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Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology

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Abstract

These guidelines from the British Association for Psychopharmacology address the scope and targets of pharmacological treatment for schizophrenia. A consensus meeting, involving experts in schizophrenia and its treatment, reviewed key areas and considered the strength of evidence and clinical implications. The guidelines were drawn up after extensive feedback from the participants and interested parties, and cover the pharmacological management and treatment of schizophrenia across the various stages of the illness, including first-episode, relapse prevention, and illness that has proved refractory to standard treatment. The practice recommendations presented are based on the available evidence to date, and seek to clarify which interventions are of proven benefit. It is hoped that the recommendations will help to inform clinical decision making for practitioners, and perhaps also serve as a source of information for patients and carers. They are accompanied by a more detailed qualitative review of the available evidence. The strength of supporting evidence for each recommendation is rated.

Keywords

Antipsychotics, evidence-based guidelines, relapse prevention, schizophrenia, treatment

Introduction

Clinical expertise in choosing and managing drug therapy for an individual patient involves an understanding of the research evidence concerning the efficacy, effectiveness and efficiency of the options, balanced with consideration of the patient's clinical circumstances, and their preferences and attitudes (Haynes et al., 2002; Morris, 2002; Woolf et al., 1999). Our hope is that these guidelines can support the implementation of evidence-based research findings into clinical practice by improving such understanding, specifically, providing an up-to-date summary of evidence regarding the benefits and risks of pharmacological interventions and highlighting areas of current uncertainty. The robustness and reliability of the evidence underlying each recommendation is indicated, and while most of the recommendations should be taken as applicable most of the time to the average patient, they do not reflect standards of care that should be rigidly adhered to; there will be occasions when unthinking observance could do more harm than good (Woolf et al., 1999). Clinicians should consider the applicability of recommendations in clinical guidelines to each patient for whom they provide care, using them to guide rather than dictate practice.

A large number of treatment guidelines for schizophrenia already exist (Gaebel et al., 2005), but those presented here differ in a few respects. They draw upon randomized controlled trial (RCT) evidence but also a broad range of other published research and the clinical experience of a consensus group. They identify areas of uncertainty where the evidence regarding particular clinical issues is not yet adequate to allow confident practice recommendations. In addition, these guidelines seek to address some areas of practice not commonly covered, such as treatment for prodromal presentations and during pregnancy and breast feeding, drug treatment for target symptoms such as persistent negative symptoms or aggression and pharmacotherapy options for treatment-resistant illness. However, they do not address rapid tranquillization, which is not specific to schizophrenia, and is fully addressed elsewhere (National Institute for Clinical Excellence, 2005; Pratt et al., 2008; Taylor et al., 2009b).

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Methodology

This document is the result of an initial meeting of a consensus group on 17 September 2008; the full membership of this group is provided in the Appendix. Brief presentations were made that reviewed key areas and highlighted recent data, with an emphasis on systematic reviews and RCTs. These were followed by a discussion among members of the group of the important issues, in order to identify areas where consensus could be reached as well as areas of uncertainty. A literature review was then assembled formally to confirm and justify the consensus points. This review together with recommendations and their strength, based on the level of evidence, were circulated to participants and other interested parties. Their feedback was, as far as possible, incorporated into the final version of the guidelines.

Identification of relevant evidence

All of the consensus points and the guideline recommendations can be linked to relevant evidence through the literature review. However, our methodology did not allow for a systematic review of all possible data from primary sources. Existing systematic reviews and RCTs were identified primarily from PubMed, Medline, Embase and PsycINFO searches.

In making recommendations that will be of practical value to clinicians who treat patients with schizophrenia, we refer to the consensus view of the evidence reviewed in this document. Clinical practice guidelines developed by other groups and organizations have also been considered, although our conclusions are not always directly in accord with these. This is largely a consequence of placing different weightings on the available evidence, and more likely to occur where the evidence itself is less than convincing.

Strength of evidence and recommendations for guidelines

Categories of evidence for causal relationships (including treatment) and grading of recommendations are taken from the methodology of the North of England Evidence-Based Guideline Development Project, undertaken by the Centre for Health Services Research, University of Newcastle upon Tyne and the Centre for Health Economics, University of York (Shekelle et al., 1999).

Evidence categories

Categories of evidence for causal relationships and treatment

(I) Evidence from meta-analysis of RCTs, at least one large, good quality, RCT or replicated, smaller, RCTs.
(II) Evidence from small, non-replicated, RCTs, at least one controlled study without randomization or evidence from at least one other type of quasi-experimental study. RCTs must have an appropriate control treatment arm; for primary efficacy this should include a placebo condition.
(III) Evidence from non-experimental descriptive studies, such as uncontrolled, comparative, correlation and case–control studies.
(IV) Evidence from expert committee reports or opinions and/or clinical experience of respected authorities.

Proposed categories of evidence for non-causal relationships

(I) Evidence from large representative population samples.
(II) Evidence from small, well-designed, but not necessarily representative samples.
(III) Evidence from non-representative surveys, case reports.
(IV) Evidence from expert committee reports or opinions and/or clinical experience of respected authorities.

Strength of recommendations

The strength of our recommendations are graded A to D, as described below. Where there was a need to extrapolate from limited available evidence or clinical opinion, the recommendations have a weaker grading (B, C or D), although they may still cover key areas of practice. Extrapolation may have been necessary because the available evidence was indirect, only partially covered the area of practice under consideration, had methodological flaws or was inconsistent. Where recommendations were predominantly derived from a consensus view, in the absence of valid, systematic evidence, they are graded as S (standard of good practice).

(A) Directly based on category I evidence.
(B) Directly based on category II evidence or extrapolated recommendation from category I evidence.
(C) Directly based on category III evidence or extrapolated recommendation from category I or II evidence.
(D) Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence.
(E) Standard of good practice.

Scope and target of the guidelines

The content of these guidelines is relevant for all prescribers treating patients with schizophrenia. We expect that in most cases these will be doctors who are specialists in psychiatry. However, the guidelines were written with an eye also to informing general practitioners, patients and their families, and other healthcare providers with an interest in the care of people with schizophrenia.

Early intervention: Prodromal/'at-risk' mental states

Incidence

The incidence of schizophrenia, relatively low at around 15 per 100,000 population a year (Saha et al., 2005) has long been held to be relatively similar worldwide, reflecting an apparent genetic aetiology. However, considerable

heterogeneity in the incidence of psychoses has now been observed (McGrath et al., 2008), related to variation in a range of factors including urban or rural setting, the level of local social capital (social cohesion and trust), and perhaps most dramatically, the proportion of migrants, a group who appear to be at greater risk compared with native populations (Cantor-Graae and Selten, 2005; Coid et al., 2008; Kirkbride et al., 2008). Data from the three-centre ÆSOP study, for example, which was one of the largest Medical Research Council (MRC)-funded studies of psychosis epidemiology, revealed an incidence for all psychotic disorders of around 30 per 100,000 person-years, the bulk of which was non-affective psychosis within the schizophrenia definition. In contrast to the commonly accepted male–female ratio of 1.4:1 (Saha et al., 2005), the condition was found to be twice as common in men (Kirkbride et al., 2006).

There is also evidence that risk factors for later illness may be evident in childhood. For example, in a study of a normal population of 6000 young boys (Jones et al., 1994), the boys were classified on the basis of whether they could toddle without support at 9 months, 10 months, 11 months or 12 months. The cumulative incidence of schizophrenia in adult life in these four groups was found to increase progressively with the age of learning to stand without support. The findings suggest that the less efficient the development of motor coordination, the greater the risk that, as an adult, an individual may develop schizophrenia. One interpretation is that there are common pathophysiological mechanisms between early developmental processes and adult cognitive function and schizophrenia.

Classification of the prodromal/'at-risk' mental state

The prodrome is a classic area of uncertainty, partly because it has only been the subject of careful research in the last 10 years or so. Definitions vary, but there are two major forms of categorization. The PACE (Personal Assessment and Crisis Evaluation Clinic) (Yung et al., 1998) and COPS (Criteria of Prodromal Syndromes) (Miller et al., 2002) criteria, commonly used in English-speaking countries, focus on what are called attenuated positive symptoms, essentially the positive symptoms that are seen in frank psychotic illness, but less severe. These criteria can also be fulfilled if there is a major recent decline in function in someone who has a schizotypal personality disorder, or a family history of psychosis. People with this syndrome are said to have an 'at-risk' mental state for psychosis, or to be at Ultra High Risk of psychosis. The German research field has developed a different approach, focusing more on subjective cognitive disturbances (termed Basic symptoms) than positive symptoms (Haefner et al., 2004; Klosterkötter et al., 2001). This work suggests that subjective disturbances in thinking, language and attention are predictive of later psychosis, but that this is not such an imminent risk as with other criteria. Early studies showed that both the PACE and COPS, and the Basic symptoms criteria, are associated with a high risk (20–40%) of progression to frank psychosis within 2 years, although rates vary between studies and some centres have reported lower rates in subsequent studies. The term 'At-risk Mental State' or 'Ultra High Risk' is therefore more appropriate than 'prodrome', as the majority of subjects will not progress to a major psychotic disorder.

Antipsychotic medication

The potential objectives of pharmacotherapy in cases that come under the care of clinical services at this early stage are threefold. First, for those individuals who are seeking help for their presenting symptoms (such as attenuated psychotic symptoms), very low-dose antipsychotic medication can be considered for short-term symptom relief, although such a prescription would be 'off-label' in terms of indication, and there are only limited trial data to inform dosage. In general, the dosages of antipsychotics prescribed for people with an At-risk Mental State are even lower than those used in first-episode psychosis, as affected individuals tend to be exquisitely sensitive to both the therapeutic effects and adverse effects of such medication (McGlashan et al., 2006; McGorry et al., 2002; Ruhrmann et al. 2007). However, individuals with an At-risk Mental State are often reluctant to take medication, and frequently express a preference for psychological intervention (Broome et al., 2005). There is preliminary evidence that both low-dose antipsychotics and cognitive behavioural therapy (CBT) can improve presenting symptoms (Ruhrmann et al., 2007; Woods et al., 2003, 2007). Only one trial has examined the combined effect of an antipsychotic plus CBT (McGorry et al., 2002). The potential for psychopharmacological interventions to facilitate the therapeutic effects of psychological treatment thus remains largely unexplored.

The second potential objective is to delay, prevent or reduce the severity of the onset of a psychotic illness. The findings of a few clinical trials (Larson et al., 2010; McGlashan et al., 2006; McGorry et al., 2002; Morrison et al., 2004) suggest that this may be possible with either low-dose antipsychotic drugs or CBT, but fall short of providing convincing evidence, as they were all modest in size (typically around 60 subjects per group), with short-term follow-up. Longer-term follow-up in two of these trials suggested that transition rates returned to high rates in the experimental groups after the treatment envelope ended (Morrison et al., 2007; Phillips et al., 2007). Ongoing multi-centre trials with much larger patient samples should be more definitive.

The third objective for treatment is to intervene as soon as psychosis develops, in order to improve the subsequent outcome. If subjects at high risk have already been engaged by mental health services before the onset of illness, the delay between the onset of frank psychosis and the initiation of treatment can be substantially reduced. For example, in South London the mean duration of untreated psychosis (DUP) in patients who developed psychosis after presenting to a service for people with an At-risk Mental State was 10 days, as compared with 12 months in patients whose first contact with mental health services was after the onset of illness (Valmaggia et al., 2009). This may account for the lower rates of hospital admission and compulsory treatment in the former group (Valmaggia et al., 2009). Whether earlier treatment improves the long-term outcome

remains controversial (Melle et al., 2008), but may be clarified by long-term, follow-up studies of those patients who developed psychosis after first presenting with prodromal symptoms.

Antidepressants

Data are also available as to whether antidepressants in the At-risk Mental State are effective, although to date these have been derived from clinical audits rather than clinical trials. Cornblatt et al. (2007) reported a very low risk of transition to psychosis in individuals with high-risk features who had been treated with antidepressants, as opposed to antipsychotics. Similar findings emerged from an audit of treatment in at-risk subjects in the UK (Fusar-Poli et al., 2007). However, it is unclear whether these low rates of transition are attributable to an effect of the drug treatment or reflect factors that might lead a clinician to choose an antidepressant as opposed to an antipsychotic or psychological treatment for someone with an At-risk Mental State.

Antidepressants and antipsychotics may also play a role in the treatment of comorbid depression and anxiety in this group, which is common (Broome et al., 2005). In clinical trials, antipsychotic treatment has been associated with an improvement in both depressive and anxiety symptoms in the At-risk Mental State (Ruhrmann et al., 2007; Woods et al., 2007).

Recommendations for the At-risk Mental State

- Encourage a therapeutic relationship to allow for further assessment, review, 'watchful waiting' and monitoring of symptoms. (S)
- Assess the nature and impact of any substance use (see the section below on 'Pharmacological strategies for comorbid substance misuse'). (S) Substance use in this group is not common and rarely leads to diagnostic confusion. There is no evidence that it has any effect on the risk of transition to psychosis.
- If antipsychotic medication is considered for symptom relief in the prodromal phase of the illness:
  - This should be treated as off-label prescribing. (S)
  - The prescription should be treated as a short-term, individual trial. (D)
  - Very low doses should be used. (D)
  - Symptom response should be monitored. (D)
  - Side effects should be carefully monitored. (D)
  - It should be prescribed by specialist psychiatric services, such as an early intervention team. (D)
- Individual CBT can be considered to be an acceptable alternative to drug treatment on the preliminary evidence available. (D)

Key uncertainties

- The value of antipsychotic medication in preventing or delaying the onset of psychotic illness.
- The value of antidepressants in reducing the risk of developing psychosis.
- The appropriate duration of treatment.
- The potential risk of stigma and self-stigmatization in prodromal/'at-risk' individuals prescribed antipsychotic medication (Corcoran et al., 2005; Corrigan et al., 2006).

First-episode psychosis

Diagnosis

Early intervention services are generally designed for first-episode psychosis, as opposed to first-episode schizophrenia or bipolar disorder, as there is often a blurring of affective and non-affective psychotic features in the early stages. A definitive diagnosis of the type of psychotic disorder is frequently postponed until 12 months or so after initial presentation, by which time differences in psychopathology and course will have emerged. Typically, within a first-episode psychosis sample, around 25% have bipolar disorder or psychotic depression, and only 30–40% will meet criteria for schizophrenia at presentation, although this latter proportion will increase over time (Singh et al., 2004; Yung et al., 2003). Schwartz et al. (2000) noted that diagnostic changes in psychosis over the 2 years after first presentation may reflect the evolution of an illness, the emergence of new information, or unreliability of measurement. Further, a definitive diagnosis using formal diagnostic criteria may be deferred as these include temporal criteria. DSM-IV diagnostic criteria for schizophrenia include continuous signs of the disturbance for at least 6 months, including at least 1 month of symptoms, and for ICD-10 diagnosis, symptoms must be clearly present for most of the time during a period of 1 month or more.

Response to antipsychotic medication

The ethos of early intervention services for first-episode psychosis is to reduce DUP, and to provide high-quality pharmacotherapeutic, psychological and psychosocial interventions in the critical early phase of the disorder (International Early Psychosis Association Writing Group, 2005). The rationale for such an approach is that people are accessed at a relatively treatment-responsive stage of illness, and the possible adverse consequences of a putative active morbid process associated with untreated psychosis may be minimized by early treatment, thus improving symptomatic and functional outcomes (Marshall et al., 2005; Perkins et al., 2005). Whether treatment with antipsychotic medication at first episode can prevent the progressive structural brain changes associated with psychotic illness remains uncertain, despite some early positive findings (Li and Xu, 2007; Lieberman et al., 2005b, 2008). However, antipsychotics are usually clinically effective in this context (Robinson et al. 2005), in that change in clinical symptoms can be appreciated shortly after starting such medication; non-response to antipsychotic medication in the first few weeks may be a predictor of eventual non-response (Correll et al., 2003; Derks et al., 2010; Jäger et al., 2009; Kinon et al., 2008a, 2010). The subsequent trajectory of response varies considerably between

patients (Lambert et al., 2008; Levine and Rabinowitz, 2010). However, the evidence is reasonably consistent that only a proportion of patients will achieve a sustained symptomatic and functional recovery during the first couple of years of the illness (Emsley et al., 2006; Malla et al., 2006; Robinson et al., 2006; Simonsen et al., 2010).

Lambert et al. (2008) assessed remission and recovery over 3 years in a cohort of 392 previously never-treated patients with schizophrenia. More than 90% were prescribed a second-generation antipsychotic (SGA) as first-line treatment. Approximately 60% of the patients in this cohort were in symptomatic remission for at least 6 months, and 52% in symptomatic recovery for at least 2 years. Only 14% never fulfilled any of the remission criteria. The European First Episode Schizophrenia Trial (EUFEST) (Kahn et al., 2008) was an open, RCT conducted in 50 sites in 14 countries. It tested the first-generation antipsychotic (FGA) haloperidol and several SGAs in first-episode schizophrenia and schizophreniform disorder. Mean symptomatic improvement (measured by total PANSS score) was more than 60%, and neither this nor rates of admission to hospital differed significantly between the drug groups. However, the patients assigned to amisulpride, olanzapine, and ziprasidone showed higher response and remission rates when compared with patients on low doses of haloperidol (Boter et al., 2009). A double-blind RCT by Sikich et al. (2008) compared the efficacy and safety of two SGAs, risperidone and olanzapine, with those of an FGA, molindone, over 8 weeks, in 116 patients with early-onset schizophrenia or schizoaffective disorder. No evidence of differential efficacy between the three antipsychotics was observed, but differences were noted in the drug side effect profiles, with more akathisia associated with molindone, and metabolic side effects being more common with risperidone and olanzapine. Similarly, in a single blind RCT of two SGAs in first episode schizophrenia, Gafoor et al. (2010) found no differences in efficacy or adverse effects.

No double-blind trial comparing an SGA with an FGA in the acute treatment of first-episode schizophrenia has shown an efficacy advantage for the SGA, with the single exception of a head-to-head, first-line treatment trial of clozapine versus chlorpromazine conducted in China which showed a small, significant advantage to clozapine (Lieberman et al., 2003a, 2003b). A meta-analysis of RCTs in the early phase of psychosis found no differences between the FGAs and SGAs tested, in terms of acute symptomatic change or long-term discontinuation (Crossley et al., 2010). However, there were differences in side-effects profiles, with a greater risk of weight gain for patients prescribed SGAs and a greater risk of extrapyramidal symptoms (EPS) in those treated with FGAs, most commonly haloperidol.

These results challenge the almost exclusive use of SGAs for the treatment of first-onset schizophrenia and schizoaffective disorder. The safety findings related to weight gain and metabolic problems (Alvarez-Jiminez et al., 2008a; Tschoner et al., 2007) raise important public health concerns, given the widespread use of SGAs in youth for non-psychotic disorders. Monitoring for metabolic disturbance may be important within the first 8 weeks of treatment, as such changes can occur early in antipsychotic treatment (Kelly et al., 2008; Zhang et al., 2004).

Given that the choice of antipsychotic medication for first-episode patients cannot, by definition, be based on known individual response to past medication, treatment recommendations tend to rest on research findings. The findings of the clinical trials discussed suggest that rates of short-term remission are high with antipsychotic treatment using both symptomatic and functional criteria (Wunderink et al., 2008). There is little to suggest any convincing superiority for any particular antipsychotic or group of antipsychotics. However, the inclusion in the study samples of various proportions of people who have been treated previously, although still experiencing their first episode, and the range of definitions of remission used, limit the generalizability of the findings to clinical practice.

Dosage

There is evidence that first-episode psychosis responds to lower doses of antipsychotic medication than those required for the treatment of established schizophrenia, even when stringent criteria for response are applied (Crespo-Facorro et al., 2006; Robinson et al. 1999; Schooler et al., 2005). There is a biological sensitivity to such medication in the early stages of the illness which applies to both the therapeutic effects and the adverse effects. Thus, there is a consensus that clinicians should use the lowest recommended dosage of an antipsychotic when initiating medication in an individual presenting with their first episode of psychosis (Lehman et al., 2004; Spencer et al., 2001; Taylor et al., 2009b).

As little difference has emerged between individual antipsychotic drugs used for first-episode psychosis, the selection of an antipsychotic drug will be more dependent on the side effect profiles as far as these are known, and the perceived susceptibility to, and tolerability of, particular side effects in the individual to be treated. Minimizing adverse effects, such as extrapyramidal and aversive subjective side effects, is particularly important at this stage given that they can be a short-term disincentive for medication adherence and have an impact on attitudes to drug treatment and mental health care over the longer term (Perkins et al., 2008; Robinson et al., 2002).

Continuation of antipsychotic medication

A key clinical question is how long antipsychotic medication should be maintained after the first episode, when the illness is in remission. Given the absence of reliable predictors of prognosis or drug response, consensus guidelines recommend continued antipsychotic medication for every patient diagnosed with schizophrenia for 1–2 years (Buchanan et al., 2010; National Institute for Health and Clinical Excellence, 2009b). Placebo-controlled trials with FGAs in first-episode samples have consistently demonstrated a substantial advantage for active medication in the prevention of relapse (Crow et al., 1986; Hogarty and Ulrich, 1998; Kane et al., 1982; Robinson et al., 2005) and the same was found to be true in a placebo-controlled RCT of the SGA quetiapine (Chen et al., 2010). There is no doubt that antipsychotic discontinuation is

strongly associated with relapse during this period (Robinson et al., 1999).

