The Treatment of Patients with Bipolar Disorder and its effects on diabetes

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Disclosures

I provided paid educational sessions and received honoraria from:
- Sanofi aventis, Lilley Diabetes, Astra Zenica & Lundbeck
Objective

• Review what is ‘Bipolar I Disorder’
• Discuss the issues and types of medication needed for Bipolar 1
• Review if there is a link between diabetes and Bipolar.
• Have an understanding of how this condition and the risks associated with it can impact on diabetes care.
What is bipolar disorder?

- Bipolar I Disorder is one of the most severe forms of mental illness
- It is also known as manic depression and is characterized by extreme mood swings between high (mania) and low (depression.)
- Bipolar can be so pronounced it interferes with everyday activities and cause uncharacteristic and/or inappropriate behaviour
The signs are diverse and can be difficult to identify. Some people swing rapidly whilst others may experience long periods between their mood swings. It can be triggered by stressful events. It is important people understand the triggers.
Diagnostic criteria for bipolar disorder (based on DSM-IV)

**Bipolar I disorder**: Presence, or history of, at least one manic (or mixed) episode

**Bipolar II disorder**: Presence, or history of, at least one major depressive episode and at least one hypomanic episode (with no history of a manic or mixed episode)

The symptoms are not attributable to physical illness or physiological effects of a drug or other substance and are not better accounted for by another psychiatric disorder

<table>
<thead>
<tr>
<th>Manic symptoms</th>
<th>Depressive symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated, expansive, or irritable mood</td>
<td>Depressed mood</td>
</tr>
<tr>
<td>Increased activity that is goal directed or</td>
<td>Markedly reduced interest in nearly all activities</td>
</tr>
<tr>
<td>psychomotor agitation</td>
<td>Increased or decreased appetite or weight</td>
</tr>
<tr>
<td>Reduced need for sleep</td>
<td>Insomnia or hypersomnia</td>
</tr>
<tr>
<td>Excessive involvement in pleasurable activities with likely adverse consequences</td>
<td>Psychomotor retardation or agitation</td>
</tr>
<tr>
<td>Inflated self esteem or grandiosity</td>
<td>Fatigue or loss of energy</td>
</tr>
<tr>
<td>Increased or pressured speech</td>
<td>Feelings of excessive worthlessness or guilt</td>
</tr>
<tr>
<td>Flight of ideas or racing thoughts</td>
<td>Impaired concentration or indecisiveness</td>
</tr>
<tr>
<td>Distractibility</td>
<td>Recurrent thoughts or actions of death or suicide</td>
</tr>
</tbody>
</table>

**Manic episode**: At least four manic symptoms including altered mood that persists for at least a week and causes marked functional impairment, hospital admission, or there are psychotic symptoms

**Hypomanic episode**: As for manic episode but less severe; symptoms persist for at least four days and functioning is noticeably altered but not enough to lead to hospital admission or to greatly impair function. There are no psychotic symptoms

**Major depressive episode**: Five or more persistent depressive symptoms (which must include depressed mood or diminished interest), which last for at least two weeks and occur on most days, and that cause serious distress or functional impairment

**Mixed episode**: Persistent mood symptoms for at least a week that meet criteria (apart from duration) for both a manic and major depressive episode, which occur at different times or rapidly alternate

**Psychotic symptoms**: These may occur during manic episodes in bipolar I disorder (but by definition not during hypomanic episodes) and during depressive episodes in either bipolar I or bipolar II disorder

*The World Health Organization classification ICD-10 does not distinguish between bipolar I and bipolar II disorder and requires another mood episode in addition to a single manic episode*
• The condition has a high rate of recurrence and if untreated, it has an approximately 15% risk of death by suicide.

• It is the third leading cause of death among people aged 15-24 years, and is the 6th leading cause of disability (lost years of healthy life) for people aged 15-44 years in the developed world.

• Disability Rights Commission. Equal treatment: closing the gap, July 2006
Bipolar I Disorder is a life-long disease and runs in families but has a complex mode of inheritance. Family, twin and adoption studies suggest genetic factors. About half of all patients with Bipolar I Disorder have one parent who also has a mood disorder, usually Major Depressive Disorder. If both parents have Bipolar I Disorder, the child has a 50%-75% chance of developing a mood disorder.

