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## **WORKING GROUP ON ACUTE PURCHASING**

### **A Review of the Use of Current ‘Atypical’ Antipsychotics in the Treatment of Schizophrenia April 1998**

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## **GUIDANCE NOTE FOR PURCHASERS 98/01**

**Series Editor: Nick Payne**

InterDEC Report No. 1/1998

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## **Trent Development and Evaluation Committee**

The purpose of the Trent Development and Evaluation Committee is to help health authorities and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise, and includes non-clinically qualified scientists and lay members. It is chaired by Professor Sir David Hull.

The Committee recommends, on the basis of appropriate evidence, priorities for:

- the direct development of innovative services on a pilot basis;
- service developments to be secured by health authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meeting on 21 April 1998 at which this Guidance Note for Purchasers (in a draft form) was considered.

### **A REVIEW OF THE USE OF CURRENT 'ATYPICAL' ANTIPSYCHOTICS IN THE TREATMENT OF SCHIZOPHRENIA**

**AUTHORS:** Beard SM, Brewin J, Packham C, Rowlands P. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield 1998. Guidance Note for Purchasers: 98/01.

**EXPERT ADVISORS TO TRENT DEC:** Mr S M Beard, ScHARR; Dr J Brewin, Consultant Psychiatrist, University Hospital, Queen's Medical Centre, Nottingham; Dr C Packham, Consultant in Public Health Medicine, Nottingham Health Authority.

**DECISION:** The Committee recommended that health districts should prepare an algorithm indicating the place for 'atypical' antipsychotic drugs in the treatment of schizophrenia. It is hoped that psychiatrists in the region will systematically evaluate the long term effects, efficacy and cost-effectiveness of the new 'atypicals' as they are introduced. This evidence would assist in any further decisions on usage in the future.

**April 1998**

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ANTIPSYCHOTICS IN THE TREATMENT OF  
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J Brewin  
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**Series Editor: Nick Payne**

Trent Institute for Health Services Research  
Universities of Leicester, Nottingham and Sheffield

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**Conflict of Interest**

None of the authors of this document has any financial interests in the drug or product being evaluated here.

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## **ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH**

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Trent Institute:

- undertakes Health Services Research (HSR), adding value to the research through the networks created by the Institute
- provides advice and support to NHS staff on undertaking HSR;
- provides a consultancy service to NHS bodies on service problems;
- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
- disseminates the results of research to influence the provision of health care.

The Directors of the Institute are: Professor R L Akehurst (Sheffield);  
Professor C E D Chilvers (Nottingham); and  
Professor M Clarke (Leicester).

Professor Clarke currently undertakes the role of Institute Co-ordinator.

A Core Unit, which provides central administrative and co-ordinating services, is located in Regent Court within The University of Sheffield in conjunction with The School of Health and Related Research (SchARR).

## **FOREWORD**

The Trent Working Group on Acute Purchasing was set up to enable purchasers to share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy. The Group is facilitated by The School of Health and Related Research (SchARR), part of the Trent Institute for Health Services Research, the SchARR Support Team being led by Professor Ron Akehurst and Dr Nick Payne, Consultant Senior Lecturer in Public Health Medicine.

The process employed operates as follows. A list of topics for consideration by the Group is recommended by the purchasing authorities in Trent and approved by the Purchasing Authorities Chief Executives (PACE) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic assisted by a support team from SchARR, which provides help including literature searching, health economics and modelling. A seminar is led by the public health consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been reviewed by the Trent DEC, chaired by Professor Sir David Hull.

In order to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions, The Trent Institute's Working Group on Acute Purchasing has joined a wider collaboration, InterDEC, with units in other regions. These are: The Wessex Institute for Health Research and Development, The Scottish Health Purchasing Information Centre (SHPIC) and The University of Birmingham Department of Public Health and Epidemiology.

**Professor R L Akehurst,**  
**Chairman, Trent Working Group on Acute Purchasing.**

## **ABBREVIATIONS**

<b>5HT</b>	Serotonin
<b>BPRS</b>	Brief Psychiatric Rating Scale
<b>CGI</b>	Clinical and Global Impression
<b>CGI -s</b>	Clinical and Global Impression - Severity of illness
<b>CI</b>	Confidence Interval
<b>CNS</b>	Central Nervous System
<b>CPMS</b>	Clozapine Patient Monitoring System
<b>DSM III-R</b>	Diagnostic and Statistical Manual of Mental Health Disorders
<b>ECG</b>	Electrocardiogram
<b>EPSE</b>	Extrapyramidal Side-effects
<b>ICD10</b>	International Statistical Classification of Diseases and Related Health Problems - Tenth Revision
<b>NMS</b>	Neuroleptic Malignant Syndrome
<b>PANSS</b>	Positive and Negative Syndrome Scale
<b>QALY</b>	Quality Adjusted Life Year
<b>QTc</b>	Measure of the time required for repolarization to occur
<b>R&amp;D</b>	Research and Development
<b>RCT</b>	Randomised Controlled Trial
<b>SADS-C</b>	Schedule for Affective Disorders and Schizophrenia - Change Version
<b>SANS</b>	Scale for the Assessment of Negative Symptoms
<b>SAS</b>	Simpson-Angus Scale
<b>TD</b>	Tardive Dyskinesia



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## EXECUTIVE SUMMARY

- Schizophrenia is a chronic relapsing psychotic disorder where the outcome is variable. It has an annual incidence of approximately two per 10,000 population per annum. More than 50% of patients may develop a chronic illness giving period prevalence rates of 4 per 1,000 over six months for the 16-64 year old population at risk.
- Acute (positive) symptoms include: hallucinations, delusions and thought disorder. Chronic or deficit states are characterised by negative symptoms including: social withdrawal, blunting of affect and lack of motivation.
- Using a population of 500,000 as a 'typical' district, evidence suggests that there may be up to 64 new patients a year diagnosed with this condition. Likewise, in any one six month period, it might be expected that there are some 1,200 -1,400 patients with active schizophrenia. There exists a growing body of evidence to suggest that the true burden of schizophrenia, in terms of relapse rates and hospitalisation rates, is more severe than has previously been generally accepted.
- Studies estimate the overall UK cost burden of schizophrenia, including the direct and indirect costs, at £2.6 billion per annum. Recent reviews have estimated the UK direct costs of schizophrenia to lie in a range somewhere between £396 million - £714 million per annum. Hospitalisation represents around 90-95% of all direct costs related to schizophrenia, with drug costs at 2% representing a much smaller proportion of total expenditure.
- The major negative points of conventional drugs are seen to be the high incidence of associated extrapyramidal side-effects and the fact that there is little observed effect on the negative symptoms of schizophrenia. Thus (in respect of conventional drugs):
  - \* 30-40% of patients do not respond during an acute episode;
  - \* they are largely ineffective against the negative symptoms of schizophrenia;
  - \* they are associated with medication compliance problems;
  - \* up to 40% of patients will relapse within two years despite prophylaxis;
  - \* up to 75% of patients will experience extrapyramidal side-effects (EPSE)
  - \* 5% of patients per year will develop tardive dyskinesia.
- The newer 'atypical' antipsychotics are now becoming increasingly prescribed for certain schizophrenic patients and represent a real alternative to conventional drugs. Available clinical evidence on the newer 'atypical' drugs shows that they:
  - \* are generally better tolerated than conventional drug therapy;

- \* have a lower observed rate of EPSE;
  - \* are at least as clinically effective as conventional drug therapy;
  - \* have the potential to influence negative symptoms;
  - \* represent a significant increase in pure drug costs.
- However, there is little long-term trial evidence related to the newer 'atypical' drugs and the projection of resource impacts remains difficult to quantify.
  - There is also a lack of direct trial comparisons of these drugs against each other, with most trials comparing with conventional drugs, such as, haloperidol. This means that making comparative statements about these drugs is difficult.
  - Up to 70% of schizophrenic patients may be suitable for treatment with 'atypical' antipsychotics, given that 30% of patients achieve a maintained response on conventional drugs.
  - The marginal drug costs for a 'typical' district are estimated at between £520,000 (if given to 20% of all schizophrenic patients) and £1,820,000 (if given to 70% of all schizophrenic patients).
  - The cost-effectiveness argument for 'atypicals' remains unproven, although, in the case of clozapine, there does appear to be good evidence showing sufficient cost savings from in-patient and other costs to off-set the high direct costs of the drug. Many of the published cost-effectiveness studies are still based on the short-term evidence base.
  - There is a need for continued randomised controlled trials (RCTs) of newer 'atypical' drugs, with more evidence of comparative efficacy and cost-effectiveness. Also a longer time period is required in the follow-up of patients.
  - The modelling of cost-effectiveness may provide a framework within which trial data can be combined with clinical experience to consider the longer-term projected impact of these drugs. A process for such an exercise is discussed in the Guidance Note.
  - Future prescribing of the newer 'atypicals' must be accompanied by a rigorous process of patient follow-up and monitoring, possibly based around a regional patient database. This would allow further evaluation of clinical impact, resource use and cost-effectiveness in real practice alongside any such trials.

# **1. INTRODUCTION**

## **1.1 General Overview**

Schizophrenia is one of the major psychiatric disorders, characterised by the presence of psychotic symptoms, thought disorders and severe disturbances of psychosocial functioning.

The illness typically presents in early adult life (median 25 years male/28 years female) and can have a devastating effect upon the lives of individuals affected by it, including both the sufferers themselves and their families and network of supporting carers.

There is no known cure for schizophrenia and all treatments are aimed at improving symptoms and delaying or preventing relapse.

Until 1989, pharmacological treatments were based on the antipsychotic (antidopaminergic) drugs: chlorpromazine, haloperidol and depot equivalents. These drugs come from a classification or drug group now commonly referred to as the conventional antipsychotics. The conventional drugs first appeared on the market in the 1950s and represented the first major pharmacological breakthrough in the treatment of schizophrenia. However, whilst some patients respond well to conventional drug treatment, a significant proportion remain either refractory to any clinical effect or cannot tolerate the associated extrapyramidal side-effects (EPSE), which are predominantly drug related.

With the initial development and later re-introduction of the antipsychotic drug clozapine, previously withdrawn due to its potential side-effects, and the subsequent introduction of other newer/novel antipsychotic compounds, there now exists a potential opportunity to improve significantly the quality of life of patients suffering from schizophrenia. This is mainly due to the claims of reduced levels of observed side-effects experienced by patients with the newer ('atypical') antipsychotics, in particular, those effects related to EPSE, and also their potential to influence both the positive and the negative symptoms of schizophrenia.

Whilst clozapine itself is restricted to treatment resistant patients, due to the recognised risk of agranulocytosis (a lowering of the white blood cell count), the other newer 'atypical' drugs have no such licensing restrictions with regard to their use. Therefore, the newer drugs are

generally considered by clinicians as an appropriate first-line treatment option for schizophrenia alongside the existing conventional drugs. There is also an increasing level of expectation for 'atypical' antipsychotics in the management of schizophrenic patients who are proved to be treatment-resistant to conventional drug therapy, although evidence for their clinical effectiveness in these patients is limited. Clozapine remains the only proven 'atypical' in treatment-refractory patients.

The currently available licensed 'atypical' antipsychotics include:

- Clozapine - (Clozaril 1990) *licensed for treatment-resistance patients only*
- Risperidone - (Risperdal 1993)
- Olanzapine - (Zyprexa 1996)
- Sertindol - (Serdolect 1996)
- Quetiapine - (Seroquel 1997) *the most recent addition to the list*

Other drugs in the late stages of development include:

- Ziprasadone
- Zotepin
- Amisulpride.

With further antipsychotic drugs now in development, and the focus of current ongoing clinical trials, this list of licensed 'atypical' antipsychotics is sure to increase, providing clinicians with a range of different and alternative treatment options. This is especially the case with the 'atypicals' as each drug has its own specific mechanism of action and underlying pharmacological basis. In pure drug cost terms, this increase in availability of newer 'atypicals' has an obvious financial implication on health authorities, as they represent a significantly more expensive treatment regimen than conventional drugs when considered on a dose equivalent basis.

There is great variation between health districts in the extent to which the newer 'atypical' antipsychotic drugs are currently used. This variation may have resulted from either an intentional policy by health authority and/or provider, or may have arisen as a result of unplanned clinical activity. There is now a great need to provide advice about effectiveness, costs and benefits, and possible models for introducing 'atypical' antipsychotic drugs and so to assist in the development of rational and consistent policies for the provision of these drugs on the basis of need.



The purpose of this Guidance Note is both to consider the current state of evidence for the clinical efficacy of the newer antipsychotics and to highlight and suggest the levels of cost-effectiveness associated with their use. The Note recommends to purchasers the most suitable place for newer antipsychotics in the treatment pathways for schizophrenia.

## **1.2 Incidence and Prevalence**

Schizophrenia is not a common illness having an annual incidence of approximately 2 per 10,000 population per annum.<sup>1,2,3</sup> This is expressed in terms of the 'at risk' population, most commonly defined as the 16-64 years age group. In terms of overall risk, the illness has a lifetime prevalence in the range of 6-12 per 1,000 population 'at risk' and is often approximated at a level of 10 per 1,000, although there is some evidence that this may be declining.<sup>4</sup>

However, more than 50% of patients may develop a chronic illness giving period prevalence rates of 4 per 1,000 over six months for the 16-64 year old population 'at risk'. The average GP is expected to be in direct contact and providing care for around 10-20 schizophrenic patients;<sup>1</sup> this obviously depends on the location and social background of individual practices.

Data from general practice suggest that the annual incidence of what the GP considers to be schizophrenia is higher than the incidence rate ascertained from secondary care studies.<sup>5</sup> These discrepancies in reported and recorded cases of schizophrenia highlight the difficulty in making consistent diagnoses, hence the need for operationally defined diagnostic criteria. A significant proportion of those presenting to primary care are of a transient nature and, therefore, would not meet these strictly defined criteria, but represent a broader range of 'psychotic' disorders. Therefore, incidence rates will be expected to vary dependent on the degree of stringency used.

## **1.3 Positive and Negative Symptoms**

Schizophrenia is a chronic relapsing psychotic disorder although the outcome is variable. It is characterised in the early stages by acute (positive) symptoms including: hallucinations, delusions and thought disorder. In a significant number of patients over time, there is the development of the chronic or deficit state characterised by negative symptoms, including; social withdrawal, blunting of affect and lack of motivation.



The following table details the typical profile of symptoms associated with schizophrenia.

**Table 1 Positive and Negative Symptoms**

<b>Positive Symptoms</b>	<b>Negative Symptoms</b>
• hallucinations	• withdrawal from social contact
• delusions	• blunted emotions
• bizarre behaviour	• lack of motivation
• hostility	• inability to experience pleasure
• thought disorder	• slowness of movement and thought

It is important to recognise that the negative symptoms of schizophrenia can have both 'primary' and 'secondary' causes, which are often difficult to identify and separate, in both the environments of clinical trial and clinical practice alike.

**Primary Symptoms** Primary negative symptoms are those which are directly related to the illness itself and have a clinical basis.

**Secondary Symptoms** Secondary negative symptoms are largely thought to be a direct consequence and effect of conventional medication. They are also thought to manifest themselves as a consequence or 'reflection' of the positive symptoms of the illness.

Clearly, the reality here is that patients are likely to have a mix of both primary and secondary negative symptoms.

Many of the newer antipsychotics show some suggestion of clinical effect and improvement in negative symptoms, even in those clinical trials conducted over a relatively short time period of 6-12 weeks. However, there are still remaining questions and clinical debate as to whether this reduction is :

- due to the removal of conventional drugs from treatment;
- due to a reduction in positive symptoms and hence a result of the clinical efficacy of 'atypicals'.

#### **1.4 Outcome Measurement and Psychiatric Rating Scales**

There are four key tools of measurement commonly used in the quantification of treatment efficacy in schizophrenia. These assessment tools are based on both the positive and negative symptoms of schizophrenia, both in isolation and also as combined symptomatic measures. There is no overall accepted standard in the measurement and assessment of clinical response to treatment alternatives in schizophrenia. All the scales are used to some degree or other in clinical trials and their assessments:

- Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987)<sup>6</sup>
- Brief Psychiatric Rating Scale (BPRS) (Overall JE et al. 1962)<sup>7</sup>
- Clinical and Global Impression (CGI) (Guy 1976)<sup>8</sup>
- Scale for the Assessment of Negative Symptoms (SANS) (Andreasen 1982)<sup>9</sup>

## **1.5 Pharmacology of Antipsychotic Drugs**

There is no cure for schizophrenia and current pharmacological treatment aims to reduce and/or control psychotic symptoms, improve functioning and delay or prevent recurrent episodes.

