Licensed Indications
Olanzapine is indicated for the treatment of schizophrenia, moderate to severe manic episodes and for the prevention of recurrence in patients with bipolar disorder.

Any Exclusions
Olanzapine is not licensed for the treatment of behavioural problems in dementia.

Therapeutic Summary
NICE guidance for schizophrenia does not specifically recommend an antipsychotic class or individual antipsychotic as first-line treatment for schizophrenia but instead emphasises the importance of patient choice (taking into account adverse effects, and carer views where possible). NICE guidance for bipolar disorder recommends an antipsychotic (e.g. olanzapine) for managing mania or hypomania. Although unlicensed, NICE recommends olanzapine as an option for moderate to severe bipolar depression (with or without fluoxetine).

Olanzapine is a second generation antipsychotic which binds to a variety of receptors including dopamine, (D1, D2, D3, D4, D5), serotonin 5HT2A/2C, 5HT3, 5HT6, cholinergic muscarinic receptors, alpha-1 adrenergic and histamine H1 receptors.

Medicines Initiation
Olanzapine should not be started in primary care unless in consultation with a specialist. Monitoring is the responsibility of the secondary care team for at least the first 12 months or until the person’s condition has stabilised.

Products Available
Available as generic 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg standard tablets, and 5mg, 10mg, 15mg, 20mg orodispersible tablets.

A long-acting depot injection is also available (ZypAdhera) although this has been classified as RED on the Joint Formulary.

Dosages and route of administration
- Initial starting dose for: schizophrenia 10mg once daily; acute mania 15mg once daily (monotherapy), 10mg once daily (in combination with other antimanic agents); for preventing recurrence in bipolar disorder initial dose 10mg/day, or if olanzapine employed for acute mania, continue with same dose for prophylaxis.
- Dosage may then be adjusted on the basis of clinical response/side-effects within the range 5-20mg daily.
- A lower starting dose of 5mg per day should be considered in those over 65 years of age when clinical factors warrant, in patients with renal and/or hepatic
impairment or in patients who have multiple factors (e.g. female, elderly, non-smoking status) which may result in slower metabolism. See "Precautions".

- Oro-dispersible tablets are bio-equivalent to standard tablets and should be placed in the mouth or dispersed in a full glass of water or other suitable beverage (e.g. orange / apple juice, milk or coffee) immediately before administration.
- Oro-dispersible tablets are no faster acting than the standard tablet preparation. Olanzapine is not absorbed sublingually or buccally but dispersed in the saliva which is when swallowed is absorbed via the gastrointestinal tract.
- If switching, other antipsychotics should gradually be discontinued whilst olanzapine is initiated.

**Duration of Treatment**
As stated in NICE guidance\(^2\), following the treatment of an acute episode of schizophrenia, the risk of relapse is high if antipsychotic medication is stopped within 1 to 2 years. For bipolar disorder treatment should be reviewed within 4 weeks of resolution of manic symptoms and if continued, reviewed every 3-6 months\(^3\).

**Monitoring Requirements and Responsibilities**
During antipsychotic treatment, improvement in the patient’s clinical condition may take several days to some weeks. During this period the patient should be closely monitored. Please note that the occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders, and in some cases has been reported early after initiation or switch of antipsychotic therapy. High risk patients should be closely supervised during treatment.

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**General Monitoring Requirements**

*Ask about compliance and side effects at every consultation.*

All patients should be offered an annual physical health check by their GP (more often if clinically indicated). A copy should be sent to the care coordinator and psychiatrist and put in the secondary care notes.

*Particular attention should be given to:*

<table>
<thead>
<tr>
<th>Lifestyle factors</th>
<th>Smoking, alcohol, substance misuse, diet, level of physical activity, sexual health, contraceptive advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to treatment</td>
<td>Including changes in symptoms and behaviour</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td>Blood pressure and lipids</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>hyperglycaemia/diabetes and hyperprolactinaemia</td>
</tr>
<tr>
<td>Other side-effects</td>
<td>Such as weight gain (monitor BMI, waist circumference), sexual dysfunction, lethargy, emergence of extrapyramidal movement disorder side-effects (including tardive dyskinesia)</td>
</tr>
</tbody>
</table>

**Schedule for Physical Monitoring\(^2,3\)**

<table>
<thead>
<tr>
<th></th>
<th>Initial Baseline Health Check &amp; During First Year by secondary care</th>
<th>Annual Health Check By GP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid Function</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Liver Function</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>
Explicit Criteria for Review and Discontinuation of Olanzapine

Acute withdrawal symptoms have been rarely described after abrupt discontinuation of olanzapine e.g. sweating, insomnia, tremor, anxiety, nausea and vomiting. It is recommended that olanzapine is discontinued gradually – ideally over a 3-4 week period – and that signs and symptoms of relapse are monitored for at least 2 years after discontinuation.²³

