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REVIEW

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 1: Acute treatment of schizophrenia

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Abstract

These guidelines for the biological treatment of schizophrenia were developed by an international Task Force of the World Federation of Societies of Biological Psychiatry (WFSBP). The goal during the development of these guidelines was to review systematically all available evidence pertaining to the treatment of schizophrenia, and to reach a consensus on a series of practice recommendations that are clinically and scientifically meaningful based on the available evidence. These guidelines are intended for use by all physicians seeing and treating people with schizophrenia. The data used for developing these guidelines have been extracted primarily from various national treatment guidelines and panels for schizophrenia, as well as from meta-analyses, reviews and randomised clinical trials on the efficacy of pharmacological and other biological treatment interventions identified by a search of the MEDLINE database and Cochrane Library. The identified literature was evaluated with respect to the strength of evidence for its efficacy and then categorised into four levels of evidence (A–D). This first part of the guidelines covers disease definition, classification, epidemiology and course of schizophrenia, as well as the management of the acute phase treatment. These guidelines are primarily concerned with the biological treatment (including antipsychotic medication, other pharmacological treatment options, electroconvulsive therapy, adjunctive and novel therapeutic strategies) of adults suffering from schizophrenia.

Key words: *Schizophrenia, acute phase treatment, evidence-based medicine, practice guidelines, biological treatment, antipsychotics*

EXECUTIVE SUMMARY OF RECOMMENDATIONS

General recommendations

Specific treatment is indicated for patients who meet diagnostic criteria for schizophrenia, a schizophrenic episode or psychotic symptoms related to schizophrenic disorder. An assessment of mental and physical health to evaluate relevant psychiatric and medical comorbid conditions, psychosocial circumstances and quality of life should be undertaken regularly. When a person presents psychotic symptoms for the first time a careful diagnostic evaluation

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should be performed, including laboratory investigation and imaging techniques (cerebral CT or MRI) in order to exclude organic brain disease. After the initial assessment of the patient's diagnosis and establishment of a therapeutic alliance, a treatment plan must be formulated and implemented. This formulation involves the selection of the treatment modalities, the specific type(s) of treatment, and the treatment setting. Periodic reevaluation of the diagnosis and the treatment plan is essential. Engagement of the family and other significant support persons, with the patient's permission, is recommended to further strengthen the therapeutic effort. The goals and strategies of treatment vary according to the phase and severity of illness. In the acute phase of treatment (lasting weeks to months), which is defined by an acute psychotic episode, major goals are to develop an alliance with the patient and family, to prevent harm, control disturbed behaviour, reduce the severity of psychosis and associated symptoms (e.g., agitation, aggression, negative symptoms, affective symptoms), determine and address the factors that led to the occurrence of the acute episode and to effect a rapid return to the best level of functioning. Special attention should be paid to the presence of suicidal ideation, intent or plan, and the presence of command hallucinations. The patient should be provided with information on the nature and management of the illness, including the benefits and side effects of the medication, in a form that is appropriate to his or her ability to assimilate the information. In the acute treatment phase, the main emphasis is on pharmacotherapeutic (and other somatic) interventions. Therefore antipsychotic therapy should be initiated as a necessary part of a comprehensive package of care that addresses the individual's clinical, emotional and social needs.

Specific treatment recommendations

In *first-episode psychosis* antipsychotic pharmacological treatments should be introduced with great care due to the higher risk of extrapyramidal symptoms (EPS). Appropriate strategies include gradual introduction of low-dose antipsychotic medication with careful explanation. The first-line use of second-generation antipsychotic medication (SGAs) (and alternatively the use of first-generation antipsychotics (FGAs) at the lower end of the standard dose range) is the preferred treatment for a person experiencing a first episode of schizophrenia. This recommendation is mainly based on the better tolerability and reduced risk of tardive dyskinesia associated with the atypical antipsychotics. Skilled nursing care, a safe and supportive environment, and regular and liberal doses of benzodiazepines may be essential to relieve distress, insomnia and behavioural disturbances secondary to psychosis, while antipsychotic medication takes effect.

In *multiple episodes* the most common contributors to symptom relapse are antipsychotic medication non-adherence, substance use and stressful life events, although relapses are not uncommon as a result of the natural course of the illness, despite continuing treatment. If nonadherence is suspected, it is recommended that the reasons for it be evaluated and considered in the treatment plan. It is recommended that pharmacological treatment should be initiated promptly, because acute psychotic exacerbations are associated with emotional distress, and a substantial risk of dangerous behaviours. Given the advantages of second-generation antipsychotics (SGAs), these antipsychotics generally seem preferable, although in principal all antipsychotics have their place in the treatment of acute schizophrenia. The selection of an antipsychotic medication is guided by the patient's previous experience of symptom response and side effects, intended route of administration, the patient's preferences for a particular medication, the presence of comorbid medical conditions, and potential interactions with other prescribed medications. The dose may be titrated as quickly as tolerated to the target therapeutic dose of the antipsychotic medication (e.g., 300–1000 chlorpromazine (CPZ) equivalents for FGAs) while monitoring the patient's clinical status. Especially when using FGAs it is recommended to keep the dose as low as possible to reduce the risk of extrapyramidal side effects. Rapid dose escalation, high loading doses and treatment with high doses above the mentioned dose range do not have proven superior efficacy, but have been associated with increased side effects. For patients presenting with high degrees of agitation in an emergency setting there is evidence for superior efficacy with the combination of benzodiazepines.

In assessing *treatment-resistant schizophrenia* (TRS) or partial response, multidimensional evaluation should consider persistent positive or negative symptoms, cognitive dysfunction with severe impairment, bizarre behaviour, recurrent affective symptoms, deficits in vocational and social functioning and a poor quality of life. The target symptoms should be precisely defined. It is important to evaluate carefully whether there is insufficient improvement in the target symptoms, despite treatment at the recommended dosage for a duration of at least 6–8 weeks with at least two antipsychotics, one of which should be an atypical antipsychotic. Adherence should be ensured, if necessary by

checking drug concentrations. In individuals with clearly defined TRS, clozapine should be introduced as treatment of choice because of clozapine's superior efficacy in this regard. Treatment alternatives in case of nonresponse may be other SGAs, augmentation strategies (antidepressants, mood stabilisers) in relation to target symptoms, combination of antipsychotics (limited evidence for risperidone or sulpiride in combination with clozapine) and, as the last treatment option, electroconvulsive therapy (ECT).

For patients presenting with *catatonic features* the option of ECT may be considered earlier when insufficient response on benzodiazepines is observed.

Treatment of *negative symptoms* begins with assessing the patient for syndromes that can cause secondary negative symptoms. The treatment of such secondary negative symptoms consists of treating their cause, e.g., antipsychotics for primary positive symptoms, antidepressants for depression, anxiolytics for anxiety disorders, or antiparkinsonian agents, antipsychotic dose reduction or switch to a SGA for extrapyramidal side effects. For primary negative symptoms treatment with SGAs is recommended. The greatest level of evidence is for amisulpride, but it has not been clearly proven to have more efficacy.

For patients with concomitant substance use disorders, a comprehensive integrated treatment is recommended in which the same clinicians or team of clinicians provide treatment for both diseases. There is limited evidence that SGAs, especially clozapine, but also risperidone and olanzapine, are beneficial for dual diagnosis patients. This may be due to reduced severity of EPS and decrease of craving.

Depressive symptoms that occur during the acute psychotic phase usually improve as patients recover from the psychosis. There is also evidence suggesting that depressive symptoms are reduced by antipsychotic treatment, with comparison trials finding that SGAs may have greater efficacy in treating depressive symptoms than FGAs. Antidepressants may be added as an adjunct to antipsychotics when syndromal criteria for major depressive episode are met.

There is evidence to suggest that both first- and second-generation antipsychotic medications may reduce the *risk of suicide*. In several studies, clozapine demonstrated the most consistent reduction of suicide rates and persistent suicidal behaviour. Further treatment strategies for medical and psychiatric comorbid conditions are extensively discussed in the full text of the guideline.

Schizophrenia

Introduction

Schizophrenia is a major psychotic disorder (or cluster of disorders) that usually appears in late adolescence or early adulthood. Despite modern treatment techniques schizophrenia still presents an enormous burden to the patients and their relatives. In most cases there is an impairment in occupational or social functioning, characterised by social withdrawal, loss of interest or ability to function at school or work, change in personal hygienic habits or unusual behaviour still in the prodromal phase (Loebel et al. 1992; Häfner and an der Heiden 2003).

Schizophrenia presents different symptoms in multiple domains in great heterogeneity across individuals and also variability within individuals over time. Due to systematic observation of psychopathology, positive and negative phenomena can be separated (Andreasen 1982; Crow 1985). *Positive symptoms* in a broader manner include delusions or delusional ideation, hallucinations, disturbance of association, catatonic symptoms, agitations, feelings of alien influence and suspiciousness. *Negative symptoms* include restricted range and intensity of emotional expression, reduced thought and speech productivity and social withdrawal associated with a reduced initiation of goal-directed behaviour. Therefore, negative components could be defined as affective flattening, alogia, anhedonia and avolition. As a third category, *disorganised symptoms* include disorganised speech, disorganised behaviour and poor attention.

The currently used diagnostic criteria for schizophrenia (DSM-IV, ICD-10) define schizophrenia as a discrete category. Schizophrenia can be diagnosed if organic brain disease has been excluded, and an essential feature of symptoms or at least one core symptom has to be present for a significant length of time during a 1-month period (or for a shorter time if successfully treated) (according to ICD-10), or for at least 6 months (according to DSM-IV) (see Table I).

According to DSM-IV or ICD-10, subtypes of schizophrenia are defined by their predominant symptoms. These subtypes include (1) the hebephrenic subtype, in which flat or inappropriate affect is prominent, (2) the catatonic subtype, in which characteristic autosymptoms (catatonia) are permanent, (3) the disorganised subtype, in which disorganised speech and behaviour dominate, (4) the paranoid subtype, in which predominantly dilutions or auditory hallucinations are present, (5) the undifferentiated subtype, which is a non-specific category, and (6) schizophrenia simplex, so-called

Table I. Diagnostic criteria of schizophrenia or schizophrenic episode.

ICD-10

Characteristic symptomatology:

1. One month or more, in which a significant portion of time is taken up by one very clear symptom or two less clear symptoms:
   - A. Thought echo, thought insertion or withdrawal, and thought broadcasting;
   - B. Delusions of control, influence, or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception;
   - C. Hallucinatory voices giving a running commentary on the patient's behaviour, or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body;
   - D. Persistent delusions of other kinds that are culturally inappropriate and completely impossible, such as religious or political identity, or superhuman powers and abilities (e.g. being able to control the weather, or being in communication with aliens from another world);

Or

2. At least two of the following:
   - E. Persistent hallucinations in any modality, when accompanied either by fleeting or half-formed delusions without clear affective content, or by persistent over-valued ideas, or when occurring every day for weeks or months on end;
   - F. Breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech, or neologisms;
   - G. Catatonic behaviour, such as excitement, posturing, or waxy flexibility, negativism, mutism, and stupor;
   - H. "Negative" symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses, usually resulting in social withdrawal and lowering of social performance; it must be clear that these are not due to depression or to neuroleptic medication;

Or

3. I. A significant and consistent change in the overall quality of some aspects of personal behaviour, manifest as loss of interest, aimlessness, idleness, a self-absorbed attitude, and social withdrawal.

Duration: One of A–D, or two of E–H present for 1 month, or I present for more than 1 year (Simple schizophrenia)

DSM-IV

A. *Characteristic symptoms:* Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):
   1. Delusions.
   2. Hallucinations
   3. Disorganised speech (frequent derailment or incoherence)
   4. Grossly disorganised or catatonic behaviour
   5. Negative symptoms, i.e., affective flattening, alogia or avolition.

Note: Only: one criterion A symptom required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices conversing with each other.

B. Social/Occupational functioning

For significant portion of time, since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to onset (or when the onset is in childhood or adolescence, the feilure to achieve expected level of interpersonal, academic, or occupational achievement).

C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least one month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or tow or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

Exclusion: The diagnosis is not made in presence of extensive depressive or manic symptoms unless it is clear that schizophrenic symptoms antedated the affective disturbance. The disturbance is not due to substance intoxication, dependence or withdrawal, or overt brain disease.

D. Schizoaffective and Mood Disorder exclusion: Schizoaffective Disorder and Mood Disorder with Psychotic features have been ruled out because wither (1) no Major depressive, Manic, or Mixed episodes have occurred concurrently with the active phase symptoms; or (2) if mood episodes have occurred during active phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. Substance/general medical condition exclusion: The disturbance is mot due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

F. Relationship to a pervasive developmental disorder: If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

due to the course and permanent negative symptoms of the disease. The subtypes of schizophrenia are listed in Table II.

These guidelines and the presented recommendations focus on the acute, and continuation and maintenance treatment of schizophrenia. The guidelines may help clinicians, service users and caregivers become aware of the different treatments that are available, and may be useful in deciding which treatment to apply as they include the level of evidence available for each treatment. The first part (Part 1) of these guidelines covers epidemiol-

Table II. Subtypes of schizophrenia.

Subtypes ICD-10
F 20.0 Paranoid schizophrenia
F 20.1 Hebephrenic schizophrenia
F 20.2 Catatonic schizophrenia
F 20.3 Undifferentiated schizophrenia
F 20.4 Post schizophrenic depression
F 20.5 Residual schizophrenia
F 20.6 Simple schizophrenia
F 20.8 Other schizophrenia
F 20.9 Schizophrenia unspecified
DSM-IV
Schizophrenia, paranoid type
Schizophrenia, catatonic type
Schizophrenia, disorganized type
Schizophrenia, undifferentiated type
Schizophrenia, residual type

ogy, course and aetiology of schizophrenia, the pharmacological properties, classification and side effects of antipsychotics and adjunctive agents, assessment before and during treatment and the management of the acute phase treatment.

Epidemiology and course of schizophrenia

Schizophrenia is a relatively common illness. Lifetime prevalence varies for methodological reasons, but the mean prevalence is estimated to be nearly one case per 100 persons (1%) in the general population. While limited to broad or narrow diagnostic criteria, the mean incidence of schizophrenia reported in epidemiological studies is 0.11–0.24 per 1000 persons (Jablensky et al. 1992). The average rates for men and women are nearly similar, but the mean age of onset is about 5 years later for women than for men (Häfner and an der Heiden 2003).

In most cases the onset of schizophrenic symptoms, according to diagnostic criteria, is preceded by a prodromal period characterised by early signs of impairment in personal and social functioning. The average length of the prodromal phase is between 2 and 5 years (Beiser et al. 1993; Häfner et al. 1993) and is often neither recognised nor treated and therefore called the duration of untreated illness (DUI). The prodromal phase is followed by the onset of acute schizophrenia, marked by characteristic positive symptoms of hallucinations, delusions and behavioural disturbances. In most industrialised countries 1–2 years pass before adequate treatment is initiated (Johnstone et al. 1986; Häfner et al. 1993). The time from the first occurrence of psychotic symptoms until treatment begins is defined as the duration of untreated psychosis (DUP) (McGlashan and Johanessen 1996). Research indicates that delayed access to health services and treatment is associated with slower or less complete recovery (Loebel et al. 1992) and increased risk of relapse in the subsequent 2 years (Johnstone et al. 1996). The acute phase refers to the presence of florid psychotic features. After positive symptoms have diminished, in a certain number of cases negative symptoms similar to the symptoms in the prodromal period remain.

The course and pattern of schizophrenia varies considerably. During the stabilisation or recovery phase, psychotic symptoms decrease in severity. The stabilisation period lasts about 6 months and is followed by the stable phase. In the stable phase negative and residual positive symptoms that may be present are relatively consistent in severity and magnitude. A certain number of patients (nearly 20–30%) display no prominent symptoms after the first episode (Häfner and an der Heiden 2003). Acute exacerbations may interrupt the stable phase and require additional treatment or interventions. Longitudinal neuropsychological assessment showed that patients with schizophrenia have considerable cognitive dysfunction in the first 4–5 years of illness, and after this period there is little evidence for deterioration (Hoff et al. 1999). Approximately 50% of people with schizophrenia treated in standard services will relapse and require readmission within the first 2 years, and up to 80% within a 5-year period (Robinson et al. 1999); about 10–25% will have no further admissions (Fenton et al. 1987; Hegarty et al. 1994). Before relapse occurs warning signs often appear, which usually consist of non-psychotic symptoms followed by emotional disturbance and mild psychotic symptoms over a period of 4–12 weeks (Birchwood et al. 1989; Gaebel et al. 1993). There is some evidence that the negative symptoms may become steadily more prominent in some individuals during the course of illness (McGlashan and Fenton 1993; Möller et al. 2002). Predictors associated, on average, with better outcomes are later age at onset, female gender, married marital status, a sociable premorbid personality, good premorbid adjustment and functioning, higher IQ, a psychoreactive trigger of onset, an acute onset of symptoms, predominantly affective or positive symptoms and no disorganised or negative symptoms at onset, fewer prior episodes, a phasic pattern of episodes and remissions, lack of family history of schizophrenia and a low level of expressed emotions in the family (Hegarty et al. 1994; Davidson and McGlashan 1997; Bottlender et al. 2000, 2002, 2003; Häfner and an der Heiden 2003).

Other, comorbid mental disorders and general medical conditions are often found with schizophrenia. After the elevated suicide risk, cardiovascular disorders, respiratory and infectious diseases, acci-

dents and traumatic injuries serve as main causes for the excess mortality of schizophrenia (Brown et al. 2000). One of the most frequent comorbid diseases is substance abuse disorder, which occurs in 15–71% of patients with schizophrenia (Soyka et al. 1993; Kovasznay et al. 1997; Bersani et al. 2002). Factors influencing the risk of abusing drugs are associated with the former and current social environment and premorbid personality (Arndt et al. 1992). Comorbid conditions can worsen the course and complicate treatment (Linszen et al. 1994).

Aetiology

Schizophrenia is a disorder with a complex aetiology. Research has attempted to determine the role of specific biological variables, such as genetic and biochemical factors und subtle changes in the brain morphology. According to the neurodevelopment hypothesis, schizophrenia appears as a result of disturbed brain development during the pre- or perinatal period, but the specificity of the nature of early brain disruption or pathogenesis is not yet defined and remains unclear (for review see Marenco and Weinberger 2000). Genetic components could only explain half of the risk to develop schizophrenia, and pre- or perinatal complications are responsible for 1–2% of the risk (Gottesman and Bertelsen 1989).

Therefore the favoured model of the illness is the 'vulnerability-stress-coping-model' (Nuechterlein and Dawson 1984). This concept proposes that vulnerability will result in the development of symptoms when environmental stresses are present and coping mechanisms fail. Vulnerability factors based on a biological component with a genetic background interact with complex physical, environmental and psychological vulnerability factors. Biochemical theories focus mainly on the 'dopamine hypothesis'. The dopamine hypothesis implies that there is an increased production of this neurotransmitter or an over-sensitivity of dopamine receptors in a certain brain region (mesolimbic system), resulting in hyperexcitability and the appearance of positive symptoms and a hypodopaminergic state in frontal brain regions, followed by negative symptoms (for review see Sedvall and Farde 1995). This hypothesis is supported by the successful treatment of psychotic symptoms by agents blocking D2 receptors in the mesolimbic system. Besides dopamine, other neurotransmitters like serotonin and glutamate seems to be involved in the pathophysiology of schizophrenia. The blockade of serotonin 5-HT_{2A} receptors and the preferential blockade of specific subtypes of dopamine receptors was hypothesised to be a relevant mechanism for the efficacy of atypical or second-generation antipsychotics in treating negative symptoms (Möller 2003).

Assessment before and during treatment

A full assessment of health and social care needs should be undertaken regularly, including assessment of social functioning and quality of life. Every patient should have a careful initial assessment, including complete psychiatric and general medical histories. In order to exclude most general medical conditions that can contribute to psychotic symptoms, physical and mental status examinations, including a neurological examination, are indicated. Basic laboratory tests should be conducted and should include CBC, measurements of blood electrolytes, lipids and glucose, tests of liver, renal, thyroid function, and additionally HIV, hepatitis, and syphilis screening, when indicated. Ordinarily, a urine screen should be performed to assess recent use of substances. In addition to establishing baselines for the administration of psychotropic medication, these tests examine the patient for illnesses that can mimic schizophrenia and illnesses that are often comorbid with schizophrenia and require modification of the treatment plan. It may be useful to assess blood levels of antipsychotic medication to establish whether the patient has been taking his or her medication. Tests to assess other general medical needs of patients should be considered (e.g., measurement of the human chorionic gonadotropin β subunit in women of childbearing age). Magnetic resonance imaging (MRI) or computed tomography (CT) and EEG should be performed in patients with a first episode and when the clinical picture is unclear, or when there are abnormal findings from a routine examination. Patients with preexisting cardiac disease need to be carefully monitored for ECG abnormalities since antipsychotic medications can be cardiotoxic. Such knowledge influences the choice of medication. Neuropsychological tests are generally not useful in making a diagnosis of schizophrenia during the acute phase but are useful after stabilisation to evaluate cognitive deficits, which can affect the treatment plan. Special circumstances (before and after the application of ECT) may require neuropsychological evaluation.

Special attention should be paid to the presence of suicidal ideation, intent, or plan, and the presence of command hallucinations, and precautions should be taken whenever there is any question about a patient's intent to commit suicide, since suicidal ideation is the best predictor of a subsequent attempt in schizophrenia (Meltzer et al. 2003). Similar evaluations are necessary when considering

the likelihood that the individual will harm someone else or engage in other forms of violence (Buckley et al. 2003).

Economic outcome, health service and stigma

Schizophrenia presents an enormous burden to the patients and their relatives and reduces the quality of life, especially due to chronic impairment. Schizophrenia has been estimated to be one of 30 leading courses of disability worldwide (Murray and Lopez 1997). Four to 15% of people suffering from schizophrenia commit suicide, and the excess mortality among people with schizophrenia is approximately 50% above that of the general population (Brown et al. 2000). The cumulative cost of the care of adults with schizophrenia is high: about 5–6% of National Health Service inpatient costs in England were attributable to schizophrenia (Knapp 1997). Schizophrenia has been estimated to account for 2.5% of annual health care expenditures in the United States of America (Rupp and Keith 1993). Over 65% of patients with schizophrenia after a second psychotic episode are unemployed, thus contributing to the high degree of so-called indirect costs of the disease (Guest and Cookson 1999). People with schizophrenia experience stigmatisation, and one of the major goals of the activities of the schizophrenia networks and health organisations is to support programs against stigma (Gaebel and Baumann 2003). It is of great importance to develop successful treatment strategies, including multidimensional approaches, in order to reduce the burden of the disease.

Goal and target audience of WFSBP guidelines

These guidelines are intended for use in clinical practice by all physicians investigating, diagnosing and treating patients with schizophrenia. Therefore an update of contemporary knowledge of various aspects of schizophrenia, especially treatment options, is provided. The aim of these guidelines is to improve standards of care, diminish unacceptable variations in the provision and quality of care, and support physicians in clinical decisions. Although these guidelines favour particular treatments on the basis of the available evidence, the treating physician remains responsible for his assessment and treatment option. These guidelines are primarily concerned with the biological (somatic) treatment of adults and address recommendations in this field. The specific aim of these guidelines is to evaluate the role of pharmacological agents in the treatment and management of schizophrenia, while the role of specific psychological interventions and specific service delivery systems is covered only briefly. The effectiveness of somatic treatment is considered.

The guidelines were developed by the authors and arrived at by consensus with the WFSBP Task Force on Schizophrenia, consisting of 37 international experts in the field.

Methods of literature research and data extraction

In the development of these guidelines the following guidelines, consensus reports and sources were considered:

American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia (APA 1997) and American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia, 2nd ed. (APA 2004).

Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde. Praxisleitlinien Psychiatrie und Psychotherapie: Schizophrenie (DGPPN 1998); Guidelines for Neuroleptic Relapse Prevention in Schizophrenia (Kissling 1991).

