

Evidence-based best practice interventions for the treatment of  
schizophrenia/psychotic disorders: Annotated Information Package

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Laura Neilson

New Zealand  
Health Technology Assessment

Department of Public Health and General Practice  
Christchurch School of Medicine and Health Sciences  
Christchurch, New Zealand

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## ACKNOWLEDGEMENTS

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This Annotated Information Package (AIP) was commissioned by the Nelson Marlborough District Health Board. It was requested by Lorraine Eade, Portfolio Manager Mental Health.

The AIP was prepared by Laura Neilson (NZHTA Assistant Research Fellow). It should be read in conjunction with the appended Information Package prepared by Susan Bidwell (NZHTA Information Specialist Manager).

## WHAT IS AN ANNOTATED INFORMATION PACKAGE?

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Annotated Information Packages (AIPs), prepared by a NZHTA Reviewer, are overviews of an appended Information Package (IP). The IP provides a folder of printed material relating to a specific topic area identified from a systematic search strategy of electronic databases and website resources. The materials include lists of abstracts, key full text papers (where readily available from local resources), and website resources.

The AIP is aimed at giving the client an informed “guided tour” of their IP to increase its usefulness. The AIP report outlines the contents of the IP, highlights information of particular interest and relevance, summarises key articles, and comments on the stage and extent of the research base. It also makes suggestions for publications that the client may wish to have retrieved, and comments on the potential of the topic for evidence-based reviews, such as NZHTA Technical Brief or Systematic Review outputs. AIPs do not involve systematic processes for the critical appraisal of identified research. Another significant limitation is that full text articles of key interest are not retrieved unless freely obtainable from local resources. As a consequence of this, comments and summaries in the AIP may be based on abstracts rather than full text papers.

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## CONTACT DETAILS

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New Zealand Health Technology Assessment (NZHTA)  
Department of Public Health and General Practice  
Christchurch School of Medicine and Health Sciences  
PO Box 4345  
Christchurch  
New Zealand

Tel: +64 3 364 3696

Fax: +64 3 364 3697

Email: [nzhta@chmeds.ac.nz](mailto:nzhta@chmeds.ac.nz)

Website: <http://nzhta.chmeds.ac.nz>

# Evidence-based best practice interventions for the treatment of schizophrenia/psychotic disorders

## RESEARCH QUESTION

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What are the best practice evidence-based interventions for schizophrenia/psychotic disorders across different age groups?

## BACKGROUND AND SCOPE OF TOPIC

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This AIP is one of a series of five reports presenting the best practice recommendations for the treatment of common mental health disorders. The other reports present recommendations for interventions treating substance-related disorders, mood disorders, anxiety disorders and adjustment disorders. Comorbid disorders are not specifically examined but are discussed in some guidelines.

### *Interventions*

Interventions for the treatment of schizophrenia and other psychotic disorders fall into two main categories. Pharmacological or drug therapies, including typical and atypical antipsychotics, are generally recommended when a person is experiencing psychotic symptoms, and to induce remission and prevent relapse. Psychosocial interventions, such as cognitive behavioural therapy (CBT), family therapy or education, and problem-solving therapy, can be useful in the management of recovery and the prevention of relapse.

People with mental health conditions may be identified and offered treatment in a variety of health settings and so interventions through primary, community and secondary or specialist care services are included in the AIP.

### *Client/population group and condition*

The population group of interest are people who present for treatment of a schizophrenic or other psychotic disorder within primary or secondary health settings. Best practice guidelines for interventions across different age groups, including adults over 18 years of age, older adults (over 60 years) and children and adolescents are presented. Where available, information was included regarding special populations, for example, pregnant or breastfeeding women.

According to DSM IV diagnostic criteria, schizophrenia/psychotic disorders include schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition, substance-induced psychotic disorder, and psychotic disorder not otherwise specified. The primary disorders included in the guidelines and reviews examined for this report were schizophrenia and general psychotic symptoms, however some guidelines included information regarding special populations and these have been included where available.

## METHODOLOGY

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### *Search strategy*

The search covered systematic reviews from 2000 onwards in English. Sources included the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), BMJ Clinical Evidence reviews, and the Health Technology Assessment database. Guidelines websites were also searched.

A search of the bibliographic databases Medline, PubMed (added in last 60 days), Embase and PsychInfo were searched for systematic reviews on treatment for schizophrenia/psychotic disorders and linked with validated filters for systematic reviews or relevant keywords where no filters were

available. Full details of the sources searched and the strategies used are given in the attached Information Package. The search was completed on 3 September 2007.

### ***Methods***

The author (LN) carefully considered the contents, including identified article abstracts, of the appended IP. An overview of its contents was provided, highlighting information of particular interest and relevance. Clinical guidelines and evidence-based reviews of key interest, where freely obtainable from local resources, were retrieved and summarised. Those not available in full were summarised based on their abstract, and information regarding how to obtain the full version given in the IP. Based on the research identified in the IP, a description of the stage and extent of the research base was prepared. Finally, a recommendation was made on whether there was potential for appraisal and evidence-based review of the topic (i.e., as a NZHTA Technical Brief or Systematic Review).

## **OVERVIEW OF FINDINGS - INTERVENTIONS FOR SCHIZOPHRENIA**

A number of recent, high quality guidelines were available which presented best practice recommendations for the treatment of schizophrenic disorders. Those that were particularly relevant or thorough are summarised in some detail below. Additional relevant systematic reviews which were not included in the guidelines or were published subsequent to them are also summarised in brief. A list of other reviews or randomised controlled trials which were not summarised in this report appears at the end of this section.

## **SUMMARY OF KEY RESEARCH**

### ***Clinical Guidelines and Standards***

#### **CORE INTERVENTIONS IN THE TREATMENT AND MANAGEMENT OF SCHIZOPHRENIA IN PRIMARY AND SECONDARY CARE. NICE CLINICAL GUIDELINE**

##### **1. (National Institute of Clinical Excellence (NICE) 2002b)**

Guideline does not cover cases of extremely early or late onset (childhood, elderly) and doesn't cover those with co-existing learning difficulties, substance misuse, significant physical or sensory difficulties or homeless persons.

#### *Care across all phases should involve*

- optimism
- getting help early
- assessment
- working in partnership with service users and carers
- consent
- providing good information and support
- appropriate language and culture
- advance directives

#### *Guidelines are comprised of three sections*

- initiation of treatment at first episode
- acute phase
- promoting recovery

#### **1. Initiation of treatment (first episode) should involve some, or all, of:**

- early referral
- early intervention services
- early treatment
- pharmacological treatment
- second opinion

#### **2. Treatment of acute episodes requires**

- service-level interventions
- pharmacological interventions
- early post-acute management

### 3. Promoting recovery through

- primary care
- secondary services
- service interventions
- psychological interventions
- pharmacological interventions
  - o relapse prevention: oral, depot
  - o treatment-resistant schizophrenia
  - o combining antipsychotics
- employment assistance

Special cases: Rapid tranquilisation should only be performed when necessary, and then only with specific:

- aims
- training
- principles
- routines
- pharmacological agents

These guidelines are provided for peoples between the ages of 18 and 65 and do not cover the treatment or management of people with childhood or very-late onset, or people with coexisting learning difficulties, substance abuse issues or significant physical or sensory difficulties.

This guideline is also under review, and an updated version is expected in October 2007.

## **GUIDANCE ON THE USE OF NEWER (ATYPICAL) ANTIPSYCHOTIC DRUGS FOR TREATMENT OF SCHIZOPHRENIA. NICE Technology Appraisal Guidance No. 43** (National Institute of Clinical Excellence (NICE) 2002a)

Issued 2002, for review in May 2005, however updated version is not yet available at time of AIP preparation. Review of 172 RCTs and around 80 other studies including head to head trials of atypical agents. Conclusions are limited by: lack of long-term follow up, high attrition rates and collection/reporting inadequacies. This report excludes elderly, treatment-resistant schizophrenia, predominant negative symptom patients, learning disabilities, co-morbid depression and substance abuse disorders, thus has limited generalisability.

### **Proposed Guidelines**

1. Choice of antipsychotic should be an informed, joint patient-clinician decision.
2. Oral atypical antipsychotics Amisulpride, Olanzapine, Quetiapine, Risperidone and Zotepine are recommended as first-line treatments for newly-diagnosed schizophrenia.
3. The above atypicals are recommended for patients taking typical antipsychotics experiencing adequate symptom control but unacceptable side-effects.
4. It is not recommended to switch to atypical antipsychotics from typical antipsychotics if a patient is experiencing adequate symptom control without unacceptable side effects.
5. Treatment-resistant schizophrenia should be managed with Clozapine at the earliest opportunity. Treatment resistance is indicated by lack of clinical improvement despite minimum two trials of antipsychotics for 6-8 weeks, one of which being atypical.
6. Depot preparations should be prescribed when appropriate following risk assessment.

