DIABETES MANAGEMENT

Manual for Health Professionals

Chronic Disease Network and Access Program 2009

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1.1 Management of Type 1 Diabetes

Diagnosis

- Random PG ≥11.1 mmol/L or FPG ≥7.0mmol/L
- Signs/symptoms: frequent urination, thirst, weight loss despite hunger, fatigue, ketoacidosis
- Usually presents in children, adolescents, or young adults

Glycemic Targets:

- A1C ≤ 7%
- FPG 4.0-7.0 mmol/L
- PPG 5.0-10.0 mmol/L

Diet counselling

- Carbohydrate intake has immediate impact on BG level
- Adjust insulin dose according to carbohydrate intake or consume a fixed amount
- Time meals and snacks to prevent hypoglycemia and optimise glycemic control

Insulin Regimens

- Adapt to patients lifestyle, diet, age, general health, motivation, ability to self-manage.
- Basal-prandial regimens or insulin pump are of choice for adults.
- Educate patient about risks, prevention, and treatment of hypoglycemia.

Prevent/Manage Complications

- Vascular protection and Blood Pressure Control
- Screen for retinopathy
- Screen for nephropathy
- Monitor neuropathy
- Foot care

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2.1 Type 1 Diabetes in Children and Adolescents

- **If diabetes is suspected in a child or adolescent, the diagnosis should be immediately confirmed.**

- **Targets:**

Age (years)	A1C	FPG	2hr PPG
<6[1]	<8.5	6.0-12.0 mmol/L	*
6-12	<8.0	4.0-10.0 mmol/L	*
13-18[2]	≤7.0	4.0-7.0	5.0-10.0

*PPG not usually measured in young children except those on pump therapy.

1. It is important to avoid hypoglycemia. Severe hypoglycemia is associated with cognitive impairment.
2. If safe to do so, attempt to reach A1C ≤6%, FPG 4.0-6.0 mmol/L; PPG 5.0-8.0 mmol/L

Insulin Therapy

- When choosing an insulin regimen, consider: age, duration of diabetes, family lifestyle, motivation and abilities of parents, socioeconomics, and family/patient preferences.
- After diagnosis, there may be a honeymoon period of up to 2 years where glycemic control is good and insulin requirements are low.
- After the honeymoon period, a more intense regimen may be required to meet targets.
- MDI (multiple daily injections) and CSII (continuous subcutaneous insulin infusion) are preferred
- LAIA seem to improve glycemic control with fewer episodes of nocturnal hypoglycemia.

Diet

- Counselling from a registered dietician or diabetes educator about nutritional considerations in diabetes is important to ensure proper growth and development of the child with optimal glycemic control

Hypoglycemia

- Management and prevention of hypoglycemia is a challenge in children.
- In some cases, administration of glucagon (20mcg/year of age up to 150mcg) is useful in managing mild or impending hypoglycemia when the child cannot or will not consume oral carbohydrate.

Ketoacidosis (DKA)

- Results from not taking insulin or improper management of sick days.
- Is the leading cause of morbidity and mortality in children with diabetes.
- Cerebral edema is a possible consequence if DKA is not properly managed.

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Comorbid Conditions

- Autoimmune Thyroid Disease – screen all children (TSH and thyroperoxidase antibodies) at diagnosis and every 2 years thereafter. If thyroid symptoms, goiter, or +ve thyroid antibodies screen every 6-12 months.
- Addison Disease – screen (Na^+, K^+, AM cortisol) whenever symptoms appear (unexplained recurrent hypoglycemia and ↓insulin requirement.
- Celiac Disease – screen (IgA, tissue transglutaminase) whenever symptomatic (recurrent GI symptoms, poor growth, poor weight gain, fatigue, anemia, poor metabolic control)

Complications

- Nephropathy – screen (ACR) yearly from 12 years of age in those with diabetes >5 years (treat as per adult guidelines if microalbuminurea persists)
- Retinopathy – screen yearly from 15 years of age in those with diabetes > 5years
- Neuropathy – screen adolescents with poor metabolic control (question about symptoms – numbness, pain, cramps, paresthesia; examine for skin sensation, light touch and ankle reflexes)
- Dyslipidemia – screen at 12 and 17 years; earlier if obese or family history of hyperlipidemia or premature CVD (treat as per dyslipidemia in adults with diabetes)
- Hypertension – all children at least twice per year (treat as per recommendations for children without diabetes)

Other considerations in Adolescents

- Eating disorders or non-compliance with insulin to avoid weight gain
- Contraception in adolescent girls
- Smoking (avoidance to prevent microvascular and macrovascular complications)
- Alcohol use (over indulgence impedes glycemic control, increases risk of hypoglycemia)

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3.1 Type 2 Diabetes in Adults

Risk Factors for Diabetes

- age ≥40 years
- family history of diabetes
- member of high-risk population
- vascular disease
- dyslipidemia
- obesity
- PCOS
- history of gestational diabetes or delivery of macosomic infant
- other[1]

Targets for Glycemic Control

- A1C ≤ 7%[2]
- FPG 4.0-7.0 mmol/L
- PPG 5.0-10.0 mmol/L[3]

Lifestyle Interventions

- Achieve and maintain healthy weight
- Healthy diet[4]
- Regular exercise[5]
- Smoking cessation[6]
- Limit alcohol intake[7]

BP test at each diabetes-related visit

- target 130/80
- reinforce lifestlye interventions
- treat with antihypertensives as per guidelines[8]

Lipid profile at diagnosis and every 1-3 years

- Primary target LDL≤ 2.0 mmol/L
- Secondary target TC/HDL ratio <4.0
- reinforce lifestyle interventions
- treat dyslipidemia as per guidelines[9]

Screen for microvascular complications

- neuropathy[10] at diagnosis then annually
- nephropathy[11] at diagnosis then annually
- retinopathy[12] at diagnosis the every 1-2 years

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3.2 Type 2 Diabetes in Adults cont'

1. Other risk factors for Type 2 diabetes include: acanthosis nigricans, history of IGT or IFG, schizophrenia, genetic defects of beta-cell function or insulin action, diseases of the pancreas, endocrine diseases such as acromegaly, drug or chemical induced, and other genetic syndromes such as Down syndrome.

2. A1C should be checked every 3 months until glycemic targets are achieved, then every 6 months thereafter. A target A1C of ≤ 6.5% may be considered for some, although there is an increased risk of hypoglycemia and mortality in patients with cardiovascular disease.

3. PPG 5.0-8.0 mmol/L may be considered if A1C target is not being met.

4. Follow 'Eat Well with Canada's Food Guide' which includes choices of foods from the four food groups that reflect personal and cultural preferences. Ensure regular timing and spacing of meals to help control blood glucose and body weight. Diet counselling is recommended.

5. 150 minutes of aerobic exercise spread over 3 days/week (moderate to vigorous aerobic exercise spread over 3 non-consecutive days with no more than 2 consecutive days without exercise). Also resistance exercise 3 times per week.

6. To minimize risk of a cardiovascular event. Use a combination of counselling and pharmacologic agents as required.

7. Patients using insulin or insulin secretagogues should be aware of hypoglycemia which can occur up to 24 hours after alcohol consumption. Excessive alcohol use limits the choices of pharmacologic agents because of drug interactions/contraindications. Patients should limit their intake to 1-2 drinks per day (≤14/week for men; ≤9/week for women).

8. Give special consideration to ACEI and ARB because of their demonstrated benefit in preventing renal failure and offering cardiovascular protection. See Section 13 for details.

9. See Section 12 for details. Special consideration should be given to statins because of their demonstrated efficacy, however if TG >10mmol/L a fibrate should be used.

10. See Section 17 (Neuropathy) and 18 (Foot Care).

11. Screen using random ACR and SCr. Nephropathy is defined as ACR ≥ 2.0mg/mmoL in men and ≥ 2.8mg/mmoL in women.

12. Ophthalmic exam by professional.

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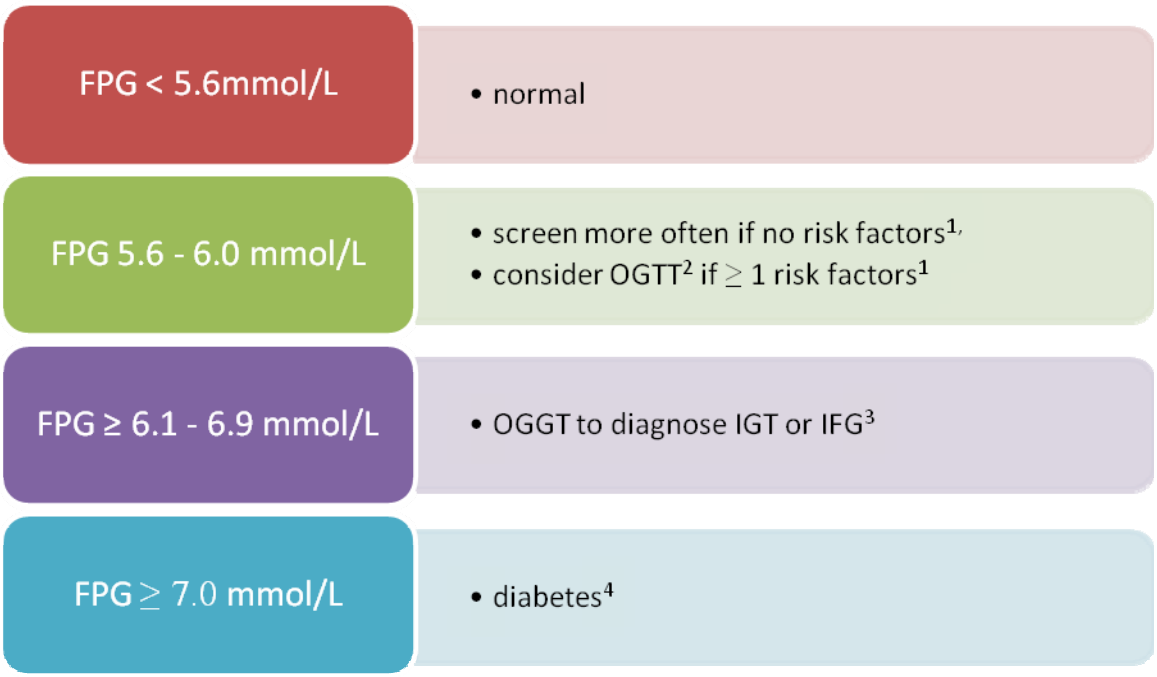
3.3 Type 2 Diabetes in Adults

Screening for Type 2 Diabetes

- All persons ≥ 40 years old: every 3 years
- Persons with additional risk factors[1]: sooner and more often



1. Risk factors for Type 2 diabetes include: family history, being a member of a high risk population, vascular disease, presence of diabetes complications, obesity, hypertension, dyslipidemia, history of gestational diabetes, IGT, IFG, and others listed on page 3.1.
2. 2 hour PG after 75g glucose load
3. IFG = OGTT <7.8; IGT = OGTT 7.8-11.0mmol/L. Note that it is possible to have both.
4. Confirm diagnosis on another day with laboratory-tested FPG or OGGT (2hourPG ≥ 11.1mmol/L) unless acute metabolic decompensation is present.

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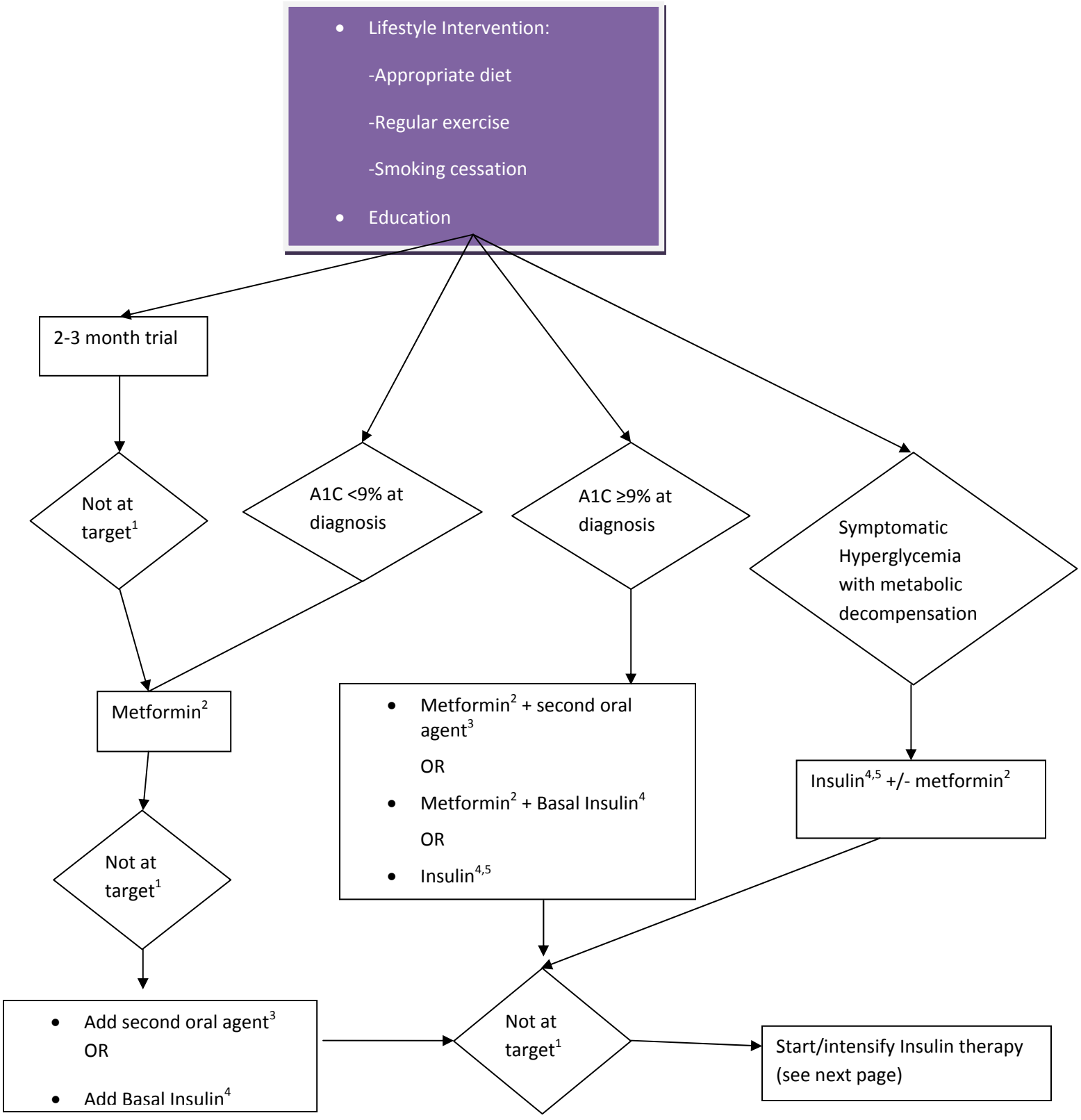
3.4 Type 2 Diabetes in Adults



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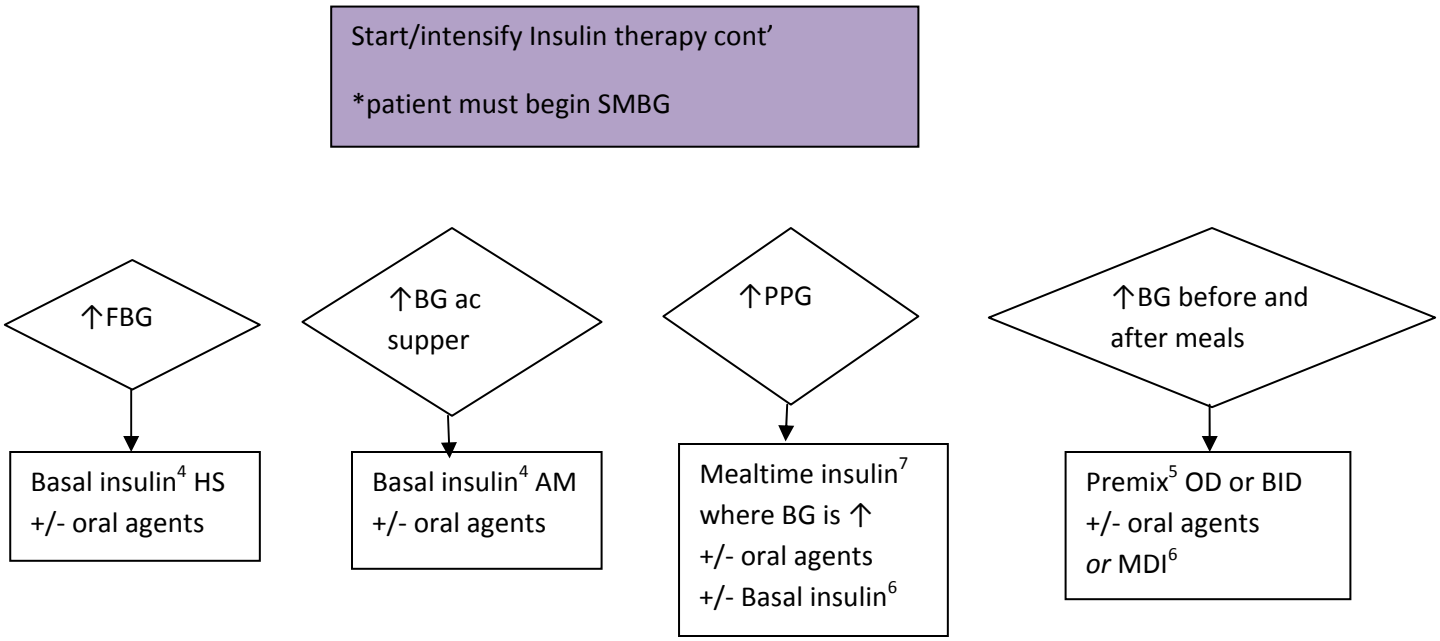
3.5 Type 2 Diabetes in Adults



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3.6 Type 2 Diabetes in Adults

1. **Targets for glycemic control: A1C <7%; FPG 4-7 mmol/L; PPG 5-10 mmol/L**

   Check A1C every 3 months when targets are not met or treatment is adjusted, then every 6 months once targets are achieved.

