GUIDELINES

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 2: Update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects

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Abstract

These updated guidelines are based on a first edition of the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia published in 2006. 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. They 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) and five levels of recommendation (1–5) (Bandelow et al. 2008a,b, World J Biol Psychiatry 9:242, see Table 1). This second part of the updated guidelines covers long-term treatment as well as the management of relevant side effects. These guidelines are primarily concerned with the biological treatment (including antipsychotic medication and other pharmacological treatment options) of adults suffering from schizophrenia.

Key words: *Schizophrenia, antipsychotics, evidence-based guidelines, long-term treatment, side effects*

Executive summary of recommendations

General recommendations

This part remains partly unchanged; it has been adopted from the WFBSP 2006 guidelines and updated where necessary. Specific treatment strategies are required not only for patients suffering from acute schizophrenia, but also in the stabilisation and stable phase of the disease. The stabilisation period follows the acute phase and constitutes a time-limited transition to continuing treatment in the stable phase. The stable phase represents a prolonged

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

Category of Evidence		Description
A		**Full Evidence From Controlled Studies is based on:**
		Two 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)
		and
		One 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)
		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 two 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.
B		**Limited Positive Evidence From Controlled Studies is based on:**
		One or more RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo")
		or
		a randomized controlled comparison with a standard treatment without placebo control with a sample size sufficient for a non-inferiority trial
		and
		no negative studies exist
C		**Evidence from Uncontrolled Studies or Case Reports/Expert Opinion**
	C1	**Uncontrolled Studies. Evidence is based on:**
		1 or more positive naturalistic open studies (with a minimum of 5 evaluable patients)
		or
		a comparison with a reference drug with a sample size insufficient for a non-inferiority trial
		and
		no negative controlled studies exist
	C2	**Case Reports. Evidence is based on:**
		1 or more positive case reports
		and
		no negative controlled studies exist
	C3	Evidence is based on the opinion of experts in the field or clinical experience
D		**Inconsistent Results**
		Positive RCTs are outweighed by an approximately equal number of negative studies
E		**Negative Evidence**
		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
F		**Lack of Evidence**
		Adequate studies proving efficacy or non-efficacy are lacking.
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**

period of treatment and rehabilitation during which symptoms are under adequate control and the focus is on improving functioning and recovery. The goals of long-term therapy have to be discussed with the patient in the context of adequate background information, as well as her/his personal goals, in order to find a common ground which will encourage an effective long-term medication strategy (shared-decision making). In this regard, a treatment plan must be formulated and implemented.

During the stabilisation phase, the main goals of treatment are to facilitate continued symptom reduction, consolidate remission, and promote the process of recovery. The main goals of treatment during the stable phase are to ensure that symptom remission or control is sustained, that the patient is maintaining or improving their level of functioning and quality of life, that monitoring for adverse treatment effects continues, and to prevent relapse. The antipsychotic pharmacological therapy should be accompanied by psychosocial interventions.

A number of psychosocial treatments, including family intervention, supported employment, assertive community treatment, skills training and

cognitive behaviour-oriented psychotherapy, have been shown to be effective during the stable phase. The selection of appropriate psychosocial treatments should be guided by the circumstances of the individual patient's needs and social context. In the same way, psychopharmacological management must be individually tailored to the needs and preferences of the patient, focusing on relapse prevention, symptom suppression and improvement of subjective wellbeing and quality of life.

Specific treatment recommendations

Long-term treatment is necessary for all patients with schizophrenia. If the patient has shown improvements with a particular medication regimen, continuation of that regimen with further monitoring is recommended for at least 6 months in the stabilisation phase. Premature dosage lowering may lead to a recurrence of symptoms and relapse, whereas this question is recently discussed controversially (Takeuchi et al. 2012). Side effects have to be assessed and, if necessary, pharmacotherapy has to be adjusted. Antipsychotic medications substantially reduce the risk of relapse in the stable phase of illness and are strongly recommended for durations of 1–2 years in first-episode patients, 2–5 years in patients who have experienced one relapse, and for over 5 years (maybe even throughout life) in multi-episode patients.

Antipsychotic monotherapy should be the preferred treatment approach. Continuous dosing strategies have shown superiority compared to intermittent-dose approaches. Deciding on the dose of an antipsychotic medication during the stable phase is complicated by the fact that there is no reliable strategy available to identify the minimum effective dose to prevent relapse.

There is no good evidence that high maintenance doses (e.g., for first-generation antipsychotics (FGAs) above 600 mg CPZ equivalents) are more effective in preventing relapse than standard doses. Therefore, a maintenance dosage below 600 CPZ equivalents is recommended. First-episode patients may require lower doses for relapse prevention than multi-episode patients.

Depot preparations (FGAs or SGAs, long-acting antipsychotics) should be the application method of choice when a patient expresses a preference for such treatment because of its convenience, or as part of a treatment plan in which the avoidance of covert non-adherence with antipsychotic drugs is a clinical priority. In certain cases, patients should be actively motivated and educated about the benefits of using depot preparations.

Antipsychotic medications are associated with differing levels of risk for various side effects, including neurological, metabolic, sexual, endocrine, sedative and cardiovascular side effects (for a detailed description see Part 1 of this guideline update). These side effects may have an even greater influence on the choice of long-term medication than in the acute phase of treatment. Monitoring of side effects is based on the side effect profile of the prescribed antipsychotic. During the stable phase, it is important to monitor all patients routinely for all extrapyramidal symptoms (EPS), weight gain, cardiovascular and metabolic side effects. Monitoring for obesity-related health problems (e.g., high blood pressure, lipid abnormalities and clinical symptoms of diabetes) and consideration of appropriate interventions are recommended if necessary (see Table III and Part 1 of these updated guidelines). Clinicians may consider regular monitoring of fasting glucose or haemoglobin A1c levels to detect emerging diabetes since patients often have multiple risk factors for diabetes, especially patients with obesity (De Hert et al. 2006, 2011a). FGAs and SGAs have specific side effect profiles and these profiles have to be considered when planning a long-term treatment. SGAs have clear advantages with respect to EPS (especially tardive dyskinesia). However, this advantage has to be weighed against other potentially dangerous side effects, e.g., metabolic or cardiac side effects (see Table II and Part 1 of these updated guidelines).

It is important to evaluate whether residual negative symptoms are in fact secondary to a parkinsonian syndrome or untreated major depression since interventions are available to address these causes of negative symptoms. For primary negative symptoms, treatment options include switching to an atypical antipsychotic or augmentation strategies. Nevertheless, it should be noted that the evidence for the efficacy of these strategies is only limited (see Part 1 of these updated guidelines). Adjunctive medications are prescribed for comorbid conditions of patients in the stable phase. Comorbid major depression and obsessive-compulsive disorder may respond to antidepressant medications, mood stabilisers may address prominent mood lability, and benzodiazepines are helpful for managing anxiety and insomnia. However, the evidence for these treatment strategies is minimal and the combination therapy of antipsychotics and benzodiazepines with a long half-time is discussed to increase mortality in schizophrenia patients (Baandrup et al. 2010) (see Part 1 of this guideline update).

Further treatment strategies, including appropriate management of side effects, are extensively discussed below.

Table II. Selected side effects of commonly used antipsychotics.

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
Hypotension	++	0	+	(+)	(+)	++	++	0/(+)	(+)	0
Agranulocytosis	0/(+)	0/(+)	0/(+)	+	0/(+)	0/(+)	0/(+)	0/(+)	0/(+)	0/(+)
Weight Gain	+	+	(+)	+++	+++	++	++	++	++	(+)
Prolactin elevation	+++	+++	0	0	(+)	+++	(+)	+++	(+)	0
Galaktorrhoea	++	++	0	0	+	+++	0	++	(+)	0
Dysmenorrhoea	++	++	0	0	+	++	(+)	+	(+)	(+)
Sedation	+	0/(+)	0	+++	+/++	+	++	(+)	(+)	0/(+)
MNS	+	?	(+)	(+)	(+)	(+)	(+)	(+)	(+)	?

Frequencies and severity of side effects refers to information obtained by drug companies, FDA, additional literature and other guidelines.
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).

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, to 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 s also 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 Psychiatry Association, Practice Guideline for the Treatment of Patients with schizophrenia (APA 1997), 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

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. Compared to the first part of these updated guidelines, this table was modified (waist circumference) as a result of an expert-based consent.

	Baseline	4 Weeks	8 Weeks	12 Weeks	Annually
Personal/Family History	x				x
Weight (BMI)	x	x	x	x	x
Waist circumference	x	x		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) and De Hert et al. (2009).

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);

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 (Hasan et al. 2012);

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 August 2012).

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 August 2012). For special questions, case reports and case series were taken into account.

Individual clinical experience by 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).

General aspects of long-term treatment of schizophrenia

Indication and goals of long-term treatment for schizophrenia

The general aspects of this section have been adopted from the last version of these guidelines and have been updated where necessary. Schizophrenia is a heterogeneous condition that has a varying course and outcome, and affects many aspects of a patient's life. The care of most patients with this disorder involves multiple efforts and a multidisciplinary team approach to reduce the frequency, duration and severity of episodes, reduce the overall morbidity and mortality of the disorder, and improve psychosocial functioning, independence and quality of life.

Specific treatment needs to be continued in the stabilisation and stable phase of schizophrenia and long-term treatment is indicated for all patients with schizophrenia. Clinical issues consist of relapse prevention and improvement of symptoms, including the reduction of the demoralising effects of persistent psychotic symptoms, treating depression and preventing suicide, reducing substance abuse and smoking, and enhancing family relationships and vocational rehabilitation.

The stabilisation period (usually lasting 3–6 months) follows the acute phase and constitutes a time-limited transition to continuing treatment in the stable phase. The primary goals in the stabilisation phase are the consolidation of the therapeutic relationship, reduction of positive symptoms, improvement of cognitive and negative symptoms, reduction of stress for the patient, improvement of social deficits and consolidation of remission, promotion of insight and compliance, supporting the development of individual coping strategies, provision of support to minimise the likelihood of relapse, enhancement of the patient's adaptation to life in the community and promotion of the recovery process.

If the patient has improved with a particular medication regimen, it is recommended that the regimen is continued for at least 6 months (Lehman et al. 2004; Falkai et al. 2006). It is also critical to assess continuing side effects that may have been present in the acute phase and to adjust pharmacotherapy accordingly in order to minimise adverse side effects that may otherwise lead to medication nonadherence and relapse.

The stable phase (lasting months to years) represents a prolonged period of treatment and rehabilitation during which symptoms are under adequate control and the focus is on improving functioning and recovery. The main goals of treatment during the stable phase are to ensure that symptom remission or control is sustained, that the patient is maintaining or improving their level of functioning and quality of life, that any increases in symptom severity or relapse occurrence are effectively treated, and that monitoring for adverse treatment effects continues. For most patients in the stable phase of schizophrenia, psychosocial interventions are recommended as a useful adjunctive treatment to pharmacological treatment to improve outcome. The main aims of pharmacological intervention in the stable phase are to prevent relapse, help keep an individual stable enough to live as normal a life as possible, and continue to promote the process of recovery (in the sense of a maintenance or continuation therapy).

The goals of long-term treatment have to be discussed with the patient and, if she/he agrees, with family members, relatives, care givers and, in some cases, advocates, with the aim of providing adequate information and with an understanding of the patient's personal goals. When an agreement is reached in the context of shared decision-making, a treatment plan must be formulated and implemented. Psychopharmacological management must be individually tailored to the needs and preferences of the patient, focusing on relapse prevention, symptom suppression and improvement of subjective wellbeing and quality of life. Psychotherapeutic interventions remain supportive but may be less directive than in the acute phase. Educational programmes during this phase have been effective in teaching a wide range of schizophrenia patients medication self-management (e.g., benefits of maintenance of antipsychotic medication, how to cope with side effects), symptoms self-management (e.g., how to identify early warning signs of relapse, develop a relapse prevention plan, refuse illicit substances and alcohol), and basic social skills (APA 1997; Lehman et al. 2004; Falkai et al. 2006).

Antipsychotic treatment

General aspects

Since the last publication of these guidelines, some new studies investigating and comparing the efficacy of FGAs and SGAs in the long-term treatment of schizophrenia have been published. Furthermore, new long-acting antipsychotics have been launched to the market, providing additional treatment options for the long-term management of schizophrenia.

The following statements are in accordance with the previous version of these guidelines and have been updated only where necessary. The efficacy of FGAs in relapse prevention was demonstrated in the 1970s (Davis 1975, 1985) and was confirmed for most SGAs later (Davis and Chen 2003; Leucht et al. 2009a, 2012a,b; NICE 2010). These efficacies have been shown for both first-episode schizophrenia patients (Kane et al. 1982; Crow et al. 1986; Bradford et al. 2003; Schooler et al. 2005; Gaebel et al. 2007) and for multiple-episode schizophrenia patients (Davis 1975, 1985; Davis et al. 1993; Jeste et al. 1993; Gilbert et al. 1995; Leucht et al. 2003). Antipsychotic therapy should be continued as part of a comprehensive package of care that addresses the individual's clinical, emotional and social needs (NICE 2002). Antipsychotic drugs are an indispensable treatment option for most people in the recovery and stable phases of schizophrenia. The main aim here is to prevent relapse and help keep a person stable enough to live as normal a life as possible (NICE 2002) with minimal side effects. Antipsychotics are also necessary for psychological treatments to be effective, and psychosocial interventions are always an essential addition to pharmacotherapy (RANZCP 2005).

Targets of long-term treatment include maintenance therapy to stabilise remission, prevent relapse, and provide symptom suppression or even continued symptom improvement. Ongoing monitoring and assessment during the stable phase are necessary to determine whether the patient might benefit from alterations to his or her treatment programme (Lehman et al. 2004), and whether potential dangerous side effects are developing. However, the frequency of assessments conducted by the psychiatrist or member of the team should depend on the specific nature of the treatment and the expected fluctuations of the illness, as well as from the health care system of the particular country. For example, patients given certain antipsychotics (e.g., clozapine) should be evaluated more frequently than patients on other antipsychotics.

