Injection Therapy in Type 2 Diabetes
### Australian Diabetes Society (ADS) HbA1c targets for T2DM

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<tr>
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Cheung et. al. MJA, 2009;191:339-344
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*Cheung et. al. MJA, 2009;191:339-344*
Therapeutic inertia

• Median HbA1c concentrations (IQR) at the review
• Before OHA - 7.7%
• Before insulin started - 9.4%
• At the next annual review, HbA1c levels in the two groups had fallen to 7.4% and 7.9% respectively
Therapies for T2DM

Traditional vs. Early Combination Approach

Potential reasons for not initiating an injectable\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Patient</th>
<th>Health Care Practitioner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear of pain</td>
<td>Fear of weight gain</td>
</tr>
<tr>
<td>Fear of weight gain</td>
<td>Fear of hypos</td>
</tr>
<tr>
<td>Fear of hypos</td>
<td>Lack of confidence</td>
</tr>
<tr>
<td>Fear of complexity of regimen, devices</td>
<td>Lack of time</td>
</tr>
<tr>
<td>Intrusive nature of testing BG, injecting, in particular if it is MDI</td>
<td>Lack of support</td>
</tr>
<tr>
<td>Fear that this is “the end”, a mark of failure</td>
<td>? Lack of interest</td>
</tr>
</tbody>
</table>

Incretin based therapies—mechanism of action GLP-1 agonists on the pancreas\textsuperscript{1,2}

GLP-1 agonists

Case study: Fred, a new patient to your clinic

- Male, aged 50 years
- Type 2 diabetes mellitus (T2DM)
- Taking metformin XR 2 g/day + gliclazide 120 mg/day
- HbA1c 8.3% [67 mmol/mol]

What further information would make you decide to initiate an injectable?
Which therapy would you choose and why?

Discussion
## Choosing an injectable

<table>
<thead>
<tr>
<th></th>
<th>GLP-1 receptor agonist</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major clinical outcomes</strong></td>
<td>No evidence to date</td>
<td>Reduces microvascular complications</td>
</tr>
<tr>
<td><strong>HbA$_{1c}$ reduction with monotherapy</strong></td>
<td>0.5% to 1.5%</td>
<td>1.5% to 3.5%</td>
</tr>
<tr>
<td><strong>Effect on weight</strong></td>
<td>Loss</td>
<td>Gain</td>
</tr>
<tr>
<td><strong>Other advantages</strong></td>
<td>• No hypoglycaemia with monotherapy</td>
<td>• Rapidly effective</td>
</tr>
<tr>
<td></td>
<td>• Simple dosing</td>
<td>• No dose limit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Extensive experience</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Long term safety and outcomes</td>
</tr>
<tr>
<td><strong>Other disadvantages</strong></td>
<td>• Long-term outcome data are lacking</td>
<td>• Hypoglycaemia</td>
</tr>
<tr>
<td></td>
<td>• Hypoglycaemia if with SU</td>
<td>• Injection</td>
</tr>
<tr>
<td></td>
<td>• GI side effects</td>
<td>• Self-monitoring required</td>
</tr>
<tr>
<td></td>
<td>• Twice-daily injection (PBS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ?Pancreatitis (rare; 1 in 10 000 people treated)</td>
<td></td>
</tr>
</tbody>
</table>

Factors in the choice of injectable\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Condition related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient preference</td>
<td>Postprandial glucose control required</td>
</tr>
<tr>
<td>Meal pattern</td>
<td>Co-morbidities</td>
</tr>
<tr>
<td>Daily routine (including occupation)</td>
<td>Unacceptable or unmanageable risk of hypoglycaemia</td>
</tr>
<tr>
<td>Capability (e.g. dexterity or cognition)</td>
<td>Unacceptable or unmanageable risk of weight gain</td>
</tr>
<tr>
<td>Willingness to self-monitor regularly</td>
<td>HbA1C level</td>
</tr>
<tr>
<td>Support from family and GP</td>
<td>Side effects</td>
</tr>
</tbody>
</table>

Revisiting the case study – you decide to initiate insulin

HbA\(_1\text{c}\) >7% on maximal oral agents: Optimise lifestyle, education and ensure adherence to oral anti diabetic medication

Commence basal analogue insulin

Commence once daily pre-mixed insulin

NB: Consider individual needs and preferences and ensure lifestyle is optimised and appropriate education is provided at every stage before altering therapy

1. RACGP Australia, Diabetes Management in General Practice. 18th edition 2012/13.
ADA/EASD position statement: sequential insulin strategies in T2DM

Adapted from: 1. Inzucchi SE et al. Diabetes Care 2012;35:1364–79.
The body’s physiologic insulin pattern

The body’s normal insulin secretory response is biphasic.