Conventional antipsychotics are dopamine (D<sub>2</sub>) antagonists and have a number of drawbacks. These include serious side-effects, particularly extrapyramidal including tardive dyskinesia; also an estimated 30% of patients remain unresponsive and their psychotic symptoms persist. Conventional drugs are also ineffective against the negative symptoms of schizophrenia and do little to prevent a chronic deficit state developing. This combination of side-effects and a failure to tackle negative symptoms leads to a recognised poor quality of life for patients, even when in a maintained state.

While the aetiology of schizophrenia remains elusive, there are well described genetic links and some evidence for possible environmental factors. The dopamine hypothesis is widely accepted - it states simply that schizophrenia is caused by an overactivity of the dopaminergic mesolimbic and mesocortical neurotransmitter systems. There is, however, little direct evidence for this from neuropharmacological and neuropathological studies. Furthermore, even if this hypothesis is correct, it does not explain the primary aetiological factor.

The dopamine hypothesis evolved simply from the observation that the conventional antipsychotic drugs, based on dopamine antagonists, were found to alleviate psychotic symptoms. Their mechanism of action was assumed to be via this dopaminergic blockade. They also block other neurotransmitter systems including, serotonin, noradrenaline, acetylcholine and histamine.

There are three main dopaminergic tracts centrally:

- mesolimbic and mesocortical (brain stem to temporal lobe);
- nigrostriatal (brain stem to basal ganglia);
- hypothalamo-pituitary.

It is thought that, while the mesolimbic system is central to the pathology of schizophrenia, conventional drugs unfortunately also block all dopamine areas and, thus, cause significant side-effects, extrapyramidal in the case of nigrostriatal blockade and hyperprolactinaemia from the effect on the hypothalamus. There are only minor variations between the different classes of conventional antipsychotics, thus, overall efficacy and incidence of side-effects is roughly equivalent.

With increasing knowledge of dopaminergic neuronal systems, and further elucidation of other neurotransmitter systems, which either act independently or through interaction with dopamine systems in the pathophysiology of schizophrenia, newer compounds have been developed. Several dopamine receptor sub-types have now been identified - D<sub>3</sub>, D<sub>4</sub> and D<sub>5</sub>. Their anatomical distribution varies, thus opening up the theoretical possibility of greater drug specificity of action. The D<sub>4</sub> receptor also shows genetic polymorphism and the variants differ in their response to antagonists.

Serotonin (or 5HT) has also emerged as a neurotransmitter of great importance for a number of reasons:

- 5HT interacts with dopaminergic neuronal systems in both brain stem and cortex;
- clozapine is a potent 5HT antagonist, a possible explanation for its antipsychotic properties;
- certain 5HT agonists cause psychotic symptoms.

Thus, there has been a proliferation of new 'atypical' antipsychotic compounds, which use these new findings in an attempt to be more efficacious and better tolerated. The potential benefits of a more targeted and selective drug therapy can be clearly seen: improved compliance; reduction in side-effects; and better management of the illness.

There are a number of different categories of 'atypical' antipsychotic compounds:

- dopamine autoreceptor agonists (that have questionable antipsychotic activity);
- 5HT antagonists;
- mixed compounds that have both dopamine and 5HT antagonistic properties.

It is important to bear in mind that these new drugs also block other neurotransmitter systems to varying degrees therefore, and, are not totally free of side-effects.

New compounds now available for treatment include clozapine, risperidone, sertindole, olanzapine and quetiapine. Three further compounds are completing phase III trials and will soon be available: ziprasadone, amisulpride and zotepine.

## **1.6 Standard Definition of 'Atypical' Antipsychotics**

In considering the definition and categorisation of 'atypicals', it is important first to clarify any confusion over the use and meaning of the two terms *antipsychotic* and *neuroleptic*, as they are commonly and inappropriately interchanged. The conventional drugs have traditionally been referred to as 'neuroleptic' as a direct description of their well documented neurological side-effects, in particular EPSE. As the newer drugs are observed to have a much lower incidence of EPSE, it is technically inaccurate to refer to them as 'neuroleptic' and the term 'antipsychotic' is commonly used.

Although the term 'atypical' has been widely used to date in labelling this group of newer antipsychotics, it is difficult to provide a clear and exact definition as to what truly represents a true atypical drug. Indeed, all these drugs have their own individual mechanisms of action and pharmacology and there is an increasing movement away from assigning an overall group name. However, it is possible to draw some overarching common features of the newer drugs for schizophrenia.

To clarify the terminology, a conventional 'antipsychotic' or 'neuroleptic' satisfies the following criteria according to Delay and Deniker (1957)<sup>10</sup>:

- 'the antipsychotic effect was not due to sedation;
- it caused a decrease in psychomotor activity;
- it induced EPSE and catalepsy'.

An 'atypical' or newer compound is less clearly defined, but would satisfy the following criteria:

- the antipsychotic effect was not due to sedation;
- causes less or no acute extrapyramidal symptoms (i.e. motor side-effects);
- causes little or no tardive dyskinesia (TD) when compared to typical drugs;
- does not produce sustained elevation in prolactin (i.e. a hormone which causes gynaecomastia - breast enlargement) above the normal range.

In addition, 'atypical' compounds could also be considered to:

- alleviate positive symptoms (i.e. delusions, hallucinations) as well as negative symptoms (i.e. blunted emotion, apathy, social withdrawal);
- alleviate neurocognitive deficits (i.e. problems in attention and information processing).

## **1.7 Prognosis and Mortality**

In terms of an overall prognosis for patients suffering from schizophrenia, it has been assumed historically that, as a general approximation, one third of patients with diagnosed schizophrenia will return to a largely symptom-free life, whilst one third will remain troubled by symptoms, but will remain independent within the community, and up to one third will have a longer-term chronic course with more serious disruption of normal social functioning over time.

However, more sophisticated cohort studies (designed specifically to uncover the true profile of schizophrenia) now indicate that there are more chronic patients than previously believed.

A recent review of schizophrenia reported data from a number of different cohort studies.<sup>11</sup> The largest and most notable of these studies suggested that in reality up to 82% of patients

will actually experience a relapse of their illness, implying, therefore, that only 18% of patients would return to an episode-free life.<sup>12</sup> This compares with the higher estimate of a third of patients experiencing no further relapse, as generally quoted. The study also suggests that 75% of patients actually will have at least one hospital re-admission due to relapse.

An earlier study, which included all schizophrenic patients, also found that only 32% of schizophrenic patients would achieve an outcome which could be considered to be relatively mild.<sup>13</sup> When restricted to those who suffer only a single episode, the proportion of patients with a mild outcome reduces to 16% of the total schizophrenic population.

Studies of patients who have repeated relapse episodes of schizophrenia report that 43% of patients experience longer-term enduring symptoms, associated with a lack of full remission and representing a chronic state. This compares with the historical view of 33% of patients experiencing a chronic illness state. Furthermore, studies also show that 9% of patients are expected to suffer a life long lasting impairment related to schizophrenia.

Therefore, there now exists a body of strong evidence both to suggest and support the view that the true burden and course of schizophrenia, in terms of relapse rates and hospitalisation rates, is more severe than has been previously generally accepted.

The true profile and prognosis of schizophrenic patients is likely to lie somewhere in the ranges suggested below, with the historical view representing the lowest estimate of those arriving at a chronic state and likely to be involved in hospitalisation and long-term clinical care.

- Single acute episode 10-20%
- Multiple acute episode 30-60%
- Chronic long-term state 30-50%

It is also widely recognised that schizophrenic patients have a much increased risk of suicide than the general population. Up to 10% of patients with schizophrenia will eventually commit suicide. A recently reported cohort study claimed that the risk of suicide increases by a factor of 20x for men and 3x for women.<sup>14</sup>

In terms of general morbidity, it is also widely accepted and recognised that schizophrenic patients have much reduced levels of good physical health. This reflects both patients' lack



of access to primary care based services and also a lack of an ability to assimilate and act on general health care advice.<sup>14,15</sup>

Another important issue is the level of schizophrenic patients who are currently cared for in forensic institutions. In a recent prevalence study of prisoners a 5% point prevalence rate was noted for psychosis.<sup>16</sup> This raises a number of questions relating to the availability of healthcare services and appropriateness of the setting of care. This level of psychosis within prisons has obvious resource consequences and presents a significant element of societal cost. This raises the question of whether an improved level of treatment/maintenance of schizophrenia within the criminal system would result in less need for secure accommodation. It is not within the scope of this Guidance Note to explore this particular issue, but the point needs highlighting as an area of expenditure, related directly to schizophrenia, where there is potential for both cost reduction and patient benefits, given more appropriate and clinically effective treatment options.

Overall, the picture of schizophrenia is one of an illness which is probably more chronic than has previously been appreciated. The advantages of achieving an early recognition and appropriate choice of treatment for schizophrenia can be summarised:

- reduction in the level and frequency of further relapse;
- minimisation of the positive aspects of the illness;
- limitation of the associated anxiety and depression;
- limitation of the cognitive deterioration associated with the illness;
- limitation to the loss of social skills and of family/social support systems; and
- reduction in the opportunity for loss of personal self care skills.

## **1.8 Cost Burden and Resource Implications**

Without doubt, schizophrenia represents a significant cost burden to the NHS, via the direct costs of drugs and supportive care, and to wider society, with implications in terms of lost employment opportunity, family support and the provision of community-based services.

Recent reviews have estimated the direct costs of schizophrenia to lie in a range somewhere between £396 million - £714 million per annum.<sup>11,17</sup> Most of this estimated direct cost is related directly to the costs of in-patient care and hospitalisation. Drug costs represent a much smaller proportion of total expenditure related to schizophrenia.

The following table breaks down the NHS direct costs, which relate directly to schizophrenia, and expresses them as a proportion of total expenditure. The figures are based on NHS data for 1992/93 and are taken from the Knapp review of schizophrenia costs.<sup>11</sup>

**Table 2 Direct Costs Related to Schizophrenia**

<b>Expenditure on schizophrenic patients: Category</b>	<b>Cost</b>	<b>Percentage of individual budget within category</b>
In-patient	£652.2m	5.37%
Out-patient	£0.9m	0.04%
Primary Care	£1.8m	0.05%
Drugs	£32.4m	1.06%
Community Care	£26.2m	0.9%
Social Services	£96.5m	1.8%
<b>TOTAL EXPENDITURE</b>	<b>£810.0m</b>	<b>2.76%</b>

The table presents the proportion of each individual NHS and Social Services budget as well as an aggregated total proportion of NHS and Social Services expenditure of 2.76%

Not surprisingly, the biggest impact of schizophrenia, in terms of both cost and proportion, lies in in-patient care. Using these figures as a cost base, the in-patient activity represents around 90-95% of the cost of schizophrenia, with drugs accounting for 1-2%. Therefore, the biggest potential for resource savings in the treatment and care of schizophrenic patients lies in the provision of in-patient care rather than with direct pharmaceutical costs.

The study estimates the overall cost burden of schizophrenia, including the direct and indirect costs, at £2.6 billion per annum.

In contrast, an alternative study, calculating the NHS and social care cost of schizophrenia, reports the total direct costs of schizophrenia in the UK as £397m per annum (1.6% of the total health care budget).<sup>18</sup> Hospital and community-based residential care accounted for 75% of these costs with drugs still representing only 5% of the overall total cost. The conservative estimate of indirect costs amounted to £1.7 billion per annum, this being based on a calculation of expected lost production and unemployment costs.

The study further stated that 97% of these direct costs were incurred by less than 50% of the schizophrenic patients. This estimate was made using published groupings which divide the schizophrenic patients into five outcome groups.<sup>19</sup>

**Table 3 Prudo & Blum 1987 - Schizophrenic Patient Classification**

Patient Group	Definition
Group 1	Only a single episode of schizophrenia, with an average duration of 22 weeks
Group 2	Episodes of major disorder lasting up to 1 year
Group 3	Episodes for 1-2.5 years
Group 4a	Episodes > 2.5 years, requiring predominantly community based care
Group 4b	Episodes > 2.5 years, requiring long-term care in either hospital or community

The mean annual direct cost per patient was estimated at £2,138 and was accounted for by items listed in table 4. Whilst this is useful information, it is important to appreciate that schizophrenic patients have a wide range of different symptoms and outcomes as the illness is extremely heterogeneous. Thus, the average cost varies enormously and is very much dependent on the outcome profile of the patient. Using the patient groupings, the cost per patient per annum varies from £1,700 in patients with a single episode of less than six months' duration (19% of all patients) to £316,000 in patients in long-term residential care (20% of all patients). It becomes self evident that the opportunity to reduce costs is greater for those patients at the severe end of the spectrum.

**Table 4 Breakdown of Mean Annual Direct Cost of Schizophrenia 1991 prices**

Item	Cost	%
Hospitals/residential care	£1,580	74%
Out-patients (OP)	£72	3%
Day-care	£292	14%
Community visits	£81	4%
Depot/other OP visits	£41	2%
Other drugs	£72	3%
<b>Total Mean Cost</b>	<b>£2,138</b>	<b>100%</b>

### 1.9 Scale of the Problem in a 'Typical' District

Using a population of 500,000 as a 'typical' district, evidence suggests that there may be up to 64 new patients a year diagnosed with this condition. This estimate is based on the 2 per 10,000 annual incidence rate and an estimated 'at risk' population, 16-64 years old, of 400,000.<sup>20</sup>

A recent review in Nottingham revealed an incidence of schizophrenia of around 30-40 patients per annum for a population 'at risk' of around 400,000. This was defined as true ICD10-F20 schizophrenia; the initial level of diagnosis was 168 new cases and included broader definitions.<sup>4</sup>

In any one six month period, it might be expected that there are some 1,200 -1,400 patients with active schizophrenia (1,300 based on a 4 per 1,000 average period prevalence rate), although these patients may not necessarily be in regular contact with psychiatric services. A point audit of schizophrenic patients in Nottingham estimated between 1,200 - 1,300 patients in contact with existing services. A lifetime risk of 1% means that, within the 'at risk' population, 4,000 persons may experience, or have been previously given, a diagnosis of schizophrenia.

Of patients in contact with services, 13% may be in-patients at any one point in time.<sup>21</sup> The rate of in-patient activity, however, can vary greatly across districts and an alternative value of 28% was also reported from a rural area study.<sup>22</sup> This variation may reflect many different influences including the extent of social services or other residential provision, differing clinical practice, institutional closure, as well as actual need based on the socio-demographic mix of the host population. There is a general consensus that the current balance in the provision of in-patient long-stay beds is inappropriate, with many chronic long-term patients occupying acute unit beds.

Recent studies have suggested that this level of recorded schizophrenia may be declining, particularly in the more pure schizophrenia diagnosis (ICD10-F20). However, overall the level of psychotic illness appears constant and it remains to be seen whether this is a valid finding or simply a reflection of changes in diagnostic behaviour.<sup>4</sup>

## **2. 'ATYPICAL' ANTIPSYCHOTICS IN THE TREATMENT OF SCHIZOPHRENIA: SUMMARY OF EVIDENCE OF EFFECTIVENESS**

In evaluating the quality and direction of evidence for the use of newer antipsychotics in the treatment of schizophrenia, it helps first to review the case for conventional drugs and then to consider the newer 'atypical' antipsychotics in further detail.

### **2.1 Clinical Effectiveness of Conventional Drug Therapy**

Effective psychopharmacological interventions for schizophrenia were introduced in the early 1950s with the discovery of chlorpromazine. Within a very short period of time this class of drugs became widely prescribed. Drugs such as chlorpromazine, haloperidol and the depot medications, flupenthixol and haldol, have been regarded previously by clinicians as the optimum pharmacological treatments for schizophrenia.

The efficacy of conventional drugs is now well established, in both reducing the positive symptoms of schizophrenia and lowering the longer-term relapse rates. There exists a wide range of published trials designed to evaluate the effectiveness of conventional drugs.

These trials tend to vary in overall quality and are generally considered to be dated and small in terms of their overall trial design, however, their key messages are not thought to be in any doubt.<sup>23</sup>

The following assessment of efficacy is drawn from this body of evidence and is well replicated and not considered clinically controversial.

#### **2.1.1 Response Rates**

Numerous studies have demonstrated the efficacy of conventional drugs in alleviating the positive symptoms of schizophrenia and in the prevention of relapse over the longer-term. Only 60-70% of patients are expected to show a clinical response to conventional antipsychotics in an acute episode.<sup>23</sup> However, the proportion who can be maintained effectively on conventional drugs remains at a much lower level (approx. 30%) due to adverse effects and treatment tolerability.

