Treatments for patients with schizophrenia

Stephen Bleakley and Marion Wetherill give an overview of current treatment options and guidelines for schizophrenia

Schizophrenia is a distressing psychiatric disorder with symptoms and long-term prognosis varying considerably between individuals. It encompasses a broad range of symptoms, including altered perception, thoughts, mood and behaviour. Although there continues to be public prejudice against people with schizophrenia many symptoms are commonly seen in the general population. For example, the lifetime prevalence of hallucinations is between 10 and 15 per cent and delusions of having special powers occurs in 4 to 8 per cent, even in the absence of a psychiatric disorder. The label “schizophrenic” adds to prejudice and should no longer be used. In truth, there are good long-term outcomes for half of sufferers. Many patients, when well, are no different from people without the illness and even those with resistant and recurrent symptoms, if given appropriate treatment and support, can lead productive lives and be integrated into society.

Schizophrenia is typically divided into acute and chronic phases. The acute phase is characterised by “positive” symptoms, such as hallucinations, paranoia, delusions and behavioural problems. It is these symptoms that often lead to admission to a psychiatric unit. The chronic phase can include reduced concentration, social withdrawal, apathy and bizarre ideas. This phase is harder to treat and can last for years. Intermittent attacks of acute illness can occur, usually depending on how successful treatment with an antipsychotic has been. A common symptom of schizophrenia is having a lack of insight to any illness. This can be a particular challenge for health professionals trying to persuade patients to take long-term antipsychotics. The formal symptomatic criteria for diagnosing schizophrenia is provided by the World Health Organization in the International Classification of Diseases currently in its 10th edition (see Panel 1, p102).

The lifetime risk of schizophrenia is between 0.4 and 1.4 per cent. The condition is encountered in all cultures across the world, with men and women equally affected. It is referred to as “youth’s greatest disabler” by the WHO because it normally occurs between the ages of 15 to 35 years. The mortality risk in those with schizophrenia is 50 per cent higher than the general population, partly as a result of a high risk of suicide — about 10 per cent will commit suicide — and the high burden of physical health problems associated with the illness and antipsychotic medication.

There is no exact cause of schizophrenia and most research suggests a complex mixture of factors is involved. These include genetic predisposition, environmental factors, such as living in an urban environment, altered brain structure, substance misuse and biochemical theories, such as the dopamine hypothesis. The dopamine hypothesis suggests that schizophrenia is caused by dopamine overactivity in the pre-frontal cortex. To support this is the observation that all antipsychotics block or partially block (as with aripiprazole) dopamine receptors, specifically D2 receptors, which are the most abundant dopamine receptors in the brain. Other neurotransmitters are also likely to be involved but are less understood. These include serotonin, glutamate and gamma-aminobutyric acid.

Non-drug treatments.

Treatment with antipsychotics continues to be the principle intervention for people with schizophrenia. However, a number of psychological approaches have been gaining favour and evidence over the past few years. They are usually tried in combination with antipsychotics or in those who are not adequately treated by antipsychotics alone. In the recently updated National Institute for Health and Clinical Excellence guidelines on schizophrenia, arts therapy, cognitive behavioural therapy (CBT) and family interventions were recommended. Arts therapy promotes self-expression and is particularly recommended for those with prominent negative symptoms. CBT enables patients to explore their thoughts and feelings towards symptoms and promotes alternative ways of coping with them. CBT should be available to all...
Panel 1: Symptomatic criteria for schizophrenia ICD-10

The normal requirement for a diagnosis of schizophrenia is that a minimum of one clear symptom (or two if less clear) from the groups listed below as (a) to (d), or symptoms from at least two groups listed (e) to (h), should have been clearly present for most of the time for a month or longer.

(a) Thought echo, thought insertion or withdrawal and thought broadcasting
(b) Delusions of control, influence or passivity, clearly described body or limb movements, or specific thoughts, actions or sensations (delusional perceptions)
(c) Hallucinatory voices giving a running commentary on the patient’s behaviour or discussing the sufferer among themselves, or other types of hallucinatory voices coming from some part of the body
(d) Persistent delusions of other kinds that are impossible and not related to cultural background or ethnicity
(e) Persistent hallucinations in any modality, when accompanied by fleeting or half-formed delusions without clear mood content, or persistent overvalued ideas, or when occurring every day for weeks or months
(f) Breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech or neologisms
(g) Catatonic behaviour, such as excitement, posturing, waxy flexibility (a tendency to remain in an immobile posture), negativism and stupor
(h) Negative symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses, usually resulting in social withdrawal and lowering of social performance (It must be clear that these are not due to depression or to antipsychotic medication.)

(i) A significant and constant change in the overall quality of some aspects of personal behaviour, manifest as a lost of interest, aimlessness, idleness, a self-absorbed attitude and social withdrawal

Adverse effects

Potential adverse effects of the antipsychotics vary considerably across the class (see Panel 2). This is in part, due to which neurotransmitters the antipsychotic affects.