The MESIFOS study (Wunderink et al. 2007) provides support for the recommendation of maintaining antipsychotic medication for at least 18 months. This randomized, open study tested an antipsychotic discontinuation strategy against a maintenance treatment regimen in a sample of people with first-episode schizophrenia in remission, with a follow-up of 18 months. The findings suggested that only a small proportion of such patients can be successfully withdrawn from antipsychotic medication without relapse.

Recommendations for first-episode schizophrenia

- If the onset of psychosis is suspected in primary care, the person should be referred to specialist mental health services, ideally an early intervention in psychosis service if this is available. (S)
- Assess the nature and impact of any substance use (see the section below on 'Pharmacological strategies for comorbid substance misuse'). (S)
- Choice of first-line antipsychotic drug should be based on:
    - The evidence for relative liability for side effects, particularly considering common and serious effects such as extrapyramidal motor syndromes and metabolic problems. (B)
    - Individual patient preference. (S)
    - Individual patient risk factors for side effects. (B)
    - Relevant medical history. (S)
- Antipsychotic medication should be initiated at the lower end of the licensed dosage range. (A)
- An individual trial of the antipsychotic of choice should be conducted:
    - The indications for oral antipsychotic medication, the expected benefits and risks, and the anticipated timeframe for improvement of symptoms and emergence of side effects should be considered and documented. (S)
    - Dosage titration should be within the dose range identified in the British National Formulary (BNF) or Summary of Product Characteristics (SmPC), and conducted gradually, based on the response of symptoms or behaviour and the nature and tolerability of side effects. (S)
    - The results of symptom and side effect review should be documented in the clinical records, with the rationale for any change in medication or its continuation. (S)
    - Aim to achieve an adequate trial: optimum dosage with good adherence for 4 weeks. (A)
    - If an FGA is selected, this probably should be a medium- or low-potency drug rather than a high-potency drug. (S)
- Following antipsychotic drug initiation, side effects should be closely monitored with regular, systematic and comprehensive assessment. Consideration should be given to the use of formal side effect checklists or rating scales. (B)

Key uncertainties

The place of antipsychotic depot/long-acting injections for first-episode schizophrenia remains uncertain (Heres et al., 2010). Non-adherence is a particular problem in this group; ironically, this is sometimes a consequence of the relatively good response to first treatment, as well as a wish of some patients to regard the episode as a brief one-off event. However, evidence on the efficacy, acceptability and tolerability of depot medication in first-episode patients is rather limited (Emsley et al., 2008; Kim et al., 2008; Weiden et al., 2009). There is an absence of long-term data comparing depot preparations with oral medication after first-episode psychosis, and its use may appear somewhat counter to the ethos of early intervention services. Only a small proportion of clinicians offer a depot preparation after a first psychotic episode (Jaeger and Rossler, 2010).

Acute psychotic episode

Placebo-controlled clinical trials with antipsychotic medication in the acute phase of schizophrenia have consistently demonstrated that the active drug is significantly more effective (Davis and Garver, 1978; Fleischhacker, 1999). The efficacy of antipsychotics in schizophrenia is not in doubt, with a systematic review and meta-analysis of 38 RCTs that compared SGAs with placebo in schizophrenic patients revealing a moderate effect size of around 0.5 and a number needed to treat (NNT) of 6 for response (Leucht et al., 2009a). With regards to differences in efficacy, the National Institute for Health and Clinical Excellence (2009b) analysed data from 72 RCTs involving 16,556 participants with an acute exacerbation or recurrence of schizophrenia, and found little evidence of clinically significant differences in efficacy between the oral antipsychotic drugs examined. Leucht et al. (2009b) also examined randomised, blind studies comparing two or more SGAs in the treatment of schizophrenia. Their analysis of 78 relevant studies with 167 relevant arms and 13,558 participants revealed olanzapine to be modestly superior to aripiprazole, quetiapine, risperidone, and ziprasidone, while risperidone was more efficacious than quetiapine and ziprasidone. These differences reflected improvement in positive rather than negative symptoms. The investigators concluded that in clinical practice the choice of antipsychotic in an individual patient should take account of differences in side effect profiles and cost in addition to any small efficacy superiorities, a conclusion echoing that of Tandon et al. (2008) who had similarly reviewed a large number of eligible RCTs.

Meta-regression in the analysis of placebo-controlled RCTs of SGAs by Leucht et al. (2009a) showed a decline in treatment response over time, and the investigators interpreted the funnel plot as possibly reflecting publication bias. Heres et al. (2006a) reviewed the results of head-to-head studies funded by pharmaceutical companies that had directly compared SGAs, and found that in 90% the reported overall outcome favoured the sponsor's drug. The potential sources of bias identified in this review, such as choice of dose ranges, study entry criteria and study populations, were considered to be subtle and remediable in future studies. However, a later meta-analysis of 150 double-blind studies comparing SGAs

versus FGAs for schizophrenia (Leucht et al., 2009c) failed to find any consistent effect of industry sponsorship as a moderator variable. A similar meta-analysis by Davis et al. (2008) of 124 RCTs found no evidence that industry sponsorship influenced the findings in relation to the relative efficacy of SGAs versus FGAs.

Early response

A key pharmacologic property of antipsychotic drugs is that they block the effects of dopamine at D2 receptors, a consistent level of dopamine blockade being achieved within a few days of starting treatment. However, studies such as that by Johnstone et al. (1978) suggested a delay of 2–3 weeks between the start of medication administration and the appearance of specific therapeutic benefits. Such findings may have partly reflected the sensitivity to change of the symptom rating scales used. Nevertheless, the notion of delayed onset has been pervasive and influential on hypotheses regarding the mechanism of action of antipsychotics. However, Agid et al. (2003) tested this premise in a meta-analysis of 42 double-blind, controlled trials of antipsychotic response during the first 4 weeks of treatment. The findings suggested that antipsychotic response begins within the first week of treatment and is cumulative over the subsequent weeks. In a multi-centre, double-blind, placebo-controlled study Kapur et al. (2005) tested how early this response might be evident; 311 patients with an acute episode of schizophrenia were randomly assigned to olanzapine (10 mg IM), haloperidol (7.5 mg IM) or intramuscular placebo. Definite improvement in psychotic symptoms was observable within the first 24 hours. Looking more closely at the dimensions of psychosis that show changes over the first few weeks of treatment, Mizrahi et al. (2006) and Menon et al. (2008) reported an early reduction of the behavioural impact of the principal psychotic symptom and decreased cognitive and emotional preoccupation, while the conviction or perspective about psychotic experience took longer to respond.

Analysis of relevant clinical trial data suggests that more improvement is seen within the first 2 weeks than in any subsequent 2-week period, and the bulk of improvement over the first year occurs in the first month (Agid et al., 2003, 2006). More specifically, response at two weeks has been found to predict subsequent response with 80% negative predicted value, which means that if an individual patient's symptoms have not shown a 20-25% improvement in symptom score after two weeks at an appropriate dosage, it is very unlikely that there will be a good clinical response to that particular drug (Ascher-Svanum et al., 2008; Chang et al., 2006; Correll et al., 2003; Kinon et al., 2008a; Leucht et al., 2007a; Lin et al., 2007). However, a study examining response and remission in patients with severe schizophrenia illness, found that lack of response by the fourth week, rather than within 2 weeks, was predictive for later non-response (Lambert et al., 2009).

Therapeutic response in clinical trials is usually defined in terms of a percentage change in total score on a psychopathological rating scale, which raises the question of how readily detectable such a change is in clinical practice if such scales are not being used. Nonetheless, the implication of these findings is that an early assessment of response to medication is worthwhile. Careful monitoring is required as symptoms fluctuate and evolve over the initial weeks, and before any change in medication is considered, time should be taken to optimize treatment with the current medication, ensuring an adequate trial in terms of dose, duration and adherence. There is no evidence that dosages above the recommended range have any advantage in the treatment of acute psychotic episodes (Davis and Chen, 2004; Kinon et al., 2008b; Mace and Taylor, 2009; Royal College of Psychiatrists, 2006; Sparshatt et al., 2009). The optimal dose for most antipsychotic drugs is below the recommended maximum, and for some drugs, such as risperidone and sulpiride, may be as little as a third of the upper limit of the licensed range (Gardner et al., 2010). It therefore follows that for the majority of patients the target dose for both acute treatment and maintenance is likely to be below the recommended maximum (Davis and Chen, 2004, Gardner et al., 2010).

Recommendations: Acute psychotic episode

- Choice of antipsychotic drug should be based on the same criteria as suggested for first-episode, but should additionally take into account:
  - Any preference a patient may have for particular antipsychotic medication. (S)
  - A patient's past experience of individual antipsychotic drugs in terms of relief of symptoms and side effects, including aversive subjective experiences. (S)
- Seek to conduct an adequate trial of the chosen antipsychotic drug in terms of dosage, duration (up to 4 weeks at optimum dosage) and medication adherence. (A)
- Dosage should be titrated against side effects and efficacy. If starting an antipsychotic that the person has not previously been prescribed, the initial dosage should be at the lower end of the licensed range and slowly titrated upwards, if indicated, to the optimal range for that drug, and not exceeding the maximum licensed dose given in the BNF or SmPC. (S)
- Initial loading doses ('rapid neuroleptization') should not be used. (B)
- The justification for dosages outside the range given in the BNF or SmPC should be documented in the clinical records. (S)
- Regular combined antipsychotic medication should not be prescribed routinely, except for short periods when switching from one antipsychotic to another. (B)
- Anticholinergic agents should not be prescribed prophylactically with antipsychotic medication, but rather their use for emergent extrapyramidal problems responsive to such medication (e.g. Parkinsonism and acute dystonia) should be determined on an individual basis, taking account of factors such as the patient's history of extrapyramidal side effects and the risk of anticholinergic side effects.
- The potential impact of comorbid substance use on the therapeutic efficacy and side effect risk should

be considered. This should be discussed with patients and carers as appropriate. (S)

- Regular review of the medication regimen should address the following:
  - Therapeutic efficacy, in terms of change in clinical domains such as symptoms, behaviour and cognition. (S)
  - Side effects of treatment. (S)
  - Medication adherence. (S)
  - Physical health. (S)
  - The need to continue, change or stop medication, and the implications of the decision taken. (S)
- The requirement for PRN ('as required') prescriptions should be regularly reviewed in relation to the clinical indications, frequency of administration, therapeutic benefits and side effects, and cumulative dosage. (S)

Maintaining response

Switching antipsychotic medication

In light of a poor response, or concern about side effects, one option is to switch to another antipsychotic. Clinicians tend to switch more often than they add another antipsychotic (Bitter et al., 2008; Kreyenbuhl et al., 2007). In a naturalistic, 1-year study of outpatients with schizophrenia, Faries et al. (2009) found that switching antipsychotic medication was relatively common, occurring in approximately one-third of patients, in line with the findings of other studies (Weiden, 2006). This is despite a relatively limited evidence base for such a strategy (Kinon et al., 1993; Weiden, 2006).

In the study by Faries et al. (2009), mentioned above, those individuals who switched antipsychotics showed poorer clinical and economic outcomes, as reflected by significantly more frequent and earlier use of a range of acute care services, than their counterparts who had remained on their initial medication regimens. This may be partly a consequence of the risk of destabilization of the illness and provocation of adverse effects following a switch (Essock et al., 2006). Such problems are potentially attributable to discontinuation of the original drug, response to the second antipsychotic and/or differences between the pharmacological profiles of the two drugs (Lambert, 2007; Weiden et al., 2007). For example, a patient switched from an antipsychotic with high antimuscarinic activity to one with low activity may have a greater risk of cholinergic rebound phenomena. To at least partly obviate such problems, gradual cross-taper of the dosages of the two antipsychotics is usually recommended rather than an abrupt switch (Lambert, 2007; Weiden et al., 2007), although there seems to be little empirical evidence to support any particular switching strategy (Remington et al., 2005; Takeuchi et al., 2008).

Older, controlled studies of switching antipsychotics in patients with an acute relapse of schizophrenia that had failed to respond to an initial course of standard antipsychotic therapy (Kinon et al., 1993; Shalev et al., 1993) yielded inconsistent results, partly related, perhaps, to the use of different criteria for response. Leaving aside studies involving clozapine, most subsequent studies of switching antipsychotics have been uncontrolled, with no comparison group who remained on their antipsychotic medication unchanged, and generally the findings have not suggested a high likelihood of a clinically relevant improvement following a switch in antipsychotic (Lindenmayer et al., 2002). Such studies have tested the effect of switching between oral antipsychotics (e.g. Alptekin et al., 2009; Lamo et al., 2005; Simpson et al., 2008) or to long-acting injectable risperidone (e.g. Fleischhacker et al., 2003; Kim et al., 2009; Lamo et al., 2005; Suzuki et al., 2007; Taylor et al., 2004). The Clinical Antipsychotic Trials of Intervention Effectiveness schizophrenia trial (CATIE) (Lieberman et al., 2005a) was a pragmatic study in which patients were randomly assigned to one of five oral antipsychotics, with a primary outcome of time to all-cause discontinuation. Most of the participants had been receiving antipsychotic medication prior to randomization, which allowed a comparison of those patients randomly assigned to stay on the same antipsychotic with those assigned to a different antipsychotic. Conducting such an analysis, Rosenheck et al. (2009) found that switching to a new antipsychotic yielded no significant advantage in terms of symptoms, neurocognition, depression, quality of life, neurological side effects or costs, except that those randomly assigned to olanzapine gained weight, whether or not they had been receiving olanzapine before randomization.

Continuing medication for relapse prevention

For the majority of first-episode patients treated with an antipsychotic there will be a satisfactory response to antipsychotic medication within 4 weeks, and the aims of continued prescription of an antipsychotic are to prevent relapse, maintain long-term control of symptoms and behaviour and improve quality of life, with minimal adverse effects. One goal is to facilitate engagement in psychosocial treatment; there is evidence that those individuals achieving greater improvement in symptoms with optimal pharmacotherapy can derive greater benefit from psychosocial interventions such as social skills training, CBT, cognitive remediation and social cognition training (Dixon et al., 2010; Hogarty et al., 1979; Kern et al., 2009; Marder et al., 2003; Rosenheck et al., 1998). For example, Guo et al. (2010) compared antipsychotic medication alone with antipsychotic medication combined with psychosocial intervention (psychoeducation, family intervention, skills training and CBT) over a year, in a sample of patients with early-stage schizophrenia. Treatment with the combination was associated with several significant advantages: a lower rate of treatment change or discontinuation, a lower risk of relapse, and improved insight, quality of life and social functioning.

Investigators in the Schizophrenia Outpatient Health Outcomes (SOHO) study (Novick et al., 2009) followed a large outpatient cohort study over 3 years. Analysis of the follow-up data on 6642 patients showed that long-lasting symptomatic remission had been achieved in a third (33%), just over a quarter (27%) had long-lasting adequate quality of life and 13% achieved long-lasting functional remission. Medium- to long-term cohort studies of this kind suggest that around 20% of people diagnosed with schizophrenia show complete recovery and, overall, 40% regain good social functioning, with 16% of early unremitting cases

achieving late phase recovery (Crumlish et al., 2009; Gaebel and Frommann, 2000; Harrison et al., 2001; Harrow et al., 2005; Hopper and Wanderling, 2000). It is uncertain to what extent a better long-term prognosis might be mediated by effective prevention of relapse. Historical reviews of response rates reported over the 20th century before and after the introduction of antipsychotic drugs (Hegarty et al. 1994; Warner, 1994) suggest that this medication may make only a limited contribution to such outcomes.

Nevertheless, the critical questions are whether relapse is associated with deterioration of the illness, at least in some patients, and if so, whether reduction in the frequency of relapse with continued antipsychotic medication prevents such a decline. Follow-up studies show that a higher frequency of relapse is associated with poorer outcome (Curson et al., 1985a). This may simply reflect that relapse is more common in the context of a worse illness with an inherently poorer prognosis, but it may indicate that following relapse, i.e. a period of unchecked, untreated psychosis, recovery is compromised (Wyatt, 1997). Repeated relapse, often associated with poor medication adherence, seems to be associated with increased difficulty or delay in achieving remission (Leucht and Heres, 2006). In a 15-year follow-up study of the natural course of schizophrenic disorders, Wiersma et al. (1998) found that two-thirds of the participants experienced at least one relapse and after each episode the illness failed to remit in one of six participants.

There is substantial evidence from clinical trials in schizophrenia that both FGAs and SGAs can reduce the risk of relapse in patients whose illness has been stabilized (Kane, 2008; Leucht et al., 2003; Marder and Wirshing, 2003). In relation to the early years of treatment, Robinson et al. (1999) found that patients continued to relapse in the 5 years after starting treatment, and that medication discontinuation increased the risk of relapse 3–5-fold. Some of the strongest evidence comes from discontinuation studies in people with established schizophrenia. An analysis of 10 studies of chlorpromazine withdrawal found that stopping this antipsychotic increased the risk of relapse over the short and longer term (Almerie et al., 2008). Reviewing the available data, Davis (1985) calculated that while untreated schizophrenia had a constant relapse rate of approximately 10% per month, this was decreased 2.5- to 10-fold with maintenance antipsychotic treatment. Reviews of other relevant studies of FGAs have concluded that, over follow-up periods of up to 2 years, relapse of illness in those patients who have withdrawn from such drugs occurs in around 50%, while for people who have continued on medication it is about 15%. In other words, for those patients stopping antipsychotic medication the risk of relapse is 2–3 times greater than it would have been if they had stayed on it, and the risk of relapse is greater with abrupt discontinuation compared with a gradual withdrawal (Davis et al., 1993; Gilbert et al., 1995; Viguera et al., 1997). However, a review of antipsychotic withdrawal studies by Viguera et al. (1997) revealed that the rate of relapse tends to level off in the 6 months or so after drug discontinuation, with few subsequent occurrences. Indeed, a proportion of the patients withdrawn from medication were drug-free at follow-up for up to 4 years, and remained clinically stable (Boshes and Manschrek, 2002). Similarly, when Gilbert et al. (1995) reviewed studies of withdrawal of FGAs they found that while 16% of the patients remaining on maintenance treatment relapsed within a year, 50% of those discontinued from their antipsychotic did not. These observations highlight the heterogeneity of response to long-term antipsychotic medication in schizophrenia, and raise the question of whether there may be a small proportion of patients for whom such maintenance treatment may be unnecessary. However, looking at treatment studies in the early stages of the illness, the consensus is that there is not a substantial minority who can maintain recovery indefinitely without medication (Carpenter, 2001; Gitlin et al., 2001; Wunderink et al., 2007).

Choice of antipsychotic for relapse prevention. Only a relatively small number of longer-term, relapse prevention trials have been conducted, and the data are insufficient to allow assessment of the relative merits of individual antipsychotics. Leucht et al. (2003) reported a meta-analysis of the data from 10 relapse prevention studies comparing FGAs and SGAs in patients with established schizophrenia. There was a modest but statistically significant reduction in relapse rate with SGAs; the overall relapse rate with the 'high-potency' FGA haloperidol was 23% while the figure for SGAs was 15%. The extent to which this possible advantage might be partly mediated by improved medication adherence remains unclear. There were methodological problems with many of the trials, such as high drop-out rates, the use of only one FGA comparator drug (haloperidol) and the failure to systematically assess adherence. Further, the definition of relapse tends to vary from study to study (Leucht and Kane, 2006), although it commonly reflects exacerbation of positive symptoms or hospital admission. In general, such studies have failed to address the impact of maintenance antipsychotic treatment more broadly, and have not considered clinically relevant outcomes such as negative and affective symptoms, cognitive impairments, disability in social and occupational functioning and comorbid problems such as substance abuse, medical illness and medication side effects.

Of relevance here are the findings of three pragmatic trials of antipsychotic treatment (EUFEST, CATIE and CUtLASS1) which although they were not designed to address relapse prevention directly, are relevant to choice of antipsychotic treatment over the medium to longer term. In the EUFEST study (Boter et al., 2009; Kahn et al., 2008), already mentioned above, 500 participants with first-episode schizophrenia or schizophreniform disorder were assigned to receive either low-dose haloperidol or one of four SGAs. The primary effectiveness outcome was discontinuation of the assigned antipsychotic for any cause, although in a non-blind study such a measure might be open to clinician bias; for example, if the psychiatrists had low expectations for haloperidol they might be more likely to discontinue it than another antipsychotic in which they had more confidence (Volavka, 2008). The main finding was that treatment discontinuation over 12 months was significantly more common in patients assigned to low-dose haloperidol than

in those treated with the SGAs, with the lowest discontinuation occurring with olanzapine. Nevertheless, there were no significant differences in therapeutic efficacy between the treatment groups in terms of symptom severity. Predictable differences in drug side-effect profiles were found. Weight gain was relatively common, being greatest with olanzapine and least with haloperidol and ziprasidone. Extrapyramidal side effects were also seen: the incidence of Parkinsonism was highest with haloperidol, despite the low-dose regimen, while akathisia was most common with ziprasidone and haloperidol.