The choice of antipsychotic drug should be made jointly by the individual and the clinician responsible for treatment, based on an informed discussion of the relative benefits of the drugs and their side effect profiles and the past experience of the patient and the physician. Antipsychotic drugs should not be prescribed concurrently and monotherapy should be favoured. For short periods of overlap in the case of switching, in the case of severe treatment resistance or in order to combine different pharmacological effects (e.g., combined treatment with low-potency FGA for sedation), a combination treatment is acceptable (NICE 2002; Lehman et al. 2004; RANZCP 2005; DGPPN 2006; Falkai et al. 2006). Psychiatrists, who treat patients with more than one antipsychotic at the same time should be aware of drug interactions and that there have been practically no studies examining the security of these combination treatments.

Methodological aspects

In contrast to the acute and short-term treatment of schizophrenia, there are only few studies that have been conducted investigating maintenance therapy and comparing FGAs and SGAs. As widely discussed in the first part of these guidelines and in other publications (Leucht et al. 2009b; Glick et al. 2011), the differentiation between FGAs and SGAs raises some problems ("pseudoclassification") and each antipsychotic has its individual side effect profile. This fact limits the comparability of different antipsychotics and needs to be considered when reading these guidelines and the underlying original publications.

Another problem is that good meta-analyses addressing questions of long-term antipsychotic treatment are still rare – a situation that can be explained by the small number of well-designed long-term clinical trials. Furthermore, main problems of meta-analyses are the comparability of the included studies (e.g., diagnostic differences, different observation periods, different dosages) and the fact that negative results are less frequently published than positive results (publication bias) (Leucht et al. 2009c). The reader should be aware about the methodological problems associated with meta-analyses and consider that meta-analyses can lead to a different interpretation of already available data (Leucht et al. 2009c). Furthermore, long-term treatment needs to address other clinical variables than psychopathology (e.g., neurocognition, drug acceptability, compliance, subthreshold episodes, substance abuse and many more) and many of the published long-term studies do have still too short observation periods, which do not allow to draw final conclusions about long-term treatment in schizophrenia patients (Altamura and Glick 2010). These methodological aspects are of great relevance for the understanding

of the original publications and of the recommendations made in these guidelines.

FGAs and SGAs

As described in the last version and in the recently updated first part of these guidelines, differences between FGAs and SGAs need to be viewed in the context of efficacy or effectiveness, side effects, the patient's symptomatology and experience. A modern antipsychotic therapy should provide a tailored therapeutic regime with great attention to the side effects. In the case of long-term maintenance therapies, intolerable side effects are an important factor related to poor treatment adherence (Goff et al. 2010).

Two pooled randomized, double-blind, multicentre 52-week studies (with similar study protocols) compared the long-term efficacy of aripiprazole and haloperidol in 1294 schizophrenia patients (Kasper et al. 2003). This study showed comparable efficacy of aripiprazole and haloperidol in reducing positive symptoms, but a superiority of aripiprazole in reducing negative and affective symptoms. Furthermore, treatment with haloperidol was associated with more motor side effects (Kasper et al. 2003).

A large double-blind, prospective long-term study in stable outpatients suffering from chronic schizophrenia (mean duration of disease over 15 years), revealed superiority of risperidone (modal daily dose 4.9 mg) with regard to treatment discontinuation, reduction of symptoms and extrapyramidal side effects when compared with haloperidol (modal daily dose 11.7 mg) (Csernansky et al. 2002).

In a large ($n = 555$) double-blind, controlled, flexible-dose RCT, risperidone (mean modal dose 3.3 mg/day) and haloperidol (mean modal dose 2.9 mg/day) were both found to lead to significant improvements in global psychopathology without difference between groups (Schooler et al. 2005). However, within the patients who achieved a clinical improvement, the patients treated with risperidone had a significantly longer time to relapse. Patients treated with haloperidol showed more extrapyramidal symptoms, while patients in the risperidone group had a greater prolactin elevation. Treatment with haloperidol resulted in less initial weight gain compared to treatment with risperidone, but this did not remain significant at the study endpoint (Schooler et al. 2005).

In a double-blind RCT with 159 remitted first-episode schizophrenia patients, no difference in the primary outcome parameter "relapse prevention" was found between haloperidol (4.1 mg/day) and risperidone (4.2 mg/day) (Gaebel et al. 2007). Both drugs showed the same efficacy in the secondary outcome parameters symptom reduction and quality of life. However, extrapyramidal symptoms were more frequent in the haloperidol group. Although the study was biased by a high drop-out rate of 68%, the drop-out rate did not differ significantly between drugs (Gaebel et al. 2007).

In a double-blind international 2-year RCT, olanzapine (mean dose 10.2 mg/day) and haloperidol (mean dose 4.82 mg/day) were shown to have the same efficacy in the primary outcome measure of symptom reduction (Green et al. 2006). However, patients treated with olanzapine were found to be less likely to discontinue the study and showed higher remission rates. It should be noted that the significantly longer duration of illness in the haloperidol group must be considered when interpreting these findings (Green et al. 2006).

Another long-term 2-year randomized, double-blind study compared haloperidol with risperidone in 63 patients with stable and chronic schizophrenia. In addition to the antipsychotic treatment, study patients received "standard behavioural skills training or enhanced training with a case manager who promoted patients' use of their skills in the community" (Marder et al. 2003). In this study, no differences in the primary outcome parameter symptom reduction (Brief Psychiatric Rating Scale) could be detected between the drugs. However, for the secondary outcome parameters, anxious-depression cluster of the Brief Psychiatric Rating Scale and the SCL-90-R self-report instrument, risperidone was superior compared to haloperidol. Furthermore, risperidone induced fewer motor side effects and patients treated with haloperidol received more anticholinergics and propanolol (for akathisia) (Marder et al. 2003).

One 12-month double-blind study from the Veterans Affairs Medical Centres (Rosenheck et al. 2003) compared olanzapine with haloperidol (plus prophylactic benztropine for motor side effects) and found no significant difference between the drugs in relation to study retention, improvement in PANSS scores, quality of life and extrapyramidal symptoms. However, this study revealed that cognitive disturbances occurred more frequently in patients treated with haloperidol and benztropine. Olanzapine induced less motor side effects, but more weight gain compared to haloperidol (Rosenheck et al. 2003). Important confounders of his study are the long diseases course (approximately 20 years), the flexible dosing scheme and the prophylactic treatment with benztropine (Moller 2008). The latter biases the study in favour of haloperidol and should not be common practice given the cognitive disturbances induced by anticholinergics.

In a flexible-dose double-blind 52-week RCT, no difference between chlorpromazine and clozapine

could be found with respect to rating scale measures of symptom severity. However, patients receiving clozapine remitted significantly faster and remained in remission longer than patients receiving chlorpromazine (Lieberman et al. 2003).

In various parts of the CATIE study (except from Part 3; for details see Part 1 of these guidelines) (Lieberman et al. 2005; Essock et al. 2006; Stroup et al. 2006, 2007) some evidence was found to suggest that olanzapine might be superior to the FGA perphenanzine, as well as to other SGAs, in the maintenance treatment of schizophrenia. The CUtLASS study (for details see Part 1 of these guidelines), with a follow-up until week 52, indicated no difference between a group of SGAs and a group of FGAs (preferentially sulpiride) in the long-term treatment of schizophrenia (Jones et al. 2006). However, both studies have important methodological restrictions which have been discussed in the first part of these updated guidelines and elsewhere (Naber and Lambert 2009; Moller 2008).

One prospective observational trial with 374 schizophrenia/schizoaffective patients and an observation period of 24 months showed that olanzapine (mean daily dose 15 mg) has some superiority compared to risperidone (mean daily dose 4.9 mg) and quetiapine (mean daily dose 588 mg) with regard to the primary outcome measure (rehospitalisation of patients after discharge from index hospitalisation) (Kilian et al. 2012). However, the quetiapine group needed higher chlorpromazine equivalent doses to show similar effects compared to the other treatment groups (Kilian et al. 2012).

The EUFEST study (Kahn et al. 2008) was conducted on first-episode schizophrenia patients and compared haloperidol with four different SGAs (amisulpride, olanzapine, quetiapine, ziprasidone) with regard to the primary outcome measure treatment discontinuation. Treatment discontinuation for any reason was significantly higher in patients treated with haloperidol. Treatment discontinuation as a consequence of insufficient efficacy was also higher in the haloperidol group, but the difference between haloperidol and quetiapine was not significant (Kahn et al. 2008).

In the SOHO study (observational and non-randomized), SGAs led to lower discontinuation rates and more remissions than FGAs and subjects reported increased subjective wellbeing following treatment with SGAs (Lambert et al. 2006; Haro et al. 2007).

In a 2003 published meta-analysis of randomised short-term efficacy trials comparing SGAs and FGAs, and comparing between different SGAs, effect sizes of clozapine, amisulpride, risperidone and olanzapine were found to be greater than those of FGAs, and the effect size of zotepine was marginally greater. Other SGAs revealed no clear superiority (Davis et al. 2003). No efficacy difference was detected when amisulpride, risperidone and olanzapine were directly compared to each other. In a more recent meta-analysis (comparing FGAs to SGAs, conducted mainly from short-term trials), SGAs were not pooled because the authors felt that they were too different to form a class (Leucht et al. 2009b, 2011b). In this new meta-analysis, only risperidone, olanzapine and sertindole (based on only one study) were superior to FGAs in terms of relapse prevention. For amisulpride, aripiprazole and clozapine, no significant difference could be detected compared to FGAs and, for the other SGAs, no data were available (Leucht et al. 2009b). However, these meta-analyses (Davis et al. 2003; Leucht et al. 2009b) primarily included short-term studies and the translation of their results to long-term studies should be undertaken only with caution.

A meta-analysis (Leucht et al. 2003) including only trials with a minimum 6 month duration showed a superiority of SGAs when grouped together and when compared to placebo, a superiority of certain SGAs (risperidone, olanzapine and sertindole), and a numeric, but not significant superiority for amisulpride and clozapine when compared to FGAs and a superiority of the grouped SGAs compared to FGAs. SGAs and FGAs showed no difference in terms of dropout-rate due to adverse effects. The authors discussed several confounding factors of this meta-analysis (e.g., the difficulty of defining relapse, the fixed-dosage regime in the included trials) and concluded that the "available data do not allow for any conclusions about whether this modest superiority for the new antipsychotics in relapse prevention is related to enhanced efficacy, better adherence, or a combination of these factors" (Leucht et al. 2003). A more recent meta-analysis of randomized trials, lasting 6 months or longer, compared FGAs with SGAs in the long-term treatment of schizophrenia (Kishimoto et al. 2011) and showed that SGAs, when grouped together, were significantly superior to FGAs with regard to relapse prevention. No study showed a superiority of the FGA comparator and this meta-analysis does not allow a conclusive comparison among SGAs (Kishimoto et al. 2011). However, the authors discuss the results concerning the questions of whether SGAs form a meaningful group and whether mid- or low-potency FGAs differ from haloperidol (Kishimoto et al. 2011).

A recent analysis of mid- and long-term outcome data of newer antipsychotics discusses some advantages of SGAs in the long-term and maintenance treatment of schizophrenia (Glick et al. 2011). The authors highlight the problems of the comparability

of different antipsychotics and that during the maintenance treatment patients and the relatives focus on other issues (e.g., relief from disabling symptoms, gaining works, building up relationships) than during the acute treatment (Glick et al. 2011). Furthermore, a consensus paper published by the European college of neuropsychopharmacology (ECNP) states that in controlled long-term studies, where the secondary negative symptoms become less prominent, certain SGAs may have some advantages in reducing negative symptoms (Montgomery and van Zwieten-Boot 2007). Please see Part 1 of these guidelines for a detailed and evidence-based discussion of the treatment of primary and secondary negative symptoms.

Another important aspect for the maintenance treatment of schizophrenia is the treatment of suicidality and there is some evidence that certain antipsychotics are superior to others in reducing suicidal behaviour in schizophrenia (Meltzer et al. 2003; Crocq et al. 2010). This important topic will be discussed in the third part of these guidelines.

In accordance to the acute treatment of schizophrenia, long-term treatment recommendations need to address the question of side effects. For long-term treatment, the risk of inducing tardive dyskinesia is lower following treatment with SGAs (Kasper et al. 2006; Naber and Lambert 2009; Leucht et al. 2011b). The metabolic side effect profile of certain antipsychotics (see Part 1 of these guidelines) should not be underestimated and long-term studies specifically addressing this question are lacking. However, increasing rates of cardiovascular diseases as consequences of metabolic syndrome are one of main reasons for excess mortality in schizophrenia patients and, therefore, special attention must be paid to these side effects (Newcomer 2007; Laursen et al. 2009; De Hert et al. 2009, 2011a).

Therefore, maintenance treatment should follow the basic rules of acute treatment: an antipsychotic maintenance therapy should be balanced between efficacy, compliance, the patient's individual side effect profile and the patient's experience with certain antipsychotics.

The risk of developing tardive dyskinesia following treatment with FGAs is well-established, but long-term complications following treatment with certain SGAs are still not fully understood. Current studies cannot negate a risk for developing metabolic syndrome, diabetes and coronary heart disease associated with long-term treatment with certain SGAs (see Part 1 of these guidelines).

