Clinical Updates

Part 1: Vitamin D Deficiency

Part 2: Atypical Antipsychotic ADRs

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Objectives

• Vitamin D Deficiency
  – Explain the risks related to vitamin D deficiency
  – Identify patients at risk for vitamin D deficiency
  – Recognize sources of vitamin D and treatment options for those who are deficient

• Atypical Antipsychotic ADRs
  – List the most common ADRs associated with atypical antipsychotics
  – Consider the community pharmacist’s role in educating patients and providers about the best management of atypical antipsychotic ADRs
Vitamin D

• A group of fat-soluble vitamins

• Three main functions
  – Bone mineralization
  – Enhances calcium and phosphorus absorption
  – Inhibits parathyroid hormone synthesis and secretion

• Likely benefits
  – Prevention and treatment of bone disease
  – Fall prevention

Australian Family Physician 2004;33(3):133-138
“Nutrient of the Decade”

- Vitamin D deficiency possibly linked to…
  - Common cancers
  - Autoimmune diseases
  - Diabetes
  - Cardiovascular disease
  - Fibromyalgia
  - Chronic fatigue syndrome
  - Depression
  - Others?
Vitamin D Sources

• Sunlight
  – 40-50% of circulating vitamin D from skin conversion
  – Sunscreens absorb UV radiation before it enters the skin
  – Short exposures are more efficient
  – Considerable seasonal variation
Vitamin D Sources

• Diet
  – Small quantities in few foods
  – High fat fish, meat, liver, eggs
  – Fortified foods (margarine and some milk)
• Supplements
  – Many with calcium + vitamin D
  – Multivitamins
  – Cod liver oil, also contains vitamin A
  – Ostelin 1000 IU (vitamin D₃)
### Adequate Intake

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Daily Adequate Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 1-18 years</td>
<td>200 IU</td>
</tr>
<tr>
<td>Men: 19-50 years</td>
<td>200 IU</td>
</tr>
<tr>
<td>Men: 51-70 years</td>
<td>400 IU</td>
</tr>
<tr>
<td>Men &gt;70 years</td>
<td>600 IU</td>
</tr>
<tr>
<td>Women: 19-50 years</td>
<td>200 IU</td>
</tr>
<tr>
<td>Women: 51-70 years</td>
<td>400 IU</td>
</tr>
<tr>
<td>Women &gt;70 years</td>
<td>600 IU</td>
</tr>
<tr>
<td>Pregnancy: 14-50 years</td>
<td>200 IU</td>
</tr>
<tr>
<td>Lactation 14-50 years</td>
<td>200 IU</td>
</tr>
</tbody>
</table>

**Fig. 1**

**Vitamin D metabolism**

- **7-dehydrocholesterol**
  - **skin**

- **cholecalciferol**
  - Vitamin D₃ (major source) is formed in the skin after exposure to sunlight

- **liver**

- **25-hydroxyvitamin D**

- **kidney**

- **1,25-dihydroxyvitamin D**

**Dietary vitamin D** (minor source):
- Vitamin D₂ – cholecalciferol is present in some fish and meat
- Vitamin D₃ – ergocalciferol is a vegetable-derived form of vitamin D, previously the main form of supplementation²

Calcium balance is maintained by parathyroid hormone and 1,25-dihydroxyvitamin D. Together they co-regulate:
- gut calcium absorption
- renal calcium reabsorption
- bone formation and breakdown
Vitamin D Deficiency

• Prevalence
  – 1 billion people worldwide with vitamin D deficiency or insufficiency

• Symptoms
  – Primarily asymptomatic
  – Muscle weakness, muscle and/or bone pain, fragility fractures

• 25(OH)D Levels – USA
  – Deficiency < 10 ng/mL (or <20 ng/mL)
  – Insufficiency: 10-30 ng/mL (or 21-29 ng/mL)

• 25(OH)D Levels – Australia
  – Deficient <25 nmol/L
  – Insufficient: 25-49 nmol/L
  – Adequate: 50-75 nmol/L
  – Optimal >75 nmol/L