National Institute for Clinical Excellence. Core Interventions in the Treatment of Schizophrenia London (NICE 2003) and National Institute for Clinical Excellence. Guidance on the use of newer (atypical) antipsychotic drugs for the treatment of schizophrenia (NICE 2002).

Royal Australian and New Zealand College of Psychiatrists. Australian and New Zealand clinical practice guideline for the treatment of schizophrenia, Draft only (RANZCP 2003), and Summary Australian and New Zealand clinical practice guideline for the treatment of schizophrenia (McGorry et al. 2003).

Scottish Intercollegiate Guidelines Network. Psychosocial Interventions in the Management of Schizophrenia (SIGN 1998).

Task Force of the World Psychiatric Association. The Usefulness and Use of Second-Generation Antipsychotic Medications–an Update (Sartorius et al. 2002).

The Expert Consensus Guideline Series. Optimizing Pharmacologic Treatment of Psychotic Disorders (Kane et al. 2003).

The Mount Sinai conference on the pharmacotherapy of schizophrenia (Marder et al. 2002).

The Texas Medication Algorithm Project (TMAP) schizophrenia algorithms (Miller et al. 1999).

Translating research into practice: the Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations (Lehman et al. 1998).

World Health Organization. WHO Guide to Mental Health in Primary Care (WHO 2000).

The Cochrane Library, Meta-analyses on the efficacy of different drugs and interventions used in schizophrenia (2004 Issues).

Reviews, meta-analyses and randomised clinical trials contributing to interventions in schizophrenic patients identified by search in the Medline data base (up to February 2004) and individual clinical experience by the authors and the members of the WFSBP Task Force on Schizophrenia.

Evidence-based classifications of recommendations

The evidence found in the literature research and data extraction was summarised and categorised to reflect its susceptibility to bias (Shekelle 1999). Daily treatment costs were not taken into consideration due to the variability of medication costs worldwide. Each treatment recommendation was evaluated and discussed with respect to the strength of evidence for its efficacy, safety, tolerability and feasibility. It has to be kept in mind that the strength of recommendation is due to the level of efficacy and not necessarily of its importance. Four categories were used to determine the hierarchy of recommendations (related to the described level of evidence):

Level A. There is good research-based evidence to support this recommendation. The evidence was obtained from at least three moderately large, positive, randomised controlled (double-blind) trials (RCTs). In addition, at least one of these three studies must be a well-conducted, placebo-controlled study.

Level B. There is fair research-based evidence to support this recommendation. The evidence was obtained from at least two moderately large, positive, randomised, double-blind trials (this can be either two or more comparator studies or one comparator-controlled and one placebo-controlled study) or from one moderately large, positive, randomised, double-blind study (comparator-controlled or placebo-controlled) and at least one prospective moderately large (sample size equal to or greater than 50 participants), open-label, naturalistic study.

Level C. There is minimal research-based evidence to support this recommendation. The evidence was obtained from at least one randomised, double-blind study with a comparator treatment and one prospective, open-label study/case series (with a sample size equal to or greater than 10 participants) showed efficacy, or at least two prospective, open-label study/case series (with a sample size equal to or greater than 10 participants) showed efficacy.

Level D. Evidence was obtained from expert opinions (from authors and members of the WFSBP Task Force on Schizophrenia) supported by at least one prospective, open-label study/case series (sample size equal to or greater than 10 participants).

No level of evidence or Good Clinical Practice (GCP). This category includes expert opinion-based statements for general treatment procedures and principles.

Indication and goals of treatment for schizophrenia

Schizophrenia is a heterogeneous condition that has a varying course and outcome and affects many aspects of the patient's life. The care of most patients with this disorder involves multiple efforts and a multidisciplinary team approach to reduce the frequency, duration and severity of episodes, reduce the overall morbidity and mortality of the disorder, and improve psychosocial functioning, independence and quality of life. The treatment of schizophrenia requires the full understanding of the patient, his or her needs and goals, conflicts and defences, coping mechanisms and resources. Therefore all those involved in treatment need to understand the biological, interpersonal, social and cultural factors which exert an influence on the patient's recovery. The major goals of treatment should be the participation of the patient and all those involved in the treatment process, co-operation with relatives, co-ordination and co-operation of the treatment institutions in terms of integrated care and the inclusion of the non-professional help and self-help systems. Facilitation of access to the healthcare system for patients suffering from schizophrenia is an additional important goal of professional work. After the initial assessment of the patient's diagnosis and clinical and psychosocial circumstances, a treatment plan must be formulated

and implemented. This formulation involves the selection of the treatment modalities, the specific type(s) of treatment, and the treatment setting. The goals and strategies of treatment vary according to the phase and severity of illness.

In the *acute phase* of treatment (lasting weeks to months), defined by an acute psychotic episode, major goals are to develop an alliance with the patient and family, to prevent harm, control disturbed behaviour, reduce the severity of psychosis and associated symptoms (e.g., agitation, aggression, negative symptoms, affective symptoms), determine and address the factors that led to the occurrence of the acute episode and effect a rapid return to the best level of functioning. A psychiatrist may see a patient who is in an acute psychotic state that renders the patient dangerous to self and others. Under these circumstances, it may be impossible to perform an adequate evaluation at the time of the initial evaluation. Given the relative safety of most antipsychotic medications, the psychiatrist may begin treatment with an appropriate medication, even in states where involuntary use of medication must be approved by a court, and perform the necessary evaluations as they become possible.

During the *stabilisation phase* (usually lasting 3–6 months), the goals of treatment are to reduce stress on the patient and provide support to minimise the likelihood of relapse, enhance the patient's adaptation to life in the community, facilitate continued reduction in symptoms and consolidation of remission, and promote the process of recovery. If the patient has improved with a particular medication regimen, it is recommended to continue that regimen for at least 6 months (APA 2004). It is also critical to assess continuing side effects that may have been present in the acute phase and to adjust pharmacotherapy accordingly to minimise adverse side effects that may otherwise lead to medication nonadherence and relapse.

The goals of treatment during the *stable phase* (lasting months to years) are to ensure that symptom remission or control is sustained, that the patient is maintaining or improving his or her level of functioning and quality of life, that increases in symptoms or relapses are effectively treated, and that monitoring for adverse treatment effects continues. For most persons with schizophrenia in the stable phase, psychosocial interventions are recommended as a useful adjunctive treatment to pharmacological treatment to improve outcome. The main aim of pharmacological intervention in the stable phase is to prevent relapse and help keep a person stable enough to live as normal a life as possible (maintenance therapy and relapse prevention).

Acute-phase treatment of schizophrenia

In the acute phase, the specific treatment goals are to prevent harm, control disturbed behaviour, suppress symptoms, effect a rapid return to the best level of functioning, develop an alliance with the patient and family, formulate short- and long-term treatment plans, and connect the patient with appropriate aftercare in the community (APA 2004). Whatever treatments are offered, it is essential to engage the patient in a collaborative, trusting and caring working relationship at the earliest opportunity (NICE 2002). Psychosocial interventions in this phase aim at reducing overstimulating or stressful relationships, environments, or life events and at promoting relaxation or reduced arousal through simple, clear, coherent communications and expectations, a structured and predictable environment, low performance requirements, and tolerant, nondemanding, supportive relationships with the psychiatrist and other members of the treatment team (DGPPN 1998; APA 2004). The patient should be provided with information on the nature and management of the illness that is appropriate to his or her ability to assimilate the information. A patient has to be informed about the benefits and side effects of the medication (NICE 2002). The psychiatrist must realise that the degree of acceptance of medication and information about it varies according to the patient's cognitive capacity, the degree of the patient's denial of the illness, and efforts made by the psychiatrist to engage the patient and family in a collaborative treatment relationship (APA 2004). Indications for hospitalisation include the patient's being considered to pose a serious threat of harm to self or others, being unable to care for self, needing constant supervision and general medical or psychiatric problems that make outpatient treatment unsafe or ineffective. Involuntary hospitalisations are indicated if patients refuse to be admitted, and if they meet the requirements of the local jurisdiction. Alternative treatment settings, such as partial hospitalisation, home care, family crisis therapy, crisis residential care, and assertive community treatment, should be considered for patients who do not need formal hospitalisation for their acute episodes (APA 2004). In the acute treatment phase, the main emphasis is on pharmacotherapeutic (and other somatic) interventions. Therefore antipsychotic therapy should be initiated as early as possible as a necessary part of a comprehensive package of care that addresses the individual's clinical, emotional and social needs. The clinician responsible for treatment and key worker should monitor both therapeutic progress and tolerability of the drug on an ongoing basis. Monitoring is particularly impor-

tant when individuals have just changed from one antipsychotic to another (NICE 2002).

Antipsychotics

Antipsychotic medications have formed the basis of schizophrenia treatment for approximately 50 years. In terms of their chemical structure, the antipsychotic medications, frequently known as *neuroleptic agents*, are a heterogeneous group of psychoactive drugs (such as phenothiazines, thioxanthenes, butyrophenones, diphenylbutylpiperidines, benzamides, benzisoxazoles and dibenzepines). They are used in the acute phase treatment, long-term maintenance therapy and in the prevention of relapse of schizophrenia.

Classification and efficacy

Conventional or *first-generation antipsychotics* (FGA) can be classified into high- and low-potency medications. The effective dose of a first-generation antipsychotic medication is closely related to its affinity for dopamine receptors (particularly D2) and its tendency to cause extrapyramidal side effects (Creese et al. 1976). *High-potency antipsychotics* have a greater affinity for D2 receptors than *low-potency medications* and the effective dose required to treat psychotic symptoms like delusions and hallucinations is much lower than for low-potency antipychotics. This dose relationship can be expressed in terms of dose equivalence (e.g., 100 mg of low-potency antipsychotic chlorpromazine has an antipsychotic effect that is similar to that of 2 mg of the high-potency antipsychotic haloperidol). Dose equivalence does not equate with equivalence of tolerability and should be considered as a general concept rather than a precise clinical guide. The side effects of high-potency agents, e.g., extrapyramidal symptoms are easier to manage than the sedation and orthostatic hypotension associated with low-potency agents. For this reason, doses of low-potency medications for a sufficient antipsychotic effect often are difficult to reach.

With the detection of clozapine as an effective antipsychotic agent that does not induce catalepsy and apomorphine antagonism, a new class of 'atypical' antipsychotics became established. Because various antipsychotics can be found on a continuum ranging from typical to atypical, the terms *second-generation antipsychotics* (SGA) or *new-generation antipsychotics* (NGA) to describe these new agents, which induce considerably fewer extrapyramidal symptoms (EPS) in a therapeutic dose range than conventional neuroleptics, have been found to be more suitable (Fleischhacker 2002).

First-generation antipychotics

Studies demonstrating the *efficacy of FGAs* (e.g., phenothiazines) in reducing psychotic symptoms in acute schizophrenia were mostly carried out in the 1960s and 1970s, comparing one or more antipsychotic medications with either placebo or a sedative agent. Nearly all of these studies found that the antipsychotic medication was superior for treating schizophrenia (NIH Psychopharmacology Service Center Collaborative Study Group 1964). A review of more than 100 trials concluded that the vast majority of double-blind studies found superior efficacy for FGAs compared to placebo and, with the exception of mepazine and promazine, all of these agents were equally effective, although there were differences in dose, potency and side effects of the different drugs (Davis et al. 1989). Superiority of FGAs over placebo was confirmed by other reviews evaluating randomised, double-blind studies (Baldessarini et al. 1990; Kane and Marder 1993; Dixon et al. 1995). Cochrane reviews and NICE reviews, including high-quality RCTs, have found the efficacy of some FGAs, e.g., chlorpromazine (Thornley et al. 2004), flupenthixol (Centre for Outcomes Research and Effectiveness, Systematic Review Flupenthixol 2002), fluphenazine (Centre for Outcomes Research and Effectiveness, Systematic Review Fluphenazine 2002), perazine (Leucht and Hartung 2004b), perphenazine (Centre for Outcomes Research and Effectiveness, Systematic Review Perphenazine 2002), pimozide (Sultana and McMonagle 2004), sulpiride (Soares et al. 2004), thioridazine (Sultana et al. 2004), trifluoperazine (Marques et al. 2004) and zuclopenthixolacetate (Fenton et al. 2004), but not of all FGAs, e.g., benperidol (Leucht and Hartung 2004a), to be similar to other conventional antipsychotics, and superior compared to placebo for, e.g., chlorpromazine, thioridazine, trifluoperazine, and with only slight superiority pimozide and sulpiride. Furthermore, FGAs (e.g., phenothiazines in this review) have proven efficacy in diminishing psychotic symptoms in long-term treatment and reducing relapse rates compared to placebo (Davis 1975).

High-potency first-generation antipsychotic agents are associated with a high risk of extrapyramidal side effects, a moderate risk of sedation, a low risk of orthostatic hypotension and tachycardia, and a low risk of anticholinergic and antiadrenergic effects.

A review of the clinical effects of haloperidol for the management of schizophrenia, given as an example for a high-potency FGA, demonstrated efficacy in short- and longer-term periods compared to placebo, but also a high propensity to cause movement disorders (Joy et al. 2004) (*Level A*).

Low-potency first-generation antipsychotic agents are associated with a lower risk of extrapyramidal effects, a high risk of sedation, a high risk of orthostatic hypotension and tachycardia, and a high risk of anticholinergic and antiadrenergic effects. Especially because of sedation and orthostatic hypotension, the dose should be increased gradually. A review of the efficacy of chlorpromazine compared to placebo as an example of a low-potency FGA supported the view that there is slight superior improvement under chlorpromazine therapy, focusing on continuous outcome data, but more side effects like sedation (Thornley et al. 2004) (*Level A*).

Second-generation antipsychotics

Although the efficacy of FGA in reducing positive symptoms and relapse was impressive the problems of only partially responding negative symptoms, cognitive dysfunction, reduced quality of life and functional impairment remained unsolved. A major shortcoming of FGA's contribution to the mentioned problems was that they produce significant adverse effects, most notably extrapyramidal effects (EPS) and subjective dysphoria in many patients, leading to reduced tolerability and adherence. These facts stimulated the development of second-generation antipsychotics (SGAs), the most significant advantage of which is the lower propensity for EPS, especially tardive dyskinesia. In addition, the SGAs demonstrated better efficacy in treating negative symptoms, cognitive disturbances, and depressive symptoms, a clinical profile that is often described as a broader spectrum of clinical efficacy (Möller 2000a,b). SGAs carry some risks like disturbances of glucose utilisation, lipid metabolism and weight gain, which are already known from some of the conventional antipsychotics, but which may be even more pronounced in some SGAs. At the time of development of this guideline the following second-generation antipsychotics (SGAs) are available either in most European countries or on the Australian and US market: *amisulpride*, *aripiprazole*, *clozapine*, *olanzapine*, *quetiapine*, *risperidone*, *ziprasidone* and *zotepine*. The available administration forms of these SGAs differ. All these medications can be administered in oral forms as pill or tablets. Amisulpride and risperidone are available as oral concentrates, olanzapine and risperidone in quick-dissolving tablets, olanzapine and ziprasidone as short-acting intramuscular preparations, and risperidone as a long-acting injectable preparation.

A meta-analysis evaluating the efficacy of SGAs compared to placebo including three RCTs of risperidone, two RCTs of olanzapine and four RCTs of quetiapine, calculated the effect size for the categorical response rate as about 0.67, and greater than 0.82 for continuous measure in favour of the SGAs, and concluded that there is statistical superiority of a SGA in therapeutic dose compared to placebo (Woods et al. 2001). Placebo response rates varied from 8 to 58% across the trials, in part explained by response definitions used in the studies. In addition, the review suggested the superiority of ziprasidone, not marketed at the time of the analysis, compared to placebo, similar to the other mentioned SGAs.

Comparing the efficacy of FGAs versus SGAs. There is still an ongoing controversial debate as to whether SGAs, as a group, are superior to FGAs in their efficacy and effectiveness in the treatment of schizophrenia. Recent meta-analyses reported the crucial points in randomised, controlled studies (Sartorius et al. 2002). In a systematic overview and meta-regression analysis of randomised controlled trials, substantial heterogeneity was observed in the study results comparing SGAs to FGAs, which was partially accounted for by the dose of the FGAs used. When the dose was about 12 mg/day of haloperidol (or equivalent), atypical antipsychotics were found to have no benefits in terms of efficacy or overall tolerability, but to cause fewer extrapyramidal side effects (Geddes et al. 2000). In a meta-analysis of randomised efficacy trials comparing SGAs and FGAs, and comparing different SGAs, effect sizes of clozapine, amisulpride, risperidone and olanzapine were greater than those of FGAs, and the effect of zotepine was marginally geater, while other SGAs revealed no clear superiority (Davis et al. 2003). No difference in efficacy was detected among amisulpride, risperidone and olanzapine when directly compared to each other. No evidence was found that the haloperidol dose (or all FGA comparators converted to haloperidol-equivalent doses) affected these results. In a review of studies evaluating efficacy and tolerability of olanzapine, risperidone, quetiapine and sertindole, superiority to placebo was reported (Leucht et al. 1999). Quetiapine and sertindole were found to be comparable to haloperidol, while olanzapine and risperidone showed slightly superior efficacy in the treatment of global schizophrenic symptoms. In addition, olanzapine and risperidone were found to demonstrate slight superiority in improvement of negative symptoms. All SGAs were noted to be associated with less frequent EPS measured as the use of antiparkinsonian medications compared to haloperidol. A meta-analysis of all randomised controlled trials in which SGAs had been compared with low-potency (equivalent or less potent than chlorpromazine) FGAs found that, as a group, SGAs were moderately

more efficacious than low-potency antipsychotics, largely irrespective of the comparator doses used (Leucht et al. 2003). Furthermore the observation has been made that low-potency FGAs in doses lower than 600 mg/day chlorpromazine (CPZ) equivalents might not induce more EPS than SGAs.

Antipsychotic monotherapy should be preferred and the minimum effective dose should be used. The optimal dose for each patient has to be found by clinical judgment. Recommended acute phase treatment dosages for commonly used antipsychotics are given in Table III.

Pharmacokinetics and pharmacogenetics

First-generation antipsychotic medications can be administered in oral forms, as intravenous applications, as short-acting intramuscular preparations, or as long-acting injectable preparations. Short-acting intramuscular medications reach a peak concentration 30–60 minutes after the medication is administered, whereas oral medications reach a peak after 2–3 hours (e.g., Dahl 1990). As a result, the calming effect of the first-generation antipsychotics may begin more quickly when the medication is administered parenterally. However, this calming effect on agitation is different from the antipsychotic effect, which may require several days or weeks. Oral concentrates are typically better and more rapidly absorbed than pill preparations, and often approximate intramuscular administration in their time to peak serum concentrations. Phenothiazines are potent inhibitors of cytochrome P450 enzyme CYP 2D6 and may therefore impair the elemination of substrates for this isoform. Zuclopenthixol is metabolised by CYP 2D6, and haloperidol by CYP 2D6, CYP 1A4 and CYP 3A4 (Spina et al. 2003).

Second-generation antipsychotics show similar pharmacokinetics to those of FGAs. SGAs are rapidly and completely absorbed after oral administration but often undergo extensive first-pass hepatic metabolism (Burns 2001). Time to peak plasma concentrations ranges from 1 to 10 hours. Atypical agents are highly lipophilic, highly protein-bound, and tend to accumulate in the brain and other tissues. The liver extensely metabolises SGAs, predominantly by cytochrome P450 enzymes. SGAs are only weak *in vitro* inhibitors of CYP isoenzymes at therapeutic concentrations and therefore not expected to interfere with elimination of coadministered medication (Spina et al. 2003). Due to large interindividual variations in biotransformation and presence of active metabolites that are not readily measured, there is often little correlation between dose, serum concentration and clinical effects (Burns 2001).

A number of medication interactions can have clinically important effects for patients treated with FGAs and SGAs (APA 2004). Coadministration of drugs that inhibit or interfere with cytochrome P450 enzymes (e.g., heterocyclic antidepressants, some β-blockers, cimetidine, caffeine, erythromycin, fluvoxamine, fluoxetine, paroxetine, sertraline) may lead to a significant increase in plasma levels and increase

Table III. Recommended dosage (orally) of selected antipsychotics in acute phase treatment.

Antipsychotic	Starting dose (mg/day)	DI[1]	Target dose first-episode (mg/day)	Target dose multi-episode (mg/day)	Maximal dosage (mg/day)[2]
SGA					
Amisulpride	200	(1)–2	100–300	400–800	1200
Aripiprazole	(10)–15	1	15–(30)	15–30	30
Clozapine[3]	25	2–(4)	100–250	200–450	900
Olanzapine	5–10	1	5–15	5–20	20
Quetiapine	50	2	300–600	400–750	750
Risperidone	2	1–2	1–4	3–6–(10)	16
Ziprasidone	40	2	40–80	80–160	160
Zotepine	25–50	2–(4)	50–150	100–250	450
FGA					
Chlorpromazine	50–150	2–4	300–500	300–1000	1000
Fluphenazine	0.4–10	2–3	2.4–10	10–20	20–(40)
Flupenthixol	2–10	1–3	2–10	10–20	60
Haloperidol	1–10	(1)–2	1–4	3–15	100
Perazine	50–150	1–2	100–300	200–600	1000
Perphenazine	4–24	1–3	6–36	12–42	56
Pimozide	1–4	2	1–4	2–12	16
Zuclopenthixol	2–50	1–3	2–10	25–50	75

[1]DI (dose intervals): recommended distribution of the daily dose – once = 1, twice = 2 etc.
[2]Maximal approved dosage in many countries. In clinical practice some SGAs are even dosed higher.
[3]Clozapine is usually not introduced to first-episode patients.

side effects like sedation, hypotension and EPS; inducers of CYP enzymes (e.g., phenytoin, nicotine, rifampicin) can significantly reduce antipsychotic levels. Barbiturates and carbamazepine decrease plasma levels through effects on cytochrome P450 enzymes and reduce antipsychotic effect. In particular, changes in smoking status may especially affect clozapine levels.

Further information about the pharmacokinetic properties of the SGAs (Prior and Baker 2003; Raggi et al. 2004) are presented in Table IV.

Pharmagenetic aspects focus mainly on different genotypes of cytochrome P450 enzymes responsible for variations in drug metabolism. In particular, CYP 2 D6 activity can vary up to 1000-fold in the population due to 70 or more genetic variants that confer a decreased, normal or increased enzyme activity (Albers and Ozdemir 2004). In 5–8% of Caucasians and 1–5% of African-Americans and Asians, the activity of the CYP 2D6 enzyme is very low or absent and they are therefore so-called 'poor metabolisers' (APA 2004). For this reason, blood levels of psychotropic agents metabolised by CYP 2D6 (e.g., risperidone) may increase and these substances may cause undesirable side effects even when administered in therapeutic doses. In contrast, ultrarapid metabolisers (due to multiple copies of the CYP 2D6 gene) have subtherapeutic drug exposure and may be incorrectly labelled as non-compliant or treatment resistant (Albers and Ozdemir 2004).

Side effects

Differences in the risk of specific side effects of antipsychotic medications are often predictable from the receptor binding profiles of the various agents. Some side effects result from receptor-mediated effects within the central nervous system (e.g., extrapyramidal side effects, hyperprolactinemia, sedation) or outside the central nervous system (e.g., constipation, hypotension), whereas other side effects are of unclear pathophysiology (e.g., weight gain, hyperglycemia). Shared side effects of FGAs and SGAs include neurological effects (i.e. acute and chronic extrapyramidal effects, neuroleptic malignant syndrome), sedation, cardiovascular effects (i.e., hypotension, tachycardia and conduction abnormalities), anticholinergic and antiadrenergic effects, weight gain and glucose and lipid metabolic abnormalities, and sexual dysfunction, all in a class- and substance-specific (often dose-related) frequency and intensity. Table V gives an overview of the estimated frequency of some important side effects of the SGAs and haloperidol. Table VI gives recommendations for monitoring.

