Metabolic & Endocrine Disorders “in Psychiatry”

M Guftar Shaikh
Endocrinologist,
RHSC Glasgow
Outline

- Effects of Psychotropics
  - Growth/Endocrine
  - Metabolic syndrome
- Assessment & Management
- Treatment
Psychotropics

- Increased use in children
- Multiple disorders
  - ADHD
  - Anxiety
  - Psychotic disorders
- Safety & efficacy - evidence limited
Anti-psychotics - problems

- Endocrine dysfunction
  - Growth
  - Thyroid
  - Puberty
  - Prolactinaemia
  - BMD
- Metabolic syndrome
### Table 4  Selected side effects of commonly used antipsychotic medications (Tandon, 1998)

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<tr>
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<tbody>
<tr>
<td>Thioridazine</td>
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*Also causes agranulocytosis, seizure and myocarditis; †possible exception of akathisia; ‡also carries warning about potential development of cataracts; §also causes nausea and headache.

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Growth- Psycho-stimulants

- Best studied in children and adolescents
- Initial reduction in growth velocity
- Can be prolonged
- Mechanism of poor growth-unclear
- ?Final Adult Height
- Variation in growth between drugs
- Ex prem 32/40 (twin 2)
- Complex congenital heart disease
- Prolonged ventilation
- Learning difficulties
- Behavioural problems (ADHD)
Does prolonged therapy with a long-acting stimulant suppress growth in children with ADHD?


Fig. 2  Z scores during the course of the study.
Does prolonged therapy with a long-acting stimulant suppress growth in children with ADHD?

Mean height velocity of 22 boys over an average of 7 years of treatment with stimulant medication to 14–15.99 years of age*

Growth and pubertal development of adolescent boys on stimulant medication for attention deficit hyperactivity disorder Alison S Poulton, Elaine Melzer, Paul R Tait, Sarah P Garnett, Chris T Cowell, Louise A Baur and Simon Clarke

Stimulants and Growth
Should we be concerned?

Long-term effects of short-acting methylphenidate on growth rates of children with attention deficit hyperactivity disorder at Queen Sirikit National Institute of Child Health.
Moungnoi P¹, Maipang P.

Comparative effects of methylphenidate and mixed salts amphetamine on height and weight in children with attention-deficit/hyperactivity disorder.
Pliszka SR¹, Matthews TL, Braslow KJ, Watson MA.

Effect of stimulants on height and weight: a review of the literature.
Faraone SV¹, Biederman J, Morley CP, Spencer TJ.

Long-Term Effects of ADHD Medication on Adult Height: Results From the NESARC
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Growth- Psycho-stimulants 2

- Height and weight plotted on chart prior to starting drug
- Previous growth data
- Regular monitoring
- Height reduction by >1SDS
  - Endocrine referral
  - Other underlying cause
- Reduction in dose
Metabolic syndrome
Metabolic Syndrome

- THE METABOLIC SYNDROME IS A CLUSTER OF THE CARDIOVASCULAR RISK FACTORS:
  - DIABETES AND PREDIABETES,
  - ABDOMINAL OBESITY,
  - HIGH CHOLESTEROL
  - HIGH BLOOD PRESSURE.
The metabolic highway