Deficiency
Mild: 25-50 nmol/L
Moderate: 12.5-25 nmol/L
Severe <12.5 nmol/L

J Clin Endocrinol Metab 2011;96:1911-1930
Interpreting Vitamin D Tests

• Variability between tests and laboratories
• Consider time of year
• Individual patient factors
  – Skin color
  – Age of individual
  – Lifestyle
Causes of Vitamin D Deficiency

- Reduced skin synthesis
- Decreased bioavailability
- Increased catabolism
- Breast-feeding
- Decreased synthesis of 25(OH)D
- Increased urinary loss of 25(OH)D
- Decreased synthesis of 1,25(OH)_2D
- Heritable disorders
- Acquired disorders
Who should be screened?

- Housebound; > 65 yo or resident of nursing home
- Naturally dark skin
- Bone disease
- Chronic kidney disease
- Wearing veils
- Malabsorption syndromes
- Obese
- Medications which interact with vitamin D
  - Phenytoin, phenobarbital, orlistat, thiazide diuretics, digoxin
## 25(OH)D Levels in Australia

<table>
<thead>
<tr>
<th>Location</th>
<th>n</th>
<th>Mean 25(OH)D level (nmol/L)</th>
<th>25(OH)D &lt; 50 (nmol/L)</th>
<th>25(OH)D &lt; 25 (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Southeast Qld</td>
<td>414</td>
<td>75 (summer), 55 (winter)</td>
<td>23%</td>
<td>8% (≤ 38 nmol/L)</td>
</tr>
<tr>
<td>Brisbane</td>
<td>126</td>
<td>57 &lt;males&gt; 52 &lt;females&gt; both in winter</td>
<td>42%</td>
<td>10%</td>
</tr>
<tr>
<td>Perth</td>
<td>197</td>
<td>58</td>
<td>34%</td>
<td>—</td>
</tr>
<tr>
<td>Maryborough (Vic)</td>
<td>113</td>
<td>54</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Geelong</td>
<td>861</td>
<td>81 (summer), 59 (winter)</td>
<td>30%</td>
<td>7% (&lt; 28 nmol/L)</td>
</tr>
<tr>
<td>Tasmania</td>
<td>262</td>
<td>53</td>
<td>49%</td>
<td>9%</td>
</tr>
</tbody>
</table>
Tropics (0° - 23°)  Subtropics (23° - 35°)  Mid-latitudes (35° - 50°)  High latitudes (50° - 70°)
Treatment

- Cholecalciferol 25 mcg
  - Equivalent to vitamin D₃ 1000 IU
  - Ostelin available without prescription {11-16 cents/capsule}
  - Not subsidised by PBS
- Daily requirements: 800-1000 IU
- Moderate deficiency (12.5-25 nmol/L)
  - 3000-5000 IU daily for 6-12 weeks
  - Maintenance dose of 1000-2000 IU daily
- Severe deficiency (<12.5 nmol/L)
  - 100,000 IU intramuscular dose, available in Australia?
  - Replenish stores quickly and effectively

Treatment

• Conflicting advice about starting treatment with a loading dose
  – Possibly an option for those with history of falls/fractures

• Sensible sun
  – 5-15 minutes (face/upper limbs) 4-6 times/week
# Recommended Sun Exposure

<table>
<thead>
<tr>
<th>Region</th>
<th>Duration (minutes)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Summer</td>
<td>Winter</td>
</tr>
<tr>
<td>Cairns</td>
<td>6-7</td>
<td>9-12</td>
</tr>
<tr>
<td>Townsville</td>
<td>5-7</td>
<td>9-13</td>
</tr>
<tr>
<td>Brisbane</td>
<td>6-7</td>
<td>15-19</td>
</tr>
<tr>
<td>Sydney</td>
<td>6-8</td>
<td>26-28</td>
</tr>
<tr>
<td>Melbourne</td>
<td>6-8</td>
<td>32-52</td>
</tr>
<tr>
<td>Adelaide</td>
<td>5-7</td>
<td>25-38</td>
</tr>
<tr>
<td>Perth</td>
<td>5-6</td>
<td>20-28</td>
</tr>
<tr>
<td>Hobart</td>
<td>7-9</td>
<td>40-47</td>
</tr>
</tbody>
</table>

