



## GUIDELINES

# World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 1: Update 2012 on the acute treatment of schizophrenia and the management of treatment resistance

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GUIDELINES FOR SCHIZOPHRENIA\*

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### Abstract

These updated guidelines are based on a first edition of the World Federation of Societies of Biological Psychiatry Guidelines for Biological Treatment of Schizophrenia published in 2005. For this 2012 revision, all available publications pertaining to the biological treatment of schizophrenia were reviewed systematically to allow for an evidence-based update. These guidelines provide evidence-based practice recommendations that are clinically and scientifically meaningful and these guidelines are intended to be used by all physicians diagnosing and treating people suffering from schizophrenia. Based on the first version of these guidelines, a systematic review of the MEDLINE/PUBMED database and the Cochrane Library, in addition to data extraction from national treatment guidelines, has been performed for this update. The identified literature was evaluated with respect to the strength of evidence for its efficacy and then categorised into six levels of evidence (A–F; Bandelow et al. 2008b, World J Biol Psychiatry 9:242). This first part of the updated guidelines covers the general descriptions of antipsychotics and their side effects, the biological treatment of acute schizophrenia and the management of treatment-resistant schizophrenia.

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

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## Preface

In 2005, the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia (Part 1: Acute treatment of schizophrenia) were published. Since 2005, new randomized clinical trials (RCT), open-label trials and meta-analyses have been conducted and published, providing new evidence for the efficacy of biological treatment in schizophrenia. Knowledge regarding the safety, tolerability and efficacy of approved antipsychotic drugs has increased and new antipsychotic drugs have been introduced. Furthermore, combination strategies and treatment with therapeutic agents other than antipsychotics have been further investigated and some new treatment strategies have been developed.

Therefore, an update of the WFSBP Guidelines for Biological Treatment of Schizophrenia is imperative.

## Executive summary of recommendations

### *General recommendations*

This part remains partly unchanged and was adopted from the WFSBP 2005 guidelines and updated where necessary. Specific treatment is indicated for patients who meet diagnostic criteria for schizophrenia, a schizophrenic episode or psychotic symptoms related to schizophrenic disorder (according to DSM-IV or ICD-10). 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 should be performed, including laboratory investigation and screening for drug abuse. Imaging techniques (preferentially MRI, if not accessible CCT), in order to exclude organic brain disease should be performed when somatic disease is clinically suspected (e.g., encephalitis, see part 3 of these guidelines "Management of special circumstances and concomitant disorders"). However, CSF should only be investigated if an organic brain disease (e.g., encephalitis, immune mediated disease) is expected.

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(s). Periodic re-evaluation of the diagnosis and the treatment plan is essential. Engagement of the family and significant others, 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 affect 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 commanding hallucinations. The patient should be informed about 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 for the acute treatment of schizophrenia and the management of treatment resistance**

The separation into first- and second-generation antipsychotics can be considered as arbitrary and there is the need to choose the suitable drug for a certain clinical condition. However, to structure the text, especially with regard to the terms used in nearly all clinical trials, the terms FGAs and SGAs are used, but the reader should be aware that these terms represent rather a pseudo-classification than a clinically and scientifically meaningful classification.

### **First-episode schizophrenia**

In first-episode schizophrenia, antipsychotic pharmacological treatments should be introduced with great care due to the higher risk of extrapyramidal symptoms (EPS). Appropriate strategies include gradual introduction of antipsychotic medication with the lowest possible effective dose, combined with careful explanation. The first-line use of both first-generation (FGA) and second generation (SGA) antipsychotic medication at the lower end of the standard dose range are possible treatments for a person experiencing a first episode of schizophrenia. Antipsychotics should be chosen individually,

respecting the patient's mental and somatic condition with special attention to side effects. However, due to the reduced risk of inducing extrapyramidal side effects, SGAs should be favoured in first-episode schizophrenia patients. When using FGAs, a close monitoring of extrapyramidal side effects (especially acute dystonic reactions, parkinsonism and akathisia at the beginning of the treatment, and tardive dyskinesia later during the treatment) is necessary. Metabolic parameters need to be closely controlled during treatment with antipsychotics. Skilled nursing care, a safe and supportive environment, and liberal doses of benzodiazepines may be essential to relieve distress, insomnia and behavioural disturbances secondary to psychosis while antipsychotic medication takes effect. However, the combination of benzodiazepines with a long half-time with antipsychotics has only little evidence and this combination strategy seems to be associated with an increased mortality in schizophrenia patients (Baandrup et al. 2010).

### Multiple episode schizophrenia (relapse)

Both, FGAs and SGAs generally have their place in the treatment of acute schizophrenia. The selection of an antipsychotic medication should be 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. Special attention needs to be given to antipsychotic-related side effects.

The dose may be titrated as quickly as tolerated to the target therapeutic dose of the antipsychotic medication while monitoring the patient's clinical status. 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.

In multiple episode schizophrenia the most common contributors to symptom relapse are antipsychotic medication non-adherence, substance use (see part 3 of these guidelines) and stressful life events, although relapses are not uncommon as a result of the natural course of the illness, despite continuing treatment. If non-adherence is suspected, it is recommended that the reasons should 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.

### Treatment-resistant schizophrenia

Treatment-resistant schizophrenia can be defined as a situation in which a significant improvement of psychopathology and/or other target symptoms has not been demonstrated despite treatment with two different antipsychotics from at least two different chemical classes (at least one should be an atypical antipsychotic) at the recommended antipsychotic dosages for a treatment period of at least 2–8 weeks per drug (Kane et al. 1988b; Lehman et al. 2004; McIlwain et al. 2011; NICE 2010).

In assessing treatment-resistant schizophrenia or partial response to medication, 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.

Adherence should be ensured, if necessary by checking drug concentrations. In individuals with clearly defined treatment-resistant schizophrenia, clozapine should be introduced as the treatment of choice because of its superior efficacy in this regard. Other treatment alternatives in case of non-response, such as other SGAs, augmentation strategies (anti-depressants, mood stabilisers) in relation to target symptoms, combination of antipsychotics and electroconvulsive therapy, can be implemented in certain cases. However, limited evidence for the efficacy of these strategies exists.

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

### Negative symptoms

The differentiation of primary and secondary negative symptoms is of particular importance for the treatment of schizophrenia. Primary negative symptoms are considered a core symptom of schizophrenia, whereas secondary negative symptoms are a consequence of positive symptoms (e.g., social withdrawal because of paranoid ideas), neurological side effects (extrapyramidal side effects, acute dystonia, antipsychotic-induced parkinsonism and tardive dyskinesia), depressive symptoms (e.g., post-psychotic or antipsychotic-induced depression) or environmental factors (e.g., social understimulation due to hospitalisation) (Carpenter et al. 1985).

For the treatment of secondary negative symptoms, both FGAs and SGAs have a modest efficacy. For primary negative symptoms treatment with certain SGAs (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, ziprasidone), but not with FGAs, is recommended with inconsistent evidence

and with the need for more studies to prove the efficacy. There is some limited evidence for the efficacy of antidepressants in the treatment of negative symptoms.

### **Treatment non-adherence**

One of the most common contributors to symptom relapse is antipsychotic medication non-adherence in schizophrenia patients. This is a general problem in all medical disciplines, because patients balance between the advantages and disadvantages of their treatment (Goff et al. 2010). In schizophrenia patients and patients with schizoaffective disorders almost half of the patients take less than 70% of the prescribed doses (Goff et al. 2010). There are many reasons for this treatment non-adherence: impaired insight, side effects associated with the antipsychotic medication, disorganized behaviour, the stigma of the diagnosis and the feeling of not being ill when symptom remission is achieved (Goff et al. 2010). Therefore, special attention needs to be paid to treatment-adherence in schizophrenia patients, because antipsychotics are only effective if they are really taken.

### **Management of side effects and long-term treatment of schizophrenia**

This is described in the second part of these guidelines, which will be published soon.

### **Concomitant substance use disorders, depressive symptoms, pregnancy and risk of suicide**

This is described in the third part of these guidelines, which will be published soon.

### **Goal and target audience of the WFSBP Guidelines**

These guidelines are intended for use in clinical practice by all physicians investigating, diagnosing and treating patients with schizophrenia. Therefore, a continuous update of contemporary knowledge of various aspects of schizophrenia, with a particular focus on 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 to 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 they 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 international experts in the field.

### **Methods of literature research and data extraction**

In the development of these guidelines, the following guidelines, consensus papers and sources were considered.

- American Psychiatric Association, Practice Guideline for the Treatment of Patients with Schizophrenia, Second Edition (Lehman et al. 2004), and APA Guideline Watch: Practice Guideline for the treatment of patients with schizophrenia (Dixon et al. 2009);
- Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde. Praxisleitlinien Psychiatrie und Psychotherapie: Schizophrenie (DGPPN 2006);
- National Institute for Clinical Excellence: The NICE Guideline on core interventions in the treatment and management of schizophrenia in adults in primary and secondary care (updated edition) (NICE 2010);
- Royal Australian and New Zealand College of Psychiatrists: Australian and New Zealand clinical practice guideline for the treatment of schizophrenia (RANZCP 2005);
- World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 1: Acute treatment of schizophrenia (Falkai et al. 2005);
- World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 2: Long-term treatment of schizophrenia (Falkai et al. 2006);
- The Schizophrenia Patient Outcome Research Team (PORT): Updated Treatment Recommendations 2009 (Kreyenbuhl et al. 2010) and The 2009 Schizophrenia PORT Psychopharmacological Treatment Recommendations and Summary Statements (Buchanan et al. 2010);
- The Cochrane Library, Meta-analyses on the efficacy of different drugs and interventions in schizophrenia (up to September 2011).

- Reviews, meta-analyses, randomised clinical trials and open label-trials contributing to interventions in schizophrenia patients identified by search in the Medline data base (up to March 2012). For special questions, case reports and case series were taken into account.
- Individual clinical experience of the authors and the members of the WFSBP Task Force on Schizophrenia.

### Evidence-based classification of recommendations

#### *Categories of evidence*

The evidence-based grading of this update is based on the WFSBP recommendations for grading evidence (Bandelow et al. 2008b), as used recently in other WFSBP Guidelines (Bandelow et al. 2008a; Grunze et al. 2009). 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 must be noted that the strength of recommendation is related to the level of efficacy and tolerability, but not necessarily importance, of the treatment. Five major categories and three minor categories were used to determine the hierarchy of recommendations (related to the described level of evidence) (see Table I).

#### *Recommendation grades*

The recommendation grades are also based on the WFSBP recommendations and adopted from the first revision of the WFSBP Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders (Bandelow et al. 2008a). The aforementioned categories of evidence “are based on efficacy only, without regard to other advantages or disadvantages of the drugs, such as side effects or interactions” (Bandelow et al. 2008a). However, these are important issues for the clinical practice, and therefore, recommendation grades were also used in these updated guidelines. For example, the evidence for the efficacy of clozapine in first-episode schizophrenia is good (Category of evidence A), but due to its side effect profile it is not recommended as a first line treatment for first-episode schizophrenia (Recommendation Grade 2). According to the publication of Bandelow and colleagues (2008a), “the recommendation grades can be viewed as steps: The first step would be a prescription of a medication with recommendation

grade 1. When this treatment fails, all other grade 1 options should be tried first before switching to treatments with recommendation grade 2” (Bandelow et al. 2008a) (see Table I).

### Acute-phase treatment of schizophrenia

This section was adopted from the first version of these guidelines and modified where necessary. In the acute phase, the specific treatment goals are to prevent harm, control disturbed behaviour, suppress symptoms, affect 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 (Lehman et al. 2004). Whichever 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 and at developing supportive relationships with the psychiatrist and other members of the treatment team (DGPPN 2006; Lehman et al. 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. 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 (Lehman et al. 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 required 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 (Lehman et al. 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

Table I. Categories of evidence and recommendation grades according to Bandelow and colleagues (2008 a,b).

Category of Evidence	Description
A	<p>Full Evidence From Controlled Studies is based on:</p> <p>2 or more double-blind, parallel-group, randomized controlled studies (RCTs) showing superiority to placebo (or in the case of psychotherapy studies, superiority to a “psychological placebo” in a study with adequate blinding)</p> <p>and</p> <p>1 or more positive RCT showing superiority to or equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control or in a well-powered non-inferiority trial (only required if such a standard treatment exists)</p> <p>In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least 2 more positive studies or a meta-analysis of all available studies showing superiority to placebo and non-inferiority to an established comparator treatment. Studies must fulfil established methodological standards. The decision is based on the primary efficacy measure.</p>
B	<p>Limited Positive Evidence From Controlled Studies is based on:</p> <p>1 or more RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a “psychological placebo”)</p> <p>or</p> <p>a randomized controlled comparison with a standard treatment without placebo control with a sample size sufficient for a non-inferiority trial</p> <p>and</p> <p>no negative studies exist</p>
C	<p>Evidence from Uncontrolled Studies or Case Reports/Expert Opinion</p> <p>C1 Uncontrolled Studies. Evidence is based on:</p> <p>1 or more positive naturalistic open studies (with a minimum of 5 evaluable patients)</p> <p>or</p> <p>a comparison with a reference drug with a sample size insufficient for a non-inferiority trial</p> <p>and</p> <p>no negative controlled studies exist</p> <p>C2 Case Reports. Evidence is based on:</p> <p>1 or more positive case reports</p> <p>and</p> <p>no negative controlled studies exist</p> <p>C3 Evidence is based on the opinion of experts in the field or clinical experience</p>
D	<p>Inconsistent Results</p> <p>Positive RCTs are outweighed by an approximately equal number of negative studies</p>
E	<p>Negative Evidence</p> <p>The majority of RCTs studies or exploratory studies shows non-superiority to placebo (or in the case of psychotherapy studies, superiority to a “psychological placebo”) or inferiority to comparator treatment</p>
F	<p>Lack of Evidence</p> <p>Adequate studies proving efficacy or non-efficacy are lacking.</p>
Recommendation Grade	Based on
1	Category A evidence and good risk-benefit ratio
2	Category A evidence and moderate risk-benefit ratio
3	Category B evidence
4	Category C evidence
5	Category D evidence

treatment and key worker should monitor both therapeutic progress and tolerability of the drug on an ongoing basis.

**Antipsychotics**

Antipsychotics are the first-line treatment in all different stages of schizophrenia. Evidence for the efficacy of antipsychotics is provided by a magnitude of

RCTs and meta-analyses published in the last 50 years. Antipsychotics are a chemically heterogeneous group and they are used in acute phase treatment, in the treatment of special circumstances, in long-term maintenance therapy and in the prevention of relapse of schizophrenia.

Since the first publication of the WFSBP Guidelines for Biological Treatment of Schizophrenia, no additional “old” first-generation antipsychotic (FGA) agents have been introduced. In 2005, amisulpride,

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aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone and zotepine were available as so called second-generation antipsychotics (SGA). This update reviews all available and published data of these drugs and, in addition, includes the data for paliperidone, iloperidone, asenapine, lurasidone and sertindole (which was reintroduced in 2005 to Europe, but has no FDA approval).

## Classification and efficacy of antipsychotics

### *First-generation antipsychotics*

The efficacy of FGAs in reducing psychotic symptoms in acute schizophrenia was mainly investigated during the period from the 1960s to 1980s, by comparing one or more antipsychotic agents with either a placebo or a sedative agent. These studies make clear that FGAs are superior to a placebo or sedative agent for the treatment of acute schizophrenia. More recently, the FGA haloperidol has been extensively investigated as a comparator in many RCTs.

An elaborate review found superior efficacy of 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). In general, superiority over placebo was confirmed by numerous double-blind studies and reviews (Dixon et al. 1995; Kane and Marder 1993). The 2005 guidelines concluded, based on Cochrane reviews and NICE reviews, that chlorpromazine, flupenthixol, fluphenazine, perazine, perphenazine, pimozide, sulpiride, thioridazine, trifluoperazine and zuclopenthixolacetate are similar in efficacy to other FGAs, and superior compared to placebo. However, this cannot be stated for some drugs, despite having a very high affinity to D2-receptors, such as benperidol, because of lacking evidence (Leucht and Hartung 2002, 2005). Moreover, thioridazine and chlorpromazine are no longer commonly used. In particular, haloperidol is a potent antipsychotic drug for the treatment of psychotic symptoms in acute schizophrenia and its efficacy and safety has been confirmed in many studies and meta-analyses over the years (Joy et al. 2006a; Kahn et al. 2008; Leucht et al. 2008, 2009b). Finally, an old, but methodologically good review, showed good efficacy of FGAs in diminishing psychotic symptoms in long-term treatment and relapse prevention in schizophrenia patients (Davis 1975). In conclusion, FGAs are effective in the treatment of schizophrenia (*Category of Evidence A, Recommendation grade 1*). Low-potency FGAs are inferior to high-potency FGAs for the treatment of acute schizophrenia (*Category of Evidence A, Recommendation grade 1*).

### *Second-generation antipsychotics*

Following the introduction of SGAs, patients and psychiatrists had hope of a new treatment period for schizophrenia. However, the postulated advantages (better efficacy for positive and negative symptoms, better outcomes for quality of life, better side effect profile) in comparison to FGAs are discussed controversially.

Effectiveness studies with some key methodological problems (Moller 2008) failed to show a clear difference between certain FGAs and SGAs (Jones et al. 2006; Lieberman et al. 2005; McCue et al. 2006; Rosenheck et al. 2006). However, two meta-analyses indicate that certain SGAs might have some advantages over other SGAs and FGAs with regard to certain dimensions (overall efficacy, specific psychopathology, relapse prevention and quality of life) (Kishimoto et al. 2011; Leucht et al. 2009b).

Since the first publication of the WFSBP Guidelines for Biological Treatment of Schizophrenia, there have been several publications (RCTs, meta-analyses) investigating the efficacy and tolerability of new SGAs (paliperidone, iloperidone, asenapine, lurasidone) in comparison to placebo (Canuso et al. 2009a,b; Citrome 2009; Cutler et al. 2008; Davidson et al. 2007; Kane et al. 2007a, 2011a; Marder et al. 2007a; Meltzer et al. 2008a; Nakamura et al. 2009; Nussbaum and Stroup 2008; Patrick et al. 2010; Potkin et al. 2007). These studies have shown that these drugs are effective in the treatment of schizophrenia and superior to placebo.

Furthermore, since the first publication of the WFSBP Guidelines for Biological Treatment of Schizophrenia, many studies and meta-analyses have compared placebo to the following established SGAs: **risperidone** (Potkin et al. 2006, 2007; Rattahalli et al. 2010a,b); **aripiprazole** (Cutler et al. 2006; El-Sayeh and Morganti 2006; El-Sayeh et al. 2006; Marder et al. 2007b; McEvoy et al. 2007; Volavka et al. 2005); **olanzapine** (Duggan et al. 2005), **quetiapine** (Arango and Bernardo 2005; Canuso et al. 2009b; Potkin et al. 2006; Small et al. 2004), **zotepine** (DeSilva et al. 2006)).

These studies provide further evidence for the efficacy of symptom reduction in schizophrenia patients and the drug's superiority over placebo. However, one Cochrane meta-analysis showed only a marginal benefit of the well-established SGA risperidone (Rattahalli et al. 2010a) in comparison to placebo, despite risperidone's efficacy and effectiveness having been proven in many RCTs and other meta-analyses (see below). In general, SGAs are effective in the treatment of schizophrenia (*Category of Evidence A, Recommendation grade 1*).

### Comparing the efficacy of FGAs versus SGAs

The most important question for the pharmacological treatment of schizophrenia is whether to treat initially and predominantly with SGAs (as recommended in nearly all guidelines released between 2004 and 2009) or to treat with FGAs. In the first version of these guidelines it was determined that SGAs generally seemed to be preferable, although all antipsychotics have their place in the treatment of acute schizophrenia.

Paradigms started to change after two large clinical trials were published: the US based **CATIE study** (funded by the National Institute of Mental Health) (Lieberman et al. 2005) and the UK-based **CUTLASS study** (funded by the National Health Service) (Jones et al. 2006). These studies discussed that certain SGAs are not superior to certain FGAs with regard to their effectiveness and that these FGAs and SGAs have an individual, but independently important side effect profile. Both RCTs included chronically ill patients that were either having an acute exacerbation of the disease or were changing their antipsychotic medication due to different reasons (e.g., no response or side effects).

However, for the correct understanding and interpretation of these two studies, as well as other such effectiveness studies, methodological problems related to effectiveness studies need to be addressed. In general, effectiveness studies (e.g., phase IV studies) do not have a placebo arm and in many cases, do have the beta-error problem (failure to detect a difference although there is one), do include patients with a long and chronic disease course (and residual symptoms) and do have problems associated with the blinding procedure (Moller 2008). Specific methodological problems that may afflict the different studies and their impact on the results are discussed separately for each study below.

One study from the **Veterans Affairs Medical Centres** (Rosenheck et al. 2003) compared the SGA olanzapine with the FGA haloperidol (in addition to the anticholinergic drug benztropine) and found no significant difference between the drugs in relation to study retention, improvement in PANSS scores, quality of life and extrapyramidal symptoms, but did show the occurrence of more cognitive disturbances in patients treated with haloperidol and benztropine. The long duration of disease (approximately 20 years), the flexible dosing scheme and the prophylactic treatment with benztropine are important confounders, and this needs to be addressed when interpreting the results (Moller 2008).

