

SIGN 131 • Management of schizophrenia

A national clinical guideline

March 2013

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

| | |
|-----------------|---|
| 1 ⁺⁺ | High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias |
| 1 ⁺ | Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias |
| 1 ⁻ | Meta-analyses, systematic reviews, or RCTs with a high risk of bias |
| 2 ⁺⁺ | High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal |
| 2 ⁺ | Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal |
| 2 ⁻ | Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal |
| 3 | Non-analytic studies, eg case reports, case series |
| 4 | Expert opinion |

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

| | |
|----------|--|
| A | At least one meta-analysis, systematic review, or RCT rated as 1 ⁺⁺ , and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1 ⁺ , directly applicable to the target population, and demonstrating overall consistency of results |
| B | A body of evidence including studies rated as 2 ⁺⁺ , directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1 ⁺⁺ or 1 ⁺ |
| C | A body of evidence including studies rated as 2 ⁺ , directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2 ⁺⁺ |
| D | Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2 ⁺ |

GOOD PRACTICE POINTS

| | |
|---|---|
| ✓ | Recommended best practice based on the clinical experience of the guideline development group |
|---|---|



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SIGN guidelines are produced using a standard methodology that has been **equality impact assessed** to ensure that these equality aims are addressed in every guideline. This methodology is set out in the current version of SIGN 50, our guideline manual, which can be found at www.sign.ac.uk/guidelines/fulltext/50/index.html. The EQIA assessment of the manual can be seen at www.sign.ac.uk/pdf/sign50eqia.pdf. The full report in paper form and/or alternative format is available on request from the Healthcare Improvement Scotland Equality and Diversity Officer.

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Scottish Intercollegiate Guidelines Network

Management of schizophrenia

A national clinical guideline



March 2013

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1 Introduction

1.1 BACKGROUND

Schizophrenia is a relatively common mental disorder, with a lifetime risk approaching one per cent. The disorder is slightly more common in men.¹ Schizophrenia typically manifests in young people in their twenties, is usually lifelong and is characterised by 'positive symptoms' such as auditory hallucinations, bizarre delusions, and disrupted speech ('thought disorder') and by 'negative symptoms' such as social withdrawal, demotivation, self neglect, and the appearance of flat affect. Subtle cognitive impairment is also a feature.²

The developmental pathways that may result in schizophrenia are highly complex and poorly understood. They include family history of schizophrenia,³ obstetric complications and developmental difficulties,⁴ abuse,⁵ major life events⁶ and parental loss.⁷ Rates of schizophrenia are also increased in urban, poor, immigrant and ethnic minority populations.⁸ Nearer to the time of onset, both cannabis use⁹ and acute life events⁶ appear relevant.

Although many people do achieve remission of symptoms, the associated difficulties can be persistent and the individual diagnosed with schizophrenia can experience repeated episodes in between periods of remission. It is increasingly recognised that recovery from schizophrenia is more than the reduction or remission of symptoms in isolation. The Scottish Recovery Network has defined recovery as "being able to live a meaningful and satisfying life, as defined by each person, in the presence or absence of symptoms."

About three quarters of people who meet diagnostic criteria for schizophrenia will experience a relapse. Unplanned disengagement from treatment is a significant risk for relapse.¹¹ Poor social integration predicts less recovery following a first or second episode of psychosis.¹² (Relapse is linked to increasing disability via loss of important relationships and work and educational opportunities. A poor outcome is more likely in men, individuals who misuse drugs, people with low intelligence quotient (IQ) or where there is long duration of untreated psychosis. Low levels of academic and social functioning prior to the onset of schizophrenia and more severe symptoms at presentation also predict poor outcome as does having more prominent negative symptoms and a poor response to antipsychotic medication.¹³⁻¹⁶

The interpersonal context is a crucial aspect of recovery. Those individuals who live in supportive home environments and have more friends experience better recovery.¹⁷⁻¹⁹ However, many individuals lose their friends' and families' support and may become subject to poverty, stigma and isolation and may face discrimination and violence. About one half will have substance misuse problems,^{20,21} and an overlapping half will have anxiety states and/or depression.²² Given the very frequent comorbidity with psychological disorders including depression (and hopelessness) and social anxiety it is important that individuals diagnosed with schizophrenia are not excluded from evidence based pharmacological and psychological treatments developed for these conditions.

People diagnosed with schizophrenia have a shorter life expectancy than the general population but with similar causes of premature death including cardiovascular disease, respiratory illness and cancer.^{14,20,23}

Stigma surrounding the diagnosis of schizophrenia exists and people diagnosed with schizophrenia are often stereotyped as violent individuals. Although violence committed by people with schizophrenia is rare and the proportion of violence in society attributable to schizophrenia is very small, there is a marginally increased risk of committing violence for someone with schizophrenia, compared to a member of the general public.^{19,24} Most of the excess risk appears to be mediated by substance abuse comorbidity.¹⁹ Individuals diagnosed with schizophrenia are more likely to hurt themselves than those in the general population. Five per cent will commit suicide, with well recognised risk factors including male sex, illness severity and comorbidity, with the only consistent protective factor being delivery of, and adherence to, effective treatment.²⁵ Incidence of attempted suicide following a first episode of psychosis amongst adolescents is 32%.²⁶ Linked to suicide are the feelings of depression and hopelessness that arise from perceptions of schizophrenia as a chronic, disabling, stigmatising diagnosis.

There is significant cost to society in relation to the care of individuals diagnosed with schizophrenia and their families. In England this was estimated as £6.7 billion in 2004/05. The direct cost of treatment was about £2 billion. Indirect costs to society amounted to nearly £4.7 billion, of which £3.4 billion was attributed to lost productivity due to unemployment, absence from work and premature mortality. The cost of informal care and private expenditures borne by families was £615 million, and that of lost productivity of carers was estimated to be £32 million. About £570 million was paid out in benefits and the cost of administering this was around £14 million.²⁷ The advent of community care has dramatically reduced the number of patients living their lives in hospital, and has not resulted in an increase in the homeless hostel population.²⁸ Many patients are now treated solely by their general practitioner without input from specialist services.²⁹

1.2 THE NEED FOR A GUIDELINE

Variation in service provision and in individual service user's outcomes suggest there is a need for evidence based recommendations on treatment of schizophrenia and to improve service users engagement with treatment. Medication is generally helpful in treating positive symptoms, but up to a third of people derive little benefit, and negative symptoms are difficult to treat. About half of people with schizophrenia do not adhere to pharmacological treatment in the short term and fewer adhere in the longer term.³⁰ This may be related to a lack of insight into their condition or to the range of adverse effects associated with medical treatments such as movement disorders, sexual problems and weight gain. The care needs of older people with schizophrenia are often neglected.³¹

Despite increasing evidence of the efficacy of discrete psychological interventions and therapies such as family intervention and cognitive behavioural therapy (CBT), delivery of such interventions has been difficult to realise in practice. Early intervention services are not available throughout Scotland or outside specialist centres and, although training may enable nurses to improve the support provided to carers,³² most professionals remain unsure how best to provide this.³³

Through providing recommendations for best practice SIGN guidelines have an important role in ensuring that all individuals with schizophrenia and their families and friends have the best opportunity to engage in evidence based treatments focused on maximising recovery and well-being.

1.3 REMIT OF THE GUIDELINE

1.3.1 OVERALL OBJECTIVES

This guideline provides evidence based recommendations for care and treatment of adults with schizophrenia. The key questions used to develop the guideline are outlined in Annex 1.

The guideline does not provide specific recommendations for the following:

- patients with at-risk or ultra-high risk mental states
- patients with specific comorbidities such as learning disabilities or autism spectrum disorders
- prodromal syndromes
- transitions from child and adolescent mental health services
- transitions to older adults services
- particular care settings (eg forensic, inpatient or outpatient units, primary or secondary care).

1.3.2 PRESENTATION OF RECOMMENDATIONS

Although the evidence and recommendations for psychopharmacology and for psychological therapies are presented separately in this guideline, the organisation and delivery of these interventions should not be disaggregated from each other. The quality of their relationships with healthcare professionals is an important determinant of an individual's attitude towards treatment and adherence to treatment including antipsychotic medication.³⁴ Services should seek to enhance the quality of their working relationships with service users and their families. All interventions for individuals diagnosed with schizophrenia and their families should be offered in an atmosphere of collaboration, optimism and information sharing. Good quality information on the nature, requirements, rationale and expected success of any interventions should be made available and, where possible, should reflect the choices available for patients and their families.

1.3.3 TARGET USERS OF THE GUIDELINE

This guideline will be of particular interest to mental health specialists working with people diagnosed with schizophrenia including psychiatrists, psychologists, specialist mental health nurses and occupational therapists providing health and social services. It will also be of relevance to general practitioners and pharmacists. The guideline will help provide direction for planning at a local and national level and will also be of interest to service users and carers.

1.4 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

1.4.1 PATIENT VERSION

A patient version of this guideline is available from the SIGN website www.sign.ac.uk

1.4.2 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off label' use.

Medicines may be prescribed off label in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

Generally the off label use of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability."³⁵

The General Medical Council (GMC) recommends that when prescribing a medicine off-label, doctors should:

- be satisfied that such use would better serve the patient's needs than an authorised alternative (if one exists)
- be satisfied that there is sufficient evidence/experience of using the medicines to show its safety and efficacy, seeking the necessary information from appropriate sources.
- record in the patient's clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice.
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the current version of the British National Formulary (BNF).³⁵ The prescriber must be competent, operate within the professional code of ethics of their statutory body and the prescribing practices of their employer.³⁶

1.4.3 ADDITIONAL ADVICE TO NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

Healthcare Improvement Scotland processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Clinical Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

SMC advice relevant to this guideline is summarised in section 9.4.

2 Key recommendations

2.1 ACCESS AND ENGAGEMENT

- A** Individuals in the first episode of psychosis should receive treatment within the context of a specialist early intervention model of care. This should be multidisciplinary and encompass:
- engagement/assertive outreach approaches
 - family involvement and family interventions
 - access to psychological interventions and psychologically informed care
 - vocational/educational interventions
 - access to antipsychotic medication.

2.2 PHARMACOLOGICAL AND RELATED APPROACHES

- ✓ Local arrangements for physical health monitoring should be put in place at the time of antipsychotic prescribing.

- A** In service users with an acute exacerbation or recurrence of schizophrenia prescribers should consider amisulpride, olanzapine or risperidone as the preferred medications with chlorpromazine and other low-potency first-generation antipsychotics providing suitable alternatives. Consideration should be given to previous response to individual antipsychotic medications and relative adverse effect profiles.

- A** Individuals with schizophrenia which is in remission should be offered maintenance treatment with antipsychotic medication for a minimum of two years.

- B** Clozapine should be offered to service users who have treatment-resistant schizophrenia.

2.3 PSYCHOLOGICAL THERAPIES

- A** Individual CBTp should be offered to all individuals diagnosed with schizophrenia whose symptoms have not adequately responded to antipsychotic medication and where persisting symptoms and/or depression are being experienced. CBTp can be started during the initial phase, the acute phase or recovery phase including inpatient settings.

- A** Family intervention should be offered to all individuals diagnosed with schizophrenia who are in close contact with or live with family members and should be considered a priority where there are persistent symptoms or a high risk of relapse. Ten sessions over a three-month period should be considered the minimum effective dose. Family intervention should encompass:
- communication skills
 - problem solving
 - psychoeducation.

3 Dual diagnosis

In this context, dual diagnosis is used to define people with schizophrenia who are also misusing drugs (including alcohol).

UK studies indicate that substance misuse is common in people with schizophrenia. A third to a half of people in the first episode of schizophrenia misuse substances, predominantly alcohol, cannabis and stimulants.³⁷The use of opiates and benzodiazepines is less common.³⁸

In a Scottish study, differences in rates of illicit drug and alcohol use between people with schizophrenia and the general population were small, unlike tobacco use which was around 50% higher than the general population.²⁰

People with schizophrenia who misuse substances have poorer outcomes for both schizophrenia and substance misuse.³⁹ There is a complex range of interactive factors such as adverse early life experience, poor educational attainment, difficult family relationships, accommodation problems, employment issues, health beliefs, general health behaviours and biological factors which could explain these poorer outcomes.

Until recently, it was common for research studies in schizophrenia to exclude people who misuse substances and this has resulted in a limited evidence base for interventions. A pharmacotherapy trial from the United States (US) showed no difference in treatment response between substance misusers and others. Poorer outcomes were due to reduced treatment adherence in those who misuse substances.⁴⁰ Although integrated motivational interviewing and cognitive behavioural therapy for people with psychosis and comorbid substance misuse reduced the amount of substance used at one year follow up, this did not have an effect on hospitalisation, symptoms or functioning when compared to treatment as usual.⁴¹

Policy reviews and implementation guidance in the United Kingdom (UK) recommends 'mainstreaming' the treatment of co-occurring mental health problems and substance misuse, with mental health services ensuring that staff have the appropriate knowledge, skills and attitudes to respond to substance misuse in people with schizophrenia, and are supported by specialist substance misuse services when required. This approach is favoured over the establishment of specialist comorbidity services.^{39,42,43}

- ✓ Comorbid substance misuse should not exclude people with schizophrenia from services or interventions. Management of severe and complex problems may require a joint consultative approach between mental health and substance use services.
- ✓ Professionals working with people with schizophrenia and comorbid substance misuse should have the appropriate competencies and support to address the needs of this service user group.

4 Access and engagement

4.1 EARLY INTERVENTION SERVICES

Early intervention (EI) services offer comprehensive multimodal and multidisciplinary care in the early phase of psychosis. Their aim is to provide quick access assertive outreach, and reduce the duration of untreated psychosis by providing a range of therapeutic approaches that minimise symptoms and maximise functioning, specifically targeting this population. Therapeutic approaches include low dose medications, family interventions, psychosocial interventions such as therapy or support groups, CBT and vocational rehabilitation. Early intervention services focus on engagement, emotional recovery and tolerance of diagnostic uncertainty, usually including service users within the spectrum of psychosis.

The majority of EI services do not exclude those who use substances and/or alcohol but no specific evidence was identified looking at outcomes for this group.

A systematic review identified four randomised controlled trials (RCTs) comparing early intervention services with standard care or hospital based rehabilitation.⁴⁴ A range of outcome measures were used and the duration of follow up varied. Meta-analysis was conducted where possible. When compared with standard care, early intervention services improved engagement (as measured by study attrition rates) and led to benefits in terms of reduced relapse rates and reduced hospital readmissions over 18 to 24 of months follow up. There was clinical benefit as measured by total symptom score (positive and negative syndrome scale, PANSS) at 18 months follow up (one study) and the intervention group had better quality of life at 18 months (one study). Early intervention services led to a greater likelihood of participants receiving family intervention (one study) or there being family involvement (one study) and a greater likelihood of receiving psychosocial therapy (two studies). One of the studies found that those in the intervention group were more likely to remain in touch with mental health services.

1+

A further meta-analysis found that early intervention services providing a combination of individual CBT and family intervention reduced hospital admission, relapse rates and symptom severity, and improved access to and engagement with treatment. For people with early psychosis, early intervention services had clinically important benefits over standard care.⁴⁵

1++

Two additional RCTs examined specific aspects of early intervention; CBT⁴⁶ and individual vocational placement and support.⁴⁷ Although both studies reported benefits in very specific outcomes such as employment, education, and use of the benefit system, studies were small (n=66 and 41) and had methodological limitations.

1-

An RCT comparing medication with a combined medication and intensive psychological intervention programme which integrated a range of therapies in 12 day-long sessions over one year found that the addition of the psychological therapies led to improved discontinuation rates.⁴⁸ The generalisability of the intervention model for services in NHSScotland is limited.