Even after the results of the CATIE and CUtLASS studies, the risk of tardive dyskinesia should not be underestimated because the widely discussed limitations of these two studies may have led to a reduced incidence of tardive dyskinesia and other motor side effects (Moller 2008; Naber and Lambert 2009). In the CATIE study patients with tardive dyskinesia were excluded from the FGA arm (selection bias) and in the CUtLASS study the most frequently chosen FGA was sulpiride. Sulpiride is an "atypical" FGA and can be considered as an SGA. Furthermore, neither of these studies used haloperidol, the mostly prescribed FGA in most developed countries, as comparator (Naber and Lambert 2009). The findings of the large European first-episode study (EUFEST) confirm that treatment with haloperidol might lead to significantly more motor side effects and a significantly higher study discontinuation rate (Kahn et al. 2008).

Keeping these conflicting points of view in mind, an evidence-based long-term treatment for schizophrenia should be based on an individually tailored medication strategy with special attention to tardive dyskinesia and metabolic side effects.

Summary statements

–   Antipsychotics (FGAs and SGAs) are effective in relapse prevention and should be offered to a patient suffering from schizophrenia *(Category of evidence A, Recommendation grade 1)*.
–   FGAs and SGAs do not show general differences in reducing symptoms with long term treatment *(Category of evidence A, Recommendation grade 1)*.
–   Some evidence is available to support superiority of certain SGAs (as outlined in these guidelines) with regard to treatment discontinuation and relapse prevention *(Category of Evidence B, Recommendation grade 3)*.
–   The reduced risk of inducing motor side effects (especially tardive dyskinesia) might favour certain SGAs *(Category of evidence C, Recommendation grade 4)*.
–   In the long-term treatment, where the secondary negative symptoms become less prominent, certain SGAs may have some advantages in reducing negative symptoms *(Category of evidence C, Recommendation grade 4)*.
–   For long-term therapy, tardive dyskinesia and metabolic side effects seem to have the greatest impact on the patient's wellbeing and health – these side effects, among others (see Part 1 of these guidelines), need to be monitored continuously and treated as soon as possible *(Category of evidence C, Recommendation grade 4)*.

  – The choice of the antipsychotic should be influenced by the same criteria recommended for starting a treatment *(Good Clinical Practice)*.
  – Maintenance treatment should be carried forward with the antipsychotic drug which led to the best response and which had the best individual side effect profile during the acute episode *(Good Clinical Practice)*.
  – Each antipsychotic selection procedure must be undertaken individually, respecting the patient's experience with certain drug classes and the individual side effect profile.

As discussed in these guidelines and in other publications, FGAs and SGAs are not two totally independent drug classes and today it is sometimes not possible to clearly categorize an antipsychotic into one particular class. Most antipsychotic agents, as long as carefully prescribed, do have their place in the maintenance therapy of schizophrenia. Antipsychotic agents with clear disadvantages, intolerable side effects and with no evidence-based data for efficacy have been described in Part 1 of these guidelines. These drugs should be avoided.

Dosages for long-term treatment

Discussions concerning the adequate dosages for long-term maintenance treatment have been controversial and evidence from dose reduction studies remains insufficient. The general statement across guidelines is that, if a first-episode patient has improved with a particular medication regimen, continuation of that regimen with monitoring are recommended, if possible, for at least 6 months in the stabilisation phase, and at least 1–2 years when a lowered dose is administered (Lehman et al. 2004; DGPPN 2006; Falkai et al. 2006). Premature lowering of dose may lead to a recurrence of symptoms and relapse. However, some authors discuss this statement controversially (Takeuchi et al. 2012) and there is a need for further studies investigating the question of dosages and dosage-reduction for long-term treatment.

In general, first-episode patients do need lower maintenance dosages than multi-episode patients *(Category of Evidence C, Recommendation grade 4)*, but the reader should be aware that the empirical basis for this recommendation is still sparse. This recommendation is based on the observations that first-episode patients are more vulnerable to developing side effects and require a lower dosage to show a response to antipsychotic treatment (see Part 1 of these guidelines).

A number of studies have investigated treatment regimens where markedly lower dosages of FGAs (oral and depot formulations) were used in maintenance therapy than during acute treatment. The results showed that, compared with continuous therapy, relapse rates increased in most studies, especially in low-dose studies (e.g., reduction of 25–50% of the standard dose (Johnson et al. 1987; Schooler et al. 1997)), but were within acceptable limits (Kane et al. 1982, 1983; Marder et al. 1984; Hogarty et al. 1988; Johnson et al. 1987; Dixon et al. 1995; Schooler et al. 1997).

However, the lower dosages were associated with a more favourable side effect profile and better compliance. Other studies have shown that high maintenance doses (e.g., more than 600 mg CPZ equivalents for FGAs) are not superior to lower dosages, and one study demonstrated that dosages below 375 mg/day CPZ equivalents are suitable for relapse prevention (Bollini et al. 1994).

In one recently published, well-designed clinical trial, dosage reduction of risperidone during maintenance treatment resulted in significantly more relapses than continuation with the initial stabilisation dose (Wang et al. 2010). As described above, there is a need for more studies aimed at ascertaining the optimal dose for maintenance therapy (especially with SGAs).

Taking the balance of relapse prevention and side effects into consideration, maintenance therapy should be designed in accordance with the stabilisation dose as long as there is a good control of relapse and no serious side effects (see Table IV) *(Category of Evidence C, Recommendation grade 4)* for at least 1 year (details for first-episode and multiple episode patients see below).

Duration of long-term treatment

Schizophrenia is a chronic disease with a recurrent disease course in the majority of cases. Therefore, the main targets of long-term and maintenance treatments are relapse prevention. The length of adequate treatment duration remains unresolved and different definitions of relapse across studies make the comparability of results difficult. Placebo-controlled RCTs and discontinuation studies have clearly shown that antipsychotics (FGAs and SGAs) are highly effective in relapse prevention (see above).

First-episode schizophrenia patients may require maintenance therapy of a shorter duration than multi-episode patients. According to Leucht and colleagues (2010), study durations in first-episode patients are restricted to 2 years and there is evidence that antipsychotic withdrawal in such a patient

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

Antipsychotic	Starting dose (mg/day)	DI[1]	Target dose first-episode (mg/day)	Target dose multi-episode (mg/day)	Maximal dosage (mg/day)[2]
SGA					
Amisulpride	200	(1)–2	100–300	400–800	1200
Asenapine[3]	5	1	5–10	5–20	20
Aripiprazole	5–15	1	15–(30)	15–30	30
Clozapine[4]	25	2–(4)	100–250	300–800	900
Iloperidone[3]	1–2	2	4–16	4–24	32
Lurasidone[3]	20–40	1	40–80	40–120	120
Olanzapine	5–10	1	5–15	5–20	20
Paliperidone[3]	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
FGA					
Chlorpromazine	50–150	2–4	300–500	300–1000	1000
Fluphenazine	0.4–10	2–3	2.4–10	10–20	20–(40)
Flupenthixol	2–10	1–3	2–10	10–20	60
Haloperidol	1–10	(1)–2	1–4	3–15	100
Perazine	50–150	1–2	100–300	200–600	1000
Perphenazine	4–24	1–3	6–36	12–42	56
Pimozide	1–4	2	1–4	2–12	16
Zuclopenthixol	2–50	1–3	2–10	25–50	75

[1]DI (dose intervals): recommended distribution of the daily dose – one = 1, twice = 2, etc.
[2]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.
[3]These antipsychotics have not been investigated in first-episode schizophrenia patients.
[4]Clozapine is usually not introduced in first-episode schizophrenia patients as first-line treatment.

group leads to significantly more relapses compared to when medication is continued (Kane et al. 1982; Crow et al. 1986; Hogarty and Ulrich 1998; Chen et al. 2010). Chronically ill patients who had been stable for years, but stopped their medications, experienced significantly more relapses than patients who stayed on their antipsychotics (Johnson 1976; Cheung 1981; Odejide and Aderounmu 1982; Sampath et al. 1992; Leucht et al. 2011b). Furthermore, a vast majority of patients who do not undergo any form of antipsychotic therapy experience a relapse within 3–5 years. Therefore, continuous antipsychotic treatment for patients suffering from multi-episode schizophrenia has been recommended by various publications (Kissling 1991; DGPPN 2006; Falkai et al. 2006). Up to 20% of individuals will only experience a single episode, while a similar or even higher percentage will experience a relapse despite continued antipsychotic drug treatment (Möller and van Zerssen 1995; Robinson et al. 1999; Moller 2004; Falkai et al. 2006). An observational study in outpatients with schizophrenia in 10 European countries revealed a constant relapse rate throughout the observation period, indicating a disease-dependent relapse rate (Haro et al. 2007). Psychiatrists may experience pressure from patients and their families to discontinue antipsychotic medication after patients recover from an episode of schizophrenia but, as discussed above, studies indicate that the rate of relapse after an acute psychotic episode is relatively high. Given the fact that there are no reliable predictors of prognosis or drug response, pharmacological relapse prevention should be considered for every patient diagnosed with schizophrenia. Possible exceptions are individuals with very brief psychotic episodes without negative psychosocial consequences, and the uncommon patient for whom all available antipsychotics pose a significant health risk (Fleischhacker and Hummer 1997; NICE 2002; 2010).

Summary statements

Recommendations for treatment durations in schizophrenia do not have a strong empirical basis and further studies are needed to provide better evidence-based recommendations. Most recommendations are based on small studies, expert's opinions and clinical experience. However, there is a high risk of relapse if patients stop their medication during the first 1–2 years following acute psychosis.

– A continuous antipsychotic for at least one year for first-episode patients is recommended *(Category of evidence C, Recommendation grade 4)*.

– For multiple-episode patients, maintenance treatment duration of at least 2–5 years (in severe cases life-long treatment) should be taken into consideration *(Category of evidence C, Recommendation grade 4)*.

– Nevertheless, the duration of treatment should be determined on an individual basis, taking into account the patient's motivation, the psychosocial situation and the additional care being given. Indefinite continuation of antipsychotic medications is recommended for patients with a history of serious suicide attempts or violent, aggressive behaviour and very frequent relapses *(Category of evidence C, Recommendation grade 4)*.

Treatment strategies (continuous treatment vs. intermittent treatment)

Intermittent dosing therapy with neuroleptic agents and incremental dose reductions until discontinuation (tapering off), careful observation and early repeated dose increases at the first signs of disease were shown to be inferior to continued treatment as they result in a higher frequency of relapse and hospital admissions in first-episode and multiple-episode schizophrenia patients (Schooler 1993; Schooler et al. 1997; Wunderink et al. 2007; Gaebel et al. 2002, 2011; Takeuchi et al. 2012).

Therefore, continuous antipsychotic treatment for relapse prevention is strongly recommended *(Category of evidence A, Recommendation grade 1)* and intermittent strategies should be avoided. The latter might only be appropriate for individuals with schizophrenia who are unwilling to accept a continuous maintenance regimen or if there are contraindications for continuous maintenance therapy (NICE 2010). Furthermore, intermittent dosing therapy requires early intervention strategies.

Early intervention

This part has been adopted from the first version of these guidelines and updated where necessary. Early intervention when prodromal symptoms appear can be effective in preventing relapse and rehospitalisation, and is part of psychiatric management. Studies have shown that relapse is usually preceded by the appearance of prodromal symptoms, which may last a few days, several weeks, or longer. The prodromal phase of relapse usually consists of moderate to severe symptoms, such as tension and nervousness, eating less, difficulty concentrating and remembering, trouble in sleeping, and depression, and it may also include mild psychotic symptoms and idiosyncratic behaviours. Such changes preceding relapse indicate either the emergence of new symptoms or increases in symptoms that were already present at baseline. In addition to these symptoms, changes in observable behaviours are noted by some patients and families. Examples include social withdrawal, wearing makeup in excessive or bizarre ways, and loss of concern for one's appearance (APA 1997).

Controlled studies have demonstrated that specific programmes designed to educate patients and families about prodromal symptoms and early intervention when symptoms occur can be helpful in reducing relapse rates (APA 1997; Lehman et al. 2004) *(Category of evidence B, Recommendation grade 3)*. One aspect of early intervention may also be to reinstall pharmacological treatment if it had been previously withdrawn, or to increase the dose of the antipsychotic currently being administered. The use of benzodiazepines may be helpful in reducing the anxiety and tension often associated with the start of a relapse (Carpenter et al. 1999; Lehman et al. 2004) *(Category of evidence C, Recommendation grade 4)*.

Long-acting depot medication (see Recommendation Table I)

Poor and partial adherence to oral antipsychotic treatment occurs in more than 40% of patients (Cramer and Rosenheck 1998) and is a major problem associated with the long-term management of schizophrenia. A direct relationship between partial medication adherence and hospitalisation risk has

Recommendation Table I. Recommendations for the antipsychotic treatment of schizophrenia patients with long-acting injectables.

Depot antipsychotic	Category of evidence[a]	Recommendation[b]
FGAs	A	1
Risperidone	A	1
Paliperidone	A	1
Olanzapine	(A)/B	(2)/3[1]

[a]Category of evidence: Category of evidence where A = full evidence from controlled studies (see Table I).
[b]Safety rating = recommendation grade derived from categories of evidence and additional aspects of safety, tolerability, and interaction potential.
[1]Olanzapine pamoate was recently launched and it is associated with the postinjection delirium sedation syndrome. Furthermore, we could not identify a comparator study between olanzapine pamoate and another depot antipsychotic. For these reasons, the highest category of evidence cannot currently be stated (see main text for details).

been demonstrated (Weiden et al. 2004). The development of long-acting depot antipsychotics has provided an important option, especially in the management of partial nonadherence. Since the initial draft of these guidelines in 2006 and in addition to the first long-acting SGA risperidone, two new long-acting antipsychotics have been launched onto the market (paliperidone palmitate and olanzapine pamoate) and some new studies and meta-analyses have been conducted.