Importantly, the available published studies show that conventional drugs have no significant effect on the negative symptoms of schizophrenia.<sup>24</sup> The functional impairment in social and

vocational activities that occurs in schizophrenia is not necessarily diminished by conventional antipsychotics, even when positive symptoms are alleviated.<sup>25</sup>

It is possible to identify poor prognosis non-responders early; as being those with a long prodromal illness and untreated psychosis and patients with structural brain abnormalities.<sup>26,27</sup>

### 2.1.2 Relapse Rates

A review of conventional drugs analysed 24 studies, which considered relapse as one of the key outcome measures.<sup>28</sup> It was concluded that 65% of patients relapse without medication, but 30% relapse even when on conventional medication. Another report, reviewing studies lasting between 10 and 24 months, noted a similar finding with a 8-40% relapse rate for patients on medication.<sup>29</sup> Up to 14% of first episode patients fail to respond to conventional medication.<sup>30</sup>

Medication non-compliance appears to be a common factor in relapsed schizophrenic patients. Compliance problems are a major difficulty with conventional drugs and it is estimated that more than half of schizophrenic patients do not take their medication correctly.<sup>31</sup>

### 2.1.3 Tolerability and Side-Effects of Conventional Drug Treatment

A major group of observed side-effects related directly to conventional drug therapy are the EPSE.

EPSE are unpleasant, stigmatising and common, and are seen by clinicians and patients alike as a major drawback to conventional antipsychotics. Up to 75% experience EPSE as a result of their treatment for schizophrenia.<sup>32</sup> EPSE represent a significant reason for non-compliance with treatment and, hence, subsequent relapse. The following table summarises the four key EPSE symptoms and presents them in the order of chronological risk.

**Table 5      Extrapyrimal Side-effects**

<b>Side Effect</b>	<b>Description</b>
Tardive Dyskinesia  (Months/Years)	This is perceived to be the most serious of the EPSE. It is characterised by a series of involuntary movements of the mouth, tongue and face. This has obvious consequences in terms of patient acceptance in the community and presents a real barrier to social interaction. Unfortunately, there is a significant proportion of patients for whom this side-effect will remain a permanent feature even after reducing their medication.
Akathisia  (Weeks/Months)	This is characterised by a restless feeling and causes patients to be continuously moving. It can be misinterpreted as a reflection of the illness itself, rather than drug-related, leading to an increase in medication.
Parkinsonian Symptoms  (Days/Weeks)	These are side-effects which present in the same form as the symptoms of Parkinsonism. They cover tremors, muscle rigidity and an overall slowing of patients' movements. The walking style of patients is invariably seen as a shuffling gait. The effects are relatively quick to manifest themselves often after only a few days or weeks of treatment.
Acute Dystonic Reactions  (Hours/Days)	These effects present as a series of involuntary muscle contractions, typically involving the neck and head. The effects are extremely distressing to patients who remain conscious and very much aware of them. These side-effects appear soon after commencing drug treatment and are dose related.

Tardive dyskinesia (TD), the most severe and debilitating EPSE, increases by 5% per year in patients on long-term medication. TD is largely untreatable and there have been lawsuits against psychiatrists in the USA by patients who developed TD when alternative drugs were available. TD represents a significant quality of life issue with schizophrenic patients on conventional medication.

Estimates of the prevalence of TD in first onset cohorts are 6.3% in first year, 11.5% at two years, 13.7% at three years and 17.5% at four years. Overall, prevalence rates vary between 15% and 50% at two years.<sup>33</sup> Risk factors for developing TD, apart from antipsychotic use, are dose of drug used, poor response to initial treatment, structural brain abnormalities, mental impairment, alcohol abuse and possibly diabetes.



TD was originally thought to be due to chronic dopamine blockade in particular D<sub>2</sub> receptors. However, it is now seen to be much more complex than this. Interestingly, patients can develop TD without ever having taken antipsychotics, while some drugs that predominantly block D<sub>2</sub> receptors, such as, sulpiride, still have very low rates of inducing TD.<sup>34,35</sup>

Conventional antipsychotics block a broad spectrum of neurotransmitters and, although EPSE are common and troublesome, there are many more adverse effects.

**Table 6 Summary of Common Adverse Effects of Conventional Antipsychotics**

<b>Side Effect</b>
<ul style="list-style-type: none"> <li>• Extrapyrimalidal (including acute dystonia, parkinsonism, akathisia, tardive dysknesia)</li> <li>• Hypotension</li> <li>• Hypothermia</li> <li>• Neuroleptic malignant syndrome (fluctuating consciousness, autonomic dysfunction and rigidity)</li> <li>• Sedation</li> <li>• Cardiac dysrhythmias</li> <li>• Endocrine effects (galactorrhoea, gynaecomastia, impotence, weight gain)</li> <li>• Agranulocytosis, leucopenia, haemolytic anaemia</li> <li>• Photosensitisation</li> <li>• Anticholinergic (dry mouth, blurred vision, constipation, urinary retention)</li> <li>• Lowering of seizure threshold</li> </ul>

#### 2.1.4 Summary of Evidence for Conventional Drug Therapy

To summarise the position with relation to the clinical effectiveness of conventional antipsychotic drugs:

- 30-40% of patients do not respond during acute episode;
- They are largely ineffective against the negative symptoms of schizophrenia;
- They are largely ineffective at increasing social/vocational activities, despite alleviating symptoms;
- They are associated with medication compliance problems;
- Up to 40% of patients will relapse within two years despite prophylaxis;

- Up to 75% of patients will experience EPSE;
- 5% of patients per year will develop TD.

## 2.2 'Atypicals': The Theoretical Case

The following sections consider in turn the existing body of trial evidence related to the clinical effectiveness of the 'atypical' antipsychotic drugs.

Before beginning to discuss the evidence behind the development and use of newer 'atypical' drug compounds, it is necessary to emphasise the two separate arguments for their use, which are commonly and erroneously amalgamated, those of treatment resistance and of the treatment of negative symptoms.

1. Newer compounds have fewer adverse effects than conventional drugs and are *probably* effective against negative symptoms.
2. Treatment resistance is not synonymous with continuing negative symptoms. To date, only clozapine has a licence for use in previously treatment-resistant patients.

## 2.3 Clinical Evidence Base: Clozapine

Clozapine is an antipsychotic drug licensed for use in treatment-resistant schizophrenic patients only (i.e. those patients who are deemed non-responsive to two or more conventional antipsychotics). The following presents the current view of strength of trial evidence for the clinical effectiveness of clozapine in this group of patients.

The majority of the published (independent) literature related to antipsychotics in general is on the use of clozapine; this is because it has now been available for nearly 10 years. Much of the trial evidence, in the form of both controlled trials and larger open labelled studies, compares clozapine to conventional drugs, typically chlorpromazine or haloperidol.

A 1993 Wessex DEC Report<sup>36</sup> considered the use of clozapine in treatment resistant schizophrenia. As part of this report consideration was given to an important review of the effectiveness of clozapine conducted by Baldessarini et al.<sup>37</sup> This study considered 14 key controlled clinical trials and identified a range of response rates which varied across the trials from 7% to 33% *above* that of the conventional treatment arms. Baldessarini

calculated that, on average, clozapine patients would achieve a 13% improvement in response rate. Of the 14 trials identified, five were deemed to be conducted in well-defined groups of schizophrenic patients.

These trials are summarised in the table below, along with two further trials, which also consider clozapine in treatment resistant patients. The table also cites additional longer-term and open studies of clozapine which, whilst not of a fully controlled and randomised design, do provide some useful information as to the longer-term potential benefits of treatment.

### 2.3.1 Response Rate

As stated, the 14 trials originally considered in the Baldessarini report provide a range of extra response of between 7-33%. The best and most respected of the considered trials from this study is the Kane study.<sup>38</sup> In this classic study of 268 treatment resistant patients, 30% responded to clozapine compared with only 4% of a chlorpromazine control group. Other studies have reported similar findings showing response rates to clozapine between 30-50%.<sup>39,40</sup>

Predicting patients who are likely to respond to clozapine is more difficult. In the Kane study,<sup>38</sup> those most likely to respond had more paranoid symptoms, less grandiosity and a higher number of admissions.

It is important to distinguish between effectiveness in refractory cases and effectiveness in the treatment of negative symptoms. Clozapine is certainly superior in the former, the latter is more controversial. Negative symptoms occur either as primary symptoms, or arise as secondary phenomena associated with a number of factors, but more importantly conventional antipsychotic drug use. Thus, as patients are transferred onto clozapine from conventional drugs, the apparent decrease in negative symptoms may be a decrease in secondary symptoms only. Kane reports some, but slower, improvement in negative symptoms probably due to decreased use of older drugs. In a 1994 report Breier describes the effects of clozapine on negative symptoms as relatively minor and largely restricted to patients with a non-deficit state.<sup>41</sup> European chlorpromazine/clozapine and haloperidol/clozapine trials support this view reporting only partial response in a severely ill (i.e. prominent negative symptoms) cohort.<sup>42</sup>

**Table 7 Supporting RCTs for Clozapine**

Trial	Design	Summary of Key Findings
Kane et al. 1988 <sup>38</sup>	Two armed multi centred randomised study. Clozapine (<900mg) vs Chlorpromazine (<1800mg) 6 week trial. 268 treatment resistant patients. (haloperidol 60mg/day).	Clozapine had significantly fewer EPSE (p<0.05) Clozapine had a significantly greater overall efficacy (p<0.05) Clozapine had a 30% clinical response rate c.f. 4% with chlorpromazine
Claghorn et al. 1987 <sup>43</sup>	Randomised double blind trial. Multi-centred. Parallel group. Clozapine (150-900mg) vs Chlorpromazine (300-1800mg). 8 weeks. 124 patients with TD / EPSE on conventional drugs.	Clozapine had fewer EPSE Clozapine had a significant greater overall efficacy (p<0.05)
Conley et al. 1988 <sup>44</sup>	Randomised double blind trial. Parallel group. Clozapine (<900mg) vs Chlorpromazine (<1800mg). 6 weeks. 24 treatment resistant patients (haloperidol 60mg/day)	Clozapine had fewer EPSE Clozapine had a significant greater overall efficacy (p<0.05)
Herrera et al. 1988 <sup>45</sup>	Double blind trial. Parallel group. Clozapine (900mg) vs Chlorpromazine (1800mg). 6 weeks. 60 treatment resistant patients (haloperidol 60mg/day).	Similar EPSE noted Clozapine had a tendency towards a greater clinical effect
Borison et al. 1988 <sup>46</sup>	Randomised double blind trial. Comparison group. Clozapine(<900mg) vs Chlorpromazine (<1800mg). 6 weeks. 27 treatment resistant patients. (haloperidol 60mg/day).	No observation on EPSE Clozapine had a significant greater overall efficacy (p<0.05)

<b>Trial</b>	<b>Design</b>	<b>Summary of Key Findings</b>
Breier et al. 1994 <sup>41</sup>	Double blind study. 10 week. Clozapine vs haloperidol. 40 schizophrenic patients.	Measures : BPRS, SANS Clozapine appeared superior in both negative and positive symptoms
Pickar et al. 1992 <sup>47</sup>	Double blind placebo control trial Clozapine vs fluphenazine or placebo 21 treatment resistant patients	Measures : BPRS, SANS Clozapine superior to both trial arms in total score, negative score and positive score
<b>Retrospective case studies</b>		
UK Clozapine Study Group 1994 <sup>48</sup>	Open study 54 chronic patients No response to 3 conventional drugs 6 month follow up	77% patients achieved a 25% improvement 42% patients achieved a 50% improvement Improvement defined at 8 weeks and maintained for 6 months Measures : BPRS/NOSIE/PSS/CGI/SARS/AIMS
Revecki et al. 1990 <sup>49</sup>	Retrospective case-controlled study of Clozapine 133 patients on clozapine	28% re-admission rate at 2 years c.f. 56% in conventional control group
Honigford et al. 1990 <sup>50</sup>	Retrospective case-controlled study of Clozapine 86 patients on clozapine	28% re-admission rate at 2 years c.f. 56% in conventional control group (NB: figures same as in Revecki study)

### 2.3.2 Relapse Rate

There is also good evidence that clozapine reduces rates of relapse and decreases the number of re-admissions.<sup>39, 51,52</sup>

### 2.3.3 Side-effects and Contra-indications

The most common side-effects of clozapine noted from the key trial evidence are: sedation; excessive salivation; weight gain and orthostatic hypotension. However, the most serious potential side-effect of clozapine is the risk of agranulocytosis.

Clozapine's ability to cause agranulocytosis is well recognised and resulted in its initial withdrawal in the 1970s. With the development of a comprehensive monitoring system, the hazards can be virtually eliminated. A study of over 11,000 patients reported an incidence

of 0.8% after one year and 0.9% at 18 months.<sup>53</sup> The incidence peaks at three months. This compares with an approximate incidence of agranulocytosis using phenothiazines of 1 in 1,300, a probable under-estimate.<sup>54</sup> The clozapine patient monitoring system (CPMS) initially requires baseline, weekly and eventually monthly white blood cell counts; medication is only provided if the counts are within a normal range. If the count falls, clozapine is stopped and the count will return to normal. This facility can currently only be provided by the manufacturer and dramatically increases the costs. However, to date there have only been two deaths reported due to agranulocytosis since the drug's re-introduction.

Clozapine also carries a risk of seizure which is noted in trials as dose related with incidence rate of 5-10% at dosage above 600mg/day.

The following table summarises the side-effect profile of clozapine and is taken directly from the Wessex DEC report.<sup>36</sup> The data are based on both published and unpublished trial results and on file data covering in total 15,000 patients.

**Table 8 Clozapine's Side-effects - Wessex DEC Report<sup>36</sup>**

<b>Side Effect</b>	<b>Incidence Rate</b>
Sedation	34%
Weight Gain	34%
Excessive Salivation	23%
Gastrointestinal symptoms	17%
Hypotension	11%
Fever	5%
Seizure	4%
Agranulocytosis	1%

#### 2.3.4 Clinical Summary

There is a wide range of clinical trial evidence now available related to the use of clozapine in treatment-resistant patients. Most studies imply a relative freedom from relapse and show better clinical response and lower re-admission rates against conventional treatment.

The Wessex report considered the evidence of effectiveness and the potential benefits to patients and the NHS of clozapine and came to the overall conclusion of recommending its use in treatment-resistant patients.

There is a general clinical consensus and support for the use of clozapine in treatment-refractory schizophrenia. It is now widely accepted that clozapine provides a better clinical response in treatment-resistant patients than conventional drugs.

## **2.4 Clinical Evidence Base: Olanzapine**

Olanzapine is a thienobenzodiazepine, which has a high affinity for the D<sub>4</sub>, D<sub>1</sub> and D<sub>2</sub> dopamine, muscarinic, alpha-1 adrenergic, 5HT<sub>2a</sub>, 5HT<sub>2c</sub> and histamine H<sub>1</sub> receptors.

It is similar to clozapine in chemical structure and in some neuroreceptor activities. However, it does not cause agranulocytosis, thus eliminating the need for weekly blood testing.

With a half-life of between 24-35 hours, irrespective of hepatic and renal impairment, olanzapine can be administered in a single daily dose.<sup>55</sup> The usual therapeutic dosage range is 5 to 20mg/day, with a recommended dose of 10mg/day. Olanzapine reaches peak plasma concentrations at about 5-8 hours after oral administration.

In terms of evidence for efficacy, many of the existing trials relate to the short-term effects of olanzapine. The key randomised controlled trials (RCTs) on olanzapine are summarised in the following table.

**Table 9 Supporting RCTs for Olanzapine**

<b>Trial</b>	<b>Design</b>	<b>Summary of Key Findings</b>
Beasley, Tollefson et al. 1996 <sup>56</sup>	Olanzapine vs haloperidol Randomised double blind 6 week trial 335 patients	More effective than placebo As effective as conventional drugs Olanzapine (15mg/day) is more effective than haloperidol in the negative symptoms
Beasley, Sanger et al. 1996 <sup>57</sup>	Olanzapine 1mg /10mg vs placebo 6 week trial Randomised double blind trial 152 patients	Olanzapine (1mg/day) equivalent efficacy to placebo EPSE not above placebo level Superior efficacy at 10mg in both positive (p<0.001) and negative symptoms
Beasley, Hamilton et al. 1997 <sup>58</sup>	Olanzapine vs haloperidol 6 week trial Double blind 431 patients	Olanzapine had equal overall efficacy to haloperidol
Tollefsson et al. 1997 <sup>59</sup>	Olanzapine(5/10/20mg) vs haloperidol(5-20mg) 1,996 patients 6 weeks	Lower levels of EPSE 66% olanzapine patients completed the study c.f. 47% haloperidol patients (p<0.05) Similar efficacy in positive symptoms Statistically greater efficacy in negative symptoms

To date, there have been four notable double blind randomised controlled clinical trials focused specifically on olanzapine. In total, approximately 3,000 patients were involved in the trials in direct comparisons with haloperidol or placebo as control arms. Dosages of olanzapine varied between 5-20mg/day, with the recommended dose set now at 10mg/day.