Neurological side effects

Extrapyramidal side effects. Extrapyramidal side effects can be divided into acute and chronic categories. Acute extrapyramidal side effects are signs and symptoms that occur in the first days and weeks of antipsychotic medication administration, are dose dependent, and are reversible with medication dose reduction or discontinuation (Goetz and Klawans 1981). *Acute dystonia* typically occurs with high-potency FGAs and more frequently in young, male patients, but has also been reported in association with SGAs, e.g., risperidone (Rupniak et al. 1986; Leucht et al. 1999). *Antipsychotic-induced parkinsonism* is thought to affect 10–80% (depending on population and doses) of patients undergoing therapy with high-potency FGAs (Bollini et al. 1994). *Akathisia* occurs with a mean frequency of approximately 20–25% in patients undergoing treatment with FGAs (Braude et al. 1983; Grebb 1995). *Tardive dyskinesia* (TD) may persist after medication dis-

Table IV. Pharmacokinetics of selected antipsychotics.

Agent	Maximal plasma level (in hours)	Elimination half-time (in hours)	CYP enzymes*
FGAs			
Chlorpromazine	2–4	30	1A2, 2D6, 3A4
Haloperidol	3–6	14–20	2D6, 3A4
SGAs			
Amisulpride	1–3	12–20	?
Aripiprazole	3–5	75–146 (94)	2D6, 3A4
Clozapine	1.5–3.6	16–23	1A2, 3A4, (2C19, 2D6)
Olanzapine	5–8	21–54	1A2, (2C19, 2D6)
Quetiapine	1.0–1.8	6.8	3A4
Risperidone	0.8–1.4	3.6	2D6, (3A4)
Ziprasidone	3.8–5.2	3.2–10	3A4, (1A2, 2D6)
Zotepine	2.8–4.5	8–16 (12)	3A4, (1A2, 2D6)

*Secondary involved enzymes in parentheses. (Burns 2001, modified).

Table V. Selected side effects of commonly used antipsychotics.

	Antipsychotic medication							
Side effect	Haloperidol	Amisulpride	Clozapine	Olanzapine	Risperidone	Quetiapine	Ziprasidone	Aripiprazole
Akathisia/ Parkinsonism	+++	0–+	0	0–+	0–++	0–+	0–+	+
Tardive dyskinesia	+++	(+)	0	(+)	(+)	?	?	?
Seizures	+	0	++	0	0	0	0	(+)
QT-prolongation	+	(+)	(+)	(+)	(+)	(+)	+	0 (?)
Glucose abnormalities	(+)	(+)	+++	+++	++	++	0	0
Lipid abnormalities	(+)	(+)	+++	+++	++	++	0	0
Constipation	+	++	+++	++	++	+	0	0
Hypotension	++	0	(+)	(+)	++	++	+	+
Agranulocytosis	0	0	+	0	0	0	0	0
Weight gain*	+	+	+++	+++	++	++	0–+	+
Prolactin elevation	+++	+++	0	(+)	++	(+)	(+)	0
Galaktorrhoea	++	++	0	0	++	0	0	0
Dysmenorrhoea/Amenorrhoea	++	++	0	0	++	(+)	0	0
Sedation	+++	0–(+)	+++	+–++	+	++	0–(+)	0
Malignant neuroleptic syndrome	(+)	?	(+)	(+)	(+)	(+)	?	(+)

Note: Frequency and severity of side effects refers to information obtained by drug companies, FDA, additional literature and other guidelines (e.g., APA 2004).

0 = no risk; (+) = occasionally, may be no difference to placebo; + = mild (less 1%); ++ = sometimes (less 10%); +++ = frequently (>10%); ? = no statement possible due to lacking data.

*Weight gain during 6–10 weeks: + = low (0–1.5 kg); ++ = medium (1.5–3 kg); +++ = high (>3 kg).

continuation and occurs with an incidence of 4(–8)% per treatment year with conventional antipsychotics (Glazer 2000). After 4 years of therapy with high-potency FGAs, approximately 20% of patients have tardive dyskinesia and the rate is higher (up to 50%) in elderly patients (Fenton 2000; Glazer 2000; Jeste 2000). Risk factors are age, female gender, the presence of drug-induced parkinsonian symptoms, diabetes mellitus, affective disturbances and higher dose and longer duration of antipsychotic therapy (Morgenstern 1993). SGAs induce fewer extrapyramidal symptoms (EPS) in a therapeutic dose range than FGAs and show a significant reduction in the risk of tardive dyskinesia compared to FGAs (Leucht et al. 1999; Correll et al. 2004). Studies provided evidence that clozapine- and probably quetiapine-induced EPS are not dose dependent (Buchanan et al. 1995; Cheer and Wagstaff 2004).

Neuroleptic malignant syndrome. Neuroleptic malignant syndrome (NMS) is characterised by dystonia, rigidity, fever, autonomic instability such as tachycardia, delirium, myoglobinuria and increased levels of creatine kinase, leukocytes and hepatic enzymes. The prevalence of NMS is uncertain; it probably occurs in less than 1% of patients treated with FGAs (Adityanjee et al. 1999) and is even more rare among patients treated with SGAs (e.g., Caroff et al. 2000). Risk factors for NMS include acute agitation, young age, male gender, preexisting neurological disability, physical illness, dehydration, rapid escalation of antipsychotic dose, use of high-potency medications and use of intramuscular preparations (Pelonero et al. 1998).

Epileptic seizures. Epileptic seizures occur in an average of 0.5–0.9% of patients receiving antipsy-

Table VI. Monitoring for patients on second generation antipsychotics*

	Baseline	4 Weeks	8 Weeks	12 Weeks	Quarterly	Annually
Personal/family history	x					x
Weight (BMI)	x	x	x	x	x	x
Waist circumference	x					x
Blood pressure	x	x		x		x
Fasting plasma glucose	x			x		x
Fasting lipid profile	x			x		x
Blood cell count	x	x		x		x
ECG	x					

BMI, body mass index; ECG, electrocardiogram.

*More frequent assessments may be warranted based on clinical status.

Note: Assessments refer mainly to American Diabetes Association and American Psychiatric Association, Diabetes Care 2004;27:596–601.

chotic medications (Devinsky et al. 1991), whereby clozapine is associated with the highest incidence rate (ca. 3%) and cumulative risk (ca. 10%) after 4 years of treatment (e.g., Devinsky et al. 1991; Buchanan et al. 1995). The dose and initial dose increases of clozapine appear to represent risk factors for epileptic seizures (Devinsky et al. 1991). Dose-dependent epileptic seizures at relevant rates (7–17%) have also been described with zotepine (Hori et al. 1992).

Cognitive side effects. Although antipsychotic medications can effectively improve cognitive functions in schizophrenic patients, memory problems and cognitive disorders represent possible side effects of antipsychotic therapy, which are particularly associated with the anticholinergic effect of antipsychotic medications and the use of anticholinergic agents such as biperiden. Drug-induced cognitive disorders have been more frequently reported in treatment with typical antipsychotic medications (Buchanan et al. 1994; Keefe et al. 1999; Meltzer and McGurk 1999; Purdon et al. 2000; Harvey and Keefe 2001; Bilder et al. 2002; Green et al. 2002; Velligan et al. 2002).

Sedation. Sedation is a common side effect of FGAs, as well as several of the SGAs, and may be related to antagonist effects of those drugs on histaminergic, adrenergic and dopaminergic receptors (e.g., Kinon and Lieberman 1996). Sedation occurs more frequently with low-potency typical antipsychotic medications and clozapine. Sedation is most pronounced in the initial phases of treatment, since most patients develop some tolerance to the sedating effects with continued administration.

Obesity and weight gain

Individuals with schizophrenia are more likely to be overweight or obese than the population at large (Marder et al. 2004). Combined with other risk factors like smoking, reduced physical activity, diabetes and hyperlipidemia the risk for cardiovascular morbidity and mortality is increased. Besides life style factors, such as poor diet and lack of exercise, treatment with FGAs and SGAs can contribute to weight gain (Marder et al. 2004). Weight gain is a multifactorial occurrence during treatment with neuroleptic agents. According to a meta-analysis, the mean weight gain associated with atypical antipsychotic medications is highest with clozapine and olanzapine, and lower with risperidone, whereas ziprasidone hardly affects body weight (Allison et al. 1999). The side effect of weight gain has to be given due consideration, as it affects therapy adherence, somatic sequelae, mortality, stigmatisation and quality of life (Allison et al. 2003). Therefore clinicians should sensitise patients and their caregivers to the health risk associated with excess weight and should encourage patients to self-monitor their weight. Body mass index (BMI) and waist size can serve as useful risk indicators (Marder et al. 2004).

Metabolic side effects

Diabetes. There is evidence that schizophrenia itself is an independent risk factor for impaired glucose tolerance, which is a known risk factor for developing type 2 diabetes, regardless of whether patients receive antipsychotic medication (Bushe and Holt 2004; Ryan et al. 2003). The interactions between schizophrenia and diabetes are likely to be multifactorial and include genetic and environmental factors. Besides endocrine stress sytems like the sympathetic–adrenal–medullary system and the hypothalamic–pituitary–adrenal axis, life style factors such as poor diet, obesity and lack of exercise are involved in the genesis of diabetes (Dinan 2004; Marder et al. 2004). Pharmaco-epidemiological studies revealed a higher rate of diabetes in patients receiving atypical antipsychotics compared with those not receiving antipsychotics or with those receiving conventional agents (Haddad 2004). Studies attempting to establish whether the association with diabetes varies between different atypical antipsychotics are inconclusive (Koro et al. 2002a; Wirshing et al. 2002; Bushe and Leonard 2004; Haddad 2004). Nevertheless clozapine and olanzapine were thought to be the agents most commonly associated with diabetes (Marder et al. 2004). As a consequence, a baseline measure of (fasting) plasma glucose levels should be collected for all patients before starting a new antipsychotic, alternatively hemoglobin A_{1c} should be measured (Marder et al. 2004). Patients and their caregivers should be informed about the symptoms of diabetes and patients should be monitored at regular intervals for the presence of these symptoms (*GCP*).

Hyperlipidemia. Retrospective reports and pharmacoepidemiological studies found a significantly greater extent of elevations of lipids (trigylcerides) in patients taking certain atypical antipsychotic medications (olanzapine and clozapine) than in patients receiving other antipsychotics (e.g., haloperidol, quetiapine, risperidone) (Koro et al. 2002b; Wirshing et al. 2002). Similar to diabetes, hyperlipidemia is linked to a multifactorial genesis and is associated with obesity and life-style factors like poor diet and lack of exercise. Elevated triglyceride and

cholesterol levels are associated with coronary heart disease, including ischaemic heart disease and myocardial infarction. Therefore total cholesterol, low-density lipoprotein (LDL) and HDL cholesterol, and triglyceride levels should be measured (Marder et al. 2004). If the LDL level is greater than 130 mg/dl the patient should be referred to an internist to evaluate whether treatment with a cholesterol-lowering drug should be initiated.

Hyperprolactinemia and sexual dysfunction

Antipsychotics–particularly FGAs, amisulpride and risperidone–can cause hyperprolactinemia by blocking dopamine D2 receptors (Mota et al. 2003; Marder et al. 2004). Hyperprolactinemia can lead to galactorrhoea, menstrual, cyclical and sexual disturbances in women, and reproductive and sexual dysfunction and galactorrhoea/gynaecomastia in men (Dickson and Glazer 1999). Plasma prolactin concentrations may remain elevated for up to 2 weeks after the cessation of oral therapy with a conventional antipsychotic, and for up to 6 months after cessation of depot therapy (Cutler 2003). Studies of SGAs (with the exception of amisulpride and risperidone) suggested that the transiently elevated prolactin levels tended to return to the normal range within a few days (Marder et al. 2004). Effects on dopaminergic, adrenergic, cholinergic and serotonergic mechanisms may also lead to sexual dysfunction, whereby it is difficult to distinguish between this and disease-related impairment of sexual activity (Baldwin and Birtwistle 1997; Fortier et al. 2000). Peripheral α-adrenergic blockade can be responsible for priapism (Cutler 2003). Of the SGAs, clozapine, olanzapine and ziprasidone were associated with only little or modest prolactin elevation (Cutler 2003), and quetiapine did not lead to hyperprolactinemia (Arvanitis et al. 1997). A clear association between prolactin elevation and sexual dysfunction has not been established (Aizenberg et al. 1995; Kleinberg et al. 1999). There is still an ongoing debate as to whether hyperprolactinemia increases the risk of breast cancer, and the studies are inconclusive to date (Marder et al. 2004). Hyperprolactinemia is suspected to cause osteoporosis if it impairs sex steroid production.

Cardiovascular side effects

Hypotension and orthostatic hypotension are related to the α-antiadrenergic effects of antipsychotic medications, and are therefore particularly associated with low-potency typical antipsychotic medications and some SGAs, e.g., clozapine (Buchanan et al. 1995; APA 2004). Patients who experience severe postural hypotension must be cautioned against getting up quickly and without assistance as falls can result in hip fractures and other accidents, particularly in elderly patients. Gradual dose titration, starting with a low dose, and monitoring of orthostatic signs minimises the risk of complications due to orthostatic hypotension. *Tachycardia* is particularly relevant in pre-existing cardiac disease. Tachycardia can result from the anticholinergic effects of antipsychotic medications, but may also occur as a result of postural hypotension. Tachycardia unrelated to orthostatic blood pressure changes that result from anticholinergic effects may occur in up to 25% of patients treated with clozapine (APA 2004). *Cardiac side effects* of antipsychotic medications registered as ECG-abnormalities include prolongation of the QT interval, abnormal T-waves, prominent U-waves and widening of the QRS complex (Haddad and Anderson 2002). The average QTc interval in healthy adults is approximately 400 ms. *QTc prolongation* (QTc intervals above 500 ms) is associated with an increased risk of torsade de pointes and transition to ventricular fibrillation (Glassman and Bigger 2001). At varying rates, all antipsychotics may cause (dose-dependent) cardiac side effects; of the FGAs, this predominantly applies to tricyclic neuroleptic agents of the phenothiazine type (e.g., chlorpromazine, promethazine, perazine and, especially, thioridazine) and to pimozide. In addition, high-dose intravenous haloperidol has been associated with a risk of QTc prolongation (Al Khatib et al. 2003). Of the SGAs, sertindole and ziprasidone were found to lengthen the QT interval in a significant manner (Glassman and Bigger 2001; Marder et al. 2004). Prior to commencement, and at subsequent increases of dose, of antipsychotic therapy with thioridazine, mesoridazine and pimozide, ECG monitoring is obligatory. This recommendation also applies to ziprasidone if cardiac risk factors, like known heart disease, congenital long QT syndrome, personal history of syncope and family history of sudden death at an early age, are present. If these risk factors are present, thioridazine, mesoridazine and pimozide should not be given (Marder et al. 2004). The application of two or more antipsychotics or other adjunctive agents could increase the risk of cardiac side effects (e.g., QTc prolongation). Case reports indicate that the use of clozapine is associated with a risk of *myocarditis* in 1 per 500 to 1 per 10,000 treated patients (Killian et al. 1999; Warner et al. 2000; La Grenade et al. 2001). If the diagnosis is probable, clozapine should be stopped immediately and the patient referred urgently to a specialist for internal medicine (Marder et al. 2004).

Other side effects

Hematological effects, like inhibition of leukopoiesis, occur in patients being treated with chlorpromazine, for example, as benign leukopenia in up to 10% and as agranulocytosis in approximately 0.3% of patients (APA 2004). The risk of agranulocytosis (defined as an absolute neutrophil count less than 500/mm^3) has been estimated at 0.05–2.0% of patients per year of treatment with clozapine (Buchanan et al. 1995). The risk is highest in the first 6 months of treatment, and therefore weekly white blood cell (WBC) and neutrophil monitoring is required. After 18 weeks, the monitoring rate may be reduced to every 2–4 weeks, as the risk of agranulocytosis appears to diminish considerably (an estimated rate of three cases per 1000 patients). WBC counts must remain above 3000/mm^3 during clozapine treatment, and absolute neutrophil counts must remain above 1500/mm^3. With maintenance treatment, patients should be advised to report any sign of infection immediately (e.g., sore throat, fever, weakness or lethargy) (APA 2004).

Allergic and dermatological effects, including photosensitivity, occur infrequently but are most common with low-potency phenothiazine medications. Patients should be instructed to avoid excessive sunlight and use sunscreen (APA 2004). *Hepatic effects* like elevated hepatic enzymes may be triggered by a number of antipsychotic medications, but this is usually asymptomatic. Direct hepatotoxicity or cholestatic jaundice occur extremely rarely and are particularly associated with low-potency phenothiazines (APA 2004). In studies involving olanzapine, reversible, mainly slight elevations in hepatic enzymes have been reported (Beasley et al. 1996a). *Ophthalmological effects* due to pigment accumulation in the lens and cornea, retinopathies, corneal oedema, accommodation disturbances and glaucoma have also been described as side effects of antipsychotic medication. To prevent pigmentary retinopathies, corneal opacities and cataracts, patients maintained on thioridazine and chlorpromazine should have periodic ophthalmological examinations (approximately every 2 years for patients with a cumulative treatment of more than 10 years), and a maximum dose of 800 mg/day of thioridazine is recommended (APA 2004). As cataracts were observed in beagles that were given quetiapine, psychiatrists should ask about the quality of distance vision and about blurry vision, and should refer to an ocular evaluation yearly or every 2 years (Marder et al. 2004). *Urinary tract problems*, such as urinary retention and urinary incontinence, may be particularly provoked by antipsychotic medications with marked anticholinergic components such as phenothiazines and those with cholinergic effects. *Dry mouth and eyes* and *constipation* may result from adrenergic and anticholinergic stimulation, often described during treatment with FGAs. *Sialorrhoea* and drooling occur relatively frequently with clozapine treatment and are most likely due to decreased saliva clearance related to impaired swallowing mechanisms, or possibly as a result of muscarinic cholinergic antagonist activity at the M4 receptor or to α-adrenergic agonist activity (Rabinowitz et al. 1996).

Adjunctive medications

Benzodiazepines. The efficacy of benzodiazepines in schizophrenia has been evaluated as monotherapy and as adjuncts to antipsychotic medications (APA 2004). In a review of double-blind studies of benozidazepines as monotherapy, superior effects compared to placebo (reductions in anxiety, agitation, global impairment or psychotic symptoms) were reported in most, but not all studies (Wolkowitz and Pickar 1991). Seven of 16 double-blind studies evaluating benzodiazepines as adjuncts to psychotic medication showed positive effects on anxiety, agitation, psychosis or global impairment; five of 13 demonstrated efficacy in treating psychotic symptoms (Wolkowitz and Pickar 1991). It was noted that benzodiazepines may improve the response to antipsychotic medications, but this effect may be limited to the acute phase and not be sustained (e.g., Altamura et al. 1987; Csernansky et al. 1988). The efficacy in patients with prominent agitation was one of the most consistent findings in retrospective and open-label studies (e.g., Salzman et al. 1991; Wolkowitz and Pickar 1991) (*Level A*). Common side effects of benzodiazepines include sedation, ataxia, cognitive impairment and a tendency to cause behavioural disinhibition in some patients.

Mood stabilisers and anticonvulsants. A recent meta-analysis including 20 double-blind RCTs using dichotomous response criteria (e.g., symptom reduction at least 50% of baseline level) found no advantage of *lithium* as a sole agent compared to placebo or to antipsychotics, but a slight superiority of lithium versus placebo augmentation to antipsychotics (focusing primarily on nonresponders) (Leucht et al. 2004a). In addition, lithium as a sole agent was inferior to antipsychotics if patients with schizoaffective disorder were excluded from analysis. Overall there is evidence for superior efficacy of lithium augmentation to antipychotics, especially in patients with mood symptoms (*Level A*) and treatment-resistant schizoprenia (*Level B*). Patients should be monitored for adverse effects that are

commonly associated with lithium (e.g., polyuria, tremor) and with its interaction with an antipsychotic medication (e.g., EPS, confusion, deterioration, other signs of neuroleptic malignant syndrome), including short-time evaluation of blood levels, particularly during the initial period of combined treatment (APA 2004).

A recent review identified five randomised, controlled studies examining the efficacy of *valproate* as an adjunct to antipsychotics in schizophrenia (Basan et al. 2004). One of these trials was single-blind (Hesslinger et al. 1999), the others double-blind (Fisk and York 1987; Dose et al. 1998; Wassef et al. 2000; Casey et al. 2003a). The overall results of this meta-analysis were inconclusive. In summary, there is limited evidence that adding valproate to antipsychotic treatment may be successful in reducing specific symptoms, e.g., hostility (Citrome et al. 2004), and therefore it may useful to introduce valproate to special patient populations, but not to use it in general when treating schizophrenia (*Level C*).

A meta-analysis including 10 double-blind RCTs found that *carbamazepine*, compared to placebo and compared to antipsychotics as the sole treatment for schizophrenia, revealed no beneficial effect (Leucht et al. 2004b). Carbamazepine augmentation of antipsychotics versus placebo was superior compared with antipsychotics alone in terms of overall improvement, but there were no differences for mental state outcomes (Leucht et al. 2004b). There is limited evidence that adding carbamazepine to antipsychotic treatment may be successful in reducing specific symptoms, e.g., aggressive behaviour or affective symptoms (Luchins 1987; Okuma et al. 1989), but not for its general use in treating schizophrenia (*Level C*).

In treatment-resistant schizophrenia, the addition of *lamotrigine* (200 mg/day) to an ongoing clozapine treatment was effective in reducing positive and general psychopathological symptoms in one RCT (Tiihonen et al. 2003); in another RCT, adding lamotrigine (400 mg/day) to conventional antipsychotics, risperidone, olanzapine or clozapine, improved positive and general psychopathology when analysing the completers, but no difference was seen in the 'primary last observation carried forward' analysis (Kremer et al. 2004). There is evidence that lamotrigine as an adjunctive treatment, especially to clozapine, can reduce schizophrenic psychopathology (*Level C*), keeping the potential elevated risk of leucopenia and agranulocytosis in mind (Kossen et al. 2001).

In an open, non-randomised trial no beneficial effect of *topiramate* added to an ongoing treatment with clozapine, olanzapine, risperidone or flupenthixol was seen in treatment-resistant schizophrenia (Dursun and Deakin 2001).

Antidepressants. Studies of antidepressants in schizophrenia focused mainly on their efficacy in treating comorbid depression or negative symptoms (APA 2004). A meta-analysis suggested some evidence for superior improvement of depressive symptoms compared to placebo, while deterioration of psychotic symptoms or worsening of adverse effects, especially EPS, was not noted (Whitehead et al. 2004), although this was described in some individual studies. An earlier review of the use of antidepressants in patients with schizoaffective disorder or schizophrenia with mood symptoms came to a positive conclusion and recommended treatment with antidepressive agents if indicated (Levinson et al. 1999). There is also some evidence for efficacy of antidepressants in negative symptoms of schizophrenia (APA 2004; Möller 2004a) (*Level B*). Since most of the studies were performed in combination with first-generation antipsychotics, findings may be different with second-generation antipsychotics (APA 2004). Clomipramine (Berman et al. 1995) and fluvoxamine (Reznik and Sirota 2000) showed advantages in treating obsessive–compulsive symptoms in schizophrenia, derived from two small open studies (*Level D*). In a crossover study, citalopram revealed efficacy in patients with a history of aggression in that it reduced the frequency of incidents (Vartiainen et al. 1995) (*Level D*).

Others. A meta-analysis of five double-blind RCTs, in which β-blockers were added to standard drug treatment in schizophrenia, found no overall efficacy for this strategy; nevertheless, several small open studies and case reports provided benefits in the outcome of treatment refractory patients (Cheine et al. 2004).