7. When more than one atypical antipsychotic is considered appropriate, the drug with the lowest purchase cost should be prescribed.
8. In absence of a full consultation between clinician and patient, an oral atypical should be considered treatment of choice due to lower risk of EPSE.
9. Antipsychotic therapy should be part of a comprehensive package of care that addresses the clinical, emotional and social needs of the patient. Long term monitoring of therapeutic progress and tolerability is vital.
10. Atypical and typical antipsychotics should not be prescribed concurrently, except for short periods to cover changeover of medications.

**RANZCP CLINICAL PRACTICE GUIDELINES FOR TREATMENT OF SCHIZOPHRENIA AND RELATED DISORDERS.** (Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for the Treatment of Schizophrenia and Related Disorders 2005)

Comprehensive literature review 1990-2003 including all Cochrane reviews, meta-analyses and international clinical guidelines. The report was reviewed by an expert committee from both Australia and New Zealand. Treatment evidence is divided into the four phases of the disease: 1. Prepsychotic, 2. First episode, 3. Recovery and 4. Prolonged/persistent schizophrenia.

**Report structure**

- I. Context and content of interventions
- II. Evidence for treatment according to stage of disease
- III. Evidence and guidelines for treatment-refractory schizophrenia and acute psychotic emergencies.

**Treatment recommendations**

- i. early detection and treatment of first episode
- ii. comprehensive and sustained interventions for 3-5 years
- iii. antipsychotics as the 'cornerstone' treatment, especially atypicals
- iv. clozapine should be used as indicated for treatment resistance (incomplete remission of positive symptomatology, pervasive negative symptoms or persistent suicide risk)
- v. routine availability of comprehensive psychosocial interventions
- vi. maintenance of social and cultural health
- vii. tailoring of interventions to phase/stage of illness, gender and culture
- viii. genuine involvement of consumers and families in service development and provision
- ix. maintenance of good physical health
- x. multidisciplinary approach with roles for both general practitioners and consultant psychiatrists.

**MANAGEMENT OF PERSONS WITH PSYCHOSES.** (Veterans Administration 2004)

FDA warnings regarding:

- Clozapine and agranulocytosis, dementia-related psychosis, paralytic ileus, hypercholesterolemia. Clozapine and Citalopram interactions
- Antidepressants and suicidal behaviour

*Search strategy*

Population: Patients with psychoses or schizophrenia

Intervention: diagnostics, screening, therapy and assessment for psychoses and schizophrenia

Control: conventional treatment for psychoses and schizophrenia

Outcome measures: morbidity, mortality, patient satisfaction, cost.

Expert consensus over recommendations sourced from high quality evidence within the literature up until 2001 (evidence-based guidelines, meta-analyses and systematic reviews of randomised controlled trials). The authors imply use of a narrow search scope and give no reference count in the summary document.

### *Guideline outline*

#### I. Interventions and practices considered

1. initial screening
2. treatment
3. management

#### II. Major outcomes considered

### **I. Interventions**

#### *1. Initial screening should involve:*

- suicide risk and level – imminent, short-term, long-term
- violence
- medical instability
- ability to cope
- legal mandates if patient refuses care
- history: psychiatric, medical, marital, family, military, past physical or sexual abuse, medication and substance use, physical examination and laboratory tests
- if indicated, neurological, neurobehavioral and/or neurocognitive examination, specialised laboratory testing, or lumbar puncture
- mental status examination
- functional and psychosocial support system
- emergent psychosocial needs
- DSM-IV diagnosis
- Agreement to treatment plan
- Treatment for cyclothymia, past history bipolar, psychotic disorder
- Psychosocial rehabilitation
- Determination of care setting
- Establishing contact with family members

#### *2. Treatment may involve:*

- Conventional antipsychotics
- Second generation antipsychotics
- Patient and family education
- Assessment of response at 6-8 weeks
- Reassessing medication if side-effects or poor response at 6-8 weeks

#### *3. Management should involve:*

- assessment of independent living skills (ILS) and providing ILS training including cognitive behavioural therapy
- assessment of housing needs
- assessment of level of family support and providing education and community-based assistance programmes
- assessment of social skills difficulties and providing supported or transitional employment
- assessment of level of case management needs – standard, intensive (ICM), mental health intensive (MHICM) or assertive community treatment (ACT)

### **II. Major outcomes considered**

- efficiency and effectiveness of initial assessment
- control of symptoms
- complications and comorbidity rate
- patient and family satisfaction regarding management of psychosis

- recovery and relapse rates
- clinical and social functioning
- quality of life
- cost of care
- need for hospitalisation, length of stay
- compliance

**APA PRACTICE GUIDELINE FOR THE TREATMENT OF PATIENTS WITH SCHIZOPHRENIA. 2<sup>ND</sup> EDITION.** (American Psychiatric Association 2004)

Updates the 1997 publication of same title

FDA warnings regarding:

- Clozapine and agranulocytosis, dementia-related psychosis, paralytic ileus, hypercholesterolemia. Clozapine and Citalopram interactions
- Antidepressants and suicidal behaviour

*Target population*

Persons aged over 18 with schizophrenia as defined in the DSM-IV

*Search strategy*

Review of 1,272 meta-analyses and systematic reviews regarding schizophrenia and schizoaffective disorder from 1994-2002. Publications were weighted for strength of evidence on a well justified rating scheme. Recommendations based on strength of evidence and agreement in literature and expert group discussion. Guidelines both internally and externally peer reviewed.

**I. Interventions and practices considered**

**Evaluation**

- Initial evaluation should involve psychiatric and medical histories, assessment for substance use and physical and mental status exams.
- Suicidal or dangerous behaviour risk should be assessed
- May require laboratory, electrophysiological and radiological assessments
- Detailed studies as indicated – eg heavy metal screening, EEG, MRI, CT.

**Treatment/Management**

- Education of both patient and family
- Psychosocial interventions significantly improve outcomes
- Antipsychotic medications – first generation agents: Phenothiazines, Butyrophenones, others: second generation agents
- Adjunctive medications – Benzodiazepines, Antidepressants, Mood stabilisers, Beta-blockers
- Other somatic therapies – ECT, rTMS
- Treatment settings and housing options

**II. Outcomes considered**

- Morbidity and mortality
- Frequency and severity of schizophrenic episodes
- Improvement in symptoms
- Improvement in functioning

**III. Major recommendations (supported with high clinical confidence)**

- Need for formulation and implementation of a treatment plan
- Establishing therapeutic alliances between patient and clinician is essential
- Appropriate acute, stabilisation and stable phase management is essential
- Special attention is required for first episode, extensive negative symptom, substance abusing, depressive and suicidal or aggressive schizophrenic

**MOH SINGAPORE CLINICAL PRACTICE GUIDELINES: SCHIZOPHRENIA.** (Singapore Ministry of Health et al. 2003)

*Key recommendations and associated evidence levels:*

- A- Level Ia, Ib (RCTs)*
- B- Level IIa, IIb, III (experimental, quasi-experimental, non-randomised)*
- C- Level IV (expert committee reports, clinical experiences)*

**Level A. Recommendations**

Antipsychotics are first-line treatment for psychotic symptoms.

Clozapine should not be used first-line because of the risk of agranulocytosis, use after other antipsychotics prove inadequate.

Most patients respond to 300-1,000 Chlorpromazine (CPZ) equivalents over a minimum of 6 weeks. First episode patients respond to lower doses than recurrent episode patients. Note: Asian patients may respond to lower doses.

Maintenance doses are generally lower than acute doses, doses should be at the lowest effective level, doses greater than 600 CPZ equivalents should be clinically justified.

Cognitive Behavioural Therapy is beneficial for schizophrenic symptom reduction.

Psychoeducation, family intervention and social skills training can reduce relapse rates.

Vocational training benefits those with competitive work as a personal goal, who are work skilled, have had previous competitive employment and minimal history of psychiatric hospitalisation.

**Level B. Recommendations**

Patients non-responsive to antipsychotics should be considered for ECT.

Patients experiencing persistent, significant anxiety or disruptive, aggressive behaviours should receive a trial of adjunctive benzodiazepines.

Antidepressants should be prescribed adjunctively for persistent depressive symptoms.

Supportive group or individual psychotherapy in combination with medications reduce relapse rates and enhance occupational and vocational functioning.

**Level C. Recommendations**

The prophylactic use of anticholinergic agents to prevent EPSE should be assessed on a case by case basis dependent on EPSE risk factors and medication risks.

**UPDATE ON 1998 SCHIZOPHRENIA PATIENT OUTCOMES RESEARCH TEAM (PORT).** (Lehman et al. 2004)

Updated treatment recommendations from the 1998 Schizophrenia PORT. Limited to schizophrenia spectrum diagnoses and comparative clinical trials or RCTs. Search yielded 294 eligible studies published since the last PORT publication. Evidence was rated and recommendations were peer reviewed by an expert panel.