1+

Five-year follow up of a 24 month RCT found that clinical benefits were not sustained.^{49,50} There were no significant quality of life differences between the groups.⁵¹ Another five-year follow-up study assessing outcomes by review of case notes found no significant benefit of EI on number or length of hospital admissions.⁵²

1++

1+

A large scale prospective cohort study identified 723 individuals who were in receipt of early intervention for the first two years after experiencing a first episode of psychosis. The median follow-up period was 7.4 years. The purpose of the study was to compare long term outcomes (of at least five years) in service users with early onset (before age 18) and those with adult onset. Within this early intervention framework, individuals experiencing early onset achieved better vocational outcome, higher quality of life, fewer psychotic symptoms, and had a more favourable illness course with fewer psychotic episodes following their treatment period.⁵³ A similar cohort study examining long term outcomes for early intervention services in 188 individuals over five years found comparable results in that initial improvements in psychotic symptoms, as well as global functioning and ongoing engagement with the service, were maintained.⁵⁴

2++

There is consistent evidence that EI services have benefit for engagement rates, readmission rates, access to family interventions and other psychological interventions and rates of functional recovery in service users in the first episode of psychosis. There is insufficient evidence on long term benefits in terms of symptom improvement. There is some indication that benefits of EI in relation to functional recovery (education/employment and independent living) are sustained at five year follow up with symptomatic and social improvements maintained up to three years.^{44,45}

The cost effectiveness of EI is uncertain largely due to difficulty in estimating the value of functional recovery, for example return to work.⁵⁵

3

- A** **Individuals in the first episode of psychosis should receive treatment within the context of a specialist early intervention model of care. This should be multidisciplinary and encompass:**
- engagement/assertive outreach approaches
 - family involvement and family interventions
 - access to psychological interventions and psychologically informed care
 - vocational/educational interventions
 - access to antipsychotic medication.

See section 5.4 for recommendations on initial pharmacological treatment.

4.2 ASSERTIVE COMMUNITY TREATMENT

Common components of assertive community treatment (ACT) include community outreach and domiciliary visits, high frequency contacts, active case management including vocational and daily living support, and seven day/24 hour availability of crisis support.

A systematic review considered ACT in the context of service level interventions for the management of schizophrenia and found that ACT improves contact with services, reduces bed usage and hospital admission, and increases satisfaction with services, when compared with standard community care. This finding is largely based on evidence from the US and should be viewed with caution when applied to a UK community treatment based setting.³⁴

1⁺⁺

There is strong evidence suggesting that those receiving ACT are more likely to remain in contact with services, adhere to medication treatments and are more likely to live independently and to be in employment than people receiving standard community care. There is further evidence suggesting that ACT decreases the likelihood of hospital admission and increases quality of life, compared with standard care.^{44,56-58}

1⁺⁺

In addition, a number of prospective cohort studies with long term follow-up periods of between three and five years, found that adherence to ACT was associated with less homelessness and fewer hospital days,⁵⁹ stronger symptomatic remission⁶⁰ and increased service engagement and adherence to medication treatment⁶¹ when compared with other service models.

2⁺

2⁺⁺

One prospective cohort study however, in a five year follow-up design comparing ACT with inpatient assessment followed by traditional community care, found no difference for individuals with schizophrenia at follow up in relation to their level of vocational and functional recovery, symptom remission and homelessness.⁶²

There is a lack of standardisation and a high level of variability in service models for ACT both within and across different countries and healthcare systems, with the evidence base continuing to be largely from outside the UK.

- B** **Assertive outreach should be provided for people with serious mental disorders (including for people with schizophrenia) who make high use of inpatient services, who show residual psychotic symptoms and who have a history of poor engagement with services leading to frequent relapse and/or social breakdown (for example homelessness).**

4.3 SPECIALIST ETHNIC MENTAL HEALTH SERVICES

A systematic review identified no evidence on the effectiveness of specialist ethnic mental health services for people with schizophrenia in terms of improving outcomes or engagement.⁴⁴

One small RCT reported benefit from a culturally specific intervention for a group of Latin Americans with persistent psychosis.⁶³ This study has limited applicability in Scotland as it is based on a very specific group intervention in a non-NHS setting. The study provides good quality but very limited evidence for improved outcomes and treatment effect where a group intervention is specifically designed and targeted at the cultural norms and values of a specific ethnic group.

1⁺⁺

The recommendations for working with people with schizophrenia from diverse ethnic and cultural backgrounds are based on expert opinion and are reproduced from the NICE guideline (NICE CG82) on core interventions in the treatment and management of schizophrenia in primary and secondary care.⁴⁴

D Healthcare professionals inexperienced in working with people with schizophrenia from diverse ethnic and cultural backgrounds should seek advice and supervision from healthcare professionals who are experienced in working transculturally.

D When working with people with schizophrenia and their carers:

- avoid using clinical language, or keep it to a minimum
- ensure that comprehensive written information is available in the appropriate language and in audio format if possible
- provide and work proficiently with interpreters if needed
- offer a list of local education providers who can provide English language teaching for people who have difficulties speaking and understanding English.

5 Pharmacological and related approaches

5.1 ANTIPSYCHOTIC TOLERABILITY

Pooled data from 138 comparisons of antipsychotics were reported in a systematic review.⁴⁴ Most of the trials were of relatively short duration, typically 12 weeks or less, and not designed to prospectively examine adverse effects. The trials provided little insight into the longer term adverse effects of treatment or whether there are clinically significant differences between antipsychotic medications. Around 5-10% of participants left the studies early specifically due to adverse effects with no apparent difference between medications.

1⁺⁺

The clinical antipsychotic trial of intervention effectiveness (CATIE) study funded by the National Institute of Mental Health, used all-cause discontinuation as the primary outcome measure and found that antipsychotics were discontinued in 60–80% of the 1,493 participants within the 18-month follow-up period, but the percentage was lower in those randomised to second-generation antipsychotics (SGA).⁶⁴ The cost utility of the latest antipsychotic drugs in schizophrenia study (CUtLASS) funded by the NHS Research and Development Health Technology Assessment Programme in England found that more service users randomised to receive an SGA than a first-generation antipsychotic (FGA) remained in their allocated treatment arm for the whole year, although the difference was not significant (65% (71/109) versus 54% (64/118)).^{65,66}

1⁺

- ✓ Healthcare professionals and service users should work together to find the most appropriate medication and the lowest effective dose. There should be detailed discussion with service users outlining the potential benefits and harms of individual medications. Service user preference should be elicited and taken into account.
- ✓ There should not be routine use of multiple antipsychotic medications. Where polypharmacy is being considered for an individual clinical situation the benefits and harms should be discussed with the service user.

5.2 PHYSICAL HEALTH MONITORING

Antipsychotic medications are associated with a range of adverse effects which can influence physical health. Table 1 outlines a proposed schedule of physical monitoring based on a systematic evaluation of guidelines for physical monitoring and the clinical experience of the SIGN guideline development group.⁶⁷

Table 1 Suggested monitoring schedule for service users taking antipsychotic medications for schizophrenia

| Test | Baseline | At 1 month | At 3 months | Annually |
|---|-------------------------|-------------------------|-------------|----------|
| Individual and family history of physical illness | ✓ | | | ✓ |
| Smoking history | ✓ | | ✓ | ✓ |
| Body mass index/ weight/waist circumference | ✓ | ✓ | ✓ | ✓ |
| Blood pressure | ✓ | As clinically indicated | ✓ | ✓ |
| HbA1C/random glucose/ fasting glucose | ✓ | As clinically indicated | ✓ | ✓ |
| Random lipids/fasting lipids | ✓ | As clinically indicated | ✓ | ✓ |
| Prolactin | As clinically indicated | | | |
| ECG | As clinically indicated | | | |

- ✓ Local arrangements for physical health monitoring should be put in place at the time of antipsychotic prescribing.

5.3 MANAGEMENT OF ADVERSE EFFECTS

- ✓ Since many adverse effects of antipsychotic medications are dose related, the minimum effective dose should always be prescribed.

5.3.1 MOVEMENT DISORDERS

Extra-pyramidal side effects

In a systematic review all SGAs were associated with fewer extra-pyramidal side effects (EPSE) than haloperidol, even with haloperidol used at low dose (<7.5 mg/day). With the exception of clozapine, (and in a small number of studies olanzapine, and risperidone), SGAs were not shown to produce fewer adverse EPSE than low potency FGAs such as chlorpromazine.⁶⁸

1++

An expert consensus guideline from the US recommends examining service users for rigidity, tremor and akathisia weekly for two weeks after initiating antipsychotic medication, or after a dose change, or until the dose has been stabilised.⁶⁹

4

- ✓ Service users should be informed of the risk of EPSE and encouraged to report any symptoms suggestive of EPSE. Healthcare professionals should be vigilant for the presence of EPSE, even if this is not mentioned by the service user for example by use of a validated side effect scale.

B If EPSE are of particular concern to a service user then SGAs or low potency FGAs should be considered.

The British Association for Psychopharmacology (BAP) consensus guidelines conclude that anticholinergic agents should not be prescribed prophylactically, but should be considered for emergent extra-pyramidal problems on an individual basis.⁷⁰

4

Tardive dyskinesia

Tardive dyskinesia (TD) is a hyperkinetic involuntary movement disorder that can affect neuromuscular function in any body region, but is most commonly seen in the orofacial region. Although typically chronic and related to treatment, TD fluctuates in severity and can occur in antipsychotic-free individuals with schizophrenia.⁷¹

A systematic review found that olanzapine was less likely to be associated with the development of TD and/or dyskinesic movements, in the short to medium term, than haloperidol, other FGAs or paliperidone. Overall TD rates were 2-3% per annum in participants on olanzapine as compared to a highly variable 5-20% for the other antipsychotics. In one trial, the rate of TD development was the same with olanzapine and risperidone.⁴⁴

1++

In a systematic review of 12 studies (n=28,051), the annual estimated incidence of TD was less with SGAs than FGAs (3.9% compared to 5.5%), and the estimated prevalences were 13.1% for SGAs compared with 32.4% for FGAs (p <0.0001).⁷²

2++

B Where tardive dyskinesia is a specific concern, an SGA should be considered.

5.3.2 SEDATION

In a systematic review clozapine and quetiapine were significantly more sedating than haloperidol (RR 1.50, 95% CI 1.01 to 2.23, p=0.043 and RR 2.07, 95% CI 1.01 to 4.27, p=0.047 respectively), whereas aripiprazole was significantly less sedating (RR 0.65, 95% CI 0.45 to 0.95, p=0.024). By contrast, compared with low-potency FGAs, only clozapine was significantly more sedating (RR 1.32, 95% CI 1.10 to 1.59, p=0.003).⁶⁸

1+

B If sedation is a concern, then haloperidol or aripiprazole should be considered.

5.3.3 WEIGHT GAIN

A systematic review found that amisulpride, clozapine, olanzapine, quetiapine and risperidone were associated with significantly more weight gain than haloperidol. The greatest weight gain was observed with clozapine (mean weight gain difference 3.4 kg, 95% CI 2.0 to 4.9, $p < 0.0001$) and olanzapine (3.3 kg, 95% CI 2.2 to 4.4, $p < 0.0001$), intermediate weight gain occurred with quetiapine (1.4 kg, 95% CI 0.7 to 2.1 $p < 0.0001$) and risperidone (1.7 kg, 95% CI 0.9 to 2.4, $p < 0.0001$), and amisulpride induced the smallest increase (0.9 kg, 95% CI 0.2 to 1.6, $p = 0.012$). Aripiprazole induced no significant weight gain. There was no significant difference between SGAs and low-potency FGAs such as chlorpromazine.⁶⁸ 1++

A Haloperidol, aripiprazole or amisulpride should be considered for service users who are particularly concerned about weight gain, or who may be at the greatest risk of weight gain.

Behavioural lifestyle approaches

A systematic review of 10 trials ($n = 482$) of non-pharmacological management of antipsychotic-induced weight gain, six of which were conducted in service users established on treatment, found that a variety of approaches (individual/group, weight management, lifestyle change, CBT, nutritional counselling) were similarly effective in reducing weight compared to treatment as usual (WMD of -2.56 kg, 95% CI -3.20 to -1.92 kg, $p < 0.001$).⁷³ 1+

SIGN guideline number 115 on the management of obesity provides evidence based recommendations on weight management.⁷⁴

A Lifestyle interventions (incorporating physical activity, dietary change and behavioural components) should be considered for service users who are experiencing weight gain on antipsychotic medications.

Metformin

A systematic review of the role of metformin in preventing weight gain in service users taking antipsychotics identified nine RCTs and two cohort studies. Possible benefits were confounded by co-administered weight and lifestyle intervention programmes, but metformin was associated with few serious adverse effects.⁷⁵ Another review examining only SGAs, and encompassing some of the same studies, reported similar conclusions.⁷⁶ 1+

Metformin is not licensed for the control of weight gain in individuals taking antipsychotic medications.

B Metformin should be considered for service users who are experiencing weight gain on antipsychotic medications.

Topiramate

A systematic review included five RCTs of topiramate for the prevention or treatment of weight gain in individuals taking antipsychotic medications. Although there was evidence of effectiveness for weight management this was often accompanied by adverse effects including worsening of schizophrenia symptoms. The review also highlighted greater drug interactions with topiramate than with metformin.⁷⁶ 1-

5.4 INITIAL TREATMENT IN FIRST EPISODE PSYCHOSIS

5.4.1 EFFICACY

The ideal minimum trial of medication duration for initial treatment is 12 weeks, reflecting the time at which 90% of individuals who respond to treatment achieve symptomatic remission. Only six of the nine trials included in a systematic review had duration of 12 weeks or more. All of the trials included service users from both inpatient and outpatient settings. None of the trials gave clear information on the rates of substance misuse in the study population.⁴⁴

The nine RCTs identified covered 12 comparisons:

- olanzapine versus haloperidol (3 trials)
- olanzapine versus quetiapine (1 trial)
- olanzapine versus risperidone (3 trials)
- risperidone versus haloperidol (4 trials)
- risperidone versus quetiapine (1 trials).

Total symptom score

Olanzapine was more effective than haloperidol but, although statistically significant, the difference was small; 0.3 on clinical global impressions (CGI) score and 6 on PANSS total score. There was no difference between risperidone and haloperidol nor any significant difference between olanzapine and risperidone.⁴⁴ A meta-analysis found no statistically significant difference at 12 weeks between olanzapine or risperidone when compared with quetiapine.⁷⁷

1⁺⁺

Rates of discontinuation

Olanzapine is less likely than haloperidol to be discontinued in studies of between 12 and 51 weeks duration, risk ratio 0.69 (95% CI 0.51 to 0.95). In short term studies of less than 12 weeks duration, risperidone was less likely to be discontinued than haloperidol, risk ratio 0.70 (95% CI 0.55 to 0.88).⁴⁴ The European first episode schizophrenia trial (EUFEST) is a pragmatic RCT conducted in individuals aged between 18 and 40 years from 15 different European countries. Although healthcare professionals were not blinded to the intervention, the trial provides generalisable data on tolerability/discontinuation outcomes.⁷⁸ Quetiapine, ziprasidone, amisulpride and olanzapine showed a lower risk of any-cause discontinuation compared with haloperidol.⁷⁸

1⁺⁺1⁺

Weight gain

In comparison with haloperidol there was significantly increased weight gain in participants on olanzapine in medium and long term studies. No significant differences were found between risperidone and haloperidol.⁷⁸

1⁺

Elevated prolactin

Prolactin was elevated in participants on risperidone compared to those on quetiapine or olanzapine. There was no statistically significant difference in prolactin level between the olanzapine and quetiapine groups. In one study there was an increased risk of elevated prolactin with risperidone compared with haloperidol.⁴⁴

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Extra-pyramidal adverse effects

A meta-analysis found a significantly lower incidence of extra-pyramidal adverse effects from SGAs as a group compared to FGAs as a group (SMD -0.38, 95% CI -0.53 to -0.24).⁷⁷

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In the short term and medium term studies olanzapine and risperidone were associated with fewer adverse effects compared to haloperidol. Olanzapine was associated with reduced incidence of treatment-emergent akathisia and parkinsonism compared to haloperidol. In examining a change from baseline extra-pyramidal symptoms, risperidone showed benefit over haloperidol. No statistically significant difference was found between risperidone and olanzapine or risperidone and quetiapine.⁴⁴

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Fasting triglycerides and fasting glucose

In one RCT there were no differences in the level of fasting triglycerides in the short or medium term in participants either on olanzapine or risperidone. There was an increased risk ratio of 2.33 (95% CI 1.01 to 5.41) for a fasting glucose greater than 100 mg/dl (5.56 mmol/l) cut-off in the olanzapine group, as well as an increased risk of fasting high density lipoprotein elevation in the medium term. Similar findings were identified for olanzapine compared to quetiapine.⁴⁴ 1⁺⁺

Summary

For individuals in the first episode of schizophrenia there is no evidence to suggest improved efficacy of SGAs over haloperidol, although discontinuation rates with haloperidol are higher than with olanzapine, risperidone, quetiapine and amisulpride.