In the **CATIE study** (Lieberman et al. 2005), the FGA perphenazine was compared with four different SGAs (olanzapine, quetiapine, risperidone,

ziprasidone) and the primary outcome measure was the discontinuation of treatment for any cause in a sample of chronic schizophrenia patients. The overall rate of discontinuation ranged from 64 to 82% and, according to the authors, this determines a limited range of effectiveness. Participants receiving olanzapine had a significantly longer time to discontinuation compared to those receiving SGAs or the FGA perphenazine. Olanzapine (64% discontinuation rate) was superior to risperidone (74% discontinuation rate), quetiapine (82% discontinuation rate) and the FGA perphenazine (75% discontinuation rate), but these results did not survive statistical corrections for multiple comparisons. The secondary outcome parameter "psychopathology scales" (PANSS positive/negative) did not differ across groups. The results of this large study need to be discussed in the context of important methodological limitations which may limit their generalizability. This study had a very high drop-out rate (overall discontinuation rate of 64%), had a significant selection bias in the FGA arm (exclusion of patients with a history of tardive dyskinesia in the FGA arm), included partially treatment refractory patients, had used olanzapine in a broader dosage range than used in clinical practice and had undergone a partial unblinding (Glick 2006; Meltzer and Bobo 2006; Moller 2008; Naber and Lambert 2009).

The **CUTLASS study** (Jones et al. 2006) showed no inferiority of a group of various FGAs (preferentially sulpiride) compared to SGAs (risperidone, olanzapine, amisulpride, zotepine, and quetiapine) in terms of quality of life (primary outcome) and symptom reduction according to PANSS (secondary outcome) in a sample of chronic schizophrenia patients. This study was criticised because of some methodological shortcomings. The study sample was quite small ( $N = 227$  included,  $N = 185$  for the follow-up after 52 weeks), a high-quality blinding procedure was not performed, SGAs and FGAs were compared as two homogenous groups, 49% of the patients received sulpiride as FGA (sulpiride is considered as the most atypical FGA) and only 59% of the patients continued taking their initial medication for 52 weeks (Moller 2008; Naber and Lambert 2009). However, the most important limitation is the use quality of life as the primary outcome parameter since it is more closely associated with negative or depressive symptoms than with psychotic symptoms (Moller 2008).

In contrast to the two aforementioned studies, the open-label **EUFEST study**, which was funded by three pharmaceutical companies without having an influence on study design, data collection, data analysis and publication (Kahn et al. 2008), was conducted on first-episode schizophrenia patients.



Haloperidol was compared with four different SGAs (amisulpride, olanzapine, quetiapine, ziprasidone) and the primary outcome measure was treatment discontinuation. A secondary outcome measure was improvement of psychopathology according to PANSS. Treatment discontinuation for any cause was significantly higher in patients treated with haloperidol. Treatment discontinuation as a consequence of insufficient efficacy was also higher in the haloperidol group, whereas the difference between haloperidol and quetiapine was not significant (Kahn et al. 2008). The secondary outcome measures, like improvement of symptoms according to PANSS and admission to hospital did not show a significant difference between groups. Haloperidol showed most extrapyramidal side effects and weight-gain was highest for olanzapine (Kahn et al. 2008).

One randomised open-label study found haloperidol, olanzapine and risperidone to be superior to aripiprazole, quetiapine and ziprasidone with regard to the time at which acute in-patient care became necessary, but found no difference concerning changes in the scores of Brief Psychiatric Rating Scale among drugs (McCue et al. 2006). Results might have been biased by the fact that the dosage of haloperidol was higher than in other studies (16 mg/day) and that 47% of the patients in the haloperidol group also received anticholinergics for the treatment of motor side effects. In contrast, no patient from the olanzapine or aripiprazole group was treated with an additional anticholinergic drug (Moller 2008).

A statement of the **World Psychiatric Association Pharmacopsychiatry Section** reviewed approximately 1600 randomized controlled trials of antipsychotic treatment in schizophrenia with regard to the effectiveness of 62 antipsychotic agents (Tandon et al. 2008). This analysis stated that both FGAs and SGAs are very heterogeneous drugs with important differences in their individual side effect profiles. A modest and inconsistent superiority for the treatment of negative, cognitive, and depressive symptoms was revealed for SGAs in comparison to FGAs. It was speculated that these differences were probably driven by the equivalent efficacy of SGAs and FGAs in the improvement of positive symptoms but fewer motor side effects in the SGA group. Finally, this analysis could not detect a different efficacy among the SGAs, but clozapine was superior to all other antipsychotic agents in treatment-resistant schizophrenia (see below) (Tandon et al. 2008).

One recently published **meta-analysis by the Cochrane schizophrenia group** compared nine SGAs with FGAs for different treatment domains, excluding all open-label studies (Leucht et al. 2009b).

With regard to the main outcome parameter (overall efficacy) and PANSS (positive and negative), amisulpride, clozapine, olanzapine and risperidone were better than FGAs with medium to small effect sizes. Aripiprazole, quetiapine, sertindole, ziprasidone and zotepine did not show superiority to FGAs in overall efficacy and in PANSS scores.

Another **meta-analysis** showed a modest superiority in relapse prevention for SGAs when compared with FGAs (Kishimoto et al. 2011). In detail, risperidone, clozapine and olanzapine were superior to FGAs with regard to the endpoint "relapse rate". After 6 months, only risperidone was superior to FGAs, but pooled SGAs were superior to FGAs with regard to long term-relapse rates (6 months). Importantly, there was no trial in which any FGA was superior to the SGA comparator (Kishimoto et al. 2011)

In the 2005 guidelines the question, as to whether SGAs, as a group, are superior to FGAs in their efficacy and effectiveness in the treatment of schizophrenia was raised. Today, there is some evidence that FGAs and SGAs are comparable with regard to efficacy and effectiveness (especially reduction of PANSS scores). However, certain SGAs have some advantages with regard to motor side effects (*Category of evidence A, Recommendation grade 1*) and certain SGAs seem to have some advantages with regard to certain treatment domains compared to FGAs (improvement of positive symptoms, treatment discontinuation, relapse prevention) (*Category of evidence C3, Recommendation grade 4*).

The side effect of each individual drug, and the specific and personal vulnerability, differ among all antipsychotic drugs and have to be taken into consideration before choosing a certain antipsychotic for administration. In the early stages of treatment, acute neurological side effects should be avoided. When designing long-term treatment (see part 2 of these guidelines) neurological side effects need to be balanced against metabolic and other side effects.

In the 2005 and 2006 guidelines, we made clear that it has never been claimed that SGAs are generally more efficacious than FGAs. We described an equal efficacy for positive symptoms, but discussed some advantages of SGAs in reducing negative, depressive and cognitive symptoms and in the better EPS tolerability of SGAs. A detailed discussion of each antipsychotic agent and the efficacy on different domains in different disease states can be found in a separate section below. However, it is important to note that SGAs do not represent a homogenous class of drugs (Leucht et al. 2009b) and that certain side effects cannot be considered as typical for the whole group of SGAs.

### Summary statements

- FGAs and SGAs are effective in reducing psychotic symptoms and in general no differences between drugs could be detected (*Category of Evidence A, Recommendation grade 1*)
- Some SGAs (as outlined and discussed in these guidelines) might have some advantages in overall efficacy over other SGAs and FGAs (*Category of Evidence B/C3, Recommendation grades 3/4*)
- Some SGAs (as outlined and discussed in these guidelines) might be superior to FGAs in relapse prevention (*Category of Evidence B/C3, Recommendation grades 3/4*)
- The increased risk of neurological side effects following treatment with FGAs could favour certain SGAs (*Category of Evidence C3, Recommendation grade 4*)
- All side effects need to be taken into consideration. Special attention needs to be given to motor side effects, metabolic side effects and cardiovascular side effects.

### Pharmacokinetics

Antipsychotics are mainly administered in oral forms, but certain FGAs and SGAs can be administered as intravenous applications, as short-acting intramuscular preparations, or as long-acting injectable preparations (see part two of these guidelines). Short-acting intramuscular FGAs reach a peak concentration 30–60 min after the medication is administered, whereas oral medications reach a peak after 2– to 3 h (Dahl 1990). As a result, the calming effect of the FGAs 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.

SGAs 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 h. Atypical agents are highly lipophilic, highly protein-bound, and tend to accumulate in the brain and other tissues. Parenteral preparations are available for various SGAs (e.g., aripiprazole, olanzapine, ziprasidone).

The times for maximal plasma levels, the elimination half-time and the metabolism pathways of certain FGAs and SGAs are presented in Table V.

### Side effects

In recent years, the specific and individual side effects of different FGAs and SGAs have received special attention (see Table II).

Differences in the risk of specific side effects of antipsychotics 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, hyperglycaemia) (DGPPN 2006).

It is important to note that both FGAs and SGAs, depending on their individual receptor binding profiles share neurological side effects (acute and long-term extrapyramidal symptoms, neuroleptic malignant symptoms), sedation, cardiovascular effects, weight gain, metabolic side effects, anticholinergic, antiadrenergic and antihistaminergic effects, hyperprolactinaemia and sexual dysfunctions.

### Neurological side effects

High-potency FGAs are known to have a high risk of inducing extrapyramidal side effects, acute dystonia, antipsychotic-induced parkinsonism and tardive dyskinesia. Tardive dyskinesia, in particular, has a close association with FGA treatment (Kasper et al. 2006) and it should be highlighted that tardive dyskinesia is often not reversible after discontinuation of the antipsychotic treatment (see part two of these guidelines). SGAs induce fewer extrapyramidal side effects in a therapeutic dose range than FGAs and show a significant reduction in the risk of tardive dyskinesia compared to FGAs (Correll et al. 2004; Leucht et al. 1999). In a recent meta-analysis, all SGAs were associated with fewer extrapyramidal side effects than the well-established FGA haloperidol (Leucht et al. 2009b). Compared to low-potency FGAs, only clozapine had the advantage of lower extrapyramidal side effects (Leucht et al. 2009b).

However, at first glance the results of the CATIE study did not show significant differences among the different antipsychotic drugs (FGA: perphenazine; SGA: olanzapine, risperidone, ziprasidone, quetiapine) in the incidence of neurological side effects. These findings are likely to have been biased by the inclusion criteria of the FGA study arm (Lieberman et al. 2005; Miller et al. 2008; Moller 2008). The **CUTLASS study** found no difference between FGAs and SGAs in neurological side effects (Jones et al. 2006), whereas the mostly administered FGA was sulpiride, a very atypical FGA (Moller 2008).

Table II. Selected side effects of commonly used antipsychotics. Frequencies and severity of side effects refers to information obtained by drug companies, FDA, additional literature and other guidelines.

Side effect	Antipsychotic medication										
	Haloperidol	Amisulpride	Aripiprazole	Clozapine	Olanzapine	Paliperidone	Quetiapine	Risperidone	Sertindole	Ziprasidone	
Akathisia/Parkinsonism	+++	0/+	+	0	0/(+)	0/+++	0/(+)	0/++	0/(+)	0/(+)	
Tardive dyskinesia	+++	(+)	(+)	0	(+)	(+)	(+)	(+)	(+)	?	
Seizures	+	0	(+)	++	0	0	0	0	(+)	0	
QT-prolongation	+	(+)	(+)	(+)	(+)	(+)	(+)	(+)	+++	++	
Glucose abnormalities	(+)	(+)	0	+++	+++	+++	+++	+++	+	0	
Lipid abnormalities	(+)	(+)	0	+++	+++	+++	+++	+++	+	0	
Constipation	+	++	0	+++	+++	+++	+++	+++	+	0	
Hypotension	++	0	+	(+)	(+)	+++	+++	+++	(+)	0	
Agranulocytosis	0/(+)	0/(+)	0/(+)	+	0/(+)	0/(+)	0/(+)	0/(+)	0/(+)	0/(+)	
Weight Gain	+	+	(+)	+++	+++	+++	+++	+++	+++	(+)	
Prolactin elevation	+++	+++	0	0	(+)	+++	+++	+++	(+)	0	
Galactorrhoea	+++	+++	0	0	+	+++	+++	+++	(+)	0	
Dysmenorrhoea	++	++	0	0	+	+++	+++	+++	(+)	(+)	
Sedation	+	0/(+)	0	+++	+/++	+	+++	+	(+)	0/(+)	
MNS	+	?	(+)	(+)	(+)	(+)	(+)	(+)	(+)	?	

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).

Haloperidol administration resulted in the presentation of more signs of parkinsonism in patients compared with SGA administration in the **EUFESt study** (Kahn et al. 2008). In one large comparison of risperidone and haloperidol in first-episode schizophrenia patients, haloperidol induced significantly more extrapyramidal signs and symptoms than risperidone (Schooler et al. 2005). These findings are supported by Cochrane reviews, providing further evidence that the frequently-used haloperidol is likely to cause neurological side effects (Joy et al. 2006a). Findings of another Cochrane review suggest that there is a dose-dependent effect of haloperidol to induce extrapyramidal side effects. High doses (> 7.5 mg/day) are associated with an increased risk of extrapyramidal side effects with no clear evidence for added efficacy (Donnelly et al. 2010).

It should be noted that low dosages of haloperidol (< 5 mg/day) might not be effective enough for the treatment of schizophrenia (Zimbhoff et al. 1997). However, one study did not show a difference between 2 and 8 mg of haloperidol (Oosthuizen et al. 2004). Furthermore, even low dosages of haloperidol can induce more extrapyramidal side effects than SGAs (Kahn et al. 2008; Leucht et al. 2009c; Moller et al. 2008; Oosthuizen et al. 2003; Schooler et al. 2005). A head-to-head comparison (meta-analysis) of different SGAs with the primary outcome parameter “use of antiparkinson medication” confirmed these findings (Rummel-Kluge et al. 2010a). Risperidone treatment was found to be especially linked to higher use of antiparkinson medication compared to other SGAs. However, this difference disappeared after exclusion of all studies with risperidone > 6 mg/day, indicating a dose-dependent effect (Rummel-Kluge et al. 2010a). In this meta-analysis clozapine and quetiapine resulted in significantly less use of antiparkinsonian medication, but these two drugs have not been compared directly (Rummel-Kluge et al. 2010a).

SGAs can cause extrapyramidal symptoms (see details below) and some studies have provided evidence that even clozapine, and probably quetiapine, can also induce dose-independent extrapyramidal side effects, but the risk is much lower compared to that associated with FGAs. Especially the risk for developing tardive dyskinesia is discussed to be lower for certain SGAs compared to FGAs (Kasper et al. 2006).

### Neuroleptic malignant syndrome (NMS)

This rare condition was described in the previous publication of these guidelines and, since 2005, some new reports and reviews have been published dealing

with this important topic. 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 and is even more rare among patients treated with SGAs (Adityanjee et al. 1999; Strawn et al. 2007). However, NMS remains a risk for susceptible patients receiving SGAs (El-Gaaly et al. 2009; Strawn 2006; Strawn and Keck 2006; Strawn et al. 2007; Trollor et al. 2009). Risk factors for NMS include acute agitation, young age, male gender, preexisting neurological disability, physical illness, dehydration, rapid escalation of antipsychotic dosage, use of high-potency medications and use of intramuscular preparations (Keck et al. 1989; Pelonero et al. 1998; Strawn et al. 2007). In special cases clinical features of NMS might be closer to those of a serotonergic syndrome when certain SGA are used and the level of severity is modest (Nisijima et al. 2007).

### Epileptic seizures

Patients suffering from schizophrenia have an increased risk of epileptic seizure and this risk is boosted by the intake of antipsychotic drugs (Alper et al. 2007). Epileptic seizures occur in an average of 0.5–0.9% of patients receiving antipsychotic medications, with clozapine being associated with the highest rate of incidence (approx. 3%) and a cumulative risk (approx. 10%) after 4 years of treatment (Buchanan 1995; Devinsky et al. 1991; Pacia and Devinsky 1994). As confirmed by the approval reports, the incidence of seizures caused by the newer antipsychotic drugs revealed the highest risk for seizures to be during treatment with clozapine. The incidence of seizures in patients assigned to newer antipsychotic drugs drug was 3.5% for clozapine, 0.9% for olanzapine, 0.8% for quetiapine, 0.4–0.5% for ziprasidone, 0.4% for aripiprazole and 0.3% for risperidone (Alper et al. 2007). For zotepine, an association with an increased risk of seizures has been described in other guidelines (DGPPN 2006). One review found that, among FGAs, the highest risk for seizure provocation is associated with chlorpromazine, and the lowest risk with haloperidol (Hedges et al. 2003). However, EEG alterations following administration of both FGAs and SGAs and in untreated schizophrenia patients are a common finding, indicating a general potential risk for seizures, independent of antipsychotic treatment-type (Alper et al. 2007; Amann et al. 2003; Steinert et al. 2011).

### Obesity, weight gain and metabolic side effects

Individuals suffering from schizophrenia are more likely to be overweight or obese than the general population. Therefore, in combination with other risk factors (e.g., smoking, reduced physical activity, diabetes, hyperlipidemia), the risk of obesity, weight gain and metabolic side effects is increased, with a consequent rise in cardiovascular morbidity and mortality (Colton and Manderscheid 2006; Marder et al. 2004; Newcomer 2005; 2007). All antipsychotics can induce weight gain, but certain antipsychotics are more prone to do it so (Casey and Zorn 2001; De Hert et al. 2009).

The results of the CATIE study indicate that olanzapine induces the highest weight gain of SGAs (clozapine was not investigated) and the same finding was revealed by the EUFEST-study (Kahn et al. 2008; Lieberman et al. 2005). In these studies, ziprasidone seemed to have a positive effect on this parameter (Kahn et al. 2008; Lieberman et al. 2005). A 24-week, open-label, three-arm multicenter study revealed a significant weight gain associated with olanzapine, risperidone and quetiapine, with no differences among these drugs (Newcomer et al. 2009). An 8-week double-blind RCT found a larger increase in metabolic parameters (BMI; total cholesterol; LDL; triglycerides) in patients treated with olanzapine when compared with risperidone, which had some small benefits on metabolic parameters. Interestingly, study discontinuation in both drug groups was linked to weight gain (Kelly et al. 2008).

One meta-analysis found that amisulpride, clozapine, olanzapine, risperidone, sertindole and zotepine have lead to more weight-gain than haloperidol (Leucht et al. 2009b). Aripiprazole and ziprasidone were not associated with greater weight gain and this meta-analysis did not find a significant difference concerning weight gain between SGA and low-potency FGAs (Leucht et al. 2009b). Another meta-analysis from the same study group revealed that, within the group of SGAs, olanzapine and clozapine lead to the most weight gain, followed by quetiapine, risperidone and amisulpride (intermediate to low weight gain) and then by ziprasidone (lowest weight gain) (Rummel-Kluge et al. 2010b). The finding of the highest weight gain in patients treated with olanzapine and clozapine is supported by other publications (Newcomer 2007; Wu et al. 2006; Zipursky et al. 2005). One meta-analysis found a small increase in the risk of diabetes in patients being treated with SGAs (clozapine, olanzapine, risperidone and quetiapine) compared to FGAs (Smith et al. 2008).

The PORT guidelines identified that clozapine and olanzapine induced the highest weight gain/metabolic

abnormalities, followed by low-potency FGAs, then followed by the group of risperidone/paliperidone/quetiapine and then by medium-potency FGAs (Buchanan et al. 2010; Kreyenbuhl et al. 2010). High-potency FGAs, aripiprazole, molindone and ziprasidone had the best profile for weight gain and other metabolic side effects (Buchanan et al. 2010; Kreyenbuhl et al. 2010). The new and recently approved SGAs have yet not been thoroughly investigated. However, asenapine seems to lead to weight gain (Kane et al. 2010), whereas lurasidone seems to have less metabolic side effects (Nakamura et al. 2009).

Schizophrenia itself is an independent risk-factor for developing diabetes mellitus and hyperlipidemia (Bushe and Holt 2004; Colton and Manderscheid 2006; Henderson et al. 2005; Newcomer 2007; Ryan et al. 2003). Enhanced glucose levels, hyperlipidemia and enhanced triglyceride levels are linked to the same drugs that induce obesity and weight gain (Buchanan et al. 2010; Kreyenbuhl et al. 2010; Leucht et al. 2009b; NICE 2010; Rummel-Kluge et al. 2010b).

Results from RCTs and meta-analysis offer a clearer picture of how these factors interact, with certain SGAs (clozapine, olanzapine, quetiapine, risperidone, paliperidone, amisulpride) leading to a significant weight gain, hyperlipidemia and glucose intolerance. However, there remains to be a lack of larger studies performing head-to-head comparison of different antipsychotics. High-potency FGAs, aripiprazole and ziprasidone seem to be superior to other SGAs and to low-potency FGAs with regard of this side effect.

A paper published jointly by the European Psychiatric Association together with the European Society of Cardiology and the European Association for the Study of Diabetes included an algorithm for the risk management of cardiovascular disease and diabetes in patients with severe mental illness (De Hert et al. 2009). This is described in detail in part 2 of these guidelines and treatment decision should be guided by this consensus paper.

### **Hyperprolactinemia and sexual dysfunction**

Hyperprolactinemia can lead to galactorrhoea, menstrual, cyclical and sexual disturbances in women, and to reproductive and sexual dysfunction and galactorrhoea/gynaecomastia in men (Dickson and Glazer 1999). Antipsychotics with a high affinity for binding to D<sub>2</sub>-receptors are more likely to induce hyperprolactinemia, while the precise mechanisms of SGAs on pituitary dopamine D<sub>2</sub>-receptors have not been fully clarified (Marder et al. 2004; Turrone

et al. 2002). For risperidone and amisulpride the risk of elevated prolactin serum levels and associated side effects is well-established (Kahn et al. 2008; Lehman et al. 2004; Leucht et al. 2009d). Cochrane Database Reviews showed that olanzapine, zotepine and ziprasidone seem to have low to moderate risk of prolactin elevation, whereas aripiprazole, quetiapine and clozapine seem to have no effect on prolactin levels (Asenjo Lobos et al. 2010; Komossa et al. 2009a,c, 2010a,b,d). A meta-analysis confirmed these findings in general (Leucht et al. 2009d).