Endogenous insulin secretion in type 2 diabetes

Loss of phase 1 response leading to postprandial excursion

Adapted from Polonsky KS et al, 1988

**Insulin profiles**

Know: Onset, peak effect, duration, when to inject

<table>
<thead>
<tr>
<th>Insulin Preparation</th>
<th>Time-action Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting human insulin (neutral)</td>
<td></td>
</tr>
<tr>
<td>Intermediate-acting human insulin (isophane)</td>
<td></td>
</tr>
<tr>
<td>Rapid-acting (analogue)</td>
<td></td>
</tr>
<tr>
<td>Basal analogue (glargine)</td>
<td></td>
</tr>
<tr>
<td>Basal analogue (detemir)</td>
<td></td>
</tr>
</tbody>
</table>

Profiles adapted from Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents by Australian Paediatric Endocrine Group. P58
Insulin profiles

Know: Onset, peak effect, duration, when to inject

25/75 premixed insulin also available

Profiles adapted from Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents by Australian Paediatric Endocrine Group. P58
INITIATING BASAL INSULIN
Starting basal insulin

**Step 1**
Add basal insulin to OADs
Aim to achieve fasting BGL of 5.0-6.0 mmol/L

**Step 2**
Starting dose: 10 U morning or at bedtime
OHAs continued at same doses

**Step 3**
Monitor Fasting BGL
Titrate Dose to achieve target
Once FBG target achieved for 6-8 weeks
Check HbA$_{1c}$
OHAs continued at same doses

**Step 4**
If pre-prandial glucose is on-target, and the HbA$_{1c}$ is not at target after 3 months, consider reviewing the full glycaemic profile and adding further mealtime injections if necessary

Fix fasting: Adjusting basal insulin

[Graph showing the adjustment of basal insulin based on home readings, with increments of 2 units over 3 days, leading to a FBG < 5.5 mmol/L.]

Davies et al, 2005.
Physician led dosage titration for once-daily basal insulin regimens

- Starting dose of basal insulin at bedtime = 10 units/day

<table>
<thead>
<tr>
<th>Average FPG Values (during last 2 days)</th>
<th>Dosage change</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0 – 5.5 mmol/L</td>
<td>No change</td>
</tr>
<tr>
<td>5.6 – 6.7 mmol/L</td>
<td>+ 2 units</td>
</tr>
<tr>
<td>6.7 – 7.8 mmol/L</td>
<td>+ 4 units</td>
</tr>
<tr>
<td>7.8 – 9.9 mmol/L</td>
<td>+ 6 units</td>
</tr>
<tr>
<td>≥10.0 mmol/L</td>
<td>+ 8 units</td>
</tr>
</tbody>
</table>

- Adjust bedtime (basal) dose based on pre-breakfast/morning value. Adjust doses weekly
- DO NOT increase dose if hypoglycaemia (<4.0 mmol/L) any time in preceding week

MIXED INSULIN
Starting pre-mix insulin

Step 1
Add pre-mixed insulin to OADs
Aim to achieve fasting BGL of 5.0-6.0 mmol/L

Step 2
Starting dose:
10 U BB or BD
OHAs continued at same doses

Step 3
Monitor Fasting BGL Titrate
Dose to achieve target

Step 4
Once FBG target achieved for 6–8 weeks Check HbA$_{1c}$
OHAs continued at same doses

If pre-prandial glucose is on-target, and the HbA$_{1c}$ is not at target after 3 months, consider reviewing the full glycaemic profile and adding further mealtime injections if necessary

**Mixed insulin**

**Example:** If your 3 most recent readings are 8.4, 8.8 and 7.6, your lowest reading will be 7.6, which falls in the range between **6.1 and 7.8** in the yellow part of the algorithm – so you would increase your next dinner dose by 2 units.

<table>
<thead>
<tr>
<th>Blood glucose levels:</th>
<th>Too low</th>
<th>Just right</th>
<th>Too high</th>
</tr>
</thead>
<tbody>
<tr>
<td>Row A:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest blood glucose level before breakfast (mmol/L)</td>
<td>Below 4.0</td>
<td>4.0 – 4.4</td>
<td>4.5 – 6.0</td>
</tr>
<tr>
<td>Row B:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change your next dinner dose by:</td>
<td>Contact doctor or diabetes educator</td>
<td>Reduce by 2 units</td>
<td>No change</td>
</tr>
</tbody>
</table>