The CATIE study (Lieberman et al., 2005a) was a double-blind, treatment trial in established schizophrenia in the USA, comparing four SGAs and one 'medium-potency' FGA, perphenazine. This study also used all-cause discontinuation as the primary outcome measure. Amongst the 1493 participants, the assigned study antipsychotic was discontinued during the follow-up period in 60–80% of cases within the 18-month follow-up period. There was a significantly lower chance of discontinuation of olanzapine over any given period compared with the other antipsychotics being tested, but the discontinuation rate for perphenazine was similar to the other SGAs: quetiapine, risperidone and ziprasidone. There were no differences in the rates of emergent extrapyramidal side effects. Caveats relevant to the interpretation of the findings are that the maximum dose of olanzapine allowed was above the licensed upper limit (Citrome and Kantrowitz, 2009); olanzapine was associated with more discontinuation due to weight gain or metabolic effects while perphenazine was more often discontinued because of extrapyramidal side effects; and those participants with tardive dyskinesia were not assigned to perphenazine.

The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS1) (Jones et al., 2006) 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 1-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.

Also relevant are meta-analyses comparing SGAs head-to-head with FGAs. Leucht et al. (2009c) analysed data from 150 double-blind studies with 21,533 participants, comparing FGAs and SGAs, and found that certain drugs in the latter group (amisulpride, clozapine, olanzapine and risperidone) appeared to possess better overall therapeutic efficacy than FGAs, albeit with modest effect sizes. Other SGAs did not emerge as superior to FGAs, even for the treatment of negative symptoms. With regards to side effects, haloperidol was the most common FGA comparator in the studies, and even at low dose (less than 7.5 mg/day) had a greater propensity to induce EPS than the SGAs. However, where the FGA comparator was a 'low-potency' antipsychotic such as chlorpromazine and perphenazine, the difference in liability for EPS was not so evident. Gain in body weight was seen with the low-potency FGAs, and when the SGAs were compared with haloperidol, the greatest weight gain was observed with clozapine, olanzapine, sertindole and zotepine, intermediate weight gain occurred with quetiapine and risperidone, and amisulpride induced less, although aripiprazole and ziprasidone induced no significant weight gain.

Leucht et al. (2009d) reviewed the three pragmatic studies discussed above as well as the findings of their own meta-analyses, and concluded that SGAs could not be considered as a homogeneous class, a view which concurred with that of an earlier meta-analysis by Davis et al. (2003). In clinical practice, any evidence for slightly greater therapeutic efficacy for some of these drugs needs to be balanced against major differences in side effects and cost. Nevertheless, other investigators still consider SGAs generally preferable, citing their lower liability for tardive dyskinesia and improved subjective tolerability (Naber and Lambert, 2009). However, amongst all of the available antipsychotic drugs none has emerged as superior in preventing relapse. In practice, choice of maintenance treatment for the individual patient may be more a question of the correct dose and formulation than of drug group.

Antipsychotic dosage for maintenance treatment. The evidence for relapse prevention with antipsychotic medication derives largely from studies of antipsychotics within their recommended dosage ranges. There are no relevant studies with dosages above the licensed range. However, there are a few clinical trials examining low dosage in first-episode patients (e.g. Schooler et al., 2005), and some older studies testing low-dose FGAs, most of which used depot preparations in order to avoid covert adherence problems confounding the results (Hogarty et al., 1988; Johnson et al., 1987; Kane et al., 1983; Marder et al., 1984, 1987). A meta-analysis of six of these double-blind, RCTs by Barbui et al. (1996) concluded that continuous low-dose treatment (defined as 50–100 mg a day chlorpromazine equivalents) was less effective than standard dosage (200–500 mg a day chlorpromazine equivalents) at preventing relapse. A multi-centre, double-blind study by Kane et al. (2002) compared four different fixed doses (monthly injections of 25, 50, 100 or 200 mg) of the depot preparation haloperidol decanoate over 1 year. The group receiving 200 mg a month showed the lowest rate of symptomatic exacerbation (15%) with minimal increased risk of adverse effects or subjective discomfort in comparison to the 100 or 50 mg doses. Nevertheless, the rates of symptom worsening with the 100 mg (23%) and 50 mg (25%) dosage regimens were not significantly greater than that observed with 200 mg. These findings add to evidence suggesting that while the recommended dose range for haloperidol decanoate is 50–300 mg IM every 4 weeks, the optimally effective dose range for many patients may be 50–100 mg IM every 4 weeks (Taylor, 2005).

The results of these trials confirm the efficacy of standard dosages of antipsychotic medication for relapse prevention, but leave the optimal dosage ranges for the available antipsychotics undetermined. In people whose schizophrenic illness is treatment-responsive, in that acute and sustained symptom

relief is achieved with antipsychotic medication, Buchanan et al. (2010) interpreted the evidence as indicating that the dosage of FGAs as maintenance dosage should be between 300 and 600 mg chlorpromazine equivalents a day, while for non-clozapine SGAs the maintenance dosage should be the dose that effectively treated positive psychotic symptoms in the acute phase of treatment. Wang et al. (2010b) examined how long the dosage of maintenance treatment should be maintained at the level required for an initial therapeutic response, and the findings suggested that clinicians should be cautious about any reduction in dosage, at least within the first year or so of follow-up. A consistent finding from the low-dose studies was that with reduced dosage there was an increased risk of relapse over time. However, some advantages with lower dosages were reported, such as a lower incidence of EPS.

Another treatment strategy tested in clinical trials has been intermittent, targeted medication (Davis et al., 1993; Schooler, 1991). Antipsychotic medication is provided only when prodromal signs of relapse occur, and so this approach depends upon the identification of a patient's characteristic early signs of a psychotic episode and their willingness to accept medication at that time. The randomized studies comparing intermittent, targeted treatment with continuous medication (Carpenter et al., 1990; Gaebel et al., 1993, 2002; Herz et al., 1991; Jolley et al., 1990; Schooler et al., 1997) found that extensive resources were required to provide support to patients and carers, and to enable the close monitoring required. The results were relatively consistent across the studies, with the intermittent strategy reducing cumulative medication dosage, but providing no social benefits and leading to a significant increase in the rate of prodromal symptoms, relapse and rehospitalization. Such an approach requires a patient to have a greater level of cooperation and collaboration with their clinical team than continuous medication, so it is unlikely to be a viable option for those patients who are generally reluctant to have treatment (Godemann et al., 2003).

Depot/long-acting injectable antipsychotic preparations. A non-randomized, national register study in Finland (Tiihonen et al., 2006) examined relapse measures such as discontinuation of medication and rehospitalization in a cohort of 2230 consecutive adults hospitalized for the first time because of schizophrenia or schizoaffective disorder. The main finding was that depot perphenazine, oral olanzapine and clozapine out-performed other antipsychotics in preventing rehospitalization. Aside from reinforcing the emerging consensus that some of the FGAs are as efficacious as the SGAs, the superiority of depot perphenazine over oral perphenazine highlights the potential value of long-acting injectable preparations, their key advantage being the avoidance of covert non-adherence (Barnes and Curson, 1994). Lack of adherence to a depot regimen, through failure to accept the injection, will be evident to the clinical team and allow the opportunity for appropriate, prompt intervention. The other potential benefits of depot antipsychotics for long-term treatment include more consistent bioavailability, removal of the need to remember to take tablets and regular contact with a healthcare professional when they administer the injection, with the opportunity for review, although the evidence base for these advantages translating into better global outcome or a reduced risk of relapse and hospitalization is relatively thin (Haddad et al., 2009; Patel and David, 2005; Robert and Geppert, 2004). Only modest differences in relapse rates have been reported in RCTs comparing oral and depot preparations in schizophrenia (Adams et al., 2001), but the findings may underestimate the potential value of the latter in clinical practice. In the majority of such trials the follow-up period, lasting a year or less, may have been too short to reveal the longer-term benefits of depot treatment. For example, in a double-blind study comparing depot and oral preparations of fluphenazine (Hogarty et al., 1979) there was no difference in the proportion of patients relapsing in the two treatment groups within the first year, but a significant advantage for depot emerged in the second year. Further, the patients for whom depot preparations are commonly prescribed are those with a history of poor medication adherence, but such patients may be under-represented in clinical trials, being less likely to consent to participate. Any bias in these studies towards the inclusion of patients who are reliable tablet-takers would serve to diminish any advantage for depot.

Clinicians may have concerns that offering a depot preparation will compromise their therapeutic relationship with a patient, partly because of assumptions that they have a greater side-effect burden than oral antipsychotics, and that patients will perceive the injections as potentially stigmatising, intrusive or ignominious (Barnes, 2005; Heres et al., 2006b; Patel et al., 2009). Certainly some patients will have negative attitudes to depot, particularly that it will constrain their autonomy, and fear that the injections might be painful (Jaeger and Rossler, 2010), but positive attitudes to depot injections are expressed generally by those patients already receiving a depot preparation (Patel and David, 2005; Waddell and Taylor, 2009). A clinical disadvantage of depot preparations is a reduced flexibility in dosage; the long half-life means that titration against response can be a protracted process (Barnes and Curson, 1994; Kane et al., 1998). One hazard is the occurrence of uncomfortable local reactions at the injection site, characterized by pain, inflammation and induration; occurring in around 15–20% of patients a year with FGA depot preparations (Bloch et al., 2001; Hay, 1995; Jones et al., 1998). However, the risk of such reactions may be minimized by the use of low-volume preparations and increasing the length of the interval between injections (Jones et al., 1998).

How long should maintenance treatment continue? In the SOHO study (Ciudad et al., 2008; Suarez and Haro, 2008), 4206 (65%) of 6516 patients achieved remission with medication, of whom 25% relapsed over a subsequent 3-year follow-up period. The rate of relapse was constant, suggesting that maintenance treatment is required long term. While some variables have emerged as having some predictive value in relation to likely drug response, such as the duration of psychotic symptoms before receiving antipsychotic medication (Emsley et al., 2006; Marshall et al., 2005; Perkins

et al., 2005), most treatment guidelines recommend continuation of antipsychotic medication for every patient diagnosed with schizophrenia (Buchanan et al., 2010; Gaebel et al., 2005; National Institute for Health and Clinical Excellence, 2009b; Smith et al., 2009), usually suggesting that this is maintained for at least 6 months to 2 years. Bosveld-van Haandel et al. (2001) criticized such recommendations for being based on medium-term studies lasting for less than 3 years, and on the basis of their own systematic review of the relevant literature concluded that it was reasonable to treat patients for longer periods than indicated by current guidelines.

Risk factors for relapse. Despite continued antipsychotic treatment, relapse rates remain high in clinical practice. While the majority of people starting on antipsychotic medication for the first time will experience remission of symptoms within 3 months or so (Lambert et al., 2008; Robinson et al., 1999), a third or more of these patients will suffer a relapse of their illness in the first 12–18 months, and around 80% within 5 years (Csernansky and Schuchart, 2002; Prudo and Blum, 1987). Perhaps the main risk factors for relapse are poor adherence to medication (Ascher-Svanum et al., 2006; Masand et al., 2009) and comorbid substance use (Buhler et al., 2002; Hunt et al., 2002; Linszen et al., 1994; Malla et al., 2008). More severe residual psychopathology and poor insight into the illness and the need for treatment have also been identified as risk factors, but these could be epiphenomena to the extent that they may be manifestations of poor medication adherence. A poor therapeutic relationship between the prescriber and patient and poor interaction between patients, their families and carers are also risk factors (Csernansky and Schuchart, 2002; Frank and Gunderson, 1990; Priebe and Gruyters, 1995), presumably partly because a poorer therapeutic alliance has been consistently found to be associated with poor medication adherence (Chue, 2006; Lacro et al., 2002; Olfson et al., 2000), and partly because environmental stress, particularly life events and high levels of expressed emotion within the family, are known to increase the risk of relapse.

Recommendations for maintaining response and relapse prevention

- Established schizophrenia requires continued maintenance with doses of antipsychotic medication within the recommended range. (A)
- The choice of antipsychotic should follow the respective recommendation for first-episode schizophrenia, but for an individual patient should include consideration of the following factors:
  - Prior treatment response. (S)
  - Experience of side effects. (S)
  - Level of medication adherence. (S)
  - Comorbid physical illness. (S)
  - Long-term treatment plan. (S)
- Each prescription of an antipsychotic should be an individual trial, following the respective recommendation for first-episode schizophrenia (S)
- Before undertaking a switch in antipsychotic medication, the current antipsychotic medication should be optimised, and an adequate trial conducted in terms of dosage, duration and adherence. (B)
- When deciding on a switch of antipsychotic medication, take account of the risk of destabilization of the illness and provocation of adverse effects, and consider conducting it as a gradual cross-taper of the dosages of the two antipsychotic drugs.
- The care plan should address reversible risk factors for relapse, such as comorbid substance use, poor adherence and a critical environment. (B)
- Any reduction in dosage should be cautious and closely monitored, given the increased risk of relapse. (C)
- An intermittent, targeted treatment approach should not be used routinely, as an alternative to continuous maintenance antipsychotic treatment. (B)
- Depot formulations should be considered where the need to monitor medication adherence is a priority within the care plan or where a patient expresses a preference for such a formulation. (S)

Key uncertainties

- Clinical predictors of safe discontinuation of antipsychotic medication have not been determined.
- Depot formulations may be associated with relatively lower rates of relapse, but evidence involving the target group, i.e. those who adhere poorly to oral antipsychotic medication, is very limited.
- While the evidence suggests that intermittent, targeted antipsychotic treatment is inadequate for relapse prevention, it is also a matter of debate whether continuous medication administration is always necessary. Boshes and Manschrek (2002) argued that depot maintenance treatment is essentially intermittent treatment, and that its therapeutic effectiveness challenges the notion that optimal risk–benefit balance is always achieved with continuous D2 dopamine receptor occupancy. Having reviewed relevant data, Remington and Kupur (2010) speculated that extended antipsychotic dosing, achieving transiently high D2 receptor occupancy, may avoid some of the negative consequences of continuous antipsychotic exposure, but further work is required to test this.

Adherence to antipsychotic medication

Frequency of poor adherence

Non-adherence with medication is common, with studies across all areas of medicine reporting that on average 50% of patients do not take their medication as prescribed (Haynes et al., 2008). Specific to people with schizophrenia, the prevalence of medication non-adherence is at least as high if not higher than that seen in people with chronic physical illness, and there is some evidence to suggest that rates vary both over time in the same patient and across settings. The average figure for poor adherence to oral antipsychotic medication is around 50%, but ranges between 20% and 90% (Bebbington,

1995; Cramer and Rosenheck, 1998; Velligan et al., 2006), while for depot antipsychotic preparations it is around 25% (Tattan and Creed, 2001; Young et al., 1999). Coldham et al. (2002), in a study of first-episode patients, found that half were poorly adherent or non-adherent within a year of starting treatment with antipsychotic medication. Valenstein et al. (2006), using medication records over a 4-year period, noted that 61% of people with schizophrenia were partially adherent or non-adherent at some point during this time, although a further study that used a combination of patient reports and prescription records found the degree of adherence to be highly variable between patients but relatively stable over time in the majority (Ascher-Svanum et al., 2006). In a review of the literature, Leucht and Heres (2006) reported that 10 days after discharge from hospital, up to 25% of patients with schizophrenia are partially or non-adherent and this figure rises to 50% at 1 year and 75% by 2 years. Overall, non-adherence is likely to be lower in hospital inpatient settings and higher in unsupervised community settings, with rates of up to 90% reported for the latter (Cramer and Rosenheck, 1998).

Although introduced with claims of greater tolerability, SGAs do not seem to have had any appreciable impact on the level of medication adherence in schizophrenia. There is little convincing evidence available to link the use of FGAs with poorer adherence, or conversely, the use of SGAs with increased adherence (Diaz et al., 2004; Lacro et al., 2002; Masand and Narasimhan, 2006; Olfson et al., 2000). No consistent difference between the two drug groups has been reported (Ren et al., 2009), measuring adherence using, for example, pill counts (Rosenheck et al., 2000) or prescription refill rates (Dolder et al., 2002), although a modest advantage for SGAs has been found in some clinical trials (García-Cabeza et al., 2001; Tollefson et al., 1997) and with analysis of pharmacy data (Al-Zakwani et al., 2003; Menzin et al., 2003).

Factors influencing medication adherence

Non-adherence can be intentional, unintentional through simply forgetting to take medication, or a mixture of both; most non-adherence is intentional. As might be expected, non-adherence is known to be more common when the patient disagrees with the need for treatment, the medication regimen is complex or the patient perceives the benefits of medication to be suboptimal or the side effects unacceptable (Byerly et al., 2007b; Mitchell and Selmes, 2007; Velligan et al., 2009). Pharmacological factors influencing adherence include the dosage regimen and type of drug formulation; a systematic review of the association between drug delivery systems and adherence in psychopharmacology concluded that adherence may be improved by switching to once-daily regimens, oral slow-release formulations and depot injections (Vergouwen et al., 2003).

Patients' attitudes to drug treatment have emerged as perhaps the strongest predictors of medication adherence, in both first-episode (Gaebel et al., 2010; Kampman et al., 2002; Mutsatsa et al., 2003; Perkins et al., 2006) and established schizophrenia (Perkins, 2002). The subjective experience of medication appears more relevant to adherence than the severity of adverse effects (Lacro et al., 2002). Adherence may therefore be medication specific, where some medicines are taken regularly, others intermittently and others not at all. This is illustrated in a study by Piette et al. (2007) where adherence rates in people with schizophrenia and comorbid physical illness were higher for antipsychotics than for antihypertensive or oral antidiabetic medication. Other factors that may impact negatively on adherence to antipsychotics are illness-related factors such as delusions, disorganisation and depression, having a poor relationship with the prescriber, denial of illness, negative attitudes towards medication from family members or peers, having comorbid substance misuse problems and being young and male (Bebbington, 1995; Mutsatsa et al., 2003; Perkins et al., 2008; Valenstein et al., 2006).

Clinical consequences of poor adherence

The clinical consequences of non-adherence with prescribed antipsychotic medication are considerable (Novick et al., 2010). It is the most common cause of relapse in people with schizophrenia (Weiden, 2007), being associated with a 3.5-fold increase in the likelihood of relapse (Robinson et al., 1999; Weiden and Olfson, 1995) which is characterized by greater difficulty or delay in achieving remission and longer duration of inpatient stay (Leucht and Heres, 2006). In recent-onset schizophrenia, non-adherence has been found to be associated with an increased frequency of relapse, persistent psychotic symptoms, and an increased risk of being admitted to hospital (Morken et al., 2008). With respect to first-episode patients, Robinson et al. (1999) reported that those who stopped taking their antipsychotic medication over a 5-year observation period were five times more likely to relapse than those who continued medication, and with respect to patients with recent-onset illness, Morken et al. (2008) reported that those who discontinued medication were 10 times more likely to relapse than those who remained on treatment. In general, the less medication that is taken, the higher the risk of relapse, and those who do not take their antipsychotic medication remain unwell for longer (McEvoy et al., 1984). In addition, hospitalization rates, which are a proxy marker for more severe relapse, are increased in non-adherent patients, with rates quoted of 150% (Knapp et al., 2004) 200% (Ascher-Svanum et al., 2006; Ward et al., 2006) and 400% (Morken et al., 2008) over those found in adherent patients. Further, non-adherent patients are more likely to use substances, be violent, be arrested (Ascher-Svanum et al., 2006), attempt suicide (Leucht et al., 2006; Tiihonen et al. 2006; Ward et al., 2006), and have poorer long-term functioning (Ascher-Svanum et al., 2006).

Assessment of adherence

In clinical practice it can be very difficult to be certain about whether or not a patient is taking prescribed medicines. Clinicians are known to overestimate adherence rates, and patients may not openly acknowledge that they are not taking all or any of their medication. Erratic adherence may make it difficult for clinicians to determine whether or not a medication is effective and the dosage appropriate, potentially

leading to unnecessary dosage increases, switching or polypharmacy (Velligan et al., 2003).

There are a number of ways to assess adherence to antipsychotic medication. The first is to use non-judgemental, direct questioning that is specific to a period of time, for example 'have you forgotten to take any of your tablets within the last week?'. There are also a number of rating scales and checklists that can be helpful in assessing a patient's medication adherence and/or their attitude to medication. The most widely used is the Drug Attitude Inventory (DAI) (Hogan et al., 1983) which consists of positive and negative statements about medication. The total score is an indicator of a patient's overall perception of the balance between the benefits and harms associated with taking medication, and therefore likely adherence. Other available rating scales that have been developed for and tested in people with schizophrenia include the Rating of Medication Influences scale (ROMI) (Weiden et al., 1994), Medication Adherence Rating Scale (MARS) (Thompson et al., 2000), Personal Evaluation of Transitions in Treatment (PETiT) (Voruganti and Awad, 2002), the Brief Adherence Rating Scale (Byerly et al., 2008), and the Brief Evaluation of Medication Influences and Beliefs (BEMIB) (Dolder et al., 2004). It is important to note that although these scales yield useful information regarding attitudes towards medication, they cannot be used to accurately assess adherence behaviour in an individual patient.

More intrusive ways of assessing adherence include pill counts, checking whether repeat medication prescriptions have been collected from the GP, and for some antipsychotics, such as clozapine and olanzapine, plasma drug levels may be useful, although the range of levels seen with the same dose in different patients means that these cannot reliably distinguish between partial and full adherence (Taylor et al., 2009b).

