Endocrinology for Psychiatrists

Brandon Orr-Walker
Agenda

• Metabolic Syndrome and “Prediabetes”
• Diabetes
• Hyperprolactinaemia
• Thyroid disease

Prevalent issues, interaction with mental health (and its treatment)
Agenda

• Metabolic Syndrome and “Prediabetes”
• Diabetes
• Hyperprolactinaemia
• Thyroid disease
“It’s time we face reality, my friends. ... We’re not exactly rocket scientists.”
“Prediabetes”

- Better termed “intermediate hyperglycaemia” or “dysglycaemia”

<table>
<thead>
<tr>
<th>Venous plasma glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO, 1965</td>
</tr>
<tr>
<td>WHO, 1980</td>
</tr>
<tr>
<td>WHO, 1985</td>
</tr>
<tr>
<td>WHO, 1999 and 2006</td>
</tr>
<tr>
<td>ADA, 1997</td>
</tr>
<tr>
<td>ADA, 2003</td>
</tr>
<tr>
<td>ADA, 2010</td>
</tr>
</tbody>
</table>

One abnormal test result defines prediabetes; no repeat testing is required.
IGT=impaired glucose tolerance. IFG=impaired fasting glucose. ADA=American Diabetes Association. HbA₁c=glycated haemoglobin A₁c. *Measurement is recommended to exclude diabetes or IGT. †12 h postload glucose measurement not recommended.

Table 1: Diagnostic criteria for prediabetes
Prediabetes

• Variable definitions, and prevalence very sensitive to definitional changes

• Heterogeneous, with minority overlap between IFG and IGT (25%)
  – IFG: hepatic insulin resistance, impaired early insulin response
  – IGT: muscle insulin resistance, impaired early and late-phase insulin secretion
“Natural History”

Secular changes

• From 1980-2008 fasting glucose has risen by 0.1mmol/l

• Small effect in large population leads to:
  – Potential large burden in disease
  – Certain significant increase in “those at risk”
2008/09 New Zealand Adult Nutrition Survey

• Diabetes 7.0%
2008/09 New Zealand Adult Nutrition Survey

- Diabetes 7.0%
- Prediabetes 18.6%
Total diabetes and pre-diabetes age-specific rates for men
Total diabetes and pre-diabetes age-specific rates for women
Pre-diabetes prevalence (Auckland)

Prevalence of prediabetes in the Auckland metro region in 2013 (out of those who had HbA1c, GTT, fasting glucose) excluding people with diabetes
Pre-diabetes + diabetes prevalence

Prevalence of prediabetes or diabetes in the Auckland metro region in 2013
(out of those who had HbA1c, GTT, fasting glucose)
## Number of people with ‘glycaemic compromise’

<table>
<thead>
<tr>
<th>DHB</th>
<th>Number with diabetes</th>
<th>Number of pre-diabetes</th>
<th>Number of people with pre-diabetes or diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waitemata</td>
<td>24,102</td>
<td>129,330</td>
<td>153,432</td>
</tr>
<tr>
<td>Auckland</td>
<td>22,470</td>
<td>105,350</td>
<td>127,820</td>
</tr>
<tr>
<td>Counties Manukau</td>
<td>34,109</td>
<td>116,293</td>
<td>150,402</td>
</tr>
<tr>
<td>Overall</td>
<td>80,681</td>
<td>350,973</td>
<td>431,654</td>
</tr>
</tbody>
</table>
“Natural History”

Progression from Prediabetes to Diabetes:

• 5-10%/yr
  – *Isolated IFG* 6-9%
  – *Isolated IGT* 4-6%
  – *Combined* 15-19%

• *Estimated lifetime risk* 70% (ADA Expert panel)
“Natural History”

Regression from Prediabetes to normoglycaemia:

- 19% DPP control group (at 10 yr FU study)
- 55-80% IFG Ely Study (UK, 10 year FU)

Progression to diabetes may not be better predicted by “prediabetes” state than other risk approaches
Interventions