Long-acting depot antipsychotics mostly consist of an ester of the antipsychotic agent in an oily solution which has to be administered by deep intramuscular injection. Following injection, the drug is slowly released from the injection site (an exception is risperidone). This results in relatively stable plasma drug levels over long periods, allowing the injections to be given every 2–4 weeks. The advantages of long-acting depot antipsychotics have to be balanced against some disadvantages. The following list has been adopted and modified from a publication by Nasrallah (2007) as well as the 2006 version of these guidelines.

Advantages of long-acting antipsychotics:

  – Improved compliance
  – Less need to remind patients to take their medication
  – Lowest effective dose principle more safely achieved (step-wise reduction)
  – Avoidance of gastrointestinal absorption problems
  – Circumvention of liver first-pass metabolism
  – Reduced risk of accidental or deliberate overdose

Disadvantages of long-acting antipsychotics:

  – Diminished flexibility of administration
  – Adjustment to the optimal dosage is a protracted and uncertain process
  – Delayed disappearance of distressing side effects after discontinuation of medication
  – Occasional local tissue reactions at the site of the injection (risk of pain, oedema, pruritis, sometimes a palpable mass).

Nevertheless, some patients already receiving depot antipsychotics prefer this method of application because they consider depot antipsychotics to be more convenient compared to oral antipsychotics (Walburn et al. 2001).

Although effective in improving treatment adherence and reducing relapse rates, these drugs are rarely prescribed in some countries like, US or France, whereas in other countries (e.g., UK and Australia) the long-acting antipsychotics are used frequently (Patel et al. 2009; Leucht et al. 2011a).

First-generation depot antipsychotics

Studies comparing the antipsychotic depot with placebo are very rare. Most reliable data are available from meta-analyses, which raise certain methodological problems (Leucht et al. 2009c). Studies comparing depot medication against placebo could only be identified for bromperidol, fluphenazine, fluspirilene and haloperidol. From one Cochrane review, there is limited evidence that bromperidol decanoate is superior to placebo, but not superior to fluphenazine or haloperidol depot (Purgato and Adams 2011). For haloperidol decanoate, only sparse data exists, but there is suggestion that it may improve symptoms in schizophrenia significantly better than placebo and there are no clear differences between the oral and the depot formulation (Quaraishi et al. 1999). Depot fluphenazine (decanoate or enanthate) has been studied extensively and a Cochrane Review included a total of 70 studies. This meta-analysis indicated that fluphenazine depot is superior to placebo with regard to long-term relapse rates, but failed to show this superiority in medium-term studies (6 months to 1 year). Furthermore, fluphenazine decanoate seems to be superior to fluphenazine enanthate, but no clear differences between the depot and oral forms of fluphenazine could be detected (David et al. 2005). In one trial, fluspirilene failed to show superiority over placebo, but a meta-analysis including 12 RCTs indicated that fluspirilene is not inferior to other depot antipsychotics (Abhijnhan et al. 2007). However, the evidence for other FGA depot formulations is assumed because their oral forms displayed sufficient effectiveness in preventing relapse. A systematic meta-review for depot antipsychotics discussed the problem of testing depot antipsychotics versus placebo because of the availability of effective treatment regimes (Adams et al. 2001). However, the limited data indicate that depot antipsychotics are effective in preventing relapse in schizophrenia, and this finding is supported from a magnitude of studies testing one depot antipsychotic against another. According to this meta-review, only a slight advantage of depot medication over oral medication could be concluded with weak evidence. Furthermore, no clear advantages of one depot over another could be found (Adams et al. 2001). This is in line with the findings of the Cochrane Reviews, but contrary to the findings of an early meta-analysis discussing a

superiority of depot formulations by assuring adherence (Davis et al. 1994).

Across the literature there has been discussion about whether the inclusion of inpatients and the short duration of trials might have reduced the advantages of depot medication (Leucht et al. 2011a). Therefore, one recently published meta-analysis (10 RCTs) focused on long-term (≥ 1 year) RCTs comparing depot (8 first-generation depots, two second-generation depots) versus oral formulations in outpatient settings (Leucht et al. 2011a). In this analysis, depot antipsychotics were superior to oral antipsychotics with regard to relapse, but not to rehospitalisation due to psychopathology, dropout rates and non-adherence (Leucht et al. 2011a). Finally, the recent PORT guidelines recommend the use of haloperidol decanoate and fluphenazine decanoate for the maintenance treatment of schizophrenia (Buchanan et al. 2010).

Summary statement

  – Currently, there is good evidence to support the use of FGA depot antipsychotics for relapse prevention in schizophrenia *(Category of evidence A, Recommendation grade 1)*, but no clear difference in efficacy between oral and depot formulations can be stated *(Category of evidence A, Recommendation grade 1)*.

Second-generation depot antipsychotics

In 2006, long-acting risperidone was the only SGA depot formulation. At the time of development of these guidelines, three different SGA depot formulations were available: risperidone microspheres, paliperidone palmitate and olanzapine pamoate.

Risperidone microspheres (risperidone depot)

The preparation consists of an aqueous suspension of microspheres comprising risperidone and a biodegradable copolymer, and the injection interval is 2 weeks. However, before applying the depot alone, there is a need for oral supplementation of oral risperidone for the first 3 weeks. With this mechanism, significant release of risperidone starts 3 weeks after the first injection, and is followed by gradual and sustained release for 4–6 weeks following the first injection (Harrison and Goa 2004). In a 12-week multicentre, double-blind RCT study, long-acting risperidone was superior compared to placebo with regard to psychopathology according to the PANSS

scale (Kane et al. 2003). This finding is supported by the results of two other 12-week, double-blind placebo-controlled studies, that demonstrated the superiority of long-acting risperidone with regard to psychopathology and treatment response compared to placebo (Ciliberto et al. 2005; Lauriello et al. 2005).

In two studies (Harrison and Goa 2004; Chue et al. 2005), no differences between oral risperidone and risperidone microspheres could be detected in terms of efficacy, whereas one 12-week RCT showed that risperidone given in the form of a long-acting injection was superior to oral risperidone with regard to the PANSS positive subscore and side effects, but not with respect to other PANSS scores (Bai et al. 2006).

In the open-label phase III of the CATIE study, no difference in efficacy between various SGAs, perphenazine, fluphenazine and risperidone, given in a long-acting injectable form, could be found (Stroup et al. 2009). Furthermore, long-acting injectable risperidone (25–50 mg) was not shown to be superior to oral olanzapine (5–20 mg) after 13 weeks of treatment and after a 12-month follow up (618 patients randomised and treated and 347 patients completed the trial) (Keks et al. 2007). In the first published naturalistic long-term 2-year-prospective study (e-STAR), a risperidone long-acting injection was found to be superior to an oral SGA (risperidone or olanzapine) in terms of Clinical Global Impression Severity and the number of hospitalizations (Olivares et al. 2009). A long-term 2-year open-label study evaluated the switch from stable treatment with oral risperidone, olanzapine, or conventional neuroleptics to long-acting injectable risperidone or to oral quetiapine. Kaplan–Meier estimates showed that the time until relapse was significantly longer for patients treated with long-action injectable risperidone compared to patients treated with oral quetiapine (Gaebel et al. 2010). However, in unstable patients, defined as those having been hospitalised within the previous 2 years or having an imminent risk for hospitalisation, other results have been reported. This was tested in a large, recently published randomized study from the Veterans Affairs Clinical Centre (Rosenheck et al. 2011). Unstable patients were either treated with long-acting injectable risperidone every 2 weeks or with a psychiatrist's choice of an oral antipsychotic. The analyses revealed that the relapse rate after randomization was not significantly lower among patients who received long-acting injectable risperidone than among those who received oral antipsychotics, but that patients treated with the depot had more adverse effects at the injection site and more motor side effects (Rosenheck

et al. 2011). One study based on observational data from the Cohort for the General study of Schizophrenia (CGS) showed that long-acting risperidone was especially prescribed in younger and more frequently hospitalised patients (regardless of disease severity). However, even after correction for these factors, long-acting risperidone was associated with a significant lower risk for hospitalisation compared to other treatment options (non-use or other depot formulations or oral formulation of FGAs or SGAs) (Grimaldi-Bensouda et al. 2011).

Three studies with long-acting injectable risperidone have been conducted in special groups of schizophrenia patients: (1) first-episode schizophrenia patients; (2) elderly patients suffering from schizophrenia; (3) schizophrenia patients with concomitant drug abuse.

In first-episode schizophrenia patients, long-acting injectable risperidone was well tolerated and led to more treatment adherence than oral risperidone in a prospective RCT (Weiden et al. 2009). Another long-term 2-year open-label study with first-episode schizophrenia patients revealed that 64% of the patients achieved remission and that 97% of the patients maintained this status until study completion (Emsley et al. 2008). A publication including subjects who participated in a foregoing 12-weeks study showed that long-acting injectable risperidone is safe and well tolerated after 12 months of treatment in schizophrenia patients (Lindenmayer et al. 2007), and safety has also been demonstrated in elderly patients (≥ 65 years) (Kissling et al. 2007). In a subsample of schizophrenia patients with comorbid substance abuse, long-acting risperidone was superior to zuclopenthixol-depot in an open, randomized, controlled 6-month study (Rubio et al. 2006).

Finally, a 52-week double-blind, randomized study showed that the combination of galantamine and long-acting injectable risperidone was not superior to the combination of placebo and risperidone depot in terms of the improvement in different cognitive domains (Lindenmayer and Khan 2011).

Summary statements

– There is good evidence to support the use of long-acting injectable risperidone for the treatment of schizophrenia *(Category of evidence A, Recommendation grade 1)*.
– There is some evidence to support a superiority of the depot compared to the oral preparation *(Category of evidence C, Recommendation grade 4)*.
– There is some evidence for the use of long-acting injectable risperidone in first-episode schizophrenia patients and elderly patients suffering from schizophrenia *(Category of evidence B, Recommendation grade 3)*.
– There is no evidence to support the combination of galantamine and risperidone depot for the treatment of cognitive symptoms in schizophrenia *(Category of evidence E)*.

Paliperidone palmitate (paliperidone depot)

Paliperidone palmitate is the depot formulation of oral paliperidone. It has low water solubility and diffuses slowly into systemic circulation following injection. Treatment with paliperidone palmitate does not require oral supplementation during the initiation of treatment (Hough et al. 2009). It was approved by the FDA according to the results of four short-term (9–13 weeks) studies comparing paliperidone palmitate with placebo (20% intralipid 200 mg/ml injectable) (Citrome 2010). These first studies, showed that paliperidone palmitate is effective in the treatment of schizophrenia in different symptom domains (Citrome 2010). In a recently published RCT, patients suffering from schizophrenia were either randomised to placebo injection, to an injection of 50 mg paliperidone palmitate or to 100 mg paliperidone palmitate on days 1, 8 and 36 (Kramer et al. 2010). Both dosages were superior to placebo with regard to reduction of total PANSS scores, CGI scores and the factor "study discontinuation". Furthermore, paliperidone palmitate was well-tolerated and did not cause more motor side effects (whereas the percentage of patients receiving medication against motor side effects was higher in the 100-mg group), but did cause significantly more weight gain than placebo (Kramer et al. 2010). In another study, schizophrenia patients were switched from a stable antipsychotic treatment to paliperidone palmitate in a 9-week, open-label phase. Patients then received two intramuscular injections of paliperidone palmitate (50mg) one-week apart, followed by subsequent injections (25, 50 or 100mg in a flexible-dose scheme) once monthly. Next, stable patients were either randomized to paliperidone palmitate (at the stabilized dose) or to placebo in a double-blind study phase. Paliperidone palmitate was superior to placebo, both in a planned interim analysis and in the final analysis, with regard to the primary endpoint time-to-relapse (Hough et al. 2010). A 13-week, double-blind study with 388 schizophrenia patients compared three different dosages of paliperidone palmitate (50, 100, 150 mg) with placebo. In this study, only 100 mg paliperidone palmitate showed a significant effect on the reduction of PANSS scores (Gopal et al. 2010b).

Another 13-week study with a comparable design (25, 100, 150 mg paliperidone palmitate vs. placebo) showed a superiority for reducing PANSS score in all treatment groups compared to placebo in a sample of acutely exacerbated schizophrenia patients (Pandina et al. 2010). One further 13-week study compared 25, 50 and 100 mg paliperidone palmitate with placebo and showed a significant improvement in all treatment groups compared to placebo (Nasrallah et al. 2010). The first open-label double-blind 1-year long-term study (extension of the double-blind study by Hough and colleagues (2010)) investigated a flexible dose of paliperidone palmitate (Gopal et al. 2011). In this study, psychopathology improved during the open-label extension and 100 mg paliperidone palmitate was administered most frequently (Gopal et al. 2011). However, the authors did not compare relapse rates across the different dosages of paliperidone palmitate.

Comparative studies (one double-blind 13-week RCT and one open-label study) have shown paliperidone palmitate not to be inferior to long-term injectable risperidone, and that both drugs seem to have a related side effect profile (Li et al. 2011; Pandina et al. 2011). A 53-week, Phase III double-blind study in acute symptomatic patients confirmed there to be no inferiority of paliperidone palmitate compared to long-term injectable risperidone (Fleischhacker et al. 2011).

A subgroup analysis with severely ill schizophrenia patients (according to CGI) showed paliperidone palmitate to be superior to placebo by day 4 of treatment (Alphs et al. 2011). A post hoc analysis of a 13-week, double-blind placebo-controlled study indicated that, in patients who received oral risperidone but who remained symptomatic, paliperidone palmitate was superior to placebo with regard to improvements in PANSS total scores, CGI scores and scores of personal and social performance (Sliwa et al. 2011).

Summary statements

- In summary, there is good evidence to support the use of long-acting injectable paliperidone for the treatment of schizophrenia *(Category of evidence A, Recommendation grade 1)*.
- There is no evidence that allows us to state a superiority of the depot compared to oral paliperidone *(Category of evidence A, Recommendation grade 1)*.
- Paliperidone depot seems to be as effective as risperidone depot *(Category of evidence A, Recommendation grade 1)*.