A Individual prescribing for service users in the first episode of psychosis should consider benefits and harms.

✓ Adverse effects should be discussed in detail with service users before the choice of medication is agreed.

5.4.2 TREATMENT STRATEGY

A systematic review identified no studies examining switching of initial treatment for individuals in the first episode of schizophrenia. The recommendations are based on consensus guidelines which concluded that while early improvement measured within two weeks is a reasonable predictor of response and remission, making the decision to change treatment in non-responders may take up to eight weeks.⁷⁰ 4

D Following initiation of an antipsychotic medication for service users in the first episode of psychosis, the medication should be continued for at least two weeks unless there are significant tolerability issues. Assessment of dose and response should be monitored during the early phase of prescribing.

D Where there is poor response to medication there should be an assessment of medication adherence and inter-current substance misuse before the lack of response can be definitively established.

D If there is no response to medication after four weeks, despite dose optimisation, a change in antipsychotic should be considered.

D Where there is partial response, this should be re-assessed after eight weeks unless there are significant adverse effects.

5.4.3 PREDICTING THE RESPONSE TO MEDICATION

Factors predicting a better response to medication include early response to treatment with antipsychotic medication, female gender and better pre-morbid social functioning. Factors that are associated with a poorer response (and poorer medication adherence) include male gender, substance misuse, forensic history and decreased level of insight.⁷⁹⁻⁸⁴ 2⁺

5.4.4 DOSE

No meta-analyses or systematic reviews were identified around dose of antipsychotic for people in the first episode of psychosis. A Cochrane review of risperidone dose identified four trials of individuals in the first episode which reflect current dosage regimens. Doses of risperidone below 2 mg daily did not have any clinical effect due to participants leaving the study early, providing weak evidence to support a dosage regimen of 2-4 mg daily.⁸⁵ An RCT identified by a meta-analysis compared risperidone with haloperidol and found that a mean risperidone dose of 3.3 mg daily was associated with remission from symptoms in three quarters of participants.⁴⁴ 1⁺⁺

There is evidence that low doses of both FGA and SGA are effective in individuals in the first episode of schizophrenia. The biological sensitivity in first episode also relates to tolerability, and lower doses of the chosen medication may reduce the adverse effect burden.⁷⁰ | 4

D Minimum effective dose of either first- or second-generation antipsychotics should be used in individuals in the first episode of schizophrenia.

5.4.5 DURATION OF TREATMENT

No meta-analyses or systematic reviews were identified which examined duration of treatment. In one RCT of guided discontinuation versus sustained antipsychotic use in 128 individuals with remitted schizophrenia following a first episode, maintenance of treatment was superior to guided discontinuation for relapse prevention over a twelve month period, odds ratio (OR) 2.91 (95% CI 1.33 to 6.37).⁸⁶ | 1+

The evidence supports treatment for at least 18 months after initial remission, although even when adherence to medication is assured, individuals recovering from a first episode of schizophrenia remain at risk of relapse.⁷⁰ | 4

D Following remission of the first episode of schizophrenia, the duration of maintenance treatment with antipsychotics should be at least 18 months.

✓ All service users in the first episode of schizophrenia should be offered a mental health review at regular intervals.

5.5 TREATING ACUTE EXACERBATION OR RECURRENCE

5.5.1 EFFICACY

A systematic review identified 72 RCTs of the use of oral antipsychotic medications in people with schizophrenia who had an acute exacerbation. Most of the comparisons were between FGAs and SGAs. Haloperidol was the most frequent comparator for the FGA class. There were 14 studies comparing risperidone with haloperidol (n=2,437) and nine comparing olanzapine with haloperidol (n=3,071). There was a broad range of outcomes at various time points and the study duration ranged from 4 to 52 weeks. Meta-analysis of studies comparing FGA with SGA in this patient group found no statistically significant differences in clinical efficacy outcomes, although there were differences related to adverse effect profiles. SGAs tended to be associated with fewer neurological adverse effects and FGA with greater metabolic adverse effects, in particular weight gain.⁴⁴ | 1++

A subsequent meta-analysis conducted across patient groups and incorporating 150 studies concluded that amisulpride, olanzapine, risperidone and clozapine, had superior efficacy when compared with FGAs in terms of overall efficacy, with small to medium effect size benefits.⁶⁸ Other SGAs were not more efficacious than FGAs.⁸⁷ A meta-analysis of head-to-head comparisons of SGAs found that while there were only small and inconsistent differences between SGAs with respect to efficacy, these need to be balanced by potentially large differences in adverse effect profiles for individual service users.⁸⁷ This is in agreement with the findings from a number of Cochrane systematic reviews comparing SGAs.⁸⁸⁻⁹⁴ | 1++

A In service users with an acute exacerbation or recurrence of schizophrenia prescribers should consider amisulpride, olanzapine or risperidone as the preferred medications with chlorpromazine and other low-potency first-generation antipsychotics providing suitable alternatives. Consideration should be given to previous response to individual antipsychotic medications and relative adverse effect profiles.

5.5.2 TREATMENT STRATEGIES

The BAP guideline examined the predictive value of early assessment of treatment response rates and concluded that an effective treatment strategy would be to commence a trial of an antipsychotic medication for an initial minimum period of four weeks before considering altering treatment, taking into account any emergent adverse effects. The guideline noted that there was no evidence to suggest that exceeding licensed doses has additional benefit and states that the optimal dose for most antipsychotics is below the recommended maximum.⁷⁰

4

D Following initiation of an antipsychotic medication for acute exacerbation of schizophrenia, the medication should be continued for at least four weeks unless there are significant tolerability issues.

D Where a partial response is seen after review at four weeks, the medication should be re-assessed after eight weeks unless there are significant adverse effects.

5.6 TREATMENT TO PREVENT RELAPSE DURING REMISSION

5.6.1 PREDICTING RELAPSE

The Remission in Schizophrenia Working Group (2005) defined remission as the absence or near absence of psychotic symptoms for at least six months. They specified this as a rating of mild or less on standard symptom severity rating scales (PANSS item scores of ≤ 3 ; brief psychiatric rating scale (BPRS) item scores of ≤ 3 , using the 1–7 range for each item).⁹⁵

Relapse has no similar definition and is variably applied in different studies, but usually refers to a clinically significant increase in the severity of psychotic, usually positive, symptoms that is sustained and requires additional clinical intervention such as an increase of treatment dose and additional support, possibly but not necessarily including re-admission to hospital.

A systematic review refers to several studies of factors which predict relapse. RCTs showed that individuals who are well stabilised on antipsychotic medications have high rates of relapse when their medication is discontinued or switched to placebo. Relapse risk is especially increased if medication is stopped abruptly, but about half of individuals will relapse within six months even if medication is withdrawn gradually. Other studies report a relatively constant rate of relapse of around 25% over three years. Predictors of relapse included persistent symptoms, poor adherence, lack of insight and substance misuse.⁴⁴

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A Cochrane review including 10 trials of chlorpromazine cessation in stable individuals (n=1,042), found that those stopping chlorpromazine had a relative risk (RR) of relapse in the short term (up to 8 weeks) of 6.8 (95% CI 3.4 to 13.5) and in the medium term (nine weeks to six months) of 4.0 (95% CI 2.8 to 5.8), compared with participants who continued medication. The RR of relapse after six months was 1.7 (95% CI 1.4 to 2.0).⁹⁶ An earlier meta-analysis of data from several large collaborative studies suggested that the number of people who do not experience relapse after discontinuing drug treatment declines by around 10% a month, but approximately 20-30% of people will not relapse after their initial episode.⁹⁷

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People with schizophrenia will benefit from reduced relapse rates if they remain on antipsychotic medication (see section 5.6.4). This benefit may only apply to one third to two thirds of people, however, and there is no reliable method of distinguishing between those who will benefit and those who will relapse in any case. The clinical factors which tend to be associated with an increased chance of relapse, such as illness severity, lack of insight, and substance misuse are also those which predict poor adherence to medication.

5.6.2 EFFICACY OF ANTIPSYCHOTICS IN SERVICE USERS WHO ARE IN REMISSION

A systematic review identified six relevant RCTs comparing SGAs (amisulpride, olanzapine, risperidone) with haloperidol to prevent relapse (variably defined, usually hospitalisation), over approximately one year. There was a trend towards increased benefit of SGAs, but only one trial result was statistically significant, showing an apparent benefit of risperidone (5 mg) over haloperidol (10 mg). Two RCTs compared olanzapine with risperidone or ziprasidone over 28 weeks. Both used 20% worsening on the PANSS and a CGI of more than 3 as defining relapse. The first study found more benefit with olanzapine but there was no difference found in the second study.⁴⁴

A meta-analysis synthesised data from 150 trials of 21,533 participants, comparing FGAs and SGAs. Amisulpride, clozapine, olanzapine and risperidone had better overall efficacy than FGAs, with modest effect sizes (varying between 0.3 and 0.5). For relapse prevention, as reported in 14 long term studies, olanzapine (4 RCTs, n=1,008, RR 0.67 (95% CI 0.49 to 0.92) and risperidone (5 RCTs, n=1,174, RR 0.74, 95% CI 0.63 to 0.87) proved to be significantly better than FGA medications.⁶⁸

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No particular drug or class is conclusively better in terms of efficacy, overall adverse effect burden, or at reducing relapse rates, than any other. RCTs tend to suggest SGAs (especially amisulpride, risperidone and olanzapine) are more effective, but methodological factors (for example choice of comparator drug and dose, and drop-out rates) could potentially account for such differences. SGAs are not demonstrably superior to chlorpromazine and other low potency FGAs.

Two pragmatic trials of antipsychotic treatment provide data on effectiveness over the medium to long term. The CATIE study had all-cause discontinuation as the primary outcome measure. Amongst the 1,493 participants, antipsychotics were discontinued in 60–80% of cases within the 18 month follow-up period. There was a significantly lower chance of discontinuation with olanzapine overall, compared to perphenazine, quetiapine, and risperidone, but olanzapine was also associated with more discontinuation due to weight gain or metabolic effects. The CULASS study was a smaller, UK trial which compared allocation to an FGA or an SGA (excluding clozapine) in 227 participants with established schizophrenia for whom a change in antipsychotic medication was considered by their psychiatrist to be clinically indicated because of inadequate clinical response or intolerance. For each participant in the study, the choice of individual drug within the assigned FGA or SGA group was the choice of the prescribing clinician. Over the one year follow up, there was no apparent disadvantage in using FGAs rather than SGAs in terms of quality of life, symptoms or the associated costs of care.⁶⁵

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In practice, the choice of maintenance treatment for a particular service user should take into account their preferences, illness severity, likely adherence, known previous drug responses, any substance misuse, levels of depression, cognitive function and adverse effect profile.⁷⁰

4

A Individuals with schizophrenia which is in remission should be offered maintenance treatment with an antipsychotic medication.

✓ This should usually be with the medication that was used during their last acute episode, assuming efficacy and tolerability.

B For maintenance treatment, prescribers should consider amisulpride, olanzapine or risperidone as the preferred medications with chlorpromazine and other low-potency first-generation antipsychotics providing suitable alternatives.

5.6.3 DOSE

A Cochrane review of chlorpromazine dose found that more people left the trial due to inefficacy of the treatment on low dose (≤ 400 mg daily) compared to medium dose (401–800 mg daily). Extra-pyramidal adverse effects, however, tended to be lower when low dose was compared with high dose (> 800 mg/day). Global state outcomes tended to be better in the high dose group, but more people in the high dose group left early due to disabling adverse effects. Less dystonia and fewer unspecified extra-pyramidal adverse effects were reported in the low dose group.⁹⁸

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A Cochrane review of risperidone dose reported that 4-6 mg daily was the optimal balance between drop-out due to inefficacy (at <4 mg) and adverse effects (at >6 mg).⁹⁸ 1⁺⁺

A meta-analysis compared the efficacy of standard dose (World Health Organisation (WHO) daily defined dose (DDD)), low dose (50-100% DDD) and very low dose (<50% DDD) for relapse prevention in people with schizophrenia. Thirteen RCTs with a follow-up duration of at least 24 weeks (n=1,395) were identified. Compared with the standard dose treatment, the low dose therapy did not show any statistically significant difference in overall treatment failure or hospitalisation, while the standard dose showed reduced risk of relapse (p=0.05). The very low dose group was inferior to the standard dose group in all efficacy parameters. No significant difference was found in the rate of drop-outs due to adverse effects between either standard dose, low dose or very low dose.⁹⁹ 1⁺⁺

Antipsychotic treatment with 50-100% DDD may be as effective as standard dose therapy but there are insufficient clinical trial data to draw firm conclusions.

B Individuals with schizophrenia, which is in remission, should be offered maintenance treatment with antipsychotic medication at low to moderate regular dosing of around 300-400 mg of chlorpromazine, 4-6 mg of risperidone, or their equivalents daily.

5.6.4 DURATION OF TREATMENT

A Cochrane review of medium term studies (six months to two years) found that chlorpromazine was more effective than placebo in reducing relapse (n=512, 3 RCTs), RR 0.57, 95% CI 0.5 to 0.7. The two long term studies lasting two to five years also found chlorpromazine to be more effective (n=394, 2 RCTs, RR 0.65, 95% CI 0.6 to 0.8) but there was significant heterogeneity in the data (I²=84%).¹⁰⁰ In a Cochrane review of haloperidol, the relapse rate in people maintained on antipsychotic treatment approached that in those withdrawn from treatment over time, but was still consistently lower in those on treatment at two years (RR 0.70, 95% CI 0.57 to 0.87).¹⁰¹ 1⁺

Although some service users will relapse despite continued treatment and others will only have one psychotic episode with or without subsequent treatment, there is evidence that individuals with schizophrenia should remain on antipsychotic medication for two and possibly up to five years after an acute episode.

A Individuals with schizophrenia which is in remission should be offered maintenance treatment with antipsychotic medication for a minimum of two years.

5.6.5 DELIVERY OF ANTIPSYCHOTIC MEDICATION

A systematic review compared first-generation antipsychotic long-acting injections (LAIs) with first- and second-generation oral antipsychotics in terms of clinical outcome. Meta-analysis of included RCTs showed no difference in relapse rate or tolerability but global improvement was twice as likely with LAIs. Four prospective observational studies were also identified; two studies reported lower discontinuation rates for LAIs while two found that outcome was either no different or better with oral antipsychotics. Mirror-image studies consistently showed reduced inpatient days and admissions following a switch from oral antipsychotics to LAIs. The authors concluded that LAIs may improve outcome compared with oral antipsychotics, but methodological issues may partly explain the variable results. Selective recruitment in RCTs and lack of randomisation in observational studies may bias against LAIs, whereas regression to the mean in mirror-image studies favours LAIs.¹⁰² 1⁺⁺

A systematic review identified ten studies with 1,700 participants and reported that various depot formulations significantly reduced relapse rates with relative and absolute risk reductions of 30% and 10%, respectively (RR 0.70, 95% CI 0.57 to 0.87) and also reduced drop-out due to inefficacy (RR 0.71, 95% CI 0.57 to 0.89). Limited data on non-adherence, rehospitalisation, drop-out for any reason and adverse events revealed no significant differences. The methodology limitations of the included studies and their potential to introduce bias were reported.¹⁰³ 1⁺⁺

In a health technology assessment (HTA) of six studies that reported a direct comparison of oral antipsychotics with depot formulation from the point of view of patient preference, five found that the majority of participants receiving LAIs preferred depot administration rather than tablet form, largely because they considered them to be more convenient.^{104,105} A subsequent review identified a further 12 studies. The most positive attitudes to depot formulation were seen in those already prescribed an LAI.¹⁰⁶ 2+

Some service users prefer depot preparations. It is difficult to predict this preference as it is those who remain on them who say they like them. Many service users realise their adherence to oral medication is variable, to their own detriment, and hence opt for depot or long-acting injection formulations.¹⁰⁷ 4

B Individuals with schizophrenia who request depot and those with medication adherence difficulties should be offered maintenance treatment with depot antipsychotic medication.

✓ Service users should be given the option of oral or depot medication, in line with their preference.

5.7 TREATMENT-RESISTANT SCHIZOPHRENIA

Most commonly treatment resistance is defined as failure to respond to an adequate trial of two different antipsychotics.