*Aust Prescr 2010;33:103-6*
Monitoring

• Serum 25(OH)D levels checked at 3-4 month intervals

• Toxicity
  – Excessive oral intake
    • Maximum daily dose of 4000 IU daily

*Pharmacotherapy* 2012; 32 (4): 354-382
Pharmacist’s Role

• Reinforce that data for vitamin D use beyond fall prevention and osteoporosis is not conclusive

• Identify those at high risk for deficiency and recommend screening

• Counsel on vitamin D dosage regimen

• Answer questions about vitamin D

  – www.nps.org.au/health_professionals/order_free_information/order_now
Atypical Antipsychotics
The Basics…

• Indications: schizophrenia, bipolar disorder, dementia, psychotic depression, autism, developmental disorders
• Receptors involved: dopamine, serotonin
• Expectations: improve positive and negative symptoms
• Some believe better tolerated and more effective than first generation antipsychotics
• Shift from typical antipsychotics
• Potential for misuse in a variety of populations

Diabetes Care 2004;27(2):596-601
# Atypical Antipsychotics

## Available in Australia
- Amisulpride (Solian)
- Aripiprazole (Abilify)
- Asenapine (Saphris)
- Clozapine (Clozaril, Clopine)
- Olanzapine (Zyprexa)
- Paliperidone (Invega)
- Quetiapine (Seroquel)
- Risperidone (Risperdal)
- Sertindole (Serdolect)
- Ziprasidone (Zeldox)

## Available in United States
- Majorit of list same as Australia, PLUS
- Iloperidone (Fanapt)
- Lurasidone (Latuda)
Use in Australia

• Atypical antipsychotics cost the PBS $334.4 million in 2007
• Olanzapine most commonly prescribed
  – Older age group for women
  – Younger age group for men
• Concern over off-label use in elderly with dementia
  – EPS and cerebrovascular events
• Question why younger women appear undertreated
  – Similar prevalence in both genders
Figure 1. Trends in selected antipsychotic drug utilization (defined daily dose (DDD) per 1000 population per day) 2002–2007 (risperidone is shown for both total and oral only use).
Figure 2. Drug utilization (defined daily dose (DDD) per 1000 population per day) for olanzapine, risperidone, quetiapine and haloperidol by gender and age (≥ 20 years) in 2006.
Problems with Patient Adherence

- Non-adherence may occur in up to 50% of patients
- Adverse effects impact quality of life
  - May cause greater distress than symptoms of illness
- One first step is assessing the patient
  - Difficult to determine if adverse effect or symptom of the illness
- Some may have an attitude that they are powerless to do anything

Aust NZ J Psychiatry 2000;34:814-821
Adverse Drug Reactions

- Extrapyramidal symptoms
  - Dystonic reactions and/or pseudoparkinsonism
  - Initiation of drug or dose increase
    - Anticholenergic treatment: benztropine, diphenhydramine
  - Akathisia
  - Tardive dyskinesia
    - Irreversible long-term effect (related to lifetime dose)
    - May need to d/c antipsychotic or switch to another Rx
  - EPS risk
    - Risperidone > olanzapine = ziprasidone > quetiapine > clozapine

Schizophr Bull 2010;36(1):71-93
Adverse Drug Reactions

• Prolactin Elevation
  – Main concern is bone mineral density
  – Associated sexual side effects
  – Risk
    • Risperidone = paliperidone > olanzapine > ziprasidone
      > quetiapine = clozapine > aripiprazole

• Sedation
  – Tolerance can develop over time
  – Olanzapine, clozapine, quetiapine most ADRs
  – May be a positive for some patients

*Schizophren Bull* 2010;36(1):71-93
Adverse Drug Reactions

• QTc prolongation
  – Monitor for CV risk factors
  – Risk
    • Ziprasidone > quetiapine = risperidone = olanzapine >> clozapine
• Neuroleptic malignant syndrome
  – Can be life-threatening
  – Risk factors: high doses, rapidly escalating dose increases, IM injections
  – D/C agent and provide supportive care
• Clozapine
  – LOTS…