In trial settings, in enrolled participants confirmed to be in “prediabetes” range (i.e. 2 tests):

• Lifestyle interventions reduce prediabetes to diabetes conversion (over 3-5 years) by 50%
  – Better than metformin
  – No additivity with metformin (DPP)
  – No additivity with pioglitazone (Indian DPP-2)

• Reduced rates of “conversion” appear robust on longer term follow-up
Interventions

Predictors of reduced risk of progressing to Diabetes:

- **Attainment of goals of intervention** (weight loss > 5%, fat intake <30%, saturated fat reduction, fibre increase, exercise >4 hr/wk)
- **Single biggest predictor of reduced risk is weight loss** (1kg reduction reduces RR by 16%)
- **Attainment of NGR** (FG <5.6 AND 2hr <7.8)
Issues with Prediabetes “intervention” in real life

• Identifying target population
• Real-world implementation
• “medicalising” a “state” in absence of hard outcome/endpoint data
• The size of the problem
How will we cope?
Metabolic Syndrome

Metabolic syndrome is the name for a group of risk factors that raises your risk for heart disease and other health problems, such as diabetes and stroke.

– Dysmetabolic syndrome
– Hypertriglyceridemic waist
– Insulin resistance syndrome
– Obesity syndrome
– Syndrome X
Metabolic Syndrome and Psychiatry

• 2/3 those with BPAD or schizoeffective disorder
• ½ with Scizophrenia
• More in woman than men.
Problems with “Metabolic syndrome”

• Lack of consensus on definition
• Validity for differing ethnicities
• No known treatment specific to the cluster
• “Binomial” approach to components
• Lack of age and gender and past history (eg of IHD) in the assessment of risk
• Doesn’t have clinical utility (ADA and EASD)
Two of the metabolic syndrome definitions

**TABLE 2. WHO Clinical Criteria for Metabolic Syndrome**

Insulin resistance, identified by 1 of the following:

- Type 2 diabetes
- Impaired fasting glucose
- Impaired glucose tolerance
- or for those with normal fasting glucose levels (<110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions

Plus any 2 of the following:

- Antihypertensive medication and/or high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic)
- Plasma triglycerides ≥150 mg/dL (≥1.7 mmol/L)
- HDL cholesterol <35 mg/dL (<0.9 mmol/L) in men or <39 mg/dL (1.0 mmol/L) in women
- BMI >30 kg/m² and/or waist:hip ratio >0.9 in men, >0.85 in women
- Urinary albumin excretion rate ≥20 μg/min or albumin:creatinine ratio ≥30 mg/g

*Derived from Alberti et al. 7,8

**TABLE 1. ATP III Clinical Identification of the Metabolic Syndrome**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity, given as waist circumference†</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&gt;102 cm (&gt;40 in)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/≥85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dL†</td>
</tr>
</tbody>
</table>

*Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated BMI. Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.

†Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, eg, 94 to 102 cm (37 to 39 in). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.

‡The American Diabetes Association has recently established a cutpoint of ≥100 mg/dL, above
"I think you should be more explicit here in step two."
Diabetes

• Epidemiology
• Association with Mental Health
  – Over-representation
  – Consequence of treatment
• Treatment of Diabetes
  – Paradigm
  – Treatment escalation
Diabetes prevalence, by age and ethnicity

Diabetes prevalence in the Auckland metro region in 2013 by age and ethnicity

- Maori
- Pacific
- Indian
- Chinese
- Other Asian
- NZ European/Other
- Grand Total
Diabetes and Mental Illness

• Mental health problems and Diabetes are common and increasing
  – Causes are complex
  – More common in most deprived
  – People with diabetes have greater risks of mental illness (2 fold, mainly associated with depression) and
  – People with mental illness have increased risk of diabetes
  – Each condition is associated with substantive comorbidity and premature mortality
  – Medications used for mental illness may increase risk of diabetes
Antipsychotic Medication and Diabetes

possible mechanisms

• Impairing insulin secretion
  – relative or absolute insulin lack

• Impairing action of insulin
  – “insulin resistance”