Olanzapine pamoate (olanzapine depot)

This depot formulation consists of a crystalline salt-formulation composed of olanzapine and pamoic acid (pamoate) (Citrome 2009). In an 8-week, double-blind study, schizophrenia patients were randomly assigned to receive 210 mg/2 weeks, 300 mg/2 weeks, or 405 mg/4 weeks of long-term injectable olanzapine or placebo/2 weeks. No other concomitant oral antipsychotic treatment was permitted (Lauriello et al. 2008). After 3 days, the high dosages were superior to placebo with regard to reduction of PANSS scores, and this superiority was reached for all three dosages after 1 week of treatment. However, olanzapine pamoate led to more sedation and weight gain than placebo (Lauriello et al. 2008). In a 24-week double-blind study, schizophrenia patients who were stable on an oral olanzapine treatment (10, 15, or 20 mg/day) were randomised to treatment with one of three different dosages of long-term injectable olanzapine (150 mg/2 weeks, 405 mg/ 4 weeks, 300 mg/2 weeks), to a low reference dose of the depot (45 mg/ 4 weeks), or to their stabilisation dose of oral olanzapine (Kane et al. 2010). Analyses showed that "the majority of oral olanzapine-treated patients (93%), as well as most olanzapine long-acting injection-treated patients receiving high (95%), medium (90%), low (84%), and very low doses (69%), remained exacerbation free, with the therapeutic 4-week regimen (medium dose) and pooled 2-week regimen (low and high doses) demonstrating efficacy similar to that of oral olanzapine as well as to each other" (Kane et al. 2010). The standard doses were superior to the very low doses, and metabolic side effects increased with increasing dosages of olanzapine (Kane et al. 2010).

Postinjection delirium sedation syndrome (PDSS)

A rare, but potential harmful, side effect was observed during the clinical trials with the long-acting olanzapine injection. The postinjection delirium sedation syndrome (PDSS) is mainly characterized by symptoms associated with olanzapine overdose. This symptom cluster includes dizziness, confusion, disorientation, slurred speech, altered gait, weakness, muscle spasms, possible seizure, and varying degrees of sedation (Detke et al. 2010). However, other symptoms of an olanzapine overdose, like hypotension or respiratory depression, have not been reported after injection of the olanzapine depot (Detke et al. 2010). It should be noted that the PDSS can occur after any injection regardless how many prior uneventful injections the patient may have had (Citrome 2009). The risk for PDSS is greatest within the first hour after injection ($<$ 1 in 1000 injections),

and the risk decreases between hours 1 and 3 (<1 in 10,000 injections after 3 h (Detke et al. 2010)). After PDSS, the median time to recovery resolve from all symptoms is between 24 and 72 h – for seven patients unconsciousness was reported and the longest period of unconsciousness was 12 h (Detke et al. 2010). As olanzapine pamoate has a higher solubility in blood than in muscle, the possibilities of accidental injections into a blood vessel or accidental entry of olanzapine pamoate directly into the bloodstream without a direct injection into the vessel (injury of a blood vessel during the injection process) have been discussed (Citrome 2009; McDonnell et al. 2010).

Therefore, a proper injection technique (aspiration of several seconds to ensure that no vessel has been hit, deep intramuscular injection) and observation of the patients for at least three hours by professional healthcare personnel must be strictly adhered to (Citrome 2009; McDonnell et al. 2010). Other rules of action are described by the manufacturer and by other reviews (Detke et al. 2010; McDonnell et al. 2010).

Summary statements

– There is good evidence to support the use of long-acting injectable olanzapine *(Category of evidence (A)/B, Recommendation grade (2)/3)*. It should be mentioned that we were not able to identify a comparator study between olanzapine pamoate and another depot antipsychotic.
– The postinjection delirium sedation syndrome needs to be considered as a possible severe side effect after every injection.
– Each injection should follow the rules of action described by the manufacturer and after each injection, a three hour observation period needs to be respected *(Category of evidence C, Recommendation grade 4)*.

Dosages of depot formulations (see Table V)

According to the PORT guidelines, the recommended dosage range for fluphenazine decanoate is 6.25 mg/2 weeks to 25 mg/2 weeks and, for haloperidol decanoate, is 50 mg/4 weeks to 200 mg/4 weeks. These recommendations have been based on both the findings of Kane and colleagues and an early review by Dixon and colleagues (Dixon et al. 1995; Kane et al. 2002).

One study investigated the equivalent switching dose from oral risperidone to long-acting risperidone injection in hospitalized patients. According to the findings of this study, switching doses are suggested as follows: patients who were originally on an oral risperidone dose of ≤ 3 mg/day should receive 25 mg of long-acting risperidone injection, those taking an oral dose of 3–5 mg/day should receive 37.5 mg, and those taking an oral dose of >5 mg/day should receive 50 mg of long-acting risperidone injection (Bai et al. 2007). A 1-year double-blind RCT compared 25 and 50 mg of long-acting risperidone in stable patients suffering from schizophrenia and found a numeric, but not a statistically significant, difference between both dosages. In total, 25–50 mg risperidone microspheres were found to be appropriate for the long-term treatment of schizophrenia and schizoaffective disorder (Simpson et al. 2006).

Treatment with paliperidone palmitate can be initiated after discontinuing previous treatment with an oral antipsychotic (no oral supplementation is required) or at the next scheduled injection, and monthly thereafter, in patients switching from another depot antipsychotic (including long-acting injectable risperidone) (Gopal et al. 2010a). Paliperidone palmitate should be initiated with 150 mg at day 1 and then with 100 mg at day 8 (± 2 days). Both injections should be applied to the same muscle to reach adequate drug concentrations quickly. After day 8, paliperidone should be injected

Table V. Recommended dosages of depot antipsychotic medications in long-term treatment.

Antipsychotic	DI (dose intervals, weeks)	First-episode patients (mg)	Multi-episode patients (mg)
SGA			
Risperidone microspheres	2	25	25–50
Paliperidone palmitate	4	25–75	25–150
Olanzapine pamoate	2–4	150–210/2 weeks	150–210/2 weeks
		300–405/4 weeks	300–405/4 weeks
FGA			
Flupentixol decanoate	2–3	20–40	20–100
Fluphenazine decanoate	2–4	6.25–37.5	12.5–50
Haloperidol decanoate	4	50–100	100–200
Perphenazine decanoate	2–4	12–100	50–200
Zuclopenthixol decanoate	2–4	100–200	200–400

every month ($\pm$ 7 days) with dosages in the range of 25–150 mg (Gopal et al. 2010a).

For long-acting olanzapine injection, the oral-to-dose correspondence was explored in a 24-week study. Patients receiving oral olanzapine in a dose of 10 mg/day can be switched to 405 mg/4 weeks, and patients receiving 15 or 20 mg/day can be switched to 300 mg/2 weeks without increasing risk of relapse (Detke et al. 2011). Further analyses of the 24-week maintenance study described earlier (Kane et al. 2010) indicate that side effects and efficacy show a dose-association in schizophrenia patients treated with long-acting olanzapine injection (Hill et al. 2011).

Other than the advice documented in this chapter, recommended dosage range might also be based on recommendations given by the manufacturers.

Summarised recommendations for long-term treatment

In first- and multiple-episode schizophrenia patients, antipsychotic medications substantially reduce the risk of relapse in the stable phase of illness and are strongly recommended. The choice of long-term medication should be made jointly by the patient and the clinician based on adequate information about the benefits and side effects (Lehman et al. 2004; NICE 2010; Leucht et al. 2011b) – for the latter, tardive dyskinesia and metabolic side effects in particular need to be addressed and monitored.

If possible, family members, caregivers and in some cases advocates should also be included in the decision process. In long-term treatment/ maintenance treatment, the antipsychotic medication which was able to achieve remission with the most favourable side effect profile should be given. Selecting the target dose of an antipsychotic medication during the stable phase is complicated by the fact that there is no reliable strategy available to identify the minimum effective dose to prevent relapse. As outlined before, there is no evidence that high maintenance doses (e.g., more than 600 mg CPZ equivalents for FGAs) are more effective in preventing relapse than standard doses (Bollini et al. 1994). However, it should be kept in mind that first-episode patients may require lower doses in relapse prevention than multiple-episode patients. The lowest dose should be chosen at which, preferably, no side effects occur, the risk of relapse seems to be optimally reduced and, if symptoms are still present, suppression of these is optimised. Side effects have to be assessed and, if necessary, pharmacotherapy has to be adjusted.

However, too rapid and too extreme dosage reduction should be avoided.

The reduced risk for tardive dyskinesia following treatment with FGAs might favour the use of SGAs, although the risk of developing metabolic and cardiovascular side effects following treatment with some SGAs needs to be taken into consideration. Certain SGAs (as described in these guidelines) might be superior in terms of relapse prevention.

The reader should keep in mind that the categorization of antipsychotics into FGAs and SGAs (or typical and atypical antipsychotics) does not follow any clear neurobiological (apart from a higher D2-binding of FGAs compared to most SGAs) or clinical rules, and that the drug with the best balance between efficacy and side effect profile and which is best tolerated (for compliance reasons) should be chosen for long-term therapy. Antipsychotics with the best profile for motor and metabolic side effects do have some advantages, but there is not enough data to make clear evidence based recommendations for a particular drug. Switching strategies and the management of treatment-resistance were described in the first part of these guidelines.

As continuous dosing strategies have revealed superiority compared to intermittent-dose strategies, continuous oral or intramuscular administration of an antipsychotic medication is preferable to other treatment strategies.

In all cases, the prodromal signs of relapse should be regularly monitored and a dose adjustment made if relapse is imminent. In stable remission, and if there are valid reasons against continuing long-term medication (e.g., due to lack of acceptance), relapse prevention with intermittent antipsychotic treatment and prodrome-based early intervention can be attempted, particularly in first-episode patients with a favourable prognosis. In this type of strategy, it is important that the patient should detect his or her own early warning signs and establish an individual crisis network.

Depot preparations should be a treatment option when a patient expresses a preference for such treatment in order to ensure compliance. As a consequence of side effects or as a result of discussions with the patient, low-dose continuous depot medication may be advisable if oral medication is added in case of early prodromal signs of relapse. For optimum effectiveness in preventing relapse, depot preparations should be prescribed within the standard recommended dosage and interval range. It may be good clinical practice that, before depot medication is applied, test doses of the oral form should be used to avoid unexpected severe side effects.

Quality of life

Apart from the improvements in psychopathology and social function, optimisation of an individual patient's subjective wellbeing and quality of life should be one of the major goals in the long-term management of schizophrenia.

A number of tools (e.g., the Quality of Life (QLS) scale, Sickness Impact Profile (SIP), Medical Outcomes Study Short-Form 36-item questionnaire (SF-36)) have been used to measure aspects of quality of life in patients. Some were developed especially for patients receiving antipsychotic treatment (e.g., the Subjective Wellbeing under Neuroleptic Treatment (SWN) scale). Regarding quality of life, this parameter is rarely the primary outcome parameter of the clinical trials and, therefore, the trials are usually not powered to detect differences between drugs for this parameter per se.

In the last version of these guidelines, we stated that **amisulpride** (Carriere et al. 2000; Colonna et al. 2000; Saleem et al. 2002), **clozapine** (Essock et al. 1996; Rosenheck et al. 1997, 1998, 1999), **olanzapine** (Hamilton et al. 1998, 2000; Revicki et al. 1999), **quetiapine** (Awad and Voruganti 2004), **risperidone** (Mahmoud et al. 1999; Voruganti et al. 2000) and **zotepine** (Voruganti et al. 2000) showed a trend towards a superiority compared to FGAs. However, even in 2006 there were inconclusive studies with inconsistent results (Falkai et al. 2006). Moreover, the findings from the CATIE and the CUtLASS questioned the superiority of SGAs in improving quality of life. The situation becomes even more complicated when considering side effects (motor side effects and metabolic side effects) which can have a great influence on quality of life. Three publications form the CATIE sample indicate that there is no difference between SGAs and the FGA perphenazine with regard to employment outcomes and participation in psychosocial rehabilitation (Resnick et al. 2008), quality of life (Swartz et al. 2007) and quality-adjusted life years (Rosenheck et al. 2006), but these parameters were not the primary outcome parameter of the study. These results were confirmed by the findings of the CUtLASS study which showed no significant difference in quality of live improvement (primary outcome parameter) between SGAs and FGAs (mainly sulpiride, which can be considered as the most atypical FGA) (Jones et al. 2006). However, limitations of these studies are well-known and need to be considered when discussing their results (Moller 2008; Naber and Lambert 2009). A small 2-year study comparing haloperidol with risperidone and another 1-year study comparing olanzapine with haloperidol did not reveal differences in improving quality of life

between FGAs and SGAs (Marder et al. 2003; Rosenheck et al. 2003). However, the findings of Marder and colleagues indicate that patients appear to feel subjectively better in the risperidone group (Marder et al. 2003). This is in line with other studies indicating an improvement in subjective wellbeing after treatment with SGAs (Wehmeier et al. 2008; Naber and Lambert 2009).

The EUFEST study used the Manchester short assessment of quality of life scale and did not find a difference between haloperidol and SGAs with regard to this secondary-outcome parameter (Kahn et al. 2008). One study conducted on first-episode schizophrenia patients did not reveal differences for quality of life measurements when comparing haloperidol with risperidone (Gaebel et al. 2007) or when comparing haloperidol with olanzapine (Strakowski et al. 2005). Furthermore, a 52-week comparison between three different SGAs (olanzapine, quetiapine and risperidone) did not indicate a superiority of any one drug over any other one with regard to quality of life (McEvoy et al. 2007). When considering all these quality of life data, it is important to bear in mind that self-reported quality of life scales might not be sensitive enough to differentiate between different treatment conditions (Moller 2008).