Schizophr Bull 2010;36(1):71-93
Adverse Drug Reactions

• Weight gain
  – Rapid increase in weight in first few months
    • After 10 weeks, 0.5-5 kg
  – Hunger and satiety altered due to drug actions
  – Check weight at each clinic visit
  – If patient gains ≥5% of initial weight, consider changing the medication

• Weight gain risk
  • Clozapine = olanzapine > risperidone = paliperidone = quetiapine > aripiprazole = ziprasidone = amisulpride
Adverse Drug Reactions

• Metabolic effects
  – Risk with/without drug therapy
  – Blood pressure, lipids, blood glucose
  – Weigh risks and benefits
    • Consider patient history and risk factors
      – Increased weight
      – Waist circumference
      – Lipids
      – Glucose
      – Blood pressure

  – Counsel patients, family, caregivers about signs/symptoms of diabetes and DKA

*Schizophr Bull* 2010;36(1):71-93
Adverse Drug Reactions

• Metabolic effects
  – Can recommend switch to different Rx
    • Cross-titration appears to be safest
  – Adding medication to promote weight loss
  – Depending on patient, consider lifestyle changes without adjusting therapy if appropriate

<table>
<thead>
<tr>
<th>Highest Risk</th>
<th>Moderate Risk</th>
<th>??</th>
<th>Lowest Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>clozapine</td>
<td>risperidone</td>
<td>asenapine</td>
<td>aripiprazole</td>
</tr>
<tr>
<td>olanzapine</td>
<td>paliperidone</td>
<td>iloperidone</td>
<td>ziprasidone</td>
</tr>
<tr>
<td></td>
<td>quetiapine</td>
<td>lurasidone</td>
<td></td>
</tr>
</tbody>
</table>

Other Considerations

• Polytherapy with antipsychotics
  – Not supported by clinical evidence
  – Risk of additional ADRs and non-adherence

• CATIE trials
  – Compared atypical and typical antipsychotics
    • Atypicals might have fewer advantages over first-generation antipsychotics than had been generally thought
    • Olanzapine had the best efficacy outcome
    • After treatment failure with an atypical antipsychotic, the most efficacious second-line medication is clozapine

• PORT Guidelines
  – Recommend monotherapy at lowest effective dose

# Monitoring Schedule

<table>
<thead>
<tr>
<th>Monitoring Parameter</th>
<th>APA/ADA Consensus Conference</th>
<th>WA Psychotropic Drugs Committee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain</td>
<td>BMI: baseline; 4, 8, 12 weeks; then quarterly&lt;br&gt;Waist circumference: baseline and annually</td>
<td>BMI: every visit or every 3 months (review tx if BMI &gt;30 kg/m²)&lt;br&gt;Waist/hip ratio: every visit or every 3 months (review tx if ratio is &gt;1.0 in males; &gt;0.8 in females)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Fasting glucose: baseline; 12 weeks; annually</td>
<td>Fasting glucose: baseline; monthly for 6 months; 3-6 monthly; when changing therapy</td>
</tr>
<tr>
<td>Lipids</td>
<td>Fasting lipid panel: baseline; 12 weeks; then every 5 years</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Blood pressure: baseline; 12 weeks; then annually</td>
<td>Blood pressure: frequently during dose titration</td>
</tr>
</tbody>
</table>

*Diabetes Care* 2004;27(2):596-601  
www.watag.org.au
Factors Impacting Medication Choice

• Nature of patient’s condition
• Specific target signs and symptoms
• Past history of drug response (safety and efficacy)
• Patient preference
• Medication effectiveness
• Comorbidities and other medications
• Availability of alternate dosage forms
• Need for special monitoring
• Cost of medication

Diabetes Care 2004;27(2):596-601
Pharmacist’s Role

- Provide education about ADRs: patients, physicians, caregivers...
- Weigh risks/benefits in making antipsychotic drug therapy selections
- Recognize monitoring schedule for metabolic syndrome-related ADRs
- Goal is to improve quality of life and facilitate adherence to medication
Questions?

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