• there is little evidence of decreased insulin release in all but those found to have Type I DM (Co-existing not causally related)
Antipsychotic Medication and Weight Gain

Described since 1950’s

• 50% of patients on chronic treatment
• commonest causes for non-compliance and/or discontinuation
• Maximal effect in 1st 3-4/12, but tends to progress
• Weight gain not restricted to those of low BMI
• Concomitant treatment with mood stabilisers and antidepressants is associated with increased weight gain
Figure 5. Antipsychotics and Weight Gain: Short-Term (10-weeks) Treatment

Reprinted with permission from Allison et al.68
Figure 2. Mean Change in Weight During Clinical Studies of Olanzapine$^a$
FIGURE 4. Changes in Body Weight at Week 8 in Participants Treated With Risperidone or Olanzapine by Body Mass Index\textsuperscript{a} Stratum at Baseline

<table>
<thead>
<tr>
<th>Body Mass Index Stratum</th>
<th>Risperidone, N=23</th>
<th>Olanzapine, N=23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;23)</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Medium (23–27)</td>
<td>71</td>
<td>59</td>
</tr>
</tbody>
</table>

\textsuperscript{a} A height-adjusted measure of body weight (kilograms per square meter).

Randomised db

Am J Psychiatry 2001; 158:765–774
Obesity Trends* Among U.S. Adults

BRFSS, 1985

(*BMI ≥ 30, or ~ 30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

**BRFSS. 1986**

(*BMI ≥30, or ~ 30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

BRFSS 1987
(*BMI ≥30, or ~ 30 lbs overweight for 5′4″ woman)

Obesity Trends* Among U.S. Adults

BRFSS, 1988

(*BMI ≥30, or ~ 30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

BRFSS, 1989

(*BMI ≥30, or ~ 30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

BRFSS, 1990

(*BMI ≥30, or ~ 30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

BRFSS, 1991
(*BMI ≥30, or ~ 30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

BRFSS, 1992

(*BMI ≥30, or ~ 30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

BRFSS, 1993

(*BMI ≥30, or ~ 30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

BRFSS 1994

(*BMI ≥30, or ∼30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

BRFSS 1995
(*BMI ≥ 30, or ~ 30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

BRFSS, 1996
(*BMI ≥30, or ~ 30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

**BRFSS 1997**

(*BMI ≥30, or ~30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

BRFSS, 1998

(*BMI ≥30, or ~ 30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

BRFSS, 1999

(*BMI ≥30, or ~ 30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

*BRFSS, 2000

(*BMI ≥30, or ~ 30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

BRFSS, 2001
(*BMI ≥30, or ~ 30 lbs overweight for 5′4″ woman)

Consensus Development Conference on Antipsychotic Drugs And Obesity and Diabetes

American Diabetes Association
American Psychiatric Association
American Association of Clinical Endocrinologists
North American Association for the Study of Obesity

J Clin Psych 65:2; 267-72 Feb 2004
Recommendations

• Consider risks when commencing antipsychotic
• Patient, family and caregiver education
• Baseline screening
• Regular monitoring
• Referral to specialised services, when appropriate

Consensus Development Conference on Antipsychotic Drugs And Obesity and Diabetes

J Clin Psych 65:2; 267-72 Feb 2004
Management of Type 2 DM

• Multifactorial
  – Glucose
  – BP
  – CVD risk
  – Reno-protection
• Lifestyle
• Pharmacotherapy
• Surgery
• Palliation
Association between mean HbA1c and complications: UKPDS

Each 1% fall in HbA1c represents a decrease in risk of...

- Lower extremity amputation or fatal peripheral vascular disease: 43%
- Microvascular disease*: 37%
- Cataract extraction*: 19%
- Heart failure*: 16%
- Myocardial infarction*: 14%
- Stroke*: 12%

† Single endpoint
# Aggregate endpoint
* p<0.05

Adapted from Stratton IM et al. on behalf of the UK Prospective Diabetes Study Group. BMJ 2000; 321:405–412.
Type 2 DM after 10 years...