Interventions to improve adherence

With respect to interventions to improve adherence, a Cochrane review (Haynes et al., 2008) concluded that all of the interventions that were effective in the longer term were complex and that even the most effective interventions had only a modest effect. Further, none were associated with predictable improvements in treatment outcome. Components of effective interventions included information giving, agreeing treatment goals, simple medicating regimens, reminders, psychological interventions and supportive care. The quality of the relationship between a patient and their treating clinician or team is critical: good engagement and a strong therapeutic alliance increase the likelihood of good medication adherence (Macneil et al., 2009; Masand and Narasimhan, 2006), as does adequate social and family support (Rabinovitch et al., 2009). When patients perceive that they have been involved in the choice of medication they are significantly more likely to adhere to that treatment (Patall et al., 2008; Wilder et al., 2010; Williams et al., 1998). Haynes et al. (2008) noted that a common thread that ran through these interventions is increased patient contact, and that there is no evidence that low adherence can be 'cured'; efforts to improve adherence must be maintained for as long as treatment is needed. Ideally interventions should be patient specific, in that they target the barriers to treatment as perceived by the patient (National Institute for Health and Clinical Excellence, 2009a).

Despite some early promise for compliance therapy, a cognitive–behavioural-based intervention, in improving insight, adherence, attitudes towards medication and re-hospitalization rates in an inpatient sample (Kemp et al., 1996, 1998), further studies have failed to replicate these positive findings (Byerly et al., 2005; O'Donnell et al., 2003). In particular, a well-conducted, adequately powered RCT found adherence therapy to be ineffective in improving adherence, psychotic symptoms or quality of life in people with schizophrenia (Gray et al., 2006).

A small proportion of patients, around 10%, are non-adherent because they simply forget to take their medication (Perkins, 2002). For this group, practical solutions such as reminder charts or texts, or compliance aids that contain compartments that accommodate up to four doses of multiple medicines each day, may have a place. Note that some medicines such as oro-dispersible formulations cannot be packaged in these devices because of stability issues, and that compliance aids are labour-intensive to fill, are associated with an increased risk of dispensing errors (Alldred et al., 2009) and are not a solution to lack of insight or lack of motivation to take medication.

As already discussed, an alternative strategy in non-adherent patients is the use of depot/long-acting antipsychotic injections. There is some evidence to support improved adherence with depot preparations in the form of longer periods until treatment discontinuation (Zhu et al., 2008), possibly because these formulations reduce the practical difficulties associated with taking medication regularly and so unintentional non-adherence. However, a proportion of patients do discontinue depot injections. With the older preparations there are reported non-adherence rates of 18% over a 3-year period (Johnson and Freeman, 1973) and 40% over a 7-year period (Curson et al., 1985b). There is no evidence that the attrition rate from SGA long-acting injections is lower than that with FGA depot preparations, with Taylor et al. (2009a) reporting that 84% of patients who started treatment with risperidone long-acting injection were no longer receiving this treatment 3 years later; note that the patients in this study may not be comparable to those recruited into RCTs of the older depots, and there were a number of reasons for treatment discontinuation in this study, in addition to non-adherence. In the UK, depot antipsychotics are prescribed for a quarter to a third of people with schizophrenia, depending on the clinical setting (Barnes et al., 2009), but there is some evidence to suggest that, in practice, their use is not always targeted towards poorly adherent outpatients (West et al., 2008).

Recommendations regarding medication adherence

- Where possible offer a choice of medication, based on the known relative liability for adverse effects. Take into account the known adverse effect profiles of individual antipsychotics, a patient's past experience of adverse

effects, and the risk of drug interactions and past medical history. (S)
- Wherever possible, the prescriber should agree jointly with the patient on the choice of, and desired outcomes from pharmacological treatment and how these can be achieved. (S)
- The medication regimen should be kept as simple as possible with respect to both the number of tablets to be taken and the number of times each day. (S)
- The efficacy of medication should be monitored and any identified side effects should be actively managed as appropriate. (S)
- The patient should be asked at regular intervals how much of their medication they have taken in the last week, and their view sought regarding the efficacy of this medication. (S)
- Consideration should be given to using one of the validated rating scales or checklists to assess a patient's attitudes towards medication. (D)
- In patients with a history of non-adherence leading to relapse, consideration should be given to using more objective methods to monitor adherence to oral medication regimens such as pill counts, and for some antipsychotics, plasma drug levels. (S)
- A depot/long-acting injection formulation should be considered when this is preferred by the patient, previous non-adherence has led to frequent relapse or the avoidance of non-adherence is a clinical priority. (S)
- Interventions to improve adherence should be patient specific, in that they should target the barriers to achieving adherence as perceived or noted by the clinical team to be present in that patient. (S)

Key uncertainty

There is evidence from controlled trials across a number of disease areas suggesting that financial incentives may have some potential to enhance medication adherence, and there is one small positive study in high-risk patients with psychotic illness (Claassen et al., 2007). Such an approach raises a number of ethical and logistical questions and a RCT further exploring the effectiveness of this intervention in people with schizophrenia in whom all conventional methods to achieve adherence have failed is underway (NIHR, 2010).

Adverse effects of antipsychotics

Clozapine aside, there are only modest differences in therapeutic efficacy between the antipsychotic drugs currently licensed, and no data available that allow for any effective targeting of particular syndromes or symptoms of schizophrenia with particular drugs in clinical practice. Thus, clinicians' and patients' perceptions of the adverse effect profiles of different antipsychotics become a major influence on drug choice. Antipsychotic drugs can cause a wide range of adverse effects (Hamer and Haddad, 2007; Ohlsen et al. 2008). If not addressed early, antipsychotic side effects can cause long-term distress and functional impairment, confound clinical assessment of the mental state and contribute to chronic physical health complications and poor adherence to treatment. Many adverse effects such as sedation, dry mouth and EPS are overt, and can be detected by careful enquiry or examination. In contrast, some adverse effects are asymptomatic and can only be detected by appropriate investigations. Examples of the latter include metabolic abnormalities (e.g. impaired glucose tolerance and dyslipidaemias), asymptomatic hyperprolactinaemia and QTc prolongation. These covert adverse effects may lead to serious consequences. For example, metabolic derangements, which differ between antipsychotics (Meyer et al., 2008), are risk factors for stroke or myocardial infarction (Casey et al., 2004; De Hert et al., 2006; Meyer and Stahl, 2009; Osborn et al., 2007, 2008).

Minimizing adverse effects

A key challenge for clinicians is to choose an antipsychotic for an individual patient that will effectively control their symptoms, while minimizing distressing or harmful side effects (Abidi and Bhaskara, 2003; Naber and Kasper, 2000). The relative liability for specific adverse effects varies significantly between individual drugs (Haddad and Sharma, 2007; Leucht et al., 2009c; Üçok and Gaebel, 2008), although the information on side effects available from published RCTs is limited in scope and detail, and methodological issues often hamper cross-study comparisons (Hamer and Haddad, 2007; Pope et al., 2010). The division of antipsychotic drugs into FGAs and SGAs is not particularly helpful in predicting liability to adverse effects in that members of each of these groups vary markedly in their adverse effect profiles. For example, among the SGAs aripiprazole has a low propensity and olanzapine a high propensity to cause weight gain (Newcomer et al., 2008; Taylor and McAskill, 2000). Similarly among the FGAs, haloperidol has a high risk and chlorpromazine a low risk of causing EPS. For this reason, it is preferable to consider the adverse effect profile of individual antipsychotic drugs rather than the group to which they may belong.

Where possible the patient should be fully involved in the selection and offered a choice of medications. In making this choice, both common and rare but potentially serious side effects that are differentially associated with individual antipsychotic drugs should be discussed and the patient's preferences sought. There are several sources for summary tables that can be used to inform such discussions (see Taylor et al., 2009b, Bazire, 2009).

Other than the anticipated adverse effect profile of individual antipsychotics, some basic points can be made with regard to predicting and so minimizing adverse effects. Most adverse effects are dose-related and so where possible the lowest effective dose of an antipsychotic should be used. The patient's medical history, including that of cardiovascular problems or epilepsy, should also be considered. Some groups are more susceptible to certain adverse effects. For example, woman of reproductive age, particularly parous women, appear to be at higher risk of hyperprolactinaemia than post-menopausal women (Haddad and Wieck, 2004; Holt and Peveler, 2010), first-onset patients seem to be particularly susceptible to weight gain (Kahn et al., 2008), young men to acute dystonias and the elderly to many adverse effects including postural hypotension, QTc prolongation and tardive dyskinesia

(Lin et al., 2004). Individuals within these groups also vary markedly in their sensitivity to develop adverse effects which reflects, at least in part, constitutional or genetic susceptibility. Adverse effects can also result from pharmacokinetic and pharmacodynamic interactions with co-prescribed medication. For example, fluoxetine can impair the metabolism of clozapine, and antihypertensive medication can increase the hypotensive effect of antipsychotics, such as risperidone, that block adrenergic alpha-1 receptors.

In summary, a patient's age and gender, medical history, co-prescribed medication and any adverse effects experienced with previous antipsychotics can help predict possible future tolerability issues and so aid selection of a new antipsychotic. A patient's perceptions of tolerability are also important, emphasizing the importance of involving the patient in the choice of medication.

Assessment and monitoring for adverse effects

If a patient raises concern about a potential side effect at any time, this needs to be addressed. Leaving this point aside, antipsychotic side effects should be reviewed routinely and regularly. There is much to be said for using a validated rating scale to achieve this rather than relying on spontaneous enquiry. The number of drug-related symptoms identified in individual patients will be greater with a structured assessment tool compared with spontaneous report or open questions about side effects and how the medication is suiting the person (Byerly et al., 2006; Yusufi et al., 2007). Clinical skill will be needed to judge whether some phenomena reflect a drug side effect, a symptom of schizophrenia, or are due to some other cause. Further, direct but sensitive questioning may be necessary to elicit more personal problems, such as sexual side effects or menstrual irregularities. Historical enquiry needs to be combined with examination and investigations as appropriate. For example, screening for EPS, particularly tardive dyskinesia, requires physical examination, and monitoring for hyperprolactinaemia and metabolic abnormalities requires blood tests.

Current guidelines differ in their recommendations as to the nature and frequency of monitoring for adverse effects associated with antipsychotics (American Diabetes Association and American Psychiatric Association, 2004; De Hert et al., 2009). It is important to emphasize that no guidance is absolute; rather it reflects expert opinion and the clinician will need to balance what is ideal against what is appropriate in a service and for a specific patient. Where blood tests are conducted, it is helpful to have measurements taken before the index antipsychotic is started, otherwise it may be impossible to know whether any subsequent abnormality preceded or followed commencement of the antipsychotic. As a general standard, systematic monitoring of adverse effects should occur prior to starting a new antipsychotic, at 3 months and then annually. The results of any monitoring should be discussed with the patient and a joint decision taken on what action is needed.

Monitoring of adverse effects in clinical practice is often poor, even for potentially serious consequences, such as metabolic side effects (Barnes et al., 2007, 2008; Morrato et al., 2010). A recent audit of nearly 6000 patients, all prescribed an antipsychotic depot and under the care of assertive outreach teams across 38 mental health trusts in the UK, found that for 35% there was no documented evidence of any assessment of side effects in the preceding 12 months (Prescribing Observatory for Mental Health, 2010). At a pragmatic level, an annual physical health check for all patients with severe mental illness, irrespective of prescribed psychotropic medication, has much to recommend it and provides a foundation on which more regular monitoring should be built. Local polices are needed to clarify the role of primary and secondary care involvement in physical health monitoring; arrangements are likely to vary in different services (Heald, 2010; Lambert and Chapman, 2004). Abnormal indices (for example, weight, blood pressure, metabolic blood screening) may not be related to prescribed medication. Clinical judgement is likely to be required to try and attribute causality and to develop a clinical management plan.

A management plan for any given side effect will need to take account of the potential benefits of the current antipsychotic in terms of treating schizophrenia in that individual, the seriousness and distress caused by the side effect and the potential risks and benefits of any intervention, particularly if a switch in antipsychotic medication is being considered. For mild side effects that cause little distress, the patient and clinicians may opt to make no change and simply monitor the situation. With more severe or distressing side effects, options for intervention will depend on the side effect in question but may include reducing the dose of the antipsychotic, prescribing a medication to treat the side effect (e.g. an anticholinergic drug to treat antipsychotic-induced Parkinsonism), lifestyle changes (e.g. dietary change for constipation caused by an antipsychotic) or a switch to an alternative antipsychotic with less of a propensity to cause the side effect in question.

Recommendations regarding medication side effects

- Use strategies to minimize the risk of adverse effects such as seeking to prescribe the minimum effective dose, the use of lower doses in first-onset and elderly patients, avoidance of inappropriate polypharmacy and monitoring and review of prn (*pro re nata)* prescribing. (D)
- Prior to starting an antipsychotic drug, inform the patient about its common side effects and less common but more serious side effects. Consider backing this up with a written patient information leaflet. (S)
- Monitor antipsychotic side effects on a regular basis using a combination of systematic enquiry (ideally use a validated rating scale), physical examination and appropriate haematological investigations. An annual physical health check and review of side effects would be the minimal standard. (S)
- An ECG is recommended (S) in the following situations:
    - There is a family history of long QTc syndrome.
    - There is a history of cardiovascular disease or arrhythmias.
    - A patient is receiving treatment with (a) a potentially cardiotoxic drug (e.g. pimozide, sertindole),

(b) high-dose psychotropic medication (i.e. a dose above the maximum licensed dose), (c) acute parenteral antipsychotic medication or (d) antipsychotic medication in combination with another drug which may prolong the QT interval or predispose to arrhythmias: see Yap and Camm (2003) for a comprehensive list of such drugs.
    - There is evidence of other factors which may predispose to arrhythmias such as electrolyte abnormalities (e.g. hypokalaemia), CNS disorders (e.g. intracranial haemorrhage) or systemic disease (e.g. liver disease): see Mackin (2008) for a more detailed account.
- Serial ECG monitoring is recommended (S) in the following situations:
    - Abnormalities are found on baseline ECG (e.g. prolonged QTc interval (greater than 440 ms for men and 470 ms for women), bundle branch block, abnormal T or U waves or frequent ventricular ectopics).
    - New onset symptoms suggestive of arrhythmia (such as syncope) or cardiovascular disease occur.
    - When a trial of high-dose antipsychotic medication or combined antipsychotics is undertaken.
    - When electrolyte abnormalities have been found.

Key uncertainties

Potential side effects. There is emerging evidence of a possible relationship between antipsychotic medication and a range of potentially serious side effects in adults with schizophrenia, including stroke in elderly patients (Kleijer et al., 2009; Sacchetti et al., 2010), venous thrombosis (Parker et al., 2010; Thomassen et al., 2001; Zornberg and Jick, 2000), myocarditis, especially with clozapine (Coulter et al., 2001), lung and breast cancer (Bushe et al., 2009; Tran et al., 2009), pneumonia in elderly patients (Trifirò et al., 2010), prolactinomas (Akkaya et al., 2009; Konopelska et al., 2008; Szarfman et al., 2006) and osteoporosis (Holt and Peveler, 2010; O'Keane, 2008). Factors other than medication are likely to be relevant, and confident recommendations regarding screening, monitoring and choice of antipsychotic to minimize these problems are not yet possible.

Mortality and antipsychotic drugs. There is consistent evidence that people with schizophrenia have an elevated mortality risk, two to three times that of the general population (Brown et al., 2010; McGrath et al., 2008). While this is partly accounted for by a higher suicide rate (Palmer et al., 2005; Qin and Nordentoft, 2005), it is also partly attributable to an increased risk for the major causes of death in the general population, such as cardiovascular and respiratory disease. Over two-thirds of people with schizophrenia die of coronary heart disease, compared with about a half of the general population (Hennekens et al. 2005). Relevant risk factors, many of which are inter-related, include cigarette smoking, diet, exercise, obesity, relative poverty and poor healthcare (Barnes and Kerwin, 2003; McCreadie, 2003). In a comprehensive meta-analysis of 42 studies, de Leon and Diaz (2005) found that up to 60% of people with schizophrenia smoke cigarettes, and such a prevalence has been found even at first episode (Harrison et al., 2008).

Considering other possible aetiological factors, in their prospective record linkage study of mortality in a community cohort of people with schizophrenia, Brown et al. (2010) noted that the introduction of SGAs coincided with the steepest rise in cardiovascular mortality. The possible association between exposure to antipsychotic medication and mortality in people with schizophrenia was explored by Weinman et al. (2009), who conducted a systematic review of eligible studies. They concluded that the data available provided some support for the hypothesis that long-term exposure to antipsychotic medication increases mortality in schizophrenia, but more rigorously designed, prospective studies were needed, which controlled for key confounding variables such as lifestyle factors, preferential prescribing and the severity of the schizophrenic illness. Tiihonen et al. (2009a) used nationwide registers in Finland to conduct an 11-year follow-up of mortality in all patients with schizophrenia treated with antipsychotics. The main finding was that long-term treatment with antipsychotic medication was associated with a lower mortality compared with no antipsychotic drug use. SGAs were a highly heterogeneous group, but clozapine seemed to have a markedly lower mortality, while with other SGAs it was neutral or increased. However, the interpretation of the findings is rendered problematic by several methodological and conceptual flaws (De Hert et al., 2010; Ghaemi and Thommi, 2010). For example, despite the collection and assessment of several potential confounding factors, other key variables known to relate to mortality, such as poverty, lifestyle and substance use, were not taken into account, and Ghaemi and Thommi (2010) identified other examples of confounding bias in this study.

The benefit identified in the Tiihonen et al. (2009a) study was driven largely by the prevention of suicide. The available evidence suggests that clozapine is associated with a reduction in suicide risk (Meltzer et al., 2003; Saunders and Hawton, 2009), although after conducting a meta-analysis of eligible studies, Hennen and Baldessarini (2005) noted that the findings were inconsistent and there were few well-designed studies.

Management of plasma prolactin elevation. Plasma prolactin elevation with antipsychotic medication is asymptomatic in some patients, while others may exhibit side effects related to the direct effects of prolactin on body tissues (galactorrhea, gynaecomastia), secondary side effects including endocrine-related sexual and reproductive dysfunction in the short term, and problems such as osteoporosis in the longer term (Byerly et al., 2007a). However, a switch to a prolactin sparing antipsychotic should be undertaken cautiously (Buchanan et al., 2010; Henderson and Doraiswamy, 2008), as the risks and benefits of such a change for an individual patient are difficult to predict, partly because the new antipsychotic may have other, unpredicted disadvantages and side effects, and partly because other factors, including genetic susceptibility and the schizophrenic illness itself, may contribute to raised prolactin (Aston et al., 2010; Houston et al., 2010).

Non-pharmacological management of antipsychotic-induced weight gain. While non-pharmacological management of antipsychotic-induced weight gain shows some promise (Pendlebury et al., 2007; Smith et al., 2007), there is insufficient evidence to support a particular therapeutic approach, such as individual or group interventions, CBT or nutritional counselling (Alvarez-Jiménez et al., 2008b). A systematic review of RCTs of physical activity or exercise for people with schizophrenia or schizophrenia-like illnesses (Gorczynski and Faulkner, 2010) was rather inconclusive, partly due to the small number of eligible trials, but suggested that regular exercise programmes may have beneficial effects on both physical and mental health. The evidence for pharmacological interventions is limited, and none has sufficient evidence to recommend widespread clinical use (Baptista et al., 2008; Bushe et al., 2009; Maayan et al., 2010). However, there is reasonable evidence that switching to an antipsychotic with a lower propensity for weight gain may lead to modest weight loss (Lin et al., 2009; Newcomer et al., 2008).

The pharmacological treatment of schizophrenia during pregnancy and breastfeeding

Pregnancy does not protect women from a first episode or recurrences of schizophrenia, and the risk of hospital admission is significantly increased in the first 1–2 months after childbirth (Munk-Olsen et al., 2006, 2009). Since ethical constraints preclude RCTs in this population, an evaluation of the reproductive safety of antipsychotic drugs has to rely on evidence of lesser stringency. In a meta-analysis of (predominantly) prospective cohort studies, Altshuler et al. (1996) found a small, but significant excess of congenital anomalies in infants exposed to phenothiazines as a group (exposed infants: $N = 2591$; non-exposed infants: $N = 71{,}746$; odds ratio: 1.21, 95% CI 1.01–1.45). The pattern of anomalies was not consistent, suggesting that the result may have been due to confounding factors. It should be noted that these early cohorts included large proportions of women who were treated for hyperemesis gravidarum with low doses of antipsychotics. In a recent Swedish population study of early pregnancy (Reis and Källén, 2008), exposure to FGAs and SGAs ($N = 552$), which were presumably used predominantly for the treatment of psychiatric disorders, was associated with a trend towards an increase of major congenital malformations (OR 1.45, 95% CI 0.99–1.41, $p < 0.055$). However, the excess was largely accounted for by cardiovascular anomalies which consisted mainly of atrial or ventricular septal defects. The results were adjusted for the confounding effect of concomitant anti-epileptic medication, but not for antidepressants, which have also been associated with small increases of cardiovascular anomalies (Oberlander et al., 2008; Reis and Källén, 2010). It is therefore currently uncertain whether or not antipsychotic drugs as a group lead to a small increase of congenital anomalies compared with the rate of 2–4% found in the general population (Nelson and Holmes, 1989). Koren et al. (2002) found reduced folate serum levels in psychiatric patients and that this was related to low dietary vitamin intake. This, as well as the higher rate of obesity in psychiatric patients, theoretically puts the offspring at an increased risk of neural tube defects although this has not been found in any existing studies.