Each of the trials lasted over a six week period, which is noticeably short when considering treatments for psychosis. Again, as is common in antipsychotic drug studies, these trials are primarily pharmaceutical company sponsored. However, they are generally considered to be of a high standard and well conducted.

#### 2.4.1 Response rate

The first trial found olanzapine to be more effective than placebo and as effective as haloperidol in the control of the positive symptoms of schizophrenia.<sup>56</sup> This observation was made using a measure of mean reduction in the BPRS from original baseline observations. Using the SANS rating scale to focus on negative symptoms in particular, the study also revealed that olanzapine was more effective than placebo and haloperidol when applied at a dosage of 15mg.



In the second trial, 152 schizophrenic patients were randomised to 1mg/day olanzapine, 10mg/day olanzapine or placebo.<sup>57</sup> The 1mg/day olanzapine was shown only to be equivalent to placebo in all efficacy comparisons. However, the 10mg dose olanzapine had statistically superior efficacy over placebo in both positive and negative symptoms of schizophrenia, when considered on both the BPRS and PANSS rating scales. EPSE levels were not noted above the placebo levels. Clinical response was defined as a 40% decrease in baseline BPRS scores or a final score  $\leq 18$ .

The third trial showed olanzapine to have equal efficacy to haloperidol in both the positive and negative symptoms.<sup>58</sup>

The fourth trial compared 5-20mg/day doses of olanzapine to a range of doses of haloperidol 5-20mg/day and, again, was based over a six week period of time.<sup>59</sup> The patient group included 1,996 schizophrenic, schizophreniform and schizoaffective patients. Interestingly, 65% of olanzapine treated patients completed the study compared to 47% in the conventional treated group. A similar efficacy in the positive symptoms was noted between olanzapine and haloperidol, with no statistically significant differences in effectiveness. Patients treated with olanzapine had statistically greater improvement in negative symptoms than their haloperidol counterparts. At study conclusion, olanzapine patients were reported to have an average decrease of 4.5 points on the PANSS negative symptom scale, compared to an average decrease of 3.2 points in patients treated with haloperidol. Patients treated with olanzapine showed comparable improvements to haloperidol patients in positive symptom improvement.

Also, Olanzapine was associated with lower levels of EPSE with scores decreasing during treatment. The percentage of patients with treatment-emergent Parkinsonism was significantly lower (14% : 28%) in the olanzapine arm, as was the percentage of patients with an overall Barnes scale global score (12% : 40%).

#### 2.4.2 Relapse rate

Much of the trial evidence for olanzapine is in acute phase studies. There is very little evidence available, as yet, about the long-term efficacy. The results of a one year follow-up study to the Tollefson trial shows rehospitalisation rates of 20% with olanzapine compared to 28% for the haloperidol group.

#### 2.4.3 Side-effects and Contra-indications

Common side-effects of olanzapine include somnolence, dizziness not related to hypotension, and weight gain. These are generally expected in around 10% of patients.

Less prevalent side-effects include: increased appetite, peripheral oedema, constipation, dry mouth, and are observed in between 1-10% of patients.

In a combination analysis of three clinical studies, patients receiving olanzapine were less likely to report treatment related EPSE symptoms. About 8.5% of olanzapine patients exhibited long-term treatment-emergent TD symptoms at any baseline visit, compared with 17.3% of haloperidol patients.

The most common side-effects associated with olanzapine reported were insomnia (10.4%), dry mouth (7.5%), akathisia or uncontrollable motor restlessness (6.6%) and nervousness (5.6%). There have been no reported cases of agranulocytosis.

There have been significant contra-indications noted:

- taking alcohol with olanzapine can increase heart rate and lead to dizziness;
- contra-indications in pregnancy and in breast feeding women;
- contra-indications in patients with a risk of narrow-angle glaucoma.

#### 2.4.4 Clinical Summary

The four trials supporting olanzapine have been relatively well received in the published literature and demonstrate the clinical equivalence to haloperidol over the short term. However, as the trials were all based over six week periods, it is very difficult to be certain over a longer time period.

Therefore:

- Olanzapine's efficacy against the negative symptoms of schizophrenia seems superior to that of conventional drugs over the short-term;
- Olanzapine should be considered to be equally effective in terms of positive aspects of schizophrenia over the short-term;

- Olanzapine demonstrates similar EPSE levels as with placebo, these being significantly lower than those with conventional drug therapy;
- Olanzapine appears to have a better compliance profile than conventional drugs;
- Efficacy in treatment-resistant patients remains unproven with a need for further trial evidence in this specific group of patients.

## **2.5 Clinical Evidence Base: Risperidone**

There is an established set of published clinical trials which relate to risperidone. Also, a Wessex DEC report, considering risperidone in treatment-resistant schizophrenia, has been published;<sup>68</sup> and, in addition, there is a recent meta-analysis conducted by Song et al.<sup>60</sup>

The following summarises the evidence for the clinical effectiveness of risperidone and refers to both these reports.

### *Song Meta-Analysis*

A meta-analysis of RCTs of risperidone in the treatment of schizophrenia was recently published.<sup>60</sup> This analysis took account of 11 double-blind trials, which were identified in a review of standard data sources (Medline, EMBASE, BIDS and PSYCLIT).

The most common comparison arms were based on haloperidol (2mg-20mg) and/or placebo. The data were apparently pooled using the approach covered by Whitehead.<sup>61</sup> Details of the individual trials are summarised in Appendix A.

The majority of patients entered into these 11 trials were hospitalised in-patients who were suffering from chronic schizophrenia. The mean time since onset was around 15 years and the mean duration of the current period on admission was six months.

In evaluating effectiveness, clinical improvement was defined as a 20% reduction from baseline (the initial scale value of each patient) in the PANSS total score or the BPRS total score. Using the total score includes clinical effects on both the positive and negative symptoms. This 20% level matched the limits used in the clinical trials. However, there is no

definitive statement as to the exact clinical relevance of this limit (i.e. how much difference in terms of treatment and/or quality of life this 20% reduction would represent).

Three specific outcome measures were explored within the meta-analysis and a summary of the main findings are presented in the following table.

**Table 10 Findings of the Meta-Analysis**

<b>Meta Analysis: Outcome Measure</b>	<b>Odds ratio with 95% confidence intervals</b>	<b>Control Group</b>	<b>Risperidone Group</b>	<b>Number Needed to Treat for One Event Difference</b>
Showing clinical improvement	1.27 (1.04-1.56)	52%	57%	20
Using anti-Parkinsonian medication	0.51 (0.41-0.63)	38%	23%	7
Drop-out before end of trial	0.75 (0.61-0.94)	34%	29%	20

Across all the trials overall clinical improvement and response rate were noted on average to be better with risperidone than with conventional therapy (57% compared to 52%); odds ratio 1.27 (1.04, 1.56). This measure includes both the positive and negative symptoms of the illness.

When considering further the individual negative symptoms of schizophrenia, there are eight trials which have specifically used the PANSS negative scores. These trials suggested that risperidone is more clinically effective than the control arm, with a pooled difference in the PANSS score between the risperidone and haloperidol groups of -0.74 (95% CI -1.50, 0.02), which has only borderline significance ( $p < 0.058$ ).

The overall drop-out rate was also reported to be statistically significant between the two arms, with risperidone patients having a 29.1% rate compared to 33.9% with the control arm; odds ratio 0.75 (0.61, 0.94).

Song discussed some of the differences found in the overall treatment effects between the trials. It was noted that one trial had a baseline PANSS score of 120.5, much higher than the other trials representing a chronic patient group, and two trials had relatively low PANSS and BPRS scores.<sup>62,63,64</sup> There were also trials which had relatively low levels of risperidone dosages (1-2mg/day), which was felt to favour the conventional arm. In order partly to allow

for these potential differences, a number of alternative sensitivity analyses were presented, which excluded those trials with either low dosage levels or very different entry baseline rating scales.

The results of the sensitivity analysis do not alter the overall outcomes of the meta-analysis when compared with an all trial based analysis. Only scenario 2 removes any of the statistical significance, however this scenario includes all sub- and supra-therapeutic dosages of risperidone.

**Table 11 Risperidone Meta-Analysis Sensitivity Analysis**

	Odds ratio with 95% Confidence Interval		
	Clinical Improvement	Drop-Out Rate	Use of EPSE medication
All Trials	1.27 (1.04, 1.56)	0.75 (0.61, 0.94)	0.51 (0.41, 0.63)
Scenario 1	1.34 (1.09, 1.64)	0.73 (0.58, 0.91)	0.57 (0.46, 0.70)
Scenario 2	1.20 (0.96, 1.49)	0.81 (0.63, 1.03)	0.55 (0.44, 0.71)
Scenario 3	1.33 (1.05, 1.68)	0.75 (0.57, 0.97)	0.54 (0.42, 0.70)

**Scenario 1:** Excludes sub-therapeutic risperidone dosage <4mg/day (Chouinard et al.<sup>65</sup>, Marder et al.<sup>66</sup> and Peuskens et al.<sup>67</sup>)

**Scenario 2:** Excludes Chouinard et al., Marder et al.

**Scenario 3:** Excludes Chouinard et al., Marder et al., all sub-therapeutic risperidone dosages <4mg.day and supra-therapeutic dosages >10mg/day (Peuskens et al.)

Wessex DEC Report

The Wessex DEC Report No 48<sup>68</sup> recently considered the use of risperidone in treatment refractory schizophrenia. Risperidone was compared to clozapine, already used in treatment-resistant patients. The report reflected on the fact that there are no suitable trials of risperidone in truly treatment-resistant patients and, only one trial exists, which places it in a direct 'head to head' comparison with clozapine.<sup>69</sup> This trial showed an equivalent efficacy but, importantly, was based on a relatively small sample size of 59 patients and, as with the other trial evidence, was very much based on a short-term time span of four weeks. The patients included were not all of a truly refractory nature.

The Wessex report concludes that the case for risperidone in refractory schizophrenia remains unproven. A summary of the trial evidence used can be found in Appendix A.

### 2.5.1 Side-effects and Contra-indications

From the meta-analysis of trials, a combination of pooled results indicated that the use of related medication related to EPSE was 23% in the risperidone group and 38.4% in the conventional haloperidol group.

Also, when combining the trial results, 18.7% of risperidone patients reported EPSE compared to 35.1% in the conventional drug patients. When compared to the levels of EPSE reported from the olanzapine trials, it was noted that there were large differences. The combined study of olanzapine reported 17.3% rates for haloperidol patients. Clearly, it is very difficult to draw any suitable comparisons of 'atypicals' without direct trials.

Risperidone was shown to be associated with significantly ( $p < 0.05$ ) more cases of weight gain and tachycardia above the rate observed for conventional antipsychotics.

Other noted side-effects include insomnia, anxiety, agitation and sedation.

### 2.5.2 Clinical Summary

The meta-analysis concludes that the short-term efficacy of risperidone is comparable to conventional antipsychotics. It can also be seen to be associated with a lower rate of EPSE, a common side-effect of conventional drugs.

There is still a need for more longer-term studies of risperidone.

- Risperidone presents less EPSE than those associated with conventional antipsychotics, although low levels of EPSE are reported at dose  $\geq 10$ mg/day.
- Risperidone appears to be more effective in respect of the negative symptoms, but this was based on a result of borderline statistical significance and has only been demonstrated over the short-term.

- Risperidone is observed to have an overall equivalent efficacy to conventional drugs when considering total rating scores in acute trials.

Risperidone mimics clozapine to some extent in showing reduced motor side-effects even though predominantly in low dose ranges, and the drug lacks most of the serious side-effects of clozapine, like agranulocytosis, cardiac effects, and seizure induction.

In terms of treatment-refractory patients, the efficacy of risperidone has not yet been demonstrated, however studies are currently underway in comparison with clozapine.

## **2.6 Clinical Evidence Base: Sertindole**

Sertindole is an 'atypical' antipsychotic, manufactured by Lundbeck as Serdolect, which is said to have a selective inhibitory effect on mesolimbic dopaminergic neurones.

Sertindole is demonstrated to be a potent antagonist at dopamine D<sub>2</sub>, 5HT<sub>2</sub>, and alpha1-receptors without activity at histaminic H1 or muscarinic receptors. This selectivity should not produce sedative effects or anticholinergic effects related to other receptors.

There are still only two published trials which have focused on the use of sertindole in the treatment of schizophrenia, these are listed in the table below.

The Van Kammen trial was a dose ranging study, which was controlled and lasted over a period of 40 days. The study involved 205 in-patients with a previous clinical response to antipsychotics. The study explored three dosages of sertindole (8,12 and 20mg/day) against a placebo control arm.<sup>70</sup>

The study found that only the 20mg dose of sertindole showed an increased effectiveness over placebo in both positive and negative symptoms, using the CGI as an outcome measurement scale.

In terms of side-effects, the incidence of EPSE was found to be no different irrespective of dosage or control arm.

The Zimbroff study was a multi-centre, double-blind, eight-week clinical trial which was designed to compare three doses of sertindole (12, 20 and 24mg/day) with three doses of haloperidol (4, 8 and 16mg/day) and also a placebo control arm. Within the study, all

sertindole doses and haloperidol doses showed significant improvement in the positive symptoms of schizophrenia compared with placebo and in reducing the total scores on the PANSS.<sup>71</sup>

**Table 12 Supporting RCTs for Sertindole**

Trial	Design	Summary of Key Findings
Van Kammen et al. (1996) <sup>70</sup>	Randomised, double blind dose ranging study. Sertindole (1mg/12mg/20mg) vs placebo. 205 schizophrenic patients. 40 day trial.	At 20mg sertindole has significantly greater efficacy on both positive and negative symptoms. 105 patients completed study.
Zimbhoff, Kane et al. (1997) <sup>71</sup>	Multi-trial, seven centre, dose ranging double blind trial. 497 patients - 20 excluded from intention to treat. 8 week study .	Sertindole has significantly greater efficacy over placebo in PANSS total score ( $p < 0.05$ ). At 20mg sertindole also reduced negative symptoms as per PANSS and SANS. No difference in reported EPSE levels.

Only sertindole, at a dose of 20mg/day, was noted as reducing the negative symptoms of schizophrenia, as measured by the PANSS Negative Symptom Sub-scale and total SANS ( $p < 0.001$ ).

On a comprehensive global scale of improvement (the CGI), all doses of sertindole and haloperidol were associated with significant improvement compared to placebo.

Within the study, EPSE rates were measured by the number of EPSE-related adverse events, use of anti-EPSE medication and three standardised movement rating scales. Patients using haloperidol experienced rates significantly higher than in the placebo arm, confirming the known relationship between conventional drugs. EPSE-profiles for sertindole were clinically and statistically indistinguishable from placebo. In addition, patients treated



with sertindole, irrespective of dose, exhibited significantly less EPSE than patients using haloperidol.

The adverse events that occurred more often with sertindole than placebo included nasal congestion and decreased ejaculatory volume. The adverse events that occurred more often with haloperidol than placebo were EPSE-related.

### 2.6.1 Side-effects and Contra-indications

In clinical trials, the most commonly noted side-effects with sertindole compared to placebo arms are prolongation of the QTc interval, reduced ejaculatory volume and nasal congestion. Also, there are a series of lesser problems associated with: weight gain; dry mouth; dizziness; postural hypotension; headache; and insomnia.

The non-sedating nature of sertindole has also been noted and is an important consideration when selecting appropriate patients for sertindole-based therapy.

The contra-indications for sertindole include:

- cardiovascular disease;
- pregnancy;
- breast-feeding;
- history of seizures.

Care is required in respect of use in:

- diabetes (adjustment to antidiabetic therapy may be needed);
- patients with hepatic impairment (may require lower dosage and slower titrations);
- patients on fluoxetine or paroxetine (may require a dosage reduction due to low metabolism rates for sertindole).