   Whenever targets are not met, check compliance and reinforce lifestyle interventions.

2. Unless contraindicated: pregnancy, excessive alcohol use, liver disease, CrCl <30mL/min, CHF. See Pharmacologic Agents for Diabetes section for alternatives.
3. See Pharmacologic Agents for Diabetes section for choices. Consider therapeutic advantages and disadvantages as well as cost to patient when choosing an agent. Also consider contraindications and comorbidities including liver disease and impaired renal function as well as lifestyle choices such as alcohol intake. It is recommended to choose agents with different mechanisms of action.
4. Basal Insulin:

   -Patient must begin SMBG and understand when/how to adjust diet/insulin dose.

   -Consider discontinuing insulin secretagogue.

   -Suggested starting dose is 10U HS. A calculated-dose (0.1-0.2U/kg) may be considered for elderly or non-obese patients where hypoglycemia is a greater risk.

   -Increase by 1 unit/day until target is reached. If target is not met at 30U/day, a more intense regimen is needed.

   -Do not increase dose if patient experiences nocturnal hypoglycemia or 2 episodes of daytime hypoglycemia in 1 week. If daytime hypoglycemia occurs, ↓dose of oral agents.

5. Premix Insulin:

   -Patient must begin SMBG and understand when/how to adjust diet/insulin dose.

   -Consider discontinuing insulin secretagogue.

   -Suggested starting dose is 5-10 units OD or BID (pre-breakfast or pre-supper).

   -Increase 1 or 2 units prebreakfast and/or presupper until target is reached. Prebreakfast dose affects presupper BG and Presupper dose affects prebreakfast (fasting) BG.

   -SMBG BID during dose titration.

   -Do not increase dose if patient experiences nocturnal hypoglycemia or 2 episodes of daytime hypoglycemia in 1 week. If daytime hypoglycemia occurs, consider ↓dose of oral agents.

6. MDI = multi-dose intensive insulin therapy = Basal + Mealtime (bolus) Insulin:

   -Patient must be motivated and capable of frequent SMBG and understand how to make necessary adjustments to insulin dose. This regimen requires more frequent testing to avoid hypoglycemia.

   -Oral agents are generally not used with MDI

   -Note that insulin plus 3 oral agents has been shown to ↑mortality.

   -Calculate total daily dose (0.3-0.5U/kg) and distribute as follows: Basal Insulin dose = 40%; Bolus insulin dose=20% at each meal. Adjust each meal dose from here if necessary.

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3.7 Type 2 Diabetes in Adults cont'

-If already on Basal Insulin and adding mealtime insulin: start with 10% of total daily dose at largest meal; 90% of total daily dose is the new Basal dose. Add more mealtime boluses in a similar way.

-Do not ↑insulin dose if patient experiences nocturnal hypoglycemia or 2 episodes of daytime hypoglycemia in 1 week

7. Discontinue secretagogues when starting mealtime insulin.

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4.1 Type 2 Diabetes in Children and Adolescents

Risk factors for Diabetes

- obesity[1]
- family history of diabetes
- member of high risk population
- exposure to diabetes in utero
- IGT
- signs of insulin resistance[2]
- use of atypical antipsychotics[3]

Targets for Glycemic Control[4]

- A1C ≤7%
- FPG 4-7 mmol/L
- PPG 5-10 mmol/L

Lifestyle Interventions

- Healthy diet
- Regular physical activity
- avoid alcohol
- no smoking
- success is increased if these initiatives are adopted by the whole family

BP test at each diabetes-related visit

- reinforce lifestyle modifications
- treat with antihypertensives as per guidelines for children without diabetes

Lipid Profile every 1to 3 years

- Familial dyslipidemia
- Family history of early CV event AND
- If LDL >4.2 mmol/L after 3-6 months of dietary intervention a statin is warrented

Screen for microvascular complications yearly

- Nephropathy: ACR
- Neuropathy: question about numbness, pain, cramps, skin sensation, light touch, ankle reflexes
- Retinopathy: eye exam

1. BMI ≥95th percentile for age and gender.
2. Signs/symptoms of insulin resistance: hypertension, dyslipidemia, acanthosis negricans
3. Risperidone (Risperdal), Olanzepine (Zyprexa), Clozapine (Clozaril), Quetiapine (Seroquel)
4. Individualize targets according to functional ability, comorbidity and other circumstances.

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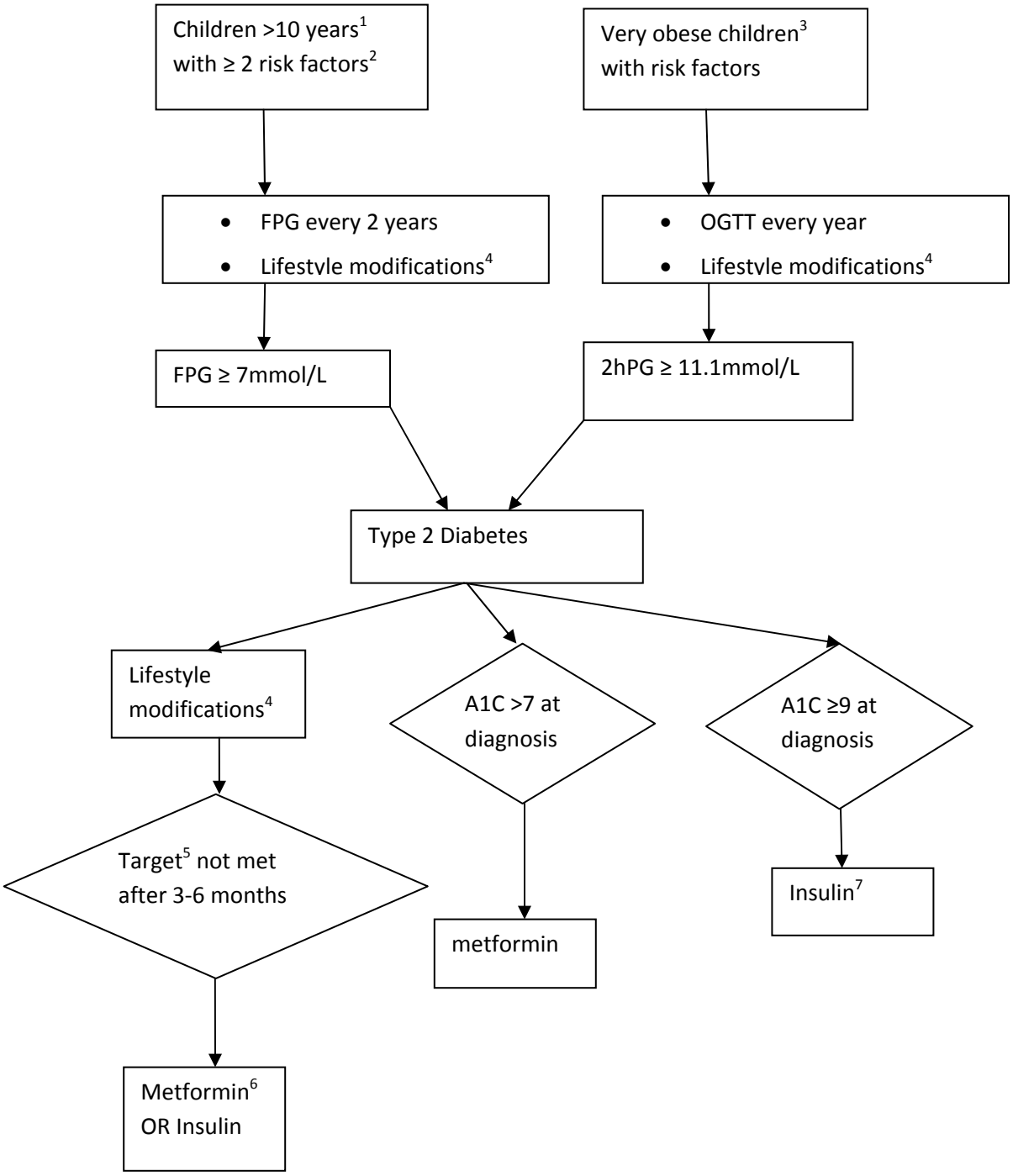
4.2 Type 2 Diabetes in Children and Adolescents



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4.3 Type 2 Diabetes in Children and Adolescents

1. Or younger if puberty has been reached.
2. Risk factors for diabetes:
    - obesity (BMI ≥95th percentile for age and gender)
    - family history of diabetes
    - member of high risk population
    - exposure to diabetes inutero
    - signs/symptoms of insulin resistance (hypertension, dyslipidemia, acanthosis nigricans); impaired glucose tolerance
    - use of atypical antipsychotics
3. BMI ≥99th percentile for age and gender.
4. Includes:
    - healthy diet (to achieve and maintain healthy weight)
    - regular exercise,
    - address avoidance of self destructive behaviours such as smoking and alcohol use.
5. Glycemic Control Targets:
    - A1C ≤7%;
    - FPG 4.0-7.0mmol/L;
    - PPG 5.0-10.0mmol/L
6. Dose of metformin for children >10 years old: 250mg-2000mg/day. Start with 250-500mg OD and titrate weekly as tolerated.
7. May be weaned off insulin once glycemic targets are achieved and lifestyle modifications implemented.

Prevention of Diabetes in Children and Adolescents

- Breastfeeding
- Healthy diet
- Regular exercise
- Involvement of the whole family in adopting a healthy lifestyle

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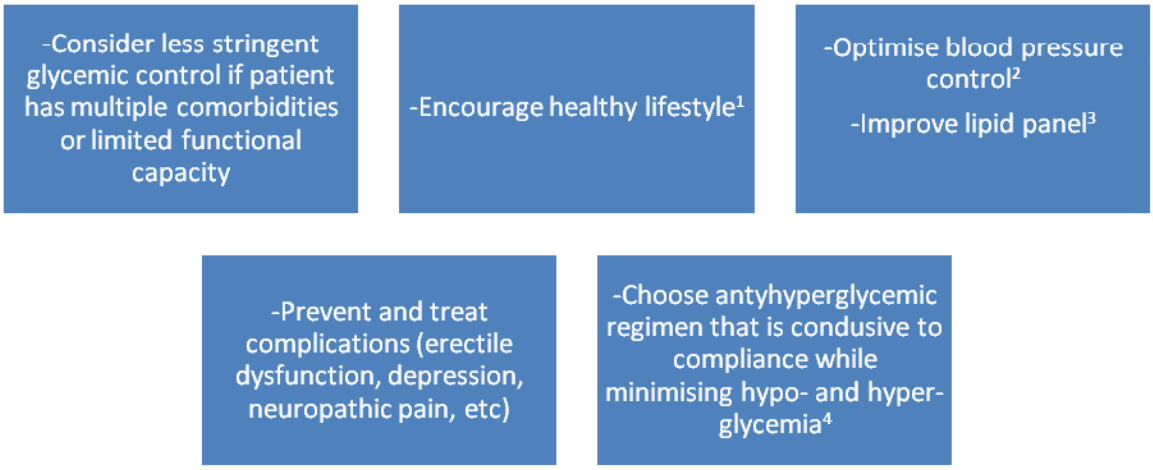
5.1 Diabetes in the Elderly



Drug	Comments
Acarbose	Moderately effective; poorly tolerated
Metformin	Good choice, especially in obese patients
Glitazones	Effective, but ↑heart failure and edema; use with caution in CVD
Sulfonylureas	↑risk of hypoglycemia with age (especially glyburide)
Repaglinide	Less hypoglycemia; preferred in people with irregular mealtimes
Lispro/Aspart Insulin	Similar kinetics to Regular insulin in the elderly
Premixed Insulins	Fewer errors (compared to mixing insulins); better glycemic control

1. Healthy diet to achieve and maintain healthy weight and optimise glycemic control; regular physical activity as permitted by comorbidities and physical limitations.
2. Treatment of isolated systolic and systolic/diastolic hypertension reduces CV morbidity/mortality and preserves renal function. ACEI, ARBs, thiazide diuretics, long acting CCB (except possibly amlodipine) are reasonable choices in the elderly. Cardioselective beta blockers and alpha blockers are not as effective in reducing CV events.
3. Statins have been shown to be effective in preventing CV events. Data on fibrates is conflicting.
4. In lean elderly patients with Type 2 diabetes, insulin secretion is impaired (an insulin secretagogue would be a good choice). In obese patients, insulin resistance is the main defect while insulin secretion is preserved (choose agents that reduce insulin resistance).

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6.1 Type 2 Diabetes in Aboriginal People

1. Programs to promote healthy diets, regular exercise, and limitation of alcohol intake should be developed in collaboration with the community so that these health recommendations are relevant to the population and more likely to be followed. These programs should focus on preventing obesity in all age groups including pregnant women as well as promoting other preventative measures such as breastfeeding.
2. These individuals may benefit from diabetes prevention strategies (weight loss, metformin, diet counselling).
3. Screen people ≥ 40 years of age every 3 years. Screen people with additional risk factors earlier and/or more frequently: first degree relative with diabetes; history of IGT or IFG; presence of complications of diabetes (retinopathy, nephropathy); history of GDM; previous delivery of macrosomic infant; hypertension; dyslipidemia; overweight; abdominal obesity; PCOS; acanthosis nigricans; use of atypical antipsychotics.
4. It is important develop treatment protocols in collaboration with the community so that cultural aspects can be incorporated.

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7.1 Pregnancy in Pre-existing Diabetes

Before Pregnancy

- Achieve A1C ≤ 7%[1]
- Start Folic Acid 5mg OD 3 months preconception
- Discontinue ACEI, ARB, statin[2]
- Discontinue oral antihyperglycemics[3]
- Screen for retinopathy[4]
- Screen for nephropathy[5]
- Quit smoking and alcohol consumption

During Pregnancy

- Targets[6]: A1C <6%

  FPG 3.8-5.2 mmol/L

  1 hour PPG 5.5-7.7 mmol/L; 2 hour PPG 5.0-6.6 mmol/L
- SMBG at least QID[7]
- Prevent hypoglycemia[8]
- Follow recommended diet and exercise plan (as glycemic control/obstetric considerations allow)
- Continue Folic Acid 5mg OD to 12 weeks gestation, then take 1mg OD
- Regular medical visits, including ophthalmology

Postpartum

- Insulin requirement returns to pre-pregnancy levels 5-7 days after delivery
- Consider breastfeeding[9]
- Resume vascular protection, hypertension treatment (as allowed by breastfeeding)
- Screen for thyroiditis 6 weeks postpartum (Type 1 diabetes)
- Continue Folic Acid 1mg OD for 6 weeks or until breastfeeding stops

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7.2 Pregnancy in Pre-Existing Diabetes

1. **Higher A1C levels are associated with poorer outcomes (spontaneous abortion, congenital malformations, pre-eclampsia, and progression of retinopathy.**
2. Control blood pressure with agents that are safe in pregnancy (CCB, beta blockers, labetolol, methyldopa, hydralazine).
3. Or switch to insulin once pregnant.
4. Risk factors for worsening retinopathy: hypertension, poor glycemic control during pregnancy, pre-eclampsia, more severe pre-existing retinopathy.
5. Microalbuminuria and nephropathy are associated with increased risk of maternal and fetal complications. In women with normal renal function, pregnancy does not affect renal function as long as blood pressure and blood glucose are optimally controlled. Women with early CKD should have their renal function monitored each trimester (ACR, estimated CrCl)
6. **Hyperglycemia poses a risk to the fetus throughout pregnancy: malformations during the first trimester; macrosomia and metabolic complications at birth**.
7. Preprandial and postprandial levels guide diet and pharmacologic therapy; testing during the night in patients on insulin to avoid nocturnal hypoglycemia
8. Normal hormone responses to hypoglycemia are blunted during pregnancy. Hypoglycemic unawareness may occur with repeated episodes of hypoglycemia (due to trying to achieve tight glycemic control) or use of certain antihypertensives (beta blockers). Hypoglycemia does not seem to affect the fetus, but can cause maternal seizures.
9. Breastfeeding offers many benefits to the mother and the baby including reducing risk of infant obesity. Glyburide and metformin appear to be safe in breastfeeding, but further studies are warranted.