When measuring the transplacental passage of several antipsychotic drugs, Newport et al. (2007) found the lowest foetal-to-maternal serum concentration ratio for quetiapine, followed by risperidone, haloperidol and olanzapine. Whether this difference is of consequence to the foetus is currently unknown. The information on the teratogenic potential of individual antipsychotics is limited, even for FGAs. When data from case reports, postmarketing surveillance, cohort studies and pregnancy registers are combined (Gentile, 2010), most outcomes have been reported for chlorpromazine, trifluoperazine, haloperidol and olanzapine (more than 400 exposures for each agent) followed by risperidone, fluphenazine, quetiapine and clozapine (200–400 exposures), and perphenazine, thioridazine and levomepromazine (50–100 exposures). If bias towards both over- and under-reporting of adverse outcomes is avoided by considering only cohort, population and surveillance studies with prospective design and only exposures in the first trimester as the most sensitive period for structural defects, then much smaller numbers of cases are available. Over 200 such cases have been reported for olanzapine, haloperidol or fluphenazine, 100–200 cases for risperidone or flupenthixol and less than 100 for all others, including chlorpromazine, clozapine, sulpiride, trifluoperazine and quetiapine (Diav-Citrin et al., 2005; Lilly, 2008; McKenna et al., 2005; Paulus et al., 2005; Reis and Källén, 2008; Rumeau-Rouquette et al., 1977; Wichman, 2009; Yaris et al., 2005). These limited data, taken together with the findings of antipsychotics as a group and the considerable number of years that several of the compounds have been available, do not suggest so far that antipsychotic drugs are major teratogens. To date, there are only four reported first trimester exposures to aripiprazole and one child was born with major congenital anomalies. No published information is currently available for sertindole, amisulpride and zotepine. There are relatively limited data on the risks of psychotropic medication during pregnancy and breastfeeding, and much more evidence is needed from prospective and controlled cohort studies of antipsychotic use in pregnancy are to arrive at more definite conclusions (National Institute for Health and Clinical Excellence, 2007).

Pregnancy can impair glucose tolerance from the second trimester onwards, and several cases of gestational diabetes associated with the use of clozapine, olanzapine and other antipsychotics during that time have been reported (Gentile, 2010; Reis and Källén, 2008). In the population-based study by Reis and Källén (2008), a significant increase from 0.9% to 2.5% was seen for all antipsychotics, but the numbers were small, no specific agent was implicated and exposure beyond the first trimester was not specified. Whether antipsychotics, and in particular olanzapine and clozapine, increase the rate of babies born large for gestational age is also an important question since this is associated with later cardiometabolic risk in the offspring (Kaaja and Rönnemaa, 2008; Owens et al., 2010). However, findings in the children of mothers who were treated with antipsychotic agents for a range of psychiatric disorders have so far been inconsistent

(Babu et al., 2010; McKenna et al., 2005; Newham et al., 2008; Newport et al., 2007; Reis and Källén, 2008). This may be explained by differences in these samples with regards to other factors that determine birth weight, such as maternal body mass index and weight gain during pregnancy, lifestyle and socioeconomic factors. Psychiatric illness may also have a role, as, for example, mothers with schizophrenia have repeatedly been shown to have children with low birthweight and small size for gestational age, an effect that appears to occur independently of psychotropic medication (Lin et al., 2010). Larger-scale prospective studies are needed to analyse the relative contribution of these factors. Similarly, rates of premature delivery have been reported to be elevated in schizophrenia (Nilsson et al., 2002), but whether psychotropic medication contributes to this outcome is not clear.

There is a remarkable absence of systematic studies of neonatal reactions to late pregnancy exposure to antipsychotics. Several cases of neonatal EPS have been reported in response to FGAs (Gentile, 2010) but there are no other consistent patterns of adverse effects in the published literature. There are also limited data regarding potential neurobehavioural sequelae of foetal exposure to FGAs. Studies have not shown differences in behavioural functioning or IQ up to 5 years (Altshuler et al., 1996; Thiels, 1987). Long-term developmental effects of SGAs have not yet been examined.

Compared with pregnancy, much smaller amounts of psychotropic drugs are transferred to the offspring during breastfeeding. Hale (2010) calculated the relative infant dose (infant dose/kg/day divided by maternal dose/kg/day) based on the best available evidence for several frequently used antipsychotics. The small case numbers to date suggest doses ingested by infants of less than 2% for quetiapine, chlorpromazine, olanzapine, and clozapine but significantly higher doses for sulpiride, haloperidol and risperidone (Hale, 2010). Several cases of lethargy or sedation have been reported but no other adverse effects (Hale, 2010). Dev and Krupp (1995) reported one infant who developed agranulocytosis during exposure to clozapine via breastmilk.

Recommendations for the pharmacological treatment of schizophrenia during pregnancy and breastfeeding

- Discussions with the patient about reproductive issues should include the partner or significant carer as appropriate. (S)
- All discussions about reproductive issues should be recorded in the clinical records. (S)
- If there is uncertainty about medication management, referral of the patient to a specialist perinatal psychiatry clinic for advice is recommended. (S)

In all women with schizophrenia of childbearing potential who are taking antipsychotic medication

- Clinicians should be aware that at least 50% of all pregnancies are unplanned. (S)
- Clinicians should regularly review family planning intentions with the patient. (S)
- Clinicians should ensure that the women receive contraceptive advice from their GP or a family planning clinic. (S)

If a woman with schizophrenia is planning a pregnancy

- The woman's psychiatric history and her response to treatment should be carefully reviewed and the risk of discontinuing medication evaluated. (S)
- The patient should be informed that there is no certainty that antipsychotic drugs are safe for the developing child, but that current evidence does not suggest that they are major teratogens. There may possibly be a small increase of cardiovascular malformations from about 1% to 1.5% for antipsychotic drugs as a group. (B)
- If the woman is taking an antipsychotic with a propensity to increase prolactin secretion, the plasma prolactin level should be measured. This should ideally be done in a state of low stress, after 4 hours of awakening and more than 1 hour after food. (S)
- If the prolactin level is significantly increased a second sample should be taken. If it is still raised and the clinician is uncertain about its impact on fertility, an opinion from an endocrinologist should be sought. (S)
- If there are risk factors for type 2 diabetes mellitus, olanzapine should be avoided unless the patient's history suggests that a switch to another medication enhances her risk of recurrence significantly. In the case of clozapine concerns about the potential for relapse usually outweigh concerns about its dysglycaemic effect. (S)
- Only prescribe aripiprazole, sertindole or zotepine if the patient's history suggests a preferential past response to this agent. Otherwise switch to another agent for which more pregnancy outcomes are available. (S)
- If a woman is successfully established on antipsychotic depot medication it should be continued if the risk of recurrence is high. (S)
- Avoid polypharmacy and use the lowest effective dose. (S)
- Diet supplementation with a high dose of folic acid (5 mg daily) is recommended in the 3 months before and after conception, especially in women who are obese or whose diet is lacking in folate. (C)

If a woman with schizophrenia is pregnant

- Clinicians should be aware that unplanned pregnancies are often discovered when the most susceptible period for teratogenicity has passed. (C)
- On discovery of the pregnancy, abrupt discontinuation of antipsychotic medication should be avoided due to the increased risk of a relapse. (C)
- Most women with established schizophrenia should continue treatment. The choice of medication should follow the respective recommendations for first-episode schizophrenia or established schizophrenia. If the woman is taking aripiprazole, sertindole or zotepine, and her history does not suggest a preferential response to this agent, consider switching to one of the

antipsychotics for which more pregnancy outcomes are available. (S)
- Depot antipsychotic medication should not be initiated in pregnancy because of the lack of flexibility in dosing. (S)
- If a woman is taking clozapine or olanzapine, screening for gestational diabetes is recommended. If the plasma glucose or Hb1ac are raised, a 2-hour 75-g oral glucose tolerance test is recommended at 24–28 weeks of pregnancy (National Institute for Health and Clinical Excellence, 2008). (S)
- Avoid polypharmacy and use the lowest effective dose. (S)

Neonatal period

- Check neonatal neutrophil count after antenatal exposure to clozapine. (S)
- If the mother was taking FGAs in pregnancy, monitor the newborn baby for extrapyramidal side effects for several days. (D)

Antipsychotic medication during breastfeeding

- Avoid polypharmacy and use the lowest effective dose. (S)
- Advise women not to breastfeed when taking clozapine. (D)
- If initiating antipsychotic therapy in a breastfeeding woman, the physical health of the infant should be taken into consideration when choosing the agent. (S)
- Advise to monitor the baby in regard to alertness and activity. (D)

Key uncertainties

- No definitive association has been found between the use of antipsychotics during pregnancy and an increased risk of birth defects or other adverse outcomes above rates in the general population (Einarson and Boskovic, 2009). However, there is a paucity of well-designed, prospective comparative studies addressing the safety of these drugs in pregnancy.
- It remains unclear whether routine ultrasound monitoring of foetal size in late pregnancy is warranted in those women who take clozapine or olanzapine during pregnancy or who gain excessive weight (Newham et al., 2008; Paton, 2008).

Pharmacological management of negative symptoms

The negative symptoms of schizophrenia reflect the absence or diminution of normal behaviours and functions. They encompass a range of deficits in communication, affect, socialization, capacity for experiencing pleasure and motivation (Buckley and Stahl, 2007), and present as deficiencies in emotional responsiveness (blunted or flat affect), poverty of speech, poor rapport, emotional and social withdrawal, anhedonia, apathy and avolition. Negative symptoms are more closely associated with poor functioning than are positive symptoms (Green, 1996); studies have shown a correlation between negative symptoms and impairments in occupational and social functioning in the community as well as a reduced likelihood of living independently (Hofer et al., 2005; Rosenheck et al., 2006).

An important clinical distinction is between primary and secondary negative symptoms (Carpenter et al., 1985). Primary negative symptoms constitute an enduring deficit state and are therefore assumed to be central to the core neurobiological deficits associated with schizophrenia; they predict poor prognosis (partly because they are a continuing phenomenon) and are stable over time. Secondary negative symptoms, on the other hand, can be consequent upon several factors, including unrecognised depression or demoralization, or medication side effects such as bradykinesia as part of drug-induced Parkinsonism. Negative features may also be the consequence of positive symptoms: social withdrawal can be caused by persecutory delusions, being distracted and preoccupied by the psychotic process, or by a patient titrating down their level of social stimulation to try to minimize intrusive psychotic experiences. Secondary negative symptoms would be expected to respond to treatment of the underlying cause. Thus, they are more likely to be manifest during acute psychotic episodes, and are not reliable predictors of prognosis. However, the judgement in practice as to whether negative symptoms in an individual patient are primary or secondary is generally a working hypothesis, the aetiology of the negative symptoms (i.e. primary or secondary) being often unclear and difficult to determine (Barnes and McPhillips, 1995; Flaum and Andreasen, 1995; Fleischhacker, 2000, Peralta et al., 2000). The characteristic of negative symptoms that is likely to prompt a change of antipsychotic drug or additional medication is their longer-term persistence despite maintenance of antipsychotic treatment. It has been estimated that some negative symptoms may be objectively identified in half to three-quarters of people with established schizophrenia (e.g. Selten et al., 2000), although the proportion with persistent primary negative symptoms is probably much less, between 15% and 20% (Bobes et al., 2010; Buchanan, 2007; Kirkpatrick et al., 2006).

Treatment of negative symptoms, particularly when these are enduring, is challenging and few intervention studies have specifically recruited such patients. Further, the findings from studies that test pharmacological strategies in patients whose negative symptoms are part of an acute exacerbation of psychosis may not be generalizable to patients who have severe and enduring primary negative symptoms.

Impact of time to first treatment

There is some debate over whether the length of time a patient has experienced psychotic symptoms before receiving treatment is positively associated with a poorer outcome in the medium to long term, or whether those with a poor prognosis, including primary negative symptoms, simply come to the attention of services later. Melle et al. (2008) compared the severity of negative symptoms in first-episode patients referred to services in an area with an early intervention

service with that in patients referred in another area without such a service, and found that the severity of negative symptoms was lower in the early intervention area where the DUP was shorter than in the service offering standard access to care: this difference between the cohorts persisted for the 2-year follow-up period of the study. This finding needs to be replicated, but suggests that early treatment may offer some protection against the development of persistent negative symptoms.

Differential effect of FGAs and SGAs

With respect to antipsychotics, improved efficacy against negative symptoms is often quoted as a feature of atypicality and has therefore been assumed to be associated with SGAs. While there is some evidence that clozapine may be effective, at least in the short-term, for negative symptoms in treatment-resistant schizophrenia (TRS) (Rosenheck et al., 1999; Wahlbeck et al., 2009), there is little evidence that SGAs have any superiority over FGAs in this respect, or that any benefit seen is demonstrably independent of an improvement in positive symptoms or medication side effects (Erhart et al., 2006; King, 1998; Rosenheck et al., 2003). To explore any differential efficacy against negative symptoms between FGAs and SGAs in non-selected populations of people with schizophrenia, Leucht et al. (2009c) conducted a meta-analysis of 150 RCTs that directly compared a FGA with a SGA and included data for more than 21,000 patients. The four most-effective SGAs overall (clozapine, olanzapine, amisulpride and risperidone) also showed the greatest differential efficacy against FGAs with respect to negative symptoms. The magnitude of this difference however was small, with the largest effect size reported being 0.32 for olanzapine. With respect to EPS, the four most effective SGAs were also better tolerated than haloperidol was in doses of more than 12 mg/day, but this association did not hold when lower doses of haloperidol were used or the comparator was a low-potency FGA. The findings of pragmatic studies comparing the clinical effectiveness of SGAs and FGAs in schizophrenia (Jones et al., 2006; Lieberman et al., 2005a) are consistent with those from the Leucht et al. meta-analysis.

Other dopaminergic strategies

Negative symptoms have been associated with the hypofunctioning of dopamine pathways in the prefrontal cortex. Selegiline, an inhibitor of MAO-B, reduces the metabolism of amine neurotransmitters including dopamine, may therefore restore these pathways to normal functioning, and is a putative treatment for negative symptoms. This has been tested in a RCT which revealed that selegiline augmentation of risperidone in acutely unwell patients had a modest advantage over placebo augmentation with respect to reducing negative symptoms, but not positive symptoms (Amiri et al., 2008). The implication of this finding for patients with enduring negative symptoms is unclear.

A further approach to the treatment of negative symptoms, based on stimulating dopamine release (Strafella et al. 2001) is repetitive transcranial magnetic stimulation (rTMS). A meta-analysis of sham–rTMS controlled studies where rTMS was administered to the left dorsolateral prefrontal cortex revealed a small, statistically non-significant, effect size for the active treatment (Freitas et al., 2009). The number of studies included was small and further exploration of this technology is warranted.

Non-dopamine strategies

While the positive symptoms of schizophrenia can largely be explained by dopaminergic mechanisms, the aetiology of negative symptoms may be more complex and a number of explanatory hypotheses have been suggested and subsequently tested in small RCTs. Candidate neurotransmitters include glutamate, serotonin and acetylcholine.

Glutamate. The observation that recreational drugs such as PCP and ketamine, that are antagonists at glutamate N-methyl-D-aspartate (NMDA) receptors, are associated with not only positive symptoms of schizophrenia but also negative and cognitive symptoms (Lahti et al., 1995), led to the hypothesis that glutamate plays an important role in the aetiology of schizophrenia. The mechanism by which glutamate may be involved remains to be fully elucidated, and this is illustrated by the fact that some of the putative treatments that have been tested such as glycine, D-serine, D-cycloserine, sarcosine and pregnenolone positively modulate the NMDA receptor, and some such as memantine are NMDA antagonists.

Strategies based on increasing glutamate. The CONSIST study (Buchanan et al., 2007) was a RCT that compared glycine, D-cycloserine or placebo augmentation of an antipsychotic in patients with moderate to severe negative symptoms. There was no difference demonstrated between treatments indicating that positive modulation of the glycine site of the NMDA receptor was not beneficial in reducing negative symptoms. A small negative RCT of modafanil (a stimulant thought to increase glutamate release) in patients with enduring negative symptoms is consistent with this conclusion (Pierre et al., 2007). It may also be relevant that LY2140023, an agonist at mGlu2/3 receptors, that was shown in a proof of concept RCT to have some efficacy in the treatment of schizophrenia, had no advantage over olanzapine in the treatment of negative symptoms (Patil et al., 2007). Further putative treatments based on glutamate underactivity that have been tested in RCTs are pregnenolone and minocycline. Both have complex pharmacological actions in addition to their effects on glutamate that may be relevant to the treatment of negative symptoms. Pregnenolone is a steroid that enhances myelination, increases neuritic outgrowth and modulates microtubule polymerization and stability. There is one small ($N = 21$) placebo-controlled trial of pregnenolone augmentation of SGAs that showed greater reductions in negative symptoms with the active drug (Marx et al., 2009). Minocycline is an antibiotic that has been shown to reverse the cognitive and behavioural disturbances induced by NMDA antagonists. It is also a potent inhibitor of microglial activation which is known to be present in schizophrenia,

at least in the early stages of the illness. A 6-month RCT of minocycline augmentation of an SGA in people with recent onset schizophrenia revealed that minocycline was superior to placebo in reducing negative symptoms with the differential increasing over time (Levkovitz et al., 2010).

Strategies based on decreasing glutamate. A meta-analysis of RCTs of lamotrigine (which inhibits glutamate release) augmentation of clozapine found the active drug to be superior to placebo augmentation in reducing both positive and negative symptoms, although the results suggested that the beneficial effect on other symptoms assessed (i.e. general psychopathological symptoms) might be even greater (Tiihonen et al., 2009b). These investigators interpreted the findings as indicating that around 20–30% of patients with a clozapine-resistant illness would obtain clinically meaningful benefit from lamotrigine augmentation. An adequately powered, placebo-controlled RCT of memantine (a NMDA antagonist) augmentation of an SGA in patients with persistent residual symptoms of schizophrenia failed to find any benefits for the active drug in reducing negative symptoms (Lieberman et al., 2009).

Serotonin. Many antipsychotics are antagonists at 5HT2a and 5HT2c receptors, and some also have affinity for 5HT1a receptors. Polymorphisms of these receptors have been shown to be associated with the poor response of negative symptoms to treatment with antipsychotics; 5HT1a (Reynolds et al., 2006), 5HT2a (Lane et al., 2005) and 5HT2c (Reynolds et al., 2005), providing support for the involvement of the serotonin system in the aetiology of negative symptoms. A number of treatment approaches based on modulating serotonin have been tested in RCTs.

Clinical trials have reported a degree of improvement in persistent negative symptoms with the addition of a selective serotonin reuptake inhibitor (SSRI) such as fluoxetine, fluvoxamine, paroxetine or citalopram, to antipsychotic medication, without exacerbating extrapyramidal side effects (Evins and Goff, 1996; Goff et al. 1990, 1995; Jockers-Scherübl et al., 2005; Salokangas et al., 1996; Silver and Nasser, 1992; Silver and Shmugliakov, 1998; Spina et al., 1994; Taiminen et al., 1997). Such benefit may not be limited to SSRIs: RCTs have also tested augmentation with monoamine oxidase inhibitors (MAOIs) (Bodkin et al., 1996; Bucci, 1987; Perenyi et al., 1992), trazodone (Decina et al., 1994) and mirtazapine (Berk et al., 2001; Zoccali et al., 2004) for the negative symptoms of schizophrenia. Many of these studies had small sample sizes and the issue of change in secondary negative symptoms was not adequately controlled for. Therefore, systematic reviews and meta-analyses (Rummel et al., 2006; Sepehry et al., 2007; Singh et al., 2010a) have reached relatively cautious conclusions. Singh et al. (2010a) analysed data from 23 trials of antidepressants added to antipsychotic medication for the treatment of negative symptoms and concluded that while antidepressants may be an effective treatment for such symptoms in established schizophrenia, further studies were required addressing issues such as side effects, adherence, cost-effectiveness and effect on quality of life. Sepehry et al. (2007) concluded that the findings of 11 eligible trials did not provide any convincing support for the addition of an SSRI antidepressant for the treatment of negative symptoms which had shown a poor response to antipsychotics alone, although perhaps a modest therapeutic effect would be seen in patients with more 'chronic' illness. Such limited potential benefit must be weighed against the risks. Tricyclic antidepressants could compound certain side effects of antipsychotics, such as sedation, postural hypotension and constipation. Pharmacokinetic interactions could also be significant. For example, fluoxetine and paroxetine are both inhibitors of the hepatic enzymes CYP2D6 and 3A4 which metabolize many psychotropic drugs, most notably clozapine (Tandon et al., 2006; Taylor et al., 2009b).

Some SGAs such as clozapine, olanzapine and quetiapine have affinity for 5HT3 receptors and it is possible that this contributes to both efficacy and the low propensity for EPS that is associated with these antipsychotics. A double-blind RCT of ondansetron (a 5HT3 antagonist) augmentation of haloperidol revealed no advantage for the active drug over placebo in the treatment of positive symptoms, but a small advantage in the treatment of negative symptoms, possible mediated through a reduction in EPS (Zhang et al., 2006).

Ginkgo biloba is a herbal medicine that can increase uptake of 5HT in the synapse. A meta-analysis of RCTs of ginkgo augmentation of a range of antipsychotics in people with schizophrenia found the active drug to be superior to placebo in improving negative symptoms with a SMD of 0.5. This was in the context of improvement in overall symptoms of a similar magnitude (Singh et al., 2010b). Ginkgo is also an antioxidant and may have immuno-stimulatory properties.