Summary statements

- Antipsychotics do improve quality of life in schizophrenia patients, but no evidence can be found in favour of one particular antipsychotic drug or a group *(Category of evidence A, Recommendation grade 1)*.
- However, it should be mentioned that side effects do influence quality of life and that both the reduction and careful management of side effects are important in order to improve quality of life *(Category of evidence C, Recommendation grade 4)*.
- There is some evidence that subjective wellbeing is greater following treatment with certain SGAs, as discussed above *(Category of evidence B, Recommendation grade 3)*.

Management of relevant side effects

In Part 1 of these guidelines, the relevant side effects of antipsychotics were described in detail. It is important to note that both FGAs and SGAs, dependent on their individual receptor binding profile share neurological side effects (e.g., acute and long-term extrapyramidal symptoms including tardive

dyskinesia, malignant neuroleptic syndrome), sedation, cardiovascular effects, weight gain, metabolic side effects, anticholinergic, antiadrenergic and antihistaminergic effects, hyperprolactinaemia, agranulocytosis and sexual dysfunctions (see Part 1 of these guidelines).

Monitoring of side effects is based on the specific side effect profile of the prescribed antipsychotic. During the stable phase it is important to monitor all patients routinely for weight gain (weight, waist circumference), extrapyramidal symptoms, cardiovascular and metabolic side effects. Great attention should be paid to monitoring of obesity-related health problems (e.g., high blood pressure, lipid abnormalities and clinical symptoms of diabetes). Therefore, clinicians should also consider regular monitoring of fasting glucose or haemoglobin A1c levels (HbA1c) to detect emerging metabolic syndrome and diabetes, since patients often have multiple risk factors for these syndromes, especially patients with obesity. SGAs have clear advantages with respect to motor side effects (especially tardive dyskinesia) compared to FGAs. These advantages have to be weighed against other side effects, for instance a higher risk of weight gain or diabetes mellitus with some agents. Adequate management of side effects may contribute to increased treatment adherence and better outcome. Therefore, strategies for the management of disabling side effects are reviewed and recommendations given in the following section. In particular, the sections "Neurological side effects" and "Metabolic side effects" received great attention during the update process due to the importance of these side effects and the volume of publications in this field. The section "Other side effects" contains statements from the last version of these guidelines, which have been updated where necessary. However, the reader should be aware that studies with high scientific quality in this area are rare and that management of side effects is still receiving less attention than improving symptomatology. Special attention should be given to the fact that many of the statements are based on meta-analytical findings, which carry certain methodological problems (e.g., comparability of included studies or underlying sample sizes), leading to different interpretations of experimental psychopharmacology studies (Leucht et al. 2009c).

Neurological side effects

Neurological side effects are a great burden for patients and it is strongly recommended that screening for these side effects takes place. Older studies have indicated that neurological side effects remain often undiagnosed and therefore untreated (Weiden et al. 1987). Clinical psychiatrists should be trained to detect these potential severe symptoms. Neurological side effects are linked to FGAs, but SGAs carry an associated risk as well.

Extrapyramidal side effects (see Table VI)

Extrapyramidal side effects can be divided into acute (acute dystonic reactions, parkinsonism, akathisia) and chronic (tardive dyskinesia) categories. Acute extrapyramidal side effects are signs and symptoms that occur in the first days and weeks of antipsychotic medication administration, are dose dependent, and are reversible with medication dose reduction or discontinuation (APA 1997).

Acute dystonic reaction

This side effect typically arises at the beginning of an antipsychotic treatment or when a dosage is increased. As outlined in Part 1 of these guidelines, it is more common in younger patients and it is related to high doses of antipsychotics (Singh et al. 1990). Acute dystonic reactions respond dramatically to the administration of anticholinergic or antihistaminic medication (APA 1997) *(Category of evidence C, Recommendation grade 4)*. Parenteral administration will have a more rapid onset of action than oral administration. If the first application does not disrupt the acute dystonic reaction, anticholinergic or antihistaminic medication can be given again.

Parkinsonism

Parkinsonism usually develops several days or weeks after initiation of an antipsychotic treatment. Antipsychotic-induced parkinsonism generally resolves itself after discontinuation of antipsychotic medication *(Category of evidence C, Recommendation grade 4)*, although some cases of persisting symptoms have been reported (Melamed et al. 1991). The primary treatment of drug-induced parkinsonism consists of preventative and therapeutic dose reductions or the administration of certain SGAs *(Category of evidence C, Recommendation grade 4)*. If this is not possible, administration of anticholinergic agents (e.g., biperiden) or dopamine agonists should be considered. However, dopamine agonists, such as bromocriptine, carry a potential risk of exacerbating psychosis, and anticholinergic drugs can cause anticholinergic side effects. Thus, excessive doses and chronic use of these agents should be avoided or minimised.

Table VI. Therapeutic options to manage antipsychotic side effects I (motor side effects and neuroleptic malignant syndrome). For categories of evidence see main text.

Side effect	Prevention	Treatment
Acute dystonic reactions	• Select antipsychotic with low rate EPS • Start with low dose • Increase dose slowly and stepwise	• Oral or intravenous application of anticholinergic drug, e.g., 2.5–5 mg biperiden, if necessary repeat procedure after 30 min, continue biperiden oral (maximal 12 mg/day)
Parkinsonism	• Select antipsychotic with low risk for parkinsonism • Increase dose slowly and stepwise	• Dose reduction or discontinuation of antipsychotic medication • Switch to SGA • Oral application of anticholinergic drug
Akathisia	• Select antipsychotic with low risk for akathisia • Increase dose slowly and stepwise	• Dose reduction • Oral application of beta-receptor-blocking agent (e.g., propranolol 30–90 mg/day) • Switch to certain SGAs • Oral application of benzodiazepines • Trial of an anticholinergic or an antihistaminic agent • Application of vitamin B6 • Application of trazodone
Tardive dyskinesia	• Select antipsychotic with low risk for tardive dyskinesia • Evaluate risk factors for tardive dyskinesia	• Switch to clozapine (alternatively to certain other SGAs) • Application of vitamin E • (Application of tiapride) • ECT (only case reports and case series) • Deep brain stimulation (treatment in severe cases) • Pallidotomy (last resort treatment in extremely severe cases)
Neuroleptic malignant syndrome (NMS)	• Select antipsychotic with low risk for NMS	• Intensive care management • Stop antipsychotic treatment • (Application of dantrolene i.v. (2.5–10 mg/kg body weight daily) • (Application of lorazepam 4–8 mg i.v./day) • In single cases ECT

Akathisia

Akathisia is linked to the initiation of antipsychotic treatment or to the switching from one agent to another. It is important not to mistake akathisia for psychotic agitation because the latter would usually be treated with antipsychotics, a strategy which would result in a further increase of akathisia. Akathisia seems to be less prevalent with SGAs than with FGAs, but akathisia can occur following treatment with every antipsychotic (Kumar and Sachdev 2009) – this finding highlights that psychiatrists should screen all patients treated with an antipsychotic for akathisia.

Several strategies have been used to decrease akathisia, but good evidence based data are still lacking. Treatment of akathisia consists of a dose reduction as a meaningful first step. In addition, effective treatments for akathisia include centrally acting beta-blockers, such as propranolol (30–90 mg/day), but the study sizes are very small and therefore should be interpreted with caution (Dupuis et al. 1987; Fleischhacker et al. 1990). However, a Cochrane Review including three studies could not confirm efficacy for beta-blockers in the treatment of akathisia (Lima et al. 2004a). There is only very limited evidence to support the use of centrally active

beta-blockers in the treatment of akathisia *(Category of evidence C, Recommendation grade 4)*. When these medications are administered, blood pressure and pulse rate should be monitored with dose changes.

In a Cochrane review, two small randomised controlled studies with a total sample size of 27 were analysed – in this analysis clonazepam was superior to placebo in reducing akathisia over a short follow-up period (7–14 days) (APA 1997; Kutcher et al. 1989; Pujalte et al. 1994; Lima et al. 2002). Therefore, some evidence exists that benzodiazepines are effective in the treatment of akathisia *(Category of evidence B, Recommendation grade 3)*, but the prolonged and extended use of benzodiazepines is associated with the risk of drug tolerance and dependence, which needs to be taken into consideration. Furthermore, the concomitant application of antipsychotics and certain benzodiazepines with a long half-time is discussed to increase mortality in schizophrenia patients (Baandrup et al. 2010).

There is no randomised, controlled trial which provides evidence for the use of anticholinergic drugs for treatment of akathisia (Rathbone and Soares-Weiser 2011). However, should a person suffer from distressing akathisia despite other treatment strategies, a trial of an anticholinergic or an antihistaminic agent may be warranted (Lima et al.

2004b; Vinson and Drotts 2001) *(Category of evidence C, Recommendation grade 4)*.

Vitamin B6 was tested for the treatment of acute neuroleptic-induced akathisia in a small placebo-controlled RCT. According to the Barnes Akathisia Scale, Vitamin B6 was superior to placebo in reducing akathisia (Lerner et al. 2004). Another small RCT in patients with neuroleptic-induced akathisia showed that both Vitamin B6 and mianserin were superior to placebo in reducing subjective distress. However, the differences reached only trend level in the objective assessments of akathisia (Miodownik et al. 2006). There is some little evidence to support the use of Vitamin B6 in akathisia *(Category of evidence C, Recommendation grade 4)*.

One small placebo-controlled, double-blind cross-over study in 13 patients indicated that trazodone might be efficient in the management of neuroleptic-induced akathisia (Stryjer et al. 2010) *(Category of evidence C, Recommendation grade 4)*.

Tardive dyskinesia

Tardive dyskinesia is a severe neurological side effect which mainly develops during long-term treatment with antipsychotics, but can also occur during a short-term treatment. SGAs, compared to FGAs have a benefit with regard to tardive dyskinesia (Tenback et al. 2005, 2010; Kasper et al. 2006; Correll and Schenk 2008). As outlined in the supplementary material of the PORT guidelines, all SGAs have been reported to be associated with new cases of tardive dyskinesia, but no difference in the incidence of tardive dyskinesia exists among various SGAs (Buchanan et al. 2010). There is good evidence to state that SGAs carry less risk for tardive dyskinesia compared to FGAs *(Category of evidence A, Recommendation grade 1)*.

Cessation of the antipsychotic is the first-line recommendation for the treatment of tardive dyskinesia in other guidelines and in textbooks, but meta-analyses of the Cochrane Schizophrenia group could not provide evidence for a positive effect of antipsychotic reduction/cessation as specific treatment for tardive dyskinesia (Soares-Weiser and Rathbone 2006). However, reducing antipsychotic dose is associated with the improvement of dyskinetic symptomatology (Kane et al. 1983; Cookson 1987) in studies with very small sample sizes. Reduction of antipsychotics is associated with a high risk of relapse and this risk must be weighed against the sparse evidence of this therapeutic approach.

The switch from one antipsychotic (usually FGA) to another one (usually SGA) has been proposed to have a beneficial effect on tardive dyskinesia. The PORT guidelines discuss this potential benefit of SGAs for the amelioration of tardive dyskinesia symptoms and state that there is no evidence to recommend SGAs for this purpose (Buchanan et al. 2010). However, there are some studies, partly reviewed in the PORT guidelines that might provide some hints towards a benefit of switching to an SGA. In a small 12-week double-blind, placebo-controlled study, the switch from an FGA to either risperidone or placebo after a 4-week washout period in patients suffering from schizophrenia and tardive dyskinesia was investigated (Bai et al. 2003). In this study, risperidone (68% responder) was superior to placebo (30% responder) in improving tardive dyskinesia (Bai et al. 2003). In a 48-week prospective follow-up study (36-week extended open-label study) by the same group, a long-term improvement of this switching strategy was detected (Bai et al. 2005). In a non-controlled blinded dose-reduction study with an observation period of 8 months, a switch to olanzapine reduced tardive dyskinesia, even after dose reduction of olanzapine (Kinon et al. 2004). In a small 12-month investigator-blinded randomized study, schizophrenia patients with tardive dyskinesia were tapered from all antipsychotics over 2 weeks and then treated with flexible doses of either quetiapine or haloperidol. The patients in the quetiapine group showed significantly more improvement in terms of tardive dyskinesia and scores of motor side effects (Emsley et al. 2004), and this positive effect of quetiapine was replicated in another small study (Cortese et al. 2008). One analysis from the CATIE sample compared 200 schizophrenia patients with tardive dyskinesia and 997 patients without tardive dyskinesia who were randomly assigned to receive one of four SGAs (olanzapine, quetiapine, risperidone, ziprasidone). This analysis did not show a significant difference between drugs in terms of a reduction of tardive dyskinesia, and most patients showed either persistence of or fluctuations in symptoms (Caroff et al. 2011). Although there are some trends towards a positive effect of switching from an FGA to an SGA on tardive dyskinesia, the evidence remains limited *(Category of evidence C, Recommendation grade 4)*. This can be explained by the lack of double-blinded RCTs and by the very small sample sizes of the published studies. Furthermore, a switch of antipsychotics can lead to worsening of symptoms.

A switch to clozapine is a frequently discussed strategy for the treatment of tardive dyskinesia. In a small open-label trial, seven schizophrenia patients with severe tardive dyskinesia were withdrawn from their antipsychotic medication for 1 week and then treated with clozapine for 24 weeks. This strategy led to an improvement in tardive dyskinetic symptoms (Bassitt and Louza Neto 1998), and these findings

were confirmed in a 5-year follow-up study (Louza and Bassitt 2005). A review including eight published studies indicated that tardive dyskinesia is responsive to clozapine, but that methodological limitations of the studies limits the quality of the data (Lieberman et al. 1991). This is in line with another small short-term study showing that clozapine might be effective for the treatment of tardive dyskinesia (Spivak et al. 1997). A study with humans and animals (oral dyskinesia; vacuous chewing movements every 5 min) showed that patients with pre-existing tardive dyskinesia responded to treatment with long-term clozapine (Tamminga et al. 1994). In summary, there is some limited evidence for a beneficial effect of clozapine on tardive dyskinesia, but double-blind RCTs are still lacking *(Category of evidence C, Recommendation grade 4)*.