The information on contra-indications and treatment considerations is well published and can be found in more detail in the Drug and Therapeutics Bulletin<sup>72</sup> and the Trent Drugs Information Service Monograph: Sertindole.<sup>73</sup>

### 2.6.2 Cardiac Conduction Changes

Sertindole can cause a prolongation of the QTc interval as measured by an ECG. This electrical conduction defect can potentially cause cardiac dysrhythmias, including torsade des pointes. The incidence of this adverse effect is approximated at 1.7% of patients taking sertindole.<sup>74</sup> The effect is most commonly observed within the first 3-6 weeks of treatment and appears not to be dose related. Since its introduction, the manufactures of sertindole have altered the prescribing and monitoring guidelines and now recommend a baseline ECG and regular ECG monitoring during dose titration and during continuing treatment. If ECG changes reach a pre-defined level, then it is advised that the drug treatment is stopped. This requirement for monitoring presents an obvious extra element of cost in using sertindole.

Some uncertainty remains over the implications of this finding. Comparative trials will probably reveal no difference in QTc between sertindole and conventional antipsychotic drugs. To date, there have been no reports of life-threatening arrhythmias in patients on sertindole.<sup>75</sup>

### 2.6.3 Clinical Summary

In summary, the two trials provide a valuable insight into the dosage effects. However, it must be said that the length of time covered by both is relatively short and it is impossible to draw any firm longer-term conclusions from their results.

In comparative terms, sertindole does present a range of contra-indications and treatment interactions, in particular, the issues around QTc interval, which are commonly seen by clinicians as a barrier to their use and acceptance by patients. This is especially the case as there are no proven efficacy benefits over any of the other 'atypical' drugs. It has also been noted that, in comparative terms, the marketing push for sertindole has been noticeably less than for its competitors.

Taking all points into consideration, the evidence for effectiveness of sertindole appears credible over the short-term but remains to be proven in a longer-term setting.

***Post DEC Meeting Note: On December 3, 1998 sertindole was withdrawn by Lundbeck due to established cardiac toxicity problems (which have been discussed above).***

## 2.7 Summary of 'Atypical' Antipsychotics

The following brings together a summary of the current clinical views on ‘atypical’ antipsychotics.

### 2.7.1 Side-effects

The real potential benefit of ‘atypical’ antipsychotics is seen as their reduced levels of side-effects when compared to the existing conventional drug treatments. Most of the reported trials compare ‘atypical’ antipsychotics with conventional and placebo control arms and make direct comparisons of side-effects, with a particular focus on the EPSE group of more serious neurological adverse effects.

The following table presents and summarises the typical range of side-effects, noted from trial evidence, for the main ‘atypical’ drugs.

**Table 13 Summary of Side-effect Profiles of Newer Antipsychotics**

<p><b>Clozapine</b></p> <ul style="list-style-type: none"> <li>• sedation</li> <li>• seizures</li> <li>• hypo-hypertension</li> <li>• hypersalivation</li> <li>• weight gain</li> <li>• constipation</li> <li>• agranulocytosis</li> </ul>	<p><b>Sertindole</b></p> <ul style="list-style-type: none"> <li>• nasal congestion</li> <li>• decreased ejaculatory volume</li> <li>• dizziness</li> <li>• dry mouth</li> <li>• orthostatic hypotension</li> <li>• weight gain</li> <li>• prolonged QTc interval</li> </ul>
<p><b>Risperidone</b></p> <ul style="list-style-type: none"> <li>• insomnia</li> <li>• agitation</li> <li>• anxiety</li> <li>• headache</li> <li>• somnolence</li> <li>• hypotension</li> <li>• EPSE (dose &gt;10 mg)</li> </ul>	<p><b>Olanzapine</b></p> <ul style="list-style-type: none"> <li>• somnolence</li> <li>• weight gain</li> <li>• dizziness</li> <li>• peripheral oedema</li> <li>• orthostatic hypotension</li> <li>• constipation</li> <li>• dry mouth</li> </ul>

Noticeably, only risperidone has shown any notable levels of EPSE, which was very much related to the higher dosage use of the drug. Even these levels were lower than in conventional therapy.

The occurrence of EPSE is extremely low in patients on clozapine and it may actually help improve TD.<sup>38,32</sup> Lieberman et al. report a 50% decrease in TD symptom severity in 40% of patients taking clozapine.<sup>76</sup> Similar findings are reported for the other new compounds.

Sertindole causes significantly less EPSE compared with haloperidol (18% vs 47%), overall the same rate as in a placebo-controlled group. There are limited data on its long-term use, but early reports suggest lower rates of TD (2% c.f. 8% at 1 year). Olanzapine produced near identical findings with rates of EPSE no different from placebo-controlled groups.

Studies on risperidone are less clear cut, at lower doses (6-8mgs) rates of EPSE are minimal, but these side-effects become more apparent with higher doses of 12-16mgs a day.

A study report, published by Casey, considered the side-effect profiles of 'atypicals' and conventional drugs.<sup>77</sup>

The report based its findings on a summary covering a number of disparate trial results. Whilst this has problems in terms of the obvious differences in clinical settings and assessment schedules, it does provide a valuable insight into the side-effect benefits and their potential to influence compliance.

The report draws out and highlights three key side-effects related to 'atypicals':

- EPSE associated with high doses of risperidone;
- agranulocytosis as a potential adverse effect of clozapine;
- the QTc interval lengthening associated with sertindole.

More generally, the report draws attention to the tendency for patients to increase weight with all the 'atypical' drugs and the general low level of sedation in the newer 'atypicals' (excluding clozapine), especially in the case of sertindole.

The study finally calls for more structured and controlled 'head-to-head' comparisons of drugs.

**Table 14 Comparative Side-effects of the New Antipsychotic Agents**

Item	Typical Neuroleptics	Clozapine	Risperidone	Olanzapine	Sertindole
CNS Extrapyrmidal side-effects	+ to +++	0	0 to ++ <sup>ab</sup>	0 <sup>a</sup>	0 <sup>a</sup>
Tardive dyskinesia (TD)	+++	0	?	?	?
Seizures	0 to +	+++	0	0	0
Sedation	+ to +++	+++	+	+	0
Neuroleptic malignant syndrome (NMS)	+	+	+	?	?
Orthostatic hypotension	+ to +++	0 to +++	+	+	+
QTc	0 to +++	0	0 to +	0	++
Liver transaminase increase	0 to ++	0 to +	0 to +	0 to +	0
Anticholinergic	+ to +++	+++	0	+	0
Agranulocytosis	0	+++	0	0	0
Prolactin increase	++ to +++	0	0 to ++	0 <sup>c</sup>	0c
Decreased ejaculatory volume	0 to +	0	0	0	++
Weight gain	0 to ++	+++	++	++	++
Nasal congestion	0 to +	0 to +	0 to +	0 to +	++

Symbols:

0 = none or not significantly different from placebo:

+ = mild

++ = moderate

+++ = marked

? = insufficient data available

<sup>a</sup> = Not significantly different from placebo-treated group, which may have received typical neuroleptics before entering the study and could have EPSE carry forward into the initial weeks of the investigation.

<sup>b</sup> = Dose-related EPSE above 6mg/day.

<sup>c</sup> = Dose related increases within the normal range.

The following table provides a helpful summary of the potential side-effects behind 'atypical' antipsychotics.

**Table 15 Adverse Effects of 'Atypical' Drugs Compared with Haloperidol**

Drug	Acute EPSE	TD	NMS	Hypotension	Hyper-prolactinaemia
Haloperidol	+++	+++	+++	+	+++
Clozapine	-	-	-	+++	-
Risperidone	+	?	++	++	+++
Sertindole	-	?	?	-	-
Olanzapine	-	?	?	-	+

### 2.7.2 Clinical Efficacy

Risperidone, sertindole, olanzapine and quetiapine have been shown to be at least equally effective as conventional antipsychotics in alleviating acute, or positive, symptoms of schizophrenia. There is evidence that they are all significantly better at improving negative symptoms, though again this may in part be due to secondary negative symptoms.

An area which would produce short-term major cost reductions would be prevention of relapse and subsequent decrease in the number of days in hospital. There is evidence from retrospective studies and mirror-group studies which begin to point towards these kinds of benefits; thus, a significant reduction in hospital days for those patients on risperidone compared with conventional treatments has been reported.<sup>87</sup> In a comparison of sertindole with haloperidol over a 12 month period, the mean number of days in hospital was 4.3 and 18.4 respectively.<sup>52</sup> There was also a decreased number of admissions in the sertindole group. Significant reductions in relapse rate for patients on olanzapine compared with haloperidol, 20% at one year compared with nearly 30% respectively has been reported.<sup>57,58</sup> There is a need for further longer-term studies on the use of 'atypical' antipsychotics.

The following table provides a helpful summary of the strength of evidence behind 'atypical' antipsychotics.

**Table 16 Efficacy of 'Atypical' Drugs Compared with Haloperidol**

<b>Drug</b>	<b>Positive symptoms</b>	<b>Negative symptoms</b>	<b>Refractory illness</b>
Haloperidol	++	+	-
Clozapine	+++	+++	+++
Risperidone	++	++	?
Sertindole	++	++	?
Olanzapine	++	+++	?

In terms of efficacy in treatment-resistant patients, the 'atypical' compounds, other than clozapine, have not as yet been shown to be any better than conventional drugs in the 30% of patients who do not respond. Therefore, any statement about the use of 'atypicals' in true treatment-resistant patients is not based on hard clinical evidence. However, this may be about to change as trials are nearing completion - in particular, for olanzapine.

### 2.7.3 Comparative or 'Head to Head' Trials

Unfortunately, the 'atypicals' have yet to be compared adequately with each other in direct clinical trials, most studies either compare with placebo or haloperidol. In comparison trials of 'atypical' drugs, there is currently very little published evidence available. There is an obvious need for a lot more direct comparative data to be made available. However, it is difficult to see how this is going to come from truly independent sources.

One trial has been identified as part of the literature search. The trial is pharmaceutical company sponsored and has received much published comment in terms of the selection of dosages and comparator arms.<sup>78</sup>

The Tran study was a double blind controlled trial of olanzapine versus risperidone in the treatment of schizophrenia. The trial took place in centres over nine countries and involved 41 investigators. The severity of the patients' psychotic disorders at their entry into the study was quantified as a minimum BPRS score of 24 (BPRS extracted from the PANSS, items 0 to 6). Patients were randomly assigned to receive either olanzapine or risperidone in a 1:1 ratio for eight weeks of acute therapy and 20 weeks of continuing maintenance.

**Table 17 'Head to Head' 'Atypical' Drug Trials**

Trial	Design	Summary of Key Findings
Tran et al. 1997 <sup>78</sup>	Randomised double blind parallel study. Olanzapine (5-20mg/day) vs Risperidone (4-12 mg/day). 8 week acute / 20 week maintenance. 297 patients randomised.	Similar drop out with olanzapine as in risperidone-treated patients. Comparable in overall efficacy. Better completion rate for olanzapine over 28 weeks. Olanzapine demonstrated lower relapse rates at 28 weeks (4% vs 9%).

Two hundred and twenty six patients completed the eight-week acute phase, with no statistically significant differences between the treatment groups in completion/drop-out rates.

Olanzapine best met the investigators' first criteria for atypicality by having fewer EPSE than risperidone (monitored using the Simpson-Angus Scale (SAS) and in the frequency of use of anti-EPSE medications).

In terms of anti-EPSE medication, a smaller proportion of olanzapine patients (17.9% vs 31.5%) requested one or more doses of anticholinergic medication. In addition, statistically fewer olanzapine-treated patients experienced elevated prolactin levels after both eight weeks and 28 weeks than did those receiving risperidone.

In efficacy measures, olanzapine and risperidone were comparable in reducing overall positive and negative symptoms of schizophrenia, although olanzapine achieved numerically superior mean changes on six of eight measures, and statistically significant superiority to risperidone in the PANSS mood sub-score at both eight and 28 weeks. In addition, at 28 weeks, a statistically significant advantage with olanzapine was evident among patients who had achieved at least a 30% improvement on the PANSS total score.

Fewer patients receiving olanzapine experienced relapse (4% at three months and 9% at six months) than did those treated with risperidone (9% at three months and 29% at six months). Relapse, a key measure of maintenance efficacy, was defined as a 20% or greater worsening in PANSS total score along with a Clinical Global Impression-Severity of Illness (CGI-S) score equal to or greater than three.



Tran concluded from this 28-week trial that olanzapine showed the key criteria for 'atypical' antipsychotic effects more often and to a greater degree than risperidone. Olanzapine was associated with fewer side-effects, less elevation of prolactin and greater efficacy in mood symptoms. At the dosages employed, he concluded that olanzapine was statistically significantly more likely than risperidone to evoke greater initial therapeutic response and less likely to be associated with relapse during maintenance therapy.

#### 2.7.4 Summary of Key Evidence

- 'Atypicals' are generally better tolerated than conventional drug therapy;
- 'Atypicals' have a lower observed rate of EPSE;
- 'Atypicals' are at least as clinically effective as conventional drug therapy;
- 'Atypicals' have the potential to influence negative symptoms;
- Clozapine is currently the only drug shown to be effective in refractory schizophrenia;
- 'Atypicals' represent a significant increase in pure drug costs;
- 'Atypicals' have been shown to reduce longer-term relapse rates and hospitalisation in non-randomised studies.

It must be re-iterated that these conclusions are based on short-term acute trials only. A summary of other 'atypical' antipsychotics is provided in the appendices.

### 3. COST AND BENEFIT IMPLICATIONS OF ADOPTING INTERVENTION

The following section considers the overall cost implications of newer antipsychotics and their potential benefits.

#### 3.1 Cost Implications of 'Atypical' Antipsychotics

##### 3.1.1 Drug Costs

The newer antipsychotic drugs are substantially more expensive than the older compounds, which is one of the reasons that their current levels of prescription are limited. The table below compares one year costs at 1996 prices for approximately equivalent doses.

**Table 18 Hospital Cost (£) for One Year Treatment, 1996 Prices.  
(Doses are approximately Equivalent)**

Drug	Dosage	Cost
Chlorpromazine	600mg/day	£33
Haloperidol	20mg/day	£117
Sulpiride	1200mg/day	£75
Trifluoperazine	30mg/day	£38
Haloperidol Decanoate	100mg/2 weeks	£79
Zuclopenthixol Decanoate	200mg/2 weeks	£85
Clozapine	450mg/day	£3,094
Risperidone	6mg/day	£1,500
Sertindole	12-20mg/day	£1,337
Olanzapine	5-20mg/day	£687-2,750

Source : BNF March 1997

It can be seen clearly that the cost of newer antipsychotics represents a significant increase over conventional drug therapy. The cost of clozapine remains high due to the requirement for regular blood testing, which is conducted centrally and funded through the drug pricing level.

### 3.1.2 Cost Burden on a 'Typical' District

Using national epidemiological data and published prevalence rates (4 per 1,000 population 'at risk') it can be predicted that an average district should realistically expect to have around 1,300 schizophrenic patients living within the community. This represents all patients and, importantly, includes those not actually known to the existing healthcare services.

Annually, a 'typical' district should expect an incidence of around 64 people experiencing first episodes of schizophrenia per annum.

Recent patient audits in Nottingham reveal that there are approximately 30 new patients, within the Trust's catchment area, with newly diagnosed pure schizophrenia every year (Brewin et al., 1997<sup>4</sup>) and this figure is reasonably steady. This value rises to around 168 when including a broader definition of schizophrenia.

Recent attempts to audit the level at which schizophrenic patients actually access services within the Nottingham area estimate the prevalence at somewhere between 1,200-1,300 patients. Although the numbers in this patient group are difficult to assess, the totals identified fit reasonably well with the national prevalence estimates.

If the generally accepted view is believed that 30% of new schizophrenics will respond well, with good prognosis, on conventional drugs, then it can reasonably be expected that the remaining 70% of the new patients will be suitable for 'atypical' antipsychotic drug therapy. Also, using haloperidol as a representative conventional drug, the marginal drug cost for these patients can be estimated at around £2,000. This cost represents the extra cost per patient spent above the cost of conventional treatment. Combining these estimates, it is seen that, for a 'typical' district, 45 new schizophrenic patients per annum (70% of 64 patients) will be suitable for treatment on 'atypical' antipsychotics at an overall marginal cost of £90,000.

If the lower Nottingham estimate of 20 suitable patients per year were to be accepted, then this value reduces to about £40,000.

However, account must also be taken of the patients already known to the service, i.e. 1,300 patients using the national figures. If the same 30%/70% split is applied to the patient

prevalence, 910 patients are identified who would not be expected to respond well to conventional drugs.