The association between prolactin elevation and sexual dysfunction is still controversial (Aizenberg et al. 1995; Kleinberg et al. 1999; Rettenbacher et al. 2010) and other outcomes of elevated prolactin levels, such as increased risk of breast cancer and osteoporosis, remain to be established.

### **Cardiovascular side-effects**

The range of cardiovascular side effects following antipsychotic treatment is within relatively harmless symptoms like tachycardia, (orthostatic) hypotension with the risk of accidents and fractures and life-threatening conditions like myocarditis, QTc prolongation with transition to ventricular fibrillation and sudden cardiac death. Furthermore, cardiac infarct as a consequence of altered metabolic risks due to treatment with antipsychotics (see above) needs to be considered, especially in the long-term treatment of schizophrenia. Risk of hypotension as well as tachycardia is typical for low-potency FGAs and for clozapine (Buchanan 1995).

Since the first publication of these guidelines, the cardiac side effects of antipsychotics have received less attention compared to extrapyramidal and metabolic side effects. Some antipsychotics have the propensity to delay cardiac repolarization and prolong the QT interval on the ECG, usually by blockade of the fast component of the delayed rectifier potassium current. This may create an arrhythmogenic substrate, increasing the risk of ventricular arrhythmias and sudden death. Risk factors for drug-induced QT prolongation and torsades de pointes include prolonged QT interval pre-treatment, female sex, electrolyte abnormalities, bradycardia, high drug doses, diuretic treatment and structural heart disease. ECG abnormalities (QTc prolongation, abnormal T-waves, prominent U-waves and widening of the QRS complex) are important and potentially dangerous side effects of antipsychotic medication and they can lead to ventricular fibrillation, torsades de pointes and sudden cardiac death (Glassman and Bigger 2001; Haddad and Anderson 2002; Zareba and Lin 2003). According

to varying rates, and dependent on the medication dose and method of application, it should be considered that all antipsychotic drugs can cause cardiac side effects. QTc prolongation (QTc intervals above 470–500 ms) is associated with an increased risk of torsade de pointes and transition to ventricular fibrillation. If this occurs under neuroleptic treatment, the medication should be discontinued and switched to an antipsychotic with a lower risk of cardiac conduction disturbances (Glassman and Bigger 2001; Marder et al. 2004; Nielsen et al. 2011). In particular, certain tricyclic antipsychotics (phenothiazine and pimozide) and certain SGAs (see Table II) are associated with a QTc prolongation, whereas the chlorpromazine-related antipsychotics seem to have a less prominent effect (Adams et al. 2007; Buchanan et al. 2010; Leucht et al. 2008; Reilly et al. 2000).

Intravenous haloperidol has been especially associated with a risk of QTc prolongation. The FDA extended the warning for intravenous haloperidol in 2007 and recommended continuous electrocardiogram (ECG) monitoring in patients receiving intravenous haloperidol (Al-Khatib et al. 2003; Meyer-Masseti et al. 2010). A recently published literature review found, that intravenous haloperidol is safe in cumulative dosages < 2 mg in patients without risk factors for QTc prolongation or torsades de pointes (Meyer-Masseti et al. 2010). Moreover, the authors state that, in patients receiving cumulative intravenous dosages > 2 mg and in patients with cardiac risk factors, ECG monitoring should take place (Meyer-Masseti et al. 2010).

With regard to SGA, sertindole and ziprasidone were found to evoke a significant QTc prolongation. However, this effect should also be taken into consideration for other frequently prescribed SGAs (Buchanan et al. 2010; Camm et al. 2012; Harrigan et al. 2004; Kreyenbuhl et al. 2010; Thomas et al. 2010). A multinational randomized, open-label, parallel-group study with blinded classification of outcomes was conducted in 9858 schizophrenic patients in order to explore whether sertindole increases all-cause mortality or cardiac events requiring hospitalization, compared with risperidone. After 14147 person-years, cardiac mortality was significantly higher with sertindole as compared with risperidone (31 vs. 12). There was no effect of treatment on cardiac events requiring hospitalization and less than 10% of the patients required add-on antipsychotic therapy (Thomas et al. 2010). A combined treatment with other drugs which increase QTc time has to be avoided (detailed lists of drugs increasing QTc can be found in textbooks of psychiatry and internal medicine or at <http://www.qtdrugs.org/>).

## Haematological side effects

Haematological side effects (e.g., leukopenia or agranulocytosis or even increased leucocytes) can occur following treatment with any antipsychotic agent. However, clozapine carries the highest risk (0.05–2%/year and patient) for life-threatening agranulocytosis, with the highest risk being within the first 6 months following treatment initiation (Buchanan 1995). Therefore, a regular blood cell count (twice a month) within the first 4–6 months is required and patients must be advised to report any signs of infection (e.g., sore throat, fever, weakness or lethargy) immediately (Lehman et al. 2004).

## Other side effects

For low-potency FGAs, allergic and dermatological side effects (e.g., allergy to sun) have been described (Lehman et al. 2004) and it should be recognized that every drug can cause an allergic reaction when administered for the first time. Elevation of liver enzymes and other hepatic effects are linked to treatment with nearly all antipsychotic agents (exception being amisulpride and paliperidone), but direct hepatotoxicity, associated particularly with low-potency phenothiazines, is rare (Lehman et al. 2004). Furthermore, interactions and drug metabolism of antipsychotics and other drugs involving cytochromes can lead to an increase of liver enzymes. Please see Table V for the pharmacokinetic properties of selected antipsychotics.

The part concerning ophthalmological side effects is adopted from the first version of these guidelines.

**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 treated with thioridazine and chlorpromazine for a prolonged period 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 (Lehman et al. 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 annually or every 2 years (Marder et al. 2004).

All antipsychotics with an anticholinergic profile can cause urinary tract problems, dry mouth and dry eyes. Constipation and bowel occlusion can be also linked to the anticholinergic effects of antipsychotics.

With SGA treatment in particular, constipation and bowel occlusion (especially associated with clozapine treatment) is underreported and often fails to be systematically assessed (De Hert et al. 2010). A meta-analysis including 48 publications revealed the highest risk for constipation to be in patients treated with clozapine or olanzapine, while for most SGAs, no data were available (De Hert et al. 2010). In very rare cases, ischaemic colitis and gastrointestinal necrosis can be associated with antipsychotic treatment (Peyriere et al. 2009). Finally, **sialorrhoea, drooling and dental problems** were frequently linked to clozapine treatment.

### First-episode schizophrenia

#### *Choice of antipsychotic medication*

Since the introduction of risperidone and olanzapine, followed by other SGAs, most guidelines have recommended the first-line use of SGAs for individuals with a newly diagnosed schizophrenia (DGPPN 2006; Lehman et al. 2004; NICE 2002; RANZCP 2005). This recommendation was based on the drug's superior tolerability and the reduced risk of EPS, especially tardive dyskinesia. However, the outcomes of several new clinical trials, meta-analyses and clinical experience question the first-line use of SGAs. Concerning efficacy and effectiveness of the treatment of positive and negative symptoms in schizophrenia, it is difficult to state a difference between FGAs and SGAs.

The choice of antipsychotic drug should be based on the drug's profile in terms of adverse effects and each patient's individual risk of developing particular associated side effects. Therefore, as far as possible, antipsychotic treatment should be specifically tailored to each patient suffering from schizophrenia. As outlined previously, FGAs have a higher risk of inducing EPS compared to SGAs, whereas metabolic and cardiovascular side effects seem to be more prominent using SGAs. However, certain FGAs, e.g., thioridazine, have a high potential for cardiac side effects (e.g., QTc prolongation), too.

First-episode schizophrenia patients carry an increased risk for developing neurological side effects and this need to be taken into consideration before starting treatment with an FGA. Furthermore, the unconfined usage of FGAs in high dosages must be avoided. Before the introduction of SGAs, serious and non-reversible motor symptoms were in the order of the day. Due to its special side effect profile (e.g., risk of agranulocytosis), clozapine should not be the drug of choice in first-episode schizophrenia.

However, only few antipsychotic drugs have been investigated in RCTs in first-episode schizophrenia patients (Fagerlund et al. 2004; Kahn et al. 2008; Keefe et al. 2004, 2006; Lieberman et al. 2003b; Merlo et al. 2002; Moller et al. 2008; Oosthuizen et al. 2004).

#### *Treatment of first-episode schizophrenia*

Patients with first-episode schizophrenia seem to be more treatment responsive and more sensitive to antipsychotic side effects than chronically ill patients. Since the first publication of these guidelines in 2005, few trials have been conducted addressing treatment response, dose finding and relapse prevention in first-episode schizophrenia. It may be possible to explain this by difficulties associated with recruiting these patients. There is a need for more trials focussing on first-episode patients to be conducted in the future.

As described in 2005, early 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). Meta-analyses and systematic reviews from both the same group and other groups confirmed that shorter duration of untreated psychosis was associated with better response to antipsychotic treatment (Marshall et al. 2005; Perkins et al. 2005).

#### *FGAs in first-episode schizophrenia patients*

Haloperidol in relatively low doses (<5 mg) was found to be suitable for the treatment of positive and cognitive symptoms in first-episode schizophrenia patients in randomized and open trials and such doses were not inferior to higher doses of haloperidol (Kahn et al. 2008; Keefe et al. 2004, 2006; Lieberman et al. 2003b; Moller et al. 2008; Oosthuizen et al. 2004; Oosthuizen et al. 2001; Remington et al. 1998; Schooler et al. 2005). In a 5-week RCT, pimozide and flupenthixol were both effective in bringing about the improvement of positive symptoms, while response to negative symptoms varied (Group TSSR 1987). In an open-label study, treatment with zuclopenthixol (median 8 mg/day) led to an improvement of psychopathological symptoms (Fagerlund et al. 2004). Therefore, a treatment recommendation can only be confirmed for haloperidol (*Category of Evidence A, Recommendation grade 2*) since other FGAs display only limited evidence (*Category of Evidence C1/D*,

*Recommendation grades 4/5*) in first-episode schizophrenia patients.

#### *SGAs in first-episode schizophrenia patients*

There are still only a few RCTs available comparing the efficacy or effectiveness of FGAs and SGAs in first-episode patients.

The EUFEST-trial did not find a significant difference in symptomatic improvement when comparing SGAs with haloperidol. However, treatment discontinuations over 12 months were more frequent and motor side effects were more severe in the haloperidol group (Kahn et al. 2008). One small non-controlled study investigated the efficacy of aripiprazole for treating first-episode schizophrenia patients in routine clinical conditions and found that aripiprazole monotherapy is effective for this population (Lee et al. 2010) This was confirmed by another open-label trial (Takahashi et al. 2009).

**Risperidone**, in contrast to haloperidol, resulted in a similar improvement in psychotic symptoms and fewer motor side effects in different double-blind RCTs (Emsley 1999; Moller et al. 2008; Schooler et al. 2005). In a non-comparative open trial, risperidone (< 6 mg/day) was found to be effective and well tolerated, whereas one RCT comparing 2 and 4 mg/day of risperidone revealed more side effects, but no better improvement in psychotic symptoms following application of 4 mg/day (Huq 2004; Merlo et al. 2002). Low-dose administration of risperidone had no superiority in terms of improvement of psychopathological and cognitive symptoms, but fewer side effects when compared with low-dose zuclopenthixol in a small randomized open trial (Fagerlund et al. 2004). Regarding relapse prevention, a 1-year follow-up, long-term study of a double-blind RCT of acute first-episode patients, found no difference between risperidone (mean dose 4.2 mg/day) and low-dose haloperidol (mean dose 4.1 mg/day) (mean dose 4.1 mg/day) regarding relapse prevention (Gaebel et al. 2007) (see part 2 of these guidelines for details).

Treatment with **olanzapine** resulted in improvement in overall, positive and negative symptoms. Furthermore, patients treated with olanzapine were less likely to discontinue treatment (Green et al. 2006; Lieberman et al. 2003b; Sanger et al. 1999). Treatment with olanzapine was associated with more weight gain, and treatment with haloperidol showed more motor side effects (Green et al. 2006; Lieberman et al. 2003b; Sanger et al. 1999). The treatment with relatively low doses of olanzapine and haloperidol entailed a significant improvement of neurocognitive functioning in first-episode schizophrenia patients with no or just small differences between

both antipsychotic agents in different double-blind RCTs (Keefe et al. 2004, 2006).

Compared to the FGA chlorpromazine (median dosages at 12 weeks were 600 mg and at 1-year follow 400 mg chlorpromazine), treatment with the SGA **clozapine** yielded more rapid improvement and remission, as demonstrated by enhanced improvement in clinical global impressions and a reduction in motor side effects. However, groups did not differ in terms of remission after 52 weeks (Lieberman et al. 2003a) (see part 2 of these guidelines for details) and clozapine should not be used as a first-line treatment in first-episode schizophrenia patients (see below).

The Cochrane schizophrenia group 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).

One recently published randomized single-blind trial found **quetiapine and risperidone** to be effective for symptom reduction, but did not reveal a significant difference between both drugs with regard to side effects (both were associated with weight gain), relative efficacies or treatment adherence (Gafoor et al. 2010).

This is in line with the results of the effectiveness **EUFEST study** (Kahn et al. 2008) and one other study showing no difference between olanzapine, quetiapine and risperidone in efficacy and treatment discontinuation rates (McEvoy et al. 2007). In contrast, one review favoured the use of SGAs in first-episode schizophrenia (Bradford et al. 2003).

Important limitations are that double-blind RCTs in first-episode patients investigating ziprasidone, amisulpiride, aripiprazole, paliperidone, sertindole and the newer SGAs are lacking and that nearly all studies used haloperidol as comparator drug.

**Other guidelines** recommend either any antipsychotic medication (other than clozapine and olanzapine) for the treatment of positive symptoms in first-episode schizophrenia (Buchanan et al. 2010; Kreyenbuhl et al. 2010) or state no significant differences in efficacy among olanzapine, quetiapine, risperidone and haloperidol (NICE 2010). In contrast to this, an initial treatment with SGAs other than clozapine was recommended by the Texas Medication Algorithm Project (Moore et al. 2007).

Based on the aforementioned findings, FGAs and SGAs are recommended for the treatment of positive symptoms in first-episode schizophrenia patients (*Category of Evidence A, Recommendation grade 1/2*). Among the FGAs only haloperidol could be recommended, whereas most other FGAs have not been



tested and the risk for motor side effects should be considered. Among the SGAs, risperidone, olanzapine and quetiapine (*Category of Evidence A, Recommendation grade 1*) could be recommended, whereas other drugs have not been tested extensively. Amisulpride and ziprasidone were clinically similar to risperidone, olanzapine, quetiapine and haloperidol in the EUFEST study (Kahn et al. 2008). Therefore, amisulpride and ziprasidone could be recommended (*Category of Evidence B, Recommendation grade 3*), but the psychiatrist prescribing these two drugs should be aware that this recommendation was based on the results of one just study (EUFEST).

In first-episode schizophrenia, SGAs might be favoured with regard to the reduced rate of neurological side effects and the finding of a reduced treatment discontinuation rate (*Category of evidence C3, Recommendation grade 4*). Furthermore, discontinuation rates seem to be significantly better following treatment with an SGA (*Category of evidence B, Recommendation grade 3*).

Clozapine is effective in the treatment of first-episode schizophrenia patients, but did not show superiority compared to chlorpromazine concerning remission after 52 weeks (Lieberman et al. 2003a). Because of the special haematological risk profile of clozapine (agranulocytosis), we do not recommend clozapine for the initial treatment of first-episode schizophrenia.

### General recommendations

These recommendations remain unmodified in relation to the first publication of these guidelines. In first-episode patients especially, other mental and non-mental disorders should be excluded before diagnosing schizophrenia and starting antipsychotic treatment (DGPPN 2006). 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. In general, the treatment setting should be based on the least restrictive environment (RANZCP 2005), but it should be adapted according to the individual patient's disease severity (see General Recommendations Table I).

### Dosage

First-episode schizophrenia patients display an increased risk of and sensitivity developing side effects (especially neurological side effects) following antipsychotic treatment compared with chronically ill patients (Buchanan et al. 2010; McEvoy et al. 1991; Naber and Lambert 2009; Remington et al. 1998). In light of these observations, patients

suffering from their first-episode should be treated with lower antipsychotic dosages compared to chronically ill patients. First-episode schizophrenia patients should receive dosages at the lower end of the standard dose range (Buchanan et al. 2010; DGPPN 2006; Moore et al. 2007).

In one double-blind RCT, relatively low dosages of risperidone (mean modal dose 3.3 mg) and haloperidol (mean modal dose 2.0 mg) led to significant symptom amelioration in first-episode patients (Schooler et al. 2005). In one 52-week, double-blind RCT, mean modal doses of 9.1 mg/day olanzapine and 4.4 mg/day haloperidol were effective in the acute reduction of psychopathological symptoms in first-episode schizophrenia in the last-observation-carried forward analyses (Lieberman et al. 2003b). In another double-blind RCT, a low dosage of haloperidol (2 mg) was found to be equally effective when compared with 8 mg haloperidol, but was better tolerated and resulted in the presentation of fewer and presented less motor side effects (Oosthuizen et al. 2004). In another study an 11.8 mg mean modal dosage of olanzapine and a 3.9 mg mean modal dosage of risperidone led to a significant symptom reduction, whereas the mean daily doses at the time of responses were lower (8.9 mg for olanzapine, 3.4 mg for risperidone) in an open-label treatment study with randomized assignments (Robinson et al. 2006). One further double-blind

Recommendation Table I. Recommendations for the antipsychotic treatment of first-episode schizophrenia patients.

Antipsychotic agent	Category of evidence <sup>a</sup>	Recommendation <sup>b</sup>
Olanzapine	A	1
Quetiapine	A	1
Risperidone	A	1
Clozapine <sup>1</sup>	A	2
Haloperidol	A	2
Amisulpride	B	2
Aripiprazole	B	2
Ziprasidone	B	2
Asenapine <sup>2</sup>	F	–
Iloperidone <sup>2</sup>	F	–
Paliperidone <sup>2</sup>	F	–
Lurasidone <sup>2</sup>	F	–
Sertindole <sup>2</sup>	F	–
Zotepine <sup>2</sup>	F	–

<sup>a</sup>Category of evidence: Category of evidence where A=full evidence from controlled studies (see Table I). <sup>b</sup>Safety rating=recommendation grade derived from categories of evidence and additional aspects of safety, tolerability, and interaction potential (see Table I). <sup>1</sup>Clozapine is highly effective in the treatment of first-episode patients, but because of its side effect profile it should be considered as recommendation grade 2. <sup>2</sup>It can be assumed that these antipsychotics are effective in the treatment of first-episode schizophrenia, but we could not identify any study to give an evidence-based recommendation.

RCT compared short-term treatment with haloperidol (mean daily dose 3.7 mg) and risperidone (mean daily dose 3.8 mg) and showed that both were effective in symptom reduction according to PANSS (Moller et al. 2008). In this study, treatment with haloperidol caused significantly more extrapyramidal side effects than risperidone. Another double-blind RCT with two different doses of risperidone (2 and 4 mg/day) showed no inferiority of the low dosage for symptom improvement in first-episode schizophrenia patients (Merlo et al. 2002). However, the higher dose resulted in more motor side effects. Olanzapine (mean modal dose 10.2 mg/day) and haloperidol (mean modal dose 4.8 mg/day) resulted both in a substantial reduction in symptom severity, whereas patients treated with olanzapine were less likely to undergo treatment discontinuation (Green et al. 2006). However, it should be noted that the lack of a significant difference between drugs and dosages in these studies does not mean that the drugs/dosages are equally efficient.

Based on the aforementioned findings, the recommendation of a treatment at the lower end of the standard dose range is mostly confirmed for haloperidol (< 5 mg/day), risperidone (< 4 mg/day) and olanzapine (< 10 mg/day) (*Category of Evidence B, Recommendation grade 3*). For other antipsychotics there is only sparse evidence for this treatment recommendation (*Category of Evidence C1/D, Recommendation grades 4/5*).

### Summary statements

- FGAs and SGAs are both effective in the treatment of first-episode schizophrenia (*Category of Evidence A, Recommendation grade 1*)
- Patients suffering from their first-episode should be treated with lower antipsychotic dosages than chronically ill patients (*Category of Evidence A, Recommendation grade 1*)
- Due to the reduced risk of inducing neurological side effects, the first-line use of SGAs in first-episode schizophrenia patients is recommended with limited evidence (*Category of Evidence C3, Recommendation grade 4*)
- Limited evidence is available to support superiority of SGAs with regard to treatment discontinuation in first-episode patients (*Category of Evidence B/C3, Recommendation grades 3/4*)
- Olanzapine, risperidone and quetiapine are the best approved SGAs in first-episode patients
- Haloperidol is the best approved FGA in first-episode patients
- Clozapine is not recommended for the first-line treatment in first-episode schizophrenia

- The treatment decision should be guided by the efficacy/effectiveness and the side effect profile of the antipsychotics and should be made individually for each patient suffering from first-episode schizophrenia

### Acute exacerbation (relapse), multi-episode patients

#### *Efficacy of FGA*

It has been demonstrated that all FGAs (with the exception of mepazine and promazine) are superior to placebo in the treatment of an acute exacerbation of schizophrenia (Davis et al. 1989; Dixon et al. 1995; Kane and Marder 1993). Haloperidol is the most investigated FGA and its efficacy for the treatment of acute schizophrenia is evident (Irving et al. 2006; Joy et al. 2006a) (*Category of Evidence A, Recommendation grade 2*). One Cochrane review displayed that low doses of haloperidol (3–7.5 mg/day) were not inferior to higher doses of haloperidol (> 7.5–15 mg/day), but caused fewer motor symptoms (Donnelly et al. 2010; Waraich et al. 2002). Perazine seems to have a similar efficacy with fewer motor side effects compared to haloperidol (Klimke et al. 1993; Schmidt et al. 1982). Zuclopenthixol acetate, which is frequently used for the treatment of acute agitation and acute psychotic symptoms, is not inferior to haloperidol in sedating at two hours (Gibson et al. 2004). However, one Cochrane Review indicates that most trials investigating zuclopenthixol acetate have methodological restrictions and that the use of this drug for the management of psychiatric emergencies should only done with caution (Gibson et al. 2004).