5.7.1 EFFECTIVENESS OF ANTIPSYCHOTIC MEDICATIONS

A systematic review included 26 RCTs (n=3,932 pts). The definition of treatment resistance varied considerably across trials. Most were short term, none being longer than 16 weeks. Clozapine had the most consistent evidence for efficacy over the FGAs in participants with an inadequate response to, or unacceptable adverse effects from current medication. It was not possible to establish equivalence between clozapine and any other SGA or to establish whether there are differences in efficacy between any of the other antipsychotics in this patient group. For comparative analysis of adverse effects, data from 138 comparisons were pooled. Most trials were of relatively short duration and not designed to prospectively examine adverse effects and so no conclusions can be drawn on the longer term adverse effects of treatment.⁴⁴ 1++

Seven subsequent Cochrane reviews conducted across heterogeneous populations provided no clear evidence that any one non-clozapine antipsychotic drug is more efficacious than another. There is evidence of differing adverse effect profiles of clinical significance between individual antipsychotics.^{92-94,108-111} 1++

A meta-analysis of 78 studies compared second-generation antipsychotics (olanzapine, aripiprazole, quetiapine, amisulpride, risperidone, ziprasidone, clozapine, zotepine and sertindole) head-to-head (n=13,558). The participants had relatively chronic courses of illness and treatment-resistant populations were analysed separately. From the analysis of treatment-resistant individuals clozapine was only shown to be superior to zotepine with respect to total symptoms, and in doses >400 mg was superior to risperidone.⁸⁷ Clozapine had the most consistent evidence for efficacy over the FGAs that were included in the trials. There was considerable variation in definitions of treatment resistance. 1++

In people with schizophrenia whose symptoms had not improved with SGA treatment, clozapine was more effective than switching to another SGA.⁴⁰ In another trial, in participants whose illness had shown a poor response to sequential trials of two or more antipsychotics there was an advantage in commencing clozapine rather than another SGA in terms of symptom improvement over a year. There was a statistically significant improvement in symptoms but not on quality of life measures.⁶⁵ 1+

A Clozapine should be offered to service users who have treatment-resistant schizophrenia.

B Clozapine should be considered for service users whose schizophrenia has not responded to two antipsychotics including a second-generation antipsychotic medication.

✓ Where treatment resistance is apparent, diagnosis and comorbidity should be reviewed.

- ✓ Monitoring of clozapine plasma levels should be considered where there are:
 - concerns around clinical effectiveness
 - emergent adverse effects
 - concerns around adherence to medication
 - introduction of or discontinuation of interacting medication
 - changes in smoking status.

5.7.2 CLOZAPINE AUGMENTATION WITH ANOTHER ANTIPSYCHOTIC

A systematic review identified six small RCTs (n=252) of clozapine augmentation. Trials were mainly short term with the longest being 12 weeks. Response was defined as a greater than 20% improvement in PANSS or BPRS scores. Augmentation of clozapine with an antipsychotic (aripiprazole, risperidone or sulpiride) improved symptoms particularly in those receiving treatment for longer than ten weeks.⁴⁴ 1⁺⁺

A meta-analysis of double blinded randomised controlled trials of clozapine augmentation identified 10 studies examining augmentation with antipsychotics. In a small study (n=28) of sulpiride augmentation there was a significant effect with respect to BPRS/PANNS (SMD 0.83, 95% CI 0.07 to 1.59). Meta-analysis of augmentation with other antipsychotics resulted in no statistically significant effects.¹¹² These findings are in agreement with previous reviews, many of which encompassed less rigorous open label studies.¹¹³⁻¹¹⁵ 1⁺⁺
1⁺

C A trial of clozapine augmentation with a second SGA should be considered for service users whose symptoms have not responded adequately to clozapine alone, despite dose optimisation. Treatment should be continued for a minimum of ten weeks.

5.7.3 CLOZAPINE AUGMENTATION WITH OTHER MEDICATIONS

Ginkgo

A review and meta-analysis of small studies of ginkgo as an adjunct therapy in chronic schizophrenia identified six studies (n=828). Response to treatment was monitored using standardised negative and total symptom rating scales. Ginkgo produced a statistically significant improvement in total (SMD -0.5, 95% CI -0.64 to -0.36) and negative symptoms (SMD -0.48, 95% CI -0.63 to -0.34).¹¹⁶ 1⁺

Despite the positive evidence it is not possible to make a recommendation for ginkgo due to concerns over dose specification and attendant regulatory and safety issues.

Lamotrigine

A meta-analysis identified five RCTs comparing clozapine augmentation with lamotrigine compared with clozapine plus placebo. Trials were one to 24 weeks duration. The primary outcome was a total score for symptoms of psychosis and the secondary outcome measures were scores for positive and negative symptoms of psychosis. Lamotrigine was superior to placebo augmentation in both the primary outcome measure SMD 0.57 (95% CI 0.25 to 0.89) and secondary outcome measures SMD 0.34 (95% CI 0.02 to 0.65) for positive symptoms and SMD 0.43 (95% CI 0.11 to 0.75) for negative symptoms. 1⁺⁺

B A trial of clozapine augmentation with lamotrigine may be considered for those service users whose symptoms have had an insufficient response to clozapine alone.

Lamotrigine is not licensed for augmentation of clozapine in service users with schizophrenia.

5.7.4 EFFECTIVENESS OF SWITCHING ANTIPSYCHOTIC

A review identified five relevant trials and concluded that, if a decision is made to switch medication, an antipsychotic with a different receptor binding profile should be chosen.¹¹⁷ | 1⁺⁺

Consensus guidelines suggest that a poorer response after switching may be due in part to the risk of destabilisation of the illness and provocation of adverse effects and notes that a gradual cross taper of the dosages of the two antipsychotics is usually recommended.⁷⁰ | 4

✓ The decision to switch antipsychotic medication should take into account the risk of destabilisation and adverse effects and the dose of medications should be gradually cross tapered.

5.7.5 HIGH DOSE ANTIPSYCHOTIC MEDICATION

Consensus guidelines found no convincing evidence that doses of antipsychotics higher than the maximum recommended are more effective than standard doses.⁷⁰ | 4

D Prescribing high dose antipsychotics should only be considered after adequate trials of antipsychotic monotherapy and augmentation, including a trial of clozapine, has failed.

✓ Local guidelines for identification and monitoring of service users receiving high dose antipsychotics should be developed and followed.

5.7.6 ELECTROCONVULSIVE THERAPY

A Cochrane review identified one small trial comparing electroconvulsive therapy (ECT) plus antipsychotics with antipsychotics alone in individuals with treatment-resistant schizophrenia. When ECT was added to antipsychotic medication, this combination was superior to medication alone over the six month trial period, global impression weighted mean difference (WMD) 19.1, 95% CI 9.7 to 28.5. Across patient groups the use of ECT was associated with greater cognitive impairment, such as memory loss, at the end of the course of treatment than the use of conventional antipsychotics but this impairment appeared to be transient.¹¹⁸ | 1⁺⁺

C ECT should only be considered in those individuals for whom other approaches to treatment have failed. It may be a useful adjunct to antipsychotic medication if there is a need for rapid improvement and reduction of symptoms, or when an individual has shown a limited response to antipsychotic medication.

5.8 SPECIFIC CLINICAL ISSUES

5.8.1 ACUTE AGITATION

In a review of two RCTs, aripiprazole was more effective than placebo in reducing agitation. The response was rapid and occurred within 45 minutes of administration. Aripiprazole (mean dose 9.75 mg) was non-inferior to haloperidol (mean dose 6.5mg). Intramuscular aripiprazole was generally well tolerated. The discontinuation rate was 0.8% with the most frequent adverse effects being headache, nausea and dizziness. The somnolence rate was $\geq 7\%$, the frequency of injection site reactions less than 5%, dystonia less than 2% and less than 5.5% of participants experienced akathisia. Aripiprazole has been associated with an increased risk of sudden death in elderly people with dementia-related psychosis and with orthostatic hypotension.¹¹⁹ | 1⁺

Systematic reviews have examined intramuscular (IM) olanzapine¹²⁰ and haloperidol plus promethazine¹²¹ for psychosis related agitation or aggression. Based on four high quality studies it was concluded that haloperidol plus promethazine was a safe and swift treatment for psychosis related agitation or aggression, whereas use of benzodiazepines alone, such as lorazepam and particularly midazolam was difficult to justify partly due to concerns over respiratory depression. Haloperidol alone led to more movement disorder adverse effects.¹¹⁷ | 1⁺⁺

5.8.2 AGGRESSION AND HOSTILITY

Two Cochrane systemic reviews found no anti-aggressive effect for either carbamazepine or valproate in people with schizophrenia.^{122,123}

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A consensus guideline concluded that clozapine is the antipsychotic with the best evidence for an anti-hostility effect in service users' schizophrenia and this is independent of any improvement in adverse effects or reduction in positive symptoms.⁷⁰

4

D The choice of medication for the treatment of irritability, hostility and aggression should be based on service user preference, past experience of antipsychotic treatment, the adverse effect profile and concurrent medical history. For individuals with treatment-resistant schizophrenia accompanied by aggression/hostility, a trial of clozapine is indicated.

5.8.3 COGNITIVE DYSFUNCTION

Antipsychotics

One systematic review of antipsychotic effects on cognition pooled the results of 18 studies (n=++1,808). SGAs offered minor benefits (effect size 0.19, 95% CI 0.04 to 0.29), compared to FGAs (usually haloperidol), on global cognitive measures, including procedural learning, language and verbal comprehension, speed of processing and both verbal and visual learning and memory.¹²⁴

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Overall, the effects of antipsychotic drugs on cognition in remitted schizophrenia are minimal. Although they may improve cognitive function, the practical benefits of this are unclear.

Acetylcholinesterase inhibitors

A review of open label and double blind studies of augmentation of antipsychotics with acetylcholinesterase inhibitors identified 13 double blind studies (six with donepezil, three with galantamine and four with rivastigmine). Significant improvement was found for various aspects of memory (by an average of 28%, in three studies, in 146 participants, 95% CI 0.06 to 0.50, p=0.014) and on the trail making test part A (by 69%, in four studies, in 93 participants, 95% CI -1.14 to -0.23, p=0.003).¹²⁵

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B Acetylcholinesterase inhibitors may be considered as adjunctive therapies to antipsychotic medication in service users where there is significant concern regarding cognitive dysfunction.

Acetylcholinesterase inhibitors are not licensed as adjunctive therapy in people with schizophrenia.

Modafinil

A review of generally poor quality studies found conflicting evidence for modafinil as augmentation of antipsychotics in people with schizophrenia.¹²⁶

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There is insufficient consistent evidence on which to base a recommendation for modafinil as adjunctive therapy in schizophrenia.

Modafinil is not licensed as adjunctive therapy in people with schizophrenia.

5.8.4 NEGATIVE SYMPTOMS

Primary negative symptoms occur in up to 20% of individuals with schizophrenia. Negative symptoms secondary to psychotic symptoms, comorbid depressive illness, or medication-related side effects are also common and disabling. In a meta-analysis the four most efficacious antipsychotics compared to haloperidol, clozapine, olanzapine, amisulpride, and risperidone, also demonstrated the greatest effect in ameliorating negative symptoms compared to haloperidol.⁶⁸ Findings of pragmatic studies are consistent with this.^{65,78,127}

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2⁺

A meta-analysis of 23 trials (n=819), concluded that antidepressants added to antipsychotic medications were superior to antipsychotics alone in the treatment of negative symptoms.¹²⁸

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Where clozapine is already prescribed, augmentation with citalopram, sulpiride, or lamotrigine is supported by the evidence base for service users with refractory negative symptoms (see sections 5.7.2 and 5.7.3).

B For service users with persistent negative symptoms despite adherence to antipsychotic medication, consider augmentation with an antidepressant, lamotrigine, or sulpiride.

5.9 MEDICATION EFFECTS ON COMORBIDITIES

5.9.1 COMORBID ANXIETY SYMPTOMS

No reviews were identified on comorbid anxiety symptoms in people with schizophrenia. Expert opinion suggests that antipsychotic drugs are associated with reductions in anxiety symptoms but there is no evidence on differential efficacy.²

✓ Individuals with schizophrenia which is in remission who have comorbid anxiety symptoms may benefit from a sedative antipsychotic medication.

✓ Individuals who meet criteria for an anxiety state should be treated according to relevant clinical practice guidelines for anxiety and panic disorders.

5.9.2 COMORBID DEPRESSIVE SYMPTOMS

✓ Individuals who meet criteria for depressive disorder should be treated according to relevant clinical practice guidelines for depression, including the use of antidepressant medication.

For people with schizophrenia, the choice of antipsychotic medication may be influenced by potential effects on depressive symptoms.

A Cochrane review of antipsychotics for people with both schizophrenia and depression identified three trials. One found no significant difference between quetiapine and haloperidol; another found that participants randomised to sulpiride had significantly lower depression scores compared with those given chlorpromazine (WMD Comprehensive Psychopathological rating scale (CPRS) -0.70, 95% CI -1.2 to -0.2). When clozapine plus antidepressant or placebo was compared with any other antipsychotic drug plus antidepressant or placebo, clozapine was associated with better Hamilton rating scores.¹²⁹

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Analysis of a subset of limited data from a systematic review (14 studies, n=1,910) showed that SGAs were more efficacious at reducing depressive symptoms than placebo (SMD -0.26, 95% CI -0.38 to -0.15), with specific evidence for amisulpride, haloperidol, olanzapine and zotepine. All but one study (of amisulpride) was in people with acute schizophrenia.⁶⁸

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In a separate review of studies conducted mainly in acute settings comparing SGAs and FGAs, amisulpride, aripiprazole, clozapine, olanzapine and quetiapine were more effective than FGAs in reducing scores on depression items on the PANSS/BPRS.⁶⁸

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B Second-generation antipsychotics should be considered for individuals with schizophrenia which is in remission who have comorbid depressive symptoms.

6 Psychological therapies

6.1 INTRODUCTION

Psychological therapies and psychosocial interventions have a role to play in supporting recovery from psychosis through a range of heterogeneous aims such as enhancing coping, reducing emotional distress, facilitating knowledge, insight and understanding, improving communication, increasing quality of life and engagement in meaningful activities, and minimising the impact of symptoms or impairments on functioning.

Psychological therapies refer to a range of interventions, based on psychological concepts and theory, which are designed to help people understand and make changes to their thinking, emotion, behaviour and interpersonal relationships in order to relieve emotional distress and to improve functioning.

Psychological therapies differ from pharmacological interventions in that the principal aim is not necessarily the reduction in psychotic experiences such as hearing voices or paranoia.¹³⁰ Psychological therapies may also influence key factors in vulnerability to, and persistence of, psychosis. A number of processes including stressful life events, the person's environment, the reactions of family and friends, and the person's thinking and behaviour play an important role in shaping recovery from schizophrenia.¹³¹ Psychological therapies have been developed to address these specific needs in relation to recovery.

A requirement of any psychological therapy is the development of a positive therapeutic relationship. The development of a shared view about the nature of the person's problems in a safe relationship free of stigma and shame is a key prerequisite.¹³² This is particularly important in the context of schizophrenia. The experience of psychosis itself (for example hostile commanding voices, persisting paranoia) or the experience of treatment (for example compulsory treatment) can create difficulties in building up a trusting therapeutic relationship.

The skills and competencies required to deliver these interventions effectively are acquired through training, and maintained through clinical supervision and practice. Training is essential in the acquisition of knowledge, competences and skills to deliver interventions.¹³³ Structuring treatment appropriately and assessing treatment fidelity, as well as measuring clinical outcomes routinely to monitor treatment response is important.¹³³ Clinical supervision is essential to the delivery of psychological therapy services, both during training and to ensure the ongoing safety and quality of subsequent practice. It is a requirement of all professional bodies accrediting psychological therapists.¹³³

A competence framework for knowledge, skills and values in implementing psychological therapies for people with psychosis is being developed.¹³⁴



Practitioners delivering evidence based psychological therapies should be trained to approved levels of competency, participate in continuing professional development and be registered with the appropriate governing body. They should be receiving ongoing clinical supervision.

A glossary in Annex 2 provides definitions of the therapies covered in this section.

6.2 ADHERENCE THERAPY

A meta-analysis of five RCTs found that although there was evidence of improved attitudes towards medication, there was no consistent evidence to suggest that adherence therapy was effective in improving critical outcomes such as symptoms, quality of life or relapse, in individuals diagnosed with schizophrenia. It concluded that there was no robust evidence for the use of adherence therapy as a stand-alone intervention.

