



*National Institute for
Clinical Excellence*

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N0106 1P 60k May 02 (ABA)

**Guidance on
the use of
newer (atypical)
antipsychotic
drugs for the
treatment of
schizophrenia**

Technology Appraisal No. 43

Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia

Issue Date: June 2002

Review Date: May 2005

Ordering Information:

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This guidance is written in the following context:

This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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11 Strand
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Web: www.nice.org.uk

ISBN: 1-84257-180-X

Published by the National Institute for Clinical Excellence

June 2002

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Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia

This section (Section 1) constitutes the Institute's guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia. The remainder of the document is structured in the following way:

- 2 Clinical need and practice
- 3 The technologies
- 4 Evidence
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- 6 Further research
- 7 Implementation
- 8 Related guidance
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Appendix A: Appraisal Committee

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A bi-lingual summary is available from our website at www.nice.org.uk or by telephoning 0870 1555 455 and quoting the reference number N0107.

Mae crynodeb ar gael yn Gymraeg ac yn Saesneg ar ein gwefan yn www.nice.org.uk neu drwy ffonio 0870 1555 455 gan ddyfynnu cyfeirnod N0107.

1. Guidance

- 1.1 The choice of antipsychotic drug should be made jointly by the individual and the clinician responsible for treatment based on an informed discussion of the relative benefits of the drugs and their side-effect profiles. The individual's advocate or carer should be consulted where appropriate.
- 1.2 It is recommended that the oral atypical antipsychotic drugs amisulpride, olanzapine, quetiapine, risperidone and zotepine are considered in the choice of first-line treatments for individuals with newly diagnosed schizophrenia.
- 1.3 The oral atypical antipsychotic drugs listed in Section 3.3 should be considered as treatment options for individuals currently receiving typical antipsychotic drugs who, despite adequate symptom control, are experiencing unacceptable side effects, and for those in relapse who have previously experienced unsatisfactory management or unacceptable side effects with typical antipsychotic drugs. The decision as to what are unacceptable side effects should be taken following discussion between the patient and the clinician responsible for treatment.
- 1.4 It is not recommended that, in routine clinical practice, individuals change to one of the oral atypical antipsychotic drugs if they are currently achieving good control of their condition without unacceptable side effects with typical antipsychotic drugs.
- 1.5 In individuals with evidence of treatment-resistant schizophrenia (TRS), clozapine should be introduced at the earliest opportunity. TRS is suggested by a lack of satisfactory clinical improvement despite the sequential use of the recommended doses for 6 to 8 weeks of at least two antipsychotics, at least one of which should be an atypical.
- 1.6 A risk assessment should be performed by the clinician responsible for treatment and the multidisciplinary team regarding concordance with medication, and depot preparations should be prescribed when appropriate.
- 1.7 Where more than one atypical antipsychotic drug is considered appropriate, the drug with the lowest purchase cost (taking into account daily required dose and product price per dose) should be prescribed.
- 1.8 When full discussion between the clinician responsible for treatment and the individual concerned is not possible, in particular in the management of an acute schizophrenic episode, the oral atypical drugs should be considered as the treatment options of choice because of the lower potential risk of extrapyramidal symptoms (EPS). In these circumstances, the individual's carer or advocate should be consulted where possible and appropriate. Although there are limitations with advanced directives regarding the choice of treatment for individuals with schizophrenia, it is recommended that they are developed and documented in individuals' care programmes whenever possible.

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- 1.9 Antipsychotic therapy should be initiated as part of a comprehensive package of care that addresses the individual's clinical, emotional and social needs. The clinician responsible for treatment and key worker should monitor both therapeutic progress and tolerability of the drug on an ongoing basis. Monitoring is particularly important when individuals have just changed from one antipsychotic to another.
 - 1.10 Atypical and typical antipsychotic drugs should not be prescribed concurrently except for short periods to cover changeover of medication.