#### *Efficacy of SGA*

The efficacy of SGAs in the treatment of acute exacerbations of multi-episode schizophrenia patients has been shown in many trials and large RTCs, and many meta-analyses have been published since the first version of these guidelines. For ease of use and retention of clarity, the cited studies are only discussed for the new SGAs, and detail is only given in cases of a significant evidence change. However, all detected studies are included into the different paragraphs giving the reader the best possible survey of evidence.

*Amisulpride.* Amisulpride was shown in RCTs and meta-analyses to be effective in the treatment of acute episodes in patients with a diagnosed schizophrenia in comparison to placebo/other antipsychotics (FGAs and SGAs (Bhowmick et al. 2010; Burns and Bale 2001; Carriere et al. 2000; Colonna et al.

2000; Delcker et al. 1990; Freeman 1997; Hwang et al. 2003; Kahn et al. 2008; Komossa et al. 2010c; Leucht 2004; Leucht et al. 2002, 2009b; Loo et al. 1997; Martin et al. 2002; Moller et al. 1997; Mortimer et al. 2004; Muller et al. 2002; Paillere-Martinot et al. 1995; Peuskens et al. 1999; Puech et al. 1998; Schlosser et al. 2002; Sechter et al. 2002; Wetzel et al. 1998). Taking these studies into consideration, there is convincing evidence for the efficacy of amisulpiride in the treatment of acute episodes of schizophrenia (*Category of Evidence A, Recommendation grade 1*).

*Asenapine.* Asenapine has been recently introduced for the treatment of schizophrenia and bipolar disorder in the USA and Europe, but has not been approved for the treatment of acute schizophrenia in Europe. We could only identify three double-blind RCTs testing asenapine versus placebo/haloperidol/risperidone. Asenapine was superior to placebo in three trials (Kane et al. 2010, 2011a; Potkin et al. 2007) and showed a similar efficacy compared to haloperidol (Kane et al. 2010) and risperidone (Potkin et al. 2007). There is evidence for the efficacy of asenapine in the treatment of schizophrenia, but further trials are required (*Category of Evidence A, Recommendation grade 1/2*).

*Aripiprazole.* When the first version of these guidelines was published, aripiprazole had been available on the market for approximately three years. From that point onwards, further RCTs, open-label studies and meta-analyses have been conducted showing that aripiprazole is effective in the treatment of acute episodes of schizophrenia (*Category of Evidence A, Recommendation grade 1*) (Bhattacharjee and El-Sayeh 2008; Cutler et al. 2006; El-Sayeh and Morganti 2004; El-Sayeh et al. 2006; Fleischhacker et al. 2009; Kane et al. 2002, 2007b, 2008a, 2009b; Kerwin et al. 2007; Komossa et al. 2009c; Leucht et al. 2009b, 2009d; Marder et al. 2003, 2007b; McCue et al. 2006; McEvoy et al. 2007; Potkin et al. 2003; Tandon et al. 2006; Wolf et al. 2007; Zimbroff et al. 2007). Finally, aripiprazole was superior to haloperidol in a 52-week long-term trial with regard to PANSS negative subscores and time to treatment discontinuation (Kasper et al. 2003).

*Clozapine.* Clozapine should be reserved for patients suffering from treatment-resistant schizophrenia (see below), despite the good efficacy of clozapine in the treatment of acute episodes of schizophrenia. This is because of its side effect profile with an emphasis on life-threatening haematological side effects (Asenjo

Lobos et al. 2010; Beasley et al. 1997; Chiu et al. 1976; Essali et al. 2009; Fischer-Cornelissen and Ferner 1976; Gelenberg and Doller 1979; Heinrich et al. 1994; Klieser et al. 1994; Lieberman et al. 2003a; McEvoy et al. 2006; Shopsin et al. 1979) (*Category of Evidence A, Recommendation grade 1/2*).

*Iloperidone.* Iloperidone was recently approved for the treatment of schizophrenia in the United States. We were able to identify one 4-week double-blind RCT (Cutler et al. 2008) comparing iloperidone with placebo/ziprasidone and showing a significant improvement in the PANSS total score compared to placebo, but no differences when compared to ziprasidone. One review with pooled data from three prospective RCTs demonstrated an equivalent long-term efficacy of iloperidone compared to haloperidol (Kane et al. 2008b). A further review identified four reports of phase III studies and showed a superiority of iloperidone compared to placebo (Citrome 2009). Therefore, iloperidone is suitable for the treatment of acute schizophrenia, but further questions concerning its efficacy and safety need to be addressed in future studies (*Category of Evidence A, Recommendation grade 1/2*).

*Lurasidone.* Lurasidone was approved for the treatment of schizophrenia in the United States in 2010. One double-blind RCT has demonstrated the superiority of lurasidone compared to placebo (Nakamura et al. 2009). In a randomized, double-blind, placebo- and olanzapine-controlled study, 40- and 120-mg doses of lurasidone were as effective as 15 mg olanzapine in improving PANSS scores in acute psychotic schizophrenia patients. However, the high lurasidone dose was associated with more side effects than the low dose, olanzapine or placebo (Meltzer et al. 2011). There is some evidence for the efficacy of lurasidone in the treatment of acute schizophrenia, but further studies comparing lurasidone to placebo and other antipsychotics are needed (*Category of Evidence B, Recommendation grade 3*).

*Olanzapine.* Olanzapine was one of the first SGAs and its efficacy in the treatment of acute schizophrenia has been proven in many RCTs, naturalistic studies and meta-analyses. There is convincing evidence for the efficacy of olanzapine for the treatment of acute schizophrenic episodes (*Category of Evidence A, Recommendation grade 1*) (Alvarez et al. 2003; Beasley et al. 1996b, 1997; Bobes et al. 2003; Carrasco et al. 2002; Chrzanowski et al. 2006; Ciudad et al. 2005; Fleischhacker et al. 2009; Hamilton et al. 1998, 1999; Hatta et al. 2009;

Ho et al. 1999; Ishigooka et al. 2001; Jones et al. 2006; Kahn et al. 2008; Kane et al. 2007a; Kraus et al. 2005; Leucht et al. 2009b, 2009d; Lieberman et al. 2003a, 2005; Martin et al. 2002; Mauri et al. 2006; McCue et al. 2006; Mortimer et al. 2004; Revicki et al. 1999; Sacchetti et al. 2008; Sanger et al. 1999; Sherwood et al. 2006; Simpson et al. 2004; Stroup et al. 2007; Tollefson et al. 1997; Villari et al. 2008).

**Paliperidone.** In two double-blind RCTs, paliperidone was found to be superior to placebo (Davidson et al. 2007; Kane et al. 2007a; Marder et al. 2007a) and presented the same efficacy as the comparator olanzapine (Kane et al. 2007a; Marder et al. 2007a). One Cochrane meta-analysis reviewed five studies comparing paliperidone with placebo and three studies comparing paliperidone with olanzapine. Paliperidone was superior to placebo and was comparable in efficacy to oral olanzapine (Nussbaum and Stroup 2008). Pooled data from three 52-week open-label studies showed that paliperidone can lead to a significant improvement in the PANSS (Emsley et al. 2008). Paliperidone showed superiority to placebo and quetiapine in a 6-week double-blind RCT (Canuso et al. 2009b). A meta-analysis confirmed the efficacy of paliperidone for the treatment of acute schizophrenia (Jones et al. 2010). **In summary**, there is good evidence for the efficacy of paliperidone in the treatment of acute schizophrenia (*Category of Evidence A, Recommendation grade 1/2*), but studies comparing paliperidone with its parent compound risperidone are lacking (Nussbaum and Stroup 2008).

**Quetiapine.** Quetiapine is one of the most frequently prescribed SGAs and there is evidence for its efficacy in the treatment of acute schizophrenic episodes (*Category of Evidence A, Recommendation grade 1*). This statement is supported by different RCTs, naturalistic studies and meta-analyses (Arvanitis and Miller 1997; Borison et al. 1996; Copolov et al. 2000; Fabre et al. 1995; Kahn et al. 2007, 2008; Komossa et al. 2010d; Leucht et al. 2009d; Lieberman et al. 2005; Mullen et al. 2001; Perez et al. 2008; Sacchetti et al. 2008; Schulz et al. 2003; Small et al. 1997; Srisurapanont et al. 2004; Stroup et al. 2007; Villari et al. 2008; Zhong et al. 2006).

**Risperidone.** Risperidone is one of the most investigated SGAs and evidence for its efficacy in the treatment of acute episodes of schizophrenia has been established in different RCTs, naturalistic studies and meta-analyses (*Category of Evidence A,*

*Recommendation grade 1*) (Addington et al. 2004; Blin et al. 1996; Borison et al. 1992; Ceskova and Svestka 1993; Chouinard et al. 1993; Claus et al. 1992; Glick et al. 2001; Hatta et al. 2009; Heinrich et al. 1994; Ho et al. 1999; Hoyberg et al. 1993; Hunter et al. 2003; Huttunen et al. 1995; Jeste et al. 1997; Jones et al. 2006; Kahn et al. 2008; Kraus et al. 2005; Leucht et al. 2009b,d; Li et al. 2009; Lieberman et al. 2005; Marder and Meibach 1994; McCue et al. 2006; Merlo et al. 2002; Nair 1998; Pajonk et al. 2005; Peuskens 1995, 1999; Potkin et al. 2007; Rattehalli et al. 2010a,b; Villari et al. 2008; Zhang et al. 2001). E

**Sertindole.** Sertindole has been shown to be superior to placebo (van Kammen et al. 1996; Zimbroff et al. 1997) and to have the same efficacy as haloperidol (Bech et al. 2010; Zimbroff et al. 1997). One Cochrane review including three studies confirmed these findings (Lewis et al. 2005). One study showed a superiority to risperidone (Azorin et al. 2006), whereas another study could not confirm this finding (Kane et al. 2011b). Sertindole seems to reduce suicidality in schizophrenia patients (see part 3 of these guidelines), but is associated with an increased cardiac mortality compared to risperidone (Crocq et al. 2010; Thomas et al. 2010). However, other comparisons to other SGAs are lacking (Komossa et al. 2009b) and meta-analyses showed no difference to other SGAs or to FGAs (Leucht et al. 2009b,d). There is evidence that sertindole is effective in the treatment of acute schizophrenia (*Category of Evidence A, Recommendation grade 1/2*).

**Ziprasidone.** Numerous RCTs, naturalistic studies and meta-analyses provide convincing evidence for the efficacy of ziprasidone in the treatment of acute schizophrenic episodes (*Category of Evidence A, Recommendation grade 1*) (Addington et al. 2004; Brook et al. 2005; Cutler et al. 2008; Daniel et al. 1999; Goff et al. 1998; Hirsch et al. 2002; Kahn et al. 2008; Keck et al. 1998; Komossa et al. 2009a; Leucht et al. 2009b,d; Lieberman et al. 2005; McCue et al. 2006; Simpson et al. 2004; Zimbroff et al. 2007).

**Zotepine.** Zotepine has been shown to be as effective as haloperidol and perazine in the treatment of acute schizophrenia (Dieterle et al. 1991; Fleischhacker et al. 1989; Hwang et al. 2001; Klieser et al. 1991; Leucht et al. 2009b; Petit et al. 1996; Wetzel et al. 1991), and more effective compared to placebo and chlorpromazine (Cooper et al. 2000b). However, it seems that zotepine has the same efficacy as other SGAs, but the evidence regarding zotepine's action

is not strong enough to draw strong conclusions (Leucht et al. 2009d; Subramanian et al. 2010). **In summary**, there is some evidence that zotepine is effective in the treatment of acute episodes in schizophrenia patients (*Category of Evidence B, Recommendation grade 3*).

#### General recommendations

These recommendations remain unmodified in relation to the first publication of these guidelines. In accordance with other guidelines, it is recommended that multiple-episode patients should receive prompt antipsychotic treatment, which will not interfere with diagnostic assessment, because acute psychotic exacerbations may be associated with emotional distress, disruptions to the patient's life, and a substantial risk of dangerous behaviour to self, others or property (APA 2004). Antipsychotic monotherapy is recommended across all guidelines in the initial treatment of acute schizophrenic episodes (APA 2004; Buchanan et al. 2010; DGPPN 2006; NICE 2010; RANZCP 2005) (*Category of Evidence C3, Recommendation grade 4*) (see Recommendation Table II).

Recommendation Table II. Recommendations for the antipsychotic treatment of multi-episode patients (acute relapse).

Antipsychotic agent	Category of evidence <sup>a</sup>	Recommendation <sup>b</sup>
Amisulpride	A	1
Asenapine <sup>1</sup>	A	1/2
Aripiprazole	A	1
Clozapine <sup>2</sup>	A	1/2
Haloperidol	A	2
Iloperidone <sup>1</sup>	A	1/2
Olanzapine	A	1
Paliperidone <sup>1</sup>	A	1/2
Quetiapine	A	1
Risperidone	A	1
Sertindole <sup>1,3</sup>	A	1/2
Ziprasidone	A	1
Lurasidone	B	3
Zotepine	B	3

<sup>a</sup>Category of evidence: Category of evidence where A = full evidence from controlled studies (see Table I). <sup>b</sup>Safety rating = recommendation grade derived from categories of evidence and additional aspects of safety, tolerability, and interaction potential (see Table I). <sup>1</sup>These drugs are not approved for the treatment of schizophrenia in all countries and therefore it should be generally considered as recommendation grade 2 in these countries. <sup>2</sup>Clozapine is highly effective in the treatment of multi-episode patients, but it is only recommended as second line treatment due to its special side-effect profile (see main text). <sup>3</sup>Sertindole has a safety rating of 1, but due to its cardiovascular side effect profile the use is restricted in some countries. In these countries, it should be considered as recommendation grade 2 for legal reasons.

#### Choice of antipsychotic medication

Antipsychotic medication should be guided by the side effect profile of the drug, the patient's experience with certain side effects, the patient's previous response experience with certain antipsychotics, and potential interactions with other prescribed medications (Buchanan et al. 2010; NICE 2010; RANZCP 2005). In contrast to the last version of these guidelines, a general and predominant use of SGAs in multi-episode patients cannot be recommended with regard to efficacy and effectiveness.

All SGAs and the established FGAs can be considered as treatment options for individuals experiencing an acute schizophrenic episode (*Category of Evidence A, Recommendation grade 1; for zotepine Category of Evidence B, Recommendation grade 3*). Clozapine should be used in cases of treatment-resistant schizophrenia (see below). SGAs carry less risk of neurological side effect, especially tardive dyskinesia. Tardive dyskinesia is a severe side effect and the reduced risk for tardive dyskinesia favours the use of SGAs over FGAs (*Category of evidence C3, Recommendation grade 4*). Furthermore, there might be some advantages of SGAs regarding treatment continuation, compliance and in other treatment domains (*Category of evidence C3, Recommendation grade 4*). Treatment compliance is from particular importance, because non-compliance is the main reason for relapse in schizophrenia patients (Goff et al. 2010).

However, the increased risk of metabolic side effects following a treatment with certain SGAs (especially in the long-term treatment) needs to be monitored and considered as part of any treatment decision (*Category of Evidence C, Recommendation grade 4*) (see Table III). With long-term treatment (especially relapse prevention), there seems to be some superiority of certain SGAs (see part 2 of these guidelines) and, therefore, initial treatment with an SGA in schizophrenia patients experiencing a relapse, could be favoured (*Category of evidence C3, Recommendation grade 4*).

In routine clinical practice, if patients are currently achieving good control of their condition without unacceptable side effects with the FGA they are taking, changing from an FGA to an oral SGA is not recommended (Buchanan et al. 2010) (*Category of Evidence C, Recommendation grade 4*).

#### Dosage

Daily doses of FGAs lower than 300 mg CPZ equivalents were found to be inadequate for optimal treatment, and doses above 940 mg CPZ equivalents produced no better responses than ranges of

Table III. Monitoring for patients on second-generation antipsychotics. More frequent assessments may be warranted based on clinical status. Especially during a long-term treatment (e.g., lifelong treatment), the monitoring process has to be adapted individually. These monitoring intervals are one suggestion which needs to be modified with regard to the administered antipsychotic and the national guidelines. Patients treated with clozapine need a special monitoring.

	Baseline	4 Weeks	8 Weeks	12 Weeks	Annually
Personal/Family History	x				x
Weight (BMI)	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				x
EEG	x				x
Pregnancy test	x				x

BMI, Body mass index; ECG, electrocardiogram; EEG, electroencephalogram. Modified according to APA (2004).

540–940 mg CPZ equivalents (Davis et al. 1989). In a Cochrane-based meta-analysis, low doses of haloperidol (3–7.5 mg/day) did not result in loss of efficacy compared to higher doses, but caused fewer neurological side effects (Donnelly et al. 2010; Waraich et al. 2002). The finding of no-inferiority of haloperidol when administered with a low dosage compared to high dosages has been confirmed in many other studies and meta-analyses (Dixon et al. 1995; Kane and Marder 1993; Stone et al. 1995; Volavka et al. 2000) and the near-maximal efficacy dose for haloperidol was shown to be 3–10 mg/day (Davis and Chen 2004). The recommendation of daily dosages between 300 and 1000 mg CPZ equivalents for FGAs in the treatment of acute schizophrenia remains stable across the guidelines and across time (APA 1997; Buchanan et al. 2010; DGPPN 2006; Lehman et al. 2004; NICE 2010) (*Category of Evidence A, Recommendation grade 1*).

The situation is more complicated for SGAs, because there is not enough data available to ensure a clear dose-response relationship of the approved SGAs and because SGAs represent a very heterogeneous class. Dosage recommendations are based on the manufacturer information, other recently published guidelines, dose ranges tested in RCTs and on reviews and meta-analyses. Details have been described earlier in these guidelines, but experience from large trials is lacking for asenapine, iloperidone and lurasidone. Clozapine is discussed in detail in an additional section below.

The following dosage ranges can be recommended for the following drugs (for details see Table IV) (Buchanan et al. 2010; NICE 2010; Schwartz and Stahl 2011):

- Amisulpride 200–800 mg/day
- Aripiprazole 10–30 mg/day
- Asenapine 5–20 mg/day
- Clozapine 100–900 mg/day, see chapter below
- Iloperidone 6–12 mg/day
- Lurasidone 40–80 mg/day (as provided by the manufacturer)
- Olanzapine 10–20 mg/day
- Paliperidone 6–12 mg/day
- Quetiapine 300–800 mg/day
- Risperidone 2–8 mg/day
- Sertindole 12–24 mg/day
- Ziprasidone 80–160 (180) mg/day
- Zotepine 75–450 mg/day (as provided by the manufacturer)

Data for higher doses is lacking and it should be noted that higher dosages rarely lead to faster or better symptom remission, but do lead to an increase of the side effects. In clinical practice higher dosages of olanzapine (e.g., up to 30 mg/day or more) are frequently used with increasing risk for inducing metabolic side effects and no evidence for a better efficacy than lower dosages. However, individual cases may require higher dosages and every treatment decision should be based on the patient's experience with certain drugs and dosages, the individual risk profile and the individual psychopathology. The approved dose ranges of the individual antipsychotics may vary across countries.

### Summary statements

- FGAs and SGAs are both effective in the treatment of acute relapse. All established FGAs and SGAs can be used in the treatment of acute

schizophrenia (*Category of Evidence A, Recommendation grade 1*)

- Each antipsychotic selection procedure must be undertaken individually, respecting the patient's experience with certain drug classes and the individual side effect profile
- All side effects need to be taken into consideration. Special attention needs to be given to motor side effects, metabolic side effects and cardiovascular side effects
- Some evidence is available to support superiority of SGAs with regard to treatment discontinuation and relapse prevention in chronically ill patients (*Category of Evidence B/C3, Recommendation grades 3/4*)
- Some SGAs (as outlined and discussed in these guidelines) might have some advantages over other SGAs and FGAs in terms of overall efficacy (*Category of Evidence B/C3, Recommendation grades 3/4*)
- The increased risk of neurological side effects following treatment with FGAs could favour certain SGAs (*Category of Evidence C3, Recommendation grade 4*)
- For FGAs and SGAs, the dose may be titrated as quickly as tolerated but as slowly as possible with special consideration of regard to uncomfortable and potentially dangerous side effects. In general, the lowest effective dose should be used to treat an acute schizophrenia episode (*Category of Evidence C, Recommendation grades 4*)
- Before switching to another antipsychotic drug, a treatment trial with the optimal dose for each patient should last for at least 2 weeks, but not longer than 8 weeks, unless there is unacceptable tolerance or contraindication for the continuation of the present drug (*Category of Evidence C, Recommendation grade 4*) (Buchanan et al. 2010; Lehman et al. 2004; NICE 2002; 2010) (see detailed discussion below)

### Specific clinical features influencing the treatment plan

#### *Treatment of primary and secondary negative symptoms*

The differentiation of primary and secondary negative symptoms is of particular importance for the treatment of schizophrenia. Primary negative symptoms are considered a core symptom of schizophrenia, whereas secondary negative symptoms are a consequence of positive symptoms (e.g., social withdrawal because paranoid ideas), neurological side effects (extrapyramidal side effects, acute dystonia, antipsychotic-induced parkinsonism and

tardive dyskinesia), depressive symptoms (e.g., post-psychotic of antipsychotic-induced depression) or environmental factors (e.g., social understimulation due to hospitalism) (Carpenter et al. 1985).