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Three subsequent small randomised pilot studies were identified. Two of the studies found that adherence interventions (adherence therapy and alliance enhancement therapy) did not result in improved clinical or treatment outcomes.^{135,136} In the third study participants recovering from their first psychotic episode and who had been in treatment for less than 12 months (n=24) were randomised to 14 sessions of adherence-coping education (ACE) or to standard treatment. Individuals who received adherence therapy had a significant improvement in positive symptoms at the end of treatment.¹³⁷

1-

In a larger study, outpatients with a diagnosis of schizophrenia who were having problems with service engagement (n=116) were randomised to either treatment-adherence therapy or treatment as usual (TAU). There were improvements in service engagement and medication adherence at the end of treatment but no significant reduction in readmissions, involuntary readmissions or improvements in symptoms and quality of life.¹³⁸

1+

Although adherence therapy influences attitudes to medication, there is no consistent evidence that this translates to improvements in symptoms or quality of life or results in reduced relapse rates.

B Adherence therapy should not be offered to individuals diagnosed with schizophrenia.

Section 5.1 covers the principles of antipsychotic prescribing.

6.3 ARTS THERAPIES

A meta-analysis of six RCTs of arts therapies versus any control found that most of the studies used group based intervention. There were three treatment modalities, music, art and body-oriented psychotherapy. The sample sizes were small (n=24-90) and many of the studies either omitted information regarding randomisation and rater blinding or reported difficulties in these areas which reduced study quality. There were high attrition rates (>40%) in half the studies and there was often no control for therapist time. Arts therapies were effective in reducing negative symptoms (SMD in score at end of treatment -0.59, 95% CI -0.83 to -0.36, from five studies), with some evidence from two of the studies that medium to large effect sizes found at the end of treatment were sustained at up to six months follow up (SMD in score -0.77, 95% CI -1.27 to -0.26). Effects remained when analysed by context of therapy indicating effectiveness when delivered via inpatient or outpatient settings. There were no significant effects on total symptom score (reported in four studies) or positive symptom score (reported in two studies), social or psychosocial functioning (one study), user satisfaction or quality of life (one study each). No RCTs of drama therapy were identified in this population group.⁴⁴

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The Multi-centre study of Art Therapy In Schizophrenia - Systematic Evaluation (MATISSE) was a three-arm, multicentre parallel group, pragmatic RCT comparing the effectiveness of referral to group art therapy plus standard care (n=140), with referral to an attention control activity group plus standard care, (n=140), or standard care alone. (n=137). The primary outcomes were global functioning and psychiatric symptoms. Group art therapy did not improve outcomes at 24 months compared with attention control activity plus standard care or standard care alone. The activity plus standard care group had fewer positive symptoms compared with those allocated to group art therapy at 12 and 24 months (adjusted mean difference 1.4, 95% CI 0.1 to 0.26, p=0.03).

1++

In this study, group art therapy and activity groups were offered on a weekly basis for 90 minutes over 12 months. Uptake of experimental and control interventions was poor. Almost 40% of study participants did not attend any art therapy sessions and amongst those who did, few attended regularly. On average participants attended 11 (0-51) art therapy groups and five (0-45) activity groups.¹³⁹

There is insufficient high quality evidence on which to base any recommendation for arts therapies in general.

B Group based art therapy should not be routinely offered to individuals diagnosed with schizophrenia.

6.4 COGNITIVE BEHAVIOURAL THERAPY FOR PSYCHOSIS

A systematic review identified 31 RCTs comparing cognitive behavioural therapy for psychosis (CBTp) with any type of control. Nineteen trials compared CBTp with standard care. There was consistent evidence (primarily from individual based interventions) that CBTp was effective in reducing rehospitalisation up to 18 months following treatment (five studies) although this was not consistently sustained at two to four years follow up (two studies). Duration of hospitalisation was also reduced at up to 12 months follow up (five studies). There was also consistent evidence that CBTp reduced total symptom score at the end of treatment (13 studies) and at up to 12 month follow up (ten studies). There were no statistically significant effects on positive symptoms at end of treatment (eight studies) or at follow up (nine studies). Meta-analysis of three studies found no benefit on relapse at up to 24-month follow up. There was some effect on hallucination-specific measures but the evidence for delusions was inconsistent. In five studies CBTp reduced depression at end of treatment and in four studies there was reduced depression at follow up. Subgroup analyses suggested that CBTp was particularly applicable to the promoting recovery phase although trials were also carried out with first episode populations (five studies) and during acute episodes (eight studies). Effects were associated with a minimum of 16 sessions.⁴⁴ 1++

Follow up of two RCTs identified in the systematic review found that benefits on symptom severity persisted up to five years following treatment,¹⁴⁰ and that effects on duration of hospitalisation persisted at two year follow up¹⁴¹ although this was not based on an intention-to-treat (ITT) analysis. 1+

In a planned post randomisation re-analysis of an RCT identified in the systematic review, the effect of aspects of CBTp received was explored. The trial aimed to deliver between 12 and 20 sessions each lasting about one hour to 133 participants randomised to the intervention. A mean of 14.3 sessions was delivered to each participant. A total of 42 participants had full therapy, 39 had partial therapy and 21 received fewer than five sessions. Full CBT with delivery of active components of treatment was associated with around six months of remission in the 12 months following randomisation and with improvements in psychiatric symptoms and depression scores. Such benefits were not seen where only assessment and engagement aspects of therapy were undertaken.¹⁴² 2+

Several subsequent RCTs were identified examining a range of interventions, primarily individually based rather than group based. Many were described as feasibility or pilot studies and there was heterogeneity in setting of treatment and in the patient groups recruited. Outcome measures varied widely.

The benefits of specific variants of CBTp were reported on outcomes such as depression,¹⁴³ aggression and violence,¹⁴⁴ trauma,¹⁴⁵ capacity to work¹⁴⁶ and functioning.¹⁴⁷ Two studies reported the benefits of CBTp on relapse and duration of hospitalisation in people with schizophrenia following a first episode of psychosis¹⁴⁸ or with those in the recovery phase.¹⁴⁹ 1+

In one study conducted over 18 months, those who received CBT had significantly more days of normal functioning compared to those who had received usual care (mean difference 77 days (95% CI 29.7 to 124.0)).¹⁵⁰ 1+

In a small study (n=33) without ITT analysis, there were no significant benefits from CBTp as an adjunct to second-generation antipsychotic medication in reducing severity of delusions.¹⁵¹ There was no benefit on auditory hallucinations when group CBT was compared with enhanced supportive therapy.¹⁵² A feasibility study reported no benefit on social functioning.¹⁵³ 1-

Three studies evaluated CBTp in routine practice. One study reported no benefit over treatment as usual,¹⁵⁴ whereas two studies found improvements in depression¹⁴³ and PANSS total scores, positive symptoms, depression, and general psychopathology.¹⁵⁵ 1-

A trial comparing CBTp with cognitive remediation found no difference between study groups in terms of improvement in negative symptoms over 12 months. Overall ITT and per-protocol analyses showed that both groups improved in terms of overall negative symptoms. There were significant differences in the effectiveness of CBTp and cognitive remediation therapy (CRT) across the three study centres which were not explained by levels of symptoms, therapeutic alliance or number of sessions conducted.¹⁴⁹ 1+

Although integrated motivational interviewing and CBT for people with psychosis and comorbid substance misuse reduced the amount of substance used at one year follow up, this did not have an effect on hospitalisation, symptoms or functioning.⁴¹ 1+

A Individual CBTp should be offered to all individuals diagnosed with schizophrenia whose symptoms have not adequately responded to antipsychotic medication and where persisting symptoms and/or depression are being experienced. CBTp can be started during the initial phase, the acute phase or recovery phase including inpatient settings.

B The minimum dose of CBTp should be regarded as 16 planned sessions.

- ✓ CBTp should be delivered according to an established treatment manual by appropriately trained therapists receiving regular supervision.
 - CBTp should be delivered in a collaborative manner such that individuals establish the relationships between thoughts, feelings and behaviour with respect to distress arising from current or past symptoms, experiences and functioning.

No good quality evidence was identified on which to base recommendations for other variants of CBTp including mindfulness, metacognitive training and acceptance and commitment therapy (ACTp) for emotional recovery and worry focused CBT for persecutory paranoia.

6.5 COGNITIVE REMEDIATION

A systematic review identified 10 trials comparing CRT with standard care and an additional seven trials with active treatment controls. The review excluded studies which examined CRT as an adjunct to vocational rehabilitation. Most of the studies were conducted in the US and typically had around 40 participants mainly from patient populations with stable schizophrenia and identified cognitive impairments. Duration of treatment varied from a few weeks to one year and there was heterogeneity in the interventions. Only five of the 17 studies provided follow-up data. Meta-analysis found that there was little evidence of sustained benefits to cognition although there were statistically significant improvements in reasoning and problem solving.⁴⁴ 1++

Of 12 additional studies identified,¹⁵⁶⁻¹⁶⁷ three presented durability or follow-up data,^{159,160,163} and two used CRT interventions as control comparisons to CBT and social cognition interventions.^{165,167} The studies each used different commercially available computer based remediation training software packages, all of which target similar cognitive domains but vary in how they have developed specific procedures to improve functioning. Some applications use ecologically valid contexts and employ additional processes that encourage metacognitive reflection rather than merely drill and practice techniques. Continual refinements to these computer based interventions could account for some of the improved outcomes over time.

Sample sizes ranged from 32 to 99 and the mean age was 40 or less in all but one study where the mean age was 47.¹⁵⁷ The duration of the intervention ranged from seven weeks¹⁶⁴ to two years,^{158,159} with most of the studies having a duration of six months or less. The total number of hours of CRT tended to be between 20 and 50 although in the study which had two years duration there were 120 hours of intervention.^{158,159} Intensity of intervention was from one to two hours per week. One to two hours per week appears practical in terms of resources and what the client group can cope with but there is variation in duration across studies. Five of the seven RCTs which directly investigated CRT as the primary intervention employed active control comparisons such as computer games or practice computer sessions and active general psychiatric rehabilitation activities, to control for service contact. 1+ 1++

There were statistically significant gains in cognitive domains, primarily verbal learning/memory, attention and cognitive flexibility measures reported in six studies at the end of treatment, although there is uncertainty around the clinical significance of these gains.^{156,158-160,162,164} Five studies provided evidence of significant additional improvements in some aspects of social functioning.^{156,158,159,161,162,166} Only two studies reported any significant improvements in psychiatric symptoms.^{158,159} One study compared CRT to CBTp and found no differences between the two groups at 12-month follow up. Both groups improved in terms of overall negative symptoms.¹⁶⁵ One study primarily investigating a social cognition remediation intervention with CRT as a control comparison, did not find any social cognition, social skills or social functioning improvement in the CRT group but did report significant non-targeted cognitive domain improvements at the end of treatment.¹⁶⁷

One of the two studies which found no benefit on clinical outcomes used a multimodal intervention incorporating social cognition training and reported improvements in personal and social functioning.¹⁶¹ The authors suggest the combination approach may have diluted the necessary focus on initially establishing improvements on cognitive functioning to a degree that enables generalisation beyond the actual intervention tasks. The other was conducted in the oldest population group which may indicate an age effect.¹⁵⁷

There was evidence from three studies, which incorporated adequate follow-up measures, of improvements in primary cognitive domains that were maintained at four, six and nine month follow-up periods.^{160,162,163} Significant improvements in some measures of daily and social functioning were found at follow up in two studies.^{162,163} One study with a three month follow-up period found no significant benefits over their control group on any neuropsychological or functional outcome measure.¹⁵⁷

Only two studies manipulated 'dose' of CRT.¹⁵⁸⁻¹⁶⁰ The first provided data after 50 and 100 hours of treatment and the second examined one and two year results. Both studies concluded that a 'higher dose' and more 'broad spectrum' training confer more benefit. This is in contrast to positive findings achieved reported in one study after only a seven week intervention.¹⁶⁴

There is evidence that CRT improves cognitive outcomes at the end of treatment and limited evidence, with inconsistencies in outcomes, that this may translate into improved social and functional outcomes. There is also some limited evidence that improvements in cognitive outcomes are maintained at follow up.

B Cognitive remediation therapy may be considered for individuals diagnosed with schizophrenia who have persisting problems associated with cognitive difficulties.

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6.6 CONTINGENCY MANAGEMENT

Contingency management programmes generally target substance use related behaviour in individuals with a diagnosis of schizophrenia and may be employed with the aim of improving treatment adherence and service engagement.

The evidence for contingency management in people with schizophrenia is based on poorly controlled studies with highly selected patient groups and, although benefits on reducing substance misuse are reported, the findings are unlikely to be generalisable to routine clinical care.^{168,169}

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6.7 COUNSELLING AND SUPPORTIVE THERAPY

A systematic review identified 17 RCTs comparing counselling and supportive therapy with any control. The therapies were defined as facilitative, non-directive and/or relationship focused, with the content largely determined by the service user. In the majority of studies counselling and supportive psychotherapy was used to control for aspects such as therapeutic relationship and regular contact with a therapist in trials of other therapies. The format of the intervention varied, and included befriending, supportive group psychotherapy, supportive individual counselling and reality adaptive supportive psychotherapy. Two trials (n=262) provided evidence of comparison with standard care/routine care (which itself is likely to encompass supportive elements), one conducted in an outpatient setting and the other focused on inpatients and day patients. Meta-analysis of the two studies found no benefit on relapse at 18 month follow up or on treatment acceptability, as measured by leaving the study early. In the hospital based study those receiving supportive

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therapy had improved positive symptoms compared to routine care which reached statistical significance at 18 month follow up, PANSS positive symptoms SMD -0.35, (95% CI-0.68 to -0.03). | 1⁺⁺

In three subsequent studies, supportive therapy was used as a control for ACE therapy,¹³⁷ group CBT for auditory hallucinations,¹⁵² individual CBT (follow-up study)¹⁴⁰ and family therapy.¹⁷⁰ | 1⁺

In an RCT of outpatients with medication-resistant auditory hallucinations, enhanced supportive therapy led to a reduction in negative beliefs about voices at one year follow up.¹⁵² | 1⁻

The counselling and supportive therapy interventions analysed included in the systematic review were disparate and did not represent any particular theoretical approach, such as person-centred, process experiential or non-directive counselling. Using supportive treatments as a 'psychological placebo' or control for therapist time potentially downplays the role of interpersonal processes in facilitating recovery amongst individuals with a diagnosis of schizophrenia.

There is insufficient consistent evidence on which to base a recommendation for counselling and supportive therapies in people with schizophrenia.

6.8 FAMILY INTERVENTION

A systematic review identified 32 RCTs of family intervention. Twenty six trials compared family intervention with standard care. Meta-analysis focusing on critical outcomes found benefits from family intervention on symptom severity (global state) at the end of treatment and at follow up and a reduction in rehospitalisation rates during the first year of treatment and reduction of duration of rehospitalisation. Subgroup analyses suggested that the service user should be included in the intervention, and interventions with greater than 10 sessions over a period of longer than 12 weeks are most effective. Although it did not reach statistical significance there was some evidence that single family format is more acceptable to service users than multiple family format as indicated by study withdrawal rates.⁴⁴ | 1⁺⁺

A subsequent Italian study randomised 40 families to 12 months of systemic family therapy or routine psychiatric treatment. The family intervention reduced relapse during the treatment period although this was not sustained at follow up.¹⁷¹ Another RCT focused on patient-caregiver dyads and noted reductions in number and length of rehospitalisations as well as improvements in family and service user functioning.¹⁷² A small Spanish RCT randomised 50 participants to family intervention plus individual counselling plus usual care or individual counselling plus routine care. Family intervention was associated with a lower rate of clinical relapse and fewer hospitalisations as well as improvement in positive and negative symptoms.¹⁷⁰ | 1⁺

A Family intervention should be offered to all individuals diagnosed with schizophrenia who are in close contact with or live with family members and should be considered a priority where there are persistent symptoms or a high risk of relapse. Ten sessions over a three month period should be considered the minimum effective dose. Family intervention should encompass:

- communication skills
- problem solving
- psychoeducation.

✓ Delivery of family intervention should take account of the whole family's preference for either single-family intervention or multi-family group intervention and should not exclude offspring.