- 2.1 Schizophrenia is a syndrome characterised by a broad range of cognitive, emotional and behavioural problems. The symptoms of schizophrenia are classified into positive and negative symptoms. Positive symptoms relate to an exaggeration of normal functions and commonly include hallucinations (principally auditory), delusions, disorganised speech/formal thought disorder and disorganised/ bizarre/catatonic behaviour. Negative symptoms relate to the loss of normal functions and include flattening of mood, emotional apathy, social withdrawal, lack of motivation and loss of pleasure.
- 2.2 Although some potential causes have been identified, the aetiology of schizophrenia remains poorly understood. The course of the disease is variable, and is influenced by the psychosocial environment of the individual. Schizophrenia can follow a relapsing and remitting course or it can be chronic and progressive. The chronic, progressive course occurs particularly in individuals who have a later onset of the disease.
- 2.3 The prevalence of the condition is estimated at between 0.2% and 1% in the general population and it is thought to be slightly more common in men. The onset of schizophrenia can occur at any age, but it is rare before puberty and peaks in late adolescence and the early twenties.
- 2.4 The most common form of presentation is an initial acute episode of floridly positive symptoms followed by the emergence and persistence of negative symptoms. Some individuals with schizophrenia have predominantly acute episodes associated with little long-term impairment. Studies suggest that about 20% of individuals with schizophrenia recover, about 70% have relapsing disease and about 10% are seriously disabled by the disease.
- 2.5 The management of schizophrenia involves a comprehensive package of care with the aim of addressing all of the person's clinical, emotional and social needs. Pharmacological management centres on antipsychotic drugs, although drug therapy currently accounts for less than 5% of total healthcare costs for schizophrenia.
- 2.6 In a substantial proportion of first episodes of acute psychosis, individuals' first contact with mental health services results in 'sectioning' under the Mental Health Act (1983). This severely limits their ability to be involved in treatment decisions, which in these circumstances are often made on their behalf by the clinician responsible for treatment.
- 2.7 Individuals experiencing a first episode of schizophrenia are known to be more susceptible to the adverse effects of treatment, which may subsequently impact on their adherence to future therapy and on their longer-term prognosis.

- 3.1 Dopamine is a monoamine neurotransmitter involved in diffuse regulatory systems in the brain. Antipsychotic drugs are considered to act by interfering with dopaminergic transmission in the brain, particularly by blockage of dopamine D2 receptors. Antipsychotic drugs may also affect cholinergic, alpha-adrenergic, histaminergic and serotonergic receptors.
- 3.2 Antipsychotics are generally subdivided into two classes: the older 'typical' agents (neuroleptics) such as haloperidol and chlorpromazine, and the newer 'atypical' agents. The parameters for the separation of these two classes are not clearly defined or agreed, but generally include the propensity to cause extrapyramidal side effects (EPS) and elevation of prolactin, the efficacy in individuals with schizophrenia who are resistant to treatment and the efficacy against negative symptoms.
- 3.3 The British National Formulary (BNF) currently lists amisulpride (Solian, Sanofi-Synthelabo), olanzapine (Zyprexa, Lilly), quetiapine (Seroquel, AstraZeneca), risperidone (Risperdal, Janssen-Cilag, Organon), sertindole (Serdolect, Lundbeck) and zotepine (Zoleptil, Orion) as atypical antipsychotics. In 2001, the Committee for Proprietary Medicinal Products (CPMP) recommended that the marketing authorisation for sertindole be re-instated. Because of ongoing concerns over cardiovascular safety, the CPMP recommended that sertindole should only be used in individuals with schizophrenia who are intolerant to at least one other antipsychotic agent (typical or atypical). It is only available direct from the manufacturers through registered centres and ongoing monitoring is a prerequisite of its use. All individuals receiving sertindole will therefore be required to enrol in post-marketing studies. It is anticipated that the CPMP will review this requirement in 2003, giving consideration to the new safety data; prescribers should therefore consult the manufacturers for further information.
- 3.4 Clozapine (Clozaril, Novartis) is also listed by the BNF as an atypical antipsychotic but its use is restricted to individuals with schizophrenia who are unresponsive or intolerant to 'conventional' antipsychotic therapy. It is the only atypical to currently have a product licence in this patient group. Non-responsiveness is defined in the Summary of Product Characteristics (SmPC) as 'a lack of satisfactory clinical improvement despite the use of adequate doses of at least two marketed neuroleptics prescribed for adequate durations'. Intolerance is defined in the SmPC as the 'impossibility to achieve adequate benefit with conventional neuroleptic drugs because of severe and untreatable neurological adverse reactions (extrapyramidal symptoms or tardive dyskinesia)'.
- 3.5 All antipsychotic agents are associated with side effects but the profile and clinical significance of these varies among individuals and drugs. These may include EPS (such as parkinsonism, acute dystonic reactions, akathisia and tardive

dyskinesia), autonomic effects (such as blurring of vision, increased intra-ocular pressure, dry mouth and eyes, constipation and urinary retention), increased prolactin levels, seizures, sedation and weight gain. Cardiac safety is also an issue because several antipsychotics have been shown to prolong ventricular repolarisation, which is associated with an increased risk of ventricular arrhythmias. Routine monitoring is a pre-requisite of clozapine use because of the risk of neutropenia and agranulocytosis. Prescribers are therefore required to ensure that effective ongoing monitoring is maintained if alternative brands of clozapine become available.