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8.1 Gestational Diabetes

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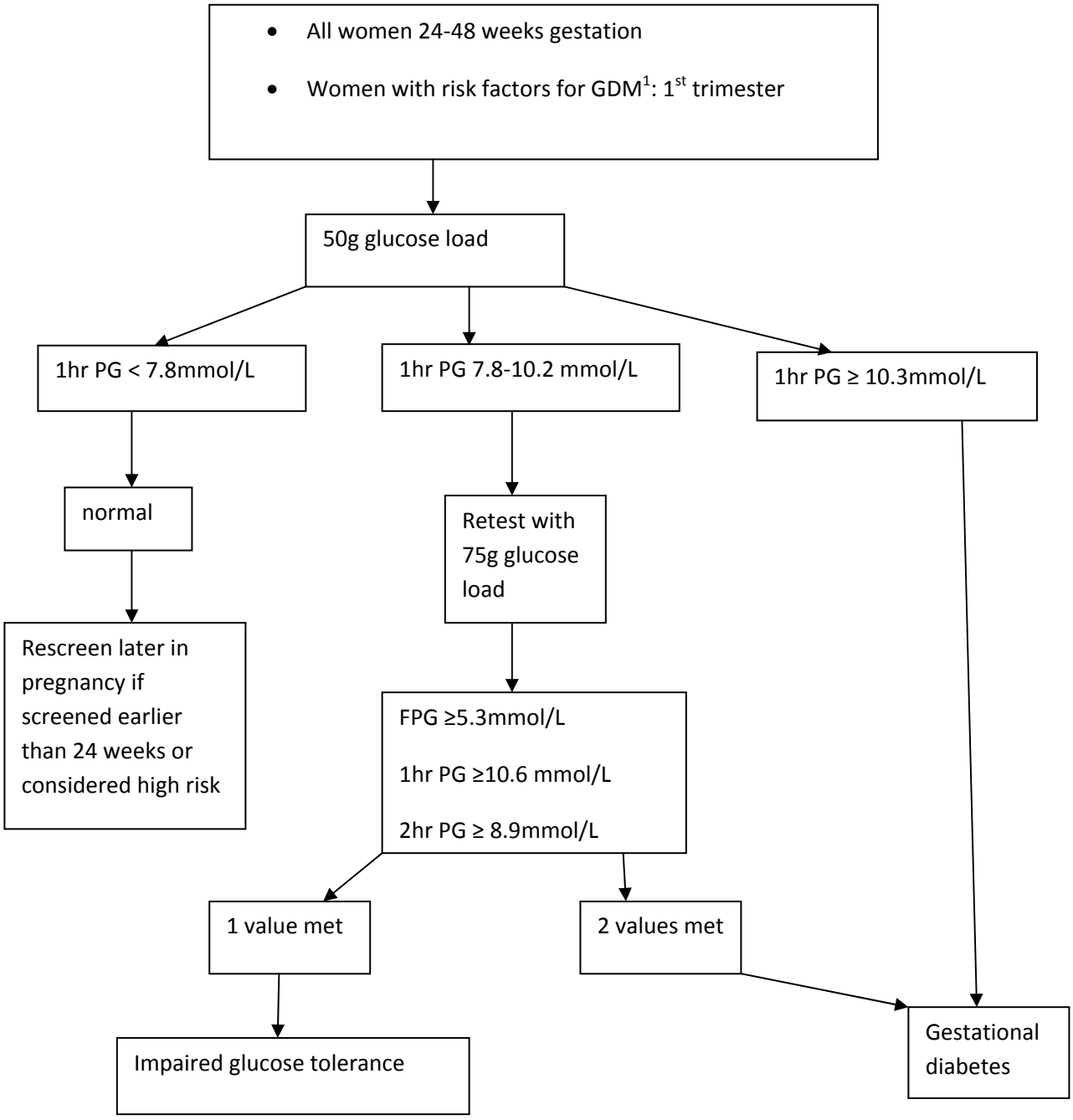
8.2 **Gestational Diabetes**



1. Risk factors for GDM: previous GDM; delivery of macrosomic infant; high-risk population (including Aboriginal); ≥35 years; obesity; polycystic ovary syndrome; corticosteroid use.

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8.3 Gestational Diabetes

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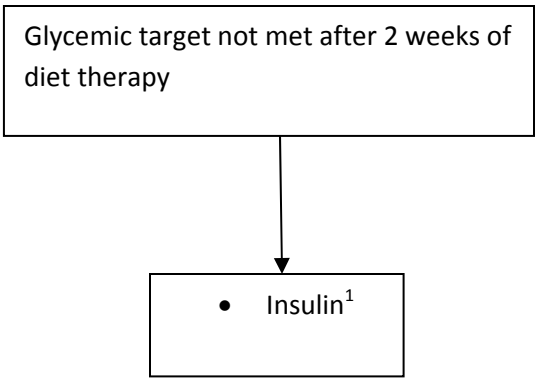

- ➢ Regular Medical visits: <20 weeks gestation – every 4 weeks
  20 – 30 weeks gestation – every 2 weeks
  >30 weeks gestation – every week
- ➢ At each visit review : SMBG including achievement of targets and episodes of hypoglycaemia
  : weight
  : medications (efficacy, compliance, side effects)
  : blood pressure
  : compliance with diet and exercise plan
- ➢ Other monitoring: ultrasound (18-21 weeks for anomalies, placenta, etc and 35 weeks for fluid and fetus; fetal movement (kick chart from 32 weeks); non-stress testing weekly from 32 weeks (fetal monitor required)

1. Glyburide or metformin may be considered if the patient refuses insulin, but their use in pregnancy is considered off-label. This decision should be made by an obstetrician.

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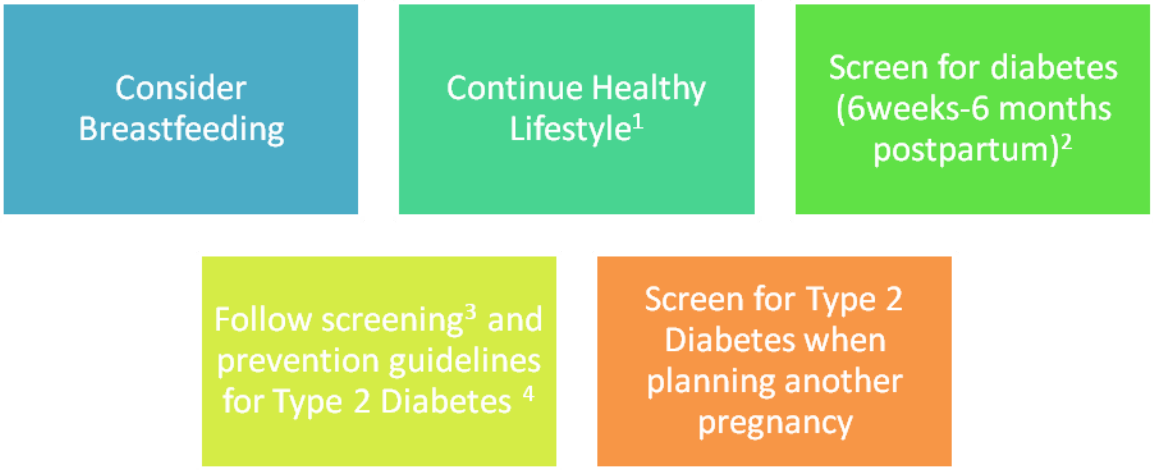
8.4 **Gestational Diabetes**

Postpartum:



1. Healthy Lifestyle: regular exercise, healthy diet, smoking cessation, limited alcohol intake.
2. Screen for diabetes with oral 75g glucose load.
3. Screening for diabetes: every 3 years for people ≥40 years old; earlier and more frequently if risk factors (family history, obesity, etc)
4. Prevention of diabetes: achieve and maintain healthy weight; low fat, high fibre diet; regular exercise; smoking cessation; limitation of alcohol intake.

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9.1 Pharmacologic Management of Diabetes in Pregnancy

Glycemic Control

Insulin Type	Comments
Regular	safe
Rapid-acting	Safe, help achieve PPG target with minimal hypoglycemia
Intermediate-acting (NPH)	Safe, but nocturnal hypoglycemia may occur
Detemir	May be considered if nocturnal hypoglycemia occurs with NPH
Glargine	Not recommended
Premixed	May not achieve tight glycemic control in Type 1

Hypertension

Drug	Trade Name	Comments
Methyldopa	Aldomet	First Line
Hydralazine		First Line
Labetolol		First Line
CCB	Nifedepine, etc	Alternative
Beta Blockers	Atenolol, etc	May cause reduced birth weight and persistent beta blockade in infant

See section on antihypertensive agents for dosing, side effects, etc.

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9.2 Pharmacologic Management of Diabetes while Breastfeeding

Medication	Compatibility (Y/N[1]/?[2])
	Hypoglycemics
Insulin	Y
Metformin	?
Sulfonylureas[3]	N
Acarbose[4]	?
Glitazones	?
Repaglinide[3]	N
	Antihypertensives
Ramipril[5]	Y
ARB	?
Norvasc, Felodipine	?
Nifedipine[6]	Y
Verapamil[6], Diltiazem[6]	Y
B-Blockers[6,7]	Only propranolol,metoprolol
Labetolol[6,8]	Y
Methyldopa	Y
Hydralazine	Y
Clonidine	N
Hydrochlorothiazide[9]	Y
Furosemide[9]	?
	Antihyperlipidemics
Statins	N
Fibrates	N
Cholestyramine[10]	?

1. Either there are potential risks to the infant, or the risks are unknown. If the mother continues to breastfeed, she should not take the medication *or* if the mother chooses to take the medication, she should not breast feed. The risks to the mother of complications of diabetes by not taking medication must be carefully weighed against risks to the baby of not being breast fed or of being exposed to the medication.
2. Safety data is unknown, or effects of exposure of infant to the medication is unknown.
3. Potential for hypoglycemia in the infant.
4. Is not appreciably absorbed by the mother, but there is no safety data available.
5. Also captopril and enalapril.
6. Consider breastfeeding 3-4 hours after taking the medication to reduce infant exposure.
7. Monitor bradycardia, respiratory depression, and hypoglycemia in the infant.
8. Monitor heart rate and blood pressure in the infant.
9. May ↓ lactation.
10. Not absorbed systemically by the mother, but does prevent absorption of fat-soluble vitamins by the mother therefore posing the risk of vitamin deficiency in the mother and the infant.

These materials were developed by the Clinical Subcommittee of the Chronic Disease Network and Access Program of the Prince Albert Grand Council and its partners and funded by the Aboriginal Health Transition Fund.

10.1 Pharmacologic Management of Diabetes

Oral Agents

Drug	Trade Name	Usual Dose	Onset	Peak	Duration
	Biguanide[1]				
Metformin	Glucophage, Glycon	500-1000mg[2]BID		3h	3-12h
	Glitazones[3]				
Pioglitazone	Actos	15-45mg OD	3-8weeks		
Rosiglitazone	Avandia	4-8mg OD[4]	3-8weeks		
	Sulfonylureas[5]				
Chlorpropamide[6]	Diabinase	100-250mg OD		6-8h	24-72h
Gliclazide[7]	Diamicron reg,MR	800mg reg BID[8] 60-120mg MR		4-6h	10-24h
Glyburide	Diabeta	5-10mg BID	<60min	2-4h	12-14h
	Meglitinides[9]				
Repaglinide	Gluconorm	0.5-4mg AC[10]	15-60min	60-90min	4-6h
	α Glucosidase Inhibitor[11]				
Acarbose	Glucobay	50-100mg TID[12]	8 weeks		
	Incretin Enhancer				
Sitagliptin[13]	Januvia	100mg OD[14]	≤4 weeks		
Saxagliptin[13]	Onlgyza	5mg OD[14]			
Liraglutide[15]	Victoza	0.6-1.8mg OD[15]			

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10.2 Pharmacologic Management of Diabetes cont'

1. Side Effects: GI upset, nausea, diarrhea (take with meals, temporarily decrease dose); metallic taste; lactic acidosis: rare but potentially fatal, (tends to occur in hepatic or renal disease; concerns with CHF, dehydration, sepsis; stop if acutely ill or hypoxic)
   Drug Interactions: alcohol; radio contrast media
   Contraindications: renal impairment (CrCl <30mmol/L), hepatic impairment, previous lactic acidosis
2. Start with 250-500mg OD and titrate up every 2 to 4 weeks to avoid GI effects. Use lower dose if elderly or CrCl <60mL/min. Maximum 850mg TID. TID is an option for higher doses to improve tolerance.
3. Side Effects: edema; heart failure (higher risk when given with insulin); weight gain; fractures; macular degeneration; monitor liver function. Note that pioglitazone has comparable A1C lowering to rosiglitazone, but is less likely to increase the risk of heart attack and more favourable effects on lipids. For these reasons some clinicians recommend pitoglitazone over rosiglitazone.
   Drug Interactions: gemfibrozil (↑effects of glitazone)
   Contraindications: avoid in heart failure
4. Can give 4mg BID. Maximum 4mg OD if on sulfonylurea.
5. Side Effects: hypoglycemia (increased risk in elderly, debilitated, malnourished, or with irregular mealtimes); sulfa skin reactions; rash; photosensitivity; GI effects; headache; dizziness; weight gain; concerns with hyperinsulinemia, hyponatremia, cardiac toxicity
   Drug Interactions: hypoglycemic effect potentiated by ASA, NSAIDs, alcohol, cimetidine, fluconazole, sulfonamides, MAOIs; beta blockers may mask symptoms of hypoglycemia; ↓effect with rifampin
   Contraindications: Type 1 diabetes; pregnancy
6. Alcohol-associated flushing; hyponatremia. Not recommended due to ↑BP and retinopathy.
7. Has antiplatelet effect; less hypoglycemia than other sulfonylureas
8. Use lower dose if renal/hepatic dysfunction or prone to hypoglycemia. Titrate up every 1-2 weeks.
9. Side Effects: hypoglycemia (less than with sulfonylureas); weight gain
   Drug Interactions: many potential including: ↑effect with azole antifungals, macrolides, HIV meds, cyclosporine; ↓effect with rifampin, carbamazepine; avoid with gemfibrozil
   Contraindications: Type 1 diabetes, pregnancy
10. Titrate every 7 days. Can start with higher dose if already on treatment or if A1C ≥8%. Take 15 minutes before eating or immediately after meal; skip if meal is skipped.
11. Side Effects: diarrhea, flatulence, GI intolerance; ↑LFT and hepatic failure; accumulates in renal failure
    Drug Interactions: may ↓absorption of metformin; ↓effect of digoxin; ↑side effects with cathartics, cholestyramine
    Contraindications: severe GI disease IBS, inflammatory bowel disease
12. Mealtime dosing. Start with 25mg OD and increase every 4 to 8 weeks. Not recommended as initial therapy if A1C ≥9%.
13. Side Effects: sore throat; headache; nausea; diarrhea; arthralgias; SJS; no safety data available yet
    Drug Interactions: ↑hypoglycemia with sulfonylurea, few known yet
14. Sitagiptin: lower dose in renal failure. Saxagliptin: not recommended in moderate or severe renal failure. Not recommended for monotherapy – to be given with metformin. No outcome or safety data available yet.
15. Side Effects: nausea, vomiting (subsides after several weeks); pancreatitis; thyroid tumors (in rodents)
16. SC injection; not yet recommended for monotherapy- give with metformin or metformin + sulfonylurea; or use instead of insulin or sulfonylurea to assist with weight loss; use instead of saxagliptin/sitagliptin to achieve further A1C lowering; do not combine with sitagliptin/saxagliptin.

