, Patient variable and short-lived.
  - Acetyl-L-Carnitine, low risk
  - Magnesium – increases insulin sensitivity and secretion
  - Conjugated linoleic acid – improves glucose tolerance & increases fasting BGL [12]

Oral Hypoglycaemic medicines: Drug-Nutrient Interactions

- Thiamin - Vitamin B1 with biguanides increased risk of lactic acidosis separate doses.
- High dose Niacin - Vitamin B3 may exacerbate diabetes mellitus [10] and coadministration with all bar the DPP-4 inhibitors may interfere with medications. The nicotinamide form doesn't interfere. [12]
- Metformin may reduce folic acid absorption so supplementation is both contraindicated and necessary [12]
- Chromium is indicated in those deficient, for treatment of Diabetes Type 2 [12]
- Chromium and Zinc potentiate ADI via additive effect with Oral Hypoglycaemic medicines except DPP-4 inhibitors [12]

CoPrescribing and Safe Practice:

- Whilst some sources suggest complete avoidance of CM for those taking oral hypoglycaemic medicines the recommended safe practice depends on cautious use, consumer education and close monitoring of patients. [2,8]
- CM can be coprescribed with pharmaceutical therapeutic agents and be of benefit to patients.
- Separating doses is advised to minimise risk of harm and retain efficacy.
- Reduction of Pharmaceutical medicines may be possible and necessary with coadministration of herbal or nutritional medicine [18]
- Clear communication of patients treatment plans between prescribers and monitoring by these prescribers, Pharmacists and Pharmacy staff reduces the potential for ADI and ADR[27]
- Pharmacists play a vital role in patient monitoring. A possible method is to succinctly note herbal supplements used by patients in Dispensary software (FRED or LOTS) to ensure continuing evaluation.

Valuable Resources and References:

- An NPS review found these sources to be the highest content and technical quality with clinical utility [28]
  - National Standard Professional Database Package - includes a CM-drug interaction checker,
  - Natural Medicines Comprehensive Database [29]
  - Natural Standard Professional Database - Professional monographs.
  - Herbal Medicines & Dietary Supplements package
  - MedlinePlus: Drugs, Supplements & Herbal Information National Prescribing Service Limited [28]
- I have found the CYP 450 lists from Evidence Based Medicine Consult to be valuable [30]
- Bone and Mills have many published works and an online Mediherb resource – Potential Herb-Drug interactions for commonly used herbs. This includes links to relevant studies. [18,26,31]
- Having these on hand will assist in all pharmacy staff providing accurate information, superior customer service and quality care provision whilst supporting, monitoring and assisting customers with queries and selection of natural health products.

In Conclusion:

- As front line health care professionals we have the opportunity and responsibility to monitor polypharmacy whether the drugs are pharmaceutical, herbal or nutritional, professionally prescribed or self selected by patients.
- With the exponential increase in availability and use of CM, whether professionally prescribed or self selected, it is essential to have knowledge of potential drug-drug, drug-herb and drug-nutrient ADIs and ADRs.
- This presentation has prepared you to ensure safe practice, answer patient queries with confidence and possibly even recommend suitable nutritional or herbal medicine products that are available in your pharmacy.
- Knowledge is true confidence
- So hopefully this presentation has given you the knowledge and confidence in nutritional and herbal prescribing and oral hypoglycaemic medicines in type 2 diabetes.
- Thank you very much for your time.