Several other agents have been investigated with regard to their efficacy for improving tardive dyskinesia. Vitamin E may have small benefits (Soares-Weiser et al. 2011) *(Category of evidence C, Recommendation grade 4)*, whereas the use of anticholinergic drugs is not recommended because of the lack of evidence and due to adverse effects (Soares and McGrath 2000; Tammenmaa et al. 2002) *(Category of evidence F)*. Furthermore, there is no compelling evidence that benzodiazepines decrease tardive dyskinesia in a sufficient manner (Bhoopathi and Soares-Weiser 2006) and the risk of developing drug dependence is another important limiting factor *(Category of evidence F)*. One Cochrane review (updated 2010 with no change of conclusion) studied the effects of a miscellaneous group of compounds (botulinum toxin, endorphin, essential fatty acid, EX11582A, ganglioside, insulin, lithium, naloxone, oestrogen, periactin, phenylalanine, piracetam, stepholidine, tryptophan, neurosurgery, or ECT) for the treatment of tardive dyskinesia and did not find any of them to be effective (Soares-Weiser and Joy 2003) *(Category of evidence F)*.

In the absence of reliable evidence, the possible benefits of calcium channel blockers in the treatment of tardive dyskinesia have to be balanced against the potential adverse effects, e.g., lowering of blood pressure and even causing symptoms of tardive dyskinesia to increase (Soares-Weiser and Rathbone 2004) *(Category of evidence F)*.

The effects of GABAegeric agonists (baclofen, gamma-vinyl-GABA, gamma-acetylenic-GABA, progabide, muscimol, sodium valproate and tetrahydroisoxazolopyridine) on tardive dyskinesia are inconclusive and their use cannot be recommended (Alabed et al. 2011) *(Category of evidence F)*.

A review including three prospective studies, eight add-on trials, one case series and eight case reports indicated that tetrabenazine might have a positive impact on tardive dyskinesia (Leung and Breden 2011) *(Category of evidence C, Recommendation grade 4)*. In a naturalistic long-term follow-up study with six patients, the combination of tetrabenazine, clonazepam and clozapine resulted in a rapid improvement of tardive dyskinesia in patients with severe, unsuccessfully controlled tardive dyskinesia (Kimiagar et al. 2011). However, good studies which would allow an evidence-based statement to be made are also lacking for tetrabenazine.

The benzamide derivate tiapride might have some beneficial effects on tardive dyskinesia, but there are insufficient well-designed studies to make a clear evidence-based statement (El-Sayeh et al. 2006) *(Category of evidence F)*.

Apart from drug treatment, biological treatments have been tested for the treatment of tardive dyskinesia. In a case series and in a case-report, ECT was shown to have a beneficial effect on severe tardive dyskinesia (Hay et al. 1990; Ucok and Ucok 1996) *(Category of evidence C, Recommendation grade 4)*. Deep brain stimulation (DBS), which is a well-established treatment option in several movement disorders, like Parkinson's disease and dystonia, has the potential for a treatment possibility in severe tardive dyskinesia (Lyons 2011). To date, there are no studies investigating DBS for tardive dyskinesia, but case reports/case series (Trottenberg et al. 2005; Sako et al. 2008) and the experience from movement disorders give theoretical, but reasonable hope, that DBS can improve tardive dyskinesia in severe cases *(Category of evidence C, Recommendation grade 4)*.

Furthermore, pallidotomy as a last resort treatment could be a promising therapeutic approach in extremely severe cases of refractory antipsychotic-induced tardive dyskinesia (Wang et al. 1997; Thobois et al. 2011) *(Category of evidence C, Recommendation grade 4)*.

In summary, treatment of tardive dyskinesia is difficult and no good data concerning different treatment strategies exists. However, in severe cases, the aforementioned strategies should be offered to patients if switching to a SGA or to clozapine has no positive effect. In doing so, psychiatrists should be aware of the relatively small amount of evidence supporting these strategies.

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (Gurrera et al. 2011) is characterised by dystonia, rigidity, fever ($>100.4°F$ or $38°C$ on at least two occasions), autonomic instability such as tachycardia $>25\%$ above baseline, tachypnea $>50\%$ above baseline, blood pressure elevation ($>25\%$ above baseline) and

fluctuation (≥ 20 mmHg (diastolic) or ≥ 25 mmHg (systolic) change within 24 h), delirium, myoglobinuria and increased levels of creatine kinase (at least 4 times the upper limit of normal) (Gurrera et al. 2011), and of leukocytes and hepatic enzymes (lactate dehydrogenase, aspartate transaminase) and a low iron serum level. However, no laboratory parameter is specific for NMS. EEG can show signs of metabolic encephalopathy like generalized slowing (Caroff and Mann 1988; Strawn et al. 2007).

Biological measurements may help to distinguish between NMS and serotonin syndrome which share the same clinical features in some patients taking neuroleptic and serotonin agonist medications simultaneously. In principle, it could possibly occur following treatment with any antipsychotic (see Part 1 of these guidelines). If malignant neuroleptic syndrome occurs, antipsychotic treatment should immediately be terminated. Despite general treatment options, specific pharmacological or somatic treatments may be considered.

Patients with a malignant neuroleptic syndrome should be admitted to an intensive care unit to enable close monitoring, stabilise vital functions and treat symptoms like hyperthermia adequately. All other drugs which can cause such a syndrome (e.g., lithium, antidepressants) should also be stopped. Good evidence for specific treatment options is still lacking. The muscle relaxant dantrolene (dosage 2.5/10 mg/kg body weight daily, intravenously applicated) seemed to be promising for the treatment of this syndrome (Sakkas et al. 1991). However, a meta-analytic review including 271 case reports from 1980 to 2006 showed that the combination of dantrolene and other drugs is associated with a prolongation of clinical recovery and that dantrolene monotherapy is associated with a higher overall mortality (Reulbach et al. 2007). Therefore, the authors state that no treatment regimen including dantrolene could be considered as evidence-based (Reulbach et al. 2007). These findings are conflicting and therefore a general treatment of neuroleptic malignant syndrome with dantrolene cannot be recommended with satisfying evidence *(Category of evidence F)*. However, in certain cases the use of dantrolene can be discussed (e.g., cases with extreme temperature elevations, rigidy and true hypermetabolism (Strawn et al. 2007)) *(Category of evidence C)*.

Electroconvulsive therapy (ECT) with a typical regime of six to ten treatments provides some benefit, but randomised controlled studies are lacking (Trollor and Sachdev 1999; Supprian 2004) *(Category of evidence C, Recommendation grade 4)*.

There is a lack of adequately powered clinical trials investigating strategies for the rechallenge of antipsychotics after NMS to provide evidence-based recommendations. One major conflict is that the restart of antipsychotic treatment after NMS is associated with a high risk (up to 30%) to develop NMS again (Caroff and Mann 1988; Pope et al. 1991; Strawn et al. 2007), but that most patients need a long-term antipsychotic treatment. One publication presented some general rules as precaution to prevent the development NMS again (Strawn et al. 2007):

– Reports of pervious episodes should be checked for accuracy
– Indications for antipsychotics should be clearly documented
– Alternative medications should be considered
– Risk factors (e.g., rapid dose titration, very high dosage of antipsychotics) should be reduced
– At least 2 weeks should be allowed to elapse after recovery from NMS before rechallenge
– Low doses of low-potency conventional antipsychotics or atypical antipsychotics should be titrated gradually after a test dose
– Patients should be carefully monitored for early signs of NMS
– Informed [written] consent should be obtained from patients and family members regarding the benefits of restarting antipsychotic therapy versus the risk of recurrence of NMS.

One review (literature search 1972–2011) stated that clozapine can be carefully reintroduced after NMS and neutropenia, but not after agranulocytosis and myocarditis (Manu et al. 2011). However, this statement for NMS is based only on five cases and the average time after NMS to reintroduce clozapine was 8.5 weeks (Manu et al. 2011). Case reports (Mendhekar et al. 2002; Norgard and Stark 2006) indicate that antipsychotics can be reintroduced after NMS, but evidence from controlled studies is lacking. Based on this very limited evidence (for case report-based reviews see Strawn et al. 2007; Wells et al. 1988) an antipsychotic rechallenge after NMS is possible *(Category of evidence C3, Recommendation grade 4)*.

Epileptic seizures

Patients suffering from schizophrenia have an increased risk of epileptic seizures 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 incidence rate (approximately 3%) and cumulative risk (ca. 10%) after 4 years of treatment

(Devinsky et al. 1991; Pacia and Devinsky 1994; Buchanan 1995).

The clinical management of seizures includes treatment with benzodiazepines and anticonvulsant agents (e.g., levetiracetam, valproic acid) and monitoring of cardiovascular parameters. Carbamazepine should not be used in combination with clozapine due to its potentiation of neutropenia and agranulocytosis. In general, in the presence of seizures, a dose reduction is recommended, or a switch from clozapine or zotepine to another antipsychotic medication if the former option is not justified for clinical and psychopathological reasons.

Obesity, weight gain and metabolic parameters

Patients should be informed about potential weight gain during antipsychotic treatment. Management of drug-induced weight gain in schizophrenia patients has to refer to the multifactorial pathophysiology of this phenomenon. Behaviour and life style are an important part of weight gain in psychiatric patients. Therefore, physicians should encourage patients to increase their physical activity gradually in a stepwise manner, in combination with dietary restriction to obtain negative energy balance (Ananth et al. 2004) (see Table VII and recommendation Table II).

Psychosocial interventions to reduce weight gain and to improve metabolic parameters

Psychosocial interventions may have a small benefit and lead to weight loss in schizophrenia patients, although the evidence for this is limited (Birt 2003; Faulkner et al. 2007a,b).

An established weight management program (including a supplemented novel food replacement program, community-based teaching about shopping and healthy food preparation), which had been modified for schizophrenia patients, was tested in a RCT and revealed that such weight management programs can stop weight gain or even reverse it in schizophrenia patients (Jean-Baptiste et al. 2007). Furthermore, there are studies indicating that behavioural therapy and educational interventions have the potential to induce weight loss in schizophrenia patients treated with antipsychotics (Mauri et al. 2006; Ganguli 2007). In the last version of these guidelines, we reviewed some studies that support the idea of dietary restriction (Heimberg et al. 1995), weight loss programs (Menza et al. 2004; Centorrino et al. 2006) and behavioural interventions (Littrell et al. 2003; Umbricht et al. 2001; Werneke et al. 2003). However, we also cited negative studies (Wirshing et al. 2002) and the evidence for a clear recommendation was limited (Falkai et al. 2006).

In summary, psychosocial interventions (weight programs, diet programs, behavioural therapy) can be recommended to treat weight gain and metabolic problems in schizophrenia patients *(Category of evidence C, Recommendation grade 4)*, but good studies fulfilling standards of evidence are still lacking. However, physicians should encourage patients with obesity to participate in psychological interventions that focus on nutrition, physical activity (aerobic exercise) and self-monitoring *(Category of evidence C, Recommendation grade 4)*.

Pharmacological interventions to reduce weight gain

The 2010 PORT guidelines describe three possible pharmacological interventions for the treatment of

Table VII. Therapeutic options to manage antipsychotic side effects II (metabolic side effects). For categories of evidence see main text.

Side effect	Prevention	Treatment
Weight gain	• Select antipsychotic with lower risk of weight gain	• Psychosocial interventions (weight programs, diet programs, behavioural therapy) • Switch to another antipsychotic with a better metabolic side effect profile (for details see main text) • Add amantadine, H2-receptor antagonists (rosaglitazone) • Add topiramate
Hyperlipidemia	• Selecting antipsychotic with low risk of inducing hyperlipidemia • Screening for risk factors, cholesterol and triglycerides	• Psychosocial interventions (weight programs, diet programs, behavioural therapy) • Switch to another antipsychotic with a better metabolic side effect profile (for details see main text)
Diabetes	• Screening for diabetes risk factors, fasting blood glucose, in some cases haemoglobin A1c • Selecting antipsychotic with low risk of inducing diabetes	• Psychosocial interventions (weight programs, diet programs, behavioural therapy) • Switch to another antipsychotic with a better metabolic side effect profile (for details see main text) • Referring to a diabetologist for special pharmacological treatment of diabetes

Recommendation Table II. Recommendations for the psychosocial and pharmacological intervention to reduce weight gain and other metabolic side effects associated with antipsychotic treatment.

Intervention/Drug	Category of evidence[a]	Recommendation[b]
Psychosocial intervention	C	4[1]
Switch to aripiprazole	A	2[2]
Switch to ziprasidone	B	3[2]
Amantadine	C	4
H2-receptor antagonists	C	4
Metformin	D	5
Modafinil	F	—
Orlistat	F	—
Rosaglitazone	F	—
Rosaglitazone + clozapine	C	4
Sibutramine	F	—
Sibutramine + olanzapine	C	4
Topiramate	C	4
Topiramate + olanzapine	B	3

[a]Category of evidence: Category of evidence where A = full evidence from controlled studies (see Table I).
[b]Safety rating = recommendation grade derived from categories of evidence and additional aspects of safety, tolerability, and interaction potential.
[1]Due to the lacking studies the category of evidence for psychosocial interventions is only C, however, they should be recommended due to their good tolerability.
[2]Switching antipsychotics carry the risk of symptom worsening and psychotic relapse. Please see main text for specific switching strategies.

antipsychotic-induced weight gain: (1) switching from one agent to another; (2) addition of another medication (see the discussed agents below) before the initiation of antipsychotic treatment; (3) addition of another medication (see below) during the antipsychotic treatment (Buchanan et al. 2010). Though some strategies seem to be promising, the evidence for these strategies is limited (Buchanan et al. 2010) and every strategy can worsen the symptomatology of the patient (Falkai et al. 2006).