## I. Psychopharmacological recommendations

### Acute positive symptom treatment in treatment-responsive patients

- antipsychotic medications other than clozapine are the first line treatment for multi-episode schizophrenics experiencing symptom exacerbation
- Choice of antipsychotic should be based on patient history, prior treatment response and side effect profile.
- Daily doses should be in the range of 300-1000 chlorpromazine or 5-20 haloperidol equivalents for first generation antipsychotics (in mg), and 10-30 aripiprazole, 10-20 olanzapine, 300-750 quetiapine, 2-8 risperidone, 120-160 ziprasidone for second generation antipsychotics (in mg).
- Treatment trials should be four to six weeks
- Antipsychotics other than clozapine, in the lower half of the recommended doses (above), are the first line treatment for first-episode schizophrenics

### Maintenance pharmacotherapy

- persons experiencing acute and sustained relief from schizophrenic symptoms should continue pharmacotherapy to reduce risk of relapse
- maintenance doses of first generation antipsychotics should be in the range of 300-600 chlorpromazine or 5-12 haloperidol equivalents
- Maintenance doses of second generation antipsychotics should be the dose found to be effective in the acute phase of treatment.
- long-acting injectable antipsychotics are indicated in persons with frequent relapse on oral medications, nonadherent persons and those who prefer the depot regimen
- Intermittent dosage maintenance strategies are not recommended, but are preferable over total non-compliance.

### Treatment-resistant schizophrenia

- Clozapine is treatment of choice for persons experiencing persistent positive symptoms despite other antipsychotic treatment. Excluding contraindications.
- Treatment resistance is defined as persistent positive symptoms after at least two adequate trials of antipsychotics, including one second generation.
- Clozapine doses should reflect the lowest possible effective dose 300-800mg.

### Pharmacotherapy recommendations for other symptom and functional domains

- Clozapine for hostility and persistent violent behaviours
- Clozapine for suicidal thoughts or behaviours
- Clozapine for persons experiencing neuroleptic malignant syndrome (NMS), persistent dystonia or tardive dyskinesia (TD) on other antipsychotics
- Prophylactic antiparkinson medications for persons being treated with first generation antipsychotics
- Adjunctive treatment with an antidepressant trial for persons experiencing an episode of depression despite positive psychotic symptom management

## II. Psychosocial treatment recommendations

### Behavioural therapies

- Family intervention over at least nine months involving education, crisis intervention plans and emotional support.
- Supported employment opportunities
- Assertive community treatment via multidisciplinary management
- Opportunities for skills training
- Cognitive behaviourally-oriented psychotherapy
- Token economy interventions

## **CANADIAN PSYCHIATRIC ASSOCIATION CLINICAL PRACTICE GUIDELINES FOR TREATMENT OF SCHIZOPHRENIA.** (Canadian Psychiatric Association 2005)

Combination of two systematic literature reviews – treatments and service delivery. Also utilised available schizophrenia clinical practice guidelines following an assessment framework (AGREE) to ensure quality. Systematic needs assessment was conducted on psychiatrists to influence the structure of the guidelines and the document was peer reviewed by a national advisory group.

Search strategy covered 1992-2004 and was limited to patients aged 18-65 years. The final database contained 2,864 quality-rated references.

### *Guideline structure*

#### I. Assessment

- Acute, stabilisation, chronic

#### II. Pharmacotherapy

- Acute, stabilisation, chronic

#### III. Psychosocial interventions

- Acute, stabilisation, chronic

#### IV. Delivery of services

#### V. Special issues

- Prodromal phase, substance use or abuse, coexisting medical conditions, pregnancy, coexisting depression, the aging patient

#### **I. Assessment**

- mental and physical symptoms, signs, ADLs, level of functioning, side effects
- collateral information from family, caregivers, health professionals
- longitudinal follow-up by the same clinicians(s)
- active, specific questioning and informed examination and investigation
- periodic assessment and recording of the patient's competency to accept or refuse treatment

#### Recommendations and indications for specific clinical assessments

- First episode
- Neuropsychological
- Genetic
- Neuroimaging
- Poorly responsive or refractory illness
- Comorbid conditions
- Physical health monitoring
- Dual diagnosis (mental retardation)

#### **II. Pharmacotherapy**

- Antipsychotics form essential components of most treatment plans
- Psychosocial interventions and simple medication regimens optimise medication adherence
- Medications must be individualised, first episode and elderly often require lower dosage, and side effect profiles will vary
- Patient involvement and agreement is critical, but medication should be recommended assertively
- Dosages should be maintained within recommended dosages and reasons for going outside this range should be documented and justified
- Combining antipsychotics is not supported by available evidence
- Second generation antipsychotics are first-line treatments with the exception of clozapine for treatment-resistant patients
- Regular evaluations are consistently necessary, standardised scales can be useful tools for baseline and ongoing assessment.

### III. Psychosocial Interventions

- optimal management requires integration of medical and psychosocial interventions
- effective psychosocial interventions improve medication adherence and relapse rate, reduce distress, improve functioning and provide support
- substance abuse, depression and anxiety disorders need to be recognised and addressed in psychosocial interventions
- psychosocial interventions need to be adjusted to fit the stage and needs of the patient and family
- attentive listening develops empathy, rapport and the therapeutic relationship and improves engagement and treatment adherence
- patient, caregiver and family education about the disorder, the course of treatment, outlook and relapse prevention is vital
- The clinical team, patient and family should develop shared, realistic goals for treatment and recovery
- All patients should have access to evidence-based programmes to develop skills, meet personal goals and cope with the wider impact of the illness
- Staff providing psychosocial interventions should be appropriately trained

#### Recommended psychosocial interventions

- vocational interventions
- skills training
- cognitive-behavioural interventions
- family interventions
- cognitive remediation
- peer support, self-help and recovery
- special situations for psychosocial interventions involve managing comorbid symptoms (stress, anxiety and depression), substance use and prenatal planning

### IV. Service delivery

- All patients should have access to comprehensive care with some continuity
- All patients in longer-term programmes should have a readily available written care plan
- The continuum of care should include crisis services, acute medical inpatient care, nonmedical crisis stabilisation, acute day hospital treatment, community-based rehabilitation, integrated addiction services, comprehensive services for early psychosis, community programmes and consumer-driven services
- All patients should have access to a continuum of housing support
- Services should be accessible in the patients' own language and own area

### V. Special issues

#### Prodromal phase

- "ultra high-risk mental state for psychosis" should be offered monitoring for at least one to two years
- If indicated, treatment for psychosis should begin without delay

#### **BMJ CLINICAL EVIDENCE: SCHIZOPHRENIA** (Nadeem et al. 2006)

Focuses on effects of drug treatments for positive and negative symptoms, relapse prevention, treatment-resistant schizophrenia and interventions to improve adherence to antipsychotic interventions. Choice of treatment is based on the trade-off between the harms and benefits of drug treatments, and therapy has the potential to improve the adherence to these drugs.

This report searched and appraised placebo versus traditional antipsychotic RCTs and comparative RCTs of atypical antipsychotics. The focus was placed on the large quantity of high quality systematic reviews. Significantly updated sections include: olanzapine, continued treatment with antipsychotic drugs, and cognitive behavioural therapy.

Review of findings:

## *Benefits and Harms of drug treatments for schizophrenia*

### **Amisulpride**

Benefits – Versus standard antipsychotics (first generation) showed an improvement in clinical impression status and a reduction in numbers of individuals exiting the trials early. Versus olanzapine (second generation) showed no significant difference in symptoms at two months. Versus risperidone (second generation) showed no significant difference in symptoms

Harms – Versus standard antipsychotics, amisulpride reduced the proportion of people experiencing at least one side effect, at least one extrapyramidal effect. Versus olanzapine, patients taking amisulpride reported less weight gain, and no significant differences in side effect profiles were seen between amisulpride and risperidone.

### **Chlorpromazine**

Benefits – Compared with placebo, chlorpromazine reduced proportion of people with no improvement or worsening symptoms over nine weeks to six months.

Harms – Again compared with a placebo, people taking chlorpromazine reported greater rates of adverse effects, including sedation, acute dystonia and parkinsonism over the same trial period.

### **Clozapine**

Benefits – Versus standard antipsychotics, clozapine improved symptoms over four to ten weeks and was less likely to cause antipsychotic-induced movement disorders. The reviews also showed a lower discontinuation rate in the clozapine versus haloperidol or chlorpromazine groups. Versus olanzapine no significant difference on effect on symptoms was found between the two groups. A separate RCT reviewing clozapine versus olanzapine in high-risk-suicide schizophrenics found a significant decrease in suicidal behaviour with clozapine. Compared to risperidone, no significant difference in symptoms was recorded.

Harms – Clozapine versus standard antipsychotics, was significantly more likely to cause hypersalivation, increased temperature and sedation but much less likely to cause dry mouth and extrapyramidal effects. Clozapine also significantly increased blood problems (leucopenia and neutropenia) compared with standard antipsychotics, however rates of agranulocytosis were lower than expected. Versus olanzapine, clozapine was associated with salivary hypersecretion, somnolence, nausea and dizziness, but olanzapine was highly associated with weight gain, meaning overall adverse effect profile differences were non-significant.

### **Depot Bromoperidol decanoate**

No significant differences were found between depot bromoperidol decanoate, depot haloperidol and depot fluphenazine decanoate in terms of needing additional medication, early exit from the trial or movement disorder symptoms. Adverse effects of bromoperidol may include parkinsonism, dystonia, cholinergic effects and weight gain: however there were no significant differences between bromoperidol and other standard depot antipsychotic treatments.