6.9 PSYCHODYNAMIC PSYCHOTHERAPY

A systematic review identified four studies of psychodynamic psychotherapy in people with schizophrenia, three of which were conducted before 1984. In only one study was there an adequate concealment method reported and, for this trial, CBT was the major focus of interest. In this small RCT, there was no benefit on mental state or global state when a psychodynamic based intervention was compared with standard care. | 1⁺⁺

No good quality RCTs of contemporary models of therapy were identified.

6.10 PSYCHOEDUCATION

Distinguishing between psychoeducation as a discrete intervention and the psychosocial approaches and family engagement which are encompassed within good quality standard care is challenging.

A systematic review identified 16 trials comparing psychoeducation with any type of control. Eight trials used standard care as the comparator. Interventions varied greatly in format, intensity and duration and most studies were conducted outside the UK limiting the generalisability of the results. Although there was no impact on relapse, one study reported improved rehospitalisation rate at 12 and 24 months when participants were offered written information and an information group for four weekly sessions followed by four monthly sessions. Two studies reported improved global assessment of functioning (GAF) at 12 months follow up and one study found improved CGI following a psychoeducation intervention with three eight week sessions, with two workbooks completed per session. One UK study measured a beneficial impact on insight at up to 12 months following a 15 minute educational video adopting a medical approach to the understanding of schizophrenia supplemented by three booklets. There was no evidence of benefit on any critical outcomes such as mortality, symptoms or quality of life.⁴⁴

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One small pilot study (n=39) of group psychoeducation conducted in a forensic setting found improvements in knowledge, self esteem and insight at three months post-intervention. However, these improvements did not translate to improved symptoms or behaviour.¹⁷³

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B Psychoeducation should not be offered as a stand-alone treatment intervention to individuals diagnosed with schizophrenia.

✓ When a diagnosis is made, professionals should ensure that service users and families/carers are informed and that clear information is given about what the diagnosis means and why it has been made.

Section 8.3 gives examples of the information service users/carers may find helpful at the key stages of the patient journey.

6.11 SOCIAL SKILLS TRAINING

A systematic review identified 20 trials comparing social skills training (excluding vocational and supported-employment based interventions) with any type of control. Most of the studies were conducted in the US. Ten trials used standard care as the comparator. Meta-analysis of three small studies (total n=125) from outside the UK found beneficial impact on negative symptoms at end of treatment. This effect was noted once multimodal studies were removed from the analysis. There was no overall evidence to suggest that social skills training was effective in improving critical outcomes.

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One subsequent study randomised 60 participants to social skills and neurocognitive individualised training (SSANIT) or structured leisure activities practised in mental health departments. After six months of treatment, personal and social functioning was significantly better in participants assigned to SSANIT. There were no differences between groups in composite secondary outcomes associated with psychopathology.¹⁶¹

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Social skills training to improve specific social interaction skills amongst individuals diagnosed with schizophrenia may be a highly relevant form of intervention for those individuals whose recovery has been blocked by problems in domains of social competence. It is less certain that these outcomes generalise to the other critical outcomes considered within this guideline.

B Social skills training may be considered for individuals diagnosed with schizophrenia who have persisting problems related to social skills.

7 Perinatal issues

7.1 INTRODUCTION

Women with schizophrenia have lower fertility rates when compared to women in the general population.¹⁷⁴⁻¹⁷⁶ They are also more likely to have unplanned and unwanted pregnancies.¹⁷⁷ They are less likely to engage with antenatal care and have more adverse outcomes of pregnancy in terms of delivery complications.¹⁷⁴ The demands of parenting may be particularly challenging, both because of the emotional demands and the requirement for greater social contact with agencies involved in child welfare. In the postpartum period, women with schizophrenia are at greater risk of not remaining the primary carer of their child.^{178,179}

7.2 RISK OF RELAPSE IN RELATION TO PREGNANCY AND CHILDBEARING

Two population based cohort studies addressed the risk of recurrence of schizophrenia in relation to first childbirth. The first found an incidence of postpartum admission (within 90 days) of 8.28% (95% CI 4.19 to 12.36) where women had any pre-pregnancy admission for schizophrenia. If women were admitted in the index pregnancy, the incidence of postpartum admission rose to 55.39% (95% CI 4.10 to 69.72).¹⁸⁰ The second found the RR of postpartum re-admission in the early period following childbirth was 5.67 (95% CI 3.23 to 9.96), when compared with risk after 180 days postpartum. Risk was significantly increased if there was an admission in pregnancy, and where there was partner psychopathology. Risk of relapse in schizophrenia remains elevated throughout the first postnatal year.¹⁸¹

✓ Healthcare professionals should be aware that women with schizophrenia have an increased risk of relapse of illness in the postpartum period, which is increased further if they are unwell during pregnancy.

7.3 INTERVENTIONS TO REDUCE RISK OF RELAPSE OF ILLNESS

There are few data on the specific benefits of interventions during pregnancy or the postpartum period to reduce the risk of relapse of schizophrenia. A small cohort study demonstrated weak evidence for an improvement in women with relapsed schizophrenia treated with antipsychotic medication and high-level social support.¹⁸² A systematic review of antipsychotic drugs for non-affective psychosis in pregnancy and the postpartum period was unable to identify any studies of adequate quality.¹⁸³

There is insufficient evidence to support a recommendation on interventions specific to pregnancy or the postpartum period to improve outcomes in schizophrenia. The following recommendation is taken directly from SIGN guideline number 127 on management of perinatal mood disorders.¹⁸⁴

D Women at high risk of postnatal major mental illness should have a detailed plan for their late pregnancy and early postnatal psychiatric management, agreed with the woman and shared with maternity services, the community midwifery team, GP, health visitor, mental health services and the woman herself. With the woman's agreement, a copy of the plan should be kept in her hand held records. The plan should identify what support should be in place and who to contact if problems arise, together with their contact details (including out-of-hours), and address decisions on medication management in late pregnancy, the immediate postnatal period and with regard to breastfeeding.

7.4 INTERVENTIONS TO REDUCE RISK OF ADVERSE OUTCOMES

No evidence was found relating to interventions to reduce unplanned or unwanted pregnancy in women with schizophrenia, or to improve child developmental outcomes. One case control study, which compared SGA with FGA or no antipsychotic use in pregnancy, found that the use of typical antipsychotics was associated with prematurity.¹⁸⁵ A small cohort study found that the quality of mother-infant interaction improved following inpatient mother and baby care for women with schizophrenia.¹⁸⁶

2+

- ✓ After individualised assessment, healthcare professionals should consider joint admission of mother and baby where a woman with schizophrenia experiences a postpartum relapse.
- ✓ Given the high risk of adverse parenting outcomes, child safeguarding issues should be routinely assessed and referral to social services considered during pregnancy.

7.5 EFFECTS OF ANTIPSYCHOTIC MEDICATION ON FETAL AND INFANT OUTCOMES

7.5.1 INTRODUCTION

The Maudsley Prescribing Guidelines suggest that the possibility of pregnancy should always be discussed and where there are known teratogenic effects women should be made aware of them even if they are not planning a pregnancy.¹⁸⁷ It is also important, when discussing risk, that women are aware that any adverse effects may be associated with the illness, factors related to the illness, or to general background risk, rather than to drugs used in pregnancy.

4

D All women with childbearing potential who take psychotropic medication should be made aware of the potential effects of the medications in pregnancy. The use of reliable contraceptive methods should be discussed.

7.5.2 PREGNANCY OUTCOMES AND FETAL DEVELOPMENT

Two systematic reviews provided no conclusive evidence that first- or second-generation antipsychotics are associated with structural teratogenicity, although they conclude that the evidence base is too limited to draw definitive conclusions.^{188,189}

2++

Two observational studies found no association between the use of antipsychotic drugs in pregnancy and particular complications such as rates of stillbirth, gestational age at birth, congenital abnormalities and perinatal syndromes. The studies considered a total of 401 pregnancy outcomes between them for women taking antipsychotics; 299 on risperidone, 60 on olanzapine, 36 on quetiapine and 6 on clozapine. There was no increased rate of any major malformation for any drug. The studies were not clear on timing or duration of exposure.^{190,191}

2+

7.5.3 NEUROLOGICAL EFFECTS ON THE NEONATE

There have been reports of self limiting extra-pyramidal symptoms or possibly withdrawal emergent syndromes in neonates exposed to risperidone in the third trimester.¹⁹¹

2+

7.5.4 EFFECTS ON FETAL GROWTH AND PREGNANCY METABOLISM

A prospective observational study focusing on infant birth weight found an association between low birth weight and the use of typical antipsychotics in pregnancy, and babies who were large for gestational age in the group of women taking SGAs, especially olanzapine and clozapine.¹⁹² A systematic review reported an increased risk of gestational diabetes with olanzapine and clozapine.¹⁸⁸ Two subsequent birth register cohort studies found an increased risk for gestational diabetes with use of antipsychotics in pregnancy, but without specificity for any individual drug.^{193,194}

2++

The evidence around potential adverse consequences from the use of antipsychotic drugs in pregnancy is conflicting and there is no clear link between individual antipsychotic medications and particular complications in pregnancy, during delivery, or for the neonate. An exception is the evidence for a link between antipsychotics and the risk of gestational diabetes.

C Women taking antipsychotics during pregnancy should be treated as high risk for gestational diabetes and monitored for blood glucose abnormalities.

7.6 BREAST FEEDING

✓ Breast feeding is an individual decision for each woman. Healthcare professionals should support women in their choice and be mindful that taking prescribed psychotropic medication is not routinely a contraindication to commencing or continuing breast feeding.

Most antipsychotic medications are excreted in breast milk but, as yet, there is no evidence to suggest that breastfed infants are at risk of toxicity or impaired development.¹⁹⁵⁻¹⁹⁹ There is little evidence on the SGAs.^{196,200} Clozapine is associated with agranulocytosis and is therefore not recommended in breast feeding.¹⁸⁸ **3**

D Women who are taking clozapine should not breast feed.

✓ All breastfed infants should be monitored for sedation and extra-pyramidal adverse effects where mothers are taking antipsychotic medications.

8 Provision of information

This section reflects the issues likely to be of most concern to service users and their carers. These points are provided for use by health professionals when discussing schizophrenia with service users and carers and in guiding the production of locally produced information materials.

8.1 SOURCES OF FURTHER INFORMATION

8.1.1 HELPLINES/WEB BASED SUPPORT

Breathing Space

0800 838 587

www.breathingspacescotland.co.uk

CarersLine

0808 808 7777

www.carersuk.org

Mental Welfare Commission

0800 389 6809

www.mwscot.org.uk

Mind

0300 123 3393

www.mind.org.uk

NHS24

08454 24 24 24

www.nhs24.com

Samaritans

0845 790 9090

www.samaritans.org

SANEline

0845 767 8000

www.sane.org.uk

8.1.2 ORGANISATIONS

The following organisations provide information and undertake work in particular areas of mental health.

Action on Depression

11 Alva Street

Edinburgh EH2 4PH

Tel: 0808 802 2020 information line Wednesdays 2pm-4pm

Tel: 0131 226 1803 administration

www.actionondepression.org

Email: admin@actionondepression.org

Carers Scotland

The Cottage, 21 Pearce Street, Glasgow, G51 3UT

Tel: 0141 445 3070

www.carersuk.org/scotland

Email: info@carerscotland.org

Health Rights Information Scotland

Scottish Consumer Council
 Royal Exchange House, 100 Queen Street
 Glasgow G1 3DN
 Tel: 0141 226 5261
 Email: hريس@scotconsumer.org.uk
www.hريس.org.uk

Mental Health Foundation Scotland

Merchants House, 30 George Square
 Glasgow G2 1EG
 Tel: 0141 572 0125
 Email: scotland@mhف.org.uk
www.mentalhealth.org.uk/

Mental Welfare Commission

Thistle House, 91 Haymarket Terrace
 Edinburgh EH12 5HE
 Tel: 0131 313 8777
 Email: enquiries@mwcscot.org.uk
www.mwcscot.org.uk

Penumbra

Norton Park, 57 Albion Road
 Edinburgh EH7 5QY
 Tel: 0131 475 2380
 Email: enquiries@penumbra.org.uk
www.penumbra.org.uk

Richmond Fellowship Scotland

3 Buchanan Gate, Buchanan Gate Business Park
 Cumbernauld Road
 Stepps
 North Lanarkshire G33 6FB
 Tel: 0845 013 6300
 Email: info@trfs.org.uk
www.trfs.org.uk

SAMH (Scottish Association for Mental Health)

Brunswick House, 51 Wilson Street
 Glasgow G1 1UZ
 Tel: 0141 530 1000
 Email: enquire@samh.org.uk
www.samh.org.uk

SANE

1st Floor, Cityside House
 40 Adler Street
 London E11EE
 Tel: 020 7375 1002
 Email: info@sane.org.uk
www.sane.org.uk

Scottish Independent Advocacy Alliance

69a George Street
Edinburgh EH2 2JG
Tel: 0131 260 5380
Email: enquiry@siaa.org.uk
www.siaa.org.uk

Scottish Recovery Network

Suites 320-323, Baltic Chambers
50 Wellington Street
Glasgow G2 6HJ
Tel: 0141 240 7790
Email: info@scottishrecovery.net
www.scottishrecovery.net

'see me'

9-13 Maritime Street
Edinburgh
EH6 6SB
Tel: 0131 624 8945
Email: info@seemescotland.org
www.seemescotland.org.uk

Support in Mind Scotland

6 Newington Business Centre
Dalkeith Road Mews
Edinburgh EH16 5GA
Tel: 0131 662 4359
Email: info@supportinmindscotland.org.uk
www.supportinmindscotland.org.uk

VOX (Voices of Experience) (Scotland)
c/o Mental Health Foundation (Scotland)

5th Floor, Merchants House
30 George Square
Glasgow G2 1EG
Tel: 0141 572 1663
Email: voxscotland@yahoo.co.uk
www.voxscotland.org.uk

8.1.3 USEFUL WEBSITES

SIGN accepts no responsibility for the content of the websites listed and does not support the use of treatments which have not been proven to be safe and effective using SIGN methodology.

www.rcpsych.ac.uk/mentalhealthinfoforall

www.bps.org.uk/psychology-public/how-can-psychology-help-you

www.dwp.gov.uk

www.direct.gov.uk

8.2 KEY MESSAGES FROM MENTAL HEALTH SERVICE USERS

A focus group was held in September 2011 with mental health service users, some of whom had received a diagnosis of schizophrenia and others who had not been given a diagnosis. The aim of the focus group was to hear about their experiences of mental health services in relation to information provision. Eight people took part, three males and five females. The people who contributed were a selected sample but their perspectives emphasise the need for adequate information provision and the importance for the involvement of service users and carers in discussions.

8.2.1 DIAGNOSIS

Some mental health service users had not received a diagnosis but it had never been explained to them why this was not possible. They felt that perhaps healthcare professionals did not inform them of their diagnosis to prevent labelling them but they expressed a need to know to allow them to get the appropriate help and understand their illness. A few service users had received a confusing diagnosis and had been given different opinions from different healthcare professionals. The group felt they were kept in the dark about their diagnosis and felt this added to anxiety and concern.

Service users felt it was important for healthcare professionals to explain what the term 'mental illness' means. The group spoke about the difficulty that people have accepting that they have a mental illness and felt it was important that healthcare professionals discussed this with them and their families.

The involvement of families in discussions regarding diagnosis was important with service users expressing a need to make families, particularly children, aware of when relatives may need to be admitted to hospital and who to contact for support.

Service users explained that they would have appreciated a healthcare professional taking the time to discuss symptoms with them and explaining why they have particular feelings, for example not wanting to go out.

Suicidal thoughts had been an issue for some service users and for some this had not been discussed with them and they reported that they did not know who to turn to for support.

8.2.2 MANAGEMENT

Some service users expressed that they did not know what help they needed and relied on healthcare professionals taking the time to discuss the options with them. Some service users felt that they would have benefitted from treatment earlier but they were not aware of where to access support.

Service users felt that they were not partners in their own care and were not aware of the treatment options. They referred to 'conveyor belt' medicine and would have appreciated time to discuss their illness and have treatments explained to them by an understanding healthcare professional. They expressed a need to involve service users and their families in treatment decisions.

Service users spoke of medication being given but did not know why they had been given it and had stopped taking it or had not started it.