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10.3 Pharmacologic Management of Diabetes cont'

Insulins[1]

Drug	Trade Name	Dosing	Onset	Peak	Duration
	Rapid Insulin[2] *(RAIA)*				
Lispro	Humalog	Just Before Meal[3]	10-15min	60-90min	3.5-6h
Aspart	NovoRapid	"	10-30min	60min	3.5-6h
Apidra	Glulisine	"		60-90min	4-5h
	Short Acting[4]				
Regular Insulin	Humulin R	20-30min AC	30-60min	2-3h	5-10h
	NovolinToronto	"	"	"	"
	Intermediate-acting[4]				
NPH	Humulin N	HS or BID	2-4h	4-10h	12-18h
	Novolin NPH	"			
	LAIA[5]				
Detemir	Levemir	OD or BID	1h	6-8h[8]	16-24h
Glargine[6]	Lantus	OD[7]	2-4h	No peak	20-24h
	Premixed[9] *Human*				
Regular/NPH	Humulin 30/70	20-30min AC	0.5-1h	Dual peak	14-28h
	Novolin 30/70[10]				
	Premixed Analogues[11]				
Lispro/Lispro-protamine	Humalog Mix 25,50	Just Before Meal			
Aspart/Aspart-Protamine	NovoMix 30	"			

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10.4 Pharmacologic Management of Diabetes cont'

1. Side Effects: hypoglycemia, weight gain, lipodystrophy
2. Less variability between sites; less need for snacks; flexible dosing; less night hypoglycemia; better control of PPG; safe in pregnancy. Rapid-acting insulin analogue.
3. Or within 20 minutes of starting meal.
4. Safe in pregnancy; more safety data in general.
5. ↓hypoglycemia
6. Some pain at injection site.
7. Split dose if >50 units.
8. Considered to have flat-action profile, but maximum serum concentration is reached 6-8 hours after injection.
9. May give OD, BID, or TID, but avoid at HS. Useful for patients with a non-intensive regimen or Type 2 diabetics with consistent foot intake and activity (ex elderly, bedridden, institutionalized). Note that the first number refers to the % of short-acting insulin and the second number refers to the % of long-acting insulin
10. Also 10/90, 20/80, 40/60, 50/50
11. Similar glycemic control to premixed human insulin. Better glycemic control than LAIA but ↑ hypoglycemia. Clinical outcome data is lacking. Note that the number refers to the % of rapid-acting insulin.

Insulin Compatibility

R + NPH: √ (draw short-acting first)

RAIA + NPH: use immediately; draw RAIA first

LAIA: do not mix with other insulins

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10.5 Pharmacologic Management of Diabetes

Combinations of Agents in Type 2 Diabetes

- Combinations with Metformin result in less weight gain than sulfonylurea combinations
- Metformin + pioglitazone has positive lipid effects, but ↑edema
- Metformin + rosiglitazone ↓A1C but↑edema
- Metformin + acarbose ↓weight and PPG, but ↑GI intolerance
- Metformin (+/-sulfonylurea) + liraglutide ↓weight and ↓A1C
- Insulin + sulfonylurea with caution in the elderly; d/c sulfonylurea when mealtime insulin is given
- Insulin + metformin superior to insulin + sulfonylurea; preferred in obese patients; allows lower dose of insulin
- Insulin + glitazone not approved in Canada (↑edema, CHF, and weight gain)
- Insulin + repaglinide is an option if ↑PPG is a problem
- Insulin + 3 oral agents ↑mortality

Special Situations: Recommended Agents *(unless otherwise contraindicated)

Renal Failure	Glitazones, Repaglinide, insulin
Hepatic Disease	Insulin, Repaglinide (use glyburide, metformin, glitazones with caution
Obesity	Metformin, Victoza
Irregular Mealtimes	Repaglinide
PPG ≥10, little ↑FPG	Repaglinide, rapid-acting insulin, diet modification
IGT, IFG	Lifestyle modifications, metformin
Hypoglycemia	Metformin, glitazones, repaglinide, gliclazide, LAIA, Incretin Enhancers
Pregnancy	Diet, exercise, insulin
Heart Failure	Metformin (unless severe renal impairment), insulin, sulfonylureas, repaglinide

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10.6 Pharmacologic Management of Diabetes

Insulin Regimens[1]

Schedule	Breakfast	Lunch	Supper	Bedtime
Conventional Regimens				
OD[2]	-	-	-	NPH/LAIA[3]
BID[4]	NPH/Detemir	-		NPH/Detemir
BID[5]	R/RAIA & NPH/Detemir	-	R/RAIA & NPH/Detemir	-
TID[6]	R/RAIA & NPH	-	R/RAIA	NPH
Multidose Intensive Regimens (MDI)				
QID[7]	R/RAIA	R/RAIA	R/RAIA	NPH
QID [8]	R/RAIA & NPH	R/RAIA	R/RAIA	NPH
Continuous SC Infusion (CSII)[9]				

1. No maximum dose for insulin. Fix low BG first and high BG later and only adjust one insulin at a time. Consider Somogyi effect with low morning BG.
2. Simple, but poor control; useful in Type 2 with oral agents during the day. Less weight gain than with insulin alone (especially with metformin). Remember insulin plus glitazone is not approved in Canada. If PM BG is↑, may need BID insulin. With ↑PPG, short-acting insulin with meals or premix may be needed.
3. Long-acting agent may be given before breakfast (rare). BID regimens are more effective with consistent food intake and activity.
4. Improved morning control and overnight coverage.
5. May use premix instead of separate injections of short-acting and long-acting agents. Using premix at bedtime should be avoided as it poses a higher risk of nocturnal hypoglycemia.
6. More likely to last until morning. Detemir or Glargine may be used instead of NPH
7. Frequent SMBG at first. Good control. Allows flexibility with meals.
8. Useful for people with varying meal schedules.
9. R or RAIA used: basal & bolus when needed. RAIA are preferred. ↑risk of rapid ketoacidosis if discontinued.

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10.7 Anti-obesity Agents[1]

Drug	Trade Name	Dosing
	GI Lipase Inhibitor[1]	
Orlistat[2]	Xenical	120mg CC (max TID)[3]

Source: RxFiles, CDA Guidelines

1. Decreases fat breakdown and absorption. Not studied in children <12 years old. Seems safe in children 12-16 years old.
2. Side Effects: Common: diarrhea, oily stools, ↑bowel movements, flatulence, abdominal pain, bloating, nausea, vomiting, dry skin, pedal edema; Serious: anaphylaxis, angioedema, urticaria
   Drug Interactions: warfarin (↑INR); cyclosporine
   Contraindications: chronic malabsorption syndromes; cholestasis
3. Start on a weekend (ie while at home) OD and slowly titrate up to TID. Give during or within 1 hour of a meal. Omit dose if meal is skipped or contains no fat. Recommend a multivitamin to prevent deficiency in fat-soluble vitamins.

AGENTS NOT OFFICIALLY INDICATED FOR WEIGHT LOSS

Drug	Trade Name	Dose[4]
	Antidepressants	
Bupropion[1] SR,XL	Wellbutrin	150mg-200mg BID 300mg XL OD
Fluoxetine[2]	Prozac	60mg OD
	Mood Stabilizer	
Topiramate[3]	Topamax	50-100mg BID

1. Not enough evidence to recommend for weight loss. May ↑seizure risk at >300mg/day. Consider if bupropion would be of other benefit to the patient besides weight loss.
2. Weight loss appears to be dose dependant and may lose effectiveness over time. May result in modest ↓A1C in type 2 diabetes. Consider if patient suffers depression +/- anxiety.
3. Weight loss may be dose related. May minimize weight gain by other psychotropics. May be beneficial in obese type 2 diabetes along with metformin and exercise, but side effects may limit its use.
4. ↓ dose in renal impairment.

10.8 Anti-obesity Agents

Herbal/Natural Products for weight loss

- Overall evidence of efficacy is weak.
- Herbal/Natural products for weight loss are often expensive and not covered by NIHB, provincial drug plans, or private health plans.
- Some have the potential for serious complications.
- **Avoid their use in CVD and hypertension**. Many contain caffeine , ephedrine, or other stimulants that may ↑BP, ↑HR, cause tremors and CNS stimulation (irritability, insomnia), and have a diuretic effect.
- **Avoid their use in patients taking medications with possible drug interactions** (ex warfarin, digoxin, statins).
- **Avoid their use in pregnancy and breast feeding.**
- Because of the lack of evidence of efficacy and possible safety concerns, generally advise against their use. If the patient insists on trying a herbal/natural product, however, encourage choosing a product with a NHP (Natural

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Health Product) number (ie regulated by Health Canada for quality) that is purchased at a pharmacy (so the pharmacist can be consulted for information).

- Common mechanisms of action:
  - Stimulant (↓appetite, ↑metabolism): caffeine, ephedra (Ma Huang), green tea products, guarana, yerba mate, kola, bitter orange, pinellia. Note safety concerns above.
  - Laxative (ie bowel cleansers): cascara sagrada, rhubarb, golden seal, fennel, ginger, marshmallow, slippery elm, probiotics, flax, psyllium. Concern with electrolyte imbalance.
  - Bulking agent (↓appetite): PGX, psyllium, flax, xanthan gum. May ↓absorption of oral medications
- **Health Canada Warnings:** (This is not a complete list. Many herbal/natural products are taken off the market because of safety concerns.)
  - Hydroxycut: nausea, tremor, dizziness, palpitations, chest pain, SOB, vomiting, insomnia, syncope, fatal MI.
  - Zantrex-3: headache, nervousness, tachycardia, nausea, diarrhea, tremor, sweating
  - Xenadrine EFX: tachycardia, abdominal cramps, nausea, vertigo, tremor, chest pain, SOB, ↑amylase
  - Ephedra (Ma Huang): banned because of MI and death
  - Ezee Slimming Patch: leucopenia, thrombocytopenia, neutropenia, ↓hemoglobin, menstrual irregularity, agitation, possible fatal jaundice, hepatitis, and clotting disorder
- Other common products:
  - Hoodia (non-stimulating appetite suppressant; evidence is weak)
  - Green Tea (conflicting evidence; contains caffeine)
  - Pyruvate (↑exercise capacity; evidence is weak)
  - Iodine (no evidence and may cause thyroid disorders)

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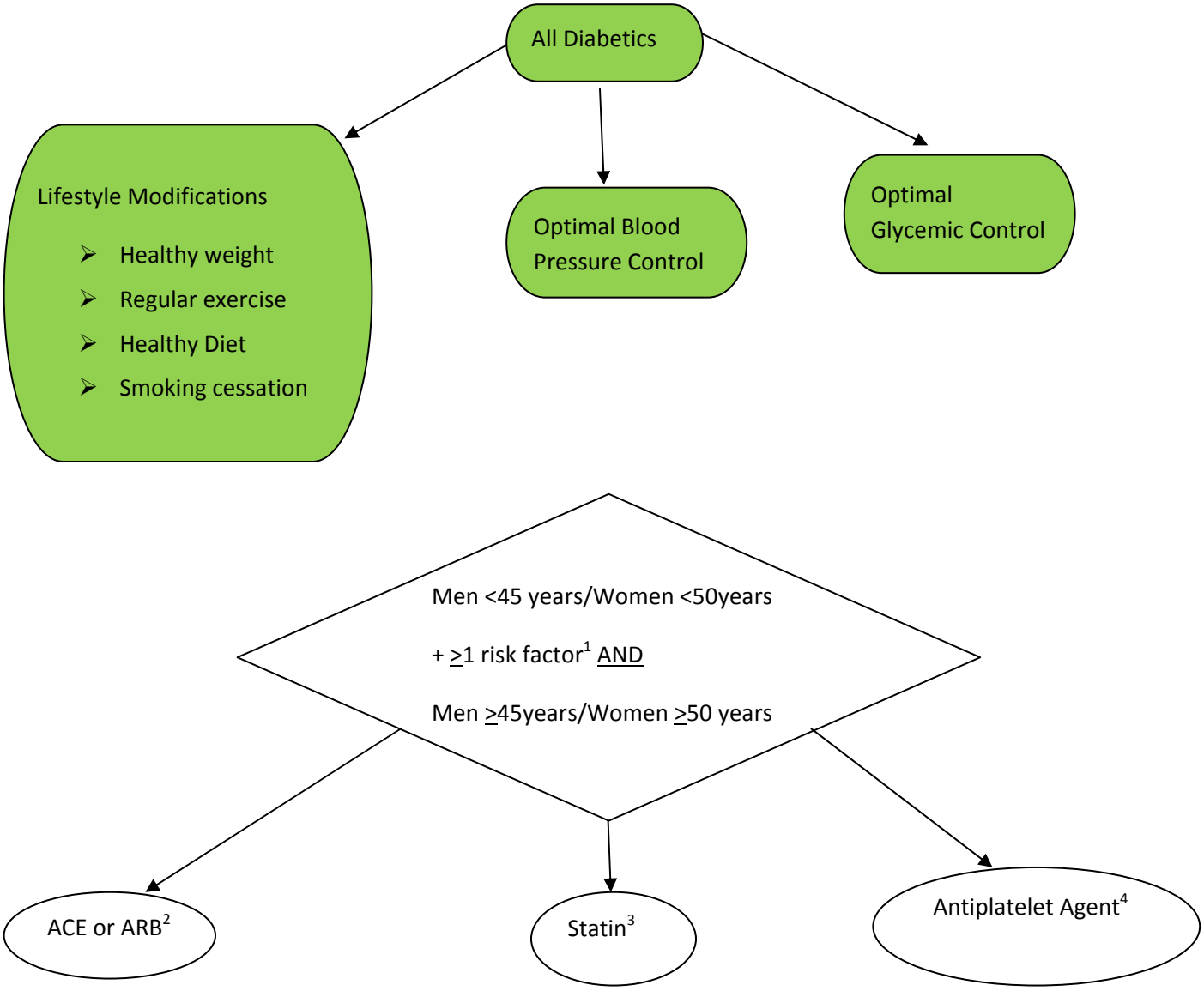
11.1 Vascular Protection



1. Macrovascular disease (MI, stroke, TIA, ischemia); Microvascular disease (retinopathy, nephropathy); LDL >5mmol/L; Systolic BP >180mmHg; Duration of diabetes >15 years and >30 years old
2. Unless contraindicated: pregnancy, history of angioedema, renal artery stenosis (solitary kidney or bilateral). See Hypertension section for alternatives
3. Unless contraindicated: pregnancy, excessive alcohol use, acute liver disease. See Dyslipidemia section for alternatives.
4. ASA 81 to 325mg OD or Clopidrogel 75mg OD if ASA not tolerated. Contraindicated in recent/active bleeding, major GI intolerance, history of ASA allergy, and persons <21 years old.

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11.2 ACEI = Angiotensin Converting Enzyme Inhibitor

ARB = Angiotensin Receptor Blocker

Drug	Trade Name	Dosing Range	Usual Dose
	ACEI[1,3,4,5]		
Benazepril	Lotensin	10-40mg OD or BID	20mg/day
Captopril	-	25-150mg/day BID or TID	25mg TID Empty stomach
Cilazapril	Inhibace	2.5- 10mg/day OD or BID	2.5-5mg OD
Enalapril	Vasotec	5-40mg/day OD or BID	10-40mg/day
Fosinopril	Monopril	10-40mg/day OD or BID	20mg/day
Lisinopril	Prinivil, Zestril	10-40mg OD	20mg OD
Perindopril	Coversyl	4mg OD or BID	-
Quinapril	Accupril	10-20mg OD or BID	-
Ramipril	Altace	2.5-10mg/day OD or BID	10mg/day
Trandolapril	Mavik	1-4mg OD	-
	ARB[2,3,4]		
Candesartan	Atacand	8-32 mg OD	8-16mg OD
Eprosartan	Tevetin	300-400mg OD or BID	-
Irbesartan	Avapro	75-300mg OD	150-300mg/day
Losartan	Cozaar	25-100mg OD or BID	25-100mg/day
Telmisartan	Micardis	40-80mg OD	-
Valsartan	Diovan	80-320mg OD	-

Source: Therapeutic Choices, RxFiles

1. Side Effects of ACEI: Dry cough; Hyperkalemia (especially with renal insufficiency, K^+ sparing diuretics, K^+ supplements, NSAIDs); angioedema, hypotension (especially if volume depleted or with diuretics); acute renal failure with bilateral renal stenosis; headache; dizziness; fatigue; rash; loss of taste; hepatotoxicity; dysguesia; pancreatitis; blood dyscrasias.
2. Side Effects of ARBS: same as ACE except no cough and less dizziness and headache.
3. Drug Interactions: K^+ supplements; K^+ sparing diuretics (assess K^+ and SCr regularly); NSAIDs; Lithium (possible toxicity)
4. Contraindications: pregnancy, history of angioedema, renal artery stenosis (solitary kidney or bilateral)
5. Use lower dose in renal impairment.
6. **Renal Function and K^+ must be monitored. Check BUN, Cr, electrolytes before starting, after 7 days, then regularly thereafter, including when dose ↑ or when a diuretic is added or ↑.**

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11.3 Statin = HMG Co-A Reductace Inhibitor

= ↓LDL, ↓TG, ↑HDL

Drug	Trade Name	Dose Range	Usual Dose
	Statin[1,2,4]		
Atorvastatin[3]	Lipitor	10-80mg OD	10-40mg HS
Fluvastatin[5]	Lescol	20-80mg/d HS or BID	20-40mg/d
Lovastatin[5]	Mevacor	20-80mg/d HS orBID	20-40mg HS
Pravastatin[3,6]	Pravachol	10-40mg HS	-
Rosuvastatin[3,6]	Crestor	5-40mg OD	-
Simvastatin	Zocor	10-80mg HS	20-40mg HS

Source: Therapeutic Choices, RxFiles

1. Side Effects of Statins: common: upper GI effects, headache, muscle pain, rash, sleep disturbances; rare: peripheral neuropathy, lupus-like symptoms, impotence, pancreatitis; ↑LFT (dose dependant); myopathy (concern if weakness accompanies muscle pain – check CK); rhabdomyolysis (increased risk with combinations of lipid-lowering agents or drug interactions that increase level of statin)
2. Drug Interactions: many potential including: ↑effect of digoxin and warfarin; increased toxicity of statin with amiodarone, clarithromycin, erythromycin, gemfibrozil, grapefruit juice, -conazole antifungals, certain HIV meds, verapamil, also transplant meds, diltiazem, ethynyl estradiol, fenofibrate, fluoxetine, niacin; decreased effect of statin with: cholestyramine (separate by 2 hours), phenytoin, phenobarb, carbamazepine, rifampin, St John's Wort, certain HIV meds **Avoid with macrolides, gemfibrozil, grapefruit, azoles, amiodarone, non-DHP CCB, cyclosporine, protease inhibitors.**
3. Few Drug Interactions with pravastatin and rosuvastatin – some transplant meds and gemfibrozil.
4. Contraindications: acute liver disease, pregnancy, excessive alcohol use
5. ↓dose in hepatic dysfunction.
6. ↓dose in renal dysfunction.