- 3.6 Individuals with schizophrenia consider the most troublesome side effects to be EPS, weight gain, sexual dysfunction and sedation. EPS are easily recognised, but their occurrence cannot be predicted accurately and they are related to poor prognosis. Akathisia is also often missed or misdiagnosed as agitation. Of particular concern is tardive dyskinesia (orofacial and trunk movements), which may not be evident immediately, is resistant to treatment, may be irreversible, and may worsen on treatment withdrawal. Sexual dysfunction can result from drug-induced hyperprolactinaemia; it is likely to be an under-reported side effect of antipsychotic treatment, as discussion of this issue is often difficult to initiate.
- 3.7 One of the main controversies regarding the use of antipsychotic drugs is the appropriate dose. High doses (particularly of the typicals) are commonly used in clinical practice. However, the prevalence of some side effects has been linked to the dose, the level of exposure and the duration of treatment, which has led to the conclusion that many individuals are exposed to unnecessarily high and potentially dangerous levels of treatment.
- 3.8 Antipsychotic drugs may take several weeks to control symptoms, and whilst some dosage adjustment may be required, the minimum effective dose possible should be used. Doses should not be normally increased above the licensed dose range when no therapeutic benefit is achieved. High doses may increase the likelihood of side effects and thus may limit benefit by reduction in concordance. Other antipsychotics should be considered rather than resorting to the use of higher than standard doses.

4

Evidence

4.1 *Clinical effectiveness*

- 4.1.1 One hundred and seventy-two randomised controlled trials (RCTs) were reviewed, which included evidence from 29 head-to-head trials of atypical agents. In addition, 53 other studies were considered, which were either case-control, had more than 2 years of follow up, or included more than 2000 participants. The overwhelming majority of RCTs were 4 to 8 weeks long, with 31 being of over 6 months duration.

- 4.1.2 The conclusions that can be drawn from the majority of the studies are limited because of the lack of long-term follow up, high attrition rates and the inadequacy of collection and reporting of adverse events. In addition, haloperidol, which may be associated with a higher incidence of EPS than other typicals, was used as the comparator in many of the trials. The generalisability of individual study results was limited by the exclusion of elderly people as well as individuals with TRS, predominantly negative symptoms, learning disabilities, co-morbid depression and substance abuse disorders.
- 4.1.3 The evidence considered suggests that the atypical antipsychotics are at least as efficacious as the typical agents in terms of overall response rates. There is evidence to suggest that they may vary in their relative effects on positive and negative symptoms and relapse rates. However, there are inadequate data to enable separate evaluation of the overall impact of individual atypicals on schizophrenia.
- 4.1.4 All atypicals are associated with a reduced incidence of EPS compared to typicals in the short to medium term (up to 26 weeks). In the long term (26 weeks or longer) there are limited data to support a reduced incidence of EPS with some of the atypicals. Additionally, there is little evidence on comparative rates of tardive dyskinesia between the atypicals or between the typical and atypicals, due to the paucity of long-term trial data. Although this may be due to the difficulties of conducting long-term studies in this patient group, this remains an important clinical research question. Whilst there is some evidence to suggest that the side-effect profiles of individual atypicals may differ, definitive statements relating to differences between them are difficult to make because of variations in the evidence base for individual drugs and in the length of treatment follow up.
- 4.1.5 The use of clozapine is restricted to individuals with schizophrenia who are unresponsive to or intolerant of 'conventional' antipsychotic therapy. Currently, it is the only atypical to have a product licence in this patient group. There is evidence that in individuals who have not responded to previous antipsychotic therapy, clozapine is associated with fewer relapses and greater clinical improvement than typical agents. Although rates of movement disorders are lower, clozapine is associated with increased drowsiness, fits and excess salivation.

4.2 Cost effectiveness

- 4.2.1 Thirty-one published economic evaluations of antipsychotic medication in the treatment of schizophrenia met the inclusion criteria for the review. Of these, 23 studies were based on clinical trials and eight involved modelling. One study compared sertindole with olanzapine and haloperidol. The remaining studies compared clozapine, olanzapine or risperidone with each other, with typicals, or with treatment before an atypical antipsychotic was given. None of the published studies looked at amisulpride, quetiapine or zotepine. All of the manufacturers' submissions contained assessments of the cost-effectiveness of their drug, mostly compared with haloperidol. The majority of studies included in the review used a cost-minimisation framework and only three studies used a cost-utility approach.
- 4.2.2 Cost-minimisation analysis is used in instances where there is evidence to suggest that the new technology is at least as effective as the technology it is seeking to replace. Using this approach, differences in cost are reported rather than estimates of cost per additional unit of clinical effect such as QALYs. Given that the evidence reviewed suggests that the atypical antipsychotics are at least as efficacious as the typical agents, the Committee considered that cost-minimisation analysis was an adequate form of evaluation of cost-effectiveness for the atypical antipsychotic drugs versus the typicals.
- 4.2.3 Comparison of the results from different studies was difficult as the studies used different assumptions regarding the outcome of treatment, different categories of cost, different time periods of treatment and information drawn from a variety of countries.
- 4.2.4 The economic model submitted by the manufacturer of clozapine showed that using this drug reduced the annual cost of treating individuals with treatment-resistant schizophrenia by approximately £7000 compared with treating these individuals with typical or other atypical antipsychotic drugs. Although annual drug expenditure increased by approximately £2000, this cost was more than offset by reducing the annual length of inpatient stays by 47 days.
- 4.2.5 The majority of studies showed that the higher costs of purchasing the atypicals were more than offset by reductions in inpatient stays. Cost savings were generally estimated to average £1000 per patient year, with an approximate range of £250 to £5000 per patient year.