Based on pathophysiological considerations and experimental research the *glutamatergic agents*, *glycine*, *d-cycloserine*, and *d-serine* have been studied as additional treatments to antipsychotics in schizophrenia, with controversial results (Tsai et al. 1998, 1999; Goff et al. 1999; Potkin et al. 1999; Evins et al. 2000; Javitt et al. 2001; Möller 2003; APA 2004). The mainly negative studies of glutamatergic substances as adjuncts to clozapine may be due to their similar action on negative symptoms via the glutamatergic pathway.

Baclofen, a $GABA_B$ agonist, did not show any relevant benefit in open and placebo-controlled double-blind trials in monotherapy or when added to standard antipychotics, following an initial successful case report (Soares et al. 2004; Wassef et al. 2003b). *Piracetam* added to haloperidol at a dose

of 3200 mg/day demonstrated beneficial effects in a placebo-controlled randomised study (Noorbala et al. 1999). *Acetylcholinesterase inhibitors* (e.g., donepezil) revealed, in case reports (Risch et al. 2001) and in an uncontrolled study, positive results on a variety of cognitive measures (Buchanan et al. 2003), but not in a randomised, placebo-controlled trial in patients with chronic schizophrenia (Friedman et al. 2002). *Oestrogen* adjunction (0.05 mg/day) to ongoing haloperidol treatment showed greater improvement in positive symptoms and general psychopathology in women with chronic schizophrenia (Kulkarni et al. 2001; Akhondzadeh et al. 2003), but not in acute schizophrenia (0.625 mg/day conjugated oestrogen added to haloperidol) (Louza et al. 2004). Augmentation with unsaturated *essential fatty acids* (EFA) (e.g., eicosapentaenoic acid) demonstrated controversial results in four randomised placebo-controlled studies with EPA (Emsley et al. 2003). A Cochrane review stated no clear effects of ω-3-fatty acids (Joy et al. 2004), but supported the suggestion of further research in this direction.

Electroconvulsive therapy (ECT)

Electroconvulsive therapy (ECT) was introduced in 1938. It involves the induction of seizures for therapeutic purposes by the administration of a variable frequency electrical stimulus to the brain via electrodes applied to the scalp. The procedure is usually modified by the use of short-acting anaesthetics and muscle relaxants (Tharyan and Adams 2004). In clinical practice the following are recommended: generalised motor seizures of 25–30 seconds duration, monitoring via EEG and by observing motor convulsions in a forearm isolated from muscle relaxants, a stimulus intensity approximately 2.5-fold the seizure threshold, treatment frequencies of twice or three times weekly and of between 12–20 treatments (Tharyan and Adams 2004). The evaluation preceding ECT should consist of a general medical evaluation to identify risk factors (including history and physical examination, assessment of vital signs, basic laboratory tests and ECG), anaesthesia evaluation addressing the nature and extent of anaesthetic risk and obtaining informed consent. Although there are no absolute contraindications to ECT, recent myocardial infarction, cardiac arrhythmias or pacemakers, congestive heart failure or severe coronary heart disease, abdominal and intracranial aneurysm, and intracranial space-occupying lesions are relative contraindications and require extreme caution and consultation of a specialist in internal medicine (APA Task Force 2001). During the informed consent process, information about the procedure, including anaesthesia, should be given and the potential risks and benefits of ECT and alternative therapeutic approaches should be described. In terms of electrode placement, two RCTs comparing bitemporal to unilateral nondominant hemisphere electrode placements in patients with schizophrenia did not show significant differences regarding mental state, global improvement or cognitive functioning (Thayran and Adams 2004). Although findings in patients with depression suggest that unilateral and perhaps bifrontal electrode placement may be associated with fewer cognitive effects, and that efficacy with unilateral electrode placement may depend on the extent to which the stimulus intensity exceeds the seizure threshold, the applicability of these observations to patients with schizophrenia is uncertain (APA 2004). An RCT assessing three different stimulus intensities with bitemporal ECT found that rates of remission and effects on cognition were comparable, but the low-dose remitter group received more ECT treatments and required more days to meet remitter status than the 2- and 4-fold seizure threshold groups (Chanpattana et al. 2001). Clinical case series, primarily from the older literature, suggest that achieving full clinical benefit for patients with schizophrenia may require a longer course of acute treatment than for patients with mood disorders (e.g., Kalinowsky 1943), and one RCT showed advantage for 20 treatments over 12 treatments (Baker et al. 1960).

The efficacy of *acute treatment* with ECT in patients with schizophrenia has been described in case series, uncontrolled studies and controlled trials. Therefore, publication details of reviews and HTA reports have been provided (Hawkins et al. 1995; Fink and Sackeim 1996; Rey and Walter 1997; Walter et al. 1999; APA Task Force 2001; Greenhalgh (UK ECT Group) et al. 2002; Tharyan and Adams 2004). One result of the cited reviews is that antipsychotic treatment alone generally produced better short-term outcomes compared with ECT alone (*Level A*). There is also evidence from at least three studies that ECT leads to a significant better global impression compared to sham (placebo) treatment (Thayran and Adams 2004) (*Level A*). Nevertheless, there are different opinions, and other reviewers did not find a significant advantage for ECT compared with sham treatment regarding mental state (APA 2004). Combined treatment with ECT and first-generation antipsychotic medications (FGAs) was observed to be more effective than treatment with ECT alone in most but not all studies (APA 2004).

A review on efficacy of ECT in *adolescents* identified no controlled trials and showed improve-

ment rates of 63% for depression, 80% for mania, 42% for schizophrenia and 80% for catatonia. In conclusion, ECT in the young seems similar in effectiveness and side effects to ECT in adults, bearing the lack of systematic evidence in mind (Rey and Walter 1997).

Side effects of ECT on the cardiovascular system are common but are typically benign and self-limited (APA Task Force 2001). Seldomly ECT may be associated with more serious cardiac arrhythmias, ischaemia and infarction, although the type, severity and likelihood of cardiac complications are generally related to the type and severity of preexisting cardiac disease (e.g., Rice et al. 1994). ECT treatment and its anaesthesia are often associated with a transient postictal confusional state, at times accompanied by postictal agitation. Cognitive side effects may also be observed with ECT, although there is much individual variation in the extent and severity of such effects (APA Task Force 2001). For most patients, however, the retrograde memory impairment typically resolves in a few weeks to months after cessation of treatment (APA 2004). Rarely do patients report more pervasive or persistent cognitive disruption that involves more distant memories (e.g., Donahue 2000). A comprehensive review concluded that there is no credible evidence that ECT causes structural brain damage (Devanand et al. 1994). ECT more often leads to improvements in concentration and attention (and in consequence memory function), parallel with clinical improvement (Prudic et al. 2000). Other side effects that are commonly noted after ECT include headache, generalised muscle aches, and nausea and/or vomiting. These effects usually resolve spontaneously or with analgesic or antiemetic medications (Datto 2000).

In catatonic schizophrenia, ECT is often the treatment of choice.

In summary, apart from in catatonia, *electroconvulsive therapy (ECT)* should only be used in exceptional cases in treatment-refractory schizophrenia, as no advantages have been consistently demonstrated compared with pharmacological treatments (*Level C*). Most studies of ECT did not conduct a comparison to monotherapy with atypical agents as an alternative. ECT should be considered in catatonia (or severe affective symptoms), as there is limited evidence in trials and clinical knowledge to confirming its efficacy in such cases, and alternative options are rare (*Level C*).

Repetitive transcanial magnetic stimulation (rTMS)

Repetitive transcranial magnetic stimulation (rTMS) is not an approved treatment for neuropsychiatric disorders to date, nevertheless this novel somatic technique has been studied in many neuropsychiatric diseases (Burt et al. 2002). In addition, there are a few controlled trials for ameliorating psychotic symptoms in schizophrenia. Repetitive TMS stimulates cortical neurons noninvasively by magnetic induction, using a brief, high-intensity magnetic field. Advantages of this technique compared to ECT are better tolerability, fewer side effects and no need for anaesthesia. Improvement in auditory hallucinations after stimulation of the left temporal–parietal cortex augmenting antipsychotic treatment was observed in a randomised, double-blind, sham-controlled trial and in two randomised, double-blind, crossover studies, each with small sample sizes (Hoffman et al. 2000, 2003; Rollnik et al. 2000). Another small, randomised, controlled study showed no effect of rTMS stimulating the right dorsolateral prefrontal cortex (Klein et al. 1999). Further research activities are required to evaluate efficacy and potential benefits of rTMS in schizophrenia.

Psychotherapy and psychosocial interventions

As mentioned earlier, these guidelines focus on biological (somatic) treatments of schizophrenia, therefore psychotherapeutic approaches alone or in combination with pharmacotherapy will only be described briefly in these guidelines. The aims of psychological treatment methods in schizophrenic diseases are to reduce the individual vulnerability, alleviate the adverse influence of external stressors, improve the quality of life, reduce the disease symptoms and promote and improve the patient's communication skills and ability to cope with the disease. Psychotherapy has to pay attention to the biological factors involved in schizophrenia and must be aimed at enabling the patient to cope with the disease and its consequences (acceptance of relapses, self-management, coping with problems). Psychotherapeutic and psychosocial interventions become more important in the long-term treatment of schizophrenia and are mostly restricted to counselling/supportive psychotherapy, psychoeducation and family interventions or cognitive behavioural therapy in the acute phase treatment. For this reason, evidence-based evaluation referring to main topics regarding guidelines, meta-analysis and systematic reviews will be presented in the long-term treatment part of these guidelines.

First-episode schizophrenia

A patient with a first episode of symptoms characterizing schizophrenia may be experiencing a schizophrenic episode or the onset of schizophreni-

form disorder, or may be having an episode of another illness or disorder that can cause similar symptoms. Therefore careful initial evaluation and assessment has to be conducted as described above. Observation of a patient, even for a short while, can provide clues to the nature of the diagnosis. In naturalistic and controlled studies, patients with first-episode psychosis were more treatment responsive than patients with multiple episodes of psychosis but, at the same time, quite sensitive to side effects, especially EPS (e.g., Lieberman et al. 1996). Incidence of tardive dyskinesia with low-dose haloperidol was seen at least as often as in other samples treated with standard doses of FGAs, and additional clinical features could not identify subjects at risk for tardive dyskinesia (Oosthuizen et al. 2003). Predictors of reduced treatment response in one study were male sex, obstetric complications in birth history, more severe hallucinations and delusions, attention deficits and development of parkinsonism during antipsychotic treatment (Robinson et al. 1999). In other studies, depressive symptoms at baseline predicted fewer negative symptoms in the course and better outcome (Oosthuizen et al. 2002), and dystonia was associated with younger age, prominent negative symptoms and higher disease severity (Aguilar et al. 1994). Earlier antipsychotic treatment (or shorter duration of untreated psychosis) was associated with better outcomes in first-episode schizophrenia, whereby poor premorbid function could indicate an illness subtype less likely to respond to antipsychotic treatment regardless of when it is initiated (Perkins et al. 2004). Cannabis use, common in first-episode schizophrenics, was noted to cause confusion and delay in treating the psychotic episode.

Efficacy of first-generation antipsychotics. In a 5-week RCT comparing flupenthixol (mean dose 20 mg/day) to pimozide (mean dose 18.8 mg/day), comparable efficacy in improvement of positive symptoms was noted, while response of negative symptoms varied. Pimozide produced a higher elevation of prolactin levels (The Scottish Schizophrenia Research Group 1987). A randomised trial found that a higher dosage of fluphenazine (20 mg/day) revealed better global improvement but more disabling side effects than lower doses (5 and 10 mg/day) (Van Putten et al. 1991). A review evaluating pharmacotherapy of first episode schizophrenia reported that in open trials with subsequent increase of dosage in case of nonresponse, haloperidol led to the best improvement (72% of cases) at doses between 2 and 5 mg daily compared to higher dosages (10–20 mg/day) (Remington et al. 1998). Open, non-comparative 6-week trials of fluphenazine (20 and 40 mg/day) and haloperidol (20–40 mg/day) found that approximately 70% of first-episode patients were stabilised within this period (Remington et al. 1998). In a randomised trial, higher doses of haloperidol (20 mg/day) demonstrated only intermittently (shorter than 2 weeks) better efficacy on psychopathology compared to lower dosages (5 and 10 mg/day), before outcome worsened due to EPS (Van Putten et al. 1990). More recent open (Oosthuizen et al. 2001) and randomised, controlled (Oosthuizen et al. 2004) studies showed low doses of haloperidol (2 mg/day or less) to be at least as effective and better tolerated (lower EPS) than higher doses of haloperidol.

Efficacy of second-generation antipsychotics. Only a few randomised controlled studies are available that compare the efficacy of SGAs with that of FGAs. *Risperidone* compared to haloperidol (mean 6 mg/day) in flexible dosing showed comparable improvement in psychotic symptoms and less EPS in a 6-week trial, demonstrating that already low dosages ($<$6 mg/day) may be successful in controlling symptoms (Emsley et al. 1999). In another RCT with two different doses of risperidone (2 vs. 4 mg/day), patients with the higher dosage demonstrated increased impairment in motor fine-tuning tasks but no better improvement in psychotic symptoms (Merlo et al. 2002). In a non-comparative open trial in first-psychotic-episode patients, low-dose risperidone (lower than 6 mg/day) was concluded to be effective and well tolerated, and significant improvements could be maintained over 1 year of treatment (Huq et al. 2004). These results underline conclusions drawn by other open studies (Kopala et al. 1997; Yap et al. 2001). A small, randomised, open trial of low-dose risperidone compared to low-dose zuclopenthixol revealed no evidence for differential effects on psychopathology or cognitive function, if corrected for the covariates EPS and anticholinergic medication (Fagerlund et al. 2004). Low-dose zuclopenthixol did, however, cause significantly more EPS compared to risperidone. First-episode patients treated with *olanzapine* had superior improvement in overall and positive symptoms and clinical response (Sanger et al. 1999), overall and negative symptoms (Lieberman et al. 2003a) and displayed a lower rate of EPS compared to haloperidol (Sanger et al. 1999; Lieberman et al. 2003a). In a randomised double-blind study comparing the neurocognitive effects of olanzapine and low doses of haloperidol, a beneficial effect on neurocognitive function could be observed for olanzapine, but the difference in benefit to low-dose haloperdiol was small (Keefe et al. 2004). In a prospective, comparative, open, non-randomised trial comparing

olanzapine to conventional agents, superior efficacy in clinical response, positive and negative symptoms, agitation and depression, and lower frequency of EPS were observed with olanzapine (Bobes et al. 2003). Patients with first-episode schizophrenia treated with *clozapine* yielded more rapid improvement and remission, demonstrated better improvement in clinical global impressions and showed a reduced EPS-rate compared to chlorpromazine (Lieberman et al. 2003b). In a Cochrane Review including two RCTs (Emsley et al. 1999; Sanger et al. 1999) the authors consistently found no superior efficacy of SGAs versus FGAs in first-episode schizophrenia, nevertheless lower EPS rates (reduced use of anticholinergics) were observed in patients treated with risperidone or olanzapine compared to haloperidol, and olanzapine revealed superior improvement in global psychopathology (Rummel et al. 2003). Another review suggested SGAs as first-line treatment for first-episode patients (Bradford et al. 2003).

In a randomised double-blind study comparing *olanzapine* (mean dose 15 mg/day) to *risperidone* (mean dose 4 mg/day) no difference in efficacy on positive and negative symptoms, and in the frequency and severity of adverse events, could be detected (van Bruggen et al. 2003).

In *summary* there is evidence for efficacy of FGAs (particularly haloperidol, flupenthixol, pimozide, chlorpromazine, all *Level C*) and SGAs (particularly clozapine, *Level C*, olanzapine and risperidone, both *Level B*) in the treatment of patients with first-episode schizophrenia.

General recommendations. In some recent guidelines, initial treatment is recommended in an outpatient or home setting if possible, because this approach can minimise trauma, disruption and anxiety for the patient and family, who are usually poorly informed about mental illness and have fears about and prejudices against inpatient psychiatric care (NICE 2002; RANZCP 2003). In other guidelines these benefits are weighed against the advantages of a hospital setting, which allows more careful monitoring of the psychotic symptoms as well as any side effects, including acute dystonia, akathisia or neuroleptic malignant syndrome arising from treatment with antipsychotic medications (DGPPN 1998; APA 2004). Inpatient care is required if there is a significant risk of self-harm or aggression, if the level of support in the community is insufficient, or if the crisis is too great for the family to manage, even with home-based support. Inpatient care should be provided in the least restrictive environment (RANZCP 2003). Unfortunately, the preceding recommendations can be followed only in an ideal situation. Often, with psychotic and possibly violent patients, an adequate diagnostic interview or physical examination cannot be conducted. Nevertheless, no matter how agitated the patient, the admitting staff should do everything they can to make sure that the patient is not suffering from another disorder that requires emergency help (APA 2004).

Pharmacological treatments should be introduced with great care in medication-naive patients. Skilled nursing care, a safe and supportive environment, and regular and liberal doses of benzodiazepines could be given to relieve distress, insomnia and behavioural disturbances secondary to psychosis, while antipsychotic medication takes effect (RANZCP 2003).

Choice of antipsychotic medication. Based on the results of the cited studies and clinical experience, first-line use of SGAs (except clozapine) is recommended for individuals with newly diagnosed schizophrenia, mostly on the basis of better tolerability and reduced risk of EPS, especially tardive dyskinesia (NICE 2002; RANZCP 2003; APA 2004). Early use of clozapine may be considered if suicide risk is prominent or persistent (RANZCP 2003), but usually clozapine should not be the drug of choice in first-episode schizophrenia. In the longer term, the risk–benefit ratio may change for some patients, for example if weight gain or sexual side effects associated with the SGA develop (RANZCP 2003).

Dosage. First SGAs, and second-line FGAs, at the lower end of the standard dose range are the preferred treatments for a person experiencing a first episode of schizophrenia (DGPPN 1998; NICE 2002; RANZCP 2003; APA 2004). Based on the mentioned findings, this dosage recommendation is mostly confirmed for haloperidol and risperidone (*Level B*), whereas for other antipsychotics there is only sparse evidence (*Level D*).

Acute exacerbation (relapse)

The most common contributors to symptom relapse are antipsychotic medication non-adherence, substance use, and stressful life events, although relapses are not uncommon as a result of the natural course of the illness, despite continuing treatment. If nonadherence is suspected, it is recommended that the reasons for it be evaluated and considered in the treatment plan (DGPPN 1998; APA 2004).

Efficacy of first-generation antipsychotics. In a review, with the exception of mepazine and promazine, all *FGAs* demonstrated superior efficacy in acute treatment compared to placebo, while there were differ-

ences in dose, potency and side effects of the different drugs (Davis et al. 1989; Baldessarini et al. 1990; Kane and Marder 1993; Dixon et al. 1995). *Haloperidol* was concluded as being efficacious in managing acute schizophrenic episodes compared to placebo, but also demonstrated high propensity to cause movement disorders (Joy et al. 2004). In two RCTs, *perazine* showed similar efficacy compared to haloperidol, but less EPS under perazine treatment was observed (Schmidt et al. 1982; Klimke et al. 1993). Two RCTs comparing perazine with the atypical antipsychotic zotepine showed controversial results; one of them found a superiority of zotepine in improving psychopathology (Wetzel et al. 1991), whereas the other found an advantage of perazine in this regard (Dieterle et al. 1991). According to these studies and one additional trial comparing perazine with amisulpride, perazine produced low EPS and had an extrapyramidal side-effect risk similar to the mentioned atypical agents (Rüther and Blanke 1988).

Efficay of second-generation antipsychotics. Patients selected in the placebo-controlled studies on *amisulpride* displayed predominantly negative symptoms (e.g., Pailliere-Martinot et al. 1995). Compared to haloperidol, fluphenazine or flupenthixol, a comparable or greater improvement of overall symptoms (Pichot et al. 1988; Delcker et al. 1990, Möller et al. 1997; Puech et al. 1998; Wetzel et al. 1998; Colonna et al. 2000), comparable improvement in positive symptoms (Delcker et al. 1990; Möller et al. 1997; Puech et al. 1998; Wetzel et al. 1998; Carriere et al. 2000, Colonna et al. 2000) and greater improvement in negative symptoms (Möller et al. 1997; Puech et al. 1998; Colonna et al. 2000) was found with amisulpride. In a small, 6-week RCT comparing amisulpride (400–800 mg/day) with risperidone (4–8 mg/day) in patients with predictive positive symptoms, no significant difference was observed in terms of efficacy or overall tolerability (Hwang et al. 2003). In a review, amisulpride was judged as being at least as efficacious as haloperidol and flupenthixol in treating acute exacerbations of schizophrenia with an optimal dose range of 400–800 mg/day (Freeman 1997). In summary, there is convincing evidence for the efficacy of amisulpride treatment in acute episodes of schizophrenia (*Level B*).

In a meta-analysis pooling data from five double-blind controlled studies comparing *aripiprazole* with placebo and haloperidol in acutely relapsed patients, aripiprazole showed a favourable safety and tolerability profile (Marder et al. 2003). Compared to placebo, significantly superior improvement in negative symptoms was observed only with 15 mg/day aripiprazole and 10 mg/day haloperidol, and not with 30 mg/day aripiprazole (Kane et al. 2002), and in another study with dosages of 20 and 30 mg/day aripiprazole, and 6 mg/day risperidone (Potkin et al. 2003). Compared to haloperidol or risperidone, randomised, double-blind controlled studies displayed comparable improvement of overall, positive and negative symptoms with aripiprazole (Kane et al. 2002; Potkin et al. 2003). In summary, there is convincing evidence for the efficacy of aripirazole in acute schizophrenic episodes (*Level B*).

For acutely ill schizophrenic patients, *clozapine* showed superiority in psychopathological improvement compared to placebo in two RCTs with small sample sizes (Shopsin et al. 1979; Honigfeld et al. 1984). In European double-blind, randomised multicentre studies the efficacy of clozapine was comparable to haloperidol, chlorpromazine, trifluoperazin and clopenthixol (Fischer-Cornelssen and Ferner 1976). In addition, other small RCTs revealed comparable efficacy (Chiu et al. 1976; Guirguis et al. 1977; Gelenberg and Doller 1979) or superior overall improvement compared to chlorpromazine (Shopsin et al. 1979). Clozapine was as efficacious as haloperidol (Klieser et al. 1994) or risperidone (Heinrich et al. 1994) in acute schizophrenic episodes and superior compared to chlorpromazine in first-episode patients (Lieberman et al. 2003). In summary, there is evidence for the efficacy of clozapine in acute schizophrenic episodes (*Level B*), but because of its side effect profile, especially haematological adverse effects, it is not recommended in first-line treatment of acute schizophrenia.

In acutely ill schizophrenic patients, *olanzapine* treatment was superior to placebo in improvement of overall and positive symptoms in a dose range of 5–20 mg/day (Beasley et al. 1996a,b; Hamilton et al. 1998). In comparison to haloperidol, similar or greater improvement of overall, positive and negative symptoms was observed (Beasley et al. 1996b, 1997; Tollefson et al. 1997; Hamilton et al. 1998; Revicki et al. 1999; Ishigooka et al. 2001; Lieberman et al. 2003). In summary, there is convincing evidence for the efficacy of olanzapine for treatment of acute schizophrenic episodes (*Level A*).

In acutely relapsed patients, treatment with *quetiapine* compared to placebo was superior in improvement of overall and positive symptoms in dosages of 150–750 mg/day (Fabre et al. 1995; Borison et al. 1996; Arvanitis et al. 1997; Small et al. 1997). There was also a significantly superior improvement in negative symptomatology, but not in all dose ranges (Fabre et al. 1995; Borison et al. 1996; Arvanitis et al. 1997; Small et al. 1997). Greater or comparable improvement of overall, positive and negative symptoms was observed with quetiapine compared to haloperidol or chlorproma-

zine in RCTs treating acutely ill patients (Arvanitis et al. 1997; Peuskens and Link 1997; Copolov et al. 2000). Therefore, evidence was revealed for the use of quetiapine in the treatment of acute schizophrenic episodes (*Level A*).