In combination with open-label diuretic, calcium channel blocker, beta-blocker, alpha-blocker, and/or centrally acting agent

*Doubling of serum creatinine, end stage renal disease, death


RENAAL Patients Reaching the Primary Composite Endpoint*

Risk reduction = 16%

Placebo

Losartan

P = 0.02

Cumulative % of patients with event

Months

0 12 24 36 48

Placebo† (n) 762

Losartan† (n) 751

689 554 295 36

583 329 52

www.hypertensiononline.org
Steno-2 Post Trial: Any CVD events

Cumulative incidence of patients with a major CVD event during follow-up

Cumulative incidence of CVD events (%)

Log-rank P=0.0002

Years of follow-up

Cumulative incidence of CVD events (%)

Numbers at risk

<table>
<thead>
<tr>
<th>Years of follow-up</th>
<th>Conventional</th>
<th>Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>1</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>47</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>31</td>
</tr>
</tbody>
</table>

Gaede et al. NEJM 2008
Steno-2 Post Trial: Mortality of any cause

Log-rank P=0.015

Numbers at risk
Conventional 80 80 77 69 63 51 43 30
Intensive 80 78 75 72 65 62 57 39

Gaede et al. NEJM 2008
<table>
<thead>
<tr>
<th>Event</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>5 patients</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>8 patients</td>
</tr>
<tr>
<td>Major cardiovascular event</td>
<td>3 patients</td>
</tr>
<tr>
<td>Progression to nephropathy</td>
<td>5 patients</td>
</tr>
<tr>
<td>Dialysis</td>
<td>16 patients</td>
</tr>
<tr>
<td>Laser treatment</td>
<td>7 patients</td>
</tr>
<tr>
<td>Death</td>
<td>5 patients</td>
</tr>
</tbody>
</table>

(from Gaede et al 2008 Steno 2, 13 year study)
Diabetes problems

- The disease progresses
- Complications accrue
- Glycaemia is dynamic, and optimising glycaemic management requires expertise
- Complications and (increasing) treatment effects can get in way of realising the improvements
- Latency for results

After median 8.5 years post-trial follow-up

<table>
<thead>
<tr>
<th>Aggregate Endpoint</th>
<th>2007</th>
<th>RRR:</th>
<th>1997</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td>9%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>P:</td>
<td>0.029</td>
<td>0.040</td>
<td></td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>24%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>P:</td>
<td>0.0099</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>15%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>P:</td>
<td>0.052</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>6%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>P:</td>
<td>0.44</td>
<td>0.007</td>
<td></td>
</tr>
</tbody>
</table>

UKPDS PTFU mean 18.5 years since diagnosis
The Era of the Guideline

For a very brief period, medieval scientists were known to have dabbled in the merits of cardboard armor.
ADA/EASD (2012): patient-centred approach

Metformin

Needs

SUs

Glinides

GLP-1 RAs

DPP-4is

Disease progression

Dopamine-2 agonists

Age

Patient

TZDs

Preferences

Bile acid sequestrants

Tolerances

Insulin

DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; TZD, thiazolidinedione

 ADA/EASD position statement (2012)

Initial drug monotherapy
- Efficacy (Δ HbA1c)
- Hypoglycemia
- Weight
- Side effects
- Costs

Two drug combinations
- Efficacy (Δ HbA1c)
- Hypoglycemia
- Weight
- Major side effect(s)
- Costs

Three drug combinations

More complex insulin strategies

Healthy eating, weight control, increased physical activity

Metformin
- high
- low risk
- neutral/loss
- GI / lactic acidosis
- low

If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):

Metformin +
- Sulfonylurea†
  - high
  - moderate risk
  - gain
  - hypoglycemia†
  - low

Metformin +
- Thiazolidinedione
  - high
  - low risk
  - gain
  - edema, HF, fx's†
  - high

Metformin +
- DPP-4 Inhibitor
  - intermediate
  - low risk
  - neutral
  - rare†
  - high

Metformin +
- GLP-1 receptor agonist
  - high
  - low risk
  - loss
  - GI†
  - high