However

• Virtually anyone can develop bipolar 1 disorder.
• Most people will develop symptoms in their teens or early 20th and nearly everyone will have develop it before the age of 50 years.
Key Priorities for bi-polar

• Assessment, recognition and diagnosis
• Treating with appropriate medication to prompt stability
• Working with family to resolve questions and discuss concerns.
• Work with healthcare teams for support with
  • Social interactions
  • Work & employment
  • Carers
  • Health & Well-being
During acute episodes of illness refer all patients with known or suspected bipolar disorder to specialist care (or if currently under a specialist team ensure access to care) to:

- Treat the acute episode
- Assess and manage risk
- Confirm the diagnosis (if necessary)
- Establish or review the longer term management plan
Patients with an established diagnosis of bipolar disorder should remain under specialist care if

- Have difficulty engaging with services or adhering to treatment
- Have frequent relapses, poorly controlled illness, or persistent symptoms
- Have severe psychiatric comorbidity, including anxiety disorders or alcohol or drug misuse
- Require management of suicide risk or risk to others
Stable patients with bipolar disorder not currently under specialist care should be referred if they:

- Are considering getting pregnant or if they are pregnant
- Have side effects or complications from treatment that may require a change in drugs
- Are considering altering or stopping treatment
- Require access to specific psychotherapies
The aim for mental health care:

• Mental well being is a dynamic state in which the individual is able to develop their potential, work productively and creatively, build strong and positive relationships with others and contribute to their community.

• It is enhanced when an individual is able to fulfil their personal and social goals and achieve a sense of purpose in society.
A Holistic Approach to Care

Mental Health

Physical Wellbeing

Social Engagement

Dr HL Millar. Personal communication, 2005
Political Drivers
The Importance Of Physical Health And Holistic Management in Mental Illness

- More likely than the general public to develop some significant health problems
- Die up to 10-15 years younger than the general public, from potentially preventable health problems
- Die faster than the rest of the population once they have health problems

Related to Disease

- Live with poorer physical health and face the challenge of symptoms of mental health
  - Subjective distress
  - Reduced cognitive ability
  - Loss of interpersonal skills
  - Anxiety and depression
  - Frequent relapses.
Causes of increased diabetes in mental health

• Reduced activity and motivation.
• Dietary choices/ sugar cravings medication induced.
• Obesity
• Dysfunctional reward systems
• Hypercorticolaemia

It’s that simple........... Or is it????????
General non-drug risk factors for diabetes

- social factors and trends
- evolution gone wrong
- severe mental illness
  - schizophrenia
  - bipolar disorder
- family history
- obesity now
- age and sex
- comorbidity
- sedentary, unhealthy lifestyle
- poor diet
- stress
- smoking
- ethnicity
- hypertension

Including pharma watchfulness, better detection, monitoring and reporting!!

• People with schizophrenia are naturally predisposed to develop diabetes, even before they have been given antipsychotic medication.

• Diabetes and disturbed carbohydrate metabolism may be an integral part of schizophrenia.
Diabetes, obesity and mental illness: beyond schizophrenia

Prevalence of diabetes in patients with Axis I psychiatric disorders.

Gaining weight is easy – losing it is not

Body Weight Simulator  http://bwsimulator.niddk.nih.gov
The general obesity issues

• As specialists in diabetes we are all too well informed of the issues with obesity
  • Food choices
  • Activity levels
  • Cooking ability
  • Etc… etc…. Etc… etc…

• However…..
Obesity, diabetes and mental illness

- US: 60% overweight (1/2 obese) - ↑risk:
  - diabetes
  - CVD
  - cancer

- Psychiatric population: increased risk
  - mental illness: schizophrenia / bipolar → increased diabetes
  - non-drug risk factors
  - drug factors: treatment itself?
Stress and weight gain

• chronic activation of HPA axis: metabolic changes

• drug-naïve first episode schizophrenics: \( \uparrow \) corticotrophin and cortisol (Ryan et al, 2004)

• older antipsychotics: cushingoid syndrome
Comorbidity
Dual diagnosis in inner London


- Smoking 60%
- Problem drinking 27%
- Non-alcohol substance use 68% (lifetime)
  - majority: multiple drug use
    - cannabis
    - amphetamines/stimulants (cocaine, ecstasy), LSD
    - opiates (heroin), barbiturates and BDZ
    - PCP, angel dust
Cannabis, a major factor for weight gain

Д-9-tetrahydrocannabinol endocannabinoids
↓
CB(1) and CB(2) receptors
↓
↑ ingestive behaviour
↓
↑ weight

new drugs to ↓ weight: CB(1) antagonists or inverse agonists in the pipeline.