### **Depot Haloperidol decanoate**

No significant differences were found in the clinical state or reporting of adverse side effects between depot haloperidol decanoate and oral haloperidol. This, however, was a very small study, running for four months only and may have lacked the power to detect significant clinical differences. Haloperidol is associated with acute dystonia, akathisia and parkinsonism, and the depot form is suggested to improve compliance, however no RCT evidence supports this.

### **Haloperidol**

Benefits – Versus a placebo, haloperidol (over a wide range of doses) significant increased global improvement in schizophrenic patients at six to 24 weeks.

Harms – Haloperidol was also associated with significantly greater rates of acute dystonia, akathisia and parkinsonism compared with a placebo, and those taking haloperidol were more likely to require anticholinergic drug treatment than the placebo group.

### **Loxapine**

No significant differences found in either efficacy or adverse effect rate or profile compared to standard antipsychotic drugs.

### **Molindone**

No significant differences found in either efficacy or proportion of individuals experiencing adverse effects. The adverse effect profile differed compared to standard antipsychotic drugs such as chlorpromazine and haloperidol, in that more people taking molindone experienced confusion and weight loss. No significant differences existed in the frequency of rigidity, tremor, akathisia, parkinsonism for participants taking molindone compared with standard antipsychotics.

### **Olanzapine**

Benefits – No significant differences in number of participants with persisting psychotic symptoms between olanzapine and haloperidol at six to eight weeks. Similarly, no significant differences were found in symptom relief or rate of drop-out of the studies between olanzapine and either amisulpride, risperidone or clozapine.

Harms – Harms of olanzapine can include parkinsonism, dystonia, cholinergic effects and weight gain. Olanzapine was shown to significantly reduce the rate of extrapyramidal adverse effects when compared with standard antipsychotics but no differences in extent or profile were found when compared to amisulpride, risperidone and clozapine.

### **Pimozide**

Benefits – A systematic review (1999) found no difference in the proportion of participants reporting no improvement or worsening of symptoms at one to three months between pimozide and standard antipsychotics including chlorpromazine, haloperidol, fluphenazine and caripramine.

Harms – Pimozide was associated with decreased sedation but increased tremor. Pimozide has been associated with sudden cardiac death at doses over 20mg/day, but RCTs found no overall difference in cardiovascular adverse effects of pimozide compared to standard antipsychotic drugs.

### **Quetiapine**

Quetiapine showed no significant difference to standard antipsychotics in terms of mental state, but was associated with reduced akathisia, parkinsonism and number of participants leaving trials early. Standard side effects can include dystonia, cholinergic effects and weight gain.

### **Risperidone**

Benefits – A systematic review associated risperidone with a statistically significant increase in reporting of improved symptoms at 12 to 26 weeks compared with standard antipsychotics. However a small additional RCT found no difference between risperidone and haloperidol in terms of mental state. No significant differences were seen either in benefits or harms between risperidone and other new antipsychotics (olanzapine, sulpiride and clozapine).

Harms – Risperidone was associated with fewer extrapyramidal side effects and proportion of people experiencing parkinsonism, but also found risperidone to be associated with significant weight gain compared to standard antipsychotics. No significant differences were seen in rates of withdrawal from studies.

### **Sulpiride**

No significant differences were found between sulpiride and standard antipsychotics in terms of symptom improvement. Sulpiride patients experienced less parkinsonism compared to those taking standard antipsychotics. Standard side effects of sulpiride can include parkinsonism (reduced), dystonia, cholinergic effects and weight gain.

### **Ziprasidone**

No significant differences existed in terms of mental status and symptoms between ziprasidone and standard antipsychotics (chlorpromazine and haloperidol), however a systematic review suggested that ziprasidone reduced akathisia and acute dystonia but increased nausea and vomiting compared to haloperidol.

### **Zotepine**

A weak systematic review (absent of RCTs) reported a clinically significant improvement in symptoms in the zotepine cohort over standard antipsychotics, but this was not robust evidence. Zotepine was also found to be associated with reduced akathisia, dystonia and rigidity when compared to standard antipsychotics.

### **Perazine**

No significant difference in global clinical impression or mental state was seen between perazine and haloperidol, or perazine and amisulpride at 28 days. Perazine, like all antipsychotic drugs is associated the side effects: parkinsonism, dystonia, cholinergic effects and weight gain, but perazine appears not to be significantly different to zotepine or amisulpride in terms of extrapyramidal side effects.

### *Interventions to reduce relapse rates*

#### **Continued treatment with antipsychotics**

- reduces relapse rates when compared with no treatment or placebo
- must continue for at least six months
- choice of drug is complex, with some systematic reviews and RCTs showing no significance and others suggesting certain drug choices
- Clozapine, depot zuclopenthixol decanoate, haloperidol, fluphenazine and risperidone were all shown to reduce relapse rates in the 12 weeks to one year following an acute episode

#### **Family interventions**

- a systematic review suggested that multiple session family interventions reduced relapse rates at 12 months when compared to usual care, single session family interventions or psychoeducational interventions.

#### **Psychoeducational interventions**

- a systematic review showed reduced relapse rates at nine to 18 months compared with usual care, however there was significant heterogeneity in both interventions and outcomes within the trials.
- a further review found a lack of evidence on psychoeducational interventions over social skills training.

#### **Cognitive Behavioural therapy**

- limited evidence suggests no significant difference in relapse rates between cognitive behavioural therapy plus standard care or standard care alone.

#### **Social skills training**

- insufficient evidence to directly assess the impact of social skills training, but one small study suggested significantly reduced relapse rates when compared to standard treatment.
- no significant differences in relapse rate were observed when comparing social skills training with psychoeducational interventions

*Interventions for treatment-resistant (to standard antipsychotics) schizophrenia*

**Clozapine**

- for individuals resistant to standard antipsychotics, clozapine was shown to significantly improve symptoms at 12 to 24 weeks and at one to two years compared with standard antipsychotics.
- Other RCTs have shown no significant difference between clozapine and risperidone, olanzapine and zotepine but studies were likely to have been too small to detect clinical significance.
- Harms of clozapine include fatigue, nausea, dizziness, hypersalivation and hypersomnia as well as increased withdrawal from studies but other RCTs show clozapine to be less likely to cause extrapyramidal adverse effects and dry mouth.

*Interventions to improve adherence to antipsychotic medication*

**Behavioural therapy**

- limited evidence that behavioural therapy improves adherence

**Compliance therapy**

- limited evidence that compliance therapy increases adherence at six and 18 months compared with supportive or non-specific counselling.
- One RCT found no significant difference in adherence between compliance and non-specific therapy over one year.

**Psychoeducational interventions**

- limited evidence of improved adherence
- evidence to suggest less improvement in adherence gained than by behavioural therapy interventions

**Family interventions**

- a systematic review showed compliance over nine to 24 months was improved by multiple family interventions compared with usual care, single family interventions or psychoeducational interventions but result was not significant.

***Special populations***

**ANTENATAL AND POSTNATAL MENTAL HEALTH: CLINICAL MANAGEMENT AND SERVICE GUIDANCE. NICE clinical guideline 45.** (National Institute of Clinical Excellence (NICE) 2007)

This document presents extensive guidelines for clinical management and service guidance for all mental disorders during the ante-, peri- and post-natal period. This summary gives general service guidelines but restricts recommendations to psychosis, schizophrenia and schizophreniform disorders.

A primary recommendation of this guideline is patient-centred care, a key element of this being good communication between healthcare professionals and women, and active involvement of women, their partners, families and carers in education and treatment choices.

*Guideline summary*

1. Principles of care

- Providing and using information effectively to improve understanding and collaboration between the woman, her family and healthcare professionals
- Support should be available for partners, families and carers
- Special consideration should be given to pregnant adolescents experiencing a mental disorder regarding confidentiality and consent

2. Prediction, detection and initial management of mental disorders

- Routine monitoring through all maternity services, especially for past or present severe mental illness, and family history.
3. Referral and initial care
- Following identification of a potential mental disorder, consider further assessment
  - mental health checks at all subsequent contacts with health services
  - Formulation of a written care plan in collaboration with the woman, partner, family, carers and relevant health professionals.
  - Inpatient care in specialist mother and baby units for the first 12 months postpartum.
4. Prevention
- Use of targeted psychosocial interventions (IPT, CBT, group psychoeducation)
  - Intensive management of mothers whose infants are stillborn or die shortly after birth.
5. Care during pregnancy and the postnatal period
- Should be the same as for anyone with a mental disorder, with specific focus on treatment decisions as they are complicated by the developing foetus, breastfeeding and the timescales imposed by pregnancy and birth
  - Benefits/harms and risks to the women and foetus/baby should be thoroughly discussed with the women being treated before starting or before stopping a psychotropic medication
  - Women being treated should be intensively followed up within one month of initial assessment.
  - Prescribers should: use lowest risk profile drugs, start at lowest effective dose, use monotherapy, and consider additional precautions for neonatal care.
6. Organisation of services
- Focus should be on the development of managed clinical networks involving linked groups of services in primary, secondary and tertiary care.
  - Each locality should have a specialist multidisciplinary perinatal service, a designated specialist inpatient service (mother and baby units, specialist staff, infant care, community integration) and access to specialist expert advice
  - Clear referral and management protocols should exist

#### *Recommendations specific to Schizophrenia*

##### **Pregnancy**

- Women pregnant or planning pregnancy should be treated according to the NICE clinical guidelines on schizophrenia
- Exception is if the women is taking an atypical antipsychotic, consideration should be given to switching to a low dose typical such as haloperidol, chlorpromazine or trifluoperazine

##### **Breastfeeding**

- Women breastfeeding should be treated according to NICE guidelines on schizophrenia
- Women receiving depot medication should be advised that their infant may show extrapyramidal symptoms several months after administration of the depot. These are usually self-limiting.