For acute-phase schizophrenia, in a dose range of 6–16 mg/day, *risperidone* demonstrated efficacy in placebo-controlled trials in the treatment of overall symptoms and positive symptoms (Borrison et al. 1992; Chouinard et al. 1993; Marder and Meibach 1994). In one short-term study, only 6 mg/day risperidone revealed a superior improvement in negative symptoms compared to placebo in a sample of chronic schizophrenic patients (Chouinard et al. 1993). Compared with haloperidol (Claus et al. 1992; Ceskova and Svestka 1993; Chouinard et al. 1993; Min et al. 1993; Marder and Meibach 1994; Peuskens et al. 1995; Blin et al. 1996), perphenazine (Hoyberg et al. 1993) and flupenthixol (Huttunen et al. 1995), there was a comparable or better response in global psychopathology and positive symptoms with risperidone in most fixed doses or with flexible dosing. There was a dose-dependent EPS rate. In most studies risperidone produced significantly less EPS than conventional comparator agents. In summary, there is convincing evidence for the efficacy of risperidone treatment in acute episodes of schizophrenia (*Level A*).

In double-blind, randomised trials, 80–160 mg/day *ziprasidone* was superior in improving overall and positive symptoms compared to placebo in acutely ill patients (Keck et al. 1998; Daniel et al. 1999). In one study there was also superior improvement in negative symptomatology (Daniel et al. 1999). Compared with haloperidol, ziprasidone showed comparable improvement in overall, positive and negative symptoms in acute phase RCTs (Goff et al. 1998; Hirsch et al. 2002). In summary there is convincing evidence for the efficacy of ziprasidone in treatment of acute schizophrenic episodes (*Level A*).

One RCT, comparing 150–300 mg/day *zotepine* to placebo, demonstrated superior improvement in overall, positive and negative psychopathology (Cooper et al. 2000a). Compared to haloperidol (Fleischhacker et al. 1989; Barnas et al. 1992; Petit et al. 1996; Hwang et al. 2001), chlorpromazine (Cooper et al. 2000a) and perazine (Dieterle et al. 1991; Wetzel et al. 1991), zotepine showed comparable or superior improvement in global psychopathology, positive and negative symptoms. In summary, there is good evidence for the efficacy of zotepine for treatment of acute schizophrenia (*Level A*).

General recommendations. It is recommended that in multiple-episode patients, antipsychotic pharmacological treatment should be initiated promptly, provided it will not interfere with diagnostic assessment, because acute psychotic exacerbations may be associated with emotional distress, disruption to the patient's life, and a substantial risk of dangerous behaviours to self, others or property (APA 2004). Antipsychotic monotherapy is recommended across the guidelines (e.g., DGPPN 1998; NICE 2002; RANZCP 2003; APA 2004) in the initial treatment of acute schizophrenic episode (*Level D*).

Choice of antipsychotic medication. The choice of antipsychotic drug should be made jointly by the individual and the clinician responsible for treatment based on an informed discussion of the relative benefits of the drugs and their side-effect profiles (NICE 2002; RANZCP 2003; APA 2004). When full discussion between the clinician responsible for treatment and the individual concerned is not possible, in particular in the management of an acute schizophrenic episode, the oral SGAs should be considered as the treatment options of choice because of the lower potential risk of extrapyramidal symptoms (EPS) (NICE 2002) and the at least comparable efficacy compared to FGAs (RANZCP 2003; APA 2004). Nevertheless, selection of an antipsychotic medication is frequently guided by the patient's previous experience with antipsychotics, including the degree of symptom response, past experience of side effects, preferred route of medication administration, the presence of comorbid medical conditions, and potential interactions with other prescribed medications (DGPPN 1998; APA 2004). All available SGAs, except clozapine (RANZCP 2003; APA 2004), should be considered as treatment options for individuals currently receiving conventional antipsychotic drugs who, despite adequate symptom control, are experiencing unacceptable side effects, and for those in relapse who have previously experienced unsatisfactory management or unacceptable side effects with conventional antipsychotic drugs. It is not recommended that, in routine clinical practice, individuals change to one of the oral atypical antipsychotic drugs if they are currently achieving good control of their condition without unacceptable side effects with conventional antipsychotic drugs (*Level D*) (DGPPN 1998; NICE 2002; APA 2004).

Dosage. An overview of studies comparing different dosages of *FGAs* concluded that daily doses lower than 300 mg CPZ equivalents were inadequate for optimal treatment and doses above 940 mg CPZ equivalents produced no better responses than in the range of 540–940 mg CPZ equivalents (Davis et al. 1989) (*Level A*). Another review found superior

improvement in nearly two-thirds of trials using doses of 300 mg CPZ equivalents or less, and consistent superiority for daily doses of 500 mg CPZ equivalents and more compared to placebo (Baldessarini et al. 1990) (*Level A*). In addition the best dose-dependent response was found in a range of 2–10 mg/day *haloperidol* (Baldessarini et al. 1990). No significant advantage was found for dosages greater than 10–20 mg/day haloperidol in acute treatment compared to lower doses (Kane and Marder 1993; Dixon et al. 1995). Recent RCTs of *FGAs* for acute treatment focusing on dosing strategies have consistently found that modest doses (mostly less than 10 mg/day haloperidol or equivalent, or plasma levels <18 ng/ml haloperidol) were as efficacious or more efficacious than higher doses (Coryell et al. 1998; Stone et al. 1995; Volavka et al. 2000) (*Level A*). Moderate doses of FGAs were noted to improve comorbid depression (Koreen et al. 1993; Volavka et al. 1996; Krakowski et al. 1997), whereas higher doses were associated with a greater risk of EPS and dysphoria (Bollini et al. 1994; Krakowski et al. 1997). In a systematic review of 16 RCTs with 19 different randomised dose comparisons of *haloperidol*, using low doses (between 3 and 7.5 mg/day compared to 7.5–15 and 15–35 mg/day, respectively) did not result in loss of efficacy, but were associated with a lower rate of clinically significant extrapyramidal adverse effects than higher doses (Wairach et al. 2004) (*Level A*). A further review stated that the near-maximal efficacy dose for haloperidol was between 3 and 10 mg/day, nevertheless high doses of haloperidol were found to be no less effective than medium doses (Davis and Chen 2004) (*Level A*). Individual adaptation of the dose, and not standard dosing, seems to be the best treatment strategy (Klieser and Lehmann 1987; Dixon et al. 1995).

In summary, the recommendation of daily dosages between 300 and 1000 mg CPZ equivalents for FGAs in the treatment of an acute symptom episode for a minimum of 6 weeks remains stable across the guidelines and over time (e.g., APA 1997, 2004; DGPPN 1998; Lehman et al. 1998; Working Group for the Canadian Psychiatric Association 1998; NICE 2002), whereby the minimum effective dose should be used. The optimal dose for each patient has to be found by clinical judgment.

For *SGAs* randomised, placebo-controlled studies which compared two or more doses of an antipsychotic were used in a review to calculate the dose–response curve (for each FGA or *SGA*, and as a group based on dose equivalence). The near-maximal effective dose was defined as the threshold dose necessary to produce all or almost all the clinical responses for each drug. It was found that the near-maximal efficacy dose for risperidone was 4 mg/day, for ziprasidone 120 mg/day, for aripiprazole 10 mg/day, for clozapine greater than 400 mg/day and for olanzapine probably greater than 16 mg/day (Davis and Chen 2004). Evidence for dose adjustment based on clinical routine, which differs from initial recommendations of approval and marketing studies, came from national surveys. From 1997 until 2001 the mean dose of risperidone used for inpatients in the New York state system decreased from 7.1 to 4.9 mg/day (Citrome et al. 2002). Additionally, based on a retrospective survey, a less rapid titration of risperidone (0.5–2 mg/day) was recommended to keep patients compliant with their medication (Luchins et al. 1998). On the other hand, doses of olanzapine in the New York state system for inpatients increased; in 2001 nearly 26% of olanzapine patients received doses greater than 20 mg/day (Citrome et al. 2002). Based upon a review of published findings and clinical experience, a more rapid initiation schedule for quetiapine was proposed than currently provided for treatment in hospitalised patients with acute schizophrenia. Additionally, higher doses (up to 1600 mg/day) of quetiapine had been well tolerated in some patients due to its favourable tolerability profile (Arango and Bobes 2004). A review concluded that there is still not enough data available to ensure a clear dose–response relationship of all approved SGAs and to make recommendations of optimal dosing strategies (Kinon et al. 2004). The dose may be titrated as quickly as tolerated to the target therapeutic dose of the antipsychotic medication, and unless there is evidence that the patient is having uncomfortable side effects (APA 2004). There is broad agreement in reviews (e.g., Davis et al. 1989; Baldessarini et al. 1990; Kane and Marder 1993; Dixon et al. 1995; Davis and Chen 2004; Kinon et al. 2004) and guidelines (e.g., DGPPN 1998; NICE 2002; APA 2004) that massive loading doses of antipsychotic medication referred to as 'rapid neuroleptisation' do not provide any advantage over standard dosing in initial treatment and may be associated with a higher risk of EPS (*Level D*). Therefore this treatment strategy should not be used in the treatment of the acute episode for people with schizophrenia.

Specific clinical features influencing the treatment plan

Treatment of predominantly positive symptoms

In common practice patients with an acute schizophrenic episode present with predominantly positive symptoms. This topic was already discussed in a

previous section of this guideline. It is recommended that in multiple-episode patients antipsychotic pharmacological treatment should be initiated promptly, provided it will not interfere with diagnostic assessment, because acute psychotic exacerbations may be associated with emotional distress, disruption to the patient's life, and a substantial risk of dangerous behaviours to self and others. For first-episode patients, short-term observation and administration of low-dose benzodiazepines may be helpful in establishing the diagnosis before antipsychotic treatment is introduced. Other psychoactive medications are commonly added to antipsychotic medications when patients continue to demonstrate active psychotic symptoms despite adequate medication trials. For persisting positive symptoms despite pharmacotherapy, treatment-resistance should be considered (*see this section in the guideline*).

In summary no specific treatment recommendations are given for patients with predominantly positive symptoms and the reader is referred to the section discussing strategies for treating acute relapse or other specific clinical features influencing the treatment plan.

Treatment of agitation

Schizophrenic patients show agitated, aggressive or violent behaviour, mostly related to psychotic symptoms (e.g., persecutory delusions, mania or hallucinations), or as a result of other symptoms, such as threatening and anxiety, when internal controls are compromised (Angermeyer 2000). Factors relating to the patient's environment or the institutions involved in treatment, such as crowded wards, lack of privacy and long waiting times, contribute to the occurrence of aggressive behaviour. The prediction of aggressive and violent behaviour during hospitalisation is difficult; however, an association was seen with hostility and thought disorders (Steinert 2002). Physician and staff confronted with an acutely ill, aggressive patient with schizophrenia should provide structure, reduce stimulation, try to verbally reassure and calm the person, and to de-escalate the situation at the earliest opportunity (Osser and Sigadel 2001). If possible, oral administration of medications is preferable to parenteral administration. The lowest effective dose should be given, and, if necessary, increased incrementally. Emergency management of violence in schizophrenia may include sedation, and as the last option restraint and seclusion. Similarly, in this context the use of drugs to control disturbed behaviour (rapid tranquillisation) is often seen as a last resort, where appropriate psychological and behavioural approaches have failed or are inappropriate. The aim of drug treatment in such circumstances is to calm the person, and reduce the risk of violence and harm, rather than treat the underlying psychiatric condition. Psychiatrists, and the multidisciplinary team, who use rapid tranquillisation should be trained in the assessment and management of service users specifically in this context: this should include assessing and managing the risks of drugs (benzodiazepines and antipsychotics), using and maintaining the techniques and equipment needed for cardiopulmonary resuscitation, and prescribing within therapeutic limits and using flumazenil (benzodiazepine antagonist) (DGPPN 1998; NICE 2002; APA 2004).

Two RCTs found that the combination of *haloperidol* (5 mg) and *lorazepam* (4 mg) intramuscularly produces an overall superior and faster clinical response than haloperidol alone (Bieniek et al. 1998; Garza-Trevino et al. 1989). Comparing monotherapy of benzodiazepines with antipychotics alone, lorazepam (or flunitrazepam) and haloperidol administered intramuscularly demonstrated similar efficacy in controlling agitation and general response to treatment (Battaglia et al. 1997; Foster et al. 1997; Dorevitch et al. 1999). In one study, lorazepam 2 mg was superior in improvement of gobal impression compared to haloperidol 5 mg (Foster et al. 1997). The administration of *midazolam* 15 mg was superior in terms of sedation (and therefore reducing agitation) compared to the combination of *haloperidol* (5 mg) and *promethazine* (50 mg), both intramuscularly, in an open, randomised, controlled study (TREC 2003).

While the use of *SGAs*, with a lower liability for extrapyramidal side effects, show promise for rapid tranquilisation, a study comparing *olanzapine* (10 mg intramuscularly) to haloperidol (7.5 mg intramuscularly) observed similar efficacy in reducing agitation at 2 and 24 hours after the first injection (Wright et al. 2001). Olanzapine demonstrated a favourable side effect profile, e.g., reduced additional need for benzodiazepines, less dystonia and EPS, and less need to receive anticholinergic drugs (Altamura et al. 2003). There is a risk of sudden death following intramuscular application of olanzapine and benzodiazepines, therefore the combined use should be avoided. An open-label study demonstrated equal efficacy of *ziprasidone* 20–80 mg intramuscularly compared to 10–40 mg haloperidol intramuscularly in acute schizophenic patients with agitation (Swift et al. 2003), and a randomised study showed comparable efficacy of ziprasidone 40 mg and haloperidol 10 mg intramuscularly (Brook et al. 2000). In addition, a dose-finding study showed superiority for ziprasidone 20 mg compared to ziprasidone 2 mg intramuscularly in

reducing acute agitation (Daniel et al. 2001). Rapid sedation may also be achieved through administration of low potency antispychotics (e.g., levomepromazine, chlorprothixene) or zuclopenthixolacetate (DGPPN 1998), but this strategy is not recommended anymore in recent guidelines (e.g., APA 2004).

If oral treatment is accepted the combination of oral risperidone (2 mg) and lorazepam (2 mg) appears to be comparable to intramuscular haloperidol (5 mg) and lorazepam (2 mg) (Currier and Simpson 2001).

Recommendations. Lorazepam and conventional neuroleptic agents showed comparable efficacy in the acute treatment of aggression and psychomotor agitation (*Level C*). Due to the more favourable side effect profile of lorazepam, initial treatment should be performed with 2–4 mg lorazepam in patients in whom no decision has yet been taken on whether to follow a medicinal or non-medicinal strategy or on which type of antipsychotic treatment to use. Administration of diazepam or other benzodiazepines (apart from lorazepam) or of low-potency neuroleptic agents, such as chlorprothixene or levopromazine, is not recommended in the treatment of agitation and excitation due to inferior efficacy or inferior tolerability. In patients whose aggressive behaviour is clearly due to psychotic symptoms, a combination treatment of lorazepam with a neuroleptic agent can be undertaken (*Level C*). Due to better tolerability, an atypical neuroleptic agent, such as olanzapine or ziprasidone, preferably in parenteral form, may be used where possible in preference to a conventional neuroleptic agent (*Level C*). There is a risk of sudden death following intramuscular application of olanzapine and benzodiazepines, therefore the combined use should be avoided. Similarly also caution has to be recommended when combining clozapine with benzodiazepines (Rupprecht et al. 2004). Clinicians must also be aware of cardiac abnormalities, especially when using ziprasidone intramuscularly.

If extremely rapid sedation is urgently required, haloperidol and lorazepam can be parenterally administered. If treatment is not sufficient to treat the symptoms of excitation/tension or anxiety, additional treatment with carbamazepine, valproate or lithium may be considered (*Level D*). Measures such as restraint and seclusion should only be used in exceptional emergency situations. They should be carefully documented and explained to the patient. In all cases, the patient should be allowed to express his or her opinions and discuss his or her experience. The physician should see a secluded or restrained patient as frequently as needed to monitor any changes in the patient's physical or mental status and to comply with local law.

Treatment of predominantly negative symptoms

Negative symptoms in schizophrenia can be differentiated into primary negative symptoms, suggesting a core symptomatology in schizophrenia, and secondary negative symptoms as a consequence of positive symptoms (e.g., social withdrawal because of paranoid ideas), due to EPS (e.g., neuroleptic-induced akinesia), depressive symptoms (e.g., post-psychotic or pharmacogenic depression) or environmental factors (e.g., social understimulation due to hospitalism) (Carpenter et al. 1985).

Due to their pharmacological profile, especially the preferential blockade of 5-HT_{2A} receptors, SGAs were concluded to possess favourable ability to treat negative symptoms compared to FGAs (e.g., Möller 2003). Unfortunately most trials were carried out in patients experiencing acute exacerbations or presenting with a mixture of positive and negative symptoms, and therefore the improvement in negative symptoms could be interpreted as a decrease in secondary negative symptoms. Overlap between adverse drug effects (EPS) and depression makes interpretation of the study results difficult. In addition most comparator doses of FGAs were retrospectively judged as too high and associated with a high EPS rate. Even when more elaborate statistical approachs, e.g., path analysis, are used, interpretation requires caution (Möller et al. 1995). On the other hand the efficacy of atypical antipsychotics in treating negative symptoms may be underestimated in meta-analysis due to methodological pitfalls inherent to such analyses (Möller 2003).

Efficacy of first-generation antipsychotics. In most studies there is also improvement of negative symptoms with FGAs but the trials focus mainly on positive symptoms (Dixon et al. 1995). Compared to placebo there is evidence for the efficacy of FGAs in treating negative symptoms (e.g., Davis et al. 1989). But even when ratings for negative symptoms are given, primary and secondary negative symptoms are not distinguished. Comparison studies to SGAs (as mentioned later) demonstrate a tendency for lower doses to be favourable in treating negative symptoms. There were no studies in patients with predominantly negative symptoms.

Efficacy of second-generation antipsychotics. Amisulpride in dosages up to 800 mg/day showed superior improvement compared to haloperidol (20 mg/day) (Möller et al. 1997) and similar efficacy compared to risperidone (8 mg/day) (Peuskens et al. 1999) in

treating negative symptoms in short-term RCTs. In a 1-year, double-blind randomised maintenance study with flexible doses, amisulpride was associated with greater improvement in negative symptomatology compared to haloperidol (Colonna et al. 2000). Selecting patients with predominantly negative symptoms a randomised double-blind long-term trial comparing six dose levels of amisulpride with haloperidol revealed better, but no significant improvement in negative symptoms after 1-year treatment in favour of amisulpride (Speller et al. 1997). Two RCTs showed superiority of amisulpride compared to placebo in improvement of negative symptoms, at dosages of 100–300 mg/day over 6 weeks (Boyer et al. 1995) and 100 mg/day over 6 months (Loo et al. 1997). Additionally, two RCTs displayed better efficacy of amisulpride in the treatment of negative symptoms compared to placebo in a patient sample suffering predominantly from persistent negative symptomatology (Palliere-Martinot et al. 1995; Danion et al. 1999). In meta-analyses (Leucht et al. 1999, 2002; Leucht 2004), amisulpride, olanzapine and risperidone were found to reveal superiority in treating negative symptoms compared to FGAs, derived from studies of acutely ill patients. In three small RCTs comparing amisulpride with FGAs in patients with predominantly negative symptoms (Pichot and Boyer 1989; Saletu et al. 1994; Speller et al. 1997), there was only a trend in favour of amisulpride but no statistical difference. Nevertheless, amisulpride is the only SGA that has been studied extensively in this patient population, and especially in regard to the placebo-controlled studies there is evidence that treatment with amisulpride is effective at a dose range of 50–300 mg/day in improving negative symptoms (Leucht 2004) (*Level A*).

Aripiprazole at a dosage of 15 mg/day, but not 30 mg/day and haloperidol 10 mg/day showed superior efficacy in improvement of negative symptoms compared to placebo in an RCT of 4 weeks duration (Kane et al. 2002). In another short-term RCT, efficacy of aripiprazole (20 and 30 mg/day) in treating negative symptoms was comparable to risperidone (6 mg/day) (Potkin et al. 2003). In a placebo-controlled RCT, aripipazole demonstrated superior efficacy in improvement of negative symptoms over 6 months (Pigott et al. 2003). Pooled data of two 52-week RCT comparing aripiprazole 30 mg/day to haloperidol 10 mg/day showed superior improvement in negative symptomatology in favor of aripiprazole (Kasper et al. 2003). In summary, although there is evidence for efficacy in treating negative symptoms (*Level A*), there is no clear experience with aripiprazole in patients with predominantly negative symptoms.

Clozapine was found to be effective in open, non-comparative trials in treatment refractory patients with more-or-less predominant negative symptoms (Meltzer et al. 1989; Meltzer 1992; Lindenmayer et al. 1994) and in a double-blind trial compared to chlorpromazine (Kane et al. 1988). In another double-blind RCT, with a small sample size, no difference between clozapine and haloperidol in the improvement of negative symptoms could be detected (Breier et al. 1994). In a double-blind multi-comparative RCT already mentioned above, clozapine (target dose 500 mg/day) revealed statistically significant superiority in impoving negative symptoms compared to haloperidol (target dose 20 mg/day) in patients with suboptimal response to previous treatment, but this effect was described as clinically modest (Volavka et al. 2002). While one meta-analysis found that there is slight significant evidence for superiority of clozapine compared to FGAs in the treatment of negative symptoms (Wahlbeck et al. 2004), another meta-analytic review reported an advantage of clozapine in this regard evaluating its efficacy in treatment-resistant patients (Chakos et al. 2001). In summary, although there is evidence for efficacy in treating negative symptoms (*Level A*), there is only little experience with clozapine in patients with predominantly negative symptoms.

Olanzapine displays evidence for superior efficacy in treating negative symptoms in acute-phase RCTs compared to placebo and haloperidol (Beasley et al. 1996a,b, 1997; Tollefson et al. 1997). Nevertheless, in an extension study after 24 weeks there was no longer a statistically significant difference between olanzapine and haloperidol in reducing negative symptoms (Hamilton et al. 1998). A path-analysis of these studies found that most of the changes in negative symptoms could not be explained by other compounds (positive symptoms, depression, EPS) (Tollefson et al. 1997). While one short-term double-blind randomised study demonstrated superiority of olanzapine (mean dose 17.2 mg/day) in improving negative symptoms compared to risperidone (mean dose 7.2 mg/day) (Tran et al. 1997), another RCT (mean dose olanzapine 12.4 mg/day versus risperidone 4.8 mg/day) could not replicate this finding, probably due to lower dosage of risperidone associated with less EPS (Conley and Mahmoud 2001). In summary, although there is evidence for efficacy in treating negative symptoms (*Level A*), there is no clear experience with olanzapine in patients with predominantly negative symptoms.

Quetiapine produced significant superior improvement in negative symptoms compared to placebo only in higher dosage (750 mg/day) acute phase

treatment in one RCT (Small et al. 1997) and in another trial in the whole dose range (75–750 mg/day), with best results at the 300-mg/day dose (Arvanitis et al. 1997). Compared to haloperidol (12 mg/day) there was no significant difference (Arvanitis et al. 1997), and compared to chlorpromazine (750 mg/day) a trend towards better efficacy in negative symptomatology could be observed (Peuskens and Link 1997). Overall, there is evidence for similar efficacy, but not for significant advantages compared to FGAs (Cheer and Wagstaff 2004) in the treatment of negative symptoms (*Level A*).

Risperidone showed significantly superior improvement in negative symptoms compared to haloperidol and placebo only at a dosage of 6 mg/day (Peuskens et al. 1995). A re-analysis using the path-analytical approach revealed a direct effect of treatment on negative symptoms in this study (Möller 2003). In partially refractory schizophrenic patients, similar efficacy was found in improvement of negative symptoms compared to clozapine and perphenazine (Möller 2003). In double-blind randomised comparisons with olanzapine there were similar results or inferior improvement in negative symptomatology (Tran et al. 1997; Conley and Mahmoud 2001). In maintenance treatment compared to haloperidol, beneficial effects of negative symptomatology were reported for risperidone (Csernansky et al. 2002). A meta-analyis of the pooled results from six double-blind RCTs comparing risperidone to FGAs found that risperidone showed significantly superior improvement in negative symptoms (Carman et al. 1995). In summary, there is evidence for efficacy in treating negative symptoms (*Level A*), but no clear experience in patients with predominantly negative symptoms.