There are only few studies investigating the efficacy of antipsychotics in the treatment of primary negative symptoms. Most studies have investigated schizophrenia patients suffering from predominantly positive symptoms, with additional secondary negative symptoms.

#### *FGAs*

FGAs are effective in the treatment of secondary negative symptoms compared to placebo, but there are differences in the necessary doses, potency and side effects of the different drugs (Davis et al. 1989; Dixon et al. 1995; Leucht et al. 2009a). In a recent meta-analysis, FGAs showed no difference in efficacy for the treatment of secondary negative symptoms when compared to certain SGAs (aripiprazole, quetiapine, sertindole, ziprasidone, and zotepine), but were inferior to four other SGAs (amisulpride, clozapine, olanzapine, and risperidone (Leucht et al. 2009b).

In comparator studies with SGAs (see below), FGAs (especially haloperidol) were either equivalent or inferior to SGAs in the treatment of secondary negative symptoms. FGAs are effective in the treatment of secondary negative symptoms (*Category of Evidence A, Recommendation grade 1*), but there is no clear evidence for the treatment of patients with primary negative symptoms (*Category of Evidence F*).

#### *SGAs*

*Amisulpride.* An efficacy for treating primary negative symptoms has been established for amisulpride and it was stated that this drug's effective dose range for improving primary and secondary negative symptoms is 50–300 mg (Boyer et al. 1995; Colonna et al. 2000; Danion et al. 1999; Loo et al. 1997; Moller 2001; Olie et al. 2006; Speller et al. 1997). One meta-analysis showed amisulpride to be effective in the treatment of secondary negative symptoms compared to placebo (Leucht et al. 2009a).

However, a comparison of amisulpride with FGAs in schizophrenia patients with predominantly negative symptoms, did not display a statistical difference (Speller et al. 1997), whereas other studies have shown a significant difference compared to placebo (Loo et al. 1997). One recent meta-analysis (based on the findings of placebo-verum studies) found significant superiority of amisulpride compared to FGAs

Table IV. Recommended dosage (orally) of selected antipsychotics in long-term treatment.

Antipsychotic	Starting dose (mg/day)	DI <sup>1</sup>	Target dose first-episode (mg/day)	Target dose multi-episode (mg/day)	Maximal dosage (mg/day) <sup>2</sup>
<b>SGA</b>					
Amisulpride	200	(1)–2	100–300	400–800	1200
Asenapine <sup>3</sup>	5	1	5–10	5–20	20
Aripiprazole	5–15	1	15–(30)	15–30	30
Clozapine <sup>4</sup>	25	2–(4)	100–250	300–800	900
Iloperidone <sup>3</sup>	1–2	2	4–16	4–24	32
Lurasidone <sup>3</sup>	20–40	1	40–80	40–120	120
Olanzapine	5–10	1	5–15	5–20	20
Paliperidone <sup>3</sup>	3–6	1	3–9	3–12	12
Quetiapine IR/XR	50	2/1	300–600	400–750	750
Sertindole	4	1	12–20	12–24	24
Risperidone	1–2	1–2	1–4	3–10	16
Ziprasidone	40	2	40–80	80–160	160
Zotepine	25–50	2–(4)	50–150	100–250	450
<b>FGA</b>					
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

<sup>1</sup>DI (dose intervals): recommended distribution of the daily dose—one = 1, twice = 2, etc.

<sup>2</sup>Maximal approved dosage in many countries (approved by national committees, these dosages may vary between different countries). In clinical practice some FGAs and SGAs are even dosed higher without sufficient evidence. This is especially the case during a long-term treatment. Increasing the dosage may result in more side effects and this would consecutively lead to a reduced compliance.

<sup>3</sup>These antipsychotics have not been investigated in first-episode schizophrenia patients.

<sup>4</sup>Clozapine is usually not introduced in first-episode schizophrenia patients as first-line treatment.

(Leucht et al. 2009b), but a head-to-head comparison of 9 SGAs did not reveal a significantly higher efficacy for amisulpride in the treatment of secondary negative symptoms (Leucht et al. 2009d).

Until today, amisulpride is, apart from olanzapine, the only SGA that has been studied extensively in patients with primary/predominantly negative symptoms. In summary, amisulpride is effective in the treatment of primary (*Category of Evidence A, Recommendation grade 1*) and secondary negative symptoms (*Category of Evidence A, Recommendation grade 1*) of schizophrenia.

*Asenapine.* In two 6-week RCTs with acute schizophrenia patients, asenapine was shown to result in a significant improvement on the PANSS negative subscale compared to placebo (Kane et al. 2010; Potkin et al. 2007) and to have the same efficacy as haloperidol (Kane et al. 2010). Therefore, asenapine is effective in the treatment of secondary negative symptoms (*Category of Evidence B, Recommendation grade 3*), but studies in patients with predominantly negative symptoms are lacking (*Category of Evidence F*). The clinical trial design and the rationale of a study testing asenapine in the treatment of primary

negative symptoms in schizophrenia has been published (Alphs et al. 2007), but no final publication has yet been provided.

*Aripiprazole.* One 4-week, double-blind, randomized study, conducted on 414 schizophrenia and schizoaffective patients showed that aripiprazole is as effective as haloperidol and superior to placebo in reducing negative symptoms (Kane et al. 2002) and in another 4-week, double-blind, randomized study including 404 schizophrenia patients was superior to placebo in reducing negative symptoms (Potkin et al. 2003). Aripiprazole was as effective as haloperidol in reducing negative symptoms in another 4-week, double-blind, randomized, parallel study conducted on 83 stable schizophrenia patients. One randomized, double-blind, placebo-controlled study investigated the efficacy of aripiprazole for the treatment of acute exacerbations of schizophrenia and showed a beneficial effect on negative symptoms (McEvoy et al. 2007). An analyses with pooled data from five, 4–6-week acute studies showed that aripiprazole is superior to placebo and as effective as haloperidol in improving PANSS subscales, including negative symptom subscale (Kane et al. 2008a). A related



analysis with pooled data from five short-term, double-blind, multicenter studies confirmed this finding (Janicak et al. 2009).

Meta-analyses (see detailed description above) that aripiprazole is not superior to other SGAs and to FGAs in reducing negative symptoms (Leucht et al. 2009b,d). The augmentation with aripiprazole in a sample of clozapine-treated patients with refractory schizophrenia was superior in reducing negative symptoms compared to placebo (Chang et al. 2008). In summary, aripiprazole is effective in treating secondary negative symptoms (*Category of Evidence A, Recommendation grade 1*), but there is only little evidence from clinical experience of its efficacy in treating predominantly negative symptoms (*Category of Evidence C3, Recommendation grade 4*).

*Clozapine.* Evidence for the efficacy of clozapine in the treatment of negative symptoms, comes from open, non-comparative trials and RCTs (Lindenmayer et al. 1994; Meltzer et al. 1989). In one study, clozapine showed the same efficacy, with a modest superiority, in the treatment of negative symptoms compared to haloperidol (Breier et al. 1994; Buchanan et al. 1998; Kane et al. 2001; Rosenheck et al. 1999; Volavka et al. 2002) and no superiority to risperidone (Bondolfi et al. 1998; Breier et al. 1999; Wahlbeck et al. 2000) or to other SGAs (Asenjo Lobos et al. 2010; Chakos et al. 2001). Recent meta-analyses reported no superiority of clozapine compared to placebo (Leucht et al. 2009a), a superiority of clozapine compared to FGAs (Leucht et al. 2009b) and no difference between clozapine and other SGAs (Leucht et al. 2009d). **In summary**, clozapine is effective in treating secondary negative symptoms (*Category of Evidence A, Recommendation grade 1*), but only little evidence of its efficacy in predominately negative symptoms is existing (*Category of Evidence C3, Recommendation grade 4*).

*Iliperidone.* Studies focussing on predominantly negative symptoms and studies showing a significant improvement of secondary negative symptoms are lacking and evidence is insufficient to recommend treatment of any negative symptoms with iloperidone (*Category of Evidence F*).

*Lurasidone.* Lurasidone was superior in improving negative symptoms in acute patients in one 6-week RCT compared to placebo (Nakamura et al. 2009), but no other studies could be identified. There is limited evidence for the efficacy of lurasidone in the treatment of secondary negative symptoms (*Category of Evidence B, Recommendation grade 3*), and no

evidence for its efficacy in treating primary negative symptoms (*Category of Evidence F*).

*Olanzapine.* As outlined in the last version of the WFSBP Guidelines, olanzapine displayed superior efficacy in treating negative symptoms in acutely ill schizophrenia patients compared to placebo, whereas its superiority compared to haloperidol remains inconclusive (Beasley et al. 1996a,b, 1997; Breier and Hamilton 1999; Buchanan et al. 2005; Gomez and Crawford 2001; Ishigooka et al. 2001; Mortimer et al. 2004; Rosenheck et al. 2003; Tollefson et al. 1997; Tollefson and Sanger 1997). Olanzapine seems to have the same efficacy in treating negative symptoms as other SGAs (Bitter et al. 2004; Canive et al. 2006; Conley and Mahmoud 2001; Gureje et al. 2003; Ho et al. 1999; Sirota et al. 2006; Volavka et al. 2002). Recent meta-analyses reported a superiority of olanzapine compared to placebo (Leucht et al. 2009a), to FGAs (Leucht et al. 2009b) and no difference compared to other SGAs (Leucht et al. 2009d).

Since the last publication of these guidelines, some studies with patients suffering from predominantly negative symptoms have been conducted. A 6-month multicenter double-blinded trial of olanzapine 5 mg/day, olanzapine 20 mg/day or amisulpride 150 mg/day showed superiority of olanzapine 5 mg/day compared to placebo in the treatment of predominantly negative symptoms, whereas olanzapine 20 mg/day and amisulpride 150 mg/day did not differ significantly from placebo (Lecrubier et al. 2006). One multicenter, randomized, monitored, open-label, parallel, dose-flexible, 1-year study of outpatients with schizophrenia found superiority of olanzapine compared to risperidone in improving negative symptoms (Alvarez et al. 2006). Olanzapine was effective in the treatment of negative symptoms in a study sample including schizophrenia patients with prominent negative symptoms in a small double-blind RCT (Sirota et al. 2006). A 12-week, double-blind, controlled study examined the efficacy of olanzapine versus haloperidol on persistent, primary negative symptoms and revealed a significant effect of olanzapine treatment on primary negative symptoms (Lindenmayer et al. 2007). **In summary**, olanzapine is effective in the treatment of primary (*Category of Evidence A, Recommendation grade 1*) and secondary negative symptoms (*Category of Evidence A, Recommendation grade 1*) in schizophrenia.

*Paliperidone.* Different studies indicate that paliperidone is effective in reducing negative symptoms in acutely ill patients (Davidson et al. 2007; Kane et al. 2007a; Marder et al. 2007a). One analyses

used pooled data from three 6-week double-blind studies included patients in an acute episode of schizophrenia who received paliperidone extended-release and made a selection of those patients who had predominant negative symptoms (Canuso et al. 2009a). This study showed that patients with and without predominant negative symptoms respond to a treatment with paliperidone (Canuso et al. 2009a). Another analysis of pooled data from three 6-week double-blind, placebo-controlled studies (Davidson et al. 2007; Kane et al. 2007a; Marder et al. 2007a) confirm these findings (Turkoz et al. 2008). In summary, paliperidone is effective in the treatment of secondary negative symptoms (*Category of Evidence A, Recommendation grade 1*), but the level of evidence is too low to recommend it for the treatment of primary negative symptoms (*Category of Evidence F*).

**Quetiapine.** Compared to placebo, quetiapine was more effective in the treatment of secondary negative symptoms in acutely ill schizophrenia patients (Arvanitis and Miller 1997; Small et al. 1997). Compared to haloperidol, quetiapine showed the same efficacy in treating negative symptoms (Arvanitis and Miller 1997) and, compared to chlorpromazine, a trend towards better efficacy could be observed (Peuskens and Link 1997). A large study with different fixed-doses of quetiapine showed superiority to placebo with high quetiapine dosage (600/800 mg/day) in the treatment of negative symptoms in a mixed sample of 588 schizophrenia patients (Kahn et al. 2007).

One 12-week double-blind, comparative study with 44 schizophrenia patients suffering from predominantly negative symptoms showed quetiapine to be as effective as risperidone in improving negative symptoms (Riedel et al. 2005) and a 12-week, randomised, flexibly dosed study showed the same efficacy for quetiapine and olanzapine (Sirota et al. 2006). Quetiapine was effective in the treatment of prominent negative symptoms in a double-blind RCT, but was inferior to olanzapine (Sirota et al. 2006). A meta-analysis including three acute, double-blind, placebo-controlled, randomised trials found that the improvement of negative symptoms in acute schizophrenia was significantly greater with quetiapine than with placebo (Small et al. 2004). In recent meta-analyses, quetiapine showed the same efficacy as FGAs and SGAs, whereas the comparison to placebo remains inconclusive (Leucht et al. 2009a,b,d).

In summary, quetiapine is effective in the treatment of primary (*Category of Evidence B, Recommendation grade 3*) and secondary negative symptoms (*Category of Evidence A, Recommendation grade 1*) in schizophrenia.

**Risperidone.** At a dosage of 6 mg/day, risperidone was superior to placebo in improving negative symptoms (Peuskens 1995; Potkin et al. 2003) and a re-analysis of this study with a path-analytical approach revealed a direct effect of treatment on negative symptoms (Moller et al. 1995). In an early meta-analysis, 4–8 mg/day risperidone was superior in terms of the treatment of negative symptoms when compared with FGAs (haloperidol, perphenazine or zuclopenthixol) (Carman et al. 1995; Glick et al. 2001), and the advantages of risperidone were greatest for negative symptoms, uncontrolled hostility/excitement, and anxiety/depression when compared to haloperidol or placebo (Marder et al. 1997). Risperidone showed the same efficacy (with some inferiority in early studies) in the treatment of negative symptoms compared to other SGAs (Conley and Mahmoud 2001; Hwang et al. 2003; Potkin et al. 2003; Tran et al. 1997; Zhong et al. 2006). Recent meta-analyses have demonstrated that risperidone is superior to some other SGAs, to FGAs and to placebo in the treatment of negative symptoms (Leucht et al. 2009a,b,d).

**In summary,** risperidone is effective in the treatment of secondary negative symptoms (*Category of Evidence A, Recommendation grade 1*), but the level of evidence is too low to recommend it for the treatment of primary negative symptoms (*Category of Evidence F*).

**Sertindole.** In one 8-week multicenter, double-blind, placebo-controlled study that investigated 497 acutely ill schizophrenia patients, sertindole was superior to placebo in reducing negative symptoms (Zimbroff et al. 1997). In one randomized, double-blind, parallel-group, flexible-dose, multi-centre study conducted on 187 schizophrenic subjects, sertindole was more effective in reducing negative symptoms than risperidone (Azorin et al. 2006). In another double-blind RCT sertindole was as effective as risperidone in reducing negative symptoms in a sample of 217 patients suffering from treatment-resistant schizophrenia (Kane et al. 2011b). One Cochrane Review and one recently published Pubmed-based review indicate that sertindole is effective in the treatment of secondary negative symptoms in schizophrenia (Azorin et al. 2010; Lewis et al. 2005). In summary, sertindole is effective in the treatment of secondary negative symptoms (*Category of Evidence A, Recommendation grade 1*), but the level of evidence is too low to recommend it for the treatment of primary negative symptoms (*Category of Evidence F*).

**Ziprasidone.** Ziprasidone was shown to be superior to placebo in the improvement of negative symptoms

in acutely ill patients in some (Daniel et al. 1999), but not all, studies (Keck et al. 1998). In a 6-week, multicenter, parallel-group, flexibly dosed study, ziprasidone was superior to haloperidol in reducing negative symptoms (Brook et al. 2005), and in one post hoc analysis in stable outpatients with schizophrenia, time to negative symptom remission was significantly shorter in the ziprasidone group compared to those administered haloperidol (Stahl et al. 2010).

In one double-blind 1-year RCT, ziprasidone was shown to be significantly more effective than placebo (Arato et al. 2002) and a 12-week double-blind RCT showed the same efficacy of ziprasidone and amisulpride in reducing negative symptoms (Olie et al. 2006) in schizophrenia patients with predominantly negative symptoms.

**In summary,** ziprasidone is effective in the treatment of secondary negative symptoms (*Category of Evidence A, Recommendation grade 1*) and there is some evidence for its efficacy for treating primary negative symptoms (*Category of Evidence B, Recommendation grade 3*).

**Zotepine.** Zotepine shows similar efficacy in the treatment of secondary negative symptoms in comparisons with FGAs, with some superiority in some studies (Cooper et al. 2000b; Moller 2003; Petit et al. 1996). Zotepine failed to show superiority compared to placebo in schizophrenia patients with predominantly negative symptoms (Moller et al. 2004) in a double-blind RCT (Cooper et al. 2000a). In a small double-blind study investigating schizophrenia patients with prevalingly negative symptoms, zotepine was superior to haloperidol (Barnas et al. 1992). Recent reviews based on the Cochrane database indicate that zotepine is more effective in the treatment of negative symptoms than placebo and that it shows the same efficacy as FGAs and SGAs (DeSilva et al. 2006; Leucht et al. 2009a,b,d).

In summary, zotepine is effective in the treatment of secondary negative symptoms (*Category of Evidence A, Recommendation grade 1*), but for the treatment of primary negative symptoms, the level of evidence is inconsistent, and therefore, it cannot be recommended (*Category of Evidence D, Recommendation grade 5*).

**Efficacy of antidepressive agents.** The general evaluation of the efficacy of antidepressive agents on negative symptoms in schizophrenia is difficult because antidepressive agents are a heterogeneous group and the differentiation between improvements in depressive or negative symptoms is

associated with problems in the diagnostic process. Furthermore, most studies have been conducted using a methodology combining antidepressants with FGAs.

In the 2005 WFSBP Guidelines some limited evidence for the efficacy of antidepressants for negative symptoms in schizophrenia was reported (Lehman et al. 2004).

Mirtazapine in addition to haloperidol/FGAs was superior to placebo in two double blind RCTs in the treatment of negative symptoms (Berk et al. 2001; Joffe et al. 2009), but, in some smaller studies, showed inconsistent results compared to placebo when combined with an SGA (especially risperidone) (Abbasi et al. 2010; Berk et al. 2009; Cho et al. 2011). Furthermore, escitalopram was not superior to placebo in the treatment of negative symptoms in patients with chronic schizophrenia (Iancu et al. 2010). Two meta-analyses indicate an efficacy of the combination of antidepressants and antipsychotics, but there are still lots of studies with negative results (Rummel et al. 2006; Singh et al. 2010). There is only very limited evidence for the efficacy of antidepressants on negative symptoms (*Category of Evidence D, Recommendation grade 5*), but the augmentation observed following administration alongside mirtazapine might be promising when combined with FGAs (*Category of Evidence B, Recommendation grade 3*).

### General recommendations and summary statements

- Since the publication of the last WFSBP Guidelines, further studies have been published that provide supporting evidence for the treatment of secondary negative symptoms with antipsychotics (*Category of Evidence A, Recommendation grade 1*)
- A general superiority of SGAs compared to FGAs for secondary negative symptoms cannot be concluded, but SGAs are superior in the treatment of primary negative symptoms (*Category of Evidence B, Recommendation grade 3*)
- Amisulpride/olanzapine display good evidence (*Category of Evidence A, Recommendation grade 1*) and quetiapine/ziprasidone some evidence (*Category of Evidence B, Recommendation grade 3*) for the efficacy of treatment of schizophrenia patients suffering from predominantly negative symptoms
- FGAs should be avoided in the treatment of schizophrenia patients suffering from primary negative symptoms, because adequate studies in these special patient groups are lacking
- The combination of antipsychotics administered with antidepressants might be promising

(Category of Evidence D, Recommendation grade 5) and mirtazapine should be favoured (Category of Evidence B, Recommendation grade 3)(see Recommendation Table III).

### Treatment of cognitive symptoms

Neurocognitive deficits are considered to be an important core deficit in 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).

#### FGAs and SGAs

FGAs demonstrated no or only minor beneficial effects on cognition, whereby inappropriately large dose ranges, combined with EPS or concomitant anticholinergic medication, may have had a negative effect (Cassens et al. 1990). In an analysis of 12 double-blind short-term trials comparing risperidone with other antipsychotics in patients with chronic schizophrenia, scores for cognition improved more for patients receiving risperidone than those

receiving other antipsychotics or haloperidol (Glick et al. 2001).

A 52-week double-blind, multicenter study with 400 schizophrenia patients early in the course of their disease showed for olanzapine, quetiapine and risperidone modest significant improvements in neurocognition, with no differences between drugs (Keefe et al. 2007b). One double-blind, 14-week trial involving 101 patients with schizophrenia showed an improvement in global neurocognitive function following treatment with olanzapine and risperidone, which was superior to the effects of haloperidol. Furthermore, improvements in memory functions were better with risperidone than with clozapine and haloperidol (Bilder et al. 2002). In other RCTs, cognitive scores improved with olanzapine, risperidone and haloperidol with a small superiority for SGAs (Harvey et al. 2005; Keefe et al. 2004). Olanzapine, risperidone and sertindole were superior to haloperidol with regard to cognitive functioning in further studies (Gallhofer et al. 2007; Lee et al. 2007). In contrast, neither risperidone nor haloperidol improved neurocognitive functioning in a 12-month follow-up study (Remillard et al. 2008).

In a study of 58 stable outpatients with schizophrenia who received a battery of cognitive tests as

Recommendation Table III. Recommendations for the antipsychotic treatment of negative symptoms in schizophrenia patients.