#### **REPRODUCTIVE MENTAL HEALTH GUIDELINE 6. MENTAL ILLNESS DURING THE PERINATAL PERIOD: PSYCHOTIC DISORDERS.** (British Columbia Reproductive Care Program 2003)

Focuses on all causes of psychosis, including, as defined by DSM-IV

- Schizophrenia – Paranoid, disorganised, catatonic, residual, undifferentiated
- Schizophreniform
- Schizoaffective disorder – bipolar type, depressive type
- Bipolar disorder – I, II, Postpartum-Onset.

##### **Risk factors**

- History of psychosis with pregnancy

- Positive family history of psychosis
- Positive family history of personality disorders
- History of bipolar disorder
- Use of drugs

#### Signs and symptoms

- Positive – Hallucinations, delusions, thought disorder
- Negative – Sleep disturbance, agitation, social withdrawal, behavioural changes, affective blunting, poverty of thought and speech, loss of motivation.

#### Course of initial episode

- Prodromal
- Acute
- Recovery

#### Assessment tools

- Mini-international neuropsychiatric interview (MINI v5.0.0)
- Brief psychiatric rating scale (BPRS)

#### Management of psychotic disorders

- Pharmacotherapy
- Electroconvulsive therapy
- Psychosocial therapies

Pharmacotherapy – requires limiting pharmacologic exposure to mother and foetus/child by using minimum effective dose and limiting total number of medications while maintaining mental health.

Electroconvulsive therapy (ECT) – ECT is an effective line of treatment with few adverse effects for mother and foetus, particularly useful for rapid treatment and when a comprehensive team of healthcare professionals are available.

Psychosocial Therapies as adjunctive treatments – psychosocial therapy used as an adjunct to pharmacotherapy or electroconvulsive therapy to assist women to recover from an initial psychotic episode. Used during the recovery phase once the initial episode is under control and the patient is thinking clearer.

### **POSTNATAL DEPRESSION AND PUERPERAL PSYCHOSIS. SIGN Guideline No. 60.**

(Scottish Intercollegiate Guidelines Network (SIGN) 2002)

Mainly focuses on postnatal depression, but limited discussion of puerperal psychosis. Defines puerperal psychosis as a mood disorder characterised by loss of contact with reality, hallucinations, severe thought disturbances and abnormal behaviour. Rates all evidence on standard grades of recommendation.

#### *Addresses*

- risk factors
- prevention
- identification and diagnosis
- management (pharmacological, physical, psychosocial, mother and baby units)
- prescribing issues in pregnancy and lactation

#### **Recommendations**

##### *Diagnosis, screening and prevention*

- Women should be screened for puerperal psychosis risk factors during the antenatal period (previous puerperal psychosis, history of affective psychosis, family history of affective psychosis).
- Primary care teams should be aware that puerperal psychosis is more likely to present following a mother's discharge home.

- Women identified at high risk of puerperal psychosis should receive specialist psychiatric review.

#### *Management*

- Puerperal psychosis should be treated. It should be managed in the same manner as psychotic disorders are at any other time, but with additional considerations regarding the use of drug treatments while breast feeding and in pregnancy.

#### *Mother and baby units*

- The option to admit mother and baby to a specialist ward should be available. Mothers and babies should not be routinely admitted to general psychiatric wards.
- Multiprofessional assessment is needed upon admission, including social work and involving family members.
- Clinical responsibility for the baby whilst the mother is an inpatient needs to be clearly determined.

#### *Prescribing – general principles for prescribing during pregnancy and breast-feeding*

- Establish clear indication for drug treatment.
- use treatments of the lowest effective dose for the shortest period necessary
- Drugs with better evidence base are preferable.
- Assess the benefit/risk ratio of the illness and treatment for both mother and baby.

### **INTERNATIONAL CLINICAL PRACTICE GUIDELINES FOR EARLY PSYCHOSIS.**

(International Early Psychosis Association Writing Group 2005)

Clinical practice guidelines developed by 29 international consultants. An update of the 2002 publication to include newly developed and registered medicines. An update of this publication (2005) is expected in 2008.

Early psychosis is often overlooked or poorly managed. Clinical care is often inadequate despite evidence that suggests good management of early psychosis can lead to substantially lower associated morbidity and mortality. Secondary prevention targets for early psychosis include: 1) the prepsychotic phase, 2) the first psychotic episode, and 3) recovery and the critical period of follow-up.

Findings and recommendations include:

- early identification and optimal treatment is likely to reduce the short and long-term burden of the disease
- community education is key to ensuring identification of onset of psychotic disorders
- phase-specific programmes of care, especially those catering to youth, are vital
- Care must be taken with pharmaceuticals in the drug-naïve patient, with emphasis on low doses and avoiding first generation antipsychotics.
- Psychosocial interventions are fundamental to recovery
- More research is needed to understand early psychosis
- Consumer and family engagement is key to developing effective treatments

#### **1) Prepsychotic period (premorbid and prodromal)**

- psychotic disorder should be considered in a young person who is becoming withdrawn, distressed, agitated and performing worse at school for a sustained period, with no apparent reason
- High-risk young people include those with DSM-IV sub-threshold positive symptoms and/or family history and significant psychosocial functioning decline over the past year
- Young persons actively seeking help must be engaged and assessed, regularly monitored, offered assistance and psychoeducation for problem areas and coping skills and offered family education and support
- Care should be carried out in a low-stigma environment
- Antipsychotics are not usually indicated unless DSM-IV criteria for psychotic disorder are met, exceptions include suicide risk, rapid deterioration, risk to others from hostility or aggressive behaviour and ineffective treatment of depressive symptoms. Antipsychotics should be low dose and considered as a short term “therapeutic trial”

- Contact with family or friends of young people not seeking help may be an appropriate strategy
- Evidence for effectiveness of treatment targeting the prepsychotic phase remains preliminary. More data are required.

## 2) First episode

- Development of community wide initiatives to address stigma
- Primary healthcare professionals should be competent in eliciting and recognising early psychosis
- Maintenance and education around linking primary and specialist services
- Provision of user-friendly and timely mental health services, ideally within outpatient services or the home environment
- Early intervention is the best strategy for effective treatment
- Inclusion of family in assessment and treatment plans
- Inpatient care may be required if family or community support is insufficient, care should be provided in small units catering to young persons and early psychosis. This symbolically communicates that young people differ in both needs and prognosis from older patients with chronic conditions.

### *First episode management*

- Rule out physical illness as cause of psychosis
- Atypical antipsychotics are first-line due to lower frequency of EPSE
- Low doses and slow titration are usually required, appropriate initial target doses include 2mg/day Risperidone, 7.5-10mg/day Olanzapine. Six to eight weeks is considered a sufficient trial period. When typical antipsychotics cannot be avoided, they should be commenced at very low doses: 1-2mg haloperidol.
- Low antipsychotic doses will not address distress, insomnia and behavioural disturbances: these must be managed with skilled nursing care, safe and supportive environments and benzodiazepines.
- Slow recovery (persistent positive symptoms following two antipsychotics over 12 weeks) is of concern and must be intensively managed, potentially using clozapine and cognitive-behaviour therapy.
- Structured and supportive crisis plans and family involvement and education are critical to recovery

## 3) Recovery (six-18 months), Critical Period (up to five years)

- High quality continuous, assertive care must be provided to prevent, rather than manage negative sequelae.
- Involvement and empowerment of consumers and families is important, and early warning signs of relapse should be discussed.
- The impact of the prodromal phase and psychosis should be assessed and managed through psychotherapy and psychosocial support
- Depression, suicide risk, substance misuse and social anxiety as well as side effects of any antipsychotic medication should be identified and actively treated.
- Antipsychotic medication reduces risk of relapse, however optimal treatment length (between 12 months and 5 years) is unknown, close monitoring should occur for any individual electing to cease medication. Long term medication is advisable for individuals who experience frequent relapses.
- Patients with persistent symptoms, or frequent relapses, who reject treatment may benefit from involuntary community treatment, with or without the use of depot medications.
- Patients should not be discharged from specialist care upon remission of symptoms, however partnerships between specialist, primary care and other agencies should be fostered

*Concludes: "First-episode psychosis is difficult to treat well, confers high levels of risk, and is the phase with the potential for greatest cost-effectiveness of treatment. To treat in a reactive manner is less effective and misses the best opportunity for enhancing outcomes and quality of life for patients and families."*

### ***Consensus Statements***

Note the following consensus guidelines should be considered to be much less robust than the guidelines and clinical evidence outlined above.