Cholinesterase inhibitors. People with schizophrenia are more likely to be tobacco smokers than the general population, lending support to the hypothesis that dysregulation of the nicotinergic system contributes to the aetiology of psychotic symptoms (Breese et al., 2000). A number of drugs that inhibit the breakdown of acetylcholine in the synapse are licensed for the treatment of Alzheimer's disease and two of these drugs have been subject to RCTs in people with schizophrenia. RCTs of galantamine (Conley et al., 2009) and donepezil (Keefe et al., 2008) augmentation of an antipsychotic found no benefit with respect to reduction of negative symptoms for the active treatments. Participants in these studies were not selected because of persistent negative symptoms.

Recommendations for the pharmacological management of negative symptoms

- Psychotic illness should be identified and treated as early as possible as this may offer some protection against the development of negative symptoms. (D)
- For any given patient, the antipsychotic that gives the best balance between overall efficacy and side effects should be used. (S)

Where negative symptoms persist beyond an acute episode of psychosis

- Ensure EPS (specifically bradykinesia) and depression are detected and treated if present, and consider the contribution of the environment to negative symptoms (e.g. institutionalization, lack of stimulation). (S)
- Consider augmentation of antipsychotic treatment with an antidepressant such as an SSRI, ensuring that choice is based on minimizing the potential for compounding side effects through pharmacokinetic or pharmacodynamic drug interactions. (D)
- If clozapine is prescribed, consider augmenting with lamotrigine or a suitable second antipsychotic. (B)

Pharmacological strategies for cognitive impairment

The severity of deficits in cognitive function in people with schizophrenia may be a key determinant of functional outcome (Addington and Addington, 2000; Gold et al., 2002; Goldberg and Green, 2002), with interventions to improve cognitive performance perhaps having the potential to improve social and occupational outcomes and quality of life (Gold, 2004; Green, 2007). To tackle the cognitive deficits commonly identified, two main pharmacological strategies have been adopted (Goldberg et al., 1993; Hutton et al., 1998; Keefe and Fenton, 2007; O'Carroll, 2000): the use of SGAs with claims for improving cognition as well as psychosis, and the prescription of specific cognitive enhancing agents as adjuncts to antipsychotic medication. With regard to the former, early studies (Keefe et al., 1999; Meltzer and McGurk, 1999) suggested that, in comparison with FGAs, several of the SGAs held promise for tackling cognitive impairment. Among the most consistent findings were an improvement in verbal fluency and attention with clozapine treatment, and working memory with risperidone (Green et al., 1997; Hagger et al., 1993; Kern et al., 1999). However, these studies had methodological problems (Keefe et al., 1999; Harvey and Keefe, 2001), including the inclusion of patients whose illnesses had responded poorly to FGAs and/or were prescribed FGAs in excessive dosage, with confounding side effects such as sedation and parkinsonian features, and perhaps also a lack of recognition of the impact of practice effects with neuropsychological tasks (Goldberg et al., 2007).

FGAs have not been considered generally to have any beneficial effects on neuropsychological performance, particularly at higher dosage (Elie et al., 2010). However, following a meta-analysis and review of the relevant literature, Mishara and Goldberg (2004) suggested that a reassessment of this view was warranted; they concluded that FGAs may provide modest-to-moderate gains across a range of cognitive domains. In line with this, an analysis of the effects on cognition in the CATIE study, which compared perphenazine, an FGA, with several SGAs, found small improvements in performance in all the treatment groups, although no significant differences between groups (Keefe et al., 2007), though the 18-month, follow-up data seemed to favour perphenazine. Thus, the initial enthusiasm for SGAs as cognitive enhancers has receded, not least because the accumulating evidence suggests that improvement in cognitive function might be expected to follow reduction of symptoms with antipsychotic drug treatment, and if there are differences between antipsychotics in improving cognitive performance, they are relatively modest, with none being shown to normalize cognitive function (Barnes and Joyce, 2001; Davidson et al., 2009). However, there is evidence that the intrinsic cholinergic activity in antipsychotic drugs and the effects of anticholinergic adjunctive medication given to tackle EPS can have deleterious effects on cognitive function in patients (Lieberman, 2004; Tracy et al., 2001; Vinogradov et al., 2009). The need for continued co-prescription of anticholinergic medication should be regularly reviewed.

The NIMH MATRICS (Management and Treatment Research to Improve Cognition in Schizophrenia) initiative adopted an expert consensus process to ascertain the drug classes most likely to yield effective cognitive enhancers in schizophrenia (Buchanan et al., 2005). The long list of drug groups that was generated partly reflects the considerable potential for future drug development in this area, and partly the lack of recognized cognitive enhancers with proven efficacy. The types of drug identified included cholinergic agents, including alpha-7 nicotinic receptor agonists and M1 muscarinic receptor agonists, alpha-2 adrenergic receptor agonists, dopaminergic agents, including D1 receptor agonists, and glutamatergic agents (Galletly, 2009). Amongst glutamatergic agents, the drugs with encouraging early findings (Heresco-Levy, 2005) were those that enhance NMDA neurotransmission, particularly those targeting the glycine sensitive site of NMDA receptors. However, a multi-centre trial comparing adjunctive glycine, D-cycloserine and placebo (Buchanan et al., 2007) found that the active drugs did not improve cognition, nor did they improve negative symptoms, despite hopes that glycine agonists and partial agonists might reduce such symptoms (Javitt, 2008).

Several drugs licensed for other clinical indications have been tested in trials as co-medications for improving cognition in schizophrenia. Modafanil is a novel, wakefulness-promoting agent that is approved for the treatment of several excess sleep disorders, and has evidence of improved cognitive function in healthy adults and adults with ADHD. A review by Morein-Zamir et al. (2007) was positive about the potential of this drug to improve attention and executive function in schizophrenia. Further studies are required; one subsequent, double-blind RCT of modafanil in clozapine-treated patients (Freudenreich et al., 2009) failed to find any improvement in cognition in comparison to placebo.

Acetylcholinesterase inhibitors have also been tested as adjunctive medication. A systematic review of studies of cholinesterase inhibitors as potential memory enhancers in patients with schizophrenia failed to find any clear evidence of benefit (Stip et al., 2007), but further RCT evidence has since been generated. In patients with schizophrenia and mild-to-moderate cognitive impairment, Keefe et al. (2008) conducted a 12-week, double-blind study of donepezil added to SGA treatment, but the drug was not effective at improving cognitive function compared with placebo. Another 12-week, double-blind, placebo-controlled trial in schizophrenia (Buchanan et al., 2008), examined the effects

of galantamine, an acetylcholinesterase inhibitor that also acts as an allosteric modulator at the alpha(4), beta(2), and alpha(7) nicotinic receptors, on a neuropsychological test battery. There was no significant treatment effect on the overall composite score of the cognitive battery used, although there were suggestions of selective benefits on processing speed and verbal memory. In a review of drug treatments for cognitive impairment in schizophrenia, Galletly (2009) commented that while acetylcholinesterase inhibition does not seem to have any impact on cognitive impairment in schizophrenia, nicotinic receptors may prove a more promising target for drug development. The overall conclusion of this systematic review was that none of the drugs tested thus far was a plausible candidate for an effective cognitive enhancer in schizophrenia.

Pharmacological strategies for comorbid substance misuse

Comorbid substance use is common in people with schizophrenia (Regier et al., 1990; Swofford et al., 2000). This is the case even at first episode (Barnes et al., 2006; Barnett et al., 2007), although the determinants of substance use in young people with recent-onset psychosis are uncertain and have only recently started to be examined (Lobbanna et al., 2010). Comorbid substance misuse in established schizophrenia is often explained as 'self-medication' for either the symptoms of schizophrenia or the side effects of the medication, although newer theories suggest that a common vulnerability exists for psychosis and substance misuse (Chambers et al., 2001). For a comprehensive review of the pharmacological management of substance misuse and comorbidity, the reader is directed to the BAP guidelines[1] by Lingford-Hughes et al. (2004; revision pending). Also of potential interest is the Cochrane Database systematic review of psychosocial interventions for people with both severe mental illness and substance misuse (Cleary et al. 2008).

Comorbid substance misuse has been shown to increase relapse rates in patients compliant with their antipsychotic medication, to a level similar to that in non-compliant patients (Hunt et al., 2002). It has also shown to be associated with a worse prognosis generally (Turner and Tsuang, 1990), including longer periods of hospitalization (Menezes et al., 1996), more severe positive symptoms (Drake and Wallach, 1989; Talamo et al., 2006), poorer adherence to medication (Olfson et al., 2000), and probably aggressive behaviour and violence (Fazel et al., 2009; Friedman, 2006; Swanson et al., 1990).

Nicotine is the substance most commonly abused by patients with schizophrenia, followed by alcohol. A survey of community mental health teams in West London found that 44% of their patients reported a problem with drug use and/or harmful alcohol use in the previous year (Weaver et al. 2003). It is therefore important to determine whether a patient is taking any substance(s) of abuse, with a comprehensive assessment and objective testing, e.g. urinalysis or oral fluid testing for illicit drugs of abuse, breathalyser and/or liver function tests for alcohol use. If a patient is using substances, then it is important to understand how and why, in order to inform their treatment plan. In the UK, there is no single model of how treatment for such a comorbid individual is managed, but a specialist psychiatric addiction services and/or 'dual disorder' team should be able to advise on management. If an individual is dependent on any substance, such that they have lost control of their use, abstinence is the most appropriate goal since it is unlikely they will regain control of their use. Pragmatically, however, whilst abstinence from their substance of abuse may be the most appropriate goal, many patients may not achieve this or will need repeated attempts. Although a challenging situation to clinical staff, substance use disorders should be seen as relapsing remitting disorders and as such relapses are the norm. It may be that as an intermediate goal, 'harm minimization' is appropriate until the time is suitable for a greater change in behaviour and attitudes to their substance misuse.

Substance-specific pharmacotherapy

Nicotine. There is a complex relationship between nicotine and schizophrenia, with some evidence that nicotine can improve symptoms (Winterer, 2010). However, smoking clearly has a negative impact on health and undoubtedly contributes to early death. Therefore, patients should be offered help to stop smoking as recommended in the NICE schizophrenia guidelines (National Institute for Health and Clinical Excellence, 2009b). A systematic review of studies of smoking cessation interventions in severe mental illness (Banham and Gilbody, 2010) concluded that the treatments for tobacco dependence that work in the general population are equally effective in those with long-term psychiatric illness. If there is a change in a patient's smoking behaviour, consideration should be given to any possible effect on their antipsychotic medication, particularly in relation to plasma clozapine levels (Rostami-Hodjegan et al., 2004). In addition, thought must be given to any interactions and contraindications or cautions for pharmacotherapy, e.g. varenicline or bupropion for smoking cessation.

Alcohol. Alcohol detoxification can be conducted following typical reducing regimens of benzodiazepines after considering the most appropriate setting. Currently in the UK, acamprosate and disulfiram are licensed for relapse prevention. In non-comorbid patients, acamprosate has been shown to help sustain abstinence (Rösner et al., 2008). There are no trials or studies of acamprosate in patients with schizophrenia. However, it is generally a well-tolerated medication with few side effects or drug interactions so can be used in patients with schizophrenia. By comparison, disulfiram has many cautions and contraindications, including psychosis, so its use in schizophrenia is generally not recommended and controversial. Nevertheless, disulfiram has been used in specialist services with good effect, and without significant worsening of psychosis (Mueser et al., 2003). Lastly, whilst not licensed in the UK, naltrexone is licensed in the USA and some European countries for relapse prevention in alcoholism.

[1]See http://www.bap.org.uk.

Unlike acamprosate, naltrexone has not been shown to improve abstinence but to reduce the risk of a lapse becoming a full-blown relapse (Rösner et al., 2008). Like acamprosate, naltrexone is generally well tolerated with few side effects or contraindications, the primary one being that it is unsuitable for use in patients who require opioids for the management of chronic pain.

There has been one trial of naltrexone and disulfiram (Petrakis et al., 2005) where these drugs were used alone or in combination for 12 weeks in motivated patients with a range of comorbidities, primarily depression with some psychoses and anxiety disorders. Both active medications showed a modest benefit over placebo, however abstinence rates were high (70%) in the placebo group. Most of the patients with a psychotic illness had bipolar disorder, with only a few having a diagnosis of schizophrenia or schizoaffective disorder. In a secondary analysis of patients with psychosis versus those without, naltrexone or disulfiram both significantly improved drinking outcomes (e.g. the number of abstinent days and heavy drinking days) with no clear advantage for either (Petrakis et al., 2006a). Notably, no difference between the treatment groups was seen in psychotic symptoms. Adverse events were more common in the psychotic group compared with the non-psychotic group, but there were no differences between the treatment groups.

There are a number of other medications whose potential role in relapse prevention is developing, e.g. baclofen, although they have not yet been studied in schizophrenia. The reader is referred to the BAP addiction guidelines for more information.

Cocaine. There have been many studies exploring pharmacotherapeutic interventions for cocaine misuse, although these have not been in samples of people with schizophrenia. These studies have failed to demonstrate robust effectiveness for any medication. Psychosocial approaches, particularly contingency management, are the most effective strategy in non-comorbid populations. Consequently, it is appropriate to use similar approaches in patients with schizophrenia.

Opioids. The common substitute medications are methadone or buprenorphine and, for relapse prevention, naltrexone. Methadone prolongs the QTc and it is advisable to check the ECG of anyone prescribed methadone who is also receiving an antipsychotic. In addition, tolerance to methadone is lost relatively rapidly, and for those patients who are disorganized, supervised consumption is required, potentially in the long term.

Other illicit drugs. There is no evidence to support the use of specific drug-targeted medication in treating other substance misuse, e.g. cannabis, ecstasy, etc., but short-term symptomatic treatment may be needed, e.g. benzodiazepines for insomnia during withdrawal.

Reviewing antipsychotic medication. Reviews of the use of FGAs have suggested that individuals with schizophrenia and comorbid substance use show a poorer response to antipsychotic medication, experience more EPS and adhere less well (e.g. Siris, 1990). The introduction of SGAs with claims for a better side-effect profile with regard to EPS has, however, not resulted in much improvement of substance misuse in many patients. A review of case records comparing substance misuse outcomes with 'conventional' antipsychotics (not further described) and certain SGAs (olanzapine, quetiapine, risperidone) found no evidence to support the suggestion that the latter are inherently more effective in reducing substance misuse (Petrakis et al., 2006b). In the CATIE study, in the subgroup of substance misusing patients with schizophrenia, there was no difference between FGAs and SGAs in terms of treatment discontinuation (Swartz et al., 2008). There were also no differences between those using and not using illicit drugs in symptom reduction and global improvement, after having adjusted for differential duration of treatment. There are a number of retrospective case note reviews, naturalistic prospective studies and a limited number of open or randomized studies generally describing some improvement in substance misuse having switched from an FGA or another SGA to an alternative SGA (e.g. olanzapine, risperidone, quetiapine, aripiprazole) (Beresford et al., 2005; Littrell et al., 2001; Stuyt et al., 2006; Swanson et al., 2007). However, improvements are not always reported (e.g. Berk et al., 2000; Brown et al., 2003). Currently, this limited evidence base suggests that no SGA has any clear benefit over FGAs or another SGA. This includes clozapine, although there are a number of case reports, naturalistic surveys or retrospective case reviews reporting beneficial effects of clozapine on reducing a range of substance misuse including nicotine, cannabis, cocaine and alcohol (e.g. Drake et al., 2000; Kelly et al., 2003; Zimmet et al., 2000). In addition to reducing use, clozapine has also been reported as useful in preventing relapse (Brunette et al., 2006), but this has yet to be tested in a prospective RCT.

With regard to depot/long-acting injection medication, the only relevant RCT compared injectable risperidone with zuclopenthixol (Rubio et al., 2006). Whilst greater improvements were seen with risperidone in drug misuse and psychiatric symptoms, these were quite small.

In conclusion, there is no evidence from prospective RCTs to support the use of a particular antipsychotic to reduce substance misuse in a patient with schizophrenia. Nevertheless, a trial of clozapine may be worth undertaking given its utility in TRS and reports of associated reductions in substance misuse.

Recommendations for patients with schizophrenia and comorbid substance use

- A comprehensive assessment, including why and how substances are taken, as well as objective biological markers of substance misuse should be undertaken routinely in all patients. (S)
- Antipsychotic medication should be optimized and clozapine considered in patients with persisting substance misuse. (D)
- Treatment focused on substance misuse should be offered. Whilst psychosocial approaches will be the mainstay,

pharmacotherapy should be considered and offered where possible, e.g. nicotine substitution/withdrawal, alcohol detoxification and relapse prevention. (D)

Pharmacological treatment of incomplete recovery

Treatment-resistant schizophrenia

It is generally asserted that in up to a third of people with schizophrenia, the illness shows a poor response to antipsychotic medication, although the proportion considered to be 'treatment-resistant' varies according to the criteria used (Barnes et al., 2003; Conley and Kelly, 2001; Juarez-Reyes et al., 1995; Pantelis and Lambert, 2003). In a minority (around 10%) of patients prescribed FGAs or SGAs, there will be a failure to achieve remission even after the first episode (Crow et al., 1986; Lambert et al., 2008; Loebel et al. 1992). More commonly, treatment resistance develops as the illness become progressively more unresponsive to medication (Wiersma et al., 1998). It remains uncertain whether TRS should be considered simply as the more severe end of the illness spectrum or as a distinct subtype of schizophrenia for which neurobiological correlates of treatment resistance should be explored (Altamura et al., 2005; Lawrie et al., 1997; Nasrallah, 1995).

Although often defined in terms of persistent positive symptoms, TRS has a heterogeneous presentation in terms of symptom and behavioural profile. One limitation of the evidence base for prescribing is that the definition of response in clinical trials involving people with TRS has tended to be a 20% or greater reduction in total BPRS/PANSS score, which may fall short of a clinically relevant change; in acutely ill, psychotic patients, a 20–30% reduction in total PANSS score corresponds to a Clinical Global Impression (CGI) rating of 'minimally improved', the smallest improvement considered clinically meaningful (Leucht et al., 2005, 2006). The clinical relevance of such a responder criterion in patients with 'treatment-resistant' illness is more uncertain. Overall symptom severity may be less relevant in this group than other outcomes, such as a reduction in 'target symptoms' that are causing distress or disability, an improvement in disturbed behaviour, or increased level of engagement in therapeutic and social activities.

Clozapine

The superiority of clozapine for TRS has been established against FGAs (Kane et al., 1988, 2001; Rosenheck et al., 1997) and SGAs (Lewis et al., 2006; McEvoy et al., 2006). There is consistent evidence that clozapine is the most effective antipsychotic for severe, refractory schizophrenia; approximately 30–60% of people with schizophrenia who fail to respond to other antipsychotics may respond to clozapine (Essali et al., 2009; Iqbal et al., 2003; Kane, 1992; Tandon et al., 2008). Similar benefit is seen in moderately refractory illness (Kane et al., 2001). Further, there is some evidence to suggest that clozapine can be effective for first-episode patients whose psychotic illness fails to remit during the early months of treatment (Agid et al., 2007; Szymanski et al., 1994), although not all studies of clozapine in first-episode patients have found evidence of superior benefit (Woerner et al., 2003), which may partly reflect the high rate of remission in such patients. There are claims for other benefits with clozapine, including improvement in cognitive function (Bilder et al., 2002; Purdon et al., 2001), a low liability for, and treatment of, tardive dyskinesia (Remington, 2007; Small et al., 1987), reduction in suicidality (Meltzer and Okayli, 1995; Meltzer et al., 2003), relief of caregiver burden (Conley, 1998), a decrease in cigarette smoking (de Leon, 2005) and possibly less requirement for adjunctive medications (Chong et al., 2000; Glick et al., 2004). There is also relatively strong evidence for an anti-hostility action (as described in the section below on Pharmacological strategies for persistent aggression and behavioural disturbance).

Large pragmatic clinical trials, such as CATIE Phase 2 (McEvoy et al., 2006) in the USA and the CUtLASS 2 study (Lewis et al., 2006) in the UK, compared the effect on TRS of switching to clozapine or a non-clozapine SGA. CUtLASS 2 found that when treating schizophrenia which has shown a poor response to sequential trials of two or more antipsychotics, there was an advantage to commencing clozapine rather than another SGA drug in terms of symptom improvement over a year. Similarly, CATIE Phase 2 found that for people whose schizophrenic illness had prospectively failed to improve with SGA treatment, clozapine proved to be more effective than switching to another SGA. The primary outcome measure for this study was time to discontinuation from the assigned SGA for any reason, and this was significantly longer for clozapine than for quetiapine or risperidone, but not olanzapine. Further, by 3-month follow-up, PANSS total scores had decreased more in patients receiving clozapine than in those treated with quetiapine or risperidone, but not in those assigned to olanzapine. Thus, olanzapine appeared to have a modest advantage over the other non-clozapine SGAs, although the findings may be confounded by the relatively high dosage of this drug used: mean modal daily doses were clozapine 332 mg, olanzapine 23.4 mg, quetiapine 642.9 mg and risperidone 4.8 mg. The recommended daily dose range for olanzapine is 10–20 mg, and there are case reports and studies suggesting that doses of olanzapine above 20 mg may be effective for TRS (Citrome and Kantrowitz, 2009; Meltzer et al., 2008; Roth, 2008). However, there does not seem to be any advantage to high-dose olanzapine in non-TRS (Kinon et al., 2008b), and a relevant Cochrane review (Duggan et al., 2005) including four RCTs exploring a range of doses of olanzapine and clozapine concluded that the limited data available in relation to olanzapine and treatment-resistant illness did not allow for definitive conclusions.