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11.4 Antiplatelet Agents

Drug	Trade Name	Dose
Acetylsalicylic Acid[1,2,4]	ASA, Aspirin, Novasen	81-325mg/day
Clopidrogel[1,3,4]	Plavix	75mg OD

Source: Canadian Journal of Diabetes September 2008

1. Side Effects: GI upset, hypersensitivity, GI bleed, major bleed, hemorrhagic stroke.
2. Drug Interactions with ASA: agents that cause GI irritation (NSAIDs, alcohol); agents that cause bleeding (warfarin).
3. Drug Interactions with Plavix: same as with ASA; also certain proton pump inhibitors ↓efficacy of Plavix (omeprazole (Losec), esoeprazole (Nexium), lansoprazole (Prevacid), rabeprazole (Pariet) – assess whether PPI treatment is necessary and change acid suppression medication accordingly.
4. Contraindications: recent bleed; active bleed; major GI intolerance; history of ASA allergy; ASA – persons <21 years of age

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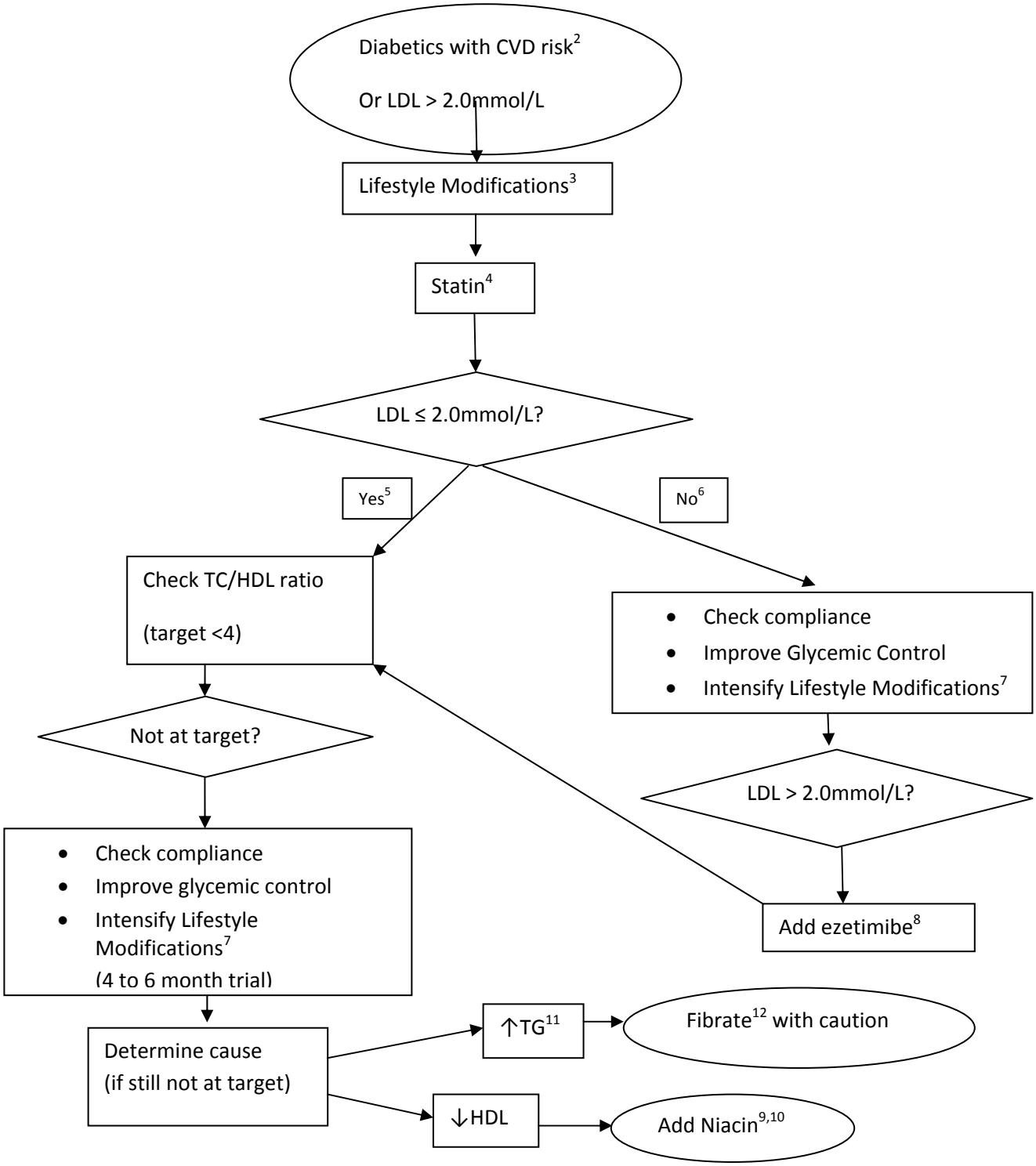
12.1 Dyslipidemia[1]



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12.2 Dyslipidemia cont'

1. Lipid profile typically shows ↑TG, ↓HDL, and normal LDL. However, the LDL particles tend to be more artherogenic.
2. CVD is the primary cause of death in persons with diabetes. Persons at high risk of CV event include: men ≥45 years and women ≥50 years;

   :men <45 years/women <50years with at least one of: macrovascular disease (MI, stroke, TIA, CVD, ischemia, etc), microvascular disease (nephropathy or retinopathy), family history of premature coronary or cerebrovascular disease in first degree relative, extreme level of single risk factor (LDL >5.0mmol/L, systolic BP >180mmHg), duration of diabetes >15 years and age >30 years.
3. **Lifestyle modifications are important in preventing CVD and managing diabetes in general. They are an adjunct to pharmacologic management and include: maintaining healthy weight, healthy diet (including restriction of alcohol and carbohydrate intake), regular exercise, smoking cessation.**
4. Unless contraindicated: pregnancy, active liver disease, excessive alcohol use.
5. Once target LDL is reached, consider lowering TC/HDL ratio to <4.0. This is more difficult to achieve and requires ongoing reinforcement of lifestyle issues and often combination with other agents.
6. If LDL remains 2.0-2.5mmol/L while on medication, the decision to further lower LDL to target should be individualized.
7. Weight loss, tight glycemic control, and restriction of alcohol and carbohydrate intake.
8. Unless contraindicated: hepatic dysfunction
9. Unless contraindicated: severe peptic ulcer disease, chronic liver disease, overt diabetes, severe gout
10. Studies are underway to determine if Niacin ↓risk of CVD in diabetics.
11. If TG >10mmol/L, a fibrate is first line to reduce the risk of pancreatitis. If TG 4.5-10mmol/L, a statin is first line in diabetics given their demonstrated benefit in reducing CV risk in this population.
12. Unless contraindiciated: severe hepatic disease, severe renal disease, smoking (gemfibrozil). When given with a statin, watch for rhabdomyolysis (CK >10x, darkened urine, renal failure).

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12.3 Statin = HMG Co-A Reductace Inhibitor

= ↓LDL, ↓TG, ↑HDL

Drug	Trade Name	Dose Range	Usual Dose
	Statin[1,2,4]		
Atorvastatin[3]	Lipitor	10-80mg HS	10-40mg HS
Fluvastatin[5]	Lescol	20-80mg/d HS or BID	20-40mg/d
Lovastatin[5]	Mevacor	20-80mg/d HS orBID	20-40mg HS
Pravastatin[3,6]	Pravachol	20-40mg HS	-
Rosuvastatin[3,6]	Crestor	5-40mg OD	-
Simvastatin	Zocor	20-80mg HS	20-40mg HS

Source: Therapeutic Choices, RxFiles

1. Side Effects of Statins: common: upper GI effects, headache, muscle pain, rash, sleep disturbances; rare: peripheral neuropathy, lupus-like symptoms, impotence, pancreatitis; ↑LFT (dose dependant); myopathy (concern if weakness accompanies muscle pain – check CK); rhabdomyolysis (increased risk with combinations of lipid-lowering agents or drug interactions that increase level of statin)
2. Drug Interactions: many potential including: ↑effect of digoxin and warfarin; increased toxicity of statin with amiodarone, clarithromycin, erythromycin, gemfibrozil, grapefruit juice, -conazole antifungals, certain HIV meds, verapamil, also transplant meds, diltiazem, ethynyl estradiol, fenofibrate, fluoxetine, niacin; decreased effect of statin with: cholestyramine (separate by 2 hours), phenytoin, phenobarb, carbamazepine, rifampin, St John's Wort, certain HIV meds. **Avoid with macrolides, gemfibrozil, grapefruit juice, azoles, amiodarone, non-DHP CCB, cyclosporine, protease inhibitors.**
3. Few Drug Interactions with pravastatin and rosuvastatin – some transplant meds and gemfibrozil.
4. Contraindications: acute liver disease, pregnancy, excessive alcohol use
5. Use lower dose in hepatic dysfunction.
6. Use lower dose in renal dysfunction.

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12.4 Other Lipid-Lowering Agents

Drug	Trade Name	Dosing	Effect on Lipids
	↓cholesterol absorption		
Ezetimibe[1]	Ezetrol	10mg OD[2]	↓LDL,↑HDL,↓TG
	Nitcotinic acid		
Niacin[3]	-	50-100mg B-TID CC, ↑ by 100mg/week to 500mg TID	↑HDL, ↓TG[4]
	Niaspan	500-750mg HS	
	Fibrate[5]		
Benzafibrate	Benzalip	200mg B-TID CC 400mg SR OD	↑HDL,↓TG[6]
Fenofibrate	Lipidil Micro	200mg OD CC	
	Lipidil Supra	160mg OD CC	
	Lipidil EZ	144mg OD	
Gemfibrozil	Lopid	300-600mg BID AC	
	Resins[7]		
Cholestyramine	Quenstran	4-8g BID AC[8]	↓LDL, ↑HDL[9]

Source: RxFiles

1. Side Effects of Ezetrol: generally well tolerated, but monitor LFT

   Drug Interactions: ↑levels with cyclosporine, fibrates

   Contraindications: hepatic dysfunction

2. When added to statin, may allow ↓dose of statin.

3. Side Effects of niacin: flushing (pre-treat with ASA or ibuprofen 30minutes prior; abates with time); dry eyes, itching; headache; GI upset; ↑LFT; torsades de pointes; ↑uric acid; ↑glucose. Monitor LFT, glucose, uric acid at 3 months, 6 months, 12 months, then yearly.

   Drug Interactions: ↑myopathy with lovastatin, ASA may ↑niacin level

   Contraindications: chronic liver disease, overt diabetes, sever gout, peptic ulcer disease

   Note: do not use No-flush Niacin b/c less effective and ↑hepatic side effects

4. Only higher doses of niacin affect LDL (ie >2g/day)

5. Side Effects of fibrates: common: GI upset, rash, abdominal pain; less common: headache, itching, ↓libido, dizziness, drowsiness, arthralgia, ↑glucose, sleep/vision changes; rare: ↓renal function, anemia, myopathy, ↑LFT, pancreatitis, gallstones

   Drug Interactions: ↑toxicity with furosemide, statins, cyclosporin, MAOIs, probenacid; ↓effect with cholestyramine; ↑levels of glitazones, sulfonylureas, warfarin (monitor INR); chlorpropamide, furosemide; monitor for rhabdomyolysis if given with statin

   Contraindications: severe hepatic disease; smoking (gemfibrozil)

   Use lower dose in renal impairment.

6. Variable effect on HDL. Benefits in persons with diabetes and hyperinsulinemia.

These materials were developed by the Clinical Subcommittee of the Chronic Disease Network and Access Program of the Prince Albert Grand Council and its partners and funded by the Aboriginal Health Transition Fund.

12.5 Other Lipid-Lowering Agents cont'

7. Side effects of resins: common: constipation (↑fluid and bulk in diet or Metamucil), nausea, bloating; rare: hyperchloremic acidosis in kids or ↓renal function; monitor LFT, TG

   Drug Interactions: separate administration of other medications by 2 hours (↓ absorption otherwise)

   Contraindications: biliary obstruction; TG >4.6mmol/l; dysbetalipoproteinemia

8. Can mix with Metamucil+orange juice/lemonade the night before; refrigerate and give the next day – ½ before breakfast and ½ before supper (shake well)

9. Possible ↑TG (monitor).

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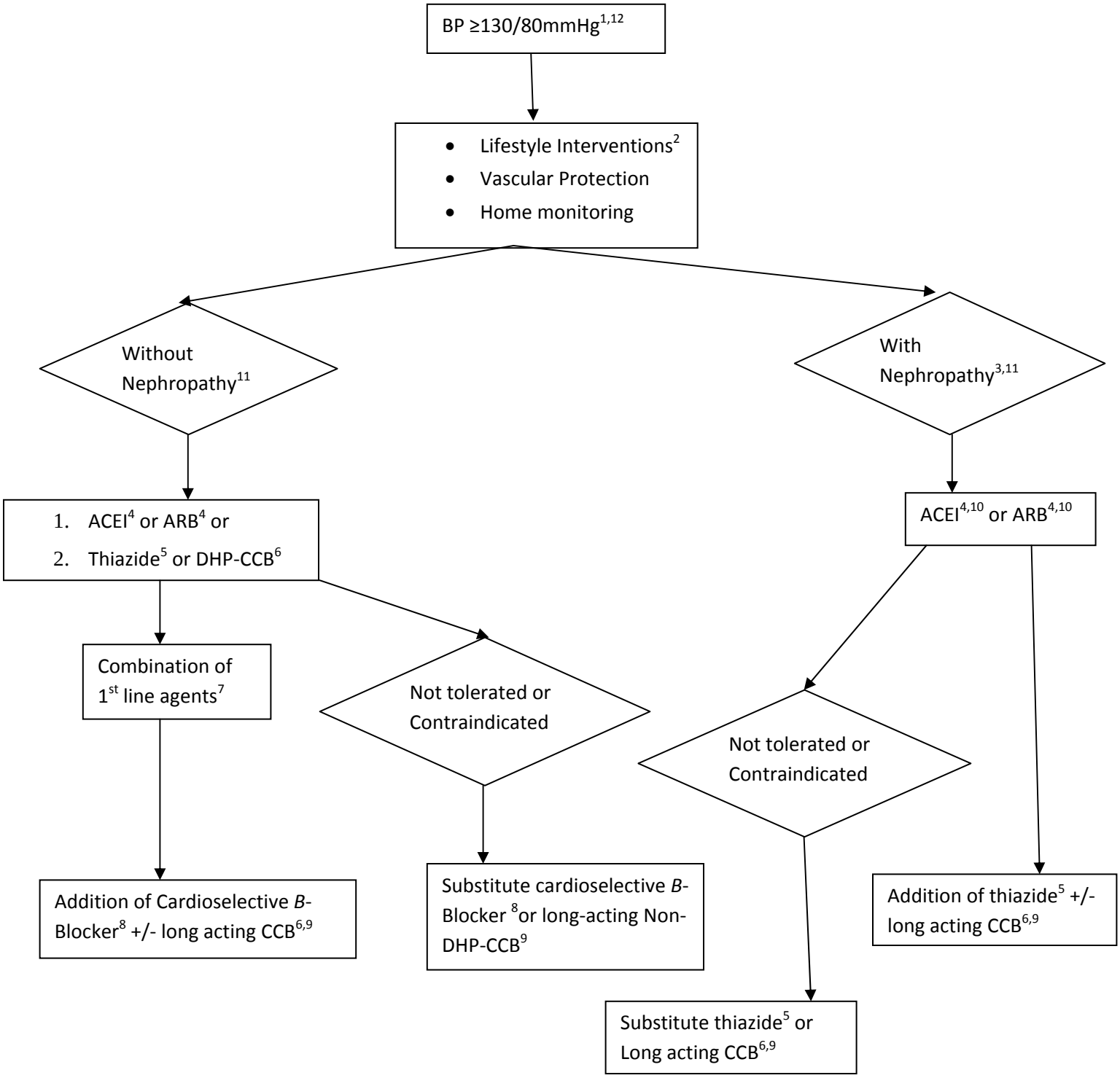
13.1 Hypertension in Diabetes