### **OPTIMISING PHARMACOLOGIC TREATMENT OF PSYCHOTIC DISORDERS. EXPERT CONSENSUS GUIDELINE SERIES. (Kane et al. 2003)**

The survey consisted of 60 questions and 994 options with written answers or scoring based on the RAND 9-pt scale. High consensus was reached on all proposed guidelines.

Issues with pharmacologic treatment of psychotic disorders with new generation antipsychotics

- medication selection
- dosing and dose equivalence
- management of inadequate response
- relapse
- co-morbidities
- compliance

#### **Initial medication selection**

- first-episode, positive symptoms – risperidone, aripiprazole, olanzapine
- first-episode, negative symptoms – risperidone, aripiprazole
- first-episode, positive and negative – risperidone
  
- depot conventional antipsychotics and long-acting injectable atypical antipsychotics were not recommended for a first-episode patient.
  
- multi-episode, positive symptoms – risperidone, aripiprazole, ziprasidone, olanzapine, quetiapine, long-acting atypical antipsychotic
- multi-episode, negative symptoms – risperidone, aripiprazole, ziprasidone
- multi-episode, positive and negative – risperidone, aripiprazole
  
- more willing to consider clozapine or long-acting injectables, mid to low-potency conventional antipsychotics were not recommended

#### **Dosage**

- dosing recommendations agreed with manufacturers recommended doses
- highest quetiapine and olanzapine doses exceeded clinical trial safety data of 800mg and 20mg respectively.
- higher doses were prescribed to multi-episode over first-episode patients
- maintenance doses were lower than acute doses

#### **Dose equivalence**

- can be calculated for conventional antipsychotics by dopamine receptor affinity
- equivalency was described relative to risperidone doses, chart can be sourced from Guideline 2.

#### **Dose adjustment indicated for certain patient characteristics**

- smokers
- cytochrome P450 polymorphisms
- age, lower dose needed in elderly and paediatric patients
- concomitant medications
- presence of hepatic or renal disease
- cardiovascular disease
- BMI or body weight

Not recommended for children <12 years old – aripiprazole, clozapine, chlorpromazine, fluphenazine, perphenazine, thioridazine, thiothixene, trifluoperazine, fluphenazine decanoate, haloperidol decanoate.

Not recommended for adolescents 13-18 years old – chlorpromazine, perphenazine, thioridazine, thiothixene, trifluoperazine.

Not recommended for elderly patients – chlorpromazine, thioridazine, thiothixene, trifluoperazine, fluphenazine decanoate, haloperidol.

#### **Adequate treatment trial time**

- little evidence for delayed onset, clinical effects appear within one week
- recommend minimum 3 weeks, maximum 6 weeks before regimen change if no response to initial or second antipsychotic was seen
- recommend 4-10 weeks and 5-11 weeks if a partial response was seen with initial or second antipsychotic, respectively.
- It was recognised that antipsychotics were likely to be trialled at an increased dose before switching agents
- The first line strategy of 70% of experts observing no response to atypicals was a switch to clozapine.
- Cross-titration was recommended as the best switching strategy between antipsychotics

Enhancing partial response

- generally seen as third line strategies (not recommended), include use of mood stabilisers, combined antipsychotics and clozapine

#### **Relapse**

- little evidence surrounding best practice
- suggest switching to long-acting injectable to ensure compliance
- relapse on injectable antipsychotic – suggest injectable atypical
- relapse on injectable atypical – suggest increased dose before switch

#### **Co-morbidities**

Different antipsychotics appear more suitable for treating schizophrenia with certain co-morbidities and associated complications.

- + suicidal behaviour – clozapine
- + aggression and violence – clozapine, olanzapine, risperidone
- + substance abuse – any long acting depot antipsychotic
- no consensus on best antipsychotics for dysphoria/depression or cognitive problems (all antipsychotics second rated), may be due to lack of empirical evidence.

Treating comorbidities

Dysphoria/depression – any SSRI, venlafaxine

Aggression/violence – lithium, valproate

Suicidal behaviour – any SSRI, venlafaxine, ECT as high second-line option

Obesity – due to weight-gain side effects of clozapine, second line options included switching antipsychotic or lowering clozapine dose. Other second line options include inclusion of topiramate and nutrition/exercise counselling. Weight loss medications (orlistat, sibutramine) or surgical interventions were not recommended

Monitoring for risk factors for diabetes, coronary heart disease, HIV, substance abuse, smoking, hypertension and obesity was strongly recommended, and may include

- weight
- blood pressure
- lipid profiles

Monitoring of response to long term antipsychotics is also recommended, including:

- endocrine work-up, especially prolactin levels
- cardiac monitoring (prolonged QTC, myocarditis)

- cataract monitoring
- EPS

### **Compliance**

- Is best monitored by caregiver and patient self-rating scales, by pill counts or blood levels
- Urine tests determined inappropriate
- Intervention recommended at or below 50% compliance
- Pharmacologic, psychosocial and programmatic interventions all highly recommended as strategies to address compliance issues, combinations of the three suggested to be the most successful

### **Long-acting Injectables**

Advantages – assured medication delivery, reduced risk of relapse, immediate knowledge of missed doses, residual medication in system despite a missed dose.

Disadvantages – lack of patient acceptance to continued injections, loss of patient autonomy

### **Indications for long-acting injectable atypical antipsychotic**

- Patient on oral atypical requesting long acting pharmaceutical
- Non-compliant patient on oral atypicals
- Patient experiencing extra-pyramidal side effects (EPSE) or tardive dyskinesia (TD) on conventional depot antipsychotics
- Involuntary outpatient commitment
- Patient on oral atypical relapsing for an unclear reason
- Patient with history of aggression and violence

Acute improvement in psychotic symptoms seen as the most important indicator of remission, sustained improvement in psychosocial functioning as most important in assessing recovery.

### **CONSENSUS STATEMENT ON HIGH-DOSE ANTIPSYCHOTIC MEDICATION.** (Royal College of Psychiatrists 2006)

Update of consensus statement published in 1993. Addresses use of high-dose antipsychotic medication in the adult mental health services only, excludes elderly or child and adolescent mental health. Recommendations are based on literature within the document and the working group consensus view. No systematic literature review was undertaken.

### **Recommendations**

1. High dose to be defined as “a single antipsychotic exceeding upper limit in the *British National Formulary*, or a combined dose which exceeds the upper limit using the percentage method”
2. Current evidence does not support the routine use of high-dose antipsychotic medication in general adult mental health services.
3. High doses should only be used after evidence-based strategies have failed and only as a carefully monitored therapeutic trial.
4. The decision to prescribe high doses should be taken explicitly and should involve an individual risk-benefit assessment in consultation with the wider clinical team, the patient and a patient advocate if desired.
5. Supplementary prescribers should not make the decision to proceed to high-dose.
6. The decision to prescribe high doses should be documented and justified, including risk-benefit analysis, aims and outcome assessment strategy.

7. Dose escalation should be in relatively small increments and allow adequate time for response.
8. Dosage should be monitored in terms of total percentage arising from drug combinations, including PRN medications. PRN medications should be closely monitored.
9. Possible contraindications and drug interactions to high-dose antipsychotics should be considered before prescription.
10. Baseline ECG should be performed and cardiac contraindications (long QT syndromes) should be excluded. ECG should be repeated as clinically indicated.
11. Services should be structured, managed and resourced to preclude or minimise perceived need for high-dose antipsychotics. Regular auditing of antipsychotic doses should become routine practice.

#### **Aggression with psychosis and rapid tranquillisation**

12. Therapeutic strategies including de-escalation, benzodiazepines and/or antipsychotics within dosage ranges are recommended.
13. Antipsychotic dose in acute violence and emergency tranquillisation can be minimised by reviewing use of alternative/adjunctive strategies, providing a suitable (well staffed) environment, and allowing sufficient time for clinical response between dosage increments.
14. Routine monitoring of a sedated patient is vital if high dose antipsychotic treatments have been used. ECGs should be carried out frequently, where possible.
15. Avoid parenteral antipsychotics if possible during acute episodes, but if used ECG monitoring should be performed.

#### **Treatment-resistant psychosis**

16. Patient should receive careful and regular psychiatrist assessment, and contributions to poor response should be considered (plasma level assay, non-compliance).
17. Local protocols, based on national guidelines should be developed for clinical management of treatment-resistance.
18. Evidence-based strategies, including Clozapine, should be exhausted before resorting to high-dose antipsychotic medication.
19. High dose antipsychotics should be treated as a limited therapeutic trial, and doses reduced back to conventional levels after a three month period unless clinical benefits outweigh risks.