4.3 Considerations

- 4.3.1 The Committee reviewed the large number of studies of the use of atypical antipsychotics, both clinical and economic, that were included in the assessment report and submissions. The evidence provided was sufficient to allow the Committee to evaluate the place of the atypicals in the treatment of schizophrenia relative to the older typical drugs. However, the Committee considered that as most of the studies were generally of short duration and inadequately reported it was not able to address the issue of differentiation between the various atypicals.
- 4.3.2 On balance, the Committee concluded that more widespread use of the atypical antipsychotics would benefit individuals with schizophrenia because of the likelihood of a reduced incidence of EPS.
- 4.3.3 However, there remain some outstanding issues that the appraised evidence was unable to address satisfactorily. These include the incidence of side effects of individual atypicals, especially in the long term, and the overall robustness of the efficacy estimates.

5

Implications for the NHS

- 5.1 Direct treatment costs of schizophrenia in England and Wales are estimated to be in excess of £1 billion, or around 3% of total NHS expenditure. Hospitalisations account for the majority of this expenditure (and for approximately 5% of total NHS inpatient expenditure), while drug costs account for 5% only of the direct costs of schizophrenia.
- 5.2 Assuming an adult population of 42 million, a prevalence for schizophrenia of 1 per 100, and that 50% of individuals with schizophrenia are diagnosed and receive antipsychotic medication, it can be estimated that in England and Wales there are 210,000 individuals who are potentially eligible for treatment with atypical antipsychotics. Approximately 30% of these individuals are classified as resistant to treatment (see Section 5.3). It is estimated that approximately 69% of individuals treated for schizophrenia receive typical antipsychotics at an average cost of £70 per person per year. If 60% of these individuals were switched to atypicals (excluding clozapine) at an average cost of £1220 per person per year (range £700 to £1900), the increase in drug costs would be in the region of £70 million per annum. Drug costs are based on BNF doses and prices.
- 5.3 Assuming a prevalence of 30% for TRS, 63,000 individuals are eligible for treatment with clozapine. Assuming that 60% respond to clozapine and approximately 13,500 individuals are already prescribed clozapine, there are an additional 24,000 potential clozapine users. Using information on resource use from the Clozaril Patient Monitoring Service, the additional

cost of clozapine is estimated to be £2920 (£2990 – £70) per person per year for individuals changing to clozapine from typicals and £1770 (£2990 – £1220) for individuals changing from treatment with other atypicals to clozapine. Taking this into account, the increase in drug costs of using clozapine for eligible individuals with TRS would be approximately £41 million per annum. This cost may reduce if a generic form of clozapine becomes available and the estimate does not take into account possible additional costs of clozapine plasma level monitoring, which is currently £20 per test.

- 5.4 Adoption of atypicals as first-line therapy is expected to involve a shift away from inpatient care to residential or community care, which are less expensive. However, overall savings are unlikely to be realised in the short to medium term because other patient groups may conceivably use the inpatient facilities. In the long term, the additional drug costs described in Sections 5.2 and 5.3 may be offset by cost reductions elsewhere.
- 5.5 In 1990/91, indirect costs of schizophrenia in the UK were estimated to be at least £1.7 billion. If the use of atypicals enables more individuals with schizophrenia to live independently and return to work, there could be substantial savings to the economy as a whole.

6

Further research

- 6.1 The Committee recognised the importance of reduction of suicide risk as a result of effective treatment. It was made aware of new data becoming available assessing the earlier use of clozapine, and the impact of this on suicide risk.
- 6.2 More long-term head-to-head RCTs of the atypical antipsychotic drugs are required, especially trials that include individuals in their first episode of schizophrenia, younger individuals and the elderly.
- 6.3 In view of the inability of interventional studies to provide answers to many of the key questions concerning the effects of atypicals, more high quality observational studies are required. In addition, observational studies would provide information on the use of atypical antipsychotics in individuals with co-morbidities and substance abuse disorders.
- 6.4 Studies are needed to assess the outcome of 'informed choice' particularly in terms of treatment adherence, treatment relapse, quality of life and cost-effectiveness.
- 6.5 Research is required to address individuals' own experiences of treatments.
- 6.6 Overall, the quality of conduct and reporting of clinical trials in schizophrenia has improved markedly over the last few years. However, future studies of antipsychotic treatments should be longer-term and should give detailed reports of reasons for discontinuation of treatment, adverse events and data on cardiac functioning. Adequate wash-out periods should be allowed before the commencement of study medications.