EPSE Dopamine blocking adverse effects include EPSEs and hyperprolactinaemia. These adverse effects depend on the affinity of the antipsychotic for striatal D2 receptors. They are routinely seen with typical antipsychotics. This is not without exception and atypical antipsychotics — clozapine, olanzapine, amisulpride and risperidone — appeared slightly more effective than others.3 Clozapine is rather unique in terms of efficacy and has been conclusively shown to be more effective in treatment resistant schizophrenia than other antipsychotics. In some patients with a severe and enduring illness it probably represents the best hope for recovery. The NICE guidelines on schizophrenia reflect these recent studies and now recommend that any antipsychotic could be used for treating the condition after considering the individual drug side effects and the views of the service user and carer if appropriate.

Antipsychotics

Antipsychotics are broadly divided into typical (first generation) and atypical (second generation). This classification is loosely based on the fact that the atypical antipsychotics are, supposedly, less likely to cause extrapyramidal side effects (EPSE) that are also referred to as movement disorders. However, this can be confusing because the antipsychotics vary considerably and are not homogenous. Many so called atypical drugs, for example, have typical-like side effects even within the normal therapeutic range. It is, therefore, probably more accurate to consider the antipsychotics as one group but with distinct differences between individual drugs.

To add to the debate, there have been a number of recent meta-analyses and naturalistic studies questioning the efficacy differences between the typical and atypical antipsychotics. In the two largest and most recent meta-analyses only four atypical antipsychotics — clozapine, olanzapine, amisulpride and risperidone — appeared slightly more effective than others.4 Clozapine is rather unique in terms of efficacy and has been conclusively shown to be more effective in treatment resistant schizophrenia than other antipsychotics. In some patients with a severe and enduring illness it probably represents the best hope for recovery. The NICE guidelines on schizophrenia reflect these recent studies and now recommend that any antipsychotic could be used for treating the condition after considering the individual drug side effects and the views of the service user and carer if appropriate.

Panel 2: Adverse effects of antipsychotic drugs6,7

<table>
<thead>
<tr>
<th>Drug</th>
<th>EPSE</th>
<th>Anticholinergic</th>
<th>Weight gain</th>
<th>Diabetes</th>
<th>Raised lipids</th>
<th>QTC prolongation</th>
<th>Raised prolactin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-*</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Clozapine</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Flupenthixol</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Quetiapine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Risperidone</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Sulpiride</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

* = unknown or limited data available; - = very low incidence; + = low; ++ = moderate; +++ = high
EPSEs include pseudoparkinsonism, dystonia, akathisia and tardive dystonias. In pseudoparkinsonism effects similar symptoms to Parkinson’s disease, such as bradykinesia, tremor and rigidity, are seen. Dystonias are a sustained or repeated involuntary muscular contraction, which, if it includes the laryngeal muscles, is an emergency requiring immediate intramuscular or intravenous procyclidine or benzatropine. Akathesia presents as a compulsion to keep moving, Tardive dyskinesias are late appearing, often irreversible, involuntary movements. Symptoms vary in severity and muscles affected but may include a constant protruding tongue, lip smacking or neck twisting.

Treating EPSEs includes either reducing or stopping the offending antipsychotic or switching to an atypical antipsychotic. If the drug cannot be switched, as is often the case with depot antipsychotics, prescribing an anticholinergic such as procyclidine or orphenadrine can be useful in pseudoparkinsonism and dystonias. Anticholinergics are not considered useful in akathesia and should be avoided in tardive dyskinesia because symptoms can worsen.

**Hyperprolactinaemia**

Hyperprolactinaemia is caused by dopamine blockade in the tuberoinfundibular pathway in the brain. Most antipsychotics cause a prolonged increase in prolactin with the exception of amisulpride, clozapine, olanzapine and quetiapine. Many patients appear asymptomatic even with a high prolactin level while others experience sexual dysfunction, menstrual changes, milk production (galactorrhoea) and breast enlargement (gynaecomastia). Persistently high prolactin over many years has been associated with a reduced bone mineral density and a higher rate of breast cancer. With the exception of menstrual changes these adverse effects can be seen in men and women.

**Neuroleptic malignant syndrome**

Neuroleptic malignant syndrome (NMS) is a rare (incidence of 0.01–0.02 per cent) but potentially fatal adverse reaction related to dopamine blockade. It is thought to be caused by the sudden blockade of dopamine in the temperature regulatory centres found in the hypothalamus and corpus striatum. It is characterised by fever, severe muscle rigidity and mental state changes. Immediate medical attention and cessation of the offending antipsychotic are essential in suspected NMS. NMS requires death results in 10 per cent of cases. Those who are newly prescribed a potent dopamine blocker should be aware of NMS, as is often the case with depot antipsychotics, pre-treatment. NMS can affect patients’ self-esteem as well as increase their risk of type 2 diabetes. An increased risk of diabetes with antipsychotics, however, can also be seen in the absence of weight gain.