Ziprasidone showed superior efficacy for improvement of negative symptoms compared to placebo in one short-term RCT (Daniel et al. 1999), but not in a statistically significant manner in another RCT (Keck et al. 1998), both in acutely ill patients. In a double-blind randomised extension study over 1 year, including patients with chronic schizophrenia presenting predominantly negative symptoms, a statistically significant superior improvement in negative symptoms was observed in favour of ziprasidone (dosage 40, 80 and 160 mg/day) compared to placebo at endpoint (Arato et al. 2002). In summary, there is evidence for efficacy in treating negative symptoms (*Level A*), and limited evidence in this regard in patients with predominantly negative symptoms (*Level C*).

Zotepine revealed inconsistent efficacy for superior improvement of negative symptoms compared to FGAs in earlier RCTs (Möller 2003), but more recent double-blind RCTs demonstrated significant advantages of zotepine compared to haloperidol (Petit et al. 1996) or chlorpromazine (Cooper et al. 2000a). A placebo-controlled study in patients with predominant negative symptoms failed to demonstrate efficacy of zotepine (Möller et al. 2004). A relapse-prevention double-blind RCT compared to placebo displayed no significant differences in regard to negative symptomatology over 26 weeks (Cooper et al. 2000b). In summary, there is evidence for efficacy in treating negative symptoms (*Level A*), and no evidence in patients with predominantly negative symptoms.

Efficacy of antidepressive agents. Despite atypical antipsychotic agents, antidepressants are used as adjunctive treatment in patients with predominantly negative symptoms (APA 2004). The role of this strategy still remains unclear, because the available studies (most of them performed with SSRI) are inconsistent and often lack high methodological standards (Möller 2004a). An earlier RCT indicated that, e.g., imipramine added to long-acting FGA, may provide benefits in negative symptoms in stable outpatients (Siris et al. 1991), whereas addition of desipramine or amitriptyline in acutely decompensated patients was associated with poorer antipsychotic response without improving depression (Kramer et al. 1989). Marprotiline revealed no significant difference in a double-blind crossover study (Waehrens and Gerlach 1980).

In six placebo-controlled studies of SSRIs for negative symptoms, one reported a modest advantage of fluoxetine 20 mg/day added to long-acting injectable antipsychotic medication (Goff et al. 1995) and another reported significant superior improvement in negative symptoms with fluoxetine (Spina et al. 1994), while four found no advantage for SSRIs, compared with placebo, in patients receiving fluoxetine combined with ongoing clozapine (Buchanan et al. 1996) and fluoxetine (Arango et al. 2000), citalopram (Salokangas et al. 1996), or sertraline (Lee et al. 1998) added to first-generation antipsychotics. Four controlled studies of adjunctive fluvoxamine (100 mg/day) have demonstrated positive results (Silver and Nassar 1992; Silver and Shmugliakov 1998; Silver et al. 2000, 2003), while there was no benefit for marprotiline (100 mg/day) added to antipsychotic treatment (Silver and Shmugliakov 1998). In a double-blind placebo-controlled study, mirtazapine demonstrated superior improvement in negative symptomatology after 6 weeks (Berk et al. 2001). In contrast, reboxetine (8 mg/day) showed no effects on negative smptoms in a double-blind placebo-controlled trial (Schutz and Berk 2001). A placebo-controlled trial found no advantage for adjunctive selegiline compared to

placebo (Jungemann et al. 1999). Overall, the evidence for efficacy of antidepressants for negative symptoms of schizophrenia is limited (*Level C*), especially when taking into consideration the fact that differentiating the improvement in depressive symptoms from negative symptoms is difficult in some cases. Since most of the studies were performed in combination with first-generation antipsychotics, it is possible that the findings might be different with second-generation antipsychotics, although this possibility seems unlikely (APA 2004). Adding–at least TCA–to acutely decompensated patients, might worsen the psychotic symptoms.

Efficacy of other medications. Earlier reports indicated that lithium augmentation to antipsychotics improved negative symptoms specifically (Small et al. 1975; Growe et al. 1979), but this finding could not be confirmed in later trials and meta-analyses (e.g., Leucht et al. 2004). There is some evidence for adding glutamatergic agents, e.g., d-cycloserine (Möller 2003; APA 2004), and the combination of adjunctive d-serine with FGAs or risperidone in treating negative symptoms (Tsai et al. 1998). In addition, there is no clear evidence for the efficacy of oestrogen augmentation or augmentation with cognitive enhancers, but pilot studies demonstrated encouraging results for improvement (Möller 2003). For further treatment strategies please refer to the section below (*see Treatment-resistant schizophrenia*).

Recommendations. For the treatment of negative symptoms, second-generation antipsychotics should be preferred (*Level A*). Of the atypical compounds, amisulpride seems to have advantages and this antipychotic is the only one that has been investigated in several studies in this special schizophrenic population (*Level A*). Clozapine may be superior compared to other antipsychotics when treating negative symptoms in the context of treatment-resistant schizophrenia (*Level B*). In cases of inadequate response comedication with SSRIs (*Level B*) and possibly mirtazapine (*Level C*) may be beneficial. The pharmacokinetic interactions with SSRIs have to be considered carefully. Add-on therapies with glutamatergic agents or oestrogen may be discussed as experimental approaches.

Treatment of cognitive symptoms

Neurocognitive deficits have been recognised as an important feature, or even a core deficit, of schizophrenia. Cognitive functioning is a correlate of global and specific functional outcome in schizophrenia and cognitive impairments account for significant variance in measures of functional status (Green 1996). SGAs have been reported to have more beneficial effects on cognitive functioning than FGAs, nevertheless the methodology used to assess cognitive deficits in schizophrenia has been deficient in many clinical studies (Harvey and Keefe 2001).

Efficacy of first- and second-generation antipsychotics. In reviews and most studies, FGAs demonstrated no or only minor beneficial effects on cognition (e.g., Cassens et al. 1990; Sharma 1999), whereby inappropriately large dose ranges, combined with EPS or concomitant anticholinergic medication, may have had a negative effect on cognition. A meta-analysis of 20 clinical trials (consisting of 11 switching studies, four comparative randomised open studies and five randomised double-blind studies) revealed evidence that SGAs show superior improvement in essential aspects of cognition compared to FGAs (Harvey and Keeefe 2001) (*Level A*). This could be confirmed for some cognitive domains in a randomised double-blind study comparing olanzapine, risperidone, clozapine and haloperidol in patients with a history of suboptimal response to conventional antipsychotics (Bilder et al. 2002). A systematic review showed superior beneficial effects on neurocognition in patients treated with SGAs (clozapine, risperidone, olanzapine, quetiapine and zotepine) compared to FGAs, although some studies provided conflicting results and there was a variety of methodological limitations (Weiss et al. 2002). In addition, a randomised double-blind study demonstrated comparable cognitive-enhancing effects relative to previous treatment (mostly haloperidol or risperidone) in acutely ill inpatients treated with olanzapine or ziprasidone (Harvey et al. 2004).

In contrast to these results, risperidone (6 mg/day) compared to low-dose haloperidol (5 mg/day) showed no superior improvement of neurocognitive deficits over a 2-year period in a randomised double-blind study (Green et al. 2002). In a randomised double-blind trial in first-episode psychosis olanzapine (mean 9.6 mg/day) demonstrated only a small advantage with respect to neurocognitive deficits compared to low-dose haloperidol (mean 4.6 mg/day) (Keefe et al. 2004).

Recommendations. In schizophrenic patients with cognitive deficits, SGAs provide an at least modest beneficial effect on neurocognitive functions compared to FGAs (*Level A*), although some studies revealed conflicting results. Adjunctive medications, previous treatments and doses of FGAs have to be

taken into consideration before switching to SGAs to improve neurocognition.

Treatment of predominantly catatonic symptoms

Significant catatonic symptoms tend to be present in close to 10% of patients admitted to psychiatric facilities (Blumer 1997). While the catatonic subtype of schizophrenia is diagnosed in approximately 5% of all first-episode patients (Jablensky et al. 1992), malignant catatonia is extremely rare. The differentiation between catatonia and neuroleptic malignant syndrome may be impossible in some cases, mentioned as 'catatonic dilemma' (Lausberg and Hellweg 1998).

Efficay of first-generation antipsychotics. Antipsychotics, especially *FGAs*, demonstrated poor efficacy in treating catatonia (e.g., Zemlan et al. 1986; Hawkins et al. 1995) (*Level C*). Additionally, patients with past or present catatonic symptoms are particularly vulnerable to neuroleptic malignant syndrome (NMS) (Lausberg and Hellweg 1998). Therefore antipsychotics with preferentially D2-blocking properties may not be beneficial for treating catatonia, and even worsen catatonic symptoms (Blumer 1997).

Efficay of second-generation antipsychotics. Some case reports suggest that *SGAs* may be more effective in treating catatonic symptoms than FGAs, e.g., amisulpride (French and Eastwood 2003), clozapine (e.g., Lausberg and Hellweg 1998; Gaszner and Makkos 2004), olanzapine (Martenyi et al. 2001), risperidone (Poyurousky et al. 1997; Kopala and Caudle 1998; Hesslinger et al. 2001; Valevski et al. 2001) and zotepine (Harada et al. 1991) (*Level D*).

Others. Benzodiazepines revealed efficacy in acute catatonic reactions (e.g., Rosebush et al. 1990; Ungvari et al. 1994; Bush et al. 1996; Lee et al. 2000) and showed benefits added to antipsychotics in chronic catatonia (Ungvari et al. 1999) (*Level C*).

Patients with prominent catatonic features seemed to derive particular benefit from treatment with *ECT*; nevertheless, the evidence is limited by the inclusion of patients with mood disorder diagnoses and consists primarily of case reports, case series and open prospective trials (e.g., Bush et al. 1996; Petrides et al. 1997; Suzuki et al. 2003) (*Level C*). Reviewing case reports and case series, ECT also appeared as efficacious as lorazepam (improvement 85 vs. 79%) and was more likely to provide a positive outcome in cases of malignant catatonia (Hawkins et al. 1995). Findings from the above cited studies confirm the clinical impression that ECT is beneficial in patients with catatonic schizophrenia who have not responded to first-line treatment with lorazepam (*Level D*) (APA 2004).

Recommendations. Benzodiazepines, e.g., lorazepam, appear to offer a safe, effective, first-line treatment of catatonia (*Level C*). ECT should be considered when rapid resolution is necessary (e.g., malignant catatonia) or when an initial lorazepam trial fails (*Level C*). When initiating antipsychotic treatment SGAs, e.g., clozapine, should be preferred in patients presenting catatonic symptoms, because of a reduced risk of developing neuroleptic malignant syndrome, and suggested higher efficacy (*Level D*).

Treatment-resistant schizophrenia

Depending upon the definition of treatment-resistant schizophrenia (TRS), about 10–30% of patients have little or no response to antipsychotic medications, and up to an additional 30% of patients have partial responses to treatment, meaning that they exhibit improvement in psychopathology but continue to have mild to severe residual hallucinations or delusion (e.g., Brenner et al. 1990; Essock et al. 1996a). Even if a patient's positive symptoms remit with antipsychotic treatment, other residual symptoms, including negative symptoms and cognitive impairment, often persist. Treatment resistance is often associated with long periods of hospitalisation. However, chronic hospitalisation may also occur in the presence of less severe psychotic symptoms and it is not a reliable indicator of poor response to antipsychotics. The use of widespread criteria for TRS, including functional level, led to prevalences of 55–65% following treatment with SGAs, a figure which would probably be even higher if cognitive deficits and poor quality of life were also included (e.g., Helgason 1990; Hegarty et al. 1994). Treatment may be completely or partially unsuccessful for a variety of reasons. The patient may receive a suboptimal dose of antipsychotic, either because an inadequate dose has been prescribed or because of at least partial non-adherence, or the prescribed antipsychotic may be partially or fully ineffective (APA 2004). Substance use may also cause or contribute to treatment resistance. Nevertheless TRS may be associated with neurobiological factors (e.g., brain-morphological abnormalities) or may depend on environmental factors (e.g., unfavourable familial atmosphere, high expressed emotions). Multidimensional evaluation of TRS should consider persistent positive or negative symptoms, cognitive dysfunction with severe impairment, bizarre behaviour, recurrent affective symptoms and suicidal behaviour, deficits in vocational and social functioning and a poor

quality of life. Therefore, in suspected TRS, the target symptoms should be precisely defined. Due to modified criteria in recent guidelines, treatment resistance is assumed if there is either no improvement at all or only insufficient improvement in the target symptoms, despite treatment at the recommended dosage for a duration of at least 6–8 weeks with at least two antipsychotics, one of which should be an atypical antipsychotic (NICE 2002; APA 2004). Compliance should be ensured, if necessary by checking drug concentrations.

Efficacy of first-generation antipsychotics. There is only limited evidence for the efficacy of FGAs for TRS. A review summarizing more than 100 trials comparing two or more different FGAs concluded that only one study found any FGA to be more effective than another (Janicak et al. 1993). As a result, in terms of efficacy, FGAs were considered interchangeable (Conley und Buchanan 1997). In most controlled trials of FGAs in patients with drug-resistant symptoms, the percentage of responders was fewer than 5% (Kane et al. 1988) or in the range of 3–7% (Kinon et al. 1993), changing the FGA once or twice if response failed. So the primary reason for choosing between drugs was to reduce side effects, provide different dosing strategies, or offer different routes of administration (Conley und Buchanan 1997). Based on neurobiochemical considerations, data from blocking 80–90% of D2 receptors by 400 mg CPZ equivalents (e.g., Farde et al. 1992) and clinical impressions from acute treatment studies (e.g., Baldessarini et al. 1988; Bollini et al. 1994; Dixon et al. 1995) suggested that higher dosages of FGA produce no therapeutic benefit for TRS, but led to a higher rate and severity of EPS and other disabling side effects (Kane 1994; Möller 1996).

Efficacy of second-generation antipsychotics. A meta-analysis summarising 12 RCTs comparing the efficacy and tolerability of *SGAs* versus FGAs for TRS found that there were more favourable outcomes when treated with clozapine reflected by superior improvement in overall psychopathology, categorical response rate, EPS and adherence rate, and when treated with olanzapine with regard to categorical response and adherence rates (Chakos et al. 2001).

The efficacy of *clozapine* for TRS could be underlined in a meta-analysis using Cochrane criteria (Wahlbeck et al. 1999) and by evaluating all available 10 RCTs comparing clozapine to other antipsychotic agents in another meta-analysis (NICE 2002). In this review, six double-blind, randomised controlled studies in TRS lasting 6–52 weeks demonstrated superior efficacy in improvement of global psychopathology and global response rate using mean doses of 176–600 mg/day clozapine compared to chlorpromazine (mean dose approximately 1200 mg/day) and haloperidol (doses between 16–28 mg/day) (Kane et al. 1988, 2001; Kumra et al. 1996; Hong et al. 1997; Buchanan et al. 1998; Rosenheck et al. 1997). In addition, an open, randomised, controlled long-term study (2 years) revealed evidence for superior global response rate with clozapine (mean dose 496 mg/day) compared to standard FGAs (mean dose 1386 mg/day CPZ equivalents) (Essock et al. 1996b). Another systematic review of clozapine in TRS including 18 prospective, controlled clinical trials (15 double-blind), 23 prospective observational studies and nine retrospective observational studies, found response to treatment in experimental designs in 36% and in retrospective analysis up to 54%, whereas dropout rates ranged from 33 to 20%, respectively (Brambilla et al. 2002). As a result of this review, clozapine was concluded also to demonstrate effectiveness and overall good tolerability in the treatment of TRS under clinical practice. Additionally superior effectiveness in adherence, quality of life and participation in psychosocial therapies was reported in further trials (Lieberman et al. 1994; Alvarez et al. 1997; Ciaparelli et al. 2003). The time course of improvement with clozapine was different and ranged from 4 to 8 weeks (Conley et al. 1997; Rosenheck et al. 1999), whereas in other trials improvement was still observed after periods of 6–12 months (Spina et al. 2000). In summary, there is good research-based evidence to recommend treatment with clozapine for treatment-resistant schizophrenic patients (*Level B*).

For *risperidone* (6 mg/day) compared to haloperidol (15 mg/day), significant superior improvement in total psychopathology was only observed in the first 4 weeks of an 8-week RCT (Wirshing et al. 1999). Predictors for response to risperidone were predominant positive symptoms and EPS at study entry. A 12-week study in patients with acute exacerbations and TRS revealed better improvement in negative and overall symptoms favouring risperidone 6 mg/day compared to haloperidol 20 mg/day (Zhang et al. 2001). Additionally treatment-resistant patients demonstrated superior improvement in verbal memory function (Green et al. 1997) and in perception of emotion (face recognition) (Kee et al. 1998) under treatment with risperidone compared to haloperidol. In a double-blind 14-week RCT comparing risperidone (mean dose 11.6 mg/day), clozapine (mean dose 527 mg/day), olanzapine (mean dose 30.4 mg/day) and haloperidol (mean dose 25.7 mg/day) superior improvement in overall psychopathology (PANSS total score) was observed in the 3 SGAs, but considering EPS reduction as a

covariate, significance was reached only for clozapine and olanzapine (Volavka et al. 2002). Comparing risperidone (3–10 mg/day) to clozapine (150–400 mg/day), one RCT showed a similar reduction in psychotic symptoms and no difference in EPS rate (Bondolfi et al. 1998). Two other RCTs revelaed superiority for clozapine in improvement of total psychopathology, positive and depressive symptoms (mean doses 5.9 mg/day risperidone vs. 404 mg/day clozapine) (Breier et al. 1999), and improvement in global impression, overall and positive symptoms (mean doses 9.0 mg/day risperidone vs. 642 mg/day clozapine) (Azorin et al. 2001). In open, prospective cross-over studies 40–80% of risperidone non-responders and solely 0–15% of clozapine non-responders improved by switching to the other agent (Cavallaro et al. 1995, Still et al. 1996), or similar efficacy was observed (Daniel et al. 1996, Konrad et al. 2000). As a result of these trials there may be an advantage for switching from risperidone to clozapine in regard to response rate. Additionally, open, comparative studies pointed towards a superior efficacy of clozapine (e.g., Flynn et al. 1998; Lindenmayer et al. 1998; Wahlbeck et al. 2002). In summary, there is evidence for superiority of risperidone compared to haloperidol, but there may be disadvantages compared to clozapine in the treatment of therapy refractory schizophrenia (*Level B*).

A meta-analysis identified two RCTs comparing *olanzapine* to FGAs in TRS and calculated an approximately 1.7-higher probability of response favouring olanzapine (Chakos et al. 2001). Patients with olanzapine treatment suffered from significantly less EPS. In an 8-week RCT, only slight superior response (7 vs. 0%) was observed in olanzapine-treated (25 mg/day) patients compared to chlorpromazine (1200 mg/day) (Conley et al. 1998). Reanalysis of an RCT focusing on TRS (defined as one unsuccesful trial with FGA) revealed a higher response rate (47 vs. 35%) for olanzapine (mean dose 11.1 mg/day) compared to haloperidol (mean dose 10.0 mg/day) (Breier and Hamilton 1999). In this study, superior improvement in overall, positive, negative and depressive symptoms was observed in the olanzapine group. As mentioned earlier, olanzapine demonstrated superior improvement in total psychopathology and negative symptoms compared to haloperidol without confounding with EPS (Volavka et al. 2002), nevertheless clinical effects of all assessed atypicals (clozapine, olanzapine, risperidone) differed only slightly from haloperidol in this randomised, double-blind trial. In another RCT compared to clozapine (mean dose 304 mg/day) there was a similar improvement of overall symptoms with olanzapine treatment (mean dose 20.5 mg/day), while olanzapine patients revealed less adverse effects (Tollefson et al. 2001). Switching from clozapine to olanzapine (5–25 mg/day) led to response in more than 40% of the patients in prospective studies (Henderson et al. 1998; Dossenbach et al. 2000), while in one study the greatest reduction in psychotic symptoms was observed in weeks 3–6 (Dossenbach et al. 2000). Further switch trials under naturalistic conditions, mainly from risperidone, revealed similar results (Lindenmayer et al. 2001, 2002; Rodriguez-Perez et al. 2002; Chiu et al. 2003; Karagianis et al. 2003). In summary, there is evidence for superiority of olanzapine compared to haloperidol or chlorpromazine, and limited evidence of similar efficacy compared to clozapine in the treatment of therapy refractory schizophrenia (*Level B*).

In an RCT lasting 12 weeks, patients with only partial response to fluphenazine treatment (20 mg/day) demonstrated a significantly higher response rate (52 vs. 38%) to *quetiapine* (600 mg/day) than to haloperidol (20 mg/day) (Emsley et al. 2000). Switching from haloperidol, olanzapine or risperidone to quetiapine (mean dose 505 mg/day) revealed clinical improvement in 69% of the patients (De Nayer et al. 2003).

Treatment with *aripiprazole* (mean dose 28.8 mg/day) compared to perphenazine (mean dose 39.1 mg/day) showed a similar response in TRS concerning recent definition (unsuccessful trial with one SGA and risperidone or olanzapine) in a randomised double-blind trial (Ebrecht et al. 2004). Significant improvement in total psychopathology was observed in both treatment conditions. In an open trial switching stable chronic patients to aripiprazole (30 mg/day), improvement in global impression, overall, positive and negative symptoms was noted (Casey et al. 2003).

Switching stable but symptomatic outpatients from conventional antipsychotics, olanzapine or risperidone to *ziprasidone* (mean dose 91 mg/day) was found to be well tolerated and associated with symptom improvement (Weiden et al. 2003).

In a double-blind RCT comparing *zotepine* (150–450 mg/day) and clozapine (150–450 mg/day) similar improvement in positive and negative symptoms, and some cognitive domains was observed during 6-week treatment (Meyer-Lindenberg et al. 1997). Two open studies found at least moderate global improvement under 1-year treatment with zotepine (50–500 mg/day), whereas response (at least 20% decrease in BPRS total score) was noted in nearly 80% of the patients occurring in the first 12 weeks (Harada et al. 1992).

In summary there is very limited evidence for efficacy of aripiprazole, quetiapine, ziprasidone and

zotepine in the treatment of therapy refractory schizophrenia (*Level D*).

General recommendations. The first step in the clinical management of treatment-resistant schizophrenia (TRS) is to establish that antipsychotic drugs have been adequately tried in terms of dosage, duration and adherence. Other causes of non-response should be considered in the clinical assessment, such as comorbid substance misuse, poor treatment adherence, the concurrent use of other prescribed medicines, polypharmacy including pharmacokinetic and pharmacodynamic interactions, physical illness and poor social environment and support (DGPPN 1998; NICE 2002, McGorry et al. 2003; APA 2004). Especially when applying SGA (lower range) it may be useful to consider the patient's weight to adjust the dose (Kane et al. 2003a). The fact that there is some delay between initiation of treatment and full clinical response complicates the evaluation of treatment response, and sometimes symptoms can continue to improve for up to 6 months. If the patient shows partial response an expert consensus agrees to extend the duration of the trial to 4–10 weeks for the initially switched antipsychotic, and approximately 5–11 weeks for the second antipsychotic prescribed (Kane et al. 2003a). Target symptoms have to be defined. If the target symptoms of schizophrenia have been unresponsive to conventional antipsychotics, treatment with an SGA should be provided; based on available evidence to date olanzapine or risperidone may be worth considering as first line (NICE 2002) (*Level B*). In individuals with clearly defined treatment resistance (including at least one adequate treatment with SGA), clozapine should be introduced as treatment of choice because of clozapine's superior efficacy in this regard (*Level B*) (DGPPN 1998; NICE 2002; APA 2004). For non-adherent patients, special efforts to enhance the therapeutic alliance should be made including psychotherapeutic and psychosocial interventions e.g., adherence therapy, psychoeducation and family interventions. Depot antipsychotics can be considered if there has been poor adherence, but clozapine may also be preferable because the improving psychopathology and the required monitoring often enhances adherence (McGorry et al. 2003). Cognitive behavioural therapy should be offered in conjunction with clozapine to improve social functioning, quality of life, and to reduce positive and negative symptoms (see section *Psychotherapy*) (*Level C*). Besides clozapine, there are limited options for patients suffering from severe and significant residual symptoms, even after antipsychotic monotherapy has been optimised without success. This may be the reason why various augmentation strategies and polypharmacy are offered, despite the fact that there is only limited or no evidence supporting this approach. Augmentation and combination strategies are reviewed and discussed below. Before switching to another agent, expert consensus agrees on increasing the dose of the current antipsychotic, unless side effects lead to earlier switching (Kane et al. 2003).