*Remember Rimonabant ........*
Cannabis, a major factor for weight gain

- Mendelson (1979) Postgraduate Medicine, 60: 111-5.
Second generation medication

Issues have been highlighted……

• weight gain
• hyperglycaemia
• new onset type 2 diabetes
• ketoacidosis
## Treatments

### Antipsychotics
- Amisulpride (Solian)
- Aripiprazole (Abilify)
- Asenapine (Sycrest)
- Olanzapine (Zyprexa)
- Quetiapine (Seroquel)
- Risperidone (Risperdal)

### Mood Stabilisers
- Carbamazepine
- Lamotrigine
- Lithium
- Sodium Valproate
Antipsychotics

• Antipsychotic drugs work by changing the activity of chemicals that transmit messages in the brain.
• The main chemical they work on are Dopamine. (selectively)
• The $5-HT_{2A}$ receptor that belongs to the serotonin receptor family
• Antipsychotic drugs are also known as ‘neuroleptics’ and (misleadingly) as ‘major tranquillisers’.
• Antipsychotic drugs generally tranquillise without impairing consciousness and without causing paradoxical excitement but they should not be regarded merely as tranquillisers. (the tranquillising effect is of secondary importance.)

• In the short term they are used to calm disturbed patients whatever the underlying psychopathology, which may be schizophrenia, mania, toxic delirium, or agitated depression.

• Antipsychotic drugs are used to alleviate severe anxiety but this be a short-term measure.
Antimanic drugs

• These are used to control acute attacks and to prevent recurrence of episodes of mania or hypomania.

• Long-term treatment should continue for at least two years from the last manic episode and up to five years if the patient has risk factors for relapse.

• Anti-depressant drugs may also be required for the co-existing depression.
Multicentre, prospective study of antipsychotic effectiveness in schizophrenia

Metabolic, symptomatic, neurocognitive and functional outcomes

Baseline data - crude prevalence of metabolic syndrome (APA, 2005):

- overall > 40%
- females > 51%
- males > 36%

(Clinical Antipsychotic Trials of Intervention Effectiveness trial)
Diabetes, obesity and mental illness: beyond bipolar


Effects of antipsychotics on fat deposition and changes in leptin and insulin level

- 46 drug-naïve Chinese schizophrenics:
  - 25 males, 19 females, mean age 26.5, vs. controls

- Assessed before and 10 weeks of treatment:
  - Risperidone 4.8 mg (n = 30)
  - Chlorpromazine 480 mg (n = 15)

- Measures:
  - abdominal fat: magnetic resonance
  - blood glucose, insulin, leptin and lipids

Results: antipsychotic treatment for 10 weeks

- ↑ intra-abdominal fat
- ↑ subcutaneous fat
- ↑↑ leptin (x3)
- ↑ lipids
- ↑ non-fasting glucose
- no change in insulin levels

Along with fat deposition, the increase in levels of fasting lipids and in non-fasting glucose may provide early signs of drug-induced progression towards the metabolic syndrome.
A number of receptors have an effect on weight gain.

- $H_1$ receptor antagonism
- $5-HT_{2C}$ receptor antagonism
- $\beta_3$ adrenoceptor antagonism
- galanin
- neuropeptide YY
- leptin
- pancreas beta-cell toxicity
Leptin and antipsychotics

Leptin, is an adipocyte-derived cytokine, crosses the blood–brain barrier to act on many regions of the central nervous system (CNS). It participates in the regulation of energy balance, inflammatory processes, immune regulation, synaptic formation, memory condensation, and neurotropic activities.
Antipsychotics: Relative adverse effects – a rough guide