Clozapine is licensed for schizophrenic illness that has proved unresponsive to adequate trials of two or more antipsychotics or where there has been intolerance of the neurological side effects. These restrictions on its use partly reflect the risk of severe, potentially life-threatening side effects,

including cardiac and metabolic abnormalities and haematological problems, particularly agranulocytosis (Fitzsimons et al., 2005; Layland et al., 2009; Schulte, 2006). Thus, if clozapine is indicated, appropriate precautions should be taken: a treatment plan should be in place to ensure compliance with the recommended starting dose titration schedule and monitoring of side effects, including the mandatory testing for haematological side effects and other necessary laboratory investigations, as well as meeting the patient's need for support from the clinical team, relatives and carers. In clinical practice in the UK, the extent to which clozapine is prescribed varies markedly across mental health services (Hayhurst et al., 2003). Psychiatrists may be reluctant to use clozapine, partly due to a lack of experience and knowledge of the drug (Nielsen et al., 2010), and would rather combine two antipsychotics or augment antipsychotic medication with a mood stabilizer, two strategies for which the supportive evidence is relatively sparse. A schizophrenic illness may often have failed to respond to standard treatment for some years before a trial of clozapine is proposed (Mortimer et al., 2010; Taylor et al., 2003).

Optimizing clozapine treatment. Despite the robust evidence for efficacy in TRS, the therapeutic response may be disappointing; even with optimum clozapine treatment, only 30–60% of patients with TRS will respond satisfactorily (Chakos et al., 2001; Iqbal et al., 2003). Considering longer-term outcome, Povlsen et al. (1985) treated 216 patients with clozapine between 1971 and 1983 for between 1 and 12 years, and reported that 47–63% of the patients 'showed no change'. Lindström (1989) conducted a retrospective study of the long-term efficacy of clozapine in 96 schizophrenic and schizoaffective patients over 13 years; over a third discontinued clozapine, the main reasons being lack of efficacy, poor adherence or the temporary withdrawal of the drug from the market in 1975.

Should the therapeutic response to clozapine prove to be disappointing, before other treatment options are considered, adherence should be checked and treatment optimized, including the systematic assessment and management of side effects (Young et al., 1998; Yusufi et al., 2007). A range of other factors that may be contributing to apparent clozapine resistance, such as continuing substance use, lack of psychosocial intervention and unrecognized depression, should be considered and addressed. In terms of the duration of an adequate trial of clozapine, evidence from clinical trials suggests an advantage to longer treatment with clozapine, although such a conclusion should be qualified as different definitions of improvement are used. The period recommended varies from 4 to 12 months (Conley et al., 1997; Meltzer, 1992). Schulte (2003) reviewed studies of plasma drug monitoring and the time to response and concluded that an adequate trial should be at least 8 weeks. However, response may be delayed longer in a proportion of patients; Meltzer (1992) concluded that 30% of patients treated with clozapine would respond by 6 weeks, another 20% by 3 months and a further 10–20% by 6 months. On this basis, Kerwin and Bolonna (2005) considered it would be reasonable to test clozapine monotherapy for 6 months.

Therapeutic drug monitoring can be helpful for assessing medication adherence and drug–drug interactions, and also when titrating clozapine dosage to achieve an adequate plasma level. The target plasma clozapine level to ensure an adequate trial is generally considered to be 350 μg/l, although clinical response is commonly seen at lower levels (Dettling et al., 2000; Flanagan, 2006). Factors influencing clozapine plasma level include the daily dose, caffeine (raises plasma level), age, gender, the co-prescription of drugs such as phenytoin and other cytochrome P-450 enzyme inducers (reduce plasma level) and cigarette smoking (de Leon, 2005; Rostami-Hodjegan et al., 2004). Smoking tobacco (but not chewing tobacco, nicotine patches or inhalers) mobilizes polycyclic aromatic hydrocarbons, which leads to an increased rate of clozapine metabolism and a corresponding decrease in the plasma level. Rostami-Hodjegan et al. (2004) provided nomograms derived from large samples of male and female patients receiving clozapine, which illustrate the relationship between such factors and clozapine plasma level. These can be helpful in the clinical management of individual patients, to guide clozapine dose adjustment and assess medication adherence. Referring to these nomograms, the extent of the effect of smoking in decreasing plasma clozapine levels is demonstrated. On average, the clozapine dose requirement will be around 50% greater in smokers (Couchman et al., 2010). If a patient stops smoking, there is a risk of toxicity with serious complications such as seizures unless the clozapine dose is promptly and appropriately reassessed.

The clozapine:norclozapine plasma level ratio can also provide information relevant to dosage adjustment. Norclozapine is a potentially active metabolite of clozapine, but has a longer plasma half-life. The mean clozapine:norclozapine ratio is around 1.33, across the dose range. A ratio of less than 0.5 suggests erratic tablet taking in preceding days while a value greater than 3 suggests that the blood was not a trough (pre-dose) sample or that clozapine metabolism is saturated, either because of the dose prescribed or because there is inhibition of clozapine metabolism due to an interaction with concurrent medication, such as fluvoxamine or ciprofloxacin (Flanagan, 2006; Couchman et al., 2010).

Abrupt withdrawal of clozapine should be avoided, except in cases where the white blood cell/neutrophil count indicates impending or actual agranulocytosis. Suddenly stopping clozapine therapy can precipitate a range of symptoms, such as nausea, vomiting, diarrhoea, sweating and headache (Durst et al., 1999; Shiovitz et al., 1996). These are generally considered to be cholinergic rebound phenomena, and an anticholinergic drug may help alleviate such symptoms. Relatively severe dystonias and dyskinesias may also be provoked by rapid withdrawal of clozapine (Ahmed et al., 1998). Further, a minority of patients may develop a withdrawal psychosis, characterized by delusions, hallucinations, hostility and paranoid reactions, which may be more severe than observed previously (Ekblom et al., 1984; Goudie, 2000; Shore et al., 2005; Tanríverdi and Yazící, 1996). If clozapine is re-introduced to treat the withdrawal psychosis, the dose

required to achieve remission may be substantially higher than that initially prescribed (Miodownik et al., 2006). While the mechanism of such 'rebound psychosis' remains unclear, attributions have been made to supersensitivity of mesolimbic dopamine receptor sites and specific properties of clozapine (Alphs and Lee, 1991; Miller, 2009; Shiovitz et al., 1996; Tanríverdi and Yazící, 1996).

Clozapine augmentation with another antipsychotic. If an adequate trial of clozapine monotherapy proves to be of limited efficacy, augmentation strategies may be considered, although few of these drug combinations have a clear rationale and none has a convincing evidence base. Clinical studies have most commonly tested the value of adding another antipsychotic. Risperidone has been most often tested as an adjunct to clozapine in RCTs (Akdede et al., 2006; Anil Yağcioğlu et al., 2005; Freudenreich et al., 2007; Honer et al., 2006; Josiassen et al., 2005), but RCTs have also investigated the addition of sulpiride (Shiloh et al., 1997), amisulpride (Assion et al., 2008) or aripiprazole (Chang et al., 2008; Fleischhacker et al., 2010) to clozapine, and there are relevant open trials and case reports regarding augmentation with ziprasidone (Henderson et al., 2009; Ziegenbein et al., 2005). The evidence from these studies is inconsistent. For example, a Cochrane review (Cipriani et al., 2009) examined three small RCTs (two lasting 8 weeks and one of 6 weeks) testing clozapine combined with risperidone, sulpiride, ziprasidone or quetiapine. It proved not to be possible to reach a conclusion as to whether any particular combination strategy was superior to another, partly because of the methodological limitations of the eligible studies. Another Cochrane systematic review specifically addressed sulpiride augmentation of clozapine (Wang et al., 2010a). Three eligible short-term trials and one long-term trial were found, all involving participants with schizophrenia that was either treatment-resistant or with prominent negative symptoms. The conclusion was that while sulpiride plus clozapine may be more effective than clozapine alone in producing clinical improvement in such a context, more robust data are required. Meta-analyses of larger numbers of relevant clinical trials have concluded that the expected benefit is at best modest, and may not be evident until at least 10 weeks of treatment (Barbui et al., 2009; Paton et al., 2007; Taylor and Smith, 2009). With regard to the nature of the possible benefit, there are some indications that clozapine augmentation with a second antipsychotic may be more effective for the reduction of negative symptoms rather than positive symptoms (Chang et al., 2008; Josiassen et al., 2005).

In relation to the risks of such a strategy, RCTs and open studies have generally found clozapine augmentation with a second antipsychotic to be relatively well tolerated. The main treatment-emergent side effects were predictable from the pharmacology of the augmenting drug, with EPS and prolactin elevation emerging as the most common problems. Nevertheless, occasional serious adverse effects have been reported with adjunctive risperidone, with published case reports of agranulocytosis, atrial ectopics and possible neuroleptic malignant syndrome (Chong et al., 1997; Godleski and Serynak, 1996; Kontaxakis et al., 2002). Augmentation with aripiprazole has been associated with nausea, vomiting, insomnia, headache and agitation in the first 2 weeks (Ziegenbein et al., 2006), and with tachycardia (Chang et al., 2008) as well as modest weight loss (Karunakaran et al., 2007; Ziegenbein et al., 2006).

The criteria guiding the choice of augmenting antipsychotic might include a complementary receptor profile, i.e. potent D2 dopamine receptor blocker, which follows a plausible neurobiological rationale (Genç et al., 2007; Kontaxakis et al., 2005). Other criteria might be a relatively low liability for extrapyramidal side effects, prolactin elevation, and a low risk of compounding characteristic side effects in people treated with clozapine such as sedation, weight gain and other metabolic problems (Josiassen et al., 2005). Use of these criteria might partly explain why clinicians commonly choose amisulpride, haloperidol and sulpiride as the antipsychotics to augment clozapine (Molina et al., 2009; Paton et al., 2007).

Recommendations for clozapine treatment

- Clozapine should be considered for patients whose schizophrenic illness has shown a poor response to, or intolerance of the neurological side effects of, trials of two antipsychotic drugs that have been adequate in terms of dosage and duration. (A)
    - One of the trials should be of an antipsychotic with an established, favourable, efficacy profile in comparison with other antipsychotics, according to relevant systematic reviews and meta-analyses. (A)
    - Poor medication adherence and comorbid substance use should be excluded as causes of the apparent poor response to antipsychotic medication. (A)
    - The treatment plan for individual patients should ensure compliance with the recommended starting dose titration schedule and the requirements for laboratory investigations and side-effect monitoring, as well as meeting the patient's need for support from the clinical team, relatives and carers. (S)
    - For an adequate trial, clozapine monotherapy should be prescribed for 3–6 months. (B)
    - Treatment-emergent side effects should be monitored and managed. (S)
    - Consideration should be given to the use of clozapine plasma levels to guide dosage and check adherence where there is suboptimal response or side effects are problematic. (D)
- A trial of clozapine should be considered for people whose schizophrenic illness is characterized by persistent symptoms of aggression and hostility. (B)
- If possible, when a patient's clozapine is to be discontinued, the dose should be gradually tapered over 1–2 weeks. (B)
- After stopping clozapine, particularly if stopped abruptly (e.g. because of agranulocytosis), a patient's physical and mental state should be monitored for symptoms reflecting cholinergic rebound or rebound psychosis, particularly in the first week. (B)
- If clozapine therapy is temporarily interrupted for more than 48 hours, it must be restarted at a dose of

12.5–25 mg/day. If this dose is well tolerated, with no cardiovascular or respiratory symptoms, and previous standard dosage titration has been uneventful, then it may be reasonable to titrate the dose to the therapeutic level more rapidly than is recommended for initial treatment. As stated in the SmPC for clozapine, if a patient previously experienced respiratory or cardiac arrest with initial dosing, but titration to a therapeutic dose was subsequently successfully achieved, re-titration should be carried out with extreme caution. (S)

- Augmentation strategies with clozapine should only be considered after optimized clozapine treatment has been administered for an adequate period of not less than 3 months. (S)
- Clozapine augmentation with a second antipsychotic:
  - An adequate trial of clozapine augmentation with another antipsychotic may need to be at least 10 weeks in duration. (B)
  - When choosing the augmenting antipsychotic, consideration should be given to antipsychotics with a complementary receptor profile to clozapine, and a side effect profile that minimises compounding recognized problems with clozapine such as sedation, weight gain and metabolic side effects. (B)

Second-generation antipsychotics other than clozapine

As mentioned above, when Leucht et al. (2009b) conducted the meta-analysis of RCTs directly comparing the SGAs approved after clozapine with each other, they found modest differences in efficacy, related to improvement in positive symptoms. One question currently unanswered is whether the rank order of efficacy for non-clozapine SGAs that emerges from this work also applies to the treatment of TRS. While early clinical reports suggested a possible role for risperidone and high-dose olanzapine in the management of TRS, controlled studies against clozapine have yielded inconsistent findings (Azorin et al., 2001; Bondolfi et al., 1998; Conley et al., 2003; Tollefson et al., 2001; Tuunainen et al., 2002; Volavka et al., 2002). Interpretation of these study findings should take account of several factors; in some cases relatively broad criteria for TRS are applied, patients with treatment intolerance rather than treatment resistance are included in some studies, while in others, doses of clozapine are used that might be considered relatively low, at least by US standards. Further, patients have generally been rendered eligible for these studies because their illness has proved to refractory to FGAs rather than other SGAs.

Case reports and open studies suggest promise for other SGAs such as quetiapine (Reznik et al., 1996; Szigethy et al., 1998), aripiprazole (Crossman and Lindenmayer, 2006; Duggal and Mendhekar, 2006; Hughes and Morcos, 2008) and ziprasidone (Deutschman and Deutschman, 2007; Loebel et al., 2007) in TRS. For some, RCTs have been conducted to test their efficacy for unresponsive illness against other non-clozapine antipsychotics. A multi-centre, double-blind, RCT compared the efficacy and safety of aripiprazole and perphenazine for schizophrenia that had demonstrably failed to respond to olanzapine or risperidone (Kane et al., 2007). Treatment with both aripiprazole and perphenazine over 6 weeks was associated with clinically relevant improvements in PANSS total scores. Conley et al. (2005) evaluated the effectiveness of risperidone (4 mg/day), quetiapine (400 mg/day) or fluphenazine (12.5 mg/day) over 12 weeks in a double-blind RCT of stringently defined TRS. The majority of patients only improved to a minimal to moderate degree, and continued to experience substantial residual symptoms. There were no significant advantages for any particular antipsychotic over the others in terms of symptom improvement or tolerability. In an RCT again involving patients with stringently defined TRS, Kane et al. (2006) compared the efficacy and tolerability of ziprasidone and chlorpromazine treatment for up to 12 weeks. Ziprasidone was more effective than chlorpromazine in improving negative symptoms and comparable in overall symptom improvement.

High-dose antipsychotics

The first step with a patient whose illness has shown a disappointing response to antipsychotic medication is to test antipsychotic drugs sequentially, in adequate trials, and address potential perpetuating factors such as comorbid substance use or poor medication adherence. If such approaches prove unsuccessful, the most common treatment options then chosen by clinicians are the prescription of high-dose or combined antipsychotic medication (Correll et al., 2009; Paton et al., 2008) although neither has much evidence for benefit (Freudenreich and Goff, 2002; Gören et al., 2008; Lehman and Steinwachs, 1998; McEvoy et al., 1991; Royal College of Psychiatrists, 2006; Tranulis et al., 2008). High dose is usually taken to mean a total daily dose of a single antipsychotic which exceeds the upper limit stated in the SmPC or BNF, or a total daily dose of two or more antipsychotics which exceeds the SmPC or BNF maximum using the percentage method (Royal College of Psychiatrists, 2006), although others have defined it as the administration of more than 1000 mg/day chlorpromazine equivalents (Diaz and de Leon, 2002; Ito et al., 2005; Lehman and Steinwachs, 1998; Marder and van Kammen, 2000; Sim et al., 2004b, 2009). Chlorpromazine equivalents in milligrams a day have been calculated for both FGAs and SGAs (Andreasen et al., 2010; Woods, 2003; WHO, 2008).

There is no convincing evidence that doses of antipsychotic drugs higher than the maximum recommended are more effective than standard doses (Davis and Chen, 2004; Kinon et al. 2008b; Royal College of Psychiatrists, 2006), although some of the earlier trials used 'mega' doses that were way above the maximum recommended dose rather than exploring the risk–benefit of doses just above the norm which would be more relevant to clinical practice. Guidelines and consensus statements have consistently recommended the routine use of a single antipsychotic drug in a standard dose in routine practice (American Psychiatric Association, 2004; Buchanan et al., 2010; Canadian Psychiatric Association, 1998; Herz et al., 1997; Royal Australian and New Zealand College of Psychiatrists' Clinical Practice Guidelines Team for the Treatment of Schizophrenia and Related Disorders, 2005; Royal College of Psychiatrists, 2006), but there is

recognition in some of this guidance that the relevant trials of high-dose antipsychotic medication provide data relevant to the mean effect in a patient sample, which does not preclude a response in particular individuals, perhaps, for example, those with rapid metabolism of these drugs. Therefore, use of high-dose antipsychotic medication is not generally precluded, provided that other evidence-based strategies have failed, there is an explicit rationale, and it is prescribed in the context of a carefully monitored, therapeutic trial. A thoughtful, risk–benefit assessment should be conducted for the individual patient, taking account of the greater risk of dose-related side effects (Mackay, 1994); for example, the risk of cardiac sudden death appears to be related to antipsychotic dose even within the licensed dose range (Ray et al., 2009). In clinical practice, maintenance antipsychotic medication at a high dosage is often the consequence of progressive increments in dosage over time, and whether such a regimen has produced any benefit may be difficult if not impossible to evaluate retrospectively.

Combined antipsychotics

The effectiveness and side-effect burden of antipsychotic drug combinations, not including clozapine, have not been systematically assessed to an extent that supports a recommendation for such a strategy over antipsychotic monotherapy in TRS (Buchanan et al., 2010; Centorrino et al., 2004; Gören et al., 2008; McCue et al., 2003; Tranulis et al., 2008), and this applies equally to combinations of non-clozapine SGAs (Chan and Sweeting, 2007; Lerner et al., 2004). There is little evidence that combining antipsychotic drugs is useful (Centorrino et al., 2004; Faries et al., 2005; Gilmer et al., 2007; McCue et al., 2005), although on the basis of a meta-analysis of 19 RCTs that had compared antipsychotic monotherapy with combined antipsychotics, Correll et al. (2009) suggested that antipsychotic combinations may be superior in some clinical situations, such as acute symptom exacerbation where co-treatment is started at the beginning of treatment, and clozapine augmentation. However, they judged the database to be too heterogeneous to allow for firm clinical recommendations. Nevertheless, even though psychiatrists apparently perceive antipsychotic polypharmacy to be generally ineffective for persistent positive psychotic symptoms (Kreyenbuhl et al., 2007), the use of antipsychotic polypharmacy, including combining non-clozapine SGAs (Freudenreich and Goff, 2002; Ganguly et al., 2004; Jaffe and Levine, 2003; Procyshyn et al., 2001; Tapp et al., 2003), is common in clinical practice. Reasons given by clinicians for antipsychotic polypharmacy include a cross-tapering switch from one antipsychotic to another and attempts to manage particularly challenging symptoms, as well as pharmacological rationales such as enhancing dopamine (D2) receptor blockade, antagonism of multiple receptors, implementing agonistic effects in the serotonergic and adrenergic system, and optimization of pharmacokinetic effects (Pandurangi and Dalkilic, 2008; Zink et al., 2010).

There are several hazards associated with the prescription of combined antipsychotics. Principally, it is a risk factor for high dosage (Barnes et al., 2009; Harrington et al., 2002; Paton et al., 2008), but also carries a greater chance of medication-related adverse events (Centorrino et al., 2004) including possibly metabolic problems (Correll et al., 2007). There is a greater risk of drug–drug interactions, and poor medication adherence due to increased treatment complexity (Carnahan et al., 2006; Freudenreich and Goff, 2002, Stahl and Grady, 2004; Weinmann et al., 2009). There are conflicting data on the question of whether combined antipsychotics may contribute to the excess mortality from natural causes in middle-aged patients with schizophrenia (Auquier et al., 2006; Baandrup et al., 2010; Joukamaa et al., 2006; Waddington et al., 1998).

Critically, if there is a therapeutic response subsequent to adding a second antipsychotic there is likely to be a problem in attribution and therefore choice of the optimal long-term treatment. Any positive response may be a consequence of more time on the first antipsychotic, related only to the second drug, due to a pharmacokinetic interaction between the two, or the effect of pharmacodynamic synergy between both antipsychotics. Determining which of these mechanisms is responsible is not likely to be feasible, although only if the last explanation were true would continuation of the combination be indicated long-term.