Antipsychotic agent	Primary negative symptoms		Secondary negative symptoms	
	Category of evidence <sup>a</sup>	Recommendation <sup>b</sup>	Category of evidence <sup>a</sup>	Recommendation <sup>b</sup>
Amisulpride	A	1	A	1
Asenapine <sup>1</sup>	F	–	B	3
Aripiprazole	C3	4	A	1
Clozapine	C3	4	A	1
Haloperidol <sup>2</sup>	F	–	A	1
Iloperidone	F	–	F	–
Lurasidone	F	–	B	3
Olanzapine	A	1	A	1
Paliperidone <sup>1</sup>	F	–	A	1
Quetiapine	B	3	A	1
Risperidone	F	–	A	1
Sertindole <sup>1,3</sup>	F	–	A	1/2
Ziprasidone	B	3	A	1
Zotepine	D	5	A	1

Primary negative symptoms are considered a core symptom of schizophrenia, whereas secondary negative symptoms are a consequence of positive symptoms (e.g. social withdrawal because paranoid ideas), depressive symptoms (e.g. post-psychotic or antipsychotic-induced depression) or environmental factors (e.g. social understimulation due to hospitalism) (Carpenter et al. 1985). <sup>a</sup>Category of evidence: Category of evidence where A=full evidence from controlled studies (see Table I). <sup>b</sup>Safety rating=recommendation grade derived from categories of evidence and additional aspects of safety, tolerability, and interaction potential (see Table I). <sup>1</sup>These drugs are not approved for the treatment of schizophrenia in all countries and therefore it should be generally considered as recommendation grade 2 or lower in these countries. <sup>2</sup>Haloperidol is the most commonly used FGA across all studies. Please see the main text for other FGAs. <sup>3</sup>Sertindole has a safety rating of 1, but due to its cardiovascular side effect profile the use is restricted in some countries. In these countries, it should be considered as recommendation grade 2 or lower for legal reasons.

part of a randomized, double-blind RCT, quetiapine at higher doses (600 mg/day) was superior to haloperidol in important domains of cognitive performance (Velligan et al. 2002).

The large EUFEST study revealed that both SGAs and FGAs showed a moderate improvement in the cognitive test performance (Davidson et al. 2009). Results from the CATIE study indicate no differences between SGAs and the FGA perphenazine in the improvement of cognitive functions in chronic schizophrenia patients (Keefe et al. 2007a).

These findings have been further confirmed in a prospective, randomized, open-label study showing that haloperidol, olanzapine and risperidone have the same efficacy in treating cognitive deficits in schizophrenia patients (Crespo-Facorro et al. 2009). A recently published study showed inconclusive results comparing aripiprazole and haloperidol with a tendency to more improvement in PANSS prosocial subscale in the aripiprazole group (Docherty et al. 2010).

In a comparison of amisulpride and olanzapine, a moderate improvement of cognitive functioning was observed for both drugs (Wagner et al. 2005) and this was confirmed in another study (Mortimer et al. 2007). An open-label comparator study with 169 patients indicates that aripiprazole was as effective as olanzapine in the treatment of neurocognitive deficits in schizophrenia patients (Kern et al. 2006). In a subanalysis of 129 patients from two double-blind and one open label trial comparing the effects of different atypical antipsychotics, no differences in efficacy between aripiprazole, olanzapine, quetiapine and risperidone in the treatment of cognitive effects could be detected (Riedel et al. 2010). A small recently published study with 24 first-episode antipsychotic-naïve patients with schizophrenia showed only minimal evidence for the efficacy of quetiapine on cognition after 6 months of treatment (Andersen et al. 2011).

Meta-analyses found that overall cognitive performance improved following treatment with haloperidol and that treatment with SGAs resulted in superior improvement in essential aspects of cognition compared to FGAs (Harvey and Keefe 2001; Woodward et al. 2007).

### General recommendations and summary statements

- A small and modest beneficial effect of antipsychotic medication in the treatment of neurocognitive disturbances can be assumed (*Category of Evidence B, Recommendation grade 3*)
- The comparison of FGAs and SGAs reveals inconclusive results with some studies favouring SGAs

and some studies showing no difference between FGAs and SGAs. However, no study favours FGAs and therefore, a predominant use of SGAs can be recommended with limited evidence (*Category of Evidence C3, Recommendation grade 4*)

### Treatment of depressive symptoms in schizophrenia patients

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 et al. 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 (Lehman et al. 2004).

The last version of these guidelines stated superiority of SGAs over FGAs in treating depressive symptoms in schizophrenia (Falkai et al. 2005). A meta-analysis revealed that SGAs and the FGA haloperidol are superior to placebo in reducing depression scores in schizophrenia (Leucht et al. 2009a). Another meta-analysis comparing FGAs with SGAs showed that most SGAs were significantly better in reducing depressive symptoms than FGAs (Leucht et al. 2009b). This topic is discussed in detail in part 3 of these guidelines.

### General recommendations and summary statements

- A small and modest beneficial effect of antipsychotic medication in the treatment of depressive symptoms can be assumed (*Category of Evidence B, Recommendation grade 3*)
- A predominant use of SGAs can be recommended with limited evidence (*Category of Evidence C3, Recommendation grade 4*)
- Antidepressive agents are effective in the treatment of comorbid depression and a detailed review and evidence-based recommendations will be provided in part 3 of these guidelines

### Treatment of agitation

#### General aspects

This part has been adopted from the last version of these guidelines and updated where necessary. 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 deescalate 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 (DGPPN 2006; Lehman et al. 2004; NICE 2002).

#### *FGAs, SGAs and benzodiazepines*

Two RCTs found that the combination of haloperidol (5 mg) and lorazepam (4 mg) intramuscularly produced an overall superior and faster clinical response than haloperidol alone (Bieniek et al. 1998; Garza-Trevino et al. 1989). Comparing monotherapy of benzodiazepines with antipsychotics alone, lorazepam (or flunitrazepam) and haloperidol administered intramuscularly demonstrated similar efficacy in controlling agitation and general response to treatment (Battaglia et al. 1997; Dorevitch et al. 1999; Foster et al. 1997). In one study, lorazepam 2 mg was superior in improvement of clinical global 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). One Cochrane review showed that the combination of haloperidol plus promethazine and other agents (lorazepam, midazolam) is an effective treatment for psychosis-induced agitation or aggression (Huf et al. 2005, 2009). However, benzodiazepine administered rapidly can cause respiratory depression and the long-term combination of antipsychotics with long-acting benzodiazepines is associated with an increased mortality (Baandrup et al. 2010).

One double-blind, placebo-controlled study compared intramuscular aripiprazole and intramuscular haloperidol and showed that both treatments exhibit the same efficacy (Andrezina et al. 2006a) and other studies and analyses confirmed these findings (Andrezina et al. 2006b; Currier et al. 2007; Daniel et al. 2007; Sanford and Scott 2008; Tran-Johnson et al. 2007).

A study comparing olanzapine (10 mg intramuscularly) with haloperidol (7.5 mg intramuscularly) observed similar efficacy in reducing agitation at 2 and 24 h after the first injection (Wright et al. 2001). Doses of 2.5–10 mg olanzapine, intramuscular administered exhibit a dose–response relationship in the treatment of acute agitation in schizophrenia which is comparable to the efficacy of haloperidol (Breier et al. 2002). One observational study showed intramuscular olanzapine to be effective in the reduction of agitation 2 h after the injection (Centorrino et al. 2007). A Cochrane review demonstrated that intramuscular olanzapine is superior to intramuscular placebo, that intramuscular olanzapine is as effective as intramuscular haloperidol and that intramuscular olanzapine is superior to and better tolerated than intramuscular lorazepam (Belgamwar and Fenton 2005). Olanzapine intramuscular induces less motor side effects than FGA short-acting intramuscular preparations (Castle et al. 2009; Chandrasena et al. 2009; Owen 2010; Wagstaff et al. 2005). There is a risk of sudden death following intramuscular application of olanzapine and benzodiazepines, therefore the combined use should be avoided. A post-hoc analysis of the EUFEST sample showed that olanzapine seems to be superior to haloperidol, quetiapine and amisulpride in reducing hostility in first-episode schizophrenia patients (Volavka et al. 2011).

A double-blind RCT demonstrated the efficacy of 20 mg ziprasidone in reducing acute agitation associated with psychosis (Daniel et al. 2001) and one study showed comparable efficacy of intramuscular ziprasidone (40 mg) and intramuscular haloperidol

(10 mg) (Brook et al. 2000). In a 6-week, multi-center, parallel-group, flexibly dosed study in acute schizophrenia intramuscularly ziprasidone followed by orally administered ziprasidone was not inferior to the combination of intramuscularly haloperidol followed by orally haloperidol, but was better tolerated (Brook et al. 2005). Furthermore, one open-label study showed that sequential intramuscular and oral ziprasidone is superior to sequential intramuscular and oral haloperidol in terms of hostility (Citrome et al. 2006).

One quantitative review compared the efficacy and safety of three SGA intramuscular formulations: ziprasidone, olanzapine and aripiprazole (Citrome 2007). This analysis revealed that intramuscular ziprasidone and olanzapine might have a small benefit compared to intramuscular aripiprazole, whereas head-to-head comparisons of these antipsychotics are lacking (Citrome 2007).

Rapid sedation may also be achieved through administration of low potency antipsychotics (e.g., levomepromazine, chlorprothixene) or zuclopentixol acetate, but this strategy cannot be recommended anymore due to potential life-threatening side effects (Lehman et al. 2004).

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

#### *New formulations*

A new formulation of the FGA (loxapine inhaled, non-invasive) has recently been investigated and the first results indicate that this formulation might be a well-tolerated and effective treatment option in acute psychotic agitation (Allen et al. 2011; Citrome 2011; 2012). However, further studies are needed to evaluate the efficacy and safety of loxapine inhaled.

#### **General recommendations and summary statements**

- Lorazepam and FGAs showed comparable efficacy in the acute treatment of aggression and psychomotor agitation (*Category of evidence C, Recommendation grade 4*)
- Administration of low-potency antipsychotic agents, such as chlorprothixene or levopromazine, is not recommended in the treatment of agitation and excitation due to inferior efficacy or inferior tolerability (*Category of evidence C, Recommendation grade 4*)
- In patients whose aggressive behaviour is clearly due to psychotic symptoms, a combination

treatment of lorazepam with an antipsychotic agent can be undertaken (*Category of evidence C, Recommendation grade 4*), whereas increasing side effects have to be taken into account

- In general the evidence of adding benzodiazepines to an antipsychotic treatment is inconclusive (see below)
- Intramuscular SGA preparations (aripiprazole, olanzapine, ziprasidone) are not inferior to intramuscular haloperidol (*Category of evidence A, Recommendation grade 1*), but do induce less motor side effects (*Category of evidence A, Recommendation grade 1*)
- However, other side effects need to be considered using intramuscular SGAs (cardiac side effects, acute metabolic side effects and others)
- There is a risk of sudden death following intramuscular application of olanzapine and benzodiazepines, therefore the combined use should be avoided
- The combination of intramuscular benzodiazepine with clozapine is associated with respiratory failure and has to be avoided (Rupprecht et al. 2004)
- New formulations (e.g., inhaled loxapine) are being developed and might be a promising non-invasive treatment possibility in future
- 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 catatonic symptoms**

No new evidence has been found since the publication of the WFSBP 2005 guidelines. Benzodiazepines should be the first-line treatment for catatonia (*Category of Evidence C*). ECT should be considered when rapid resolution is necessary (e.g., malignant catatonia) or when an initial lorazepam trial fails (*Category of Evidence C, Recommendation grade 4*). Details and further recommendations can be found in the WFBSP 2005 guidelines (Falkai et al. 2005).

#### **Treatment-resistant schizophrenia**

The definitions and descriptions of treatment-resistant schizophrenia are based on the 2005

WFBSB guidelines, other guidelines and a publication from Kane and colleagues (Falkai et al. 2005; Kane et al. 1988a):

Treatment-resistant schizophrenia can be defined as a situation in which a significant improvement of psychopathology and/or other target symptoms has not been demonstrated despite treatment with two different antipsychotics from at least two different chemical classes (at least one should be an atypical antipsychotic) in the previous five years at the recommended antipsychotic dosages for a treatment period of at least 2–8 weeks per drug (Kane et al. 1988a; Lehman et al. 2004; McIlwain et al. 2011; NICE 2002; 2010).

The following section was adopted from the 2005 WFBSB guidelines and updated where necessary. 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 (Brenner et al. 1990; Marder 1995; Meltzer 1990). 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 treatment-resistant schizophrenia, including functional level, led to a prevalence 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 (Hegarty et al. 1994; Helgason 1990).

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 due to at least partial non-adherence or the prescribed antipsychotic being partially or fully ineffective (APA 1997; Lehman et al. 2004). Especially non-adherence to antipsychotic treatment is the main cause of treatment-resistance (Goff et al. 2010).

Substance abuse may also cause or contribute to treatment resistance. Nevertheless, treatment-resistant schizophrenia may be associated with neurobiological factors (e.g., morphological brain abnormalities), may depend on environmental factors (e.g., unfavourable familial atmosphere, high expressed emotions) or pharmacodynamic reasons. Multidimensional evaluation of treatment-resistant

schizophrenia 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 treatment-resistant schizophrenia, the target symptoms should be precisely defined. Compliance should be ensured, if necessary by checking drug concentrations.

#### FGAs

No new evidence for FGAs and treatment-resistant schizophrenia published since the release of the last version of these guidelines could be found. Meta-analyses from many clinical trials and reviews indicate that, in terms of efficacy, FGAs are interchangeable and that changing from one FGA to another FGA resulted in fewer than 5% of the patients achieving a satisfying therapeutic response (Conley and Buchanan 1997; Conley and Kelly 2001; Janicak et al. 1993; Kane et al. 1988a; Kinon et al. 1993). Doses higher than 400 CPZ (blocking of 80–90% of D2 receptors) do not lead to more efficacy in treatment-resistant schizophrenia, but do cause more side effects, with an emphasis on extrapyramidal motor symptoms (Kane 1994).

#### SGAs

SGAs, especially clozapine, were discussed to be more effective in the management of treatment-resistant schizophrenia than FGAs.

An open, multicenter RCT (CUtLASS 2 trial), showed an advantage of clozapine in reducing positive and negative symptoms in treatment-resistant schizophrenia compared to four established SGAs (ziprasidone, olanzapine, quetiapine, amisulpride). However, clozapine did not differ from these SGAs with regard to quality of life, but presented a trend towards inducing fewer motor side effects (Lewis et al. 2006).

Phase II of the CATIE-study (CATIE-II) (McEvoy et al. 2006) investigated patients who discontinued treatment with olanzapine, quetiapine, risperidone or ziprasidone in CATIE-I/IB due to lacking efficacy. A total of 99 patients were randomly assigned to a blinded treatment with olanzapine/quetiapine/risperidone (but not to the drug the individual patients received in the first trial), or to an open-label treatment with clozapine. Patients treated with clozapine underwent a significantly longer treatment period time before treatment discontinuation for any reason as well as a greater improvement when compared to quetiapine and risperidone, but not to olanzapine (McEvoy et al. 2006). However,



olanzapine was used at a higher dosage compared to the other psychotics in the CATIE study (Lieberman et al. 2005; Naber and Lambert 2009).

In the last part of the CATIE-study (CATIE-III), patients who had discontinued antipsychotic treatment in phases 1 and 2, were included in a phase in which they could select one of nine antipsychotic regimens (aripiprazole, clozapine, olanzapine, perphenazine, quetiapine, risperidone, ziprasidone, long-acting injectable fluphenazine decanoate) in monotherapy or a combination of any two drugs (Stroup et al. 2009). Discontinuation rates due to lack of efficacy were lower for clozapine (5%), risperidone, quetiapine, and ziprasidone (0–5%) than for olanzapine, aripiprazole and combination treatment (13–18%) (McIlwain et al. 2011; Stroup et al. 2009).

These study extensions indicate that clozapine (and olanzapine) are promising in schizophrenia patients who do not respond to treatment with other antipsychotics, but the limited sample sizes and the methodological limitations of the primary studies are important confounders.

A meta-analysis of 12 controlled trials (involving 1916 independent patients), showed that SGAs exhibit superiority in the management of treatment-resistant schizophrenia compared to FGAs. However, the results, except for clozapine, are inconclusive (Chakos et al. 2001).

*Amisulpride.* Amisulpride is frequently used in combination with another SGA in different clinical trials (see below), but studies with amisulpride monotherapy remain to be lacking. One small (seven patients) study indicated that switching to amisulpride monotherapy (final mean dosage was  $1085.7 \pm 226.8$  mg/day) in cases of treatment-resistant schizophrenia might be promising (Kontaxakis et al. 2006).

*Aripiprazole.* In one study, only patients who completed an open-label period (olanzapine or risperidone) and failed to respond to this medication entered a 6-week, double-blind treatment phase with aripiprazole or perphenazine. Both drugs improved psychopathology in this treatment-resistant group, but perphenazine resulted in more motor side effects (Kane et al. 2007c).

A case report with very high dosages of aripiprazole (60 mg/day) lead to a significant improvement of psychopathology with no increase in side effects (Duggal and Mendhekar 2006). Furthermore, aripiprazole has been used in some combination trials with clozapine in treatment resistant-schizophrenia (see below).

*Clozapine.* Clozapine has been shown to be the most effective antipsychotic agent in treatment-resistant schizophrenia (Buchanan et al. 1998; Essock et al. 1996; Hong et al. 1997; Kane et al. 1988a; Kumra et al. 2008; NICE 2002; Wahlbeck et al. 1999). Its side effect profile in the range between metabolic dysfunctions and severe agranulocytosis is an important limitation of its first-line usages in not-treatment-resistant schizophrenia.

Clozapine was superior to some other SGAs, not including olanzapine, in the CATIE-II and CULASS-2 trials (Lewis et al. 2006; McEvoy et al. 2006). As outlined in the sections of the other drugs, the superiority of clozapine compared to other SGAs and FGAs has been shown in many studies, but the evidence in comparison with olanzapine has been inconsistent. However, different methodological problems (small sample sizes, low dosage range of clozapine, incorrect definition of treatment-resistance) may explain the non-inferiority of olanzapine compared to clozapine (Buchanan et al. 2010).

In other guidelines, clozapine has been recommended as first-line treatment in treatment-resistant schizophrenia (Buchanan et al. 2010; DGPPN 2006; Lehman et al. 2004), but a recent meta-analysis using the Cochrane criteria failed to show the superiority of clozapine over other SGAs (Asenjo Lobos et al. 2010). However, 21 of 27 trials included in this review were with either olanzapine or risperidone as comparator. Moreover, this review did not focus on treatment-resistant schizophrenia patients and the mean clozapine dosages may have been too low.

In most studies and in clinical practice, the mean dosage of clozapine may frequently be too low to manage treatment-resistant schizophrenia. We recommended in the last version of these guidelines a mean dosage of 400 mg/day clozapine and highlighted that some patients might respond to 100–200 mg/day, whereas other patients may need doses of up to 900 mg/day (Falkai et al. 2005). The recent PORT-guidelines discussed the importance of an adequate dosage range of clozapine (300–800 mg/day) and of sufficient treatment duration (at least 8 weeks) (Buchanan et al. 2010). Furthermore, the authors of the PORT guidelines recommend obtaining plasma levels above 350 ng/ml in patients who have failed to demonstrate an adequate response following treatment with clozapine (Buchanan et al. 2010). This PORT evidence statement is supported by five studies showing an association of high clozapine blood levels and a positive symptom response (Buchanan et al. 2010; Hasegawa et al. 1993; Kronig et al. 1995; Perry et al. 1991; Potkin et al. 1994; VanderZwaag et al. 1996). However, it should be recognized that clozapine is not popular in all countries. For example, one analyses showed that the

prescription rates of clozapine are very variable among different Asian countries (Xiang et al. 2011).

*Olanzapine.* In two meta-analyses, olanzapine was superior to FGAs in the management of treatment-resistant schizophrenia (Chakos et al. 2001; Leucht et al. 2009b). This has also been demonstrated by different RCTs (Altamura et al. 2002; Breier and Hamilton 1999; Conley et al. 1998) and in open-label studies (Chiu et al. 2003; Karagianis et al. 2003; Lindenmayer et al. 2002; Martin et al. 1997). One RCT indicated the same efficacy in the management of treatment resistant for olanzapine compared to haloperidol (Buchanan et al. 2005) and to clozapine (Tollefson et al. 2001). Switching from clozapine to olanzapine led to response in more than 40% in prospective studies (Dossenbach et al. 2000; Henderson et al. 1998). However, recent studies found that high dosages of olanzapine have, at most, the same efficacy or are inferior to clozapine in treatment-resistant schizophrenia (Bitter et al. 2004; Kumra et al. 2008; Meltzer et al. 2008b).

*Quetiapine.* Schizophrenia patients, who had only a partial response to fluphenazine treatment, demonstrated a significantly higher response rate to quetiapine than to haloperidol in a 12-week RCT (Emsley et al. 2000). In addition to this, a double-blind 12-week RCT, comparing quetiapine, risperidone and fluphenazine in a sample of treatment-resistant schizophrenia patients, showed more treatment adherence with both SGAs, but no differences in the psychopathology change among the three different drugs (Conley et al. 2005). A recently published randomized parallel-group, fixed-dose, clinical trial in patients who failed to demonstrate an initial therapeutic response during a 4-week run-in phase with quetiapine at 600 mg/day and were then treated with either 600 mg/day for 8 weeks or alternatively with 1200 mg/day, did not show an improved efficacy of the higher quetiapine dosage (Lindenmayer et al. 2011).