Some service users reported that they had taken the initiative to learn about mental illness and treatments themselves via websites and libraries. They thought it would have been helpful to have received written information from healthcare professionals to help them to understand mental illness and learn about the available treatments. They did acknowledge that written information may not be useful for everyone as some people may not be able to take the information in or it may cause more anxiety. They also acknowledged that some people may not want information and that healthcare professionals should take this into account.

8.2.3 HOSPITAL CARE

Service users recalled waking up in psychiatric wards with no explanation as to how they got there or what behaviours they had displayed. They felt that an explanation would help people understand why they were being detained in hospital. They expressed a need to be informed if they were in hospital voluntarily or if they had been admitted under the Mental Health Act. They felt it was important to explain the term 'sectioned' as there were some misunderstandings around what this actually meant. Those who had been admitted to hospital under the Mental Health Act felt it was important to explain how long they would be detained in hospital and what the routines would be. They felt that not being properly informed added to the confusion.

Service users reported that they were never told why they were receiving particular treatments or why some procedures were in place. One individual described their knowledge of mental illness, treatments and psychiatric ward procedures being gained from films.

8.2.4 DISCHARGE AND FOLLOW UP

The majority of service users reported leaving hospital not knowing "what would happen to them." They expressed a need for healthcare professionals to discuss their care plan with them and their families.

Service users expressed a need for both verbal and written information. It was important for a named contact for support to be given.

8.3 CHECKLIST FOR PROVISION OF INFORMATION

Schizophrenia can be very distressing for service users and their families. There are many issues which families have to cope with and they need information, support and reassurance from healthcare professionals throughout the patient journey. Service users and carers will need to be provided with information and support according to their particular circumstances and needs. The information which service users and carers are given about their condition and care should be culturally appropriate.

This section gives examples of the information service users/carers may find helpful at the key stages of the patient journey. Although items appear under specific headings, information needs are rarely linear and points may apply at various stages of the patient journey. The list was developed by members of the guideline group based on their experience and their understanding of the evidence base. It is neither exhaustive nor exclusive.

| General points for professionals providing information to service users and carers |
|--|
| <ul style="list-style-type: none"> • Information provided may need to be repeated for service users and carers on more than one occasion and should be available through 1:1 discussion backed up by written material and details of sources of further information and support (including voluntary organisations). • Information needs to be communicated in an accessible way that people can understand and service users and carers may require time for questions and discussion, at the time or at a later date. • Families and carers will include children who are carers. • Potential issues about self harm and/or suicidal thinking should be explored sensitively and guidance given about what measures may be helpful. |
| Presentation and diagnosis |
| <ul style="list-style-type: none"> • Where appropriate, explain that a diagnosis cannot be made straight away and advise of the value of early intervention and how this may prevent the development of some of the more debilitating problems associated with schizophrenia (for example social withdrawal and occupational breakdown). • When a diagnosis is made, ensure that services users and families/carers are informed and that clear information is given about what the diagnosis means and why it has been made. • Include information about some commonly held misconceptions about the diagnosis. For example it is not a 'split personality'; not a life sentence with no hope; not automatically accompanied by violent behaviour; does not automatically mean people will never work again, nor have loving relationships. • Acknowledge that everyone's experience of schizophrenia is different and that symptoms and experiences will vary between individuals. • Inform service users and carers about access to independent advocacy. • Discuss confidentiality issues including whether, and in what circumstances, any information given by the carer can remain confidential from the service user. This should be re-visited at regular intervals. Practitioners' Guidance on these issues is contained in the publication 'Carers and Confidentiality' produced by the Mental Welfare Commission for Scotland (www.mwscot.org.uk). • Provided carers with information about sources of information and support for themselves. • Discuss: <ul style="list-style-type: none"> - recovery and hope. Describe how recovery is defined (www.scottishrecovery.net) and clarify that this is not synonymous with 'cure' from the illness, nor is it always a linear process. Allow for an opportunity to talk about what possible barriers to recovery people may experience (one of these might be social isolation) - relapse prevention, including information about wellness recovery action planning - treatments, including any unwanted effects the service user may experience as a result of treatment with medication and what steps should be taken should these occur - where appropriate, the impact of medication on psychomotor skills (for example driving and the requirement to contact the DVLA) and how this can/should be addressed. • The following quality of life issues should be discussed: <ul style="list-style-type: none"> - physical health - lifestyle issues such as the use of tobacco, alcohol and non-prescription drugs - any feelings of guilt, shame and stigma and how the person can be helped to address these - the value of social support - employment/education worries - difficulties related to family and children. - Discuss the impact of diagnosis on life in general, not only for the service user but also the potential impact for example on family dynamics; siblings; and carers' own mental health. |

Management

- Advise service users and carers that treatment and care is generally provided in the community but some people may have to be admitted to hospital for a short time.
- Acknowledge that service users sometimes do not realise or accept that they are unwell and discuss that they may have to be admitted to hospital for treatment under the Mental Health (Care and Treatment) (Scotland) Act 2003. Ensure that good quality information is provided verbally and in written form about mental health legislation, including safeguards and rights and details about the Mental Welfare Commission for Scotland.
- Provide sufficient information on treatments to enable service users to make an informed choice. The following information should be discussed:
 - negative and positive aspects of all treatments
 - timescale for symptom improvement.
- Advise service users to speak to their healthcare professional if they are considering stopping medication.
- Ensure that carers/families are aware of the possible consequences of stopping medication in a non-managed way.
- Advise service users to discuss pregnancy planning and contraceptive advice with their healthcare professional, in order that risks in pregnancy or of relapse of illness are minimised.

Discharge from hospital

- Service users and carers should be kept fully informed and consulted at each stage of the discharge process.
- Provide information on useful national and local organisations and websites and where service users can find information on financial issues/benefits.
- Service users and carers should be given a named telephone contact to deal with any immediate problems following discharge.
- Describe how recovery is unlikely to be linear. Ensure that service users and carers have been provided with information on useful organisations and websites and where they can find information on financial issues.

9 Implementing the guideline

9.1 IMPLEMENTATION STRATEGY

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

Implementation of this guideline will be encouraged and supported by SIGN. The implementation strategy for this guideline encompasses the following tools and activities:

- identification of the key recommendations that should be prioritised for implementation
- description of recommendations likely to have significant resource implications
- audit tools
- guideline and supporting materials available to download from the SIGN website
- dissemination of a quick reference guide to all appropriate healthcare professionals
- electronic dissemination of the full guideline to all NHS Boards
- iPhone, iPad and Android apps
- patient version of the guideline.

9.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

| | Guideline Section | Resource Implication | |
|----------|--|----------------------|--|
| A | <p>Individuals in the first episode of psychosis should receive treatment within the context of a specialist early intervention model of care. This should be multidisciplinary and encompass:</p> <ul style="list-style-type: none"> • engagement/assertive outreach approaches • family involvement and family interventions • access to psychological interventions and psychologically informed care • vocational/educational interventions • access to antipsychotic medication. | 4.1 | Service development costs. Early intervention services not routinely offered in Scotland |
| ✓ | Local arrangements for physical health monitoring should be put in place at the time of antipsychotic prescribing. | 5.2 | Investment costs in physical health monitoring |
| A | <p>In service users with an acute exacerbation or recurrence of schizophrenia prescribers should consider amisulpride, olanzapine or risperidone as the preferred medications with chlorpromazine and other low-potency first-generation antipsychotics providing suitable alternatives. Consideration should be given to previous response to individual antipsychotic medications and relative adverse effect profiles.</p> | 5.5.1 | No significant resource implication |
| A | Individuals with schizophrenia which is in remission should be offered maintenance treatment with antipsychotic medication for a minimum of two years. | 5.6.4 | Potential for increased prescribing costs |
| B | Clozapine should be considered for service users whose schizophrenia has not responded to two antipsychotics including a second-generation antipsychotic medication. | 5.7.1 | Potential for increased prescribing costs |
| A | Individual CBTp should be offered to all individuals diagnosed with schizophrenia whose symptoms have not adequately responded to antipsychotic medication and where persisting symptoms and/or depression are being experienced. CBTp can be started during the initial phase, the acute phase or recovery phase including inpatient settings. | 6.4 | Current provision of psychological therapy services across Scotland is variable. NHS Education for Scotland is working in partnership with the Scottish |
| A | <p>Family intervention should be offered to all individuals diagnosed with schizophrenia who are in close contact with or live with family members and should be considered a priority where there are persistent symptoms or a high risk of relapse. Ten sessions over a three month period should be considered the minimum effective dose. Family intervention should encompass:</p> <ul style="list-style-type: none"> • communication skills • problem solving • psychoeducation. | 6.8 | Government, NHS Boards and other service providers to increase the capacity within the current NHS workforce to deliver psychological therapies, to support service change, and to ensure that the new resource is used effectively in practice. |

9.3 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

9.4 ADDITIONAL ADVICE TO NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

In 2007 NHS Quality Improvement Scotland developed standards for integrated care pathways for mental health. Three standards are specific to care of individuals with schizophrenia:

- In the early stages of schizophrenia an early intervention model of care is delivered.
- Psychoeducational, psychological and psychosocial therapies, which should include cognitive behavioural therapy (CBT) where indicated, are offered and delivered in a timely manner.
- Medication, including for drug treatment-resistant schizophrenia, is recorded.

Table 2 summarises SMC advice for antipsychotics indicated for schizophrenia.

Table 2 SMC advice to NHSScotland.

| Drug | Product/formulation | Indication | Date | SMC Decision |
|------------------------|---|---|-----------|--|
| Aripiprazole | orodispersible tablets and oral solution (Abilify®) | Treatment of schizophrenia in adolescents 15 years and older | Aug 2010 | Accepted for restricted use within NHSScotland. |
| Aripiprazole | intramuscular injection (Abilify®) | Rapid control of agitation and disturbed behaviours in patients with schizophrenia, when oral therapy is not appropriate | Dec 2008 | Accepted for use in NHSScotland. |
| Aripiprazole | tablets 5 mg (Abilify®) | Treatment of schizophrenia | July 2005 | Accepted for restricted use in NHSScotland. |
| Aripiprazole | (Abilify®) | Treatment of schizophrenia | Aug 2004 | Accepted for use within NHSScotland. |
| Olanzapine | long-acting injection (ZypAdhera) | Maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine | Aug 2010 | Not recommended for use within NHSScotland. |
| Olanzapine | intramuscular use (Zyprexa®) | Acute agitation in schizophrenia or acute mania | July 2004 | Accepted for use within NHS Scotland. |
| Paliperidone palmitate | prolonged-release suspension for injection (Xeplion) | Maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone. In selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, it may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed | Nov 2011 | Accepted for use within NHS Scotland. |
| Paliperidone | prolonged-release tablets (Invega®) | Treatment of schizophrenia | Apr 2008 | Not recommended for use within NHSScotland. |
| Quetiapine | prolonged-release tablet (Seroquel XL®) | Treatment of schizophrenia in adults (18 years and over) | Nov 2008 | Accepted for use within NHSScotland. |
| Risperidone | 3 mg, 4 mg orodispersible tablets (Risperdal Quicklet®) | Treatment of acute and chronic schizophrenia and similar psychosis and treatment of mania in bipolar disorder | Sept 2007 | Accepted for restricted use within NHSScotland. |
| Risperidone | orodispersible tablets (Risperdal Quicklet®) | Acute and chronic schizophrenic psychoses | May 2003 | Recommended for restricted use within NHSScotland. |

10 The evidence base

10.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. The evidence base underpinning NICE guideline CG82 Schizophrenia: core interventions in the treatment and management of schizophrenia in adults in primary and secondary care (March 2009)⁴⁴ was updated to form the evidence base for development of this guideline. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2008-2011. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group.

10.2 RECOMMENDATIONS FOR RESEARCH

- The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline (see Annex 1). The following areas for further research have been identified:
- RCTs of arts therapies including the use of art therapy in individual rather than group settings
- RCTs examining the effectiveness of contemporary models of process experiential-based psychotherapy as primary intervention as opposed to comparison treatment
- RCTs of contemporary models of psychodynamic psychotherapy
- Development and evaluation of psychological therapies in the perinatal phase with outcomes specified for mothers and the mother-infant relationship
- RCTs of third wave cognitive and behavioural therapies
- Effectiveness of SGAs and low-potency FGAs in both oral and depot forms
- RCTs of clozapine as a second line treatment
- Behavioural and biological predictors of treatment response/resistance
- RCTs of pharmacological/psychosocial augmentation strategies in clozapine non- and partial response
- Studies of the differential effects of antipsychotics on anxiety/cognitive dysfunction/sexual dysfunction and different treatments for them
- Studies of the efficacy of various physical health monitoring regimes
- Development of novel approaches to physical ill health in schizophrenia.

10.3 REVIEW AND UPDATING

This guideline was published in 2013 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: www.sign.ac.uk

11 Development of the guideline

11.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in "SIGN 50: A Guideline Developer's Handbook", available at www.sign.ac.uk

11.2 THE GUIDELINE DEVELOPMENT GROUP

| | |
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The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive.

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive. All members of the SIGN Executive make yearly declarations of interest and further details of these are available on request.

| | |
|----------------------|--|
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| | |
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11.4 CONSULTATION AND PEER REVIEW

11.4.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held on 22 November 2011 and was attended by 164 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

11.4.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewer's comments.

SIGN is very grateful to all of these experts for their contribution to the guideline.

| | |
|-------------------------|---|
| Dr Alison Brabban | <i>Clinical Lead, Early Intervention in Psychosis, Tees, Esk and Wear Valleys NHS Trust</i> |
| Dr Patrick Convery | <i>Head of Mental Health and Learning Disability, The Regulation and Quality Improvement Authority, Belfast</i> |
| Ms Donna Dunlop | <i>Senior Pharmacist, Ailsa Hospital, Ayr</i> |
| Dr Fiona Gaughran | <i>National Psychosis Service, South London and Maudsley NHS Foundation Trust, London</i> |
| Professor Louise Howard | <i>Professor in Women's Mental Health, Institute of Psychiatry, London</i> |
| Professor Eve Johnstone | <i>Professor of Psychiatry, Royal Edinburgh Hospital</i> |
| Ms Rachel King | <i>British Association of Art Therapists, London</i> |
| Mrs Kirsty Macfarlane | <i>Principal Pharmacist, Scottish Medicines Consortium, Edinburgh</i> |
| Dr Peter McKenna | <i>Research Psychiatrist, Benito Menni, Complex Assistencial en Salut Mental, Barcelona</i> |
| Dr Hamish McLeod | <i>Programme Director, Mental Health and Wellbeing Research Group, University of Glasgow</i> |
| Ms Rachel Rogers | <i>Dramatherapy Scotland and The British Association of Dramatherapists</i> |

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|-----------------------------|---|
| Ms Chloe Swift | <i>Policy Officer, Royal College of Nursing, Edinburgh</i> |
| Professor Elizabeth Twamley | <i>Associate Professor of Psychiatry, University of California, San Diego</i> |
| Professor Peter Tyrer | <i>Professor of Community Psychiatry, Imperial College, London</i> |
| Professor Til Wykes | <i>Professor of Clinical Psychology and Rehabilitation, Institute of Psychiatry, London</i> |

All expert referees made declarations of interest and further details of these are available on request from the SIGN Executive.