Premature death and loss of 20-30 years of normal lifespan

Metabolic highway

Diabetes
Cardiovascular events
Prediabetes

Beta cell failure

Insulin resistance

Obesity and increased BMI

Beware: cardiometabolic risk ahead

On ramp

↑ Appetite weight gain

↑ Triglycerides

↑ Triglycerides

Insulin

Adipose
Liver
Muscle

Pancreas
Hyperinsulinemia

# Metabolic Syndrome Definitions

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Journal and Year</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Cook et al.</td>
<td><em>Arch Pediatr Adolesc Med</em>, 2003; 157, 821-74</td>
<td>Three or more of the following:</td>
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<tr>
<td>de Ferranti et al.</td>
<td><em>Circulation</em>, 2004; 110, 2494-721</td>
<td>1. Fasting glucose ≥110 mg/dL (≥110 mg/dL)</td>
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<td>Cruz et al.</td>
<td><em>J Clin Endocrinol Metab</em>, 2004; 89, 108-1322</td>
<td>1. Fasting glucose ≥6.1 mmol/L (≥110 mg/dL)</td>
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<td>Ford et al.</td>
<td><em>Diabetes Care</em>, 2005; 28, 878-8144</td>
<td>1. Impaired glucose tolerance (ADA criterion)</td>
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<td>2. WC ≥90th percentile (age- and sex-specific, NHANES III)</td>
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<td>2. WC &gt;75th percentile (age- and sex-specific, NHANES III)</td>
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<td>2. WC ≥90th percentile (age- and sex-specific, NHANES III)</td>
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<td>2. BMI –Z score ≥2.0 (age- and sex-specific)</td>
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<td>2. WC ≥90th percentile (sex-specific, NHANES III)</td>
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<td>3. Triglycerides ≥110 mg/dL (age-specific, NCEP)</td>
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<td>3. Triglycerides &gt;95th percentile (age-, sex- and race-specific, NGHS)</td>
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<td>4. HDL-C ≤40 mg/dL (all ages/ sexes, NCEP)</td>
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<td>4. HDL-C &lt;1.3 mmol/L (&lt;50 mg/dL)</td>
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<td>4. HDL-C ≤10th percentile (age- and sex-specific, NHANES III)</td>
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<td>4. HDL-C &lt;5th percentile (age-, sex- and race-specific, NGHS)</td>
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<td>5. Blood pressure ≥90th percentile (age-, sex- and height-specific, NHBPEP)</td>
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### Metabolic Syndrome

**IDF Definition**

The IDF consensus definition of metabolic syndrome in children and adolescents

<table>
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<th>Age group (years)</th>
<th>Obesity* (WC)</th>
<th>Triglycerides</th>
<th>HDL-C</th>
<th>Blood pressure</th>
<th>Glucose (mmol/L) or known T2DM</th>
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</thead>
<tbody>
<tr>
<td>6–&lt;10</td>
<td>≥90th percentile</td>
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<td>Metabolic syndrome cannot be diagnosed, but further measurements should be made if there is a family history of metabolic syndrome, T2DM, dyslipidemia, cardiovascular disease, hypertension and/or obesity.</td>
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<tr>
<td>10–&lt;16 Metabolic syndrome</td>
<td>≥90th percentile or adult cut-off if lower</td>
<td>≥1.7 mmol/L (≥150 mg/dL)</td>
<td>&lt;1.03 mmol/L (&lt;40 mg/dL)</td>
<td>Systolic ≥130/ diastolic ≥85 mm Hg</td>
<td>≥5.6 mmol/L (100 mg/dL) (If ≥5.6 mmol/L [or known T2DM] recommend an OGTT)</td>
</tr>
<tr>
<td>16+ Metabolic syndrome</td>
<td>Use existing IDF criteria for adults, ie: Central obesity (plus any two of the following four factors): • raised triglycerides: ≥ 1.7mmol/L • reduced HDL-cholesterol: &lt;1.03mmol/L (&lt;40 mg/dL) in males and &lt;1.29mmol/L (&lt;50 mg/dL) in females, or specific treatment for these lipid abnormalities • raised blood pressure: systolic BP ≥130 or diastolic BP ≥85mm Hg, or treatment of previously diagnosed hypertension • impaired fasting glycemia (IFG): fasting plasma glucose (FPG) ≥5.6 mmol/L (≥100 mg/dL), or previously diagnosed type 2 diabetes</td>
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Metabolic Syndrome