The available evidence does not allow for any endorsement of antipsychotic polypharmacy in routine practice, but on the other hand, it cannot be confidently stated that such a strategy would never have a reasonable risk-benefit balance in an individual case (Lerner et al., 2004; Pandurangi and Dalkilic, 2008). Thus, combined antipsychotics tend to be advocated only as a closely monitored, time-limited trial, to be considered only after a lack of response to several adequate trials of antipsychotic monotherapy, and other evidence-based treatments, including clozapine, have been exhausted (Langan and Shajahan, 2010; Miller, 2004; Stahl and Grady, 2004).

Pharmacological strategies for persistent aggression and behavioural disturbance

Hostile and aggressive behaviour is not uncommon in people with unresponsive schizophrenia. It presents a major management challenge for clinicians, who are likely to consider a pharmacological treatment with only a limited potential benefit to still be clinically worthwhile. However, the evidence base for such interventions is weak. This is partly because clinical trials of medication for persistent aggression face a number of methodological difficulties. For example, aggressive episodes tend to occur infrequently so large trials may be necessary to find any statistical differences, patients with severe aggression and hostility may be unlikely to consent to participate in a research study, and indeed from an ethical point of view might warrant immediate treatment rather than participation in a trial with the risk of assignment to a placebo or a drug whose potential efficacy for aggression is still under examination. Further, outcomes are hard to define, persistent aggression being a broad term covering a range of behaviours from physical violence, impulsivity and verbal aggression through to an intimidating, threatening demeanour. For people with schizophrenia, Volavka and Citrome (2008) have recognized various drivers of aggressive, violent behaviour, such as positive symptoms, impulsivity and

comorbid psychopathy. The inconsistent findings of clinical trials testing anti-aggression medication may partly reflect this heterogeneity; for some potential drug treatments, the proportion of these subtypes within the trial sample may be a determinant of the degree of anti-aggressive efficacy found, but their representation among study participants is not generally known.

Antipsychotic medication for persistent aggression. Clozapine has long been recognized as having some anti-aggression properties, possibly linked to its serotonergic effect (Hector, 1998; Volavka, 1999). For example, in a study of clozapine in state hospital inpatients, Wilson and Claussen (1995) reported the occurrence of fewer violent episodes during the first 6 months of treatment. Subsequent reviews of the relevant literature have generally concluded that clozapine is the antipsychotic with the best evidence for an anti-hostility effect in schizophrenia (Volavka and Citrome, 2008). The findings of more recent RCTs (Citrome et al. 2001; Krakowski et al., 2006; Volavka et al., 2004) suggest that reduction in hostility and aggression with clozapine is independent of any improvement in side effects, such as akathisia or sedation, or reduction in positive symptoms. However, the observation of a decrease in hostility despite little apparent change in the severity of psychotic symptoms does not preclude some relief of the affective impact of such symptoms, which may be relevant to an anti-aggression effect (Taylor and Estroff, 2003), although such a notion has not been tested.

A specific anti-aggression effect has not been as consistently demonstrated for antipsychotic drugs generally (Citrome et al., 2001; Swanson et al., 2008; Volavka and Citrome, 2008), and some years ago the evidence for antipsychotics other than clozapine reducing violent behaviours was judged by Lehman et al. (2004) as suggestive but inconclusive. Krakowski et al. (2006) randomized 110 patients with recent episodes of aggression to receive clozapine, olanzapine or haloperidol, and found clozapine to be superior to both olanzapine and haloperidol in reducing overall aggression and the number and severity of physical assaults. A further, double-blind RCT conducted by these same investigators (Krakowski et al., 2008) was claimed as being the first double-blind comparative study of SGAs specifically designed to investigate aggression in physically assaultive subjects. The finding suggested different pathways for the anti-aggressive effects of clozapine and olanzapine. When treatment with clozapine, olanzapine and haloperidol was compared over 12 weeks, clozapine reduced aggression most effectively, although this change was not associated with improvement in cognitive functioning, while olanzapine was associated with better neurocognitive functioning relative to the other two antipsychotics, and this improvement was related to a decrease in aggressive behaviour.

Swanson et al. (2008) in the context of the CATIE study, examined the reduction in the risk of violence with 6 months of treatment with one of four SGAs (olanzapine, risperidone, quetiapine or ziprasidone) compared with an FGA (perphenazine). An intention-to-treat analysis was carried out on a sample of 1445 patients with relevant baseline data, and there was also analysis of data from a subgroup of 653 patients (retained sample) who completed the 6 months of treatment with the medication initially assigned. No differences between antipsychotic drugs were found, except for a greater reduction in violence with perphenazine compared with quetiapine in the retained sample only. Adherence to medication reduced violence, although not in those patients with a history of childhood antisocial conduct. More generally, better adherence to antipsychotic treatment seems to be associated with lower levels of aggression (Arango et al., 2006; Grinshpoon et al., 1998; Swanson et al., 2004, 2008; Swartz et al. 1998). Arango et al. (2006) randomized 46 previously violent patients to either depot zuclopenthixol (233 mg IM every 14 days) or oral zuclopenthixol (35 mg a day) for 1 year, and found significantly fewer violent episodes among those participants assigned to the depot preparation. Violence during the 1-year follow-up was inversely proportional to the degree of treatment adherence over that period. Thus, any reduction in aggressive behaviour reported with either clozapine or long-acting depot preparations may be at least partly attributable to the greater medication adherence consequent upon the necessarily close and regular monitoring by health professionals with both of these treatments. Nevertheless, a proportion of patients will continue to show aggressive behaviour despite adherence to antipsychotic medication, although this may be more likely to be verbal rather than physical (Bobes et al., 2009).

Other adjunctive medication for persistent aggression. Clinicians commonly add other classes of drugs to antipsychotic medication in the hope of reducing aggression and the risk of violence. Benzodiazepines are commonly prescribed, and augmentation with lithium or anticonvulsant drugs such as valproate, carbamazepine and lamotrigine is often considered. Small studies have also tested a beta-blocker (pindolol) (Caspi et al., 2001) and the SSRI antidepressant, citalopram (Vartiainen et al., 1995). However, the evidence that such adjunctive strategies provide long-term benefit in terms of reduced risk of aggressive behaviour is inconsistent and uncertain (Volavka and Citrome, 2008). Cochrane database systematic reviews could not document an anti-aggressive effect for either carbamazepine or valproate in schizophrenia (Leucht et al., 2007b; Schwarz et al., 2008).

There is an older literature suggesting that carbamazepine may be indicated for patients exhibiting symptoms such as impulsivity and behavioural dyscontrol, and EEG abnormalities (Schulz et al., 1990; Simhandl and Meszaros, 1992). Such notions may continue to have an influence on prescribers, who will consider adding anticonvulsant medication to combat impulsive aggression (Arey and Marder, 2008; Volavka and Citrome, 2008), with the hope of consequent improvement in social behaviour and engagability. A Cochrane review (Huband et al., 2010) evaluated the trial evidence for anti-epileptic drugs in aggression across all clinical groups, though none of the eligible studies identified included people with schizophrenia: the evidence summarized was insufficient to allow any firm conclusion about the use of

anti-epileptic medication in the treatment of aggression and associated impulsivity.

Valproate is one of the anticonvulsant drugs most commonly prescribed (Citrome et al., 2000). Small, early studies and uncontrolled observations held promise for valproate as an anti-aggressive agent for schizophrenia (Afaq et al., 2002; Chong et al., 1998; Citrome et al., 2004; Dose et al., 1998; Littrell et al., 2004; Moriñigo et al., 1989), but this was not realized in later controlled studies (Schwarz et al., 2008; Volavka and Citrome, 2008), although a randomized double-blind study in personality disorders found some reduction in aggression with valproate (Hollander et al., 2003). The doubtful evidence regarding benefit must be weighed against potentially serious side effects. The drug can be associated with marked weight gain, and is a known human teratogen (Wyszynski et al., 2005), with recent clinical guidelines (National Institute for Health and Clinical Excellence, 2006) warning against its routine prescription for women of child-bearing age.

Augmentation of antipsychotic medication with other classes of medication

TRS commonly attracts adjunctive treatment with other classes of medication, such as antidepressants, mood stabilizers, anti-epileptic drugs and benzodiazepines. In general, there is a lack of persuasive, consistent evidence for efficacy from the relevant RCTs, which share several limitations. For example, the targets for treatment in TRS clinical practice are likely to be those associated with distress or impairment of interpersonal functioning, and tend to be within one of three domains: cognitive/perceptual problems, affective dysregulation and impulsive/behavioural dysfunction. However, improvement in such key problems may not be clearly reflected in a percentage reduction in overall mental state score, the outcome measure adopted by most studies in this area. Further, although clinicians are inclined to choose particular adjunctive drug treatments for particular target indications, this is rarely reflected in the selection criteria for patient samples for RCTs of these drugs. Finally, the studies tend to be short, so there is a lack of longer-term efficacy and safety data, and pharmacokinetic issues are not systematically addressed.

Antidepressants for depressive features. Antidepressant medication may have a significant role in the treatment of poorly responsive schizophrenia if this concept is broadened to include persistent depressive and negative symptoms. Depressive features in people with schizophrenia are associated with poorer outcomes, including a higher incidence of relapse and readmission to hospital (Herz and Lamberti, 1995; Johnson, 1988), poorer social functioning and quality of life (Conley et al., 2007; Sim et al. 2004a), and increased suicidality and risk of suicide (Barnes et al., 1989; Fenton, 2000; Hawton et al., 2005). A series of studies conducted by Siris et al. (1987, 1990, 2000) addressed the differential diagnosis of such comorbid depressive features, and demonstrated some value for tricyclic antidepressants, or at least imipramine, in their treatment. Otherwise, the potential benefit of adjunctive antidepressants for comorbid depressive symptoms has not received the attention it might seem to warrant, given how often depression occurs as a distinct syndrome within schizophrenia (Buckley et al., 2009; Siris, et al. 2001), and how commonly antidepressants are prescribed in addition to antipsychotic treatment in clinical practice (Buckley et al., 2009; Kasckow and Zisook, 2008; Micaleff et al., 2006). Nevertheless, older reviews of this area have generally concluded that antidepressant treatment can be beneficial in this context (Levinson et al., 1999; Plasky, 1991).

Whitehead et al. (2003) were only able to identify 11 RCTs investigating the clinical effectiveness of antidepressant medication in the treatment of depression in people with schizophrenia. However, these trials had methodological problems including small sample sizes and limited data reported, so meta-analysis could only be performed on a subset. A range of antidepressants were tested in these studies, but only one investigated a SSRI, namely sertraline (Mulholland et al., 2003). The meta-analysis results provided weak evidence for the efficacy of antidepressants in this context, although the possibility of publication bias was acknowledged. These investigators wondered whether a fair conclusion might be that the use of antidepressants is 'unproven'. Further research is required to determine the best treatment approach to treating depression in patients with schizophrenia, with more methodologically robust clinical trials of antidepressants with longer follow-up periods (Micaleff et al., 2006; Whitehead et al., 2003).

Lithium. A Cochrane review (Leucht et al., 2007c) of controlled trials of augmentation of antipsychotics with lithium in schizophrenia was inconclusive. Although there were more responders with lithium, this was not consistent across different response criterion thresholds. Further, this advantage lost statistical significance when schizoaffective patients were excluded from the analysis. A large trial of augmentation with lithium in people with schizophrenia lacking affective symptoms would be a valuable contribution to the evidence base. There is tentative evidence that lithium is effective in reducing affective symptoms in individuals with schizophrenia or schizoaffective illness (Atre-Vaidya and Taylor, 1989; Keck et al., 1996) and that it may be a helpful treatment for patients with aggression or agitation (Arey and Marder, 2008). With regard to TRS, the evidence is thin. In a 4-week, single-blind, randomized trial, Collins et al. (1991) found no improvement in forensic patients with such a diagnosis when lithium was added as an adjunctive treatment to antipsychotic medication. Overall, these reviews suggest that a therapeutic trial of adding lithium to an antipsychotic, weighing up the limited evidence for benefit with the potential side effects, may only be worth considering for patients with schizophrenia who exhibit affective symptoms, particularly signs of excited behaviour.

Carbamazepine. Like lithium, carbamazepine does not appear to be effective as monotherapy for schizophrenia (Arey and Marder, 2008). Eight RCTs testing carbamazepine

as an adjunctive treatment were reviewed by Leucht et al. (2007b). While there was some indication of benefit (criterion reduction in BPRS total score), this was not statistically significant. A review of the literature by Volavka and Citrome (2008) concluded that while carbamazepine might possess some anti-aggressive activity, the evidence was 'rather sparse'. When interpreting the published study findings, it is important to bear in mind the potential increase in the metabolism of some antipsychotics that carbamazepine can induce. This can lead to a lowering of their plasma concentrations and potentially compromise their antipsychotic effect.

Valproate. As mentioned above, valproate is commonly prescribed in clinical practice as an adjunct to an antipsychotic for schizophrenia (Citrome et al., 1998). A meta-analysis of five relevant trials of valproate augmentation in schizophrenia by Basan et al. (2004) found inconsistent evidence of benefit, and no overall superiority for the combination. Similarly, a Cochrane systematic review (Schwarz et al., 2008) examined seven studies of augmentation with valproate and found little evidence of a favourable effect on mental state. One multi-centre trial of acutely hospitalized patients (Casey et al., 2003) was relatively positive, finding that valproate led to more rapid improvement in patients receiving risperidone or olanzapine, with the suggestion of some reduction in excitement in this patient sample. This accords with hints from smaller studies and case reports that valproate may be helpful for managing mood symptoms, particularly excitement (Citrome, 2009a, 2009b). However, a 12-week, double-blind RCT of valproate augmentation of risperidone or olanzapine, in 402 patients with an acute psychotic episode, showed no efficacy advantage for valproate: antipsychotic monotherapy was actually superior to adjunctive valproate on negative symptoms (Citrome, 2009a). It is difficult to extrapolate these effects in acutely psychotic individuals to treatment of treatment-resistant illness with persistent symptoms, particular as any possible benefit must be weighed against some potentially serious adverse effects, as noted above.

Valproate also has a role in the prophylaxis of clozapine-induced seizures. Clozapine lowers the seizure threshold (Taner et al., 1998; Welch et al., 1994), and grand mal seizures are not uncommon (1–10%) in people treated with the drug; risk factors include rapid upward titration of dosage and the concurrent prescription of other medications that lower the seizure threshold (Devinsky et al., 1991; Liukkonen et al., 1992). Guidance on the clinical management of such seizures (Phansalker and Osser, 2009; Taylor et al., 2009b) includes reduction in the dose of clozapine, plasma-level monitoring, and the co-prescription of valproate.

Lamotrigine. The ability of lamotrigine to attenuate the behavioural effects of ketamine suggested that it might improve persistent symptoms in schizophrenia. The use of lamotrigine augmentation was first reported by Dursun et al. (1999) in six patients with schizophrenia refractory to clozapine. An initial dose of 12.5 mg/day of lamotrigine, subsequently titrated according to response, was added to the maximum tolerated dose of clozapine, and was associated with a consistent improvement in symptom scores. This publication was followed by modestly encouraging findings from several small trials (Kremer et al., 2004; Poyurovsky et al., 2010; Zoccali et al., 2007). For example, in a 10-week, placebo-controlled study, Kremer et al. (2004) found improvement in TRS with the addition of up to 400 mg of lamotrigine daily to FGAs or SGAs. The advantage over placebo was not significant in the primary LOCF statistical analysis, although a completers' analysis revealed significant reductions in positive and general psychopathology symptoms with lamotrigine. A Cochrane systematic review (Premkumar and Pick, 2006) identified five eligible randomized trials of lamotrigine augmentation in schizophrenia and concluded that the evidence for use of adjunctive lamotrigine in schizophrenia was not robust, and large, well-designed, pragmatic, randomized trials were required. Subsequently, Goff et al. (2007) provided an account of two relatively large double-blind studies, with a combined total of 429 participants, in which lamotrigine or placebo was added for stabilized patients who continued to show psychotic symptoms despite maintaining treatment with an SGA. One of the studies found an advantage for lamotrigine for negative symptoms while the other found an advantage for cognition. However, the findings were inconsistent. The conclusion must be that, in routine clinical practice, the usefulness of lamotrigine augmentation of antipsychotics other than clozapine for the management of schizophrenia that has proved refractory to standard medication remains to be determined.

However, specifically in regard to lamotrigine augmentation of clozapine, a more positive conclusion may be warranted. Trials focusing on lamotrigine augmentation in patients with persistent positive symptoms despite adequate clozapine treatment (Dursun and Deakin, 2001; Tiihonen et al., 2003; Zoccali et al., 2007) have yielded more robust evidence of benefit. Tiihonen et al. (2003) conducted such a trial in schizophrenic inpatients with clozapine-refractory symptoms: augmentation with lamotrigine (200 mg/day) was associated with a small but statistically significant attenuation of positive symptoms and general psychopathology ratings, but not negative symptoms. A systematic review (Tiihonen et al. 2009b) of five studies, including the clozapine-treated patients from the Goff et al. (2007) trials described above, concluded that there was an advantage for lamotrigine augmentation of clozapine over placebo for both positive and negative symptoms, with an effect size of 0.57. Why the therapeutic effect appears to be more impressive in clozapine-refractory patients is uncertain. Lamotrigine does not appear to alter the steady state blood levels of clozapine (Spina et al. 2006), but perhaps acts synergistically with clozapine, possibly via glutamatergic pathways (Large et al. 2005).

Recommendations for the management of incomplete recovery, for drugs other than clozapine

- High-dose and combined antipsychotic prescribing for TRS should only be used after the failure of several, adequate,

sequential trials of antipsychotic monotherapy, and other evidence-based treatments for TRS including optimised treatment with clozapine, have been exhausted. (B)
- Poor medication adherence and comorbid substance use and should be excluded as causes of the apparent poor response to antipsychotic medication. (A)
- The use of high-dose antipsychotic medication for TRS should be treated as a limited therapeutic trial, with close monitoring of side effects and therapeutic response. The high dosage should be continued after 3 months only if there is evident clinical benefit that outweighs any risks. (S)
- The use of combined non-clozapine antipsychotics for TRS should also be in the context of a closely monitored, time-limited trial. (D)

Areas of uncertainty

Given the relative lack of rigorous data on the risks and benefits of combination antipsychotic therapy in schizophrenia, further RCTs and head-to-head-trials are warranted. Further, the evidence base regarding the risks and benefits of pharmacological augmentation strategies in relation to the treatment of particular clinical domains or persistent symptom clusters is generally too limited to allow for confident recommendations for clinical practice.

Electroconvulsive therapy. On the basis of data from 25 relevant RCTs, the NICE guideline on the use of electroconvulsive therapy (ECT) (National Institute for Clinical Excellence, 2003) concluded that the evidence for the general use of ECT in the management of schizophrenia was inconclusive, but conceded that it may be effective in acute episodes of certain types of schizophrenia and reduce the occurrence of relapses, and that the combination of ECT and pharmacotherapy might be more effective than pharmacotherapy alone. A subsequent Cochrane review of ECT for schizophrenia by Tharyan and Adams (2005) included 26 trials with 50 reports, and concluded that ECT combined with antipsychotic medications was an option to be considered when the treatment aim was rapid global improvement and symptomatic reduction, and for patients whose illnesses had shown only a limited response to medication alone. The authors acknowledged that any benefit might not last beyond the beyond the short term. Reviewing the relevant published literature led Braga and Petrides (2005) and Haskett and Loo (2010) to much the same opinion: the combination of ECT and antipsychotic medication may be a useful option for patients with schizophrenia that has proved unresponsive to pharmacological interventions, and its adverse effect profile does not seem different from that seen with ECT alone. Johns and Thompson (1995) considered that there was a need for further research to delineate the specific role of ECT in schizophrenia, with studies targeting illness characterized by affective symptoms or a poor response to standard treatment, and seeking to establish whether it potentiates the effects of antipsychotic medication.

The particular combination of ECT and clozapine was proposed and tested as a treatment strategy a couple of decades ago (Fink, 1990; Klapheke, 1991, 1993; Meltzer, 1990) and has been reported as being safe. Evidence derived from a relatively small sample of patients suggests that adjunctive ECT may produce benefit when a schizophrenic illness has shown only a poor response to clozapine monotherapy (Bhatia et al., 1998; Bonator et al., 1996; Havaki-Kontaxaki et al., 2006; Kales et al., 1999; Kho et al., 2004), the combination being more effective than ECT or clozapine alone (Kupchik et al., 2000; Masoudzadeh and Khalilian, 2007). However, a trial directly comparing combined clozapine and ECT therapy with clozapine alone in 10 patients with clozapine-refractory schizophrenia or schizoaffective disorder found no statistical differences between the two treatment groups on any clinical outcome (Koen et al., 2008). Any benefit achieved with this combination may not be maintained after ECT is discontinued (Kales et al., 1999), and the risks and benefits of maintenance ECT remain unknown.

Specifically, case reports have been published in support of the notion that ECT can provide some stabilization of a patient with TRS to allow for a re-trial of clozapine (Green et al., 1994; James and Gray, 1999), this being particularly justified perhaps when there is evidence of a previous good therapeutic response to the drug. It has been proposed that in such cases the rapid, although short-lived, response to ECT might provide a window of opportunity to engage with the patient who would otherwise be too disturbed to accept blood tests and co-operate with a clozapine regimen (Barnes, 1999).

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Conflict of interest statement

All attendees completed conflict of interest statements that are held at the British Association for Psychopharmacology office according to BAP policy.

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