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13.2 Hypertension in Diabetes cont'

1. This includes isolated systolic hypertension. BP should be measured at each diabetes-related visit.
2. Maintenance of healthy weight, healthy diet (low fat, high fibre), regular exercise, limitation of salt and alcohol intake, and stress management.
3. Nephropathy = urinary albumin:creatinine ratio ≥2.0mg/mmoL in men / ≥2.8mg/mmoL in women or chronic kidney disease. Refer to specialist.
4. Unless contraindicated: pregnancy, history of angioedema, renal artery stenosis (solitary kidney or bilateral).
5. Unless contraindicated: gout, sulfa allergy, anuria, hyponatremia. If CrCl <30mL/min or SCr > 150umol/L furosemide should be used instead.
6. Unless contraindicated: SBP<90mmHg, recent MI, pulmonary edema, AV block, sick sinus syndrome
7. Combination of ACEI and ARB not recommended except in proteinuric nephropathy.
8. Unless contraindicated: 2nd or 3rd degree heart block (in absence of pacemaker). Avoid in patients with asthma, severe peripheral artery disease, and patients > 60years. Efficacy is uncertain in smokers or patients with no previous MI or angina.
9. Use with caution in heart failure or 2nd or 3rd degree heart block without pacemaker.
10. Monitor K^+ and SCr carefully in patients with CKD taking an ACEI or ARB. Consider d/c ACEI/ARB during acute illness that results in intravascular volume depletion (fever, diarrhea).
11. A combination of 2 first line agents may be considered as initial therapy if SBP ≥20mmHg above target or DBP ≥10mmHg above target. Do not combine ACEI and ARB in absence of proteinuria.
    Preferred Combinations: ACEI or ARB + thiazide (ACEI increases efficacy of the thiazide and reduces hypokalemia); ACEI or ARB + DHP-CCB (ACEI reduces possible edema from DHP-CCB)
    Acceptable Combinations: CCB + thiazide; thiazide + potassium-sparing diuretic; aliskiren + thiazide or CCB; *B*-blocker + diuretic or DHP-CCB
    Combinations *not* recommended: ACEI + ARB; *B*-blocker + ACEI or ARB; *B*-blocker + nonDHP-CCB; *B*-blocker + centrally-acting agent (clonidine)
12. Three or more agents may be required to reach target BP. For resistant hypertension, consider other causes: obstructive sleep apnea; renal artery stenosis; aldosteronism; NAIDs; white-coat hypertension.

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13.3 ACEI = Angiotensin Converting Enzyme Inhibitor

ARB = Angiotensin Receptor Blocker

Drug	Trade Name	Dosing Range	Usual Dose
	ACEI[1,3,4,5,6]		
Benazepril	Lotensin	10-40mg OD or BID	20mg/day
Captopril	-	25-150mg/day BID or TID	25mg TID Empty stomach
Cilazapril	Inhibace	2.5- 10mg/day OD orBID	2.5-5mg OD
Enalapril	Vasotec	5-40mg/day OD or BID	10-40mg/day
Fosinopril	Monopril	10-40mg/day OD or BID	20mg/day
Lisinopril	Prinivil, Zestril	10-40mg OD	20mg OD
Perindopril	Coversyl	4mg OD or BID	-
Quinapril	Accupril	10-20mg OD or BID	-
Ramipril	Altace	2.5-10mg OD or BID	10mg/day
Trandolapril	Mavik	1-4mg OD	-
	ARB[2,3,4,6]		
Candesartan	Atacand	8-32 mg OD	8-16mg OD
Eprosartan	Tevetin	300-400mg OD or BID	-
Irbesartan	Avapro	150-300mg OD	-
Losartan	Cozaar	25-50mg OD or BID	50-100mg/day
Telmisartan	Micardis	80mg OD	-
Valsartan	Diovan	80-320mg OD	-

Source: Therapeutic Choices, RxFiles

1. Side Effects of ACEI: Dry cough; Hyperkalemia (especially with renal insufficiency, K^+ sparing diuretics, K^+ supplements, NSAIDs); angioedema, hypotension (especially if volume depleted or with diuretics); acute renal failure with bilateral renal stenosis; headache; dizziness; fatigue; rash; loss of taste; hepatotoxicity; dysguesia; pancreatitis; blood dyscrasias
2. Side Effects of ARBS: same as ACE except no cough and less dizziness and headache.
3. Drug Interactions: K^+ supplements; K^+ sparing diuretics (assess K^+ and SCr regularily); NSAIDs; Lithium (possible toxicity)
4. Contraindications: pregnancy, history of angioedema, renal artery stenosis (solitary kidney or bilateral)
5. Use lower dose in renal impairment.
6. **Renal function and K^+ must be monitored. Check BUN, CrCl, electrolytes before starting, after 7 days, then regularly thereafter, including when dose ↑ or when a diuretic is added or ↑.**

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13.4 Diuretics

Drug	Trade Name	Dose Range	Usual Dose
	Thiazides[2,3,4,12]		
Hydochlorothiazide	HCTZ	6.25-100mg OD[1]	12.5-25MG OD
Chlorthalidone[5]	-	12.5-25mg OD[1]	12.5-25mg OD Or 25mg EOD
Indapamide[6]	Lozide	1.25mg-5mg OD[1]	1.25-5mg OD
Metolazone[8]	Zaroxolyn	2.5mg-10mg OD	5mg OD
	Loop Diuretics[3,4,7,12]		
Furosemide	Lasix	20-240mg/day OD or BID	
	K^+sparing[12]		
Spironolactone[9,10,11]	Aldactone	12.5-200mg/day[1] OD or BID	25-50mg OD

Source: RxFiles, Therapeutic Choices

1. Lower dose in renal impairment. Use furosemide if CrCl ≤30mL/min (SCr > 150mmol/L)
2. Side Effects: lower doses are well-tolerated; rash; allergic reaction; photosensitivity; ↑calcium; ↑uric acid; ↑cholesterol; ↑glucose; ↓sodium; ↓potassium; ↓magnesium;↓zinc; pancreatitis; sexual dysfunction.
3. Drug Interactions: Digoxin (toxicity if K^+ is low); ↑lithium; NSAIDs (loss of BP control), corticosteroids (↓K^+)
4. Contraindications: symptomatic hyperuricemia (gout); sulfa allergy; anuria; hyponatremia
5. More potent and longer acting than HCTZ. Minimal lipid/electrolyte changes.
6. Other side effects: headache, dizziness. Less effect on lipids and glucose.
7. Side Effects: dehydration; ↓(K^+, magnesium, calcium); ↑(glucose, uric acid, glucose, lipids); azotemia; nausea; anorexia; weakness; fatigue; rash; ototoxicity at high doses
8. Is effective in patients with mild to moderate renal dysfunction; beneficial in CHF +/- furosemide
9. Effective in CHF, hyperaldosteronism, edema, cirrhosis, systolic dysfunction (alternative first line)
10. Side Effects: ↑K^+ (especially in renal failure, diabetes; avoid if K^+ >5mmol/L); ↓Na; dehydration; rash; gynecomastia; abnormal menstruation; GI ulcers
11. Drug Interactions: ↑K^+ with ACEI, ARB, potassium supplements; ↓diuretic effect, worsening renal function with NSAIDs
12. **Electrolyte disturbances can be life-threatening. Electrolytes and renal function must be monitored regularly.**

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13.5 CCB = Calcium Channel Blockers

Drug	Trade Name	Dose Range	Usual Dose
	DHP (long acting)[1,2,3,4]		
Amlodipine[5]	Norvasc	2.5-10mg OD	5-10mg OD
Felodipine[6]	Renedil, Plendil	2.5-20mg OD[7]	5-10mg OD
Nifedipine	Adalat XL[8]	30-120mg OD	30-60mg OD
	Non-DHP[9,10,11]		
Diltiazem[13]	Cardizem reg	120-420mg/day[12]	240-360mg/day
	Cardizem CD,ER,SR	(reg TID; SR give BID;	Reg TID; SR- give BID;
	Tiazac reg, XC	CD, ER, XC give OD)	CD,ER,XC give OD)
Verapamil[14]	Isoptin reg, SR	120-480mg/day	180-240mg/day
	Chronovera (SR)	(reg TID; SR give OD)	(reg TID; SR give OD)

Source: RxFiles, Therapeutic Choices

1. DHP = dihydropyridine. Relatively more peripheral vasodilation and less heart effect than non-DHP.
2. Side Effects: dizziness; headache; flushing (dose-related); rash; peripheral edema; gingival hyperplasia; gynecomastia; dyspnea and pulmonary edema in LV dysfunction (may worsen HF); ↑heart rate.
3. Drug Interactions: carbamazepine; cyclosporine; azole antifungals; macrolides; HIV meds; many other potential
4. Contraindicatins: SBP <90mmHg; recent MI; AV block; sick sinus syndrome; pulmonary edema
5. ↑toxicity with grapefruit. May be effective in diastolic dysfunction.
6. ↑toxicity with grapefruit. Less negative inotropic effects than nifedipine. Safe in heart failure
7. Do not crush or chew tablets.
8. Do not use short-acting formulations for essential hypertension. Can be used in pregnancy. Potential negative inotropic effects
9. Side Effects: as per DHP except ↓heart rate, AV block, HF
10. Drug Interactions: ↑negative inotropic effects with amiodarone, *B*-blockers, digoxin; ↑level of carbamazepine, cyclosporine, digoxin; ↑myopathy with simvastatin, lovastatin; ↑level with HIV meds, cimetidine; ↓level with rifampin; many other potential
11. Contraindications: as per DHP plus systolic dysfunction, CHF; use with caution in 2nd or 3rd degree heart block without pacemaker
12. Can sprinkle contents of capsule but do not crush tablets.
13. May also cause lupus-like rash.
14. May also cause constipation. Most negative inotropic and chronotropic

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13.6 *B*-Blockers ("oprolols")

Drug	Trade Name	Dose Range	Usual Dose
	Cardioselective[4,5,6]		
Acebutolol[3]	Sectral	100-800mg/day[1] OD or BID	400mg/day
Atenolol	Tenormin	25-100mg/day [1] OD or BID	50mg/day
Bisoprolol	Monocor	2.5-20mg OD[1,2]	5-10mg OD
Metoprolol	Lopressor	12.5mg-400mg/day[2] (reg BID, SR give OD)	100-200mg/day
	Non-Cardioselective[4,5,6]		
Nadolol	-	20-320mg/day[1]	160mg/day
Pindolol[3]	Viskin	5-30mg BID[2]	15mg BID
Propranolol[7]	Inderal	80-320mg/day[2] (reg BID, LA give OD)	160-320mg/day
Timolol	-	5-30mg BID[2]	20mg BID

Source: Therapeutic Choices

1. Lower dose in renal impairment.
2. Lower dose in liver impairment.
3. Also ISA (intrinsic sympathomimetic actvitiy) IE less bradycardia, lipid changes and cold extremities; NOT recommended in angina or with history of MI
4. Side effects: fatigue, ↓HR; ↓exercise capacity; headache; impotence; vivid dreams; hallucinations; worsens PAD, CHF, Reynauds syndrome; cold extremities; dyslipidemia (↑TG, ↓HDL); may mask/delay symptoms of hypoglycemia; less common: hyperglycemia, depression, heart failure, heart block; acebutolol may cause +ve antinuclear antibody test and Lupus
5. Drug Interactions: ↓HR with digoxin, nonDHP-CCB; ↑effect of amiodarone; ↑toxicity with cimetidine; clonidine (hypertensive crisis); insulins, NSAIDs (↓hypotensive effect); ↓level of B-Blocker with phenobarb
6. Contraindications: severe or poorly controlled asthma/COPD; 2nd or 3rd degree heart block; uncompensated heart failure; severe peripheral artery disease
   Use with caution in persons >60 years. Sudden withdrawal may exacerbate angina/MI: taper dose before discontinuing.
7. Possibly more CNS effects and lipid effects. Also used for anxiety; migraine prophylaxis; thyrotoxicosis; GI bleed.

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13.7 Other Antihypertensive Agents

Drug	Trade Name	Dose Range	Usual Dose
	B&α Blockers		
Labetolol[4]	Trandate	100mg BID-400mg TID[2]	200mg BID
	á Blockers[5,7]		
Doxazosin	Cardural	2-8mg HS	8mg HS
Prazosin	Minipress	0.5-5mg BID	2mg BID
Terazosin[6]	Hytrin	1mg HS-10mg BID	5mg HS
	Centrally Acting[8]		
Clonidine[9]	Catapres, Dixarit	0.1mg BID-0.2mg TID	0.1-0.2mg BID
Methyldopa[10]	Aldomet	125mg BID-500mg QID[2]	250mg BID
	Vasodilators[11]		
Hydralazine[12]	Apresoline	10-50mg QID[1]	25mg QID
Minoxidil[13]	Loniten	2.5-50mg BID[1]	10mg BID
	Renin Inhibitor		
Aliskiren[14]	Rasilez	150-300mg OD[3]	-

Source: Therapeutic Choices, RxFiles

1. Lower dose in renal impairment.
2. Lower dose in liver impairment.
3. Absorption decreased by high fat meal.
4. Side Effects: see non-selective B- Blockers but no effect on lipids; also: edema, dizziness, nasal congestion, postural hypotension
   Drug Interactions: see non-selective B- Blockers
   Contra Indications: see non-selective B- Blockers
   Used in pregnancy.
5. Side Effects: orthostatic hypotension; headache; drowsiness; palpitations; nasal congestion;
   Drug Interactions: Add other hypotensives with caution (syncope).
6. ↑level with verapamil
7. Do not use for initial treatment (3rd line agent). Not recommended for hypertension in diabetes. May be beneficial in pheochromocytoma or prostatism.
8. 2nd or 3rd line agents (if alternatives are contraindicated or in refractory hypertension). May worsen depression, impotence. An option for pheochromocytoma or prostatism
9. Causes rebound hypertension if abruptly stopped. Has a greater role in psychological conditions (ADHD)
   Side Effects: sedation; dry mouth; ↓HR
   Drug Interactions: cyclosporine, mirtazapine, TCAs
   Contraindications: CHF, heart block, diabetes (neuropathy)
10. First line for hypertension in pregnancy
    Side Effects: sedation; dry mouth; depression; nasal congestion; orthostatic hypotension; palpitations; sexual dysfunction; sodium and water retention; drug fever; hepatotoxicity;
    Drug Interactions: ↓absorption with iron (separate by 2 hours); ↓BP with levodopa; ↑BP with TCAs; ↑side effects of lithium
11. 2nd or 3rd line. Consider adding a B-blocker or centrally acting agent to minimize reflex tachycardia and a diuretic to prevent sodium and water retention.
12. Side Effects: reflex tachycardia; headache; edema; Lupus syndrome (at high doses); aggravate angina; dizziness; hepatitis
    Contraindications: left ventricular hypertrophy
13. Side Effects: reflex tachycardia; edema; pericardial effusion; lupus; rash; ↑facial hair
14. Side Effects: diarrhea; headache; ↑K^+; rash; allergy; sore throat; rare: cough, angioedema, gout
    Drug Interactions: cyclosporine; furosemide; irbesartan; ketoconazole
    Contraindications: pregnancy

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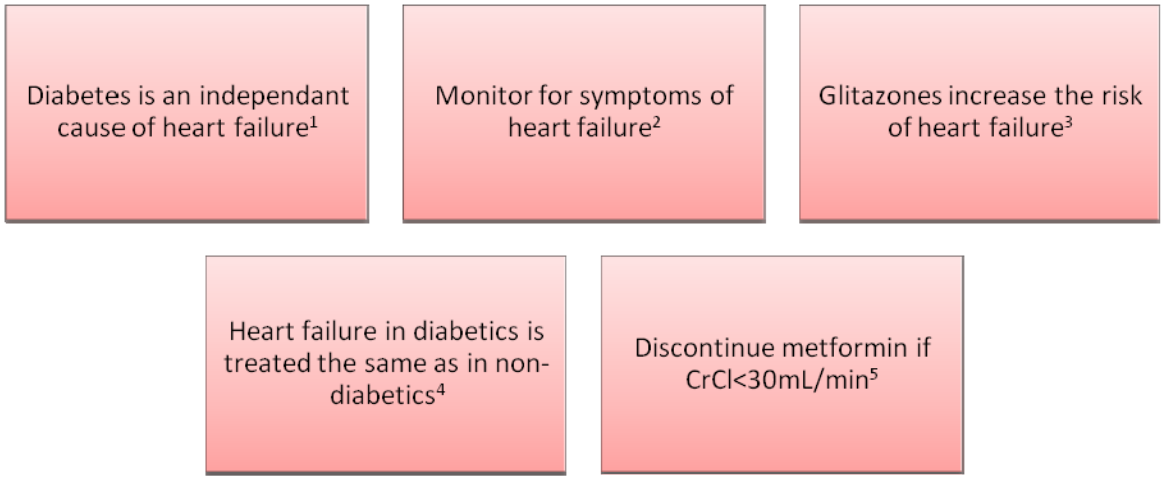
14.1 **Heart Failure**



1. Diabetes can cause a cardiomyopathy which results in a decline in cardiac function. Microalbuminuria is also an independent risk factor for heart failure. ACEI, by reducing kidney albumin excretion, lower the risk of new-onset heart failure.
2. Shortness of breath, peripheral edema, fatigue. Heart failure is sometimes misdiagnosed as COPD, pneumonia, varicose veins, etc.
3. Glitazones should not be given to patients with unstable or severe heart failure; close monitoring is required for patients with mild-moderate heart failure. Use of glitazones plus insulin is not recommended nor approved in Canada.
4. Persons with renal failure may require lower doses of medications for heart failure and slower titration. Monitor electrolytes, creatinine, BP, body weight more frequently.
5. Heart failure patients taking metformin are at increased risk of lactic acidosis if they have impaired renal function.