*Risperidone.* Risperidone was superior to haloperidol with regard to improvements of psychopathology and cognition (Green et al. 1997; Kee et al. 1998; Wirshing et al. 1999; Zhang et al. 2001) and showed the same efficacy in improving positive symptoms compared with olanzapine and clozapine in treatment-resistant schizophrenia (Bondolfi et al. 1998; Volavka et al. 2002). However, other RCTs have shown an inferiority of risperidone compared to

clozapine in such patients (Azorin et al. 2001; Breier et al. 1999). In a multicenter, randomized, double-blind, parallel-group study with schizophrenia patients who had failed to undergo an adequate response to antipsychotic treatment within the previous 6 months and who had not responded positively to haloperidol, sertindole and risperidone showed the same efficacy in improving overall psychopathology (Kane et al. 2011b).

*Ziprasidone.* A recently published 18-week randomized, flexible-dose, double-blind trial compared ziprasidone and clozapine in treatment-resistant schizophrenia patients and showed comparable efficacy of both drugs, with a more favourable metabolic profile of ziprasidone (Sacchetti et al. 2009). A prospective, 1-year open-label study in patients with treatment-resistant schizophrenia revealed ziprasidone to be effective and well-tolerated (Loebel et al. 2007). Furthermore, a symptom improvement in stable but symptomatic schizophrenia was achieved by switching from FGAs/olanzapine/risperidone to ziprasidone (Weiden et al. 2003). Additionally, ziprasidone is one frequently-used combination partner of clozapine in treatment-resistant schizophrenia (see below).

*Zotepine.* In a small double-blind RCT, zotepine was as effective as clozapine in the improvement of positive/negative symptoms and in some cognitive domains (Meyer-Lindenberg et al. 1997). In an open-label study a moderate global improvement after 1 year of treatment was noted in treatment refractory patients treated with zotepine (Harada et al. 1991). A more recent open-label study with 30 treatment-refractory patients showed that treatment with zotepine resulted in a decrease in all PANSS subscores (Hashimoto et al. 2006).

#### *General recommendations*

The first step in the clinical management of treatment-resistant schizophrenia 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 (see part 3 of these guidelines), 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 2006; Lehman et al. 2004; NICE 2002; RANZCP 2005).

The treatment with one antipsychotic should be maintained for a sufficient long time period and a continuous re-evaluation of symptomatology is necessary. It should be considered that sometimes symptoms can continue to improve over the course of 6 months and that, if the patient is showing a partial response to treatment, expert consensus recommended to extend the duration of the trial somewhat to 4–10 weeks for the initial antipsychotic and 5–11 weeks for the second antipsychotic prescribed (Kane et al. 2003). If a patient is having little or no response to the initial or to the second antipsychotic prescribed, the expert committee recommended waiting for between a minimum of 3 weeks and a maximum of 6 weeks before making a major change in treatment regimen (Kane et al. 2003). One analysis of seven pooled RCTs (including studies with amisulpride, risperidone, haloperidol and flupenthixol) indicated that, if a patient with schizophrenia shows no symptom reduction in the first two weeks of antipsychotic treatment, a further improvement after four weeks seems to be unlikely (Leucht et al. 2007a). However, large RTCs with other antipsychotic drugs are needed to address this question more specifically in order to allow an evidence-based statement.

### Summary statement

- In cases of treatment-resistant schizophrenia treatment adherence needs to be controlled
- A switch from an initially unsuccessful FGA to another FGA seems to be ineffective (*Category of Evidence A, Recommendation grade 1*) and a switch to an SGA should instead be taken into consideration (*Category of Evidence B, Recommendation grade 3*)
- In individuals with a diagnosed treatment-resistant schizophrenia according to recent definitions, clozapine should be considered as first-line treatment (*Category of Evidence B, Recommendation grade 3*)
- Dependent on the national regulations, patients treated with clozapine should be monitored frequently with regard to haematological side effects/EEG-alterations/cardiac side effects, and a dosage range of 100–900 mg or a blood level of more than 350 ng/ml should be aimed for (*Category of Evidence B/C3, Recommendation grades 3/4*) (Buchanan et al. 2010; Falkai et al. 2005)
- In cases of clozapine intolerance a switch to another SGA, preferentially olanzapine or risperidone, should be performed (*Category of Evidence B, Recommendation grade 3*)
- There are few data to support amisulpride, aripiprazole and quetiapine being effective in

monotherapy for the management of treatment-resistant schizophrenia (*Category of Evidence C, Recommendation grade 4*)

- There is no evidence for the efficacy of asenapine, iloperidone, lurasidone and paliperidone in the treatment of these patients (*Category of Evidence F*)
- Dose escalation, unless side effects lead to an earlier drug switching, was previously recommended by an expert consensus statement (Kane et al. 2003), but recent studies do not support this statement (see above)
- Apart from these treatment strategies, special psychotherapeutic (especially cognitive behavioural therapy) and psychosocial interventions to enhance the therapeutic alliance (e.g., adherence therapy, psychoeducation and family interventions) and the usage of long-acting depot antipsychotics should be taken into consideration

### Switching strategies

In the literature three main strategies for switching from one antipsychotic agent to another are described (Falkai et al. 2005), but few studies have discussed this question with an appropriate methodological approach:

1. Cross-titration (gradually tapering off the dose of the first antipsychotic while gradually increasing the dose of the second).
2. Overlap and taper (continuing the same dose of the first antipsychotic while gradually increasing to a therapeutic level and then tapering the first).
3. Abrupt change of the antipsychotics.

The first two switching modalities, in particular, are considered as equally effective and tolerable (Kane et al. 2003), and cross-titration is preferred among guidelines. With regard to the switching to clozapine, there are different possibilities. Tapering the first medication before starting with clozapine in order to reduce the probability of haematological side effects is seen alongside cross-titration, probably reflecting the need for relatively slow titration of clozapine (Kane et al. 2003).

The results of switching between different SGAs are inconsistent and one post-hoc analysis of the CATIE-I study indicated that the probability of experiencing a benefit from a medication switch is a function of both the medication being switched from and the medication being switched to (Essock et al. 2006). Furthermore, switching had only modest success rates among the medications used in CATIE-I (Essock et al. 2006). Another analysis of the CATIE-results showed no difference between

switching and staying on a particular drug for neurocognition, quality of life, neurological side effects, weight (exception for olanzapine) and health cost among the investigated drugs (Rosenheck et al. 2009).

A post-hoc analysis of a naturalistic 1-year open-label randomized cost-effectiveness study of atypical and conventional antipsychotics revealed that individuals who switched antipsychotics were significantly more likely to use a range of acute care services, and did so significantly earlier, compared with those remaining on their initial regimens (Faries et al. 2009).

One open-label study showed only a modest effect of switching from one SGA to another (Suzuki et al. 2007), while another open-label study indicated that the switch from risperidone to olanzapine might lead to an improvement in clinical and social parameters (Faries et al. 2008). An additional open-label study showed that the switch from olanzapine to risperidone was associated with significant improvement in symptomatology, independent of the switching strategy, but that gradual reduction of olanzapine was associated with higher rates of retention compared with abrupt or less gradual discontinuation (Ganguli et al. 2008). A randomized, 14-week, open-label trial compared two switching strategies (A: add-on of aripiprazole on a current regimen, wait for 4 weeks, and the tapering of prior antipsychotics; B: add-on of aripiprazole and the simultaneous tapering of prior antipsychotics in patients with schizophrenia) showing that both strategies were effective, safe and well tolerated (Takeuchi et al. 2008). A 12-week multicenter naturalistic open-label switching study evaluated the overall clinical efficacy, safety, and tolerability of aripiprazole in stable patients and the symptom worsening when switching from D2 receptor antagonists to aripiprazole (Kim et al. 2009). Symptomatically stable patients showed, in this naturalistic study, a clinically meaningful treatment benefit after being switched to aripiprazole (Kim et al. 2009). Another study compared an aripiprazole titrated-dose (starting dose 5 mg/day) or fixed-dose (dose 15 mg/day) switching strategy with risperidone down-tapering and showed no difference between both strategies (Ryckmans et al. 2009).

An analysis of three open-label, flexible dose, 1-year extension studies showed that a switch from a FGA, olanzapine or risperidone to ziprasidone resulted in significant improvement in metabolic parameters and in movement disorder assessments (Simpson et al. 2008). A 6-week open-label, randomized study of 54 patients with persistent schizophrenia or schizoaffective disorder compared three strategies for switching from FGAs to ziprasidone (A: abrupt discontinuation of conventional antipsychotics on day 1; B: fast taper:

50% of conventional antipsychotic dosage on days 1 through 7, followed by discontinuation; C: slow taper: 100% of conventional antipsychotic dosage on days 1 and 2, followed by 50% on days 3 through 7, then discontinuation) (Stip et al. 2010). In the early study phase, the slow-taper strategy was superior to the other strategies (reduction of total psychopathology), but at the study endpoint no significant differences between the three strategies could be detected (Stip et al. 2010).

### Summary statements

- There is insufficient evidence to provide clear general treatment strategies (*Category of Evidence D, Recommendation grade 5*)
- Some studies indicate that a switch from FGAs/SGAs to certain SGAs might be promising (*Category of Evidence C, Recommendation grade 4*)
- In the future, large RCTs are needed to address the question as to which switching strategy might be best and how to switch from one antipsychotic to another

#### *Switching from antipsychotic polypharmacy to monotherapy*

Antipsychotic monotherapy is recommended through all guidelines but, in clinical practice more, than two-thirds of schizophrenia patients are treated with a combination of two or more antipsychotic agents (see below). One RCT addressed this question, showing that the switch from antipsychotic polypharmacy to monotherapy leads to more treatment discontinuation on the one hand but, on the other hand, successful treatment switching in two-thirds of the patients. Furthermore, the switch to monotherapy was associated with significant weight loss, without worsening of symptom control and without an increase in hospitalisation (Essock et al. 2011). The authors compare these findings with the results of a nonrandomized open-label trial showing that discontinuation of polypharmacy with a switch to monotherapy resulted in 54% remaining stable, 23% showing symptom improvement and 23% showing a worsening of symptoms (Essock et al. 2011; Suzuki et al. 2004).

In conclusion, some positive evidence exists for a switch from antipsychotic polypharmacy to antipsychotic monotherapy (*Category of Evidence B/C, Recommendation grades 3/4*).

### Combining antipsychotics

In general, antipsychotic monotherapy should be the first-line treatment in schizophrenia and the

combination of antipsychotics should be a strategy of last resort for treatment-resistant schizophrenia (Barnes and Paton 2011). However, the combination of two or more antipsychotics in clinical practice is a frequently observed phenomenon (10–50%) (Barnes and Paton 2011; Clark et al. 2002; Freudenreich and Goff 2002) and this trend towards polypharmacy in schizophrenia patients is increasing (Ganguly et al. 2004; Paton et al. 2008). Despite this trend, few RCTs with a good study design and appropriate sample-sizes have been conducted to evaluate the efficacy of combining strategies (Freudenreich and Goff 2002). Problems following antipsychotic polypharmacy are the risk of non-adherence, increasing side effects, drug-to-drug interactions and the exposure to high-dosage antipsychotic medications (Barnes and Paton 2011; Paton et al. 2008). Furthermore, other neuroactive drugs, like antidepressants, anxiolytics and sedatives/hypnotics, are commonly used concomitantly during an antipsychotic treatment. For example, one post-hoc analysis of the CATIE sample showed that 14.6% of schizophrenia patients received concomitant antidepressants, 13.7% received concomitant anxiolytics and 11.2% received concomitant sedative/hypnotics (Chakos et al. 2011). These combinations raise the same problems (safety, interaction, unknown efficacy) as discussed for the combination treatment of different antipsychotics.

A large meta-analysis investigating antipsychotic combinations for schizophrenia (Cochrane Review) is planned, but has not yet been published (Maayan et al. 2011). Another Cochrane meta-analysis investigated the combination of clozapine with different antipsychotic drugs for treatment resistant-schizophrenia and displayed that there is only limited evidence for this combination and that no combination strategy is superior to the other (Cipriani et al. 2009). One further meta-analysis from the Cochrane schizophrenia groups compared antipsychotic combination therapy with monotherapy in schizophrenia showing that antipsychotic cotreatment was superior to monotherapy with regard to the number needed to treat and the clinical global impression (Correll et al. 2009). Furthermore, the authors detected, that this superiority was apparent in studies lasting longer than 10 weeks, but not in studies with a duration smaller than 10 weeks. Another important point to recognise is that combination from the beginning of the antipsychotic treatment and that the combination with clozapine was superior to other combination strategies (Correll et al. 2009). However, data of specific psychopathology and adverse event data were insufficient and it was not possible to determine a definite statement that combinations using antipsychotics other than clozapine are more effective

than monotherapy. Furthermore, this meta-analysis was biased by a regional effect in that patients from Chinese studies predominated in many of the trials with characteristics that were also associated with superiority of antipsychotic polypharmacy (Correll et al. 2009).

A systematic review of current evidence of the combination therapy with non-clozapine atypical antipsychotics up until 2007 found that there is lacking evidence for combination strategies and that, due to a lack of safety data, caution is recommended (Chan and Sweeting 2007). Furthermore, one systematic review stated that there is a lack of convincing evidence for a superior benefit for an antipsychotic combination when monotherapy has proven to be ineffective (Barnes and Paton 2011), which is in line with previously published reviews (Pandurangi and Dalkilic 2008; Wolff-Menzler et al. 2010).

In one multicenter, double-blind, 16-week, placebo-controlled study with 323 schizophrenia or schizoaffective patients, the combination of aripiprazole (2–15 mg/day) or placebo in addition to a stable regimen of quetiapine (400–800 mg/day) or risperidone (4–8 mg/day) was investigated (Kane et al. 2009a). Combining aripiprazole with either risperidone or quetiapine did not lead to a significant improvement in psychopathology compared to placebo, but was well tolerated and reduced prolactin levels in the risperidone group (Kane et al. 2009a). A small open-label study investigated 17 schizophrenia patients, who failed to respond to a sequential monotherapy with olanzapine, quetiapine and risperidone and who were subsequently treated with a combination therapy with olanzapine plus risperidone, found a significant improvement in symptomatology (Suzuki et al. 2008).

Antipsychotic polypharmacy involving clozapine is very common, but the results of these combination treatments are inconsistent. The combination of clozapine with chlorpromazine in treatment-resistant schizophrenia patients revealed no benefit (Potter et al. 1989), but the combination of clozapine and sulpiride improved psychopathology and was superior to placebo (Shiloh et al. 1997). In a small study, schizophrenia patients on a steady dose of clozapine randomly received either the combination of clozapine/amisulpride (400 mg/day,  $n = 7$ ), clozapine/amisulpride (600 mg/day,  $n = 6$ ) or clozapine/placebo ( $n = 3$ ) (Assion et al. 2008). The combination with amisulpride improved the secondary outcome parameters (GAF, CGI, MARDS), but failed to reduce the BPRS total score due to the lack of power of the study (Assion et al. 2008). Another small study ( $n = 50$ ) compared the effectiveness and tolerability of the combination of amisulpride/clozapine with the combination of quetiapine/clozapine in patients who

were only partially responsive to clozapine monotherapy and revealed that both combinations are effective with some superiority for the amisulpride/clozapine combination (Genc et al. 2007).

The combination of clozapine and risperidone has been shown to be inferior to superior compared to the combination of clozapine and placebo or to clozapine alone (Akdede et al. 2006; Anil Yagcioglu et al. 2005; Freudenreich et al. 2007; Honer et al. 2006; Josiassen et al. 2005; Weiner et al. 2010). In another small randomized trial ( $n = 24$ ), the combinations of clozapine/ziprasidone and clozapine/risperidone were effective, with a slight increase of akathisia in the clozapine/ziprasidone group (Kuwilsky et al. 2010). Aripiprazole was combined with clozapine in two double-blind, placebo controlled RCTs and this combination did not improve total symptom severity, but improved negative symptoms, CGI and reduced metabolic risk factors (Chang et al. 2008; Fleischhacker et al. 2010).

One case study with three cases indicated that the combination of olanzapine/sulpiride might improve positive and negative symptoms (Raskin et al. 2000), but a small RCT could not confirm these findings (Kotler et al. 2004).

We could not identify a double-blind, placebo-controlled RCT for the combination clozapine/ziprasidone, but case series and open-label studies have presented inconclusive results that this combination might be a promising treatment alternative (Henderson et al. 2009b; Ziegenbein and Calliess 2006).

A 10-week placebo-controlled, double-blind crossover study examined the impact of aripiprazole on weight, lipids, glucose metabolism, and psychopathology in overweight and obese schizophrenia and schizoaffective disorder subjects treated with a stable dose of olanzapine and showed that the combination olanzapine/aripiprazole can improve some, but not all, metabolic parameters (Henderson et al. 2009a).

The combination of the FGA pimozide and clozapine was shown to improve psychotic symptoms with an increase of side effects in open trials (Freudenreich and Goff 2002; Miller and Craig 2002). In a recent double-blind, placebo-controlled, parallel-designed 12-week trial, pimozide was found to be not better than placebo in combination with clozapine in reducing positive, negative and general psychopathology scores (Friedman et al. 2011).

In some countries (e.g., France or Belgium: Bret et al. 2009; Broekema et al. 2007) the combination of cyamemazine (cyamemazine), a typical antipsychotic with anxiolytic properties, with other antipsychotics (especially risperidone) is common in schizophrenia patients to reduce agitation and anxiety (Lancelin et al. 2010). One European study

indicates that cyamemazine is prescribed up to 7.1% concomitantly to other antipsychotics (Broekema et al. 2007). However, we were not able to detect open studies or RCTs investigating this combination strategy in schizophrenia patients.

One final important, but underrepresented topic is the concomitant prescription of long-acting injectables (see part 2 of these guidelines) and oral antipsychotics. Long-acting injectables are discussed to be a monotherapeutic alternative to oral medication, but one study shows that almost half of the patients receiving long-acting injectables are concomitantly treated with oral antipsychotics (Aggarwal et al. 2012). This form of combination treatment needs to be investigated in future prospective studies to identify the benefits and risks of this strategy (Aggarwal et al. 2012).

### Recommendations and summary statements

There is still only limited evidence for the efficacy of combining different antipsychotics in treatment-resistant schizophrenia. An important question is whether to add one antipsychotic to an ongoing treatment or to lower the dosage of the first antipsychotic agent when combining with another agent. The first strategy would lead to an increase of CPZ, whereas the second strategy would result in the same effective CPZ, or even in lower dosages. Due to this important point, combination studies are often not comparable, meaning that adequately designed RCTs are needed to address this question.

Large, double-blind and placebo controlled RCTs and head-to-head comparisons of different SGAs are still lacking. Furthermore, there is only limited knowledge about side effects and drug-interactions when combining different antipsychotics.

- The combination of clozapine with another SGA (possibly risperidone) might have some advantage compared to monotherapy (*Category of Evidence C, Recommendation grade 4*)
- Antipsychotic monotherapy should be the preferential treatment strategy and, in cases of preferential-resistant schizophrenia, the recommendations set out in our and other guidelines for the management of this disease state should be followed (*Category of Evidence C3, Recommendation grade 4*)
- In certain individual cases an antipsychotic combination therapy might be advisable (*Category of Evidence C3, Recommendation grade 4*) and, in these cases, side effects and clinical responses should be monitored at frequent intervals (*Category of Evidence C3, Recommendation grade 4*)

### Augmentation strategies

Augmentation strategies with lithium, anticonvulsants, benzodiazepines, beta-blockers, *N*-methyl-D-aspartate (NMDA) receptor agonists, cholinergic agonists and others have been investigated in schizophrenia patients, but only limited efficacy for these strategies was available in the last version of these guidelines. The recent PORT guidelines described only little or no evidence to support the efficacy of lithium and any anticonvulsant for the management of treatment-resistant positive symptoms (Buchanan et al. 2010). However, differences among the anticonvulsive drugs/mood stabilizers and their combination partners should be considered when judging evidence.

#### *Mood stabilizers and anticonvulsants*

**Carbamazepine.** The combination of carbamazepine and haloperidol resulted in a worsening of symptoms in one study (Hesslinger et al. 1999), but results from a small case series indicate that carbamazepine has the potential to improve symptoms in treatment-resistant schizophrenia (Simhandl et al. 1996). A meta-analysis from the Cochrane schizophrenia group concluded that carbamazepine cannot be recommended for the routine clinical use (treatment or augmentation) in patients with schizophrenia (Leucht et al. 2007c). In this meta-analysis (Leucht et al. 2007c), the majority of studies showed a non-superiority of carbamazepine in comparison with placebo.

**In summary,** there is negative evidence for the usage of carbamazepine in the general treatment of schizophrenia (*Category of Evidence E*) but, for patients who had positively responded to carbamazepine and in other specific circumstances (e.g., aggressive behaviour), a trial of the drug might be warranted (*Category of Evidence C, Recommendation grade 4*) (Leucht et al. 2007c; Luchins 1984; Okuma et al. 1989; Thibaut and Colonna 1993b).

**Lamotrigine.** Early case reports displayed that the combination of lamotrigine and clozapine reduced psychotic symptoms (Dursun and Deakin 2001; Dursun et al. 1999; Saba et al. 2002) and two RCTs showed that lamotrigine was superior to placebo when combined with clozapine or different FGAs and SGAs (Kremer et al. 2004; Tiihonen et al. 2003). A 2007 published, 24-week double-blind, randomized, placebo-controlled trial explored the efficacy of a lamotrigine add-on in treatment-resistant schizophrenia patients who were treated with clozapine. Lamotrigine had a positive effect on negative,

positive and general psychopathological symptomatology and on some cognitive domains (Zoccali et al. 2007). One meta-analysis including five different trials indicated that lamotrigine augmentation may be an effective treatment for patients with clozapine-resistant schizophrenia (Tiihonen et al. 2009), whereas another meta-analysis is more reluctant (Premkumar and Pick 2006).