Interestingly, the recent Nottingham Trust audit of proposed antipsychotic prescribing estimated that there were approximately 250 patients, out of a total of 1,200 -1,300, in need of these newer drugs, either because of intolerable side-effects or treatment resistance. This equates to roughly 20% of the current case-load. This lower level of suitable patients may be a direct reflection of the current restrictions in prescribing 'atypicals' rather than any real measure of need, but this remains unclear.

The following presents the expected marginal cost for varying proportions of the current case-load being suitable for 'atypical' drugs.

**Table 19 Extra Direct Costs for a 'Typical' District due to 'Atypical' Drug Prescribing**

<b>Proportion of Caseload Suitable for 'Atypical' Drugs</b>	<b>Number of Patients Suitable for 'Atypical' Drugs</b>	<b>Marginal Cost per Patient</b>	<b>Total Marginal Cost</b>
20%	260	£2,000	£520,000
30%	390	£2,000	£780,000
40%	520	£2,000	£1,040,000
50%	650	£2,000	£1,300,000
60%	780	£2,000	£1,560,000
70%	910	£2,000	£1,820,000

The total revenue for the Nottingham Healthcare NHS Trust in 1996/97 was £51 million. Approximately £752,000 or 1.6% of the total was spent on drugs. Antipsychotics accounted for only £225,000 and, within this figure, only 48 patients received the newer drugs, at a cost of £120,000; which emphasises the additional financial burden of the newer drugs.

### **3.2 Potential Benefits of Antipsychotics**

The overall benefits of prescribing 'atypical' antipsychotic medication to schizophrenic patients are difficult to quantify in terms of direct health service costs.

There appears to be a potential for a significant reduction in the level of serious side-effects for patients receiving these drugs. There may be very substantial benefits in terms of the natural history of the disease of a few patients, but the current evidence is unclear on this matter. Better compliance, partially due to improved tolerance, may also reduce relapse and re-admission rates and may have knock-on cost saving effects.

However, some evidence suggests that patients receiving this medication may be more able to utilise existing rehabilitation services and, hence, have a cost increasing effect.

Finally, these drugs may have the effect of improving quality of life, and that of families and carers but, as yet, these effects on quality of life are very difficult to quantify.

### **3.3 Existing Cost-effectiveness Studies**

In terms of published studies which focus on the relative cost-effectiveness of newer antipsychotics, there is very little evidence currently available.

One study, currently in press and funded by Eli Lilly,<sup>79</sup> has considered the use of olanzapine in non-treatment resistant patients who have experienced multiple episodes. This study is based on a decision-tree model of patient pathways simulating the symptom characteristics of patients and repeatedly considering a three-monthly cycle of treatment over a five year time span. The study uses a decision tree structure based on a previous approach<sup>49</sup> and has populated the model using data from literature, olanzapine trial data and UK clinical opinion. Results are expected to present a positive cost argument for olanzapine over haloperidol and, also, an advantage in clinical effectiveness, when considering the time spent by patients below a BPRS threshold of 18, which indicates a relatively good mental state. The authors are very clear in their description of the model as a theoretical estimate, listing out the range of assumptions necessarily taken. They also highlight the fact that health resource use data are extremely difficult to identify in mental health cases. The described process of expert panel and wide literature review highlights the levels of research resource required to conduct modelling exercises of this nature and stresses the need for clinical involvement.

All remaining economic studies are centred on clozapine and its use in treatment resistant schizophrenic patients.

A recent editorial in the British Journal of Psychiatry helps to reiterate the overall view of the cost-effectiveness evidence with relation to drug treatments in schizophrenia.<sup>80</sup> In commenting on a recent open small-sample study, it notes the real lack of large scale fully randomised and blinded study data in relation to schizophrenia and mental health generally. It also stresses the need for more longer-term studies, as much of the existing evidence is focused on the more immediate impact of drugs and their side-effects. This need for better and clearer evidence is stressed even more with the obvious cost implications of the 'atypical' drugs. The article essentially continues the open debate regarding the relative ethics of short naturalistic studies and the longer-term prolonged randomised studies in mental health issues.

Aitchison et al.<sup>81</sup> recently considered the cost-effectiveness of clozapine in a UK based study comparing the three year history of patients not treated with clozapine to a following period of clozapine treatment. The study involved 26 patients who had either chronic schizophrenia or schizoaffective disorder. The study claimed that the mean cost per annum of the patients on clozapine was £32,836 compared to £36,604 pre-clozapine, representing an annual net saving of £3,768. In terms of patient values, this represents a saving of £145 per annum on an original patient cost of £1,407, an overall decrease of 10%. These costs included: hospitalisation/accommodation, drug cost and service use. The study also showed a lower level of unemployment following the introduction of clozapine (12 patients compared to 21). The study identified a reduced level of hospitalisation costs per patient with £19,740 (60.1% of total mean cost post-clozapine) compared to £29,072 (79.4% under conventional treatment).

Revicki et al.<sup>49</sup> published a study of cost-effectiveness using clozapine in treatment-resistant patients compared to standard antipsychotic medication. The study was based on a retrospective comparison of two patient groups taken from seven centres in the USA. The cost study considered only the direct costs associated with the treatment and did not expand into the consideration of wider society costs, such as, unemployment, carer effects etc. The study was based on patients who were treatment-resistant to conventional drugs. The study claims that, although more costly in the first year, clozapine would be cost beneficial by the end of year 2 with a net saving of \$12,622 (£8,000) when comparing a clozapine treated group to a non-clozapine comparator arm.

Questions were raised with regard to this study, in particular about the possibility of non-resistant patients being included in the control arm and the exclusion of some hospitalisation costs. Overall, the study, even in a later re-worked form, remained inconclusive.

Davies and Drummond<sup>17</sup> published a study which considered further the cost-effectiveness of clozapine in treatment refractory schizophrenia. The basis of the paper was an economic model based on a decision tree developed from the Revicki retrospective cohort study. The study was not randomised and potential for bias remained. The underlying model was adapted to the UK in terms of cost and treatment management via the use of standard costings and clinical Delphi consensus exercises. The outcomes of the study suggested that clozapine remained cost-neutral and that, under the central estimates used, it actually reduced direct costs. A £91 per annum saving (£1,333 per lifetime) is forecast under the base case analysis. Also, a net gain of 5.87 years with mild disability is predicted as a benefit per patient lifetime. The paper concludes that prospective economic studies are necessary to confirm the results.

Meltzer et al.<sup>82</sup> published a further study of cost-effectiveness of clozapine in treatment-resistant patients. This study was based on a cohort of 96 treatment-resistant patients with a two year history of schizophrenia prior to study. The study noted that the cost of treatment was significantly reduced if patients continued clozapine treatment for > 2 years. These cost savings were primarily due to the reduction in levels of hospitalisation.

Chouinard et al.<sup>83</sup> produced a utility analysis on the cost-effectiveness of risperidone. The basis for the analysis was the results of a multi-centred RCT by the same author, which compared risperidone with oral haloperidol. The original study was dose ranging and showed that risperidone at 6-16mg/day was superior to 20mg/day haloperidol on several of the symptom measures in PANNS. This study is different from the other published economic analyses of 'atypicals' as it does not claim a net cost reduction due to the drug, but does predict that a real benefit is achievable for the patient. The analysis uses the concept of Quality Adjusted Life Years (QALYs) to measure patient benefit. The utilities were calculated using the linear analogue and standard gamble techniques on patient profiles with ratings made by psychiatric nurses and not patients. The study reported an annual gain to patients of 0.075 QALYs per annum compared to conventional treatment. By comparing an incremental cost of £690 (Can \$1600) to a gain of 0.075 QALYs, the estimated cost per QALY was stated as £10,057 (Can \$23,333). Again, it must be said that the basis of this

was a short-term trial but, with a randomised design, having a clearer underlying methodology to its analysis than in the other studies.

Glazer et al.<sup>84</sup> looked specifically at 'revolving door' schizophrenic patients and the potential effects of depot medication and 'atypical' drugs. The study was based on a clinical decision analysis model, which was based on a collection of assumptions regarding compliance rates and re-hospitalisation rates. The paper compared the three treatment options (depot conventionals, oral conventionals and oral 'atypicals') under a variety of different scenarios. The study used the annual direct treatment costs as the primary outcome measure, including drug cost, clinic and case management cost as well as in-patient costs. The model used a standard rate of 80% chance of a stable management given patient compliance under all three options; this reduces to 15% in non-compliance cases. The key difference between the treatment options was in the default compliance rates used: 50% oral conventional, 80% depot and 65% oral 'atypical'.

The conclusion was that depot medication provided a better outcome in all but one of the scenarios used. However, under this scenario, in which compliance rates of 'atypicals' increased to 80% and the cost of 'atypicals' reduced by 25%, 'atypicals' became the cheapest option. The quality of evidence presented in this report is limited due to the level of assumptions taken and the very much simplified model structure. The authors themselves again recognised the need for prospective trial evidence.

In a review of cost-effectiveness studies, Meltzer considered three published studies.<sup>85</sup> Meltzer's conclusion was that clozapine had been found to be clinically superior to conventional therapy. He recognised the observed lower costs in treatment-resistant patients associated with lower hospitalisation rates, even when including drop-outs from clozapine treatment. Overall, he concludes that if drop-outs from clozapine treatment are in the range 30-50% and occur within 1-4 months of treatment, then clozapine is likely to be cost-effective. Meltzer calls for more focused studies on specific patient groups.

Hargreaves et al. also reviewed the pharmacoeconomics of antipsychotics in the treatment of schizophrenia.<sup>86</sup> This review considered both clozapine and risperidone before widening out into a discussion around the inclusion of economic measurement in randomised controlled trials. The review comments on the Revicki paper, pointing out the inconclusive nature of the report and the fact that follow-up analysis had also failed to provide an overwhelming case for clozapine in treatment-resistance. The paper also comments on the



modelling work of Davies and Drummond which took the Revicki decision tree into a UK setting using a consensus panel. Hargreaves confirms the apparent cost-effectiveness of clozapine in this study, but also comments on the sensitivity of this result to slight changes in assumptions.

The Hargreaves review also cited a number of studies which considered the cost-effectiveness of risperidone. All of these were mirror-image studies, which matched the test group with a selected group of control patients.<sup>87</sup> The studies all reported an observed reduction in the number of hospitalised days under risperidone and, therefore, implied a cost-benefit over standard treatment. However, all fell short of providing a true cost analysis. This type of study has a number of associated problems with no true randomisation and no blinding within the study design. They are also retrospective by definition. It is very difficult to generalise beyond the study in these cases. The review finally considered a retrospective study comparing two treatments: risperidone and clozapine. The arms were of a small number of patients with a mixture of diagnoses (some of which in the clozapine arm were not pure schizophrenia), all of whom had a history of in-patient treatment. Comparisons were made with the costs in the year prior to treatment.

In summary, there exists only a limited body of economic information related to 'atypical' antipsychotics. This is based on a mix of retrospective studies and pharmacoeconomic modelling. There is a clear and identified need for more RCT-based analysis with cost-effectiveness analysis built into the studies, wherever possible.

Table 20 summarises the cost-effectiveness studies for 'atypical' antipsychotics. These are primarily focused on clozapine, although there are a limited number relating to risperidone.

### Conclusions

Whilst there appears to be some consideration of cost-effectiveness now reaching the published literature, a great deal of this is still focused on the use of clozapine, specifically in treatment-resistant patients. Often there is still some confusion over exactly what costs are included within the analyses and, generally, the results are difficult to generalise to a wider schizophrenic population. A small number of analyses adopt modelling approaches, given the lack of focused trial evidence with cost-effectiveness designed as a clear primary objective.

From the review of cost-effectiveness evidence, we can draw the following conclusions:

- There is suggestive evidence, in the case of clozapine, that there are sufficient cost savings from in-patient and other costs to off-set the high direct costs of the drug itself and the patient monitoring requirements.
- Although this claim of cost saving has also been made in the case of the other 'atypical' drugs, there is less evidence for this, and it is certainly a more contentious issue. Nevertheless, there may be something in the claims and the NHS ought to be taking very seriously the possibility of improving the health state of this group of people at zero, or negative net cost.
- The implication of this is that this is a very strong case for some further trial work targeted at an economic analysis. A process for starting such analysis is suggested in section 3.4 via the use of healthcare modelling.

### **3.4 Cost-effectiveness Modelling**

Given the current lack of cost-effectiveness evidence for the newer 'atypical' drugs, from either cohort studies or as a product of clinical randomised controlled trials, we are currently faced with the need to adopt other analytical approaches. Without doubt, cohort study data will become available once these drugs become more widely used and following enough of a time period to observe their real health resource impact. However, until this point is reached within what framework should we consider the cost-effectiveness of these drugs?

In the absence of such hard study evidence, a modelling approach would seem to provide the most appropriate way to address these real present day prescribing issues and to make some level of judgement as to the overall strength of argument for the 'atypicals'. The use of modelling allows the combination of the existing trial evidence with current clinical opinion in order to take a view of schizophrenia reflecting the best of current knowledge. A modelling approach also enables values and parameters to be challenged, using sensitivity analysis, which in turn provides a better appreciation of expected ranges for key outcomes, such as, cost-effectiveness. Modelling is also particularly useful in making judgements as to the strength of relationship between parameters and to identify those assumptions on which the model outcomes rely. Indeed, the Lilly modelling work, described in the review of cost-effectiveness studies, takes this lead and certainly adds value to the overall debate.

In producing this Guidance Note, the authors have considered the type of modelled analysis which could be designed. However, they have stopped short of actually conducting any model themselves, as the resources required to conduct such an exercise are clearly beyond the scope of this document.

The model presented is very much a simplification of the overall treatment management of schizophrenia and should be interpreted with the same level of caution and caveats as with any other healthcare modelling exercise. The main purpose of the model is to present a framework around which to present the known evidence and to facilitate purchasers to begin to consider their options.

The model represents three possible treatment pathways for schizophrenic patients, based on the three possible scenarios for the use of 'atypicals'.

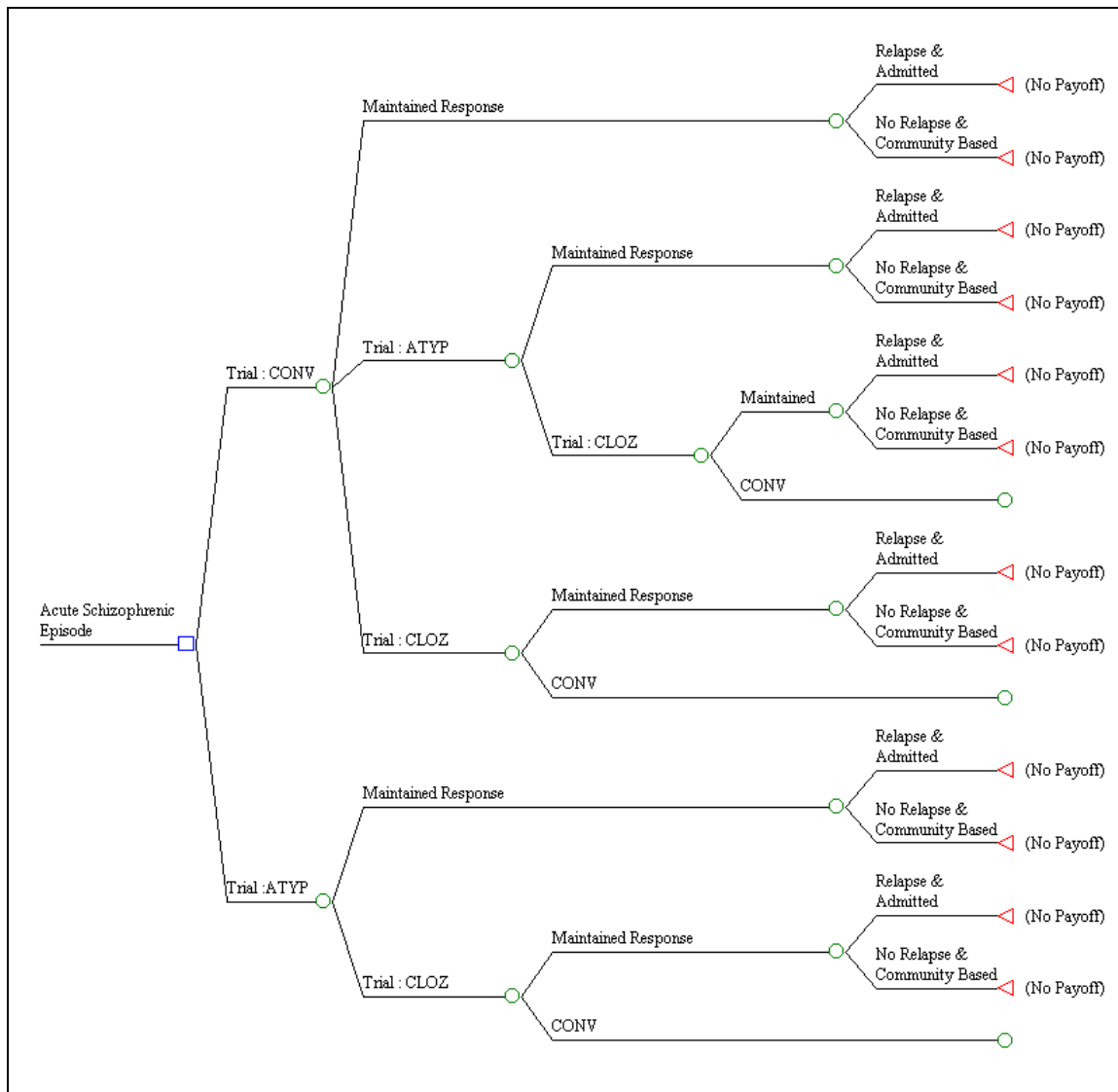
- Scenario 1: Do not use 'atypicals' at all in the treatment of schizophrenia (i.e. use conventional drugs as first line, with clozapine reserved for treatment resistant patients).
- Scenario 2: Use 'atypicals' as a treatment option after reasonable trial with conventional therapy (either 1 or 2 iterations).
- Scenario 3: Use 'atypicals' in place of conventional drugs as a first line therapy.