Metformin +
- Insulin (usually basal)
  - highest
  - high risk
  - gain
  - hypoglycemia variable

If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference):

Metformin +
- Sulfonylurea†
  - +
  - TZD
  - or
  - DPP-4-i
  - or
  - GLP-1-RA
  - or
  - Insulin†

Metformin +
- Thiazolidinedione
  - or
  - SU†
  - or
  - DPP-4-i
  - or
  - GLP-1-RA
  - or
  - Insulin†

Metformin +
- DPP-4 Inhibitor
  - or
  - SU†
  - or
  - DPP-4-i
  - or
  - GLP-1-RA

Metformin +
- GLP-1 receptor agonist
  - or
  - SU†
  - or
  - DPP-4-i
  - or
  - GLP-1-RA

Insulin (?)
(multiple daily doses)

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:

ADA/EASD Position Statement. Available at: http://care.diabetesjournals.org/content/early/2012/04/17/dc12-0413.full.pdf
Management algorithm for blood glucose control in type 2 diabetes

The algorithm includes only therapeutic agents available through the PBS
If HbA₁c > 7% consider intensifying treatment provided hypoglycaemia is not a problem
# Authorised only as dual therapy with metformin or sulphonylurea where combination of metformin and sulphonylurea is contraindicated or not tolerated
* Rosiglitazone is not authorised for triple therapy or for use with insulin, but is approved only as dual therapy with metformin or sulphonylurea where combination metformin and sulphonylurea is contraindicated or not tolerated

Colagiuri et al. National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes. Diabetes Australia and the NHMRC, Canberra 2009
Individualising HbA$_{1c}$ goals

Approach to management of hyperglycaemia:

- More stringent
  - Patient attitude and expected treatment efforts
  - Highly motivated, adherent, excellent self-care capacities
  - Risks potentially associated with hypoglycaemia, other adverse events
  - Low
  - Disease duration
  - Newly diagnosed
  - Life expectancy
  - Long
  - Important comorbidities
  - Absent
  - Established vascular complications
  - Absent
  - Resources, support system
  - Readily available

- Less stringent
  - Patient centred care
  - Less motivated, non-adherent, poor self-care capacities
  - High
  - Long-standing
  - Short
  - Few / mild
  - Severe
  - Limited

Inzucchi et al. Diabetes Care 2012;35:1364–79
Glycaemic Medications

• Metformin
  – Insulin sensitiser
• Sulphonylureas
  – Insulin secretagogue
• Glitazones
  – Insulin sensitiser
• Acarbose
  – Reduce rapid postprandial CHO absorption
• Insulin
NICE (Oct 2008)

• Initiation:
  – NPH insulin at bedtime or twice daily
  – Other insulin:
    • long-acting insulin analogue,
    • human or analogue premixed insulin (esp if HbA$_{1c}$ >9)

• Intensification:
  – from basal to premixed or mealtime plus basal
  – from premixed once to twice or further prandial injection or eventual change to mealtime plus basal regimen
Other agents (unfunded currently)

DPP4 inhibitors (eg sitagliptin)
• Additive with metformin
• No weight gain and no hypoglycaemia (monoTx or with MF)

GLP-1 agonists (eg exenatide)
• Weight loss, satiety. No hypoglycaemia
• Greater glucose effect than DPP4 agents
• Appear more durable effect than sulphonylurea
Other agents (unfunded currently)

SGLT2 inhibitors (eg dapagliflozin, canagliflozin)

- insulin-independent
- Weight loss, natriuresis, glycosuria
- No hypos
- Reduced CVD endpoints
- Lower genito-urinary infections
Lipids

• In NZ we think of CVD risk
• Either:
  – Calculated (www.nzsssd.org.nz/cvd/)
  – Clinical high risk
Lipid Management

• Risk relates to LDL, and LDL lowering reduces risk, but residual high risk remains:
  – LDL particle number (eg assoc with high Apo B)
  – Low HDL (Framingham, ProCam, TNT, Prove-IT)