11.4.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. All members of the SIGN Editorial group make yearly declarations of interest and further details of these are available on request from the SIGN Executive. The editorial group for this guideline was as follows.

| | |
|---------------------------|--|
| Dr Keith Brown | <i>Chair of SIGN; Co-Editor</i> |
| Dr Roberta James | <i>SIGN Programme Lead; Co-Editor</i> |
| Dr Tahir Mahmood | <i>Royal College of Obstetricians and Gynaecologists in Scotland</i> |
| Professor Ronan O'Carroll | <i>British Psychological Society</i> |
| Dr Sara Twaddle | <i>Director of SIGN; Co-Editor</i> |

Abbreviations

| | |
|----------------|--|
| ACE | adherence-coping education |
| ACT | assertive community treatment |
| ACTp | acceptance and commitment therapy |
| BAP | British Association for Psychopharmacology |
| BNF | British National Formulary |
| BPRS | brief psychiatric rating scale |
| CATIE | clinical antipsychotic trial of intervention effectiveness |
| CBT | cognitive behavioural therapy |
| CBTp | cognitive behavioural therapy for psychosis |
| CGI | clinical global impression |
| CI | confidence interval |
| CPRS | Comprehensive Psychopathological rating scale |
| CRT | cognitive remediation therapy |
| CUtLASS | cost utility of the latest antipsychotic drugs in schizophrenia study |
| DDD | daily defined dose |
| ECT | electroconvulsive therapy |
| EI | early intervention |
| EPSE | extra-pyramidal side effects |
| EUFEST | European first episode schizophrenia trial |
| FGA | first-generation antipsychotic |
| GAF | global assessment of functioning |
| GMC | General Medical Council |
| HTA | health technology assessment |
| IM | intramuscular |
| IQ | intelligence quotient |
| ITT | intention-to-treat |
| LAI | Long-acting injection |
| MA | marketing authorisation |
| MATISSE | Multi-centre study of Art Therapy In Schizophrenia - Systematic Evaluation |
| MTA | multiple technology appraisal |
| NICE | National Institute for Health and Clinical Excellence |
| OR | odds ratio |
| PANSS | positive and negative syndrome scale |
| RCT | randomised controlled trial |
| RR | relative risk |
| SGA | second-generation antipsychotic |

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| SIGN | Scottish Intercollegiate Guidelines Network |
| SMC | Scottish Medicines Consortium |
| SMD | standardised mean difference |
| SPC | summary of product characteristics |
| SSANIT | social skills and neurocognitive individualised training |
| SZ | schizophrenia |
| TAU | treatment as usual |
| TD | tardive dyskinesia |
| UK | United Kingdom |
| US | United States |
| WHO | World Health Organisation |
| WMD | weighted mean difference |

Annex 1

Key questions used to develop the guideline

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search. The questions outlined are adapted from NICE guideline CG82; Schizophrenia: core interventions in the treatment and management of schizophrenia in adults in primary and secondary care (March 2009).⁴⁴

| Key question | See guideline section |
|---|-----------------------|
| DUAL DIAGNOSIS | |
| 1. For people with psychosis and comorbid substance misuse (dual diagnosis) what is the evidence around access and engagement to services and the effectiveness of treatment (psychological or pharmacological) at all stages of the illness? | 3 |
| ACCESS AND ENGAGEMENT | |
| 2. For people with psychosis, do early intervention services improve clinical outcomes or improve the number of people remaining in contact with services when compared with standard care? | 4.1 |
| 3. For all people from black and minority ethnic groups with psychosis, do specialist ethnic mental health services (culturally specific or culturally skilled) improve clinical outcomes or improve the number of people remaining in contact with services? | 4.3 |
| PERINATAL ISSUES | |
| 4. Does pregnancy or childbearing increase the risk of developing first episode or relapse of schizophrenia? | 7.2 |
| 5. What pharmacological or psychological interventions during pregnancy or the postpartum period improve outcome in terms of relapse of illness? | 7.3 |
| 6. What pharmacological or psychological interventions during pregnancy or the postpartum period improve outcomes for mothers and infants in terms of: <ul style="list-style-type: none"> • adverse obstetric or neonatal outcomes • proportion pre-term or low birth weight babies • requirement for stays in neonatal units • proportion infants on at-risk register or taken into care on delivery • proportion failure to thrive in neonatal period • proportion babies needing detox • improved mother-infant relationship as measured by the child remaining with the mother/attachment/ bonding • improved child development • reduced unplanned or unwanted pregnancies? | 7.4 |

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| 7. What adverse effects on fetal and infant development are associated with antipsychotic medications? | 7.5 |
| PHARMACOLOGICAL THERAPY | |
| 8. For people with first episode or early schizophrenia, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared with another oral antipsychotic drug at the initiation of treatment? The analysis will compare each of the SGAs (amisulpride, aripiprazole, olanzapine, paliperidone, quetiapine, sertindole and zotepine) with each other, as well as with haloperidol and any non-haloperidol FGA. | 5.4 |
| 9. For people with first episode or early schizophrenia in whom initial oral antipsychotic medication is not fully effective, what is the most effective treatment strategy and when do you decide to alter initial treatment? | 5.4 |
| 10. For people with first episode or early schizophrenia, are there any relevant factors (including patient populations) which predict the nature and degree of response to initial antipsychotic medication? | 5.4 |
| 11. For people with first episode or early schizophrenia, what should be the dose/duration (and, where relevant, frequency) of initial antipsychotic medication? | 5.4 |
| 12. When antipsychotic-naïve patients are started on antipsychotic medication, are relatively low doses required for a therapeutic response? | 5.4 |
| 13. For people with first episode or early schizophrenia, what is the most appropriate treatment strategy to manage known side effects of antipsychotic medication? | 5.4 |
| 14. For people with first episode or early schizophrenia, what non-pharmacological (lifestyle) measures are of benefit in management of side effects. Consider dietary interventions, weight management, exercise and sleep hygiene. | 5.4 |
| 15. For people with first episode or early schizophrenia, what baseline measurements should be taken before initiating antipsychotic medication? | 5.4 |
| 16. For people with an acute exacerbation or recurrence of schizophrenia, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared with another oral antipsychotic drug? | 5.5 |
| 17. For people with an acute exacerbation or recurrence of schizophrenia who have an inadequate or no response to oral antipsychotic medication, what is the most effective treatment strategy and when do you decide to alter treatment? | 5.5 |
| 18. For people with an acute exacerbation or recurrence of schizophrenia, are there any relevant factors (including patient populations) which predict the nature and degree of response to initial antipsychotic treatment? | 5.5 |
| 19. For people with an acute exacerbation or recurrence of schizophrenia, what should be the dose/duration (and, where relevant, frequency) of initial antipsychotic treatment? | 5.5 |
| 20. For people with an acute exacerbation or recurrence of schizophrenia, what is the optimal dose range for antipsychotic medication? | 5.5 |
| 21. Does rapid escalation of dosage/relatively high dosage yield any advantage in terms of speed of onset or degree of therapeutic response? | 5.5 |
| 22. Does intramuscular antipsychotic improve speed of onset or degree of therapeutic response? Consider haloperidol, olanzapine and aripiprazole | 5.5 |
| 23. For people with an acute exacerbation or recurrence of schizophrenia, what is the most appropriate treatment strategy to manage known side effects of antipsychotic medication? | 5.5 |

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| 24. For people with an acute exacerbation or recurrence of schizophrenia, what baseline measurements should be taken before initiating antipsychotic medication? | 5.5 |
| 25. For people with schizophrenia that is in remission, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared with another oral antipsychotic drug? | 5.6 |
| 26. For people with schizophrenia that is in remission, is any depot or long-acting antipsychotic medication associated with improved relapse prevention over time? | 5.6 |
| 27. For people with schizophrenia that is in remission, are there any relevant factors (including patient populations) that predict continuing remission? | 5.6 |
| 28. For people with schizophrenia that is in remission, what should be the dose/duration (and, where relevant, frequency) of antipsychotic medication? | 5.6 |
| 29. For people with schizophrenia that is in remission, who have had long term antipsychotic drug treatment, is there any evidence that patients have a preference for either depot/long-acting or oral preparations? | 5.6 |
| 30. For people with schizophrenia that is in remission and comorbid depressive features, is antipsychotic medication associated with an enhanced therapeutic response? | 5.6 |
| 31. For people with schizophrenia that is in remission and comorbid anxiety and depressive features, is antipsychotic medication associated with an enhanced therapeutic response? | 5.6 |
| 32. For people with schizophrenia that is in remission, is any antipsychotic medication associated with improved cognitive function in relevant domains? | 5.6 |
| 33. For people with schizophrenia that is in remission, is there any evidence that switching to a particular antipsychotic medication is associated with a lower liability for tardive dyskinesia? | 5.6 |
| 34. For people with schizophrenia that is in remission, what is the most appropriate treatment strategy to manage known side effects of antipsychotic medication? | 5.6 |
| 35. For people with schizophrenia whose illness has not responded adequately to treatment, what are the benefits and downsides of continuous oral antipsychotic drug treatment when compared with another oral antipsychotic drug? | 5.7 |
| 36. For people with schizophrenia whose illness has not responded adequately to treatment and who have had long term antipsychotic drug treatment, is there any evidence that patients have a preference for either depot/long-acting or oral preparations? | 5.7 |
| 37. For people with schizophrenia whose illness has not responded adequately to clozapine treatment, is augmentation of clozapine with another antipsychotic medication associated with an enhanced therapeutic response? | 5.7 |
| 38. For people with schizophrenia whose illness has not responded adequately to clozapine treatment, is augmentation of clozapine with another medication associated with an enhanced therapeutic response? (triglycerides, antidepressants, anticonvulsants, antipsychotics) | 5.7 |
| 39. For people with schizophrenia whose illness has not responded adequately to treatment, when do you decide to change antipsychotic medication? | 5.7 |
| 40. For people with schizophrenia whose illness has not responded adequately to treatment, are there any relevant factors (including patient populations) that predict poor response to antipsychotic medication? | 5.7 |

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| 41. For people with schizophrenia whose illness has not responded adequately to treatment, what should be the dose/duration (and, where relevant, frequency) of antipsychotic medication? | 5.7 |
| 42. For people with schizophrenia whose illness has not responded adequately to treatment, do high (mega) doses of antipsychotic medication offer any therapeutic advantage over standard (recommended) dosage? | 5.7 |
| 43. For people with schizophrenia whose illness has not responded adequately to treatment, is clozapine more effective than other antipsychotic medications? | 5.7 |
| 44. For people with schizophrenia and comorbid depressive features whose illness has not responded adequately to treatment, is antipsychotic medication associated with an enhanced therapeutic response? | 5.8 |
| 45. For people with schizophrenia and comorbid anxiety and depressive features whose illness has not responded adequately to treatment, is antipsychotic medication associated with an enhanced therapeutic response? | 5.8 |
| 46. For people with schizophrenia with persistent negative symptoms, is any antipsychotic medication (including adjunctive treatments) associated with an enhanced therapeutic response? | 5.8 |
| 47. For people with schizophrenia with persistent symptoms of irritability, hostility and aggression, is any antipsychotic medication (including adjunctive treatments) associated with an enhanced therapeutic response? | 5.8 |
| 48. For people with schizophrenia whose illness has not responded adequately to treatment, is any antipsychotic medication associated with improved cognitive function in relevant domains? | 5.8 |
| 49. For people with schizophrenia whose illness has not responded adequately to treatment, is augmentation of antipsychotic medication with another antipsychotic associated with an increased risk of/severity of treatment-emergent adverse events? | 5.7 |
| 50. For people with schizophrenia whose illness has not responded adequately to treatment, is augmentation of antipsychotic medication with another medication associated with an increased risk of/severity of treatment-emergent adverse events? (triglycerides, anticonvulsants, antidepressants, antipsychotics). | 5.7 |

| PSYCHOLOGICAL THERAPIES | |
|---|----------|
| <p>For people with schizophrenia what is the effectiveness of psychological therapies?</p> <p>Consider the following patient groups:</p> <ul style="list-style-type: none"> • people with first episode or early schizophrenia • people with an acute exacerbation or recurrence of schizophrenia • people with schizophrenia that is in remission • people with schizophrenia whose illness has not responded adequately to treatment • people with schizophrenia and comorbid anxiety and depressive features whose illness has not responded adequately to treatment. <p>Consider the following interventions:</p> <ul style="list-style-type: none"> • adherence therapy • arts therapies • cognitive behavioural therapy • cognitive remediation • contingency management • counselling and supportive psychotherapy • family intervention • psychodynamic psychotherapy and psychoanalysis • psychoeducation • social skills training <p>with attention to:</p> <ul style="list-style-type: none"> • format • dose • factors that may predict the nature and degree of response to a psychological intervention • any advantages of combining particular psychological/psychosocial interventions with an antipsychotic medication, either concurrently or sequentially. | 6.2-6.11 |

Annex 2

Glossary of Psychological Therapies

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| Adherence therapy | Adherence therapy is a brief intervention which explores an individual's ambivalence to treatment and maintenance medication. It refers to any discrete and structured programme, tailored to the individual's needs, involving interaction between service provider and service user, during which service users are provided with support, information and management strategies to improve their adherence to medication and/or with the specific aim of improving symptoms, quality of life and preventing relapse. |
| Arts therapies | Arts therapies (art, body-oriented or music) combine psychotherapeutic techniques with activities aimed at promoting creative expression. Arts therapies aim to enable people diagnosed with schizophrenia to experience themselves differently and to develop new ways of relating to others; help people express themselves and to organise their experience into a satisfying and 'containing' aesthetic form; and to help people to accept and understand feelings that may have emerged during the creative process. |
| Cognitive behavioural therapy (CBT) also referred to as CBT for psychosis (CBTp) | A structured and collaborative therapeutic approach, CBT is a discrete psychological intervention which aims to make explicit connections between thinking, emotions, physiology and behaviour with respect to current or past problems, primarily through behavioural experiments and guided discovery. CBT seeks to achieve systemic change through the re-evaluation of perceptions, beliefs or reasoning thought to cause and maintain psychological problems. The aim is to help the individual normalise and make sense of their psychotic experiences, and to reduce the associated distress and impact on functioning. Targeted outcomes include symptom reduction (positive or negative psychotic symptoms and general symptoms including mood), relapse reduction, enhancement of social functioning, development of insight, amelioration of distress, and the promotion of recovery. |
| Cognitive remediation | Cognitive remediation is a behavioural treatment for people who are experiencing cognitive impairments that may interfere with daily functioning. Cognition refers to a broad set of abilities that together allow us to perceive process, manipulate, and respond to information. Examples of cognitive functions are attention, memory, organisation and functioning. Many people with schizophrenia experience some problems in these domains and this may limit their recovery in areas such as daily living, social or vocational functioning. Cognitive remediation programmes employ a variety of methods, but increasingly rely on computerised learning, in order to help people develop particular cognitive skills. |
| Contingency management | Contingency management strategies refer to behavioural programmes in which specific target behaviours are positively reinforced through monetary incentives or other reward systems. |
| Counselling and supportive therapy | Counselling and supportive therapy are psychological interventions which are facilitative, non-directive and/or relationship focused, with the content largely determined by the individual receiving counselling. The aims are to promote self knowledge, emotional acceptance and growth, and develop personal resources in order to live more fully and satisfyingly. Counselling and supportive therapy may be concerned with addressing and resolving specific problems, making decisions, coping with crises, working through inner feelings and inner conflict, or improving relationships with others. The current guideline refers to counselling and supportive therapy offered to people diagnosed with schizophrenia as discrete interventions, as distinct from the importance of the therapeutic alliance and supportive elements in the provision of all good quality standard care. |

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| Family intervention | Family intervention is a discrete psychological intervention with a specific supportive, educational or treatment function which involves problem solving/crisis management and/or intervention with the identified service user. Family intervention for individuals diagnosed with schizophrenia has developed out of the consistent finding that the emotional environment within a family was an effective predictor of relapse. In this context, 'family' includes people who have a significant emotional connection to the individual, such as parents, siblings and partners. Different models of family intervention aim to help families cope with their relative's problems more effectively, provide support and education for the family, reduce levels of distress, improve the ways in which the family communicates and negotiates problems, and try to prevent relapse by the service user. |
| Psychodynamic and psychoanalytic therapies | These therapies are based on psychodynamic and psychoanalytic theories of development and of the mind and include attention to unconscious as well as conscious mental processes. The approaches place emphasis on the importance of the therapeutic relationship, including transference and counter transference, how difficulties from the past can be repeated in the therapeutic relationship as well as in current relationships and therefore understood and changed. Modern psychodynamic therapies include mentalisation based treatments which draw heavily from attachment theory and aim to promote reflective functioning, the capacity to be aware of the mental states of self and others. |
| Psychoeducation | Psychoeducational interventions include any discrete programme involving interaction between an information provider and service users or their carers which has the primary aims of offering information about the condition and the provision of support and management strategies. The current guideline refers to psychoeducation that is offered as a specific intervention, as distinct from the provision of good quality and accessible information to all people with schizophrenia and their carers which is considered to be a requirement of good standard care. |
| Social skills training | Social skills training is a structured psychosocial intervention that aims to enhance social performance and reduce distress and difficulty in social situations. Interventions include behaviourally-based assessments of a range of social and interpersonal skills and place importance on both verbal and non-verbal communication, the individual's ability to perceive and process relevant social cues, and respond to and provide appropriate social reinforcement. The current guideline does not include vocational and supported employment-based interventions within the definition of social skills training. |

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