- obese children and young people with ≥2 of the following cardiovascular risk factors are very likely to constitute a high risk group:
  - i. impaired fasting glucose or impaired glucose tolerance
  - ii. hyperinsulinaemia
  - iii. abnormal lipids – low HDL or high total cholesterol, LDL or TG
  - iv. hypertension
Psychiatry and Metabolic Syndrome

- Psychiatry patients often gain weight
- Factors
  - Sedentary lifestyle
  - Poor diet
  - Medication
- Excessive weight gain
  - Social withdrawal
  - Poor compliance
Increased risk of MS
Atypical anti-psychotics and risk

Table 1. Atypical antipsychotics and risk of weight gain: FDA and experts agree on three tiers of risk (48)

<table>
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<tr>
<th>Antipsychotic</th>
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<td>Aripiprazole</td>
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FDA, US Food and Drug Administration.
†Risperidone’s active metabolite paliperidone probably has the same risk of weight gain as risperidone itself.
Atypical anti-psychotics and risk

Table 2. Atypical antipsychotics and cardiometabolic risk: FDA and experts disagree on one vs. three tiers of risk

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Expert consensus</th>
<th>CATIE</th>
<th>FDA</th>
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<tbody>
<tr>
<td>Clozapine</td>
<td>Definite risk</td>
<td>ND</td>
<td>Diabetes warning</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Definite risk</td>
<td>Definite risk</td>
<td>Diabetes warning</td>
</tr>
<tr>
<td>Risperidone†</td>
<td>Inconclusive</td>
<td>Intermediate</td>
<td>Diabetes warning</td>
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<td>Inconclusive</td>
<td>Definite risk</td>
<td>Diabetes warning</td>
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<td>Ziprasidone</td>
<td>±Limited data</td>
<td>Low risk</td>
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ND, not done (clozapine and aripiprazole not studied in early phases of this trial). CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; FDA, US Food and Drug Administration.

†Risperidone’s active metabolite paliperidone probably has the same cardiometabolic risk as risperidone itself.
Definition of Obesity
Definition
Body Mass Index

- BMI = Weight (kg) / [Height (m)^2]

- Adults
  - 25-30 - overweight
  - >30 - obese
  - >40 - morbidly obese
Body Mass Index

- BMI = Weight (kg) / [Height (m)^2]
- NOT A MEASURE OF ADIPOSITY!!
- Adults
  - 25-30 - overweight
  - >30 - obese
  - >40 morbidly obese
Referred guidelines

Consider referred for repeat unless BMI falls above the 90th centile/below the 5th centile as significantly overweight/underweight even on the basis of a single measurement. It is important that the boy whose BMI falls in the central range should also be referred. However, having obesity may lead to transient changes in posture and water retention due to the shape of the charts, and these should be normal. It should be remembered that the higher the age of the second M, the greater the risk of future obesity. Remember also that while BMI has a high correlation with relative fatness or bonelessness it is actually assessing the weight to height relationship; it may not give misleading results in boys who are very stocky and muscular who might appear obese on the BMI alone.

How to calculate BMI

Deduce weight (kg) by square of height (m²)

\[ \text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m)}^2} \]

<table>
<thead>
<tr>
<th>Age</th>
<th>Height</th>
<th>Weight</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

Reference


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Wickford Close, Southend
Tipton & West 1. 0559-370-01
# SDS calculator

<table>
<thead>
<tr>
<th>SD</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
<th>+1</th>
<th>+2</th>
<th>+3</th>
</tr>
</thead>
<tbody>
<tr>
<td>centile</td>
<td>0.1</td>
<td>2.5</td>
<td>15.8</td>
<td>50</td>
<td>84</td>
<td>97.6</td>
<td>99.7</td>
</tr>
</tbody>
</table>

http://www.phsim.man.ac.uk/SDSCalculator/SDSCalculator.aspx
Management of Obesity

- BMI > 98th centile
  - Child/family seeking help
  - Risk factors
  - Underlying pathology
  - Future co-morbidity
  - Extreme obesity
Who Should be referred to a Paediatrician