• In FIELD and ACCORD in those with high TG and low HDL (on statin) the addition of fenofibrate reduced CVD rates, and reduced maculopathy
Lipid Management

- Statins are very effective, but dose increases (doublings) result in modest further improvement. Need increased potency or add on therapy.
- FDA has warned about simvastain at 80mg day: better will be atorvastatin or simvastatin 40mg plus ezetimide
Statins

• Rhabdomyolosis risk approx 2-3 /million scripts
• Statin associated with increased risk of T2DM (HR 1.09)
  – But risk benefit favourable.
• Increased reports of “confusion” on statin meds, reversible, (median 3 weeks) and not progressive or dementia (HPS outcome data)
Prolactin

• Normal physiology
• Disease and Prolactin
• Antipschotics
• Does hyperprolactinaemia matter? How?
• Approaches to manage or minimise hyperprolactinaemia
Prolactin

- Anterior pituitary hormone
- Discovered in early 1970s
- Inhibited by dopamine released from hypothalamus via D$_2$ receptors
- Other neurotransmitters/hormones may have stimulatory effect on PrL release including VIP and serotonin
- Normal range 40-600 mIU/l
Prolactin physiology

- Episodic secretion with sleep-dependent diurnal variation
- Increase 10 fold during pregnancy principally in response to oestrogen
- 4-6/52 postpartum remains elevated, with suckling triggering episodic release
- 6-12/52 postpartum basal levels fall to normal, but suckling produces high peaks
- Other physiologic stimuli for release include exercise, sexual activity, acute psychological stress
Prolactin in pregnancy
Prolactin levels postpartum
Disease and Prolactin

• Pituitary Disease
• Drugs
• Stress
• Nipple stimulation/chest wall trauma
• Hypothyroidism
• Oestrogen (high dose)
• Renal disease/clearance of prolactin
Consequences of elevation of PrL:

- Hypogonadism
- Galactorrhoea
- (mild androgenic effects)
Hyperprolactinaemia by Aetiology

![Bar chart showing serum prolactin concentration in ng/mL for different causes of hyperprolactinaemia: Lactotroph macroadenoma, Lactotroph microadenoma, Other pituitary and hypothalamic disease, Pregnancy, Stress, Drugs.]
(Partial) list of drugs known to cause hyperprolactinemia and/or galactorrhea

- **Typical antipsychotics** Phenothiazine drugs (*eg*, chlorpromazine, clomipramine, fluphenazine, prochlorperazine, thioridazine) haloperidol, pimozide
- **Atypical antipsychotics** risperidone, molindone, olanzapine
- **Antidepressant agents** clomipramine, desipramine
- **Gastrointestinal drugs** cimetidine, metoclopramide
- **Antihypertensive agents** methyldopa, reserpine, verapamil
- **Opiates** codeine, morphine
<table>
<thead>
<tr>
<th>Drug</th>
<th>PRL elevation</th>
<th>Clinical symptoms of hyperprolactinaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>early&lt;sup&gt;a&lt;/sup&gt;</td>
<td>sustained&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Traditional</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>↑↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td><strong>Atypical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>⇔</td>
<td>⇔</td>
</tr>
<tr>
<td>Risperidone&lt;sup&gt;d&lt;/sup&gt;</td>
<td>↑↑</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>⇔</td>
<td>⇔</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>↑</td>
<td>⇔</td>
</tr>
<tr>
<td>Sertindole</td>
<td>⇔</td>
<td>⇔</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

<sup>a</sup> Following single oral dose or first week of therapy.

<sup>b</sup> After some weeks of therapy.

<sup>c</sup> Incidence estimated from the literature.

<sup>d</sup> Lower risperidone doses may have minimal effects since elevation of PRL level is dose-related (see text).