**Table 20 Summary of Cost-effectiveness Studies**

Trial	Design	Findings
Aitchison et al. 1997 <sup>81</sup>	Small sample cohort study. 29 patients. Direct/indirect costs.	Using clozapine, the patient group achieved a £3,768 annual marginal cost saving - £145 per patient (10% reduction). Reduced hospitalisation cost £19,740 c.f. £29,072 for the cohort. Lower levels of unemployment.
Revicki et al. 1990 <sup>49</sup>	Retrospective study of clozapine vs conventional antipsychotics. Direct costs.	Cohort study suggests clozapine reduces costs at the end of year 2 by £7,800 (\$12,622).
Davies et al. 1994 <sup>18</sup>	Model based analysis. Used Revicki US study as basis.	Suggested a cost benefit with clozapine of: £91 per annum patient cost saving £1,333 per patient lifetime saving
Meltzer et al. 1993 <sup>82</sup>	Cohort study of treatment resistant schizophrenic patients.	Cost savings observed using clozapine
Chouinard et al. 1996 <sup>83</sup>	Utility analysis. Risperidone. Based on a multi-centred randomised control trial (short term) Canadian based.	Original study showed that risperidone had significantly greater efficacy (6-16mg/day) compared with haloperidol (20mg/day) using PANSS scale. Used QALYs with ratings made by psychiatric nurses £10,000 per QALY predicted.
Glazer et al. 1996 <sup>84</sup>	Pharmacoeconomic modelling based analysis of oral vs depot vs 'atypical' antipsychotic drugs in chronic schizophrenia. Costs limited to direct : drugs, clinic, monitoring, side-effects and inpatient costs.	Suggests that depot medication can provide cost benefits when challenging assumption of compliance and hospitalisation rates are taken. Base-case suggests :- <ul style="list-style-type: none"> <li>• £5,752 annual cost on oral</li> <li>• £4,595 annual cost on depot</li> <li>• £7,162 annual cost on 'atypical'.</li> </ul>
Hargreaves et al. 1996 <sup>86</sup>	Review of pharmacoeconomics considering clozapine and risperidone.	Identifies the need for more longer-term studies and recognised limitations of mirror-studies/ small cohort studies-

The following diagram shows the structure underpinning the proposed model.

**Figure 1 Schematic Decision Tree**



The model would need to be populated with data on:

- drug prescribing
- relapse rates
- community resource use (Community Psychiatric Nurse visits)
- lengths of stay
- drop-out rates
- drug costs
- hospitalisation rates
- resource costs
- suicide rate
- treatment switching.

It may also prove appropriate to expand the model out to consider treatment switching and to reflect patient symptoms. There may also be a case for developing alternative model

structures for specific patient groups to reflect the real variety in resource use that can be experienced by schizophrenic patients.

As a next step, it may be appropriate for such modelling work to be taken up as part of a Regional research programme or even from within a national research co-ordinated approach such as the Health Technology Assessment Programme. It would also be worth considering the merits of involving the support of the pharmaceutical companies directly, as in the Lilly project. However, it is more likely that modelling would be focused on specific drugs if this were to be the case.

In summary:

- A modelling approach appears to be the most appropriate way forward given the early stage in 'atypical' prescribing;
- Initial investigations have identified a potential structure to a model and the type of data required;
- Initial investigations have shown that the resources required in the process of gathering these data and refining a model structure are significant;
- The lack of any long-term evidence behind the drugs makes the predicting of benefits, and, more importantly, resource impact, difficult and suggests the need for a significant amount of clinical opinion gathering;
- The conducting of such a modelling project lies outside of the scope of a Guidance Note;
- The ways in which this requirement can be taken forward need to be considered.

#### 4. OPTIONS FOR PURCHASERS AND PROVIDERS

There is insufficient evidence to allow a definitive statement about a best option approach to the use of 'atypical' neuroleptic medications at the present time.

This is due to:

- the lack of direct comparisons of 'atypical' drugs;
- the relatively short time period of the existing trials;
- the lack of detailed and established economic analysis.

It is not possible, therefore, to be confident about the longer-term benefits of these drugs and it is also difficult to make comparisons between them, other than in summarising side-effects.

There are a number of different options which commissioning groups may wish to adopt:

**Option 1: Do Nothing**

This perpetuates an unsatisfactory and inequitable situation within, and between, health authority populations.

**Option 2: Accept fully the use of these drugs for all patients with new onset and resistant schizophrenia within the health district.**

This assumes that the evidence of the use of these drugs in this way is uncontroversial and that evidence of effectiveness in all cases is available, which it is not.

**Option 3: Set a limit on the resources allocated to prescribing, based on an incremental or staged introduction.**

This may be achieved by the pragmatic use of modelling processes, which allow for a range of priority groups to receive these medications under agreed care protocols. This approach should be developed with local discussion.

Newer antipsychotics are more extensively researched and, therefore, safer than conventional drugs, indeed chlorpromazine and haloperidol may have difficulty in obtaining licences in today's climate. Therefore, there exists an opportunity to encourage greater use

of these new drugs in primary care. Dosage administration and monitoring are all relatively straightforward apart from clozapine which will not be considered here.

Current protocols for Nottingham and North Derbyshire Districts are presented at Appendix C.



## 5. DISCUSSION AND CONCLUSIONS

To summarise the key points from the review:

- Evidence of clinical benefit is generally good for all the 'atypical' drugs, although still short-term in the case of the majority of trials. The majority of evidence relates to the use of clozapine in treatment-resistant patients.
- A potential for offsetting drug costs exists from the reduction in hospitalisation costs and the avoidance of treatment for relapsed patients.
- There are huge impacts on health authority drug budgets if 'atypicals' are to be introduced for all schizophrenic patients.
- There remains no clear statement on the cost-effectiveness of the 'atypicals', other than clozapine, with evidence of cost-effectiveness based on short-term trials of simple modelling.
- There remains an issue of exactly which groups are going to be given the 'atypical' drugs and when. This question is not really answered from trial evidence alone.

Access to the type of data required to make cost-effectiveness statements remains a real problem, with the lack of longer-term studies.

Some patients would rather accept some degree of illness than exposure to certain side-effects. However, this is only anecdotal and is not a specific area explored within the Guidance Note itself.

In terms of further work:

- There is a need to be more explicit and clearly map out the treatments for schizophrenia, with the model structure suggested as the beginning of this process.
- Data gaps need to be clearly identified as a result of the modelling process; we already know that much of this will be related to resource use and long-term relapse rates.

- Studies are needed to enable 'missing' data to be gathered via direct data trawls from existing sources or via more primary research. Clinical debate and consensus would also play a major role.
- Once data become more readily available, the schizophrenia model can then be re-populated and evaluated in the light of a revised evidence base.
- Once fully populated, the model can be used to conduct a realistic cost-effectiveness analysis.

## 6. USE OF CURRENT 'ATYPICAL' ANTIPSYCHOTICS IN THE TREATMENT OF SCHIZOPHRENIA: SUMMARY MATRIX

PATIENT GROUP	PATIENT CRITERIA (GUIDELINES NOT PROTOCOLS)	ESTIMATED FUTURE ACTIVITY	OPPORTUNITY FOR COST SAVING	AUDIT POINTS	EFFECTS THAT COULD BE EXPECTED IN RELATION TO STARTING POINT	COST-EFFECTIVENESS
Use of 'atypicals' (excluding clozapine) in Multiple Relapse + First Episode schizophrenic patients.	<p>These are patients who:</p> <ul style="list-style-type: none"> <li>do not respond clinically to conventional treatment, or</li> <li>remain responsive to first line treatments, but who may have problems with side-effects of conventional treatment.</li> </ul> <p>Together this is estimated at 70% of patients, with the remaining 30% maintained on conventional drugs.</p>	<p>Within a 'typical' district a six month prevalence of 900-1,000 patients fitting this criteria would be expected.</p> <p>Annual increase in drug cost estimated at £1.8 million from around £200-300,000 on conventionals.</p>	<p>Potential to increase the time between subsequent relapse, lowering hospitalisation costs.</p> <p>Also indications that problems related to EPSE are reduced significantly.</p>	<p>Information would need to be compiled on:</p> <ul style="list-style-type: none"> <li>compliance</li> <li>relapse rates</li> <li>drop-out</li> <li>side-effects</li> <li>resource use</li> <li>admission rates</li> <li>suicide attempts.</li> </ul>	<p>An effect on the negative symptoms of the illness.</p> <p>At least an equal efficacy related to the positive symptoms.</p>	<p>No information on cost-effectiveness currently available.</p>

## APPENDIX A TRIAL SUMMARIES

### Song Meta Analysis: Double-blind, randomised clinical trials: risperidone versus other neuroleptics<sup>60</sup>

Study	Antipsychotic drugs and daily dose	No. of patients	Duration (weeks)	Diagnoses	Baseline mean scores	Length of current hospitalisation (weeks)	Mean length of illness (years)
Marder et al. (1994) <sup>66</sup>	Risperidone 2, 6, 10, 16mg Haloperidol 20mg placebo	256 66 66	8	Chronic (DSM-III-R), PANSS total score 60-120	PANSS: 92.1 dBPRS: 53.7	29.7	15.8
Chouinard et al. (1993) <sup>65</sup>	Risperidone 2, 6, 10, 16mg Haloperidol 20mg Placebo	92 21 22	8	Chronic (DSM-III-R), PANSS total score 60-120	PANSS: 94.2 dBPRS 54.4	100.5	16
Peuskens. (1995) <sup>67</sup>	Risperidone 1, 4, 8, 12, 16mg Haloperidol 10mg	1136 226	8	Chronic (DSM-III-R) PANSS total score 60-120	PANSS: 89.7 dBPRS: 48.7	17.8	15.3
Blin et al. (1995) <sup>62</sup>	Risperidone 4-12mg Haloperidol 4-12mg Methotrimprazine 50-150mg	21 20 21	4	(DSM-III-R) with an acute exacerbation and psychotic anxiety	PANSS: 120.5 dBPRS: NA	NA	NA
Hoyberg et al. (1993) <sup>88</sup>	Risperidone 5-15mg Perphenazine 16-48mg	55 52	8	Chronic patients with acute exacerbation (DSM-III-R)	PANSS: 94:5 dBPRS: 53	NA	NA
Claus et al. (1992) <sup>89</sup>	Risperidone 1-10mg Haloperidol 1-10mg	22 22	12	Chronic patients (DSM-III)	PANSS : 86.2 dBPRS : NA	NA	14.1
Min et al. (1993) <sup>63</sup>	Risperidone 5-10mg Haloperidol 5-10mg	16 19	8	Chronic (DSM-III-R), PANSS total score 60-120	PANSS: 89.9 dBPRS: 50.9	22	10.6

Huttenen et al. (1995) <sup>90</sup>	Risperidone 4-10mg Zuclopenthixol 20-50mg	48 50	6	Chronic (DSM-III-R), with acute psychotic symptoms	PANSS: 93.3 dBPRS: 53.9	0.9	12.5
Ceskova et al. (1993) <sup>91</sup>	Risperidone 2.5-9.5mg	31	8	Schizophrenia (ICD-()) and schizoaffective psychosis	BPRS: 44.3	23.8	10.4
Mesotten et al. (1991) <sup>64</sup>	Risperidone 2-10mg Haloperidol 2-10mg	28 32	8	Schizophrenic, paranoid, other psychotic patients (DSM-III)	BPRS: 50.6	NA	>5.8
Borison et al. (1992) <sup>92</sup>	Risperidone 2-10mg Haloperidol 4-20mg Placebo	53 53 54	6	(DSM-III-R) BPRS >30	BPRS: 51.3	NA	15.1

PANSS: Positive and Negative Symptom Rating Scale

BPRS: Brief Psychiatric Rating Scale

dBPRS: PANSS-derived BPRS

DSM-III: Diagnostic and Statistical Manual of Mental Disorder (3rd edn), the American Psychiatric Association (1980).

DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders (3rd edn - Revised), the American Psychiatric Association (1987)

ICD-9: International Classification of Diseases (9th revision)

NA: not available.

## Risperidone Trial Data: Wessex Report No 48

### Randomised Double-Blind Studies of Risperidone

Author	Study Population	Design <sup>a</sup> (all double-blind studies)	Duration weeks	No. patients	Main efficacy assessment <sup>b</sup>	End-point improvement (R versus H or M or P or C)	
						Overall	EPSE
Borison et al., 1991 <sup>64</sup> <small>Error! Bookmark not defined.</small>		R vs. H vs. PL, 1-10mg	6	160	BPRS	Tendency to greater effect	Lesser effect (p<0.05)
Borison et al., 1992 <sup>92</sup>	DSM-III-R schizophrenics minimum score 30 on BPRS	Titration to effect: r 2-10mg/day vs. H4-20mg/ day vs.pl	6	36	BPRS SANS	Tendency to greater effect	Lesser effect (p<0.05)
Chouinard et al., 1993 <sup>65</sup>	DSM-III-R chronic schizophrenics, PANSS scores 60-120	Fixed dose: r 2, 6, 10 or 16mg/day vs. H 30mg/day vs. pl	8	135	PANSS	Identical or greater effect	Lesser or identical effect
Marder et al., 1991	DSM-III-R chronic schizophrenics, PANSS score 60-120	Fixed dose: r 2,6,10 or 16mg/day vs. H 20mg/ day vs.pl	8	523	PANSS	Greater effect (p>0.05)	Lesser effect (p<0.05)
Marder et al., 1994 <sup>66</sup>		R vs. H vs. PL, 2-16mg	8	388	PANSS	Identical or greater effect	Tendency to lesser effect
Peuskens et al., 1992 <sup>67</sup>	DSM-III-R chronic schizophrenics, PANSS scores 60-120	Fixed dose: R 1, 4, 8, 12 or 16mg/day vs. H 10mg/ day vs pl.	8	1362	PANSS	Identical or greater effect	Lesser or similar effect

<b>Risperidone vs. Haloperidol</b>							
Mesotten 1991 <sup>64</sup>		H vs. R 2-20mg	8	60	BPRS	Similar effect	Tendency to lesser effect
Claus et al., 1992 <sup>89</sup>	DSM_III-R chronic schizophrenics, previously optimised on last treatment	Titrated to effect in first 6 weeks: H 2-20mg/ day vs. R 2-20mg/ day; dose maintained for last 6 weeks	12	44	PANSS SADS-C	Tendency to greater effect	Identical
<b>Risperidone vs. Haloperidol vs. Methtrimapazine</b>							
Tatossian et al., 1991	DSM-III-R acute schizophrenics	Titrated to effect: R 4-12mg/day vs. H 4-12 mg/day vs. M 50-150mg/day.	4	62	PANSS	Greater effect (p>0.05) than both	Similar to M; M lesser effect than H (p<0.05)
<b>Risperidone vs. Haloperidol</b>							
Remvig, 1991		R vs. P, 5-15mg	8	107	PANSS	Greater effect (p<0.05) than both	Similar effect
Hoyberg et al., 1993 <sup>88</sup>	Acute exacerbations in chronic DMS-III-R schizophrenics	Double-blind dose titrated to effect in first 4 weeks; R 5-15mg/day vs. P 16-48 mg/day; dose maintained for the final 4 weeks	8	107	PANSS	Tendency to greater effect	Identical

<sup>a</sup> = R: risperidone, H: haloperidol, PL: placebo, M: methtrimapazine, P: perphanzine, C: clozapine

<sup>b</sup> = BPRS: Brief Psychiatric Rating Scale, SANS: Scale for Assessment of Negative Symptoms, PANSS: Positive and Negative Syndrome Scale, SADS-C: Schedule for Affective Disorders and Schizophrenia - Change Version.