Switching strategies

There are three main strategies for switching from one agent to another: cross-titration (gradually tapering off the dose of the first antipychotic while gradually increasing the dose of the second), overlap and taper (continuing the same dose of the first antipsychotic while gradually increasing the second to a therapeutic level and then tapering the first), and abrupt change of the antipsychotics. Some studies compared these strategies, especially the two first mentioned switching modalities, and found no difference in efficacy and tolerability (Kane et al. 2003a). Most guidelines prefer cross-titration, with the exception of switching to clozapine (e.g., APA 2004). In this case tapering off of the first antipsychotic should be completed before introducing clozapine due to potential haematological side effects. Nevertheless many experts prefer also cross-titration, probably reflecting the need for relatively slow titration of clozapine (Kane et al. 2003a).

Switching to clozapine

As previously discussed, a substantial number of studies have consistently demonstrated that clozapine is superior to conventional neuroleptic agents in the treatment of refractory schizophrenia (*Level B*). In this case no general dosage recommendations can be given; however, although the mean dose in the studies was 400–500 mg clozapine daily, some patients responded well to only 100–200 mg/day and others benefited from doses of up to 900 mg/day. According to clinical practice a target dose of up to 400 mg/day may be selected. After nonreponse, despite continuing treatment over 4–6 weeks and obtaining sufficient blood levels of clozapine, the next step should consist of increasing the dosage up to 900 mg/day and closely monitoring for adverse effects (*Level D*). If there is still no adequate response augmentation or combination strategies should be considered (*Level D*).

Switching to other SGAs

As mentioned, a few studies have produced evidence of the superiority of SGAs other than clozapine, mainly risperidone and olanzapine, compared with

typical neuroleptic agents in treatment-refractory schizophrenia (*Level B*). There is some evidence from switch studies that switching from clozapine to other SGAs, e.g., olanzapine in the case of inadequate response may provide benefits (*Level D*). More future research is urgently needed to develop evidence-based switching strategies, especially from clozapine.

Combining antipsychotics

Despite the frequent combination of two and more antipsychotics in clinical practice (e.g., in more than 50% of hospitalised patients), there are few randomised controlled studies available evaluating the efficacy of combining strategies (Freudenreich and Goff 2002). In patients with TRS adding an antipsychotic to *clozapine* was mentioned as a reasonable treatment option. To date, four double-blind, placebo-controlled randomised trials have been published evaluating combination therapy with clozapine. While combining clozapine with chlorpromazine revealed no benefit (Potter et al. 1989), adding sulpiride to clozapine led to a more than 20% decrease in psychopathology (BPRS total score) and superior improvement compared to placebo (Shiloh et al. 1997). In addition to earlier open studies and case reports, a recent double-blind RCT showed significantly superior improvement of positive, negative and total psychopathology when *adding risperidone* for up to 6 mg/day to clozapine (mean dose 400 mg/day) (Josiassen et al. 2005). In contrast to these results another RCT revealed a significantly inferior improvement of positive symptoms by adding risperidone compared to placebo (Yagcioglu et al. 2005). In open trials *pimozide* (mean dose 4 mg/day) combined to clozapine demonstrated improvement in psychotic symptoms, but also increased or changed side effects (Freudenreich and Goff 2002; Miller and Craig 2002). It was discussed if an increased serum level of clozapine may be responsible for better outcome (e.g., in combination with risperidone) (Tyson et al. 1995). The effect of increasing clozapine levels could not be replicated in another study over 4 weeks in TRS (Henderson und Goff 1996). A significant decrease in psychopathology was found without changes of clozapine serum level. Further case series revealed evidence for the efficacy of adding risperidone to clozapine (McCarthy and Terkelsen 1995; Morea et al. 1999; Raskin et al. 2000; Taylor et al. 2001). Case reports and open label studies revealed success with the combination of clozapine and *olanzapine* (Gupta et al. 1998), clozapine with *amisulpride* (Allouche et al. 1994) and clozapine with *ziprasidone* (Kaye 2003).

In a case series, improvement of positive and negative symptoms was reported in patients receiving *olanzapine* in combination with sulpiride (Raskin et al. 2000). However, in a randomised controlled study with small sample size of patients with TRS, the addition of sulpiride (600 mg/day) to olanzapine monotherapy over 8 weeks did not reveal relevant benefits in positive and negative symptomatology, but led to improvement of depressive symptoms (Kotler et al. 2004). A small case series showed efficacy of combining olanzapine and risperidone (Lerner et al. 2000).

Recommendations. Overall there is only very limited evidence for the efficacy of combining antipsychotics in TRS. The combination of clozapine with risperidone, and clozapine with sulpiride may reflect the best treatment options, based on successful RCT (*Level C*). Nevertheless in clinical practice it may be useful to select the antipsychotic with which the best previous response could be obtained for further combination (*Level D*). On a theoretical pharmacodynamic basis, antipsychotics with different receptor profiles may be selected for combination therapy (e.g., clozapine combined with amisulpride) (*Level D*). Last but not least clinicians should be aware of potentiating side effects when combining two or more antipsychotics and may select agents with decreased interaction risk.

Augmentation strategies

Augmentation strategies have to be selected in regard to the defined target symptoms in TRS. Depending on the type of predominantly presented residual symptom (e.g., aggressive behaviour, anxiety, positive, negative, cognitive or mood symptoms), augmentation includes adding lithium, anticonvulsants, benzodiazepines and β-blocking agents, and in some exceptional cases undertaking more or less experimental approaches with *N*-methyl-d-aspartate (NMDA) receptor agonists (e.g., d-serine, glycine, d-cycloserine) or cholinergic agonists (APA 2004).

To avoid risking side effects and potential drug interactions, effectiveness of current treatment with the chosen adjunctive medications has to be evaluated at short time intervals, and adjunctive medications that do not produce clinical benefits should be discontinued. Randomised controlled studies with greater sample sizes of augmentation strategies for TRS are still lacking, therefore recommendations are based mainly on clinical experience (Freudenreich and Goff 2002).

Mood stabilisers and Anticonvulsants. A meta-analysis evaluating the efficacy of *lithium* in schizophrenic patients included 20 randomised, controlled studies. Eleven of these trials studied the efficacy of lithium as add-on treatment to ongoing antipsychotic medication (Leucht et al. 2004). Overall the combination strategy revealed better response, but superiority compared to antipsychotic monotherapy could not be found consistently in all trials and disappeared if patients with mood symptoms were excluded. In small case series augmentation with lithium showed improvement in TRS (Simhandl et al. 1996).

As mentioned earlier, adding *valproate* to haloperidol, olanzapine and risperidone in randomised controlled trials demonstrated inconsistently positive effects only on different specific response aspects, e.g., negative symptoms and global impression (Wassef et al. 2000), hostility (Dose et al. 1998; Citrome et al. 2004) and more rapid onset of action (Casey et al. 2003a), while another study reported no benefit in any outcome measure (Hesslinger 1999). In one small case series improvement in patients with TRS was reported (Morinigo et al. 1989).

The addition of *carbamazepine* revealed controversial results. In combination with haloperidol, a worsening of symptoms was reported, possibly due to pharmacokinetic reasons (decrease of haloperidol plasma level) (Hesslinger 1999). A meta-analysis concluded that there is no evidence for the efficacy of combining carbamazepine with antipsychotics in schizophrenia (Leucht et al. 2002). Overall in the eight evaluated placebo-controlled trials significantly better improvement was noted only in a minority of patients in the active substance group, and there was no superiority in regard to response criteria (reduction above 50% of BPRS total score). Patients augmented with carbamazepine showed less EPS and similar tolerability compared to placebo. In a small case series augmentation with carbamazepine showed improvement in TRS (Simhandl et al. 1996).

Lamotrigine was observed, in case reports, to reduce psychotic symptoms in combination with clozapine (Dursun et al. 1999; Dursun and Deakin 2001; Saba et al. 2002). When lamotrigine was added to risperidone or haloperidol, case reports were controversial (Dursun and Deakin 2001; Kolivakis et al. 2004). No significant improvement was observed in addition to olanzapine or flupenthixol (Dursun and Deakin 2001). In two RCTs the addition of lamotrigine (200 mg/day) versus placebo to an ongoing clozapine treatment (Tiihonen et al. 2003), or to conventional antipsychotics, risperidone, olanzapine or clozapine in a dose of 400 mg/day, was slightly effective (Kremer et al. 2004) in reducing positive and general psychopathological symptoms in treatment-resistant schizophrenic patients. In both trials lamotrigine was well tolerated.

In an open, non-randomised trial no beneficial effect of *topiramate* added to an ongoing treatment with clozapine, olanzapine, risperidone or flupenthixol was seen in treatment-resistant schizophrenia (Dursun and Deakin 2001).

Antidepressive agents. When augmenting antidepressive agents, the potential exacerbation of psychotic symptoms due to increased adrenergic and dopaminergic transmission has to be considered (Siris et al. 2000). Beyond treating depressive symptoms (*see previous section*), persisting negative symptomatology is the target of adding antidepressive agents. It is noteworthy that, in a recent review, fluvoxamine and fluoxetine demonstrated improvement of negative symptoms independent of the influence on depressive mood (Silver 2003). In addition, e.g., a recent double-blind, placebo-controlled study augmenting mirtazapine 30 mg/day to ongoing clozapine treatment showed significant reduction of negative symptoms and total psychopathology in 8 weeks (Zoccali et al. 2004). The efficacy in treating schizophrenic patients with predominantly negative symptoms is reported elsewhere in this guideline (*see Section 3.3.3*). Other studies were mainly conducted only in postpsychotic depression, and therefore no recommendation for treatment-resistant schizophrenia could be extrapolated.

Benzodiazepines. Additional benzodiazepine treatment consistently showed no superiority to antipsychotic monotherapy in patients with TRS. Two double-blind RCTs demonstrated superior improvement in total psychopathology (Lingjaerde et al. 1979; Wolkowitz et al. 1992), while other trials revealed no benefit (Holden et al. 1968; Hanlon et al. 1970; Ruskin et al. 1979; Pato et al. 1989). In the subsample of patients with catatonia the benzodiazepines oxazepam and clonazepam revealed efficacy in acute catatonia, while for lorazepam no superiority could be observed in a placebo-controlled RCT in chronic catatonic patients (Ungvari et al. 1999). In general, lorazepam may provide some advantages for combination approaches, because good absorption of the oral preparation and less muscle relaxation than with other benzodiazepines was observed (APA 2004).

β-Blocking agents. A systematic review and meta-analysis concluded that β-blockers did not reveal clear evidence for their use as adjunctive medication in schizophrenia and also in patients with TRS

(Cheine et al. 2004). A placebo-controlled RCT demonstrated only slight, non-significant improvement for the combination with nadolol (80–120 mg/day) over 3 weeks (Allan et al. 1996). In a 16-week, randomised clinical trial, patients showed no significant difference when augmented with propranolol (up to 1920 mg/day) (Myers et al. 1981). Further RCTs reported no clinical improvement with augmentation of oxprenolol (160–640 mg/day) (Karniol and Portela 1982), or propranolol in the dose range of 80–640 mg/day (Pugh et al. 1983) or in a mean dose of 450 mg/day (Yorkston et al. 1977) over 12-week treatment.

Recommendations. In summary, there is very limited evidence that augmentation with mood stabilisers or anticonvulsants reveals benefits for patients with TRS. Therefore, administration of valproic acid, carbamazepine or lamotrigine should only be considered after other therapy options have been exhausted. There is evidence that lamotrigine as an adjunctive treatment, especially to clozapine, can reduce schizophrenic psychopathology (*Level C*). Adding valproate may be a therapy option if aggression and hostility is predominantly present (*Level C*), and lithium may reveal benefits if depressive symptoms are predominant (*Level D*). Carbamazepine should not be administered together with clozapine due to a potential increased risk of haematological side effects. In excited, anxious and catatonic patients, the use of adjunctive benzodiazepines is beneficial (*Level C*). Patients presenting with persisting negative (*Level C*) or depressive symptoms (*Level B)* may be treated with antidepressants.

Electroconvulsive therapy (ECT) in TRS

In patients with *treatment-resistant schizophrenia* (*TRS*), reports and case series suggest that ECT may augment response to FGAs (e.g., König and Glatter-Götz 1990; Sajatovic and Meltzer 1993; Chanpattana et al. 1999) and increase therapeutic benefit in combination with SGAs (e.g., Kupchik et al. 2000; Hirose et al. 2001). Therefore the combination of neuroleptics and ECT may be recommended (APA 2004) (*Level C*). Reviewing randomised controlled studies (RCTs) there is only one study using stringently defined criteria for TRS comparing ECT with sham-ECT, both groups on concurrent antipsychotics. In this study no significant advantage for ECT was found (Thayran and Adams 2004). Nevertheless another RCT examining continuation ECT for TRS revealed responder rates for remission above 50% (Chanpattana et al. 1999). There is only inconsistent evidence that mood symptoms or a diagnosis of schizoaffective disorder suggest a better response to ECT (e.g., Folstein et al. 1973; Dodwell and Goldberg 1989) (*Level D*). Some reports suggest that greater benefits are observed in patients with younger age (Chanpattana et al. 1999), predominantly positive symptoms (Landmark et al. 1987), shorter illness and episode durations (50–70% for patients who have been ill for less than 1 year but less than 20% for patients who have been continuously ill for more than 3 years) (e.g., Kalinowsky and Worthing 1943; Chanpattana et al. 1999; Thayran and Adams 2004), or fewer paranoid or schizoid premorbid personality traits (Dodwell and Goldberg 1989) (*Level D*). The available evidence suggests that antipsychotic medications should be continued during and after ECT when it is used in the treatment of schizophrenia (APA 2004) (*Level D*). A review of case series stated that the addition of ECT to clozapine for patients who did not respond to either traditional medication or a trial of clozapine alone had been reported as well tolerated and effective in 67% of cases (Kupchik et al. 2000) (*Level D*).

In summary there is only limited evidence for the efficacy of ECT in TRS. Therefore, ECT may be a treatment option in patients not responding to clozapine or when a trial with clozapine is not recommended, e.g., because of harmful side effects (APA 2004) (*Level C*). The available evidence suggests that antipsychotic medications should be continued during and after ECT (APA 2004) (*Level D*). After successful ECT treatment in TRS, maintenance ECT has to be considered (APA 2004) (*Level C*).

Combining with psychotherapy

A review stated that cognitive behaviour therapy techniques may have value in improving positive symptoms and therefore effectiveness in treatment-refractory schizophrenia (Cormac et al. 2004). In addition, cognitive remediation may be useful as a therapeutic strategy to reduce the severity of cognitive deficits (Bark et al. 2003). For persistent positive symptoms or disabling negative symptomatology, a CBT programme may lead to superior improvement compared to standard care or supportive counselling (Lewis et al. 2002). In another RCT, cognitive behavioural strategies (individual or group therapy), including elements of family intervention, proved efficacy in improvement of delusions and hallucinations (Drury et al. 2000). To date, some other randomised controlled trials are underway to assess efficacy of CBT in acutely ill patients (Wiedemann and Klingberg 2003). CBT was effective compared to standard care in increasing adherence and treatment (Kemp et al. 1998). In a meta-analysis it was

concluded that some RCTs showed efficacy in symptom improvement for family intervention compared to standard care (Falloon 2003). In summary, especially CBT and family intervention are helpful as adjuncts to antipsychotic treatment in patients with TRS (*Level B*).

Treatment in special circumstances

Psychiatric comorbidity

Suicidal behaviour. Common estimates are that 10% of people with schizophrenia will complete suicide, and that the rate of suicide attempts is 2–5-fold higher (e.g., Siris 2001). Cohort studies have shown that approximately 10% of patients with first-episode schizophrenia attempted suicide within 1 year, whereby hallucinations and previous suicidal behaviour represented the greatest risk factors (Nordentoft et al. 2002). Demographically associated with suicidality in schizophrenia are young age, being early in the course of the illness, male gender, coming from a high socioeconomic family background, being highly intelligent, having high expectations, not being married, lacking social supports, having awareness of symptoms, and being recently discharged from the hospital. Also associated are reduced self-esteem, stigma, recent loss or stress, hopelessness, isolation, treatment non-adherence and substance abuse (e.g., Siris 2001). Clinically, the most common correlates of suicidality in schizophrenia are depressive symptoms and the depressive syndrome, although severe psychotic and panic-like symptoms may contribute as well (e.g., Siris 2001). Suicide attempts by schizophrenic patients are more frequently fatal, indicating that more violent methods are used (Beautrais 2001). Different genetic and neurobiological factors are thought to influence suicidal behaviour, perhaps independently of genetic factors due to schizophrenia (Meltzer 2002). Suicide is the leading cause of premature death among patients with schizophrenia (e.g., Meltzer 2002). Suicidal ideas or threats should be judged in the context of a patient's history as provided by the patient and by relatives and the current therapist, if they are available (APA 1997). There should be close monitoring of vulnerable patients during times of personal crisis, significant environmental changes, or heightened distress or depression during the course of illness. The frequency of outpatient visits may need to be increased during vulnerable periods, including recent discharge from the hospitals (APA 1997).

In some open and randomised controlled studies comparing SGAs with FGAs, a protective effect may be observed for the prevention of suicide. This effect could not be demonstrated consistently (Keck et al. 2000; Tondo et al. 2001; Barak et al. 2004). Therefore it was concluded to date that no significant difference has emerged between atypical and typical neuroleptic agents as substance groups in the prevention of suicidal behaviour (*Level C*). If there is an increased risk of suicide, clozapine has proved to be superior to other neuroleptic agents in the reduction of suicidal behaviour in randomised controlled and open studies (Meltzer and Okayli 1995; Meltzer et al. 2003; Wagstaff and Perry 2003) (*Level B*).

Recommendations. For patients at high risk for suicide hospitalisation should be considered, and suicide precautions should be instituted. It is important to maximise the somatic treatment of psychosis and depression and address the patient's suicidality directly, with an empathic and supportive approach (APA 2004). Clozapine therapy should be considered if there is a significant and continuously increased risk of suicide (*Level B*).

Depression and anxiety

Depressive symptoms may occur in all phases of schizophrenia, e.g., prodromal phase, first episode, during the early course and after remission, and depression may contribute to the residual symptoms of schizophrenia, whereby the proportion of patients with schizophrenia who also manifest depression ranges from 7 to 75% (Siris 2000). Depressive symptoms have to be distinguished from side effects of antipsychotic medications (including medication-induced dysphoria, akinesia and akathisia), and the primary negative symptoms of schizophrenia (APA 2004). If antipsychotic medication-induced dysphoria is suspected, then antipsychotic dose reduction may be effective, or alternatively a switch to an antipsychotic with a lower risk of inducing extrapyramidal symptoms (e.g., SGA) may be considered. Some FGAs (e.g., thioridazine) (Dufresne et al. 1993) and SGAs have been suggested to be effective in treating depressive symptoms in schizophrenia. SGAs are suggested to be superior in this regard compared to FGA; however, evidence is limited (e.g., Tollefson et al. 1998; Peukens et al. 2000; Möller 2005a) (*see also Section 2.3.1.2. Efficacy of SGA*). Depressive symptoms in acute episodes may improve parallel with psychosis due to antipsychotic treatment (Möller 2005b). Due to potential worsening of psychosis by antidepressive agents during the acute phase, antidepressants are advocated primarily as adjunctive treatment in the stable phase of schizophrenia (Mulholland and Cooper 2000). Treatment with antidepressants added as an adjunct to antipsychotics is indicated when the

symptoms meet the syndromal criteria for major depressive disorder or are severe and causing significant distress (e.g., when accompanied by suicidal ideation) or interfering with function (DGPPN 1998; APA 2004). Tricyclic antidepressants (TCAs) have been primarily examined in the treatment of postpsychotic depression (Siris et al. 2000) (*Level B*). Other antidepressants, e.g., SSRIs and dual reuptake inhibitors, have also been found to be useful in the treatment of depression in schizophrenia (Siris 2000) (*Level B*). Nevertheless, one RCT observed no significant advantage with sertraline compared to placebo and demonstrated high placebo response (Addington et al. 2002). A small RCT comparing sertraline and imipramine in postpsychotic depression revealed comparable efficacy, but more rapid onset with sertraline (Kirli and Caliskan 1998). However, very few studies have examined the effects of antidepressants in patients treated with SGA, making it difficult to evaluate the current utility of adjunctive antidepressant agents. When prescribed, antidepressants are used in the same doses that are used for treatment of major depressive disorder (APA 2004). There are, however, potential pharmacokinetic interactions with certain antipsychotic medications; for example, the SSRIs (such as fluoxetine, paroxetine, and fluvoxamine) are inhibitors of cytochrome P450 enzymes and thereby increase antipsychotic plasma levels. Similarly, the blood levels of some antidepressants may be elevated by the concomitant administration of antipsychotic medications.

Aggressive behaviour

In observational and retrospective cohort studies violent behaviour occurred more frequently (nearly 4-fold) in those with schizophrenia than in persons with no form of psychiatric disease (Angermeyer 2000). In a meta-analysis, younger age, higher rehospitalisation rate, comorbid antisocial personality disorder and former involvement in criminal acts were predictors of violence in schizophrenic people living in the community (Bonta et al. 1998). Other risk factors for violence in schizophrenia include prior arrests, substance abuse, the presence of hallucinations, delusions or bizarre behaviours, the presence of neurological impairment, and being male, poor, unskilled, uneducated and unmarried (APA 1997). Often relatives, e.g., parents, are frequent targets of violence when it occurs (Angermeyer 2000). Identifying risk factors for violence and violent ideation is part of a standard psychiatric evaluation. When a patient is found to pose a serious threat to other people, the psychiatrist must exercise his or her own best judgement, in accord with the legal requirements of the jurisdiction, to protect those people from foreseeable harm (APA 1997). Effective management of aggression and assaultiveness in patients with schizophrenia can often be achieved through behavioural treatment, limit-setting and 'talking down' techniques (APA 2004). Antipsychotic medications are the mainstay of management; anticonvulsants (e.g., Citrome et al. 2004), lithium and high-dose β-blockers (e.g., propranolol, pindolol) (e.g., Caspi et al. 2001) have also been reported to provide some utility (*Level C*) (APA 2004). SGAs, e.g., risperidone (e.g., Chengappa et al. 2000; Aleman and Kahn 2001) and especially clozapine (e.g., Chengappa et al. 2002) reveal efficacy in the treatment of hostility and aggressive behaviour (*Level C*). The emergency management has been already discussed in a previous section (*see Section 3.2. Treating agitation*).