- Possible Underlying Pathology
  - Dysmorphic features
  - Short for degree of obesity
  - Learning difficulties
Who Should be referred to a Paediatrician

- Risk for Co-Morbidity
  - Hypertension
  - Obstructive Sleep Apnoea
  - Insulin resistance/(Diabetes)
  - Mobility/Joint problems
  - Dyslipidaemia
  - NAFLD
  - PCOS
  - Psychological concerns
  - Family Hx of T2DM/CVD
**Extreme Obesity**

- **Extreme Obesity**
- **BMI ≥3.5 SD**
- i.e. BMI (kg/m2) over the following:

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 yrs</td>
<td>22.7</td>
<td>22.7</td>
</tr>
<tr>
<td>5 yrs</td>
<td>22</td>
<td>23.5</td>
</tr>
<tr>
<td>10 yrs</td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td>15 yrs</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>18 yrs</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

http://www.phsim.man.ac.uk/SDSCalculator/SDSCalculator.aspx
Examination & History

Height, Weight, BMI

- Note obesity pattern:
  - generalised, abdominal, buffalo hump
- Blood pressure
  - using appropriate cuff
- Pubertal assessment,
  - menstrual history
Examination & History

- Acanthosis nigricans
- Signs of endocrinopathy
  - Hypothyroid/cushings
- Dysmorphisms
  - PWS, Bardet-Biedl
Don’t forget!!!

- The Most Important Information
ACCURATE Diet & Exercise!!!
Prolactin
Physiology

- Prolactin
  - Lactotrophes
  - Pregnancy & lactation
  - Hypothalamic GnRH
- Sex
- Age
- Reproductive status
- Stress
Weighted Summary: Effects of Antipsychotics on Prolactin Levels

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Prolactin Response Weighted Score*</th>
<th>Hyperprolactinemia APA Guidelines Weighted Risk†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Clozapine</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Risperidone</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>++/+</td>
<td>0</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Insufficient data</td>
<td>+</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Insufficient data</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*+++ = robust elevation; ++ = moderate elevation; + = mild, transient elevation; 0 = no elevation.

†APA guidelines 2004 weighted score: +++ = frequently causes side effect at therapeutic doses; ++ = sometimes causes side effect at therapeutic dose; + = mild or occasionally causes side effect at therapeutic doses; 0 = no risk or rarely causes side effect at therapeutic dose; NA = not available.

APA indicates American Psychological Association.

Adapted from Tandon.95
<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Study design</th>
<th>Effect on serum prolactin levels</th>
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</thead>
<tbody>
<tr>
<td>Aripiprazole vs. olanzapine (Chrzanoski et al., 2006)</td>
<td>52-week, open-label, extension study of patients with acute relapsing or chronic schizophrenia</td>
<td>Higher mean prolactin levels with olanzapine than aripiprazole at study endpoint (9.30 ng/mL vs. 0.78 ng/mL; p=0.003)</td>
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<td>3-week, randomized, double-blind study of patients with bipolar I disorder</td>
<td>Risperidone-treated patients more likely to experience elevated prolactin levels than olanzapine (51.73 ng/mL vs. 8.23 ng/mL; p&lt;0.001)</td>
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<td>Risperidone vs. olanzapine vs. quetiapine (Staller, 2006)</td>
<td>Naturalistic, cross-sectional study for ≥6 months in outpatient youths with psychiatric disorders</td>
<td>Significantly higher mean prolactin levels among risperidone-treated patients than controls or quetiapine- or olanzapine-treated patients (22 ng/mL vs. 6.4, 10.4, 6.7 ng/mL; p&lt;0.05)</td>
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<td>Risperidone vs. haloperidol (Schooler et al., 2005)</td>
<td>Long-term (median duration of treatment=206 days), double-blind, randomized study in patients with first-episode psychosis</td>
<td>Higher mean prolactin levels in risperidone-treated patients than those treated with haloperidol (73.69 ng/mL vs. 48.16 ng/mL for women, p&lt;0.003; 34.08 ng/mL vs. 21.81 ng/mL for men, p&lt;0.0001)</td>
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<td>Clozapine vs. olanzapine vs. risperidone vs. haloperidol (Volavka et al., 2004)</td>
<td>14-week, randomized, double-blind study of patients with schizophrenia or schizoaffective disorder</td>
<td>Elevation of prolactin levels with risperidone (p&lt;0.05 vs. comparators) and haloperidol (ns); Decreased prolactin levels with clozapine and olanzapine</td>
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ns, non significant.
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Hyperprolactinemia