## APPENDIX B ICD 10 CLASSIFICATION OF SCHIZOPHRENIA

<b><u>Code</u></b>	<b><u>Disorder</u></b>
F20	Schizophrenia
F22	Persistent delusional disorder
F23	Acute and transient psychotic disorder
F25	Schizoaffective disorders
F30	Manic episode
F31	Bipolar affective disorder

Source : *WHO ICD10 Classification System of Mental Health and Behavioural Disorder*



## **APPENDIX C            CURRENT PROTOCOLS FOR 'ATYPICAL' PRESCRIBING**

The following presents two examples of suggested treatment protocols for the use of 'atypical' antipsychotics. These protocols have both been developed locally by clinicians within the North Derbyshire and Nottingham Districts. As such, it is understood that they are not a statement of health authority policy, but do provide useful input into the development of such protocols.

### **North Derbyshire**

#### **PROTOCOL FOR USE OF 'ATYPICAL' NEUROLEPTICS**

##### **Background**

It is tempting to reserve the use of these drugs for cases where all other treatments have failed. However they are not licensed for use in treatment resistance and logic dictates that they are much more likely to benefit patients at an earlier, less intractable, stage of illness. Their price and relative novelty would suggest that they could not currently be recommended as first line treatment. The following protocol suggests a way that the drugs can be apportioned sensibly whilst monitoring reasons for use and measuring effectiveness in the local population.

##### **Protocol**

- Diagnosis of Schizophrenia
- and
- Treatment with accepted therapeutic dose of standard neuroleptic for minimum of six weeks
- and
- Lack of response or inability to tolerate drug
- Quantify with HONOS/BPRS/AIMS/GAF then
- Use Risperidone/Olanzapine/Sertindole at therapeutic dose for minimum of six weeks
- Register patient on database
- Repeat database
- Repeat baseline measures after six weeks

##### **Note:**

HONOS - a scale for measuring the overall outcome of patients with psychiatric illness.

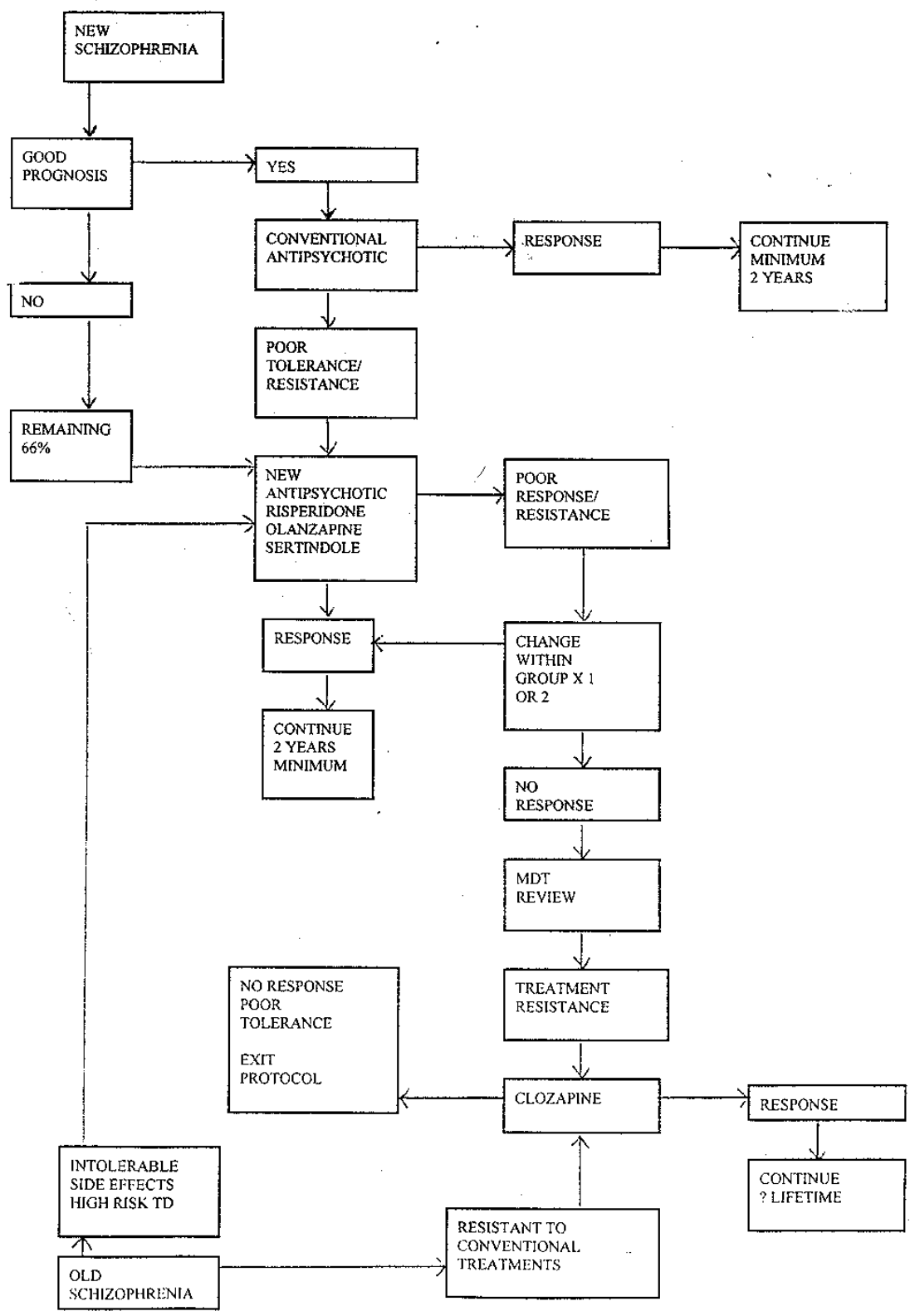
BPRS - a measure of the severity of psychotic symptoms.

AIMS - a measure of the extra pyramidal symptoms produced by neuroleptics.

GAF - a global measure of overall functioning.

# Nottingham

## ALGORITHM FOR ANTIPSYCHOTIC PRESCRIBING IN SCHIZOPHRENIA



## APPENDIX D ASSESSMENT OF OTHER NEW ANTIPSYCHOTIC DRUGS

The following information was provided by the Trent Drug Information Service through ADIs R&D Insight (1998).

The tables provide further detail on other new 'atypical' antipsychotic drugs which are beginning to be marketed (Amisulpride; Quetiapine; Ziprasidone; Zotepine).

<b>Approved name</b>	<b>Amisulpride</b>
<b>Manufacturer</b>	Lorex
<b>Status in UK</b>	Marketed November 1997
<b>Pharmacology Indications/use</b>	Dopamine D <sub>2</sub> /D <sub>3</sub> antagonist Licensed in UK for treatment of acute and chronic schizophrenic disorders in which positive or negative symptoms are prominent
<b>Cost/month</b>	£60-£120 (400-800mg daily) for acute episodes £8-£45 (50-300mg) for predominantly negative symptoms
<b>Clinical evidence</b>	A bell-shaped dose-response curve was observed with amisulpride 100-1200 mg/day in a 4-week dose-ranging study, which used haloperidol 16 mg/day as a positive control, and involved 317 patients with acute exacerbation of schizophrenia. Amisulpride 400 and 800 mg/day were the most effective doses for positive symptoms. A similar, but non-significant effect, was seen with negative symptoms [1].  Amisulpride was at least as effective as haloperidol in the treatment of acute exacerbations of schizophrenia, and was more effective in the treatment of negative symptoms, in a multicentre, double-blind European study in which 191 patients were randomised to treatment with amisulpride 800 mg/day or haloperidol 20 mg/day bid for 6 weeks [2].  Equivalent antipsychotic effects of amisulpride (1000 mg/day) and flupenthixol (25 mg/day) were observed in a 6-week, randomised, double-blind trial involving 132 patients with acute schizophrenia with predominantly positive symptomatology. There was no difference between treatments in the time course of improvement [3].
<b>Adverse effects</b>	Agitation, amenorrhoea, anxiety, extrapyramidal disorders, galactorrhoea, sleep disorders

### References

- 1 Puech A et al.. Amisulpride, an atypical antipsychotic, in the treatment of acute episodes of schizophrenia: a dose-ranging study vs. haloperidol. *Acta Psychiatrica Scandinavica* 1998; 98: 65-72.
- 2 Möller HJ et al.. Improvement of acute exacerbations of schizophrenia with amisulpride: a comparison with haloperidol. *Psychopharmacology* 1997; 132: 396-401.
- 3 Wetzel H et al.. Amisulpride versus flupenthixol in schizophrenia with predominantly positive symptomatology - a double-blind controlled study comparing a selective D2-like antagonist to a mixed D1-/D2-like antagonist. *Psychopharmacology* 1998; 137: 223-232.

<b>Approved name</b>	<b>Quetiapine</b>
<b>Manufacturer</b>	Zeneca
<b>Status in UK</b>	Marketed October 1997
<b>Pharmacology Indications/use</b>	Dopamine D <sub>2</sub> /5HT <sub>2</sub> antagonist Indicated for the treatment of schizophrenia ( <i>no qualifications</i> )
<b>Cost/month</b>	£113-142 (300-450mg daily)
<b>Clinical evidence</b>	<p>In a large phase II double-blind study, 106 patients with chronic or subchronic schizophrenia received at least 1 week of either quetiapine (mean dosage 307 mg/day) or placebo. Quetiapine was more effective than placebo in treating psychotic symptoms in patients. [4]. In a double-blind multicentre study, 361 patients with an acute exacerbation of chronic or subchronic schizophrenia were randomised to receive quetiapine 75, 150, 300, 600 or 750 mg/day, haloperidol 12 mg/day or placebo for 6 weeks. There were no significant differences between quetiapine and haloperidol in any of the efficacy parameters [5].</p> <p>In a phase III study of 618 patients with schizophrenia, the efficacy and tolerability of quetiapine at 3 different dosages and dosing regimens (50-450 mg/day bid-tid) for 6 weeks was evaluated. A significantly greater improvement in various rating scores was found after quetiapine 225mg bid compared with 25mg bid. Quetiapine 150mg tid was significantly superior to 25mg bid with respect to BPRS total score. The 225mg bid and the 150mg tid dosage groups were not significantly different with respect to any efficacy measure [6].</p> <p>In a multicentre US and European study, 286 patients with acute exacerbation of chronic or subchronic schizophrenia received PO high-dose quetiapine (maximum daily dose 750mg; n = 96), low-dose quetiapine (maximum daily dose 250mg; 94), or placebo (96), for 42 days. High-dose quetiapine therapy (mean daily dose 360mg) resulted in significant improvements rating scores compared with placebo. The significant changes in the BPRS positive-symptom cluster score showed the consistent effect of quetiapine in reducing positive symptoms, but its effect on negative symptoms was less consistent [7].</p> <p>201 patients with an acute exacerbation of chronic or subchronic schizophrenia or schizophreniform disorder were randomised to receive quetiapine or chlorpromazine (titrated up to a maximum dosage of 750 mg/day) for 6 weeks. Both treatments were associated with marked improvements in BPRS total score and CGI Severity of Illness score, although the clinical significance of some measures were variable [8].</p>
<b>Adverse effects</b>	Agitation, amenorrhoea, anxiety, dizziness, drowsiness, dry mouth, extrapyramidal disorders, galactorrhoea, headache, sleep disorders, tachycardia. Cataract potential in animals has not been confirmed in humans.

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- 4 Borison Riet al.. ICI 204,636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. *Journal of Clinical Psychopharmacology* 1996; 16: 158-169.
- 5 Arvanitis LA et al.. Multiple fixed doses of Seroquel (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Biological Psychiatry* 1997; 42: 233-246.
- 6 King Djet al.. A comparison of bd and tid dose regimens of quetiapine (Seroquel) in the treatment of schizophrenia. *Psychopharmacology* 1998; 137: 139-146.
- 7 Small JG et al.. Quetiapine in patients with schizophrenia: a high- and low-dose double-blind comparison with placebo. *Archives of General Psychiatry* 1997; 54: 549-557.
- 8 Peuskens J and Link CGG. A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. *Acta Psychiatrica Scandinavica* 1997; 96: 265-273.

<b>Approved name</b>	<b>Ziprasidone</b>
<b>Manufacturer</b>	Pfizer
<b>Status in UK</b>	Phase III trials in USA. FDA approval withheld pending further data. Earliest UK marketing 2000/1
<b>Pharmacology Indications/use</b>	Dopamine D <sub>2</sub> /5HT <sub>2</sub> antagonist Treatment of schizophrenia ( <i>qualifications unknown</i> )
<b>Cost/month</b>	Unknown
<b>Clinical evidence</b>	In a multicentre, double-blind study which enrolled 302 patients with schizophrenia, a 6-week treatment with ziprasidone 80 or 160 mg/day significantly improved positive and negative symptom and other rating scores [9]. Another double-blind study compared the efficacy of ziprasidone with that of placebo in the treatment of 139 patients with schizophrenia or schizoaffective disorders. After a 28-day treatment period with ziprasidone 40 or 120 mg/day, a significantly larger number of ziprasidone 120 mg/day recipients (48.8%), compared with ziprasidone 40 mg/day (37.2%) or placebo recipients (25.5%) experienced <sup>3</sup> 30% reduction in BPRS total score, or had Clinical Global Impression (CGI) severity scores of 1-2 (33.3%, 20.9% and 12.8%, respectively) [10]. In a preliminary report from a randomised, double-blind, placebo-controlled study involving 294 patients with schizophrenia reduced the rate of psychotic relapse over a 1-year period (6% relapse rate vs 35% placebo) and demonstrated a continuing improvement in negative symptoms and functioning over the course of the study  The IM formulation of ziprasidone produced marked improvement in psychopathology and symptoms of psychomotor agitation by day 3 in a pilot study involving 12 acutely ill patients with schizophrenia. These patients received fixed doses of IM ziprasidone 20-80 mg/day for 3 days, followed by PO ziprasidone on days 4 and 5[12].
<b>Adverse effects</b>	Anxiety, agitation, dizziness, extrapyramidal symptoms, GI disorders, headache, skin rashes, sleep disorders,

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- 10 Small JG et al.. Quetiapine in patients with schizophrenia: a high- and low-dose double-blind comparison with placebo. Archives of General Psychiatry 1997; 54: 549-557.
- 11 Goff DC et al.. An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. Journal of Clinical Psychopharmacology 1998; 18: 296-304.
- 12 Elwood W. Atypical antipsychotics lining up to help in schizophrenia. Inpharma 1110: 13-15, 25 Oct 1997.

<b>Approved name</b>	<b>Zotepine</b>
<b>Manufacturer</b>	Orion Pharma
<b>Status in UK</b>	Marketed November 1998
<b>Pharmacology Indications/use</b>	Dopamine D <sub>2</sub> /D <sub>3</sub> antagonist:Noradrenaline reuptake inhibitor Treatment of positive and negative symptoms in schizophrenia
<b>Cost/month</b>	£35-£99 (75-300mg daily)
<b>Clinical evidence</b>	In a placebo-controlled study comparing zotepine (150-300mg) to chlorpromazine (300-600mg) it was demonstrated that zotepine was clinically and statistically superior to chlorpromazine in symptom control, and was also associated with a lower risk of extrapyramidal symptoms [13]. A study in patients with acute exacerbation of chronic schizophrenia which compared zotepine (150-300mg) to haloperidol (10-20mg) demonstrated that zotepine was as effective as haloperidol in improving the positive symptoms of schizophrenia, significantly more effective on the negative symptoms, and induced significantly less extrapyramidal symptoms and treatment-emergent adverse events [14].
<b>Adverse effects</b>	Asthma, dizziness, dry mouth, sleep disorders, tachycardia, weight increase.

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