- **Contact your doctor or diabetes educator**
- **Reduce your next dinner injection dose as shown**
- **No change**
- **Increase your next dinner injection dose as shown**
Hands on with devices

Insulin
Insulin device demonstration

• Step 1: Read instructions!
• Step 2: Place needles, pens, sharps container in front of you.
• Step 3: Put needle on pen.
• Step 4: Roll, rock (pre-mix only) and air shot.
• Step 5: Dial up dose.
• Step 6: Injection site selection (avoid lumps and bumps!).
• Step 7: Inject!
• Step 8: Needle removal and disposal
Needles and injection sites

- Size does matter!
- 4–6 mm preferable
- Can use longer needle if large dose and/or sc fat
- One needle, one shot

Injection sites

- **Abdominal wall**: Generally fastest and the most uniform rate of absorption
- **Legs**: Slowest absorption (unless exercising). Acceptable site
- **Arms**: Not recommended
- Injections should be subcutaneous


1. RACGP Australia, Diabetes Management in General Practice. 18th edition 2012/13.
Hypoglycaemia management

Have some easily-consumable quick acting carbohydrate
e.g. 1/2 can of regular soft drink (not ‘diet’) OR
1/2 glass of fruit juice OR
3 teaspoons of sugar or honey OR
6-7 jellybeans OR
Glucose tablets equivalent to 15 grams carbohydrate.

Wait 10-15 minutes. If BG isn't rising, eat another quick-acting carbohydrate from the list above.

If the next meal is >20 minutes away, eat some longer acting carbohydrate. This could be one of the following:
A sandwich OR
1 glass of milk or soy milk OR
1 piece of fruit OR
2-3 pieces of dried apricots, figs or other dried fruit OR
1 tub of natural low fat yoghurt OR
6 small dry biscuits and cheese.

Adjusting other therapies when initiating insulin

• Dependent on the mode of action
  – Insulin sensitiser (metformin): no change
  – Secretagogue: no change unless adding a second dose of insulin
  – DPP-4 inhibitors: no change but not currently PBS listed for use with insulin (TGA approved only)

Revisiting the case study: Fred

• Male, aged 50 years
• Type 2 diabetes mellitus (T2DM)
• Metformin XR 2 g/day + gliclazide 120 mg/day
• HbA$_{1c}$ 8.3% [67 mmol/mol]
• Additional benefits when compared with gliptins:
  o reduce body weight
  o lower blood pressure
  o slow gastric emptying
  o promote satiety

• Neither gliptins nor GLP-1 agonists cause hypoglycaemia as monotherapy
GLP-1 receptor agonists for T2DM – 4

- Gastrointestinal adverse events, especially nausea, are the most common type of adverse event; associated with 5–10% discontinuation rate in clinical trials
- Should not be used in patients with a history of severe gastrointestinal disease such as gastroparesis or inflammatory bowel disease
- Rare reports of acute pancreatitis
You decide to initiate a GLP-1 agonist

GLP-1 agonists available in Australia

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<tr>
<th>Exenatide&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Long-acting exenatide&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Liraglutide&lt;sup&gt;3&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>• TGA approved</td>
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</tr>
<tr>
<td>• PBS reimbursed</td>
<td>• Not PBS reimbursed</td>
<td>• Not PBS reimbursed</td>
</tr>
<tr>
<td>• Twice daily</td>
<td>• Once weekly</td>
<td>• Once daily</td>
</tr>
<tr>
<td>• SC injection</td>
<td>• SC injection</td>
<td>• Once daily</td>
</tr>
<tr>
<td>• BMS/AstraZeneca</td>
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GLP-1 agonists available in Australia: indications

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<th>Long-acting exenatide</th>
<th>Liraglutide</th>
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| • As adjunctive therapy to improve glycaemic control in patients with T2DM who are taking:  
  – metformin  
  – a SU  
  – a combination of metformin and a SU  
  – a combination of metformin and a basal insulin but are not achieving adequate glycaemic control. | • Treatment of T2DM in combination with:  
  – metformin  
  – SUs  
  – metformin and a SU  
  in patients who have not achieved adequate glycaemic control. | • As an adjunct to diet and exercise for treatment of adults with T2DM to achieve glycaemic control:  
  – in dual combination, added to metformin or a SU, in patients with insufficient glycaemic control despite the use of maximally tolerated or clinically adequate doses of metformin or SU monotherapy.  
  – in triple combination, added to metformin and a SU in patients with insufficient glycaemic control despite dual therapy. |