6.7 Authors and peer reviewers of reports relating to antipsychotic drugs should ensure that manuscripts adhere to the CONSORT (Consolidated Standards of Reporting Trials) statement for all outcomes. Reports should also include full details of randomisation procedures, allocation concealment, blinding procedures and details of participants' baseline characteristics. Statistical analyses for trials designed to show differences should be based on the 'intention-to-treat' principle.

7.1 All clinicians treating individuals with schizophrenia should review their current practice of prescribing antipsychotic drugs in line with the guidance set out in Section 1.

7.2 To enable clinicians to audit their own compliance with this guidance, it is recommended that a system for identifying individuals with schizophrenia and the drugs prescribed for them be maintained at a local level.

7.3 An individual with schizophrenia should have a comprehensive package of care that addresses his or her clinical, emotional and social needs. The package of care should be based on a complete and current assessment carried out by the clinician responsible for treatment and the multidisciplinary team, including a risk assessment that considers concordance with medication, and should include an up-to-date treatment plan.

7.4 To measure compliance locally with the guidance set out in Section 1, the following criteria should be used. Further details of suggestions for audit are presented in Appendix D.

- If an individual with schizophrenia is currently being treated with a typical antipsychotic drug and is experiencing good control of the condition without unacceptable side effects, as determined through discussion between the individual and the clinician responsible for treatment, current drug therapy is ordinarily maintained.
- An oral atypical antipsychotic drug is considered for prescription in the following circumstances:
 - an individual is newly diagnosed with schizophrenia
 - an individual's symptoms are adequately controlled on a typical antipsychotic but he or she is experiencing unacceptable side effects
 - an individual is in relapse but has previously experienced unsatisfactory management or unacceptable side effects with typical antipsychotic drugs.
- An individual with TRS is prescribed clozapine at the earliest opportunity, within its licensed indications.

- When an individual with schizophrenia is able to discuss with the clinician responsible for treatment about drug therapy:
 - the individual and the clinician decide jointly, with consultation with the individual's advocate or carer where appropriate or possible, on the choice of antipsychotic drug based on an informed discussion of the relative benefits of each drug and its side-effect profile
 - an advance directive is developed and documented in the individual's care programme, whenever possible, on the choice of antipsychotic to be prescribed in the circumstance of an acute psychotic episode.
- When an informed discussion between the clinician responsible for treatment and an individual with schizophrenia is not possible, an oral atypical antipsychotic is prescribed, in consultation with the individual's carer or advocate where possible and appropriate.
- Monitoring both therapeutic progress and tolerability of the drug on an ongoing basis is carried out by the clinician responsible for treatment and the individual's key worker.
- Depot preparations are prescribed when appropriate.
- Atypical and typical antipsychotic drugs are not prescribed concurrently except for short periods to cover changeover of medication.

8

Related guidance

- 8.1 It is anticipated that NICE Guidance on the use of electroconvulsive therapy for schizophrenia will be published in late 2002 and NICE clinical guidelines on the management of schizophrenia in December 2002.

9

Review of guidance

- 9.1 This guidance will be reviewed in May 2005.

Andrew Dillon
Chief Executive

June 2002

APPENDIX A

Appraisal Committee members

The Appraisal Committee is a statutory committee whose members sit for 3 years. Two meetings are held per month and the majority of members attend one or the other. Declared interests may also exclude a member from individual technology appraisals. The Committee are supplemented by technology specific experts as indicated in Appendix B.

Dr Jane Adam
Radiologist
St George's Hospital

Dr Sunil Angris
General Practitioner
Waterhouses Medical Practice

Professor David Barnett (Chair)
Professor of Clinical Pharmacology
University of Leicester

Professor Carol Black
Consultant Physician
Royal Free Hospital & University
College London

Professor John Brazier
Health Economist
University of Sheffield

Professor Bruce Campbell
Consultant Surgeon
Royal Devon & Exeter Hospital

Professor Mike Campbell
Statistician
Institute of General Practice & Primary
Care, Sheffield

Dr Karl Claxton
Health Economist
University of York

Professor Jack Dowie
Health Economist
School of Hygiene & Tropical Medicine

Dr Paul Ewings
Statistician
Taunton & Somerset NHS Trust

Sally Gooch
Director of Nursing
Mid-Essex Hospital Services Trust

Professor Trisha Greenhalgh
Professor of Primary Health Care
University College London

Liz Heyer
Chief Executive
Barnet & Chase Farm Hospitals
NHS Trust

Dr Diane Ketley
Research into Practice Programme
Leader
NHS Modernisation Agency

Ruth Lesirge
Patient Representative
Director, Mental Health Foundation

Dr George Levvy
Patient Representative
Chief Executive, Motor Neurone
Disease Association