- Atypical
- May be transient
- More pronounced in adolescents
  - Number of receptors
  - Young children - other medication
- Women greater PRL levels
- (macroprolactin)
Puberty/Hypogonadism

- Mediated through elevated prolactin
  - Hypothalamic dysregulation

- Sex hormone dysregulation
  - Pulsatile release of GnRH
  - Reduced sex steroids
  - Hypogonadism
Short term consequences

- **Galactorrhea**
  - Women > men
  - 10-90% reported

- **Gynaecomastia**
  - Rare
  - 1-2% (11%)
Antipsychotic treatment decreases dopaminergic activity, leading to increased prolactin. Prolactin inhibits release of hypothalamic GnRH, resulting in decreased gonadotropins and testosterone. This leads to decreased estrogen and symptomatic hyperprolactinemia.
Figure 2  Management options for antipsychotic-induced hyperprolactinaemia (Haddad and Wieck, 2004).
Bone Mineral Density

- Prolactinomas
  - Reduced BMD
- ?antipsychotics
- Sex steroids
- Hypogonadism
- ?Benefit from oestrogen

- Decreased bone mineral density in male schizophrenia patients
- Bone mineral density changes over a year in young females with schizophrenia: relationship to medication and endocrine variables.
- Meaney AM¹, O'Keane V. Schizophr Res. 2007 Jul;93(1-3):136-43.
Other Problems

- Breast Cancer
- Pituitary Adenomas
- BMD
Children & Adolescents

- Duration of therapy
- Degree of elevation of prolactin
- Consequences
- Limited evidence
Careful patient history; Query patient before beginning treatment and yearly thereafter*

Query:
- Changes in menstruation?
- Changes in libido?
- Breast milk secretion?

If clinically indicated or if positive response is given to any question

Measure prolactin level
- If possible, rule out nonpharmacologic etiology

If patient is hyperprolactinemic

Consider switch to antipsychotic with lower potential to elevate prolactin

Query:
- Changes in libido?
- Erectile dysfunction?
- Ejaculatory dysfunction?
Management

- Baseline levels
- Growth measurement
- Pubertal development
- Rule out
  - Hypothyroidism/renal failure
- Change medication
- Persistently elevated PRL - ?MRI pituitary
- Sex steroids /bisphosphonates
- Dopamine agonists???
Thyroid

- Lithium, (Valproate & Quetiapine)
- Inhibition of release of thyroxine
  - Elevated TSH
  - Transient
  - Goitre (reversible)- thyroxine/stop Lithium
Thyroid

- Baseline TFTs
- Re-check 1-2 months
- Then 6-12 months
- If hypothyroid start thyroxine
Baseline

- U+Es, calcium, TFTs, prolactin
- Height, weight
- (BMI-chart)
- Pubertal status
  - Menstruation, gynaecomastia, galactorrhea
- Diet/Physical activity
Monitoring

- TFTs & calcium
- 1-2 months, 6,12, annually
- Prolactin
  - Reduce dose or change to PRL sparing
- BMD
  - Back pain, low trauma fracture
  - DXA scan
  - Vitamin D/calcium supplementation
Any Questions?