### ***Additional Cochrane reviews published since the release of Clinical Evidence***

#### ***Pharmacological interventions***

##### **Chlorpromazine versus placebo for schizophrenia.** (Adams et al. 2007)

Review of 302 excluded and 50 included studies. Chlorpromazine found to

- reduce rate of relapse over short, medium and long term
- provide global improvement in functioning
- assist in retention of participants in study for full term

- have many adverse effects including: sedation, acute movement disorders, parkinsonism, lowering of blood pressure, dizziness and weight gain.

Rates of akathisia were not significantly different between chlorpromazine and placebo. Results of the review confirmed much that clinicians and recipients of care already know but aimed to provide quantification to support clinical impression. Authors concluded that their findings did not threaten the position of chlorpromazine as a “benchmark” treatment for psychoses, and that chlorpromazine is a well established, but imperfect treatment. They stated that judicious use of this best available evidence should lead to improved evidence-based decision making by clinicians, carers, and patients.

#### **Antidepressants for the negative symptoms of schizophrenia.** (Rummel et al. 2006)

Review of the efficacy of combining antipsychotic and antidepressant drug treatment for management of negative symptoms of schizophrenia. Five studies were included, and it was shown combined antipsychotic-antidepressant therapy resulted in the following clinical responses

- statistically significant greater improvement
- significantly lower severity at endpoint
- clinically significant improvement in negative symptoms – affective flattening, avolition, avolition
- no statistically significant differences were seen in leaving the study early, adverse events or movement disorders.

These data appear to justify the combined use of antipsychotics and antidepressants to manage the negative symptomatology of schizophrenia but no data are available in the mid to long term, and no data on outcomes such as compliance, cost or quality of life. The amount of information is currently too limited to allow firm conclusions, but warrants further study.

#### **Aripiprazole for schizophrenia.** (El-Sayeh and Morganti 2006)

A review of 15 randomised trials to examine the effects of aripiprazole for people with schizophrenia and schizophrenia-like psychoses. Compared with a placebo, aripiprazole is associated with a significant decrease in relapse in the short and mid term, as well as better compliance. Aripiprazole decreased prolactin levels below that of a placebo. Compared to typical and atypical antipsychotics, no difference in global or mental state was observed. The adverse effect profile was similar between trial arms, although aripiprazole reported decreased akathisia and need for anti-parkinson medication compared to typicals as well as a lower incidence of increased prolactin levels and elongated QT intervals compared with atypical antipsychotics. More robust and long term studies are required.

#### **Benzodiazepines for schizophrenia.** (Volz et al. 2007)

Comparison of benzodiazepines to a placebo or antipsychotics for the treatment of schizophrenia, either as a sole agent or an adjunct to antipsychotic medication. Due to poor data reporting and inconsistencies, conclusions regarding benzodiazepines as sole agents cannot be drawn. Further comparisons of benzodiazepines in comparison to antipsychotics were also limited but antipsychotics were associated with a lower relapse rate. In combined antipsychotic-benzodiazepine versus antipsychotic alone studies, patients benefited within the first hour but this effect was subsequently lost. Final conclusions could not be made upon the efficacy of benzodiazepines, beyond temporary sedation, in the treatment of schizophrenia.

#### **Depot fluspiriline for schizophrenia.** (Abhijnhan et al. 2007)

Clinical, social and economic outcome comparison between depot fluspiriline and placebo, oral antipsychotics, and depot antipsychotics for schizophrenia and schizophrenia-like psychoses. Included 12 randomised studies. No clear differences were found between fluspiriline and oral medication or other depots, and no differences were found for movement disorders in one short term study. Overall, the advantages of fluspiriline as a depot over oral preparations and the advantages of depot fluspiriline over other depot medications cannot be informed from such few, short term studies. More RCT research is required.

### **Glutamatergic drugs for schizophrenia.** (Tuominen et al. 2006)

A review of the efficacy of glutamatergic drugs in the treatment of schizophrenia. Generally, no reduction in positive symptoms was observed in any glutamatergic drug trial. Glycine and D-serine may have improved negative symptoms but results were inconsistent and studies were not robust enough to allow firm conclusions.

### **Haloperidol versus placebo for schizophrenia.** (Joy et al. 2006)

Twenty-one trials were reviewed and consensus showed haloperidol to be an effective antipsychotic, particularly in short term trials: most improvements were seen in the first six weeks. Adverse effect data suggest haloperidol is significantly associated with movement disorders – acute dystonia, akathisia and parkinsonism. Therefore, where there is no other treatment option, haloperidol is justified, but prescription of an alternative antipsychotic with less likelihood of adverse effects is always preferable.

### **Lamotrigine for schizophrenia (Premkumar and Pick 2006)**

Lamotrigine was compared as an adjuvant with either a placebo or other antipsychotic augmentation strategy. Data were poor but suggested no significant difference in proportion of people whose mental state did not improve. Lamotrigine was associated with a reduction in PANSS total scores, positive symptom scores and negative symptom scores. The only significant side effect experienced in the lamotrigine group was nausea (9%). More research is needed to determine the place of lamotrigine in everyday clinical practice.

### **Molindone for schizophrenia and severe mental illness** (Bagnall et al. 2007)

A review of fourteen clinical trials involving molindone and schizophrenia and schizophrenia-like psychoses. Current data do not allow conclusions on comparative efficacy of molindone over a placebo, although molindone was found to be at least equally effective as other typical antipsychotics. Molindone causes similar rates of movement disorders but causes significantly more weight loss. There is no suggestion for consideration of molindone as an atypical antipsychotic.

### **Oral fluphenazine versus placebo for schizophrenia.** (Matar and AlMerie 2007)

Reviews of literature with strict selection/inclusion criteria. Short-term global state outcomes of ‘not-improved’ were not significantly different than the placebo. Fluphenazine also increases the rate of extrapyramidal effects (akathisia, rigidity). Fluphenazine is still an effective treatment for psychoses, but is imperfect and associated with significant adverse effects.

### **Penfluridol for schizophrenia.** (Soares and Lima 2006)

Comparison of the long-acting penfluridol to a placebo, other antipsychotics and no treatment to review the effects as an antipsychotic. Found the efficacy and adverse effects profile to be similar to other typical antipsychotics.

- penfluridol was superior in mental state outcomes to a placebo
- no differences were seen between penfluridol and other oral antipsychotics
- penfluridol was as safe and efficacious as other depot antipsychotics and was superior in keeping patients in treatment.

### **Perazine for schizophrenia.** (Leucht and Hartung 2006)

This was an analysis of six trials, one of which showed perazine to be superior to trimipramine (active placebo) at five weeks. However, lack of information and incomplete reporting meant results on efficacy were controversial and further assessment by RCT is needed. No higher risks for adverse

effects (extrapyramidal effects) were seen compared with other antipsychotics (haloperidol, zotepine and amisulpride). Insufficient data exists to present firm conclusions.

#### **Risperidone versus olanzapine for schizophrenia** (Jayaram et al. 2006)

A review of all clinical trials comparing risperidone to olanzapine for schizophrenia and schizophrenia-like psychoses. Most mental state data showed the drugs to be equally effective. Both drugs commonly cause adverse effects (75%) including anticholinergic symptoms (20%), sleepiness (30%), as well as insomnia, extrapyramidal symptoms and weight gain. People allocated to risperidone were less likely to gain weight compared to olanzapine, and were less likely to leave the study because of metabolic side effects. Both drugs were associated with high attrition rates, with 66% and 56% of participants leaving the study early for risperidone and olanzapine groups, respectively.

#### **Zotepine for schizophrenia** (DeSilva et al. 2006)

A review of 11 short term randomised clinical trials (four to 12 weeks). Compared with placebo, Zotepine improved mental state. Zotepine may be as successful as older typical antipsychotics, mental state measures of 'no improvement' decreased in the Zotepine group. Zotepine may also result in less movement disorder adverse effects compared with typical antipsychotics.

### *Non-pharmacological interventions*

#### **Problem solving skills for schizophrenia.** (Xia and Li 2007)

This study reviewed the effectiveness of problem solving therapy compared with other comparable therapies or routine care for those with schizophrenia. Three small trials were evaluated and it was concluded insufficient evidence was present to confirm or refute the benefits of problem solving therapy.

#### **Cessation of medication for people with schizophrenia already stable on chlorpromazine.** (Almerie et al. 2007)

Ten trials were reviewed and it was found in the short term, those remaining on chlorpromazine were less likely to experience a relapse than those who ceased their medication. Long term data were similar. This review highlights the risks of stopping chlorpromazine for those with established illness. Cessation of medication for schizophrenia must be carefully considered by both the patient and clinician in terms of potential harms and benefits

#### **Compliance therapy for schizophrenia.** (McIntosh et al. 2006)

A single trial was analysed to assess the effects of compliance therapy on antipsychotic medication adherence for people with schizophrenia. No significant differences were seen between the groups receiving compliance therapy or non-specific counselling. Mental state, insight, quality of life and global functioning appeared to be unaffected by compliance therapy, however rates of hospitalisation at one and two years were non-significantly reduced. No clear evidence suggests a benefit of compliance therapy but good evidence is required for accurate evaluation.