Dr Gill Morgan
CEO
North & East Devon Health Authority

Professor Miranda Mugford
Health Economist
University of East Anglia

Siân Richards
General Manager
Cardiff Local Health Group

Professor Philip Routledge
Professor of Clinical Pharmacology
University of Wales College of
Medicine

Dr Rhiannon Rowsell
Pharmaceutical Physician
AstraZeneca UK Ltd

Dr Stephen Saltissi
Consultant Cardiologist
Royal Liverpool University Hospital

Professor Andrew Stevens
Professor of Public Health
University of Birmingham

Professor Ray Tallis
Consultant Physician
Hope Hospital, Salford

Professor Mary Watkins
Head of Institute of Health Studies
University of Plymouth

Dr Norman Waugh
Public Health Consultant
University of Southampton

APPENDIX B

Sources of evidence

The following documentation and opinion was made available to the Committee.

- a. **Assessment Report:**
prepared by the NHS Centre for Reviews and Dissemination, Centre for Health Economics, University of York (*A Rapid and Systematic Review of Atypical Antipsychotics in Schizophrenia*, 21 September 2001)
- b. **Manufacturer/ sponsor submissions:**
 - AstraZeneca
 - Janssen-Cilag Ltd
 - Lilly
 - Lundbeck
 - Novartis Pharmaceuticals (UK) Ltd
 - Orion Pharma (UK) Ltd
 - Pfizer Ltd
 - Sanofi-Synthelabo
- c. **Professional/specialist group submissions:**
 - Royal College of Psychiatrists
 - British Association for Psychopharmacology
 - Institute of Psychiatry
 - Pharmaceutical Schizophrenia Initiative
 - UK Psychiatric Pharmacy Group
- d. **Patient group submissions:**
 - The Zito Trust
 - Mental Health Charities in NICE (MHCiN) comprising of:
 - National Schizophrenia Fellowship (NSF)
 - Mind
 - Manic Depression Fellowship
 - SANE
 - Voices Forum
 - Mental After Care Association (MACA)
 - National Schizophrenia Fellowship
 - Mind
 - The Schizophrenia Association of Great Britain (SAGB)
 - SANE
- e. **Trade associations submissions:**
 - There were no submissions for this category
- f. **External expert and patient advocate submissions:**
 - Dr David Taylor, Chief Pharmacist, South London and Maudsley NHS Trust and Honorary Senior Lecturer, Institute of Psychiatry
 - Professor Thomas Barnes, Professor of Clinical Psychiatry, Imperial College School of Medicine
 - Professor Robert Kerwin, Professor of Clinical Neuropharmacology, Institute of Psychiatry
 - Emma Harding and Dennis Preece on behalf of MHCiN

APPENDIX C

Patient information

Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia

The patient information in this appendix has been designed to support the production of your own information leaflets. You can download it from our website at www.nice.org.uk where it is available in English and Welsh. If you would like printed copies of the leaflets please ring the NHS Response Line on 0870 1555 455 and quote reference number N0108 for the English patient leaflet and N0109 for the bi-lingual patient leaflet.

What is NICE guidance?

The National Institute for Clinical Excellence (NICE) is a part of the NHS. It produces guidance for both the NHS and patients on medicines, medical equipment, diagnostic tests and clinical and surgical procedures and where they should be used.

When the Institute evaluates these things, it is called an appraisal. Each appraisal takes around 12 months to complete and involves the manufacturers of the drug or device, the professional organisations and the groups who represent patients.

NICE was asked to look at the available evidence on newer (atypical) antipsychotic drugs and provide guidance that would help the NHS in England and Wales decide where they should be used in the treatment of schizophrenia.

What is schizophrenia?

Schizophrenia has a wide range of symptoms. These include hallucinations (often hearing voices), delusions (false ideas that do not respond to reasoned argument), muddled speech and thoughts, and, very rarely, catatonia (prolonged rigid postures or outbursts of repeated movement). People with schizophrenia may also experience 'flattening' of their moods, which means that they don't have any strong emotions, don't feel motivated to do anything and become detached from their social situation.

Schizophrenia can follow a 'relapsing and remitting course', which means that symptoms come and go, or it can be 'chronic and progressive', which means that symptoms are persistent (are present all the time) and get worse over time. Schizophrenia can occur at any age, but it is rare before puberty and most common in late adolescence and the early twenties. It affects between about 2 and 10 people in every 1000 in the general population. Schizophrenia is thought to be slightly more common in men than in women.

The treatment and care of people with schizophrenia involves a comprehensive package of care that aims to address all of the person's clinical, emotional and social needs. Antipsychotic drugs are the most common type of medicines used to treat schizophrenia, but they form just a small part of the overall care given.

What are newer (atypical) antipsychotics?

Antipsychotic drugs are believed to work by changing the activity of chemicals that transmit messages in the brain. The main chemical they work on is called dopamine.