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sedation</th>
<th>Weight gain</th>
<th>Extrapyramidal</th>
<th>Anticholinergic</th>
<th>Hypotension</th>
<th>Prolactin increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+++</td>
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<tr>
<td>Aripiprazole</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Asenapine</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>_</td>
<td>-</td>
<td>+/-</td>
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<tr>
<td>Chlorpromazine</td>
<td>+++</td>
<td>++</td>
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<td>+++</td>
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<tr>
<td>Clozapine</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Olanzapine</td>
<td>++</td>
<td>+++</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Quetiapine</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>-</td>
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<tr>
<td>Risperidone</td>
<td>+</td>
<td>++</td>
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<td>+</td>
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<td>+++</td>
</tr>
</tbody>
</table>

Diabetes risk in the bipolar population

- Increased prevalence across the general population
- Exacerbating factors
  - sedentary lifestyle
  - junk food
  - smoking
  - cannabis abuse
- cohort effect in bipolar disorder
  - genetic association
  - secondary neuroendocrine changes
- better clinical monitoring and ‘pharma’-attentiveness
- antipsychotic-induced symptom improvement
- antipsychotic-induced weight gain
Multifactorial aetiology of diabetes risk in severe mental illness

- Antipsychotics
- Neuro-endocrine changes
- Severe mental illness
- Chronically mentally ill
- General population

- Prevalence

- Genetic association
- Family history

- ↑ Obesity
- ↑ Detection

- Sedentary lifestyle
- Unhealthy diet
- Cannabis

- HPA
- Chronic cortisol

- Leptin receptors
- 5-HT2C receptors
- Pancreas
- Peripheral effects

Cumulative effects
## Schedule for physical monitoring

<table>
<thead>
<tr>
<th>Test</th>
<th>Initial check</th>
<th>Annual check</th>
<th>Anti psychiatric</th>
<th>Lithium</th>
<th>Valproate</th>
<th>Carbamazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>TFTs</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>Start and every 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFTs</td>
<td>✓</td>
<td></td>
<td></td>
<td>Start and every 6 months</td>
<td>Start and every 6months</td>
<td>Start and every 6months</td>
</tr>
<tr>
<td>Renal function</td>
<td>✓</td>
<td></td>
<td></td>
<td>Start and every 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBC</td>
<td>✓</td>
<td></td>
<td></td>
<td>Only if clinically indicated</td>
<td>Start and every 6months</td>
<td>Start and every 6months</td>
</tr>
<tr>
<td>Plasma Glucose</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>Start and at 3 months (and 1 month for olanzapine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid</td>
<td>✓</td>
<td>Over 40s only</td>
<td></td>
<td>Start and at 3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>Initial check</td>
<td>Annual check</td>
<td>Anti psychotic</td>
<td>Lithium</td>
<td>Valproate</td>
<td>Carbamazepine</td>
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<tr>
<td>Blood Pressure</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight &amp; Height</td>
<td>√</td>
<td>√</td>
<td>Start and every 3 months for first year</td>
<td>Start and if there is weight gain</td>
<td>Start and every 6 months</td>
<td>Start and every 6 months</td>
</tr>
<tr>
<td>Smoking</td>
<td>√</td>
<td>√</td>
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<tr>
<td>Prolactin</td>
<td></td>
<td></td>
<td>Risperidone only</td>
<td></td>
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<tr>
<td>Children &amp; adolescents only</td>
<td></td>
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<tr>
<td>ECG</td>
<td></td>
<td></td>
<td>Review CVD risk factors</td>
<td>Review CVD risk factors</td>
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<tr>
<td>If indicated by CVD risk factors</td>
<td></td>
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<tr>
<td>Drug screening &amp; C X-ray</td>
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<tr>
<td>Review clinical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum drug level</td>
<td></td>
<td></td>
<td>1 week after initiation and 1 week after every dose change</td>
<td>To review if ineffective</td>
<td>Every 6 months</td>
<td></td>
</tr>
<tr>
<td>EEG, MRI or CT scan</td>
<td>To rule our differential diagnosis</td>
<td></td>
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</tr>
</tbody>
</table>
A Holistic Approach to Care

Mental Health

Physical Wellbeing

Social Engagement
To conclude

• Bi-polar is a significant mental health condition.
• The diagnosis of diabetes and bipolar have increased health risks.
• There are treatments available; however recognition that some have worse outcomes for diabetes than others.
• Mental health services are there for your help.
Thank you

Any questions??