   CrCl can be calculated using the Cockroft/Gault equation: GFR (men)= (140-age) * weight(kg)/72 * SCr; GFR (women)= calculate as per men then multiply by 0.85.

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15.1 Hypoglycemia

Severity	Symptoms[1]	Treatment
Mild	• Patient can self-treat • Trembling, palpitations, sweating, anxiety, hunger, nausea, tingling	• 15g carbohydrate[3](CHO) • Wait 15 minutes, retreat if BG <4.0mmol/L • Monitor BG until stable at >4mmol/L
Moderate	• As above • Also confusion, difficulty concentrating, weakness, dizziness, drowsiness, headache, vision changes, difficulty speaking	• As above
Severe[4]	• Patient requires assistance • May be unconscious[2] • BG usually <2.8mmol/L • Call 911 • Discuss episode with diabetes nurse ASAP	• Conscious: 20g CHO • Wait 15 minutes, re-treat with 15g CHO if BG <4.0mmol/L • Unconscious: 1mg Glucagon[4] IM or SC • IV access: glucose 10-25g Over 1-3 minutes • Once alert give meal or snack

1. Hypoglycemia is most often drug-induced, especially if trying to meet tight glycemic target and can remain problematic for several hours. **Repeat BG every 15 minutes until stable at >4mmol/L**. To prevent repeated hypoglycemia, offer the usual meal or snack that is due once hypoglycemia is reversed. If the next meal is > 1hour away, give a snack that includes protein and 15g carbohydrate.

   It occurs in about 20% of persons taking insulin secretagogues. It is rarely fatal, but can cause immediate danger if the patient is driving, operating machinery, etc when the episode occurs.

2. Prolonged coma is associated with transient paresis, convulsions, and encephalopathy.

3. **Glucose tablets/solution are preferred to glucose gel (gel has slower onset). Alternatives to glucose: ¾ cup regular pop or juice; 6 'Lifesavers'; 1 tablespoonful honey; 3 teaspoonfuls table sugar dissolved in water**. 15g CHO raises BG by 2.1mmol/L within 20 minutes – enough to bring symptom relief. Glucose gel, orange juice, and milk have slower onset.

4. Glucagon raises BG 3.0-12.0mmol/L within 60 minutes. With advanced liver disease and after 2 standard alcoholic drinks, the effect of Glucagon is impaired.

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16.1 Erectile Dysfunction

Affects 45% of men with diabetes

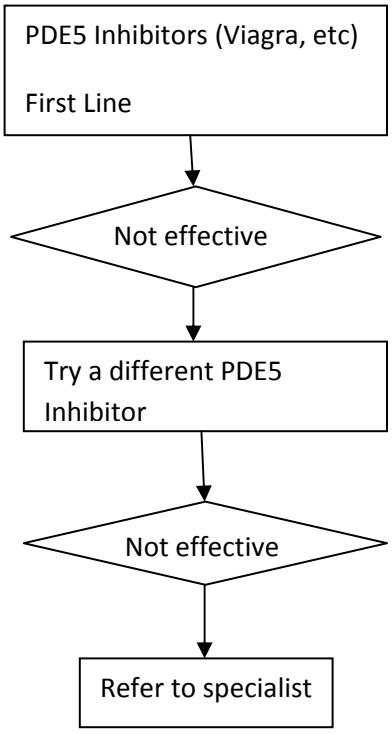
Risk Factors: ↑age, longer duration of diabetes, poor glycemic control, smoking, hypertension, dyslipidemia, CVD, ↓androgen

- May be first sign of CVD
- retinopathy may correlate with erectile dysfunction

Due to micro/macrovascular disease and neuropathy

- May be side effect of medication used to manage diabetes

May be psychological and situational influences



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16.2 PDE5 Inhibitors = Phosphdiesterase-5 Inhibitor

Drug	Trade Name	Dosing	Onset	Duration
Sildenafil[1]	Viagra	25-100mg[2,3,4]	30-60 minutes[6,7]	4-12 hours (peak effect in 1 hour)
Tadalafil[1]	Cialis	10-20mg/event OR 2.5-5mg OD[4]	30-60 minutes	36 hours (peak effect in 2hours)
Vardenafil[1]	Levitra	5-10mg[2,5]	30-60 minutes[6,7]	As per Viagra

1. Side Effects: common: flushing, headache, dyspepsia, nasal congestion; diarrhea, GI upset (dose related); blurred vision (more with Viagra, Levitra); rash; myalgia; ↓smell; hearing loss; amnesia; rare but serious: QT prolongation (Levitra), MI, priapism, vision loss

   Drug Interactions: ↑hypotension with alpha-1 blockers (ex prazosin – avoid or space by 4hours), antihypertensives, alcohol; ↑toxicity of PDE5I: azole-antifungals, cimetidine, macrolides, ciprofloxacin, doxycycline, grapefruit, isoniazid, HIV meds, quinidine, verapamil (use lowest dose of PDE5I and maximum interval of Q24H for Viagra and Levitra, Q72H for Cialis); ↓effect of PDE5I: carbamazepine, phenytoin, phenobarb, rifampin

   Contraindications: concurrent use of nitrates (NitroDur, ISDN, etc) may cause serious ↓BP leading to fainting, stroke, or MI (allow nitrate washout of 24 hours before Viagra or Levitra and 48 hours before Cialis); concurrent use of alpha-blocker (prazosin, terazosin); symptomatic hypotension or any condition where lowering of BP would not be tolerated; previous priapism or conditions predisposing to priapism; seek emergency care if chest pain occurs within 24 to 48 hours of taking PDE5I
2. Take 30-60 minutes prior to intercourse.
3. Maximum dose 100mg once in 24 hours.
4. Lower dose in renal or liver disease
5. Lower dose in liver disease
6. Possible onset in 10-15 minutes.
7. Onset may be delayed by high-fat meal.

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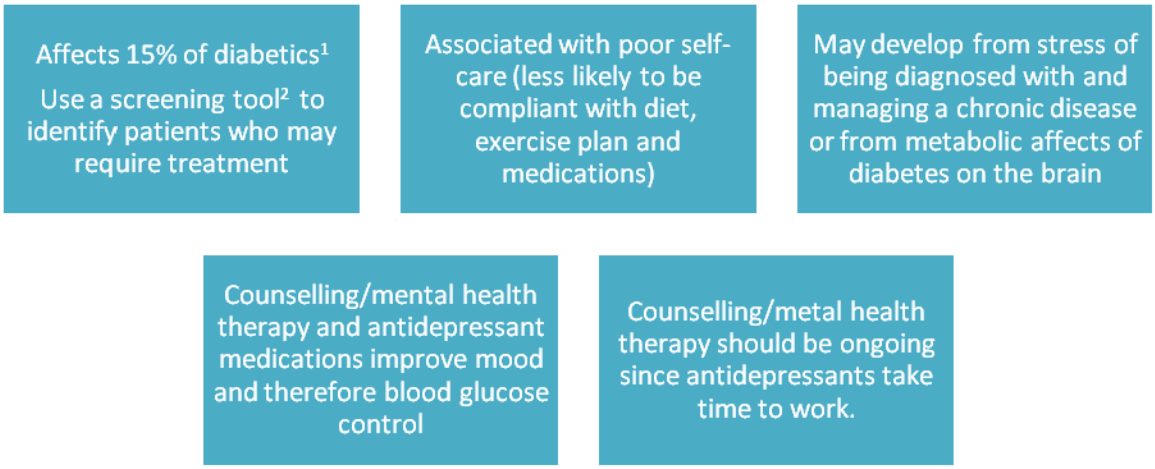
17.1 Depression in Diabetes



1. Consequences include suboptimal glycemic control and increased risk of health complications (from poor self-care), decreased quality of life, increased family problems, and increased health care costs.

2. Ex PHQ-9 (Patient Health Questionnaire-9 for depression) or other screening tool to identify patients who may be depressed. Treatment (mental health counselling with or without medication) can then be prescribed according to the patient's assessed severity of depression.

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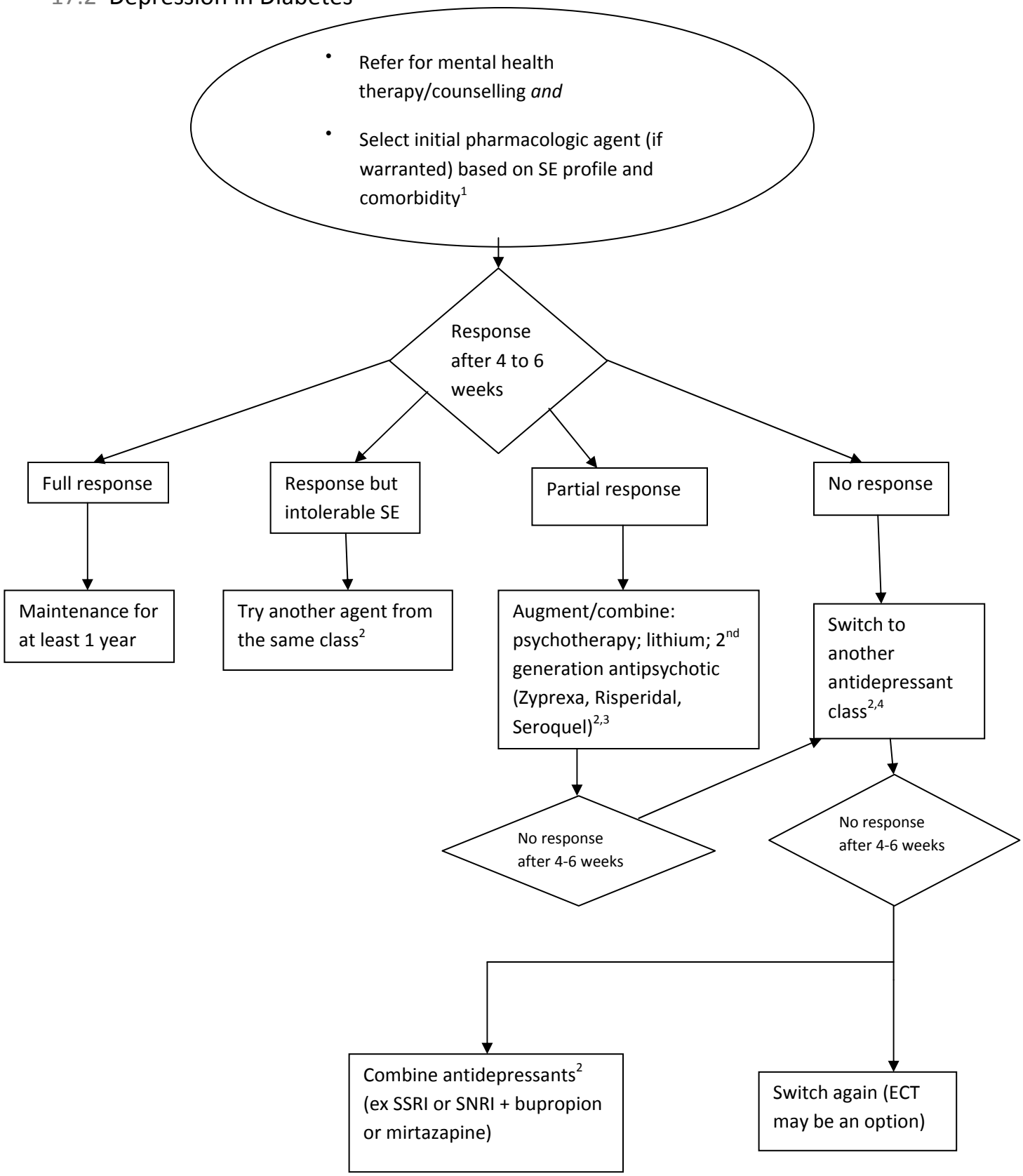
17.2 Depression in Diabetes



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17.3 Depression in Diabetes cont'

1. Antidepressants are generally well-tolerated and safe for diabetics.

   SSRIs, Venlaflaxine, RIMAs, Duloxetine, Bupropion may be good choices because they cause less weight gain.

   Bupropion, Mirtazapine, Moclobomide, Venlaflaxine (lower doses), cause less sexual dysfunction.

   Duloxetine, Venlaflaxine, TCAs are also used to treat neuropathic pain.

   Whichever agent is chosen, optimize dosing during the first 4 to 6 weeks.

2. Once a response is achieved, treatment should be maintained for at least 1 year.
3. These are best prescribed by a specialist. Use the 2nd generation antipsychotics with caution in diabetics because of their tendency to cause weight gain and insulin resistance.
4. Generally there is no need for a washout period, but one agent can be tapered while the other is titrated up. An exception is when switching from MAOI, moclobamide, or fluoxetine to another agent. If any agent is discontinued, it slow tapering is recommended to prevent withdrawal symptoms.

Adolescents: Safety and efficacy is not well-established (concerns with suicide ideation; aggression; agitation). Fluoxetine, clomipramine, fluvoxamine, or sertraline may be possible options.

Pregnancy: Must consider risks to baby and benefits to mother. TCA and SSRI's have the most data. Use the lowest dose and if possible, taper 5-10 days before delivery. Fluoxetine is the agent most studied.

Breastfeeding: Sertraline, paroxetine, and fluvoxamine show lower levels in breast milk and no reported adverse effects in the infant.

Elderly: Dose according to renal function; start low and titrate slowly.