There are two groups of antipsychotic drugs: the older 'typical' drugs such as haloperidol and chlorpromazine, and the newer 'atypical' drugs. The main difference between these two groups of drug is the side effects they may cause.

All antipsychotic drugs can cause side effects but these will be different for each patient and each drug. The side effects may include shaking or trembling, and muscle twitches or spasms, these side effects can be permanent or they can disappear after a person stops taking the drugs. Antipsychotic drugs can also cause blurred vision, increased pressure inside the eye, dry mouth and eyes, constipation, urinary retention, sexual dysfunction (for example impotence and loss of sex drive) increased levels of prolactin (a hormone), fits, sedation and weight gain. Some antipsychotics are also associated with heart problems, for example changes to the heartbeat.

What has NICE recommended about the use of atypical antipsychotics?

NICE has made the following recommendations.

Your doctor should discuss with you which antipsychotic drug you should take. Your doctor should explain the benefits and side effects of the drugs, and if appropriate consult your advocate or carer. Decisions about which drugs you are prescribed should be made jointly with you and your doctor, and you should understand what the side effects of the medicine might be.

If you have been newly diagnosed with schizophrenia then your doctor should consider prescribing you one of the following atypical (newer) oral antipsychotic drugs: amisulpride, olanzapine, quetiapine, risperidone or zotepine.

If you are currently taking typical (older) antipsychotic drugs that are controlling your symptoms of schizophrenia but are causing side effects that you and your doctor agree are unacceptable, then your doctor should consider prescribing you an oral atypical antipsychotic (amisulpride, olanzapine, quetiapine, risperidone, sertindole or zotepine).

NICE does not recommend that you change to one of the atypical (newer) antipsychotic drugs if you are currently taking typical (older) antipsychotics that are controlling your symptoms of schizophrenia and are not causing unacceptable side effects.

If there is evidence that you have what is known as treatment-resistant schizophrenia or TRS (where the drugs you are taking are not controlling your symptoms of schizophrenia), then your doctor should prescribe you clozapine.

It is important to take antipsychotic drugs regularly at the doses that have been prescribed. Some people with schizophrenia have problems keeping to a regular dosing regimen and may be prescribed a depot preparation – that is an injection of an antipsychotic in a form that allows it be released slowly into the body over a few weeks. Your doctor and other professionals responsible for your care should assess and discuss with you whether a depot preparation would be appropriate.

If more than one of the atypical antipsychotic drugs is suitable for you, your doctor should prescribe the least expensive drug.

If it is not possible for you to have a full discussion with your doctor about which drug should be prescribed, for example because you are having a relapse or acute schizophrenic episode, then your doctor may prescribe an atypical antipsychotic because of the lower risk of side effects. In these circumstances, your doctor should discuss your drug treatment with your carer or advocate if possible and appropriate.

It is recommended that ‘advanced directives’ are developed and kept in your care programme. Advanced directives are instructions written by you and your healthcare team, that describe what you would like to happen if you are not able to be involved in a discussion with your doctor at a time you require treatment (for example during a relapse or acute schizophrenic episode).

Treatment with antipsychotic drugs should be part of an overall package of care that addresses your medical, emotional and social needs. Your doctor and key worker should monitor, on an ongoing basis, your progress and how well the drugs you are taking are working, and any side effects you are experiencing. This is particularly important if you have just changed from one antipsychotic to another.

Atypical and typical antipsychotic drugs should not be prescribed at the same time except for short periods if you are changing drugs.

What should I do?

If you, or someone you care for, have schizophrenia then you can discuss this advice with the doctor or key worker at your next appointment.

Will NICE review its guidance?

Yes. The guidance will be reviewed in May 2005.




**Further
information**

Further information on NICE, and the full guidance issued to the NHS is available on the NICE website (www.nice.org.uk).

The guidance can also be requested by phoning 0870 1555 455, quoting reference N00106.

If you have access to the Internet and would like to find out more about schizophrenia, visit the NHS Direct website: www.nhsdirect.nhs.uk. If you would like to speak to NHS Direct, phone 0845 46 47.

APPENDIX D

Technical detail on criteria for auditing the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia

Objectives for an audit

One or more audits can be carried out in different care settings to ensure that:

- individuals with schizophrenia are involved in the choice of the drugs prescribed for their condition
- atypical antipsychotic drugs are prescribed appropriately for individuals with schizophrenia.

Individuals to be included an audit

A single audit could include all individuals with schizophrenia. Alternatively, individual audits could be undertaken on specific groups of individuals such as the following:

- people newly diagnosed with schizophrenia
- people previously diagnosed with schizophrenia
- people with treatment-resistant schizophrenia.

The audits described can be carried out on a suitable sample of individuals and can be carried out jointly by mental health and primary care teams.

Measures to be used as a basis for the audit

In any audit of individuals diagnosed with schizophrenia, the following measures can be used.