#### **Drama therapy for schizophrenia or schizophrenia-like illnesses.** (Ruddy and Dent-Brown 2007)

A review of drama therapy as adjunct to antipsychotic medication treatment compared to standard care or other psychosocial interventions. Five studies met inclusion criteria, but had no significant findings on the value of drama interventions for keeping inpatients engaged in treatment. No conclusive data on harms or benefits of drama therapy for inpatients with schizophrenia were found.

#### **Family intervention for schizophrenia.** (Pharoah et al. 2006)

This update builds on a 2002 study with a further 15 trials. Family intervention is shown to

- decrease the frequency of relapse
- reduce hospital admissions
- encourage compliance with medications, and

- may improve social functioning and expression of emotion within the family setting  
No data were found to suggest family intervention either prevents or promotes suicide. It does not obviously affect the tendency to leave care. As this method of care is widely practiced, there should be further study to determine short and long term outcomes.

#### **Supportive therapy for schizophrenia.** (Buckley et al. 2007)

This study aimed to estimate the effects of everyday clinical care supportive therapy for people with schizophrenia. Twenty-one studies were included, and no significant differences favouring other psychological or psychosocial treatments over supportive therapy were found. General functioning was improved most by cognitive behavioural therapy in the short, mid and long term, and user satisfaction was also greater for cognitive behavioural therapy over supportive therapy but the clinical significance of these findings based on a small data set is unclear.

#### *Other reviews*

#### **Electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania.**(Greenhalgh et al. 2005)

Review of the clinical and cost effectiveness of ECT for mental illness. Two randomised systematic reviews and four non-randomised systematic reviews were included. Special populations including older people, children and adolescents, catatonics and women with postpartum exacerbation were not included. Specifically for schizophrenia, ECT is indicated for treatment resistance, however little information exists on its efficacy and modelling shows clozapine treatment to be more cost efficient

#### **American Society of Health System Pharmacists Therapeutic Position Statement on the use of second-generation antipsychotic medications in the treatment of adults with psychotic disorders.** (Noel and American Society of Health-System Pharmacists 2007)

ASHP encourages health professionals to consider second-generation or atypical antipsychotics as first-line treatment for persons with psychotic disorders. The efficacy of treatment and tolerability profile improves treatment adherence and reduces the severity of short and long-term motor effects. It should be noted that second-generation antipsychotics are associated with cardiovascular and metabolic risks, so, as with any treatment option, should be carefully considered for use and monitored throughout the course of treatment. Adverse effects can include:

- Motor symptoms: dystonia, parkinsonism, akathisia, tardive dyskinesia
- Prolactin elevation
- Weight gain
- Diabetes mellitus, new onset hyperglycaemia
- Dyslipidemias
- Cardiac toxicity
- Cerebrovascular events
- Hematologic toxicity, respiratory depression and seizures

#### ***Additional reviews included in the appended AIP but not summarised in this report:***

The summary pages for these reviews, including objectives, main findings and clinical implications are included in Folder II of the appended IP. Instructions for their retrieval in full are given in the location information.

#### Pharmacotherapy

##### *Cochrane reviews*

*Very recently updated in the latest issue of the Cochrane Library (i.e. since the search date)*

Fenton et al (2007) Thioridazine for schizophrenia

Leucht et al (2007) Carbamazepine for schizophrenia.

Leucht et al (2003) Lithium for schizophrenia.

Rathbone & McMonagle (2007) Pimozide for schizophrenia or related psychoses.

*Other reviews of peripheral interest or reviews published before the BMJ Clinical Evidence review*

Arunpongpaisal et al (2003) Antipsychotic drug treatment for elderly people with late-onset schizophrenia.

Bagnall et al (2000) Ziprasidone for schizophrenia and severe mental illness.

Basan and Leucht (2003) Valproate for schizophrenia.

Chua et al (2005) Estrogen for schizophrenia.

David et al (2004) Depot fluphenazine decanoate and enanthate for schizophrenia.

David et al (2005) Depot perphenazine decanoate and enanthate for schizophrenia.

Dinesh et al (2004) Depot pipotiazine palmitate and undecylenate for schizophrenia.

Duggan and Brylewski (2004) Antipsychotic medication versus placebo for people with both schizophrenia and learning disability.

Duggan et al (2005) Olanzapine for schizophrenia.

Gibson et al (2004) Zucloperthixol acetate for acute schizophrenia and similar serious mental illnesses.

Gilbody et al (2000) Risperidone versus other atypical antipsychotic medication for schizophrenia.

Hartung et al (2005) Perphenazine for schizophrenia.

Hosalli and Davis (2003) Depot risperidone for schizophrenia.

Kumar and Strech (2005) Zucloperthixol dihydrochloride for schizophrenia.

Leucht and Hartung (2005) Benperidol for schizophrenia.

Lewis et al (2005) Sertindole for schizophrenia.

Marques et al (2004) Trifluoperazine for schizophrenia.

Marriott et al (2006) Antipsychotic medication for elderly people with schizophrenia.

Mota Neto et al (2002) Amisulpride for schizophrenia.

Murphy et al (2000) Loxapine for schizophrenia.

Nolte et al (2004) Amphetamines for schizophrenia.

Punnoose and Belgamwar (2006) Nicotine for schizophrenia.

Rummel et al (2003) New generation antipsychotics for first episode schizophrenia.

Tuunainen et al (2000) Newer atypical antipsychotic medication versus clozapine for schizophrenia.

Srisurapanont et al (2004) Quetiapine for schizophrenia.

Waraich et al (2002) Haloperidol dose for the acute phase of schizophrenia.

Whitehead et al (2002) Antidepressants for people with both schizophrenia and depression.

Wong et al (2004) Depot bromperidol decanoate for schizophrenia.

*Other reviews*

Bagnall et al (2003) Systematic review of atypical antipsychotic drugs in schizophrenia. Health Technology Assessment Vol.7 No.13

David and Adams (2001) Depot antipsychotic medication in the treatment of patients with schizophrenia: 1) Meta-review; 2) patient and nurse attitudes. Health Technology Assessment Vol.5 No. 34.

Lewis et al (2006) Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment. Health Technology Assessment Vol.10 No. 17.

### Non-pharmacological

#### *Cochrane Reviews*

Berner et al (2007) Management of sexual dysfunction due to antipsychotic drug therapy.

Cheine et al (2001) Beta-blocker supplementation of standard drug treatment for schizophrenia.

Crawford-Walker et al (2005) Distraction techniques for schizophrenia.

Faulkner et al (2007) Interventions to reduce weight gain in schizophrenia.

Gold et al (2005) Music therapy for schizophrenia or schizophrenia like illnesses.

Hayes and McGrath (2000) Cognitive rehabilitation for people with schizophrenia and related conditions.

He (2007) Morita therapy for schizophrenia.

Izquierdo de Santiago and Khan (2004) Hypnosis for schizophrenia.

Jones et al (2004) Cognitive behaviour therapy for schizophrenia.

Joy et al (2006) Polyunsaturated fatty acid supplementation for schizophrenia.

Joy and Saylan (2007) Mother and baby units for schizophrenia.

Malmberg and Fenton (2001) Individual psychodynamic psychotherapy and psychoanalysis for schizophrenia and severe mental illness.

McMonagle and Sultana (2000) Token economy for schizophrenia.

Pekkala and Merinder (2002) Psychoeducation for schizophrenia.

Rathbone et al (2005) Chinese herbal medicine for schizophrenia.

Rathbone and Zia (2005) Acupuncture for schizophrenia.

Ruddy and Milnes (2005) Art therapy for schizophrenia.

Tharyan and Adams (2005) Electroconvulsive therapy for schizophrenia.

#### *Other reviews*

Adams (2000) Psychosocial interventions for schizophrenia. Effective Health Care Bulletin Vol.6 No. 3.

Durham et al (2005) Long-term outcome of cognitive behaviour therapy clinical trials in Central Scotland. Health Technology Assessment Vol.9 No.42.

Marshall et al (2001) Systematic reviews of the effectiveness of day care for people with severe mental disorders: 1) acute day hospital admission; 2) vocational rehabilitation; 3) day hospital versus outpatient care. Health Technology Assessment Vol.5 No.21.

## **CONCLUDING COMMENTS**

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### ***Research base and stage***

The research base was in general of very high quality and multiple guidelines and Cochrane Collaboration reviews were identified and retrieved. There is however, a paucity of research in

culturally-based conceptions of mental health and how these conceptions might affect response or adherence to treatment for schizophrenic or other psychotic disorders. Even where reference is made to cultural considerations for treatment, this is not specifically relevant to the ethnic variation in New Zealand. Generally, more robust evidence is available for pharmacological interventions than for psychological or the combination of psychological and pharmacological interventions.

### ***Potential for Technical Brief or Systematic Review***

Recent high quality evidence on the treatment of psychotic disorders has been identified in the AIP. The guidelines identified and reviewed briefly are underpinned by recent, comprehensive high quality systematic reviews of evidence. A major update of the National Institute of Clinical Evidence (NICE) guidance is currently in progress, expected to report about this time next year and be released early in 2009.

The information provided in this AIP may be sufficient for the needs of the Nelson-Marlborough DHB, given the availability of the full text of the relevant documents that have been produced by well respected groups.

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