An analysis of two randomized, double-blind, 12-week, parallel-group trials investigating flexibly dosed lamotrigine versus placebo as an add-on treatment in schizophrenia patients with stable, residual psychotic symptoms did not support the additional use of lamotrigine for treatment in combination with atypical antipsychotics (Goff et al. 2007). A more recent double-blind randomized trial with three treatment groups (A: lamotrigine; B: divalproex sodium; C: placebo) did not reveal a significant difference among groups with regard to psychopathology, quality of life and other scores (Glick et al. 2009). This is in line with older studies showing inconsistent and negative results for the combination of lamotrigine with risperidone, haloperidol, olanzapine or flupenthixol (Dursun and Deakin 2001; Kolivakis et al. 2004).

**In summary,** there is inconsistent evidence for the usage of lamotrigine in schizophrenia (*Category of Evidence D, Recommendation grade 5*), whereas the combination of lamotrigine with clozapine in treatment-resistant schizophrenia might improve symptoms (*Category of Evidence B, Recommendation grade 3*).

**Lithium.** Two meta-analyses evaluating the efficacy of lithium revealed no evidence that lithium alone is an effective treatment for patients with schizophrenia, and only inconclusive results for it as an add-on treatment (Leucht et al. 2004, 2007b). With regard to the side effect profile of lithium and the inconclusive data (*Category of Evidence D/E*), an add-on treatment with lithium in schizophrenia cannot be recommended. However, in patients with mood symptoms and in schizoaffective patients, there is some evidence for the efficacy of lithium augmentation (Leucht et al. 2004) (*Category of Evidence B, Recommendation grade 3*).

**Pregabalin.** In one case report and in a case series of 11 schizophrenia patients with treatment resistant anxiety, an augmentation with pregabalin resulted in an improvement in general psychopathology, positive and negative symptoms and in a reduction of concomitant benzodiazepine treatment (Englisch et al. 2010; Schonfeldt-Lecuona et al. 2009).

There is some limited evidence for the benefits add-on treatment with pregabalin in schizophrenia patients with treatment-resistant anxiety (*Category of Evidence C2, Recommendation grade 4*).

**Topiramate.** The combination of topiramate and clozapine in treatment-resistant schizophrenia showed inconclusive results – in two studies the add-on of topiramate was superior to placebo (Afshar et al. 2009; Tiihonen et al. 2005), whereas other studies with a larger sample size and a longer treatment period could not replicate this finding (Behdani et al. 2011; Muscatello et al. 2011). A 12-week naturalistic, open-label study showed a positive effect of the combination of clozapine/topiramate with regard to psychopathology and metabolic parameters (Hahn et al. 2010). However, no beneficial effect of topiramate added to an ongoing treatment with clozapine, olanzapine, risperidone or flupenthixol was seen in a naturalistic case-series outcome study (Dursun and Deakin 2001).

A 12-week, randomized, placebo-controlled prospective study investigated the efficacy of 100 or 200 mg/day topiramate on weight gain in hospitalized schizophrenia patients and found that a 200-mg/day dose of topiramate significantly decreased body weight, body mass index, waist measurement, and hip measurement compared to a dose of 100 mg/day and placebo (Ko et al. 2005). In a 12-week, randomized, open-label, parallel-group trial of topiramate in outpatients suffering from schizophrenia, topiramate add-on limited weight gain in patients treated with olanzapine (Kim et al. 2006). However, as a relevant side effect, a dose-dependent depressogenic effect of topiramate in patients with a personal or family history for mental illness has been described (Celano et al. 2011; Mula et al. 2003). The use of valproate in schizoaffective patients is subject of a controversial discussion and the empirical basis for the application of valproate is small (Schwarz et al. 2008).

**In summary,** there are only inconsistent results for the add-on treatment of topiramate (*Category of Evidence D, Recommendation grade 5*) in treatment-resistant schizophrenia, but there is limited positive evidence for the efficacy of topiramate in reducing weight gain in schizophrenia (*Category of Evidence B, Recommendation grade 3*).

**Valproate.** The combination of valproate and haloperidol, olanzapine or risperidone in different RCTs demonstrated inconsistent results concerning negative symptoms and clinical global impression (Wassef et al. 2000), hostility (Citrome et al. 2004; Dose et al. 1998), treatment-resistant schizophrenia (Morinigo et al. 1989) and more rapid onset of

action (Casey et al. 2003), but one study did not find any benefit of an add-on of valproate (Hesslinger et al. 1999). In an 8-week open-label randomized parallel-group clinical trial in hospitalized adults diagnosed with schizophrenia and hostility, the combination of valproate/risperidone was not superior to a risperidone monotherapy (Citrome et al. 2007). A large 12-week randomized, double-blind, parallel-group tested the efficacy of the following four combinations for treatment of acute schizophrenia: A: olanzapine/placebo; B: olanzapine/valproate; C: risperidone/placebo; D: risperidone/valproate (Casey et al. 2009). All four treatments were effective in the reduction of the PANSS total score, with no difference among groups. However, with regard to the PANSS negative score, antipsychotic monotherapy was superior to the combination therapy (Casey et al. 2009). In another 12-week, double-blind randomized trial, no difference between the add-on therapy with valproate, lamotrigine and placebo could be detected (Glick et al. 2009). However, one small open-label study investigated the add-on treatment of valproate on atypical antipsychotics for severely ill patient needing treatment in a closed ward and showed an improvement in global functioning and psychopathology (Suzuki et al. 2009). One meta-analysis from the Cochrane schizophrenia group found inconclusive data for valproate monotherapy in schizophrenia and for a positive effect of valproate on aggression and tardive dyskinesia (Schwarz et al. 2008).

In summary, there is no general evidence for the usage of valproate in schizophrenia (*Category of Evidence E*), but the combination of valproate and antipsychotics might have an effect in severely ill patients, especially by targeting aggression and hostility (*Category of Evidence D, Recommendation grade 5*).

#### *Antidepressive agents*

This was partly described in a previous section. There is only very limited evidence for the efficacy of antidepressants on negative symptoms (*Category of Evidence D, Recommendation grade 5*), but it appears that the augmentation with mirtazapine might be promising when combined with FGAs (*Category of Evidence B, Recommendation grade 3*). An augmentation with antidepressive agents should be performed carefully because the increase of adrenergic and dopaminergic transmission can result in an exacerbation of psychosis (Siris et al. 2000). However, adequate RCTs testing the efficacy of add-on treatment with antidepressive agents in treatment-resistant schizophrenia are lacking (*Category of Evidence F*) and, therefore, their usage cannot be recommended.



*Benzodiazepines*

In a review of double-blind studies, benzodiazepines administered in monotherapy showed in most, but not all, of the studies a superior effect compared to placebo (Wolkowitz and Pickar 1991). A meta-analysis performed by the Cochrane schizophrenia group included 11 studies and addressed the question of whether benzodiazepines are effective in the treatment of psychosis-induced aggression or agitation (Gillies et al. 2005). The data were inconclusive and large RCTs are lacking, but benzodiazepines do not induce motor side effects which may provide a reason to choose them over the older antipsychotics in patients suffering from aggression and agitation (Gillies et al. 2005). This is in line with an older review showing that seven of 16 double-blind studies revealed a positive effect on anxiety, agitation, psychosis and global impairment following benzodiazepine add-on treatment (Wolkowitz and Pickar 1991).

Furthermore, data from two small RCTs found benzodiazepines (clonazepam) being superior to placebo in reducing antipsychotic-induced acute akathisia (Lima et al. 2002). One double-blind study demonstrated that there are advantages in improving akathisia and psychotic excitement using the combination of the FGA haloperidol and the benzodiazepine clonazepam (Altamura et al. 1987).

A case series showed a successful reversal of catatonia in two patients treated with benzodiazepines (Ungvari et al. 1994), but lorazepam failed to show efficacy in a randomized, double-blind, placebo-controlled cross-over study with catatonic patients (Ungvari et al. 1999). Despite the fact that no published RCT exists for acute catatonia, results from many open-label studies and clinical experience have had led to a consensus for benzodiazepines as first-line treatment of acute catatonia (England et al. 2011; Francis 2010; Gibson and Walcott 2008).

Older studies investigating benzodiazepines as an add-on treatment to antipsychotic treatment also showed inconsistent results (Hanlon et al. 1970; Holden 1968; Pato et al. 1989; Ruskin et al. 1979; Wolkowitz and Pickar 1991; Wolkowitz et al. 1992).

In general, lorazepam may provide some advantages for combination approaches because good absorption of the oral preparation and less muscle relaxation was observed than with other benzodiazepines (Lehman et al. 2004). However, as discussed before an increased mortality following the combination treatment of antipsychotics with long-acting benzodiazepines has been described in a Danish population study (Baandrup et al. 2010).

*NMDA-agonists and other glutamatergic drugs*

Based on the glutamate hypothesis of schizophrenia, therapeutic approaches with glutamate-modelling agents have been tested in some studies. One large ( $n = 138$  patients) double-blind, placebo-controlled study compared the adjunctive treatment of either memantine or placebo to the standard SGAs treatment and did not find a significant difference between both groups (Lieberman et al. 2009). Another smaller ( $n = 21$ ) double-blind, placebo-controlled study with treatment-resistant schizophrenia patients tested the efficacy of add-on memantine or placebo to clozapine and revealed reduction of positive and negative symptoms in the memantine group (de Lucena et al. 2009).

Other glutamatergic drugs (glycine, D-serine, D-cycloserine, ampakine (CX516)) were ineffective in reducing positive symptoms as add-on treatment to antipsychotics. However, some limited evidence exists that glutamatergic drugs may have a positive impact on negative symptoms (Tuominen et al. 2006). However, recent meta-analyses and studies using metabotropic glutamate receptor agonists indicate that modulation of the glutamatergic neurotransmission might be promising treatment approaches in the future (Conn et al. 2009; Fell et al. 2012; Singh and Singh 2011), but well-designed clinical trials are needed to confirm these findings.

*Other neuroactive agents*

A multitude of different neuroactive agents has been investigated as add-on treatments or therapeutic alternatives in the management of schizophrenia. For beta-blockers, cannabis/cannabinoid compounds, estrogens and polyunsaturated fatty acids, only limited and inconsistent evidence exists for the treatment of schizophrenia Akter et al. 2012; Chua et al. 2005; Joy et al. 2006b; Rathbone et al. 2008; Shek et al. 2010; Thibaut and Colonna 1993a). 3-(2,4-Dimethoxybenzylidene)-anabaseine (DMXB-A), a partial agonist at the alpha-7 nicotinic receptor has recently be discussed as a novel therapeutic agent (Tregellas et al. 2011), but corresponding clinical trials are not available yet. Finally, one meta-analysis including five double-blind, randomized, placebo-controlled trials (in total 264 patients) indicates that nonsteroidal anti-inflammatory drugs, like ibuprofen, diclofenac, naproxen sodium or acetylsalicylic acid have the potential to improve psychopathology and to reduce comorbid somatic diseases (Sommer et al. 2011).

### Summary statements

- The augmentation with certain stabilizers and anticonvulsants as outlined above might be promising, whereas certain drugs could not be recommended for augmentation anymore (*Category of evidence B to E, see details above*) (see Recommendation Table IV)
- There is only little evidence that the augmentation with antidepressants is effective, whereas mirtazapine seems to be an exception (*Category of evidence B to F*)
- There is only little evidence supporting the add-on treatment with benzodiazepines in schizophrenia, in catatonic schizophrenia and in antipsychotic-induced acute akathisia (*Category of Evidence C, C1–C3, Recommendation grade 4*). However, benzodiazepines have a prominent effect of agitation (*Category of Evidence B, Recommendation grade 3*)
- There is only inconsistent data for memantine and other glutamatergic drugs in the treatment of schizophrenia (*Category of Evidence D, Recommendation grade 5*)
- There is only inconsistent data for other neuroactive agents in the treatment of schizophrenia (*Category of Evidence D, Recommendation grade 5*)
- New neuroactive drugs as discussed above have the potential to improve the therapy of schizophrenia, but there is a need for well-designed clinical trials to confirm the initial findings

### Electroconvulsive therapy (ECT) in treatment resistant schizophrenia

In the last version of the WFSBP Guidelines and in the APA guidelines, ECT was recommended only with limited evidence for the management of treatment-resistant schizophrenia (Lehman et al. 2004).

This recommendation was based on inconsistent findings comparing verum-ECT and sham-RCT in treatment-resistant schizophrenia (Chanpattana et al. 1999; Tharyan and Adams 2005).

However, ECT as an add-on to antipsychotic treatment does have its place in certain cases (Tharyan and Adams 2005). ECT may be a treatment option in patients not responding to clozapine or when clozapine is not tolerated (Lehman et al. 2004). A recently published meta-analysis including systematic reviews with meta-analyses published since 2000 found a significant effect of ECT on global symptoms in patients with or without concurrent antipsychotics (Matheson et al. 2010). However, as a methodological limitation, the limited sample of studies (only five reviews/meta-analyses were included in the analyses) should be taken into consideration. A retrospective chart review of 19 patients indicates that maintenance ECT combined with antipsychotic treatment might provide some benefit compared to pharmacological treatment alone (Levy-Rueff et al. 2010). One recent review revealed that catatonic patients are the most responsive to ECT and that ECT combined with antipsychotics, especially clozapine might be preferable (Zervas et al. 2011). A retrospective analysis of charts from 79 patients diagnosed with schizophrenia, persistent delusional disorders and schizoaffective disorders showed that most patients had an excellent/good outcome (66), whereas eight had a moderate outcome and five had a poor outcome (Kristensen et al. 2011).

### Summary statements

- There is limited evidence for the general efficacy of ECT in treatment-resistant schizophrenia (*Category of Evidence D, Recommendation grade 5*)

Recommendation Table IV. Recommendations for the augmentation of antipsychotic treatment.

Augmentation strategy	Category of evidence <sup>a</sup>	Recommendation <sup>b</sup>	Application for
Carbamazepine add on	E	–	Treatment-resistant schizophrenia
Lamotrigine ad on	D	5	Treatment-resistant schizophrenia
Lamotrigine + Clozapine	B	3	Treatment-resistant schizophrenia
Lithium add on	D/E	–	Treatment-resistant schizophrenia
Lithium add on	B	3	In patients with mood symptoms
Pregabalin add on	C2	4	Treatment-resistant anxiety
Topiramate add on	D	5	Treatment-resistant schizophrenia
Topiramate add on	B	3	Reducing weight gain <sup>1</sup>
Valproate	E	–	Treatment-resistant schizophrenia
Valproate	D	5	Targeting aggression and hostility

<sup>a</sup>Category of evidence: Category of evidence where A = full evidence from controlled studies (see Table I).

<sup>b</sup>Safety rating = recommendation grade derived from categories of evidence and additional aspects of safety, tolerability, and interaction potential (see Table I). <sup>1</sup>See part 2 of these guidelines.

- In certain cases ECT add-on to antipsychotic treatment may be appropriate (*Category of Evidence C3, Recommendation grade 4*) and in catatonia ECT is an important therapeutic alternative (*Category of Evidence C, Recommendation grade 4*)

### Repetitive transcranial magnetic stimulation (rTMS) in treatment resistant schizophrenia

Since the last version of these guidelines, new studies investigating the efficacy of rTMS in the management of treatment-resistant schizophrenia (persistent auditory hallucinations and persistent negative symptoms) have been conducted.

The recently published PORT-guidelines recommend the application of low-frequency (1 Hz) rTMS over the left temporoparietal cortex for the treatment of auditory hallucinations that have not responded to adequate antipsychotic therapy (Buchanan et al. 2010). This statement was based on a meta-analysis of 10 studies, which found a significant advantage of active rTMS compared to sham (placebo) TMS in the treatment of persistent auditory hallucinations (Aleman et al. 2007). However, there are negative studies, the localisations of the target brain area are not comparable across studies and the sham condition in some of the studies cannot be compared with a placebo in a drug trial. Therefore, because of the good side effect profile of rTMS, a treatment attempt with low-frequency rTMS in persistent auditory hallucination can be recommended with limited evidence (*Category of Evidence C/D, Recommendation grades 4/5*).

High-frequency rTMS (especially at 10 Hz) applied to the dorsolateral prefrontal cortex was shown in several studies to be a promising technique to improve such negative symptoms, although studies with a negative outcome do also exist (Dlabac-de Lange et al. 2010; Freitas et al. 2009). One large RCT including schizophrenia patients with predominantly negative symptomatology to confirm the efficacy and tolerability of 10 Hz rTMS will be published soon (Cordes et al. 2009). In summary, there is some limited evidence for the efficacy of high-frequency rTMS (preferentially 10 Hz) to the DLPFC for the treatment of negative symptoms (*Category of Evidence D, Recommendation grade 5*). However, there is the need for future investigations, especially to evaluate the intensity and duration of treatment and the need for a maintenance treatment (see Tables III–V).

### Conclusion

This update of the WFSBP Guidelines for the biological treatment of schizophrenia and the management of treatment resistance summarizes the available publications in this field and provides evidence-based treatment recommendations.

For the clinical psychiatrist, the knowledge about the efficacy of different antipsychotic drugs, their combinations and different augmentation strategies is of particular importance. Especially the consistent finding that SGAs are not “magic bullets” and have their own and individual side effect profile, requires particular consideration when treating patients with

Table V. Pharmacokinetics of selected antipsychotics.

Antipsychotic	Maximal plasma level (in hours)	Elimination half-time (in hours)	CYP enzymes <sup>1</sup>
<b>SGA</b>			
Amisulpride	1–3	12–20	Mainly eliminated by renal route
Asenapine	1	24	1A2, (3A4, 2D6), UGT1A4
Aripiprazole	3–5	75–146 (954)	2D6, 3A4
Clozapine	1.5–3.6	16–23	1A2, 3A4, (2C19, 2D6)
Iloperidone	2–5	25.5–37.3	2D6, 3A4
Lurasidone	1–3	12.2–18.3	3A4
Olanzapine	5–8	21–54	1A2, (2C19, 2D6)
Paliperidone	24	23	Mainly eliminated by renal route
Quetiapine	1.0–1.8	6.8	3A4
Risperidone	0.8–1.4	3.6	2D6 (3A4)
Sertindole	10	55–90	2D6, 3A4
Ziprasidone	3.8–5.2	3.2–10	3A4, (1A2, 2D6)
Zotepine	2.8–4.5	8–16 (12)	3A4, (1A2, 2D6)
<b>FGA</b>			
Chlorpromazine	2–4	30	1A2, 2D6, 3A4
Haloperidol	3–6	14–20	2D6, 3A4

<sup>1</sup>Secondary involved enzymes in parentheses. Modified and extended according to Burns (2001).

these agents. There is no evidence for a general difference between FGAs and SGAs in terms of efficacy and effectiveness. However, some studies and meta-analyses indicate superiority of SGAs with regard to some symptom domains and treatment continuation (the latter in first-episode patients especially). FGAs have a higher risk of inducing neurological side effects, especially tardive dyskinesia, which is often irreversible after stopping medication (see part 2 of these guidelines), and is a non-tolerable side effect. Some SGAs and some FGAs carry an increased risk for developing a metabolic syndrome with consequent associated diseases.

Therefore, the consideration of side effects is becoming increasingly important. Clinicians must keep in mind that most patients may need lifelong treatment and so require treatment strategies with the optimal balance between efficacy and tolerability.

To make these guidelines more comprehensive, we have separated the guidelines in three parts, which will be published consecutively. The second part will address the long-term treatment of schizophrenia and the third part will include specific treatment circumstances (e.g., depression, pregnancy or substance-abuse). Furthermore, we have included evidence-based recommendation statements at the beginning of the guidelines and at the end of each chapter to give a fast, accessible and easy overview.

Even today, there is unsatisfying evidence for different questions in the treatment of schizophrenia and these questions need to be addressed in large well-designed clinical trials. In recent years some important trials (e.g., CATIE, CUtLASS, EUFEST) have been published, but each of them has important methodological limitations.

Several aspects, like the well-known link between sponsorship and study outcome, the usage of various dosage-ranges among studies, the unpopular publication of negative results, different exclusion criteria (especially when investigating treatment-resistant schizophrenia) as well as many other factors could bias the results of published studies.

However, there is a need for evidence-based national and international treatment recommendations and clinical psychiatrists and researchers need to re-evaluate their knowledge and their treatment strategies regularly to provide the best possible treatment for the patient.

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### Statement of Interest

Alkomiet Hasan has been invited to scientific meetings by Lundbeck, Janssen-Cilag and Pfizer. Peter Falkai was honorary speaker for Janssen-Cilag, AstraZeneca, Eli Lilly, Bristol Myers-Squibb, Lundbeck, Pfizer, Bayer Vital, SmithKline Beecham, Wyeth, and Essex. During the last 2 years, but not presently, Peter Falkai was a member of the advisory boards of Janssen-Cilag, AstraZeneca, Eli Lilly, and Lundbeck. He received research support by AstraZeneca. Thomas Wobrock has been a member of a speaker bureau for Alpine Biomed, AstraZeneca, Bristol Myers Squibb, Eli Lilly, I3G, Janssen-Cilag, Novartis, Lundbeck, Sanofi-Aventis and Pfizer. He received research support by AstraZeneca, I3G and AOK. Jeffrey Liebermann was/is a member of the advisory boards of Bioline, Intracellular Therapies, Alkermes, Lilly and Pierre Fabre. He received research support/grants by Allon, GlaxoSmithKline, Lilly, Merck, Novartis, Pfizer, Psychogenics, LTD, Sepracor and Targacept. He holds a patent by Repligen. Birte Glenthøj and Wagner F. Gattatz report no conflict of interest. Florence Thibaut is a member of the Sertindol Study International Safety Committee. Hans-Jürgen Möller has received grants or is a consultant for and on the speakership bureaus of AstraZeneca, Bristol-Meyers Squibb, Eisai, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Lundbeck, Merck, Novartis, Organon, Pfizer, Sanofi-Aventis, Schering-Plough, Schwabe, Sepracor, Servier and Wyeth.

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