<table>
<thead>
<tr>
<th>SIDE EFFECTS</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very Common (≥10%)</strong></td>
<td></td>
</tr>
<tr>
<td>Weight gain and increased appetite</td>
<td>Encourage a healthy balanced diet and regular exercise. Monitor and refer to a dietician and/or Consultant if appropriate.</td>
</tr>
<tr>
<td>Increase in prolactin levels</td>
<td>Refer to Consultant. If symptomatic (eg sexual dysfunction, galactorrhoea, gynaecomastia, disturbances of menstrual cycle/amenorrhoea, consider dose reduction or switching to an alternative atypical antipsychotic.</td>
</tr>
<tr>
<td>Somnolence / Drowsiness</td>
<td>Give as a single night-time dose. Consider temporary dose reduction. Advise patients not to drive/operate machinery if affected.</td>
</tr>
<tr>
<td>Orthostatic hypotension and dizziness</td>
<td>Initiate slowly. Consider dose reduction or dividing the dose. Advise patient to take time to stand up. Advise patient not to drive.</td>
</tr>
<tr>
<td><strong>Common (≥1% and &lt;10%)</strong></td>
<td></td>
</tr>
<tr>
<td>Elevated glucose, glucosuria</td>
<td>Manage according to local diabetes guidelines. Refer to Consultant if appropriate.</td>
</tr>
<tr>
<td>Elevated cholesterol and triglyceride levels.</td>
<td>Manage according to local guidelines.</td>
</tr>
<tr>
<td>Extrapyramidal symptoms</td>
<td>Consider a dose reduction. An anticholinergic (eg procyclidine) maybe helpful for symptoms of stiffness, tremor and dystonia.</td>
</tr>
<tr>
<td>Akathisia (may include physical &amp; /or psychological restlessness)</td>
<td>Refer to Consultant. A reduction in dose, discontinuation or change to an alternative atypical antipsychotic maybe required. Review use of anticholinergics as these can worsen symptoms.</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>Refer to Consultant if appropriate.</td>
</tr>
<tr>
<td>Leucopenia, neutropenia</td>
<td>Check FBC if sore throat, fever or other signs of infection. Refer to Consultant if appropriate.</td>
</tr>
<tr>
<td>Constipation</td>
<td>Recommend a high fibre diet, good fluid intake and regular exercise. Consider a bulk-forming laxative.</td>
</tr>
</tbody>
</table>
Oedema
Refer to Consultant if appropriate.

Dry mouth
Recommend chewing sugar-free gum. If severe and persistent consider prescribing artificial saliva.

Raised ALT/AST/AP levels
Usually transient and asymptomatic, especially in early treatment. See ‘Cautions’. Monitor and refer back to Consultant if appropriate.

Uncommon (≥ 0.1% and <1%)

Tardive dyskinesia
Refer to Consultant. A reduction in dose, discontinuation or change to an alternative atypical antipsychotic maybe required. Review use of anticholinergics as these can worsen Tardive Dyskinesia. Please note that these symptoms can temporarily deteriorate or can even arise after abrupt discontinuation of treatment

Others:
QT prolongation, bradycardia, photosensitivity reaction, alopecia, urinary incontinence, increased creatine phosphokinase levels, increased total bilirubin, thromboembolism, dystonia, seizures (especially where history exists or risk factors for seizures reported, development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, urinary hesitination/incontinence/retention

Rare (≥ 0.01% and < 0.1%)

Neuroleptic malignant syndrome (NMS) - hyperthermia, muscle rigidity, autonomic instability, altered consciousness, ↑CPK levels
Very rare. Discontinue ALL antipsychotic(s). If suspected immediate referral to an acute hospital is required.

Others:
Ventricular tachycardia / fibrillation, sudden death, thrombocytopenia, pancreatitis, rhabdomyolysis, priapism, hepatitis, hypothermia. Discontinuation reactions (e.g. sweating, insomnia, tremor, anxiety, nausea, vomiting) if stopped abruptly so withdraw gradually ideally over 4 weeks.

Contraindications
- Patients with a known hypersensitivity to any ingredient or known risk of narrow angle glaucoma

Precautions
- Pregnancy, breastfeeding.
- Patients below the age of 18 years.
- Olanzapine is not licensed for the treatment of dementia-related psychosis and/or behavioural disturbances. Refer to local BPSD guidelines
- Antipsychotic use maybe associated with an increased risk of venous thromboembolic events (VTE), all possible risk factors for VTE should be identified before and during antipsychotic treatment and preventative measures undertaken
- Consider carefully the risk of cerebrovascular events before treating any patient with a previous history of stroke or Transient Ischaemic Attack or high baseline risk of cerebrovascular disease (e.g. hypertension, diabetes, smoking, atrial fibrillation).
- Patients with prostatic hypertrophy or paralytic ileus and related conditions
- Patients with diabetes and patients at risk require appropriate clinical monitoring - hyperglycaemia and/or development or exacerbation of pre-existing diabetes occasionally associated with ketoacidosis or coma has been reported, including some fatal cases
- Renal impairment

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DATE APPROVED BY THE NOTTINGHAMSHIRE APC: January 2015
Author: John Lawton
Patients with low leucocyte and/or neutrophil counts, patients with bone marrow depression (caused by, for example, medicines including chemotherapy, radiation therapy, concomitant illness)

Patients with eosinophilic conditions or with myeloproliferative disease

Patients with a history of seizures or subject to factors that may lower seizure threshold.

Patients with raised ALT and/or AST, hepatic impairment or taking potentially hepatotoxic drugs. Where hepatitis has been diagnosed, olanzapine should be discontinued

Patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia, and hypomagnesaemia.

Dopamine agonist-associated psychosis in Parkinson’s disease

Clinically Relevant Medicine Interactions and Their Management

Smoking and carbamazepine increase metabolism of olanzapine via CYP1A2 enzyme induction

Use with caution in those who consume alcohol or receive medicines that can cause central nervous system depression

Dopamine agonists / anti-Parkinsonian medicines (effects antagonised)

Medicines known to increase the QTc interval

Medicines known to cause neutropenia eg carbamazepine, sodium valproate

CYP1A2 inhibitors e.g. ciprofloxacin / fluvoxamine may inhibit the metabolism of olanzapine

Please consult the manufacturers Summary of Product Characteristics (SPC) for further information.

References

1. Zyprexa SPC, Last updated 04/06/2014
2. NICE Clinical Guideline 178, Psychosis and schizophrenia in adults. February 2014
3. NICE Clinical Guideline 185, Bipolar Disorder. September 2014
5. NAPC Managing Behavioural and Psychological Problems in Patients with Diagnosed or Suspected Dementia. January 2012 (pending review).