Criterion	Standard
1. There is a notation in the individual's patient record that the individual and the clinician responsible for treatment jointly decided on the antipsychotic drug prescribed, in consultation with the individual's advocate or carer if possible	100% of individuals with schizophrenia
2. There is an advance directive in the individual's patient record on the agreed choice of antipsychotic to be used in the case of acute psychotic illness	100% of individuals with schizophrenia
3. There is evidence in the individual's patient record that therapeutic progress and drug tolerability are being monitored on an ongoing basis	100% of individuals with schizophrenia
4. Depot preparations are prescribed for any of the following circumstances: <ol style="list-style-type: none"> Concordance is identified as an issue in the individual's risk assessment The individual expresses a preference for a depot preparation 	100% of individuals with schizophrenia at risk of non-compliance with medications or who express a preference for depot preparations
5. Typical and atypical antipsychotic drugs are not prescribed concurrently	100% of individuals with schizophrenia

If an audit includes individuals diagnosed with schizophrenia for the first time, the following additional measure can be included.

1. The individual who is diagnosed with schizophrenia for the first time is prescribed an oral atypical antipsychotic drug	100% of individuals newly diagnosed with schizophrenia
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Exception	Definition of Terms
<p>A. The individual with schizophrenia is not able to participate in an informed discussion with the clinician responsible for treatment at the time of prescription and an advocate or carer is not available</p>	<p>The notes should indicate that the clinician responsible for treatment discussed benefits and side effects of antipsychotic drugs and the individual participated in making a choice or that the individual was not capable of participating in making a choice at the time. The notes should refer to involvement of the individual's advocate or carer where applicable.</p> <p>For audit purposes, a list of typical and atypical antipsychotic drugs should be available.</p> <p>Where no choice is clearly indicated, note if the purchase cost of drugs (taking into account daily required dose and product price per dose) was considered.</p>
<p>A. There is a notation in the patient record that it has not been possible to develop an advance directive with the individual or their carer/ advocate</p>	<p>The advanced directive should indicate that the clinician responsible for treatment discussed with the individual what drug to prescribe in the circumstance of acute psychotic illness and the individual participated in making that choice.</p>
<p>None</p>	<p>Local teams should agree on shared-care protocols for individuals on antipsychotic drugs and should agree on what constitutes concordance with the agreed protocols for audit purpose</p>
<p>None</p>	<p>If drug concordance is identified as an issue in the individual's risk assessment, check the individual's patient record to see if depot preparations have been considered by the clinician responsible for treatment.</p>
<p>A. The concurrent prescriptions are for a short period to cover changeover of medication</p>	<p>Check the individual's patient record for reference to more than one drug prescribed at the same time.</p> <p>Local teams should agree on what constitutes a changeover period for audit purposes.</p>
<p>A. Local teams may define exceptions that preclude the use of an oral atypical antipsychotic or favour the use of a typical antipsychotic</p>	<p>See patient prescription record and list of typical and atypical antipsychotic drugs in <i>BNF</i>. Oral atypical drugs = amisulpride, olanzapine, quetiapine, risperidone and zotepine.</p>

Continued overleaf

If an audit includes individuals with a previously established diagnosis of schizophrenia, the following additional measure can be included.

Criterion	Standard
1. For an individual with a previously established diagnosis of schizophrenia, consideration is given to prescription of an oral atypical antipsychotic drug	100% of individuals with established diagnosis of schizophrenia

If an audit includes individuals with TRS, the following additional measure can be included.

1. The individual with TRS is prescribed clozapine at the earliest opportunity	100% of individuals with TRS
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Calculation of compliance with the measure

Compliance with each measure described in the table is calculated as follows:

$$\frac{\text{Number of individuals whose care is consistent with the criterion plus number of individuals who meet any of the exceptions listed}}{\text{Number of individuals to whom the measure applies}} \times 100$$

Clinicians should review the findings of measurement, identify if practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that desired improvement is being achieved.

Exception	Definition of Terms
<p>A. The individual's symptoms are adequately controlled by current therapy without unacceptable side effects</p> <p>B. Local teams may define additional exceptions that preclude the use of an oral atypical antipsychotic or favour the use of a typical antipsychotic</p>	<p>This criterion applies to individuals being treated actively and individuals in relapse.</p> <p>Local teams should agree on what constitutes evidence of consideration of prescribing an oral atypical antipsychotic drug.</p> <p>See individual's prescription record and list of typical and atypical antipsychotic drugs.</p> <p>For first exception, see notes of individual's progress.</p> <p>Unacceptable side effects are as noted following discussions between the individual and clinician responsible for treatment.</p>

TRS is suggested by a lack of satisfactory clinical improvement despite sequential use of the recommended dose for 6 to 8 weeks of at least two antipsychotics, typical or atypical. See individual's prescription record. If the individual has not been prescribed clozapine, note if there is a plan to switch drug therapy in the near future.