# GLP-1 agonist dosing

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<tr>
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<th>Exenatide&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Once-weekly exenatide&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Liraglutide&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Lixisenatide</th>
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<tr>
<td><strong>Starting dose</strong></td>
<td>5 μg bd</td>
<td>2 mg once weekly</td>
<td>0.6 mg od</td>
<td>10mcg od</td>
</tr>
<tr>
<td><strong>Dose range</strong></td>
<td>5–10 μg bd</td>
<td>2 mg once weekly</td>
<td>0.6–1.8 mg od</td>
<td>20mcg od</td>
</tr>
<tr>
<td><strong>Dose titration</strong></td>
<td>Increase dose to 10 μg bd after 1 month (where necessary)</td>
<td>Not required</td>
<td>After ≥1 week, dose should be increased to 1.2 mg od After an additional ≥1 week, the dose can be increased to 1.8 mg (where necessary)</td>
<td>Increase to 20 mcg after 14 days</td>
</tr>
<tr>
<td><strong>Dose timing</strong></td>
<td>Within 60 mins prior to morning and evening meals (or the two main meals of the day, ~≥6 hours apart). Exenatide <strong>should not</strong> be administered after a meal</td>
<td>Any time of day, independent of meals</td>
<td>Any time of day, independent of meals</td>
<td></td>
</tr>
</tbody>
</table>

Hands on with devices

GLP-1 agonists
GLP-1 agonist device demonstration (exenatide and liraglutide)

- Step 1: Read instructions!
- Step 2: Place needles, pens, sharps container in front of you
- Step 3: Put needle on pen
- Step 4: Dial up dose (NB. different from insulin pen)
- Step 5: Injection site selection (avoid lumps and bumps as per insulin)
Adjusting other therapies when initiating a GLP-1 agonist

- Metformin can be continued unchanged\(^1-^3\)
- A reduction in the dose of SU may be considered to reduce the risk of hypoglycaemia\(^1-^3\)
- The dose of insulin should be evaluated. In patients at increased risk of hypoglycemia consider reducing the dose of insulin\(^1\)

Note: GLP-1 agonists are not indicated in combination with DPP-4 inhibitors (similar mode of action).

Combination of basal insulin and GLP-1 agonists

• Complementary modes of action
• Benefits include:
  – Minimising weight gain
  – Managing both fasting and prandial glucose excursions
  – Insulin sparing
  – Relatively low risk of hypoglycaemia
• Exenatide is TGA approved, but not PBS funded in combination with insulin

NDSS registration and needle disposal

• Free pen-needles and syringes are provided through the National Diabetes Services Scheme (NDSS) for all Australians with diabetes
  – Patients can register at www.ndss.com.au

• Patients can dispose of sharps in an approved sharps disposal container
  – Arrangements for the collection of sharps vary in different States and Territories (e.g. local council, hospital)
  – Patients can contact their State or Territory Diabetes Organisation for advice

1. RACGP Diabetes Management in General Practice Guidelines for Type 2 Diabetes, 2012/2013.
Driving

• Diabetes is identified as one of the medical conditions that may impair driving ability
  – Drivers with diabetes must meet certain medical standards
  – Medical standards for licensing and clinical management guidelines in assessing fitness to drive for commercial and private vehicle drivers March 2013 can be found at www.austroads.com.au/assessing-fitness-to-drive

1. RACGP Diabetes Management in General Practice Guidelines for Type 2 Diabetes, 2012/2013.
Sick days

• Patients need to have a plan for sick days negotiated in advance. This plan should include:
  – When to call the doctor
  – How often to measure blood glucose and urinary ketones
  – What medicines to take
  – How to eat

• It is important that telephone access to a resource person is available

1. RACGP Diabetes Management in General Practice Guidelines for Type 2 Diabetes, 2012/2013.
Discussion: trouble shooting with injectables

- Painful injections – technique issues
- Bruising and bleeding – injection technique issues
- Site rotation
- Storage
- Travel
- Eating out

Back to decision matrix
Conclusions

• It’s easier and safer the earlier you initiate injectables\textsuperscript{1-3}

• The increasing number of injectables available offers more choice for you and your patients

• Utilising support from a multi-disciplinary team is key\textsuperscript{4}

• Regular review and adjustment of therapies is critical

Intensifying

- Add short acting if on basal
- Increase number of mixed injections
Headache – GLP1 vs Insulin

• Balance evidence
• +ve side effects - weight
• Control
• Durability
• -ve side effects
• Evidence
• Hypos – more as intensify therapy
Role of OHAs with insulin

• Don’t stop oral hypoglycaemic agents (OHAs) immediately

• Get A1C under control and consider stopping later

• Sulphonylureas (insulin secretagogues) will ultimately need to be removed

• Metformin (sensitisers) – seriousness of side effects increase with renal failure