Substance use disorders

Substance abuse in individuals with schizophrenia is very common and has risen to the most prevalent comorbid psychiatric condition associated with schizophrenia (Cuffel et al. 1993). Estimated life-time prevalence rates for substance abuse in schizophrenia range from approximately 15 to 65% (Kovanaszay et al. 1997; Regier et al. 1990; Wobrock et al. 2004). Prevalence rates vary with different screening instruments, evaluation settings (inpatient or outpatient) and depend on different social and cultural factors. In more recent studies the 6-month and lifetime prevalence of substance abuse or dependence among people with schizophrenia was found to be ca. 27 and 60%, respectively (Fowler et al. 1998), whereas comorbid non-alcohol lifetime substance misuse was reported in 16% of the overall population, and cannabis abuse was reported in 60% of male schizophrenics under the age of 36 years (Duke et al. 2001). Comorbid substance use disorder (SUD) has been associated with more frequent and longer periods of hospitalisation and other negative outcomes, including higher relapse rate, even in first-episode patients, higher non-compliance, elevated EPS-rate in general and during antipsychotic treatment, unemployment, homelessness, violence, incarceration, suicide and HIV infection (e.g., Mueser et al. 1990; Olivera et al. 1990; Soyka et al. 1993; Linszen et al. 1994; Blanchard et al. 2000; Mueser et al. 2000; Goldham et al. 2002; Hunt et al. 2002; Lacro et al. 2002). Besides the legal substances tobacco and alcohol, cannabis seems to be the most illicit drug abused in schizophrenics and has been discussed as an important risk factor for developing schizophrenia (Bersani et al. 2002; Caspari and Wobrock 2004). The presence of

substance abuse or dependence is often missed in assessments, especially if such a patient is seen during an acute psychotic episode. Because self-report may often be unreliable, corroborating evidence from all sources including laboratory tests (liver function) and drug screening (urine and blood) should be sought. The effects of abused substances on schizophrenic symptoms vary, making the differentiation of substance abuse-related symptoms from those related to functional psychosis difficult (APA 2004). The abused substances may lead to increased hallucinations, paranoid symptoms or anxiousness in patients with pre-existing schizophrenic psychoses (e.g., Dixon et al. 1991). Antipsychotics may not necessarily neutralise these psychomimetic effects (e.g., Gawin 1986). In some cases it may be extremely difficult to distinguish between schizophrenia and drug-induced psychosis.

The key issue in providing treatment for this population is developing a dual disorder approach that integrates treatment of substance abuse and schizophrenia (Ridgely and Jerrel 1996; Drake and Mueser 2000; Wobrock et al. 2004). Many programmes are now providing this integration through interdisciplinary teams with expertise in the treatment of schizophrenia and substance abuse. This form of treatment features assertive outreach, case management, family interventions, housing, rehabilitation and pharmacotherapy. It also includes a stagewise motivational approach for patients who do not recognise the need for treatment of substance use disorders, and behavioural interventions for those who are trying to attain or maintain abstinence. Studies show that combined treatment programmes with motivational elements, psychoeducation and cognitive-behavioural approaches avoiding direct confrontation can be effective in reducing substance abuse and in decreasing frequency and severity of psychotic decompensations (e.g., Hellerstein et al. 1995; Addington and El-Guebaly 1998; Drake and Mueser 2000; Barrowclough et al. 2001; Clark 2001; Baker et al. 2002).

Although prospective randomised controlled studies for schizophrenic patients with comorbid substance use are lacking, recommendations for antipsychotic treatment are mostly derived from studies in schizophrenia where drug abuse was an exclusion criteria. In older reviews, haloperidol at a dose of 5–10 mg/day (maximal 20 mg/day), or alternatively flupentixol 5–20 mg/day, were recommended as drugs of choice for antipsychotic treatment (Soyka 1996; Wilkins 1997). Antipsychotics with extensive anticholinergic side effects should be avoided since anticholinergic effects of used substances could be potentiated. Additional positive symptoms caused by substances usually remit quickly with abstinence; hence, schizophrenic patients with concomitant substance use do not require higher doses of antipsychotics than schizophrenic subjects without comorbid substance use (Richard et al. 1985; Siris 1990; Wilkins 1997). In schizophrenic patients using cocaine, a possible intensification of cocaine-induced hyperthermia must be taken into account during antipsychotic treatment (Kosten and Kleber 1988). Prolonged absorption, e.g., of cannabis from visceral fat tissue, may be responsible for prolonged psychomimetic effects and pharmacokinetic interactions, especially in the initial stages of therapy. Alcohol, for example, has been reported to reduce the serum levels of antipsychotic agents (e.g., fluphenazine) (Soni et al. 1991).

Open trials with *FGAs*, in particular *flupentixol*, and case series suggest an effectiveness in the reduction of comorbid substance use. In schizophrenic patients with comorbid alcohol dependence, alcohol consumption and craving was markedly reduced by flupentixol decanoate (10–60 mg i.m. every 2 weeks), while psychopathology was hardly affected (Soyka and Sand 1995; Soyka et al. 2003). In addition to an improvement in mental state, schizophrenic patients with comorbid substance dependence (alcohol, cocaine, marijuana, benzodiazepines and amphetamines) receiving flupentixol decanoate displayed a reduction in substance intake (Schilkrut et al. 1988; Levin et al. 1998). In contrast to these findings, treatment with flupentixol decanoate (compared to placebo) was associated with more relapses in alcoholics without comorbid schizophrenia (Wiesbeck et al. 2001). In a cross-sectional study, treatment with SGAs compared with conventional antipsychotic agents was associated with a reduction in alcohol consumption, although no differences were seen in psychopathology or extrapyramidal side effects (Scheller-Gilkey et al. 2003).

Of *SGAs* the largest body of evidence has been gathered for *clozapine* in the treatment of schizophrenic patients with comorbid substance use. In case records, case series, retrospective analysis of treatment-resistant patients and cross-sectional studies, reduced substance consumption (particularly alcohol and cocaine) associated with clozapine treatment has been reported. Reduced substance use was associated with improvement in (particularly negative) schizophrenic symptoms in most case series (Albanese et al. 1994; Yovell & Opler, 1994; Marcus and Snyder 1995; Tsuang et al. 1999) and retrospective or cross-sectional studies (Lee et al. 1998; Drake and Muser 2000; Zimmet et al. 2000), but not in all retrospective analysis (Buckley et al. 1994a,b). Controlled studies for maintenance therapy and relapse prevention in patients with this dual

diagnosis are not available. In clozapine-treated patients with treatment-resistant schizophrenia, no difference was found in the comparison of patients with and without comorbid substance use regarding readmission rate in a prospective observational trial (Kelly et al. 2003). In cocaine addicts, administration of clozapine can increase serum concentrations of cocaine and induce cardiovascular side effects, therefore close monitoring during the dose titration phase of clozapine is indicated (Farren et al. 2000). For patients showing persistent psychotic symptoms or developing side effects to classical antipsychotics, treatment with clozapine at doses of 50–600 mg/day is recommended (Soyka 1996; Wilkins 1997). In addition, retrospective, cross-sectional and prospective studies (switching from haloperidol to clozapine) revealed evidence for the reduction of cigarette smoking in schizophrenic patients (McEvoy et al. 1995; Procyshyn et al. 2001, 2002). For *risperidone*, case records and an open prospective study with small sample size revealed evidence for reduction of substance use, craving, symptomatology and relapse in comparison with typical antipsychotics (haloperidol, fluphenazine, chlorpromazine) (Gupta and Basu 2001; Smelson et al. 2002). In a prospective pilot study with small sample size comparing *olanzapine* with haloperidol, reduction in cocaine consumption parallel to an improvement in psychopathological condition and adverse drug effects was observed (Tsuang et al. 2002). Open prospective clinical trials showed that switching antipsychotic treatment from conventional antipsychotic drugs to olanzapine could decrease substance use and improve schizophrenic symptoms (Noordsy and O'Keefe 1999; Littrell et al. 2001). Substantial weight gain was noted as an adverse effect. One open prospective study demonstrated that olanzapine at doses of 10–25 mg/day is as effective on psychiatric symptoms in treatment-resistant schizophrenic patients without comorbid substance use as in those with additional substance use (Conley et al. 1998). An open prospective trial and case reports suggested that *quetiapine* may be successful in reducing alcohol and cocaine craving, relapse and symptom improvement in patients with comorbid substance use (Brown et al. 2002; Weisman 2003). In a retrospective study comparing the efficacy of *clozapine* and *riperidone* on alcohol and cannabis use in schizophrenic patients, treatment with clozapine led to more abstinence (Green et al. 2003).

Since depressive symptoms are frequent in patients with schizophrenia and comorbid substance use, studies with tricyclic *antidepressants* (TCAs) were undertaken. Besides the antidepressant effect a decrease of substance consumption and craving could be detected in cocaine-dependent schizophrenic patients. This observation was made either in an open study (Ziedonis et al. 1992) or in a placebo-controlled study administering desipramine (Wilkins et al. 1997) or imipramine concurrently to neuroleptic treatment (Siris et al. 1993). Because of their anticholinergic effects, treatment with TCAs should not be started until drug-detoxification is completed. Other adverse effects of treatment with TCAs may be the precipitation of hypertensive crises during concomitant use of substances with adrenergic stimulation and the exacerbation of psychotic symptoms (Siris 1990).

For *anticraving agents*, e.g., acamprosate (modulating NMDA receptors) and naltrexone (opioid receptor antagonist), there are no controlled studies available for patients with schizophrenia and drug dependencies. Naltrexone has been reported in research abstracts to be potentially helpful (Sernyak et al. 1998; Maxwell and Shinderman 2000). Nevertheless, because of their excellent tolerability these medications may be administered to alcohol-dependent schizophrenic patients (Noordsy and Green 2003). Disulfiram may itself induce psychosis, presumably by blocking dopamine β-hydroxlyase (Ewing et al. 1977; Major et al. 1978; Noordsy and Green 2003). Therefore, and due to the possible acceleration of antipsychotic drug metabolism, discussion is controversial regarding the use of disulfiram in patients with schizophrenia and comorbid alcohol dependence, although therapeutic success in doses 250–500 mg/day has been reported in case records and chart reviews (Kofoed et al. 1986; Mueser et al. 2003).

Since the frequency of *EPS* is increased in schizophrenic patients with comorbid substance use disorder, concomitant or early administration of anticholinergic agents, for instance biperiden, could be considered (Soyka 1996). The higher risk for EPS in this population could argue for SGAs as the first-line treatment option in schizophrenic patients with comorbid substance use. The benzamide antipsychotic tiapride could become the treatment of choice for dyskinesias, as tiapride may have anticraving properties and is used in the treatment of alcohol withdrawal syndromes (Soyka 1996).

Based on very limited evidence but supported by theoretical neuropharmacological considerations (e.g., lower EPS, ameliorating brain reward dysfunction, reducing impulsivity) and growing clinical practice, SGAs may be recommended as first-line treatment in patients with schizophrenia and comorbid substance use disorder (Krystal et al. 1999; Noordsy and Green 2003; Potvin et al. 2003) (*Level D*). It may be favourable for patients with this dual diagnosis to lower the threshold for recommending a trial with clozapine than in patients without comor-

bid substance use disorder (*Level D*). Because of frequent non-adherence, extended use of depot antipsychotics such as haloperidol or flupentixoldecanoate may be a favourable therapeutic option for this patient group (Soyka 1996) (*Level D*).

Somatic comorbidity

Epidemiological surveys demonstrate that patients with schizophrenia suffer to a higher extent from a variety of somatic comorbidities, including cardiovascular disease, respiratory disease, diabetes and infectious diseases. Somatic comorbidities are determined by multiple factors, including associations with schizophrenia itself, lifestyle (e.g., smoking, substance use, obesity, lack of exercise), environment and medications (e.g., Jeste et al. 1996). Therefore treatment selection and clinical management of patients with schizophrenia must consider the patient's past medical history and general medical status when determining the treatment plan (APA 2004). Because patients with psychosis and *mental retardation* are at increased risk for extrapyramidal side effects and tardive dyskinesia, second-generation antipsychotics, and particularly those with minimal risk of EPS (e.g., quetiapine), are recommended (APA 2004). For patients with preexisting *osteopenia* or *osteoporosis*, an antipsychotic with minimal effects on prolactin should be prescribed if possible. In addition, for women with *breast cancer*, antipsychotics with prolactin-elevating effects should be avoided or prescribed only after consultation with the patient's oncologist. In such instances, aripiprazole, which partially suppresses prolactin release, may be specifically indicated (APA 2004). For *obese* patients special treatment considerations may be useful (*see the section on management of side effects in Part 2 of these guidelines*). Treatment selection should always weigh the expected benefits of antipsychotic treatment against its potential to exacerbate or contribute to the development of specific medical conditions. Patients with prolonged QT syndrome, bradycardia, certain electrolyte disturbances, heart failure or recent myocardial infarction and patients who are taking drugs that prolong the QT interval should not be treated with an antipsychotic that could further prolong the QT interval or increase the risk of the arrhythmia torsades de pointes. These antipsychotics include thioridazine, pimozide, droperidol and ziprasidone (Marder et al. 2004). Medications with low affinity for α-adrenergic receptors should be used for patients who are vulnerable to orthostatic hypotension, including elderly patients, patients with peripheral vascular disease or compromised cardiovascular status, and other severely debilitated patients (APA 2004). For patients with acute angle-closure glaucoma, severe constipation, history of a paralytic ileus, urinary retention, prostate hypertrophy or delirium/dementia, antipsychotics with little or no antagonism for cholinergic receptors should be prescribed. Studies demonstrated evidence that patients with severe dementia may be at increased risk of stroke when treated with risperidone or olanzapine compared to placebo. Nevertheless this elevated risk may also exist for FGAs or other SGAs, but has not been systematically investigated. Clozapine should not be used in patients with haematological diseases, especially when presenting with neutropenia ($<1500/mm^3$) or low white blood cell (WBC) count ($<3000/mm^3$) or a history of such sensitivities to prior medications (e.g., chlorprothixene, mianserine). Patients with hepatic disease may have impaired metabolism of antipsychotic medications and are at risk for toxicity. It is important to note that all antipsychotic medications lower the seizure threshold, with increased risks for chlorpromazine, clozapine and zotepine.

Elderly patients

Among middle-aged and elderly persons with schizophrenia, approximately 20% have late-onset schizophrenia (onset after age 40) or very-late-onset schizophrenia-like psychosis (onset after age 60) (APA 2004). The approach to the treatment of older persons with schizophrenia is similar to that for younger patients and involves combining pharmacotherapies with psychosocial interventions (NICE 2002; APA 2004). Several age-related physiological changes, e.g., reduced cardiac output, reduced glomerular filtration rate, possible reduction in hepatic metabolism, and increased fat content alter absorption, distribution, metabolism and excretion of medications. Compared to younger patients, geriatric patients show greater variability of response and greater sensitivity to medications. While an exaggerated response is more common in the elderly, some patients manifest diminished idiosyncratic, and even paradoxical effects of medications. In general, recommended starting doses in older patients are one-quarter to one-half of the usual adult starting dose (APA 2004). Elderly patients tend to be more sensitive to the therapeutic and toxic effects of antipsychotic medications, partly because of age-related decreases in dopamine and acetylcholine neurotransmission in the brain. This sensitivity is especially higher in older patients with structural brain abnormalities. Side effects of antipsychotic medications that occur more frequently in older subjects include sedation, orthostatic hypotension, anticholinergic reactions, extrapyramidal symptoms

(akathisia and parkinsonism but not acute dystonia), and tardive dyskinesia (e.g., Jeste 2000). Because nearly all the commonly prescribed antipsychotic medications are equally efficacious for older patients with schizophrenia, selection of an antipsychotic medication should be based primarily on the side effect profile (*for concomitant somatic comorbidity see previous section in this guideline*) (APA 2004). In six double-blind controlled studies that included schizophrenic patients with a mean age of more than 45 years, the mean rate of relapse for the groups whose antipsychotic medication was withdrawn was 39.9% over an average 6-month follow-up period, while the relapse rate for the groups whose antipsychotic medication was maintained was 11.4% (Jeste et al. 1993). This result may suggest to continue with medication. Especially in elderly people, unnecessary polypharmacy has to be avoided, and anticholinergic side effects of antipsychotic drugs become more prominent and important. This should be taken into consideration when prescribing an antipsychotic or adjunctive agent.

Gender differences

In the clinical presentation and course of schizophrenia, numerous gender differences are obvious (e.g., Goldstein and Tsuang 1990; Häfner 2000). The mean age of onset in women is later (3–4 years) than in men and the peak of illness onset is two-tailed, with a second peak after menopause (Häfner 2000). Probably due to the later onset, a better premorbid history and potential protective effects of oestrogens, women present a favourable course with less negative and more affective symptoms, and are more likely to show response to neuroleptics than men with schizophrenia (Seeman 1986; Goldstein and Tsuang 1990; Castle et al. 1993, Häfner 2000). Other than biologically mediated factors including family and societal expectations, lower pre- and postadmission levels of substance abuse and better support from family members may also positively affect outcome. In addition, traditional socialisation practises may allow greater dependence on the family and greater acceptance of family treatment among female schizophrenic patients. Also, it has been observed that, even after body weight is considered, women with first-episode schizophrenia responded to lower doses of antipsychotic medication than men (Szymanski et al. 1995; Leung and Chue 2000), although there is evidence that postmenopausal women may require higher doses (Leung and Chue 2000). Women tended to develop more EPS and higher prolactin levels during antipsychotic treatment than men (Leung and Chue 2000). Due to hormonal changes, women may need reduced dosage of neuroleptics in the middle of the menstrual cycle and increase of dosage during menstruation (Castle et al. 1995). Women with schizophrenia have a higher risk of physical and sexual abuse than healthy women and men, therefore careful exploration and special help may be required (Goodman et al. 1997).

In summary, there is limited evidence that women may be treated with lower doses of antispychotic medications than men (*Level D*). Additional information on contraception, protection against physical and sexual violence and potential gender-specific risks of antipsychotics (e.g., osteoporosis, breast cancer) should be given (*Level D*).

Pregnancy and lactation

Antipsychotic treatment of the pregnant or lactating women with schizophrenia has to balance the risks of various psychotropic medications to the foetus, newborn and breast-fed infant, against untreated psychotic symptoms and inadequate prenatal care (APA 2004). Controlled studies of antipsychotic drugs during pregnancy are not available, for obvious ethical reasons. Therefore knowledge of the risks of these agents arises from animal studies and from uncontrolled exposures in humans. Two periods of high risk to the foetus or newborn are identifiable– the first trimester with highest teratogenic risk and the time of birth with the highest withdrawal risk (APA 2004). Psychotropic drug exposure in the first trimester is only under full control of the physician and patient in planned pregnancies. Concerning *FGAs*, there is relatively little evidence of harmful effects, especially with high-potency agents, related to their former widespread use (Cohen and Rosenbaum 1998; American Academy of Pediatrics 2000; Gold 2000). Reports of the use of psychotropic medications during pregnancy had focused mainly on chlorpromazine and haloperidol. Less information is available regarding foetal exposure to *SGAs*. In a review, spontaneous abortion, stillbirth, prematurity, foetal abnormalities, unwanted perinatal reactions, gestational complications, including new-onset diabetes and preeclampsia, were reported under treatment with olanzapine (Ernst and Goldberg 2002). There were reports of elective terminations, new-onset or worsening gestational diabetes, floppy infant syndrome, neonatal seizures, gastro-oesophageal reflux disease and one intrauterine foetal death under treatment with clozapine (Gentile 2004). Elective terminations (MacKay et al. 1998) and one case of corpus callosum agenesis has been observed with risperidone treatment (Gentile 2004). Two case reports treating a pregnant schizophrenic patient with quetiapine revealed no complications

(Tenyi et al. 2002; Taylor et al. 2003). Case reports are lacking for aripiprazole and ziprasidone, while possible teratogenic effects have been described in animal studies (Gentile 2004). In a sytematic review it was concluded that olanzapine and clozapine do not increase the teratogenic risk compared to outcomes in the general healthy population; knowledge about quetiapine, risperidone, aripiprazole and ziprasidone is limited or lacking (Gentile 2004). Treatment with olanzapine and clozapine may be associated with a greater risk of hyperglycemia (Gentile 2004). In addition, pregnant women with schizophrenia taking SGAs were found frequently to be obese and have an inadequate intake of folic acid (related to an increased risk of neural tube defects), even suggesting indirect effects rather than a direct medication effect (Koren et al. 2002). Further, a number of studies demonstrated that pregnant women with schizophrenia receive relatively poor prenatal care, have more obstetric complications, and their offspring are more likely to have low birth weight and stillbirth (APA 2004). Contributing factors may be, e.g., low socioeconomic status and high rates of smoking or substance use disorders. Compared with antipsychotic medications, mood stabilisers and benzodiazepines are much more closely associated with foetal malformations and behavioural effects, the teratogenic effect of sodium valproate is especially well known (Ernst and Goldberg 2002; American Academy of Pediatrics 2000; Gold 2000). Thus, their risk/benefit ratio is different, and the need for their continuation during pregnancy and breast-feeding requires strong clinical justification.

Based on the reported findings and considerations it is recommended to insist on early involvement of an obstetrician who can help reduce the risks of the pregnancy and with whom the risks and benefits of pharmacological treatment options can be discussed. When possible, non-pharmacological management of schizophrenia should be undertaken during pregnancy (RANZCP 2003), although there nevertheless may be more risk to the mother–infant dyad from psychosis than benefit from stopping medication (Working Group for the Canadian Psychiatric Association 1998). If antipsychotic treatment is necessary, the minimum effective dose should be used and special attention paid to lowering the dose during the month before delivery or terminating 5–10 days before anticipated delivery (APA 1997; Working Group for the Canadian Psychiatric Association 1998). Because there is still more experience with FGAs in pregnancy, no advantage of SGAs in this condition has been demonstrated (Gentile 2004). Some high-potency agents appear to be safe (e.g., haloperidol), and they should be used preferentially but as briefly as possible, and the dose should be low enough to avoid EPS and therefore the necessity of antiparkinsonian medications (APA 1997; DGPPN 1998; Working Group for the Canadian Psychiatric Association 1998). Antiparkinson medication should especially be avoided in the first trimester (APA 1997), and treatment with phenothiazines should not be conducted (DGPPN 1998). After delivery, resumption of the full dose of FGA or SGA has to be considered, because there may be an increased risk of psychosis postpartum (APA 1997; Working Group for the Canadian Psychiatric Association 1998).

The efficacy of *ECT* during pregnancy in schizophrenia is assumed to be similar to that in non-pregnant women, while randomised evidence is lacking (UK ECT Group 2002). The rate of complications based on over 300 case reports and summarised in reviews (Miller 1994; UK ECT Group 2002) tended to be low (around 1%), and included four cases of premature labour, five cases of miscarriage, five cases of congenital abnormalities and three cases of still birth or neonatal death. Therefore ECT is recommended as a possible treatment option in several guidelines if pharmacological antipsychotic treatment is not appropiate (APA 1997; DGPPN 1998).

Because antipsychotics can accumulate in breast milk, especially observed with clozapine medication, and based on only sparse literature reports, *breast feeding* could not be recommended for women taking antipsychotic drugs (Gentile 2004). There is consensus among different guidelines to avoid breast feeding during psychotropic treatment of the mother (APA 1997; DGPPN 1998; Working Group for the Canadian Psychiatric Association 1998).

Early intervention in the initial prodromal phase

Subthreshold psychotic features combined with the onset of disability, especially if there is a family history, indicate a very high risk to develop psychosis (McGorry et al. 2003). Therefore persons with high risk in their family should be actively engaged in assessment and regular monitoring of mental state and safety. This should be carried out in a home-, primary care- or office-based setting, if possible, to reduce stigma (McGorry et al. 2003). Concurrent syndromes such as depression and substance abuse, and problem areas such as interpersonal vocational and family stress, should be appropriately managed. Information about the level of risk should be carefully provided, conveying a sense of therapeutic optimism. It should be emphasised that current problems can be alleviated, progression to psychosis

is not inevitable, and if psychosis does occur then effective and well-tolerated treatments are readily available. Engagement at this early stage will help to reduce any subsequent delay in accessing treatment for first-episode psychosis. The use of antipsychotic medication during the prodrome is the subject of research. At present it should be reserved for patients who display clear psychotic symptoms (*Level D*) (McGorry et al. 2003).

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