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17.4 Pharmacologic Management of Depression in Diabetes

Drug	Trade Name	Dose Range
	SSRI[1]	
Citalopram	Celexa	10-40mg OD
Fluoxetine	Prozac	10mg AM to start 20-60mg AM
Fluvoxamine	Luvox	25mg HS to start, 100-150mg HS
Paroxetine	Paxil	10mg AM[2 to] to start; 20-60mg AM
Sertraline	Zoloft	25-50mg AM[3] to start; 50-100mg AM
	Dual Action	
Bupropion[8]	Wellbutrin SR	150-300mg/day
	Wellbutrin XL	150-450mg OD[1]
Mirtazapine[9]	Remeron	15-45mg OD
Trazodone[10]	Desyrel	50-400mg HS or BID
	SNRI[4]	
Venlaflaxine	Effexor XR	37.5mg OD to start; 112.5-225mg/day[2,3]
Duloxetine	Cymbalta	30-60mg/day[2]
	TCA[5]	
Amitriptyline	Elavil	10mg HS to start 50-200mg HS
Clomipramine	Anafranil	As per Amitriptyline
Desipramine	-	As per Amitriptyline
Imipramine	Tofranil	As per Amitriptyline[3]
Nortriptyline	Aventyl	10mg HS to start 25-100mg HS
	RIMA[6]	
Moclobamide	Manerix	100-300mg/day to start 450-600mg/day BID PC
	MAOI[7]	
Phenelzine	Nardil	15-30mg/day to start; 30-75mg/day B-TID
Tranylcypromine	Parnate	10-20mg/day to start; 20-60mg/day B-TID

Source: RxFiles, Therapeutic Choices

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17.5 Depression in Diabetes cont'

1. Selective Serotonin Reuptake Inhibitor
   Side Effects: nausea, dry mouth, sexual dysfunction, ↑risk of GI bleed
   Citalopram: also somnolence, sweating; Fluoxetine also nervousness, anorexia, insomnia;
   Fluvoxamine also: drowsiness, sweating, anorexia, most nauseating, constipating,sedating;
   Paroxetine also: drowsiness, fatigue, sweating dizziness more weight gain and sexual dysfunction;
   Sertraline also diarrhea, tremors, most sexual dysfunction
   Drug Interactions: many possible including : MAOI; NAIDs (↑bleeding); ↑SSRI level with cimetidine, clarythromycin, erythromycin, azole antifungals, isoniazid, some HIV meds; ↓level of SSRI with carbamazepine, phenytoin, phenobarb, rifampin; fewest DI with Citalopram; ↑ toxicity of clozapine, methadone, mexelitine, phenytoin, pimozide, propafenone; more drug interactions with Fluoxetine and Fluvoxamine
2. Lower dose in renal dysfunction
3. Lower dose in hepatic dysfunction
4. Serotonin/Norepinephrine Reuptake Inhibitor
   Side Effects: nausea, drowsiness, nervousness, dizziness, dry mouth, ↑BP if >300mg/day, tremor, agitation,headache, sleep disturbances
   Duloxetine also: diarrhea, ↑LFT, ↓appetite, urinary retention
   Drug Interactions: few
5. Tri-cyclic Antidepressants
   Side Effects: anticholinergic (dry mouth, blurred vision, constipation, urinary hesitancy, tachycardia, delirium); antihistaminergic (sedation, weight gain); orthostatic hypotension; lower seizure threshold; sexual dysfunction;
   Fewer with Nortriptyline and Desipramine
   Drug Interactions: many including: MAOI; ↑toxicity with cimetidine, antipsychotics, ↓effect with carbamazepine, phenobarb, rifampin; antiarrythmics; clonidine (↓hypotensive effect); thiazides (↑hypotensive effect)
6. Reversible Inhibitor of Monoamine Oxidase A
   Side Effects: nausea, insomnia, dizziness
   Drug Interactions: avoid sympathomimetics, meperidine; caution with opioids, antihypertensives, antipsychotics, SSRIs, selegiline, excessive alcohol; cimetidine
7. Monoamine Oxidase Inhibitor
   Side Effects: edema, postural hypotension, insomnia, sexual dysfunction, edema
   Drug Interactions: sympathomimetics, meperidine, SSRIs, TCAs, levodopa, tyramine foods
8. Side Effects: agitation, insomnia, anorexia,
   Contraindications: anorexia or bulimia nervosa; seizure disorders; situations that ↓seizure threshold
9. Side Effects: weight gain, sedation, dry mouth, edema, arthralgias
10. Side Effects: drowsiness, nausea, headache, dry mouth, priapism, ↓BP
    Drug Interactions: may potentiate effects of other CNS depressants and hypotensive effects of antihypertensives

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18.1 Neuropathy

Risk Factors[1]: ↑BG; ↑TG; high BMI; smoking; hypertension

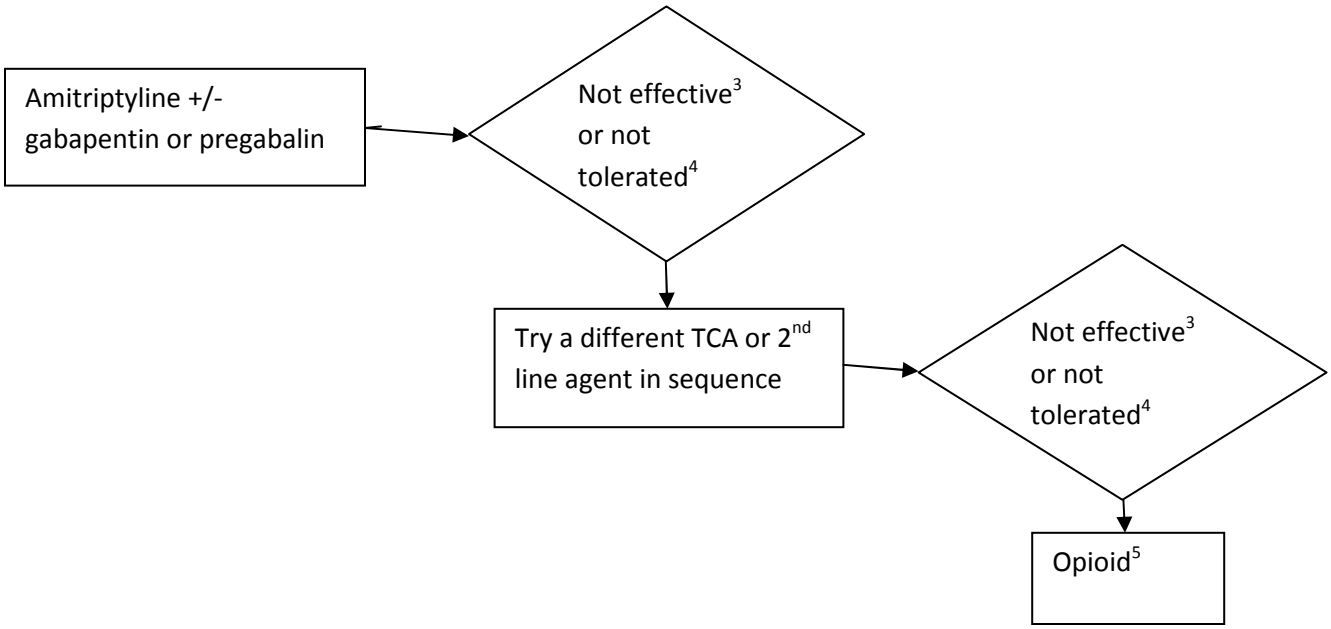
<50% will develop neuropathy within 10 years of onset of diabetes

Type2 diabetics may already have neuropathy at diagnosis

Neuropathic pain can be severe

Foot ulcer and amputation are serious consequences

Other body systems can be involved[2] and should be assessed by a specialist



1. Note that metformin can cause vitamin B12 deficiency, which has similar symptoms to diabetic nephropathy. Patients taking metformin may require vitamin B12 supplementation.
2. Cardiovascular (affects innervations of the heart and cardiac vessels and contributes to exercise intolerance, LV dysfunction, silent MI); gastrointestinal (slows gastric emptying leading to abdominal discomfort and delayed absorption of medications and glucose); genitourinary (incontinence and sexual dysfunction).
3. A reasonable trial duration of a medication to determine efficacy is 2 to 3 months. Ensure patient has realistic expectations of treatment (ie improved functioning and reduced pain by 30%).
4. Ensure patient understands that some side effects are inevitable, but may be tolerable or treatable.
5. Consider tramadol or codeine for mild to moderate pain; morphine or hydromorphone for more severe pain.

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18.2 Pharmacologic Management of Neuropathic Pain

Drug	Trade Name	Initial Dose	Titration
	First Line Agents[1,2,3,4]		
Amitriptyline[6]	Elavil	10mg HS	↑10mg weekly to 150mg HS (max)
Gabapentin[7]	Neurontin	100mg TID[8]	↑300mg weekly to 1200mg/day max
Pregabalin[7]	Lyrica	75-150mg/day[8]	↑150mg weekly to 300mg/day
	Second Line Agents[1,2,3,4]		
Venlaflaxine[9]	Effexor	37.5mg/day[8]	↑37.5mg weekly to 150-225mg/day
Duloxetine[10]	Cymbalta	60-120mg/day	
Topical Lidocaine	Xylocaine	5% gel/cream On 12 hours-off 12 hours	
	Third Line Agents[1,2,3,4]		
Tramadol[11]	ZytramXL,Tridural,Ralivia	150mg OD[8]	↑weekly to 200-400mg OD
Morphine[5,12]	-	5mg Q6H PRN[13]	↑slowly until relief of symptoms or intolerable SE
Hydromorphone[5,12]	Dilaudid	1mg Q4H PRN[13]	As for morphine

Source: Canadian Pain Society; Therapeutic Choices; RxFiles

1. Combinations of agents are often required; be aware of additive side effects (ex sedation) and drug interactions. Do not combine agents from the same class.
2. Try alternate drugs within a class before determining that the class is ineffective or intolerable (ex TCA) .
3. For continuous pain, consider administering the agent(s) regularly to prevent pain and allow tolerance to side effects to develop. For intermittent pain, administer the agent just prior to the pain trigger.
4. Make one change at a time so drug therapy benefits/adverse effects can be accurately assessed.
5. Ensure adequate trial of non-opioid analgesics and adjuncts (at target dose and for appropriate duration) before using opioids.
6. Side Effects of TCA: drowsiness, confusion, constipation, dry mouth, urinary retention, arrhythmia, orthostatic hypotension. Desipramine and Nortriptyline may have fewer side effects.
   Contraindications of TCA: glaucoma, prostatism, CVD.
7. Side Effects: drowsiness, dizziness, peripheral edema, blurred vision, diarrhea, nausea.
8. Adjust dose in renal failure.
9. Side Effects: nausea, drowsiness, dizziness, constipation, hypertension
   Drug Interactions: possible ↑effects with macrolides, azole-antifungals, grapefruit, MAOIs
10. Side Effects: sedation, nausea, constipation, dry mouth. Contraindicated in glaucoma.
11. Side Effects: sedation, ataxia, constipation, seizures (use with caution in epilepsy), orthostatic hypotension.
    Drug Interactions: possible Drug Interactions: possible ↑toxicity with paroxetine, azole-antifungals, macrolides. MAOI
12. Side Effects of opioids: nausea, constipation (requires bowel regimen), allergic reaction, drowsiness. Addiction is unusual unless patient has past history of substance abuse.
13. After 1 or 2 weeks, switch to equivalent daily dose of controlled-release agent (ex MS Contin, Hydromorph Contin). If management of breakthrough pain is required, use the immediate-release formulation of the same agent (ex Statex and MS Contin; Dilaudid and Hydromorph Contin). If the opioid is to be discontinued, slow tapering is required to prevent withdrawal effects.

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19.1 Foot Care

Prevention and Management of Diabetic Foot Problems Includes:

1. Diabetic foot problems can be prevented by optimising glycemic control; implementing vascular protection strategies; treating renal disease and peripheral vascular disease; smoking cessation; optimising nutritional status; and managing neuropathy. Patients should be educated to adopt lifestyle modifications accordingly and be compliant with prescribed treatment. Patients should also be educated about daily foot care including:

   -what to watch for when inspecting the feet;

   -how to inspect the feet if mobility is limited;

   -proper cleansing and moisturising of the feet;

   -proper nail trimming;

   -how to prevent injury to the feet (ex not walking barefoot, etc);

   - to report swelling, redness, warmth, pain or injury to the feet right away.

2. Patients should be educated about how to choose appropriate footwear including: instruction to change the socks daily; not to wear tight socks, garters, or knee-highs; to try on new shoes late in the day (when the feet may be slightly swollen); to choose shoes with a low heel (<5cm); to avoid over-the-counter insoles (which may cause blisters); purchase a shoe from a reputable store (fitted properly). Professional orthotics are recommended for persons with loss of sensation in the feet, vascular insufficiency, or foot deformities.

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19.2 Foot Care cont'

3. Diabetics should have their feet inspected by a professional at least annually or more often if there is a high risk for ulceration. The inspection should include assessment for:

-structural abnormalities (range of motion of ankles and toes, callus pattern, bony deformities, skin temperature);

-neuropathy using a 10-g Semmes-Weinstein Monofilament;

-peripheral artery disease;

-ulceration;

-and evidence of infection.

At this time, the professional should also evaluate the patient's choice of footwear and educate the patient about proper foot care as above.

4. Risk Categories for Ulceration/Amputation (with use of 10-g monofilament)

> 0 – no loss of protective sensation in the feet (continue daily foot care routine; follow up for nail/callus care as needed; annual professional foot inspection)
>
> 1 – loss of protective sensation (continue daily foot care routine; orthotics may be warranted; follow up in 3-6 months for foot/shoe exam and nail/callus care)
>
> 2 – loss of protective sensation in the feet with high pressure (callus/deformity) or poor circulation (continue daily foot care routine; orthotics recommended; follow up in 1-3 months for foot/shoe/activity evaluation and nail/callus care)
>
> 3 – history of plantar ulceration or neuropathic fracture (continue daily foot care routine; orthotics recommended; follow up in 1-12 weeks)

Warning signs for increased risk of complications: previous ulceration; neuropathy; structural deformity; limited joint mobility; peripheral vascular disease; microvascular complications.

5. Non-ulcer diabetic foot complications should be managed according to the etiology of the problem (ex treatment of neuropathic pain with pharmacologic agents; referral to vascular surgeon for severe peripheral vascular disease; referral to orthopaedic surgeon or podiatrist for structural deformities). **If further investigation or specialist-referral is warranted, the patient should not weight-bear on the affected limb to prevent further deformity.** Foot ulcers should be assessed for signs of infection and adequate circulation for wound-healing. **Note that an important indicator of infection is pain in a previously insensate foot.** A wound-care specialist should be consulted. Non-infected foot ulcers with adequate circulation should be debrided if necessary and treated as per recommendations for moist wound healing. Non-infected foot ulcers with poor circulation should be kept dry. Foot infections should be treated aggressively, though current studies do not identify any particular antibiotic agent as being of choice in treating foot infections. The initial agent should be empiric and broad-spectrum. Deep tissue cultures may identify the appropriate agent to use. Uncontrolled diabetes may blunt cellular response to infection: the patient may not present with fever or leukocytosis. Deep infections require surgical debridement as well as antibiotic treatment. Studies suggest that the time limit for healing is 4 weeks (ie if a wound is not healed by week 4, it is not likely to heal at all).

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20.1 Index of Pharmacologic Agents

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20.2 Index cont'

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20.3 Index cont'

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20.4 Index of Pharmacologic Agents

Trade Name (Drug Name) and Section(s)

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20.5 Index cont'

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20.6 Abbreviations

A1C – glycosylated haemoglobin A1C

ACR – Albumin Creatinine Ratio

ADHD – Attention Deficit Hyperactivity Disorder

BG – blood glucose

BMI – body mass index

BP – blood pressure

CHF – congestive heart failure

CKD – chronic kidney disease

CNS – Central Nervous System

COPD – Chronic Obstructive Pulmonary Disease

CrCl – creatinine clearance

CSII – continuous subcutaneous insulin infusion

CV – cardiovascular

CVD – cardiovascular disease

DBP – diastolic blood pressure

DHP – dihydropyridine

DKA – diabetic keto acidosis

ECT – electroconvulsive therapy

FPG – fasting plasma glucose

GDM – gestational diabetes mellitus

GI – gastrointestinal

HDL – high density lipoprotein

HF – heart failure

HIV – human immunodeficiency virus

HR – heart rate

IFG – impaired fasting glucose

IGT – impaired glucose tolerance

INR – International Normalised Ratio

K^+ - potassium

LAIA –long acting insulin analogue

LDL – low density lipoprotein

LFT – liver function test

MDI – multiple daily injections

MI – myocardial infarction

Na – sodium

NSAID – nonsteroidal anti-inflammatory drug

OGTT – oral glucose tolerance test

PAD – Peripheral Artery Disease

PCOS – polycystic ovary syndrome

PG – plasma glucose

PPG – post prandial glucose

PPI – proton pump inhibitor

SBP – systolic blood pressure

SCr – serum creatinine

SE – side effects

SJS – Stevens Johnson Syndrome

SMBG – self-management of blood glucose

TC – total cholesterol

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20.7 Abbreviations cont'

TCA – tricyclic antidepressants

TG – triglyceride

TIA – transient ischemic attack

↑ - increased

↓ - decreased

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20.8 Benefit Status with NIHB

Agents that require prior approval for coverage as a benefit with NIHB:

Bupropion (Wellbutrin): depression in patients not responsive to or intolerant of other antidepressants

Clopidrogel (Plavix): 1 year duration after implantation of intracoronary stent OR acute coronary syndrome (unstable angina or non-STEMI MI) in combination with ASA

Ezetimibe (Ezetrol): for use with a statin when the maximally tolerated dose of statin does not achieve target LDL level OR as monotherapy when statin is not tolerated

Hydromorph Contin: moderate to severe chronic pain not controlled by other agents OR other agents are not tolerated

Insulin-detemir (Levemir)

Insulin-glargine (Lantus)

Pioglitazone (Actos); Rosiglitazone (Avandia): Type 2 diabetes not controlled by metformin or a sulfonylurea OR patient cannot tolerate metformin or sulfonylurea OR metformin or sulfonylurea is contraindicated

Agents that are not a benefit from NIHB:

Aliskiren (Rasilez)

Duloxetine (Cymbalta)

PDE5 Inhibitors (Viagra, Cialis, Levitra)

Pregabalin (Lyrica)

Sitagliptin (Januvia)

Tramadol (Zytram, Relivia, Tridural)

Other agents relevant to the management of Diabetes that are not a benefit from NIHB:

Anti-obesity drugs

Alternative therapies (St John's Wort)

Selected OTC products

Regular soaps, shampoos, and moisturizers

Megavitamins

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20.9 Benefit Status with NIHB cont'

All other items in this publication are at time of printing covered by NIHB. Note that the benefit status of pharmacologic agents is subject to change. For further information about benefit status, prior approval criterion or NIHB in general, please contact the local pharmacy or consult the Health Canada website (www.hc-sc.gc.ca) and follow the links to NIHB from Aboriginal Health.

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