⇔ = no or minimal elevation; ↑ = mild elevation; ↑↑ = moderate elevation; ↑↑↑ = marked elevation; -= minimal frequency; + = low frequency; ++ = moderate frequency; +++ = high frequency; ? = currently no published data.
Acute dose comparison

FIGURE 1. Mean Plasma Prolactin Level Changes Over 24 Hours in 18 Patients After Taking Clozapine, Olanzapine, or Risperidone and in Five of the Same Patients After Not Taking the Drugs$^a$

$^a$ One of the patients taking clozapine, two taking olanzapine, and two taking risperidone had their prolactin levels measured twice: first after taking their usual dose of the medication and second, at least 1 month later, after not taking their usual dose.

Am J Psychiatry 2002; 159:133–135
# Novel Antipsychotics

<table>
<thead>
<tr>
<th>Agent</th>
<th>( D_2 ) blockade</th>
<th>( 5 \ HT_2 ) Blockade</th>
<th>Other effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>weak</td>
<td>potent</td>
<td>Anti muscarinic histamine blockade</td>
</tr>
<tr>
<td>Risperidone</td>
<td>potent</td>
<td>potent</td>
<td>Anti muscarinic</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>weak</td>
<td>potent</td>
<td>Alpha blockade, histamine blockade</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>weak</td>
<td>moderate</td>
<td></td>
</tr>
</tbody>
</table>
Hyperprolactinaemia in patients on antipsychotics

• *May be physiological*
• *May be due to other illness*  
  *(hypothyroidism, pituitary disease)*
• *May not be associated with symptoms*
• *Symptoms may not be problematic*  
  *(eg hypogonadism in a women on COC or DP)*
With respect to pituitary disease:

- Elevated prolactin does not always require treatment:
- Few/no sx (esp postmenopausal woman)
- Small tumor not invasive or compressing structures
With respect to pituitary disease:

• Normal prolactin does not exclude pituitary disease
• Elevated prolactin does not usually interfere with gonadal function if PrL < 1000
• Elevated prolactin due to dopamine blockade is not known to cause pituitary tumor development or growth

• However, markedly elevated prolactin levels in a pt with a pituitary tumor may be an indication for urgent medical treatment
Indications for medical management of Prolactinomas

**Mass Effects**
- Hypopituitarism
- Visual field defects due to pressure on the optic chiasm
- Cranial nerve deficits
- Headaches

**Effects of Hyperprolactinemia**
- Hypogonadism
- Amenorrhea or oligoamenorrhea
- Infertility
- Impotence
- Osteoporosis or osteopenia

**Relative indications:**
- Bothersome hirsuitism
- Bothersome galactorrhea

Gillam et al, Endocrine Reviews 2006
Management of Antipsychotic-induced hyperprolactinaemia

• Exclude other causes
  – (Pre-treatment level, TFT’s)

• Treat if problematic symptoms/s-e
  – Oestrogen/progesterone
  – substitution
  – combination Tx
  – addition of dopaminergic agents
“It’s no good, Dawson! We’re being sucked in by the sun’s gravitational field and there’s nothing we can do! ... And let me add those are my sunglasses you’re wearing!”
Thyroid function

- Thyroid normally under tonic stimulus and negative feedback (ie TSH dependent)
- Hypothyroidism associated with weight gain and hyperprolactinaemia
- Lithium has complex effects on thyroid function
Lithium and Thyroid

noted that patients with psychiatric disease treated with lithium carbonate developed hypothyroidism and goiter.

Lithium:

• increases intrathyroidal iodine content,
• inhibits the coupling of iodotyrosine residues to form iodothyronines (thyroxine [T4] and triiodothyronine [T3]), and
• inhibits release of T4 and T3
Lithium and Thyroid

- Goitre 40-50% usually in first 2 years
- 20-30% may develop hypothyroidism
  - May be associated with thyroid autoimmunity
  - More rarely with hyperthyroidism or thyroiditis (transient thyrotoxicosis)
Summary

- Endocrine conditions are common in patients with psychiatric illness
  - Should be screened for

- These conditions may affect patient care and long term morbidity and mortality
  - Require attention (monitoring and management)

- Psychiatric treatment may predispose to endocrine problems (and other physical disease aspects)
  - Duty of care
Thanks for your attention!!!