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Further reading

- The Choice and Medication website offers peer-reviewed, patient friendly advice on all medicines used in mental illness. www.choiceandmedication.org.
- Rethink is a leading National charity for anyone affected by a serious mental illness (www.rethink.org; tel 020 7840 3188).

**Panel 3: Suggested monitoring with antipsychotics**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Every six months to yearly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea and electrolytes</td>
<td>Urea and electrolytes</td>
</tr>
<tr>
<td>Liver function test</td>
<td>Liver function test</td>
</tr>
<tr>
<td>Full blood count*</td>
<td>Full blood count</td>
</tr>
<tr>
<td>Lipid profile</td>
<td>Lipid profile</td>
</tr>
<tr>
<td>Weight and body mass index</td>
<td>Weight and BMI†</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>Blood pressure and pulse</td>
</tr>
<tr>
<td>Blood pressure and pulse</td>
<td>Fasting plasma glucose</td>
</tr>
<tr>
<td>Electrocardiogram††</td>
<td>ECG (if clinically indicated)</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Prolactin (if symptomatic)</td>
</tr>
</tbody>
</table>

Three months after initiation

| Lipid profile |
| Weight and BMI‡ |
| Fasting plasma glucose |
| Blood pressure and pulse§ |

* A full blood count is mandatory for clozapine, every week for the first 18 weeks, then every two weeks for one year then every four weeks; † For all antipsychotics, with cardiovascular risk factors and those on haloperidol, pimozide, sertindole and clozapine; ‡ Weight, BMI and fasting plasma glucose should be measured more frequently with olanzapine and clozapine; § Blood pressure and pulse should be repeated frequently during first few months of treatment.

**Panel 4: General advice from NICE updated schizophrenia guidelines**

- GPs and other primary healthcare professionals should monitor the physical health of people with schizophrenia at least once a year.
- Before starting antipsychotic medication, the patient should be offered an ECG if specified in the drug’s summary of product characteristics, if he or she has cardiovascular risks or if he or she is being admitted to inpatient facilities.
- The drug should be chosen by the service user and healthcare professional together, considering potential side effects of the individual antipsychotic.
- The antipsychotic should be tried for at least four to six weeks at an optimum dose before switching to an alternative choice.
- Clozapine should be offered to people with schizophrenia whose illness has not responded adequately to at least two different antipsychotic drugs, one of which should be an atypical antipsychotic.
CONTINUING PROFESSIONAL DEVELOPMENT

Other

Other adverse effects associated with antipsychotics include sedation, anticholinergic effects (eg, constipation, urinary retention and confusion), a reduced seizure threshold, hypotension and QT prolongation. The QT interval represents the time taken to complete the depolarisation and repolarisation cycle of the ventricles. QT prolongation is suggested as a risk factor for torsade de points and sudden cardiac death, although other factors may also be involved. The risk of QT prolongation and other cardiovascular complications have prompted NICE in their latest guidance to recommend an electrocardiogram for all those starting on an antipsychotic as an inpatient or in those with any underlying cardiovascular risk.

Despite these adverse effects antipsychotics remain the principle intervention for treatment and long-term prevention of schizophrenia.

Depot preparations

Antipsychotics are available as liquids, oral dispersible tablets and both short and long-acting intramuscular injections. Depot preparations of atypical antipsychotics produce a predictable release of drug over two to five weeks.

Risperidone is the only atypical long acting injection (LAI) currently available. The drug is encapsulated in a polymer to form microspheres and the formulation takes three to four weeks to break down, meaning there is a three-week lag after administration, before risperidone is released. Therefore patients on risperidone LAI require additional antipsychotic cover for the first three or four weeks of treatment which is usually tapered down and stopped over the following two weeks. Olanzapine LAI has recently been granted a European medicine licence but will not be launched in the UK until mid 2010. There are reports of an unpredictable post-injection syndrome (where similar symptoms to olanzapine overdose are seen) so it will be restricted to use in health care facilities only and are insulated in a polymer to form microspheres and the injection (LAI) currently available. The drug is encapsulated with another antipsychotic such as amisulpride or aripiprazole.10 Where clozapine cannot be used (eg, in those refusing blood tests) higher than usual doses of some antipsychotics are occasionally tried.

Combining antipsychotics or using higher than usual doses carries a significant health risk, with additive adverse effects.

Summary

People with schizophrenia experience distressing symptoms which may alienate them from family, friends and society. Antipsychotics remain the mainstay of treatment but are associated with a multitude of adverse effects, which, accompanied by the illness itself, can increase cardiovascular risk and reduce life expectancy. Regular and timely health monitoring is essential for all those suffering schizophrenia.

General advice from the updated NICE guidelines appears in Panel 4 (p103).

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist’s CPD portfolio.

1. Help reduce the stigma associated with mental illness by downloading materials and a toolkit from the time to change website. Find out if there is a local event happening near you.

2. Check if your clients on antipsychotics have had an annual physical healthy check?

3. Discuss adherence and potential adverse effects with a client on a long term antipsychotic.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?

References