Switching antipsychotics

In a multicentre, double-blind RCT, 173 overweight schizophrenia patients were randomly assigned to a switch from olanzapine to aripiprazole or to stay on olanzapine – the switch to aripiprazole resulted in an improvement in metabolic parameters and weight (Newcomer et al. 2008).

A randomized trial examined the effects of switching from olanzapine, quetiapine or risperidone to aripiprazole on metabolic parameters and showed that patients switching antipsychotics ($n = 89$) had significantly weight reductions and an improvement of metabolic parameters compared to patients staying on their antipsychotic drug ($n = 98$) (Stroup et al. 2011). In open-label

short term trials the switch from various antipsychotics to aripiprazole reduced weight gain or resulted in a significant weight loss (Casey et al. 2003; Ganguli et al. 2011). The switch from olanzapine to quetiapine resulted in a decline of mean weight gain and the switch from olanzapine/risperidone to ziprasidone was promising in open-label studies (Weiden et al. 2003a,b; Gupta et al. 2004). In a long-term observation study, the switch from olanzapine/risperidone to ziprasidone was associated with sustained improvements in weight and metabolic parameters (Weiden et al. 2008). However, the switch from an FGA to ziprasidone did not change any metabolic parameter (Weiden et al. 2008). Results from phase I of the CATIE study show that switching from olanzapine to any other antipsychotic resulted in no weight gain/weight loss, but staying on a treatment with olanzapine led to a significant weight gain (Rosenheck et al. 2009). This may lead back to the situation that weight gain/change of weight gain was not the primary outcome parameter of the CATIE study. Furthermore, in the analyses of the CATIE study, aripiprazole (which seems to be a promising switching partner (see above)) was not available.

A Cochrane review indicates that switching antipsychotics to an agent with fewer metabolic side effects can result in an improvement of these parameters (Mukundan et al. 2010).

The recently published results for aripiprazole allow us to state that a switch to aripiprazole is a promising approach for treating antipsychotic-induced weight gain *(Category of evidence A, Recommendation grade 2)*. The switch to ziprasidone might have some advantages compared to staying on risperidone/olanzapine, but the evidence is limited *(Category of evidence B, Recommendation grade 3)*. Before switching drugs, it should be taken into consideration that switching from one antipsychotic to another carries the risk of symptom worsening, as indicated by the findings of the CATIE study, for example (Essock et al. 2006; Rosenheck et al. 2009).

Drug therapy for obesity

In non-psychiatric populations specific drug therapies for obesity are recommended exclusively as part of an integral treatment plan in patients with a BMI above 30 kg/m^2, or in combination with obesity related risk factors or diseases with a BMI above 27 kg/m^2. Different drugs have been tested to reduce weight gain and improve metabolic parameters in schizophrenia patients, but most studies did not show a benefit.

Amantadine

Amantadine, a dopamine agonist, has a risk of worsening psychosis (Ananth et al. 2004). Weight reduction was reported with an open-label add-on treatment of amantadine after 2 weeks in 10 patients taking FGAs (Correa et al. 1987). The effect of weight loss was also shown by an add-on treatment with 100–300 mg/day amantadine for 3–6 months in 12 patients who gained excessive weight while taking olanzapine (Floris et al. 2001). In a small double-blind, placebo-controlled study, amantadine was superior to placebo as an addition to olanzapine with regard to weight loss (Graham et al. 2005). This was confirmed by a placebo-controlled double-blind, 16-week trial examining 60 patients with schizophrenia, schizophreniform or bipolar disorder. However, the effect was no longer significant after 24 weeks (Deberdt et al. 2005).

There is some minimal evidence to suggest that amantadine can reduce antipsychotic-induced weight gain *(Category of evidence C, Recommendation grade 4)*.

H2-receptor antagonists

Nizatidine, a peripheral H2-receptor blocker, which probably acts by inducing early satiety related to increased cholecystokinine and reduced production of gastric acid, has been reported to reduce weight gain in doses of 300 mg/day in a patient taking olanzapine (Sacchetti et al. 2000). In 8-week, randomised, double-blind, placebo-controlled studies, nizatidine confirmed its weight-loosing effect in patients treated with olanzapine (mean weight decrease 1.0 kg) (Atmaca et al. 2003), and stopped weight gain in patients treated with quetiapine (Atmaca et al. 2004). A further double-blind RCT in patients treated with olanzapine (5–20 mg/day) demonstrated significantly less weight gain after 4 weeks add-on treatment with doses of 300 mg nitazidine twice daily without presenting significant differences in adverse events, but the difference was not statistically significant after 16 weeks (Cavazzoni et al. 2003). In a 16-week, randomised, open-label trial, positive effects in preventing weight gain were observed with treatment of ranitidine (300–600 mg/day) added to olanzapine (Lopez-Mato et al. 2003), while famotidine failed to show significant effects in a double-blind placebo-controlled study (Poyurovsky et al. 2004).

Currently, there is limited evidence to recommend the H2-receptor antagonists for the treatment of antipsychotic-induced weight gain *(Category of evidence C, Recommendation grade 4)*.

Metformin

Metformin is an antidiabetic drug, used to treat type II diabetes, that increases sensitivity for insulin and can lead to consecutive weight loss in subjects without diabetes (Buchanan et al. 2010; Desilets et al. 2008). The combination of metformin with olanzapine was either superior or inferior to placebo with regard to weight gain and metabolic parameters (Baptista et al. 2006, 2007; Chen et al. 2008; Wu et al. 2008). However, the combination of metformin with olanzapine might be promising in the subpopulation of first-episode patients, who are more receptive for side effects (Wu et al. 2008). In another study, no effect of metformin was reported in five patients who were undergoing long-term treatment with haloperidol, fluphenazine, trifluperazine or risperidone (Baptista et al. 2001). A meta-analysis including 12 studies indicated a small and modest positive effect on weight gain and metabolic parameters for the combination of metformin and olanzapine (Praharaj et al. 2011). Furthermore, the combination of metformin plus the oral anorexiant sibutramine was not superior to placebo with regard to metabolic parameters, except for preventing a triglyceride increase (Baptista et al. 2008). A very complex randomized open-label study compared metabolic parameters in patients treated with either olanzapine in monotherapy or olanzapine plus one of two possible algorithms (A: olanzapine + amantadine 200 mg/day with possible switches to metformin 1000–1500 mg/day and then to zonisamide 100–400 mg/day; B: olanzapine + metformin 1000–1500 mg/day with possible switches to amantadine 200 mg/day and then to zonisamide 100–400 mg/day) (Hoffmann et al. 2012). This study showed a potential benefit from algorithm B.

A randomized double-blind and placebo-controlled 12-week RCT in children and adolescents with schizophrenia did not show a benefit of the combination risperidone + metformin compared to risperidone + placebo (Arman et al. 2008). In a case report, the combination of metformin and risperidone in a 20-year-old woman resulted in worsening of psychotic symptoms (thought broadcast symptoms) (Venkatasubramanian et al. 2010).

The data for metformin are inconsistent and therefore no clear evidence-based recommendation can be given for the combination of metformin and antipsychotics *(Category of evidence D, Recommendation grade 5)*.

Modafinil

One pilot study assigned schizophrenia patients, who had been previously treated with clozapine, to

either modafinil or placebo. No effect on metabolic parameters in patients treated with modafinil was found (Henderson et al. 2011). One case report and one study have investigated the impact of the psychostimulant modafinil on antipsychotic-induced weight gain and other metabolic parameters. The case report showed that the addition of modafinil to treatment with clozapine resulted in a significant weight loss (Henderson et al. 2005b). Currently, the addition of modafinil administration to clozapine treatment with the aim of reducing antipsychotic-induced weight gain cannot be recommended *(Category of evidence F)*.

Orlistat

Orlistat prevents the absorption of fats without influencing appetite. In a 16-week randomized double-blind, placebo-controlled trial, treatment with orlisat was found to be associated with a weight-loss only in males treated with clozapine or olanzapine (Joffe et al. 2008). In a later 16-week open-label extension phase of this study, the long-term application of orlisat did not improve metabolic parameters in patients who did not respond within the first 16 weeks (Tchoukhine et al. 2011). One case report suggests moderate weight loss after adding orlistat, a lipase inhibitor reducing intestinal fat absorption, to amisulpride (Anghelescu et al. 2000).

There are insufficient data to give a good evidence-based recommendation for orlisat *(Category of evidence F)*.

Rosaglitazone

In a small double-blind, placebo-controlled 12-week RCT, the antidiabetic agent rosaglitazone was not superior to placebo when combined with olanzapine with regard to metabolic parameters (Baptista et al. 2009). However, another small 8-week double-blind, placebo-controlled RCT showed that the addition of rosaglitazone to a treatment with clozapine is promising with regard to insulin resistance and other metabolic parameters (Henderson et al. 2009).

There is only minimal evidence that the combination of clozapine and rosaglitazone might be helpful with regard to metabolic parameters *(Category of evidence C, Recommendation grade 4)*, but there is not enough evidence to make a general statement *(Category of evidence F)*.

Sibutramine

Sibutramine is approved for the treatment of obesity. It was tested in two double-blind, placebo-controlled

RCTs combined with either olanzapine (Henderson et al. 2005a) or clozapine (Henderson et al. 2007). The combination with olanzapine reduced weight and improved metabolic parameters, whereas the combination with clozapine did not show a benefit (Henderson et al. 2005a; Barinas-Mitchell et al. 2006; Henderson et al. 2007).

There is little evidence that the combination of olanzapine and sibutramine might be helpful with regard to metabolic parameters *(Category of evidence C, Recommendation grade 4)*, and the amount of data is insufficient to permit the formulation of a general statement *(Category of evidence F)*. However, sibutramine can induce psychotic symptoms and this limits its application for this purpose.

Topiramate

The anticonvulsant topiramate was superior to placebo in reducing antipsychotic-induced weight gain and improving metabolic parameters in a 12-week, randomized, placebo-controlled prospective study with 66 schizophrenia in-patients. This effect was dose-dependent as 200 mg/day of topiramate was found to be superior to a 100-mg/day dosage (Ko et al. 2005). In a randomised, double-blind, placebo-controlled clinical trial, topiramate was superior to placebo in controlling antipsychotic-associated weight gain (Afshar et al. 2009). In another 12-week, randomized, open-label, parallel-group trial of topiramate in outpatients subjects with schizophrenia, topiramate limited the olanzapine-induced weight gain (Kim et al. 2006). This was further confirmed in a 12-week, double-blind, parallel-group study in drug-naive first-episode schizophrenia patients. In this study 100 mg/day topiramate added to olanzapine was significantly more effective in improving metabolic parameters and reducing weight gain than placebo added to olanzapine (Narula et al. 2010). The combination of topiramate with clozapine did not lead to a weight loss in a double-blind, placebo-controlled RCT in which weight gain was not the primary outcome parameter (Muscatello et al. 2011). In a report, topiramate, given at a dose of 125 mg/day over 5 months, led to weight loss in a patient taking clozapine (Dursun and Devarajan 2000). However, in another 12-week RCT in which weight gain was not the primary outcome parameter, topiramate and placebo did not differ with regard to this parameter (Tiihonen et al. 2005).

There is some evidence that topiramate might improve metabolic parameters and antipsychotic-induced weight gain *(Category of evidence C, Recommendation grade 4)*, and that especially the combination of topiramate with olanzapine seems to

be beneficial *(Category of evidence B, Recommendation grade 3)*. However, cases of agitation and/or aggressive behaviour associated with topiramate therapy have been documented and psychiatrists need be cautious when using topiramate (Farinde 2011).

Other drugs

In an 8-week double-blind, placebo-controlled RCT, the melatonergic agent *ramelton* was added to schizophrenia patients' medication regimen. Ramelton decreased serum cholesterol levels and reduced intra-abdominal fat, but did not improve anthropometric measurements, glucose metabolism, or inflammatory markers (Borba et al. 2011). Fluoxetine was not superior compared to placebo in reducing olanzapine-induced weight gain (Poyurovsky et al. 2002; Bustillo et al. 2003), but fluvoxamine could prevent clozapine-induced weight gain (Lu et al. 2004). However, both SSRIs have a high interaction potential and could not be recommended for use for this purpose.

General aspects

The use of agents like phentermine, chlorphentermine, sibutramine or phenylpropanolamine in individuals with mental illness is limited because these drugs can lead to an exacerbation of psychotic symptoms. For this reason, these agents cannot be recommended in patients with schizophrenia. As stated in the 2010 PORT guidelines (Buchanan et al. 2010) and in a review from the schizophrenia research group (Faulkner et al. 2007b), a general recommendation for a drug intervention to reduce antipsychotic-induced weight gain cannot be given. Furthermore, the aspect of worsening psychosis after adding one or two other agents to the present antipsychotic medication needs to be addressed in future studies. However, as discussed above and in the first part of these updated guidelines, a switch from one antipsychotic with an unfavourable metabolic profile to one with a better profile (e.g., aripiprazole, ziprasidone) might be a promising therapeutic alternative.

However, despite the fact that there is only limited evidence that weight programmes (including cognitive behavioural elements) lead to significant weight loss, physicians should encourage patients with obesity to participate in psychological interventions that focus on nutrition, physical activity and self-monitoring *(Category of evidence C, Recommendation grade 4)*. Furthermore, families and relatives should be informed about metabolic side effects and metabolic parameters should be checked regularly (see Table III).

Monitoring metabolic side effects

Monitoring metabolic side effects during the treatment with antipsychotics is of particular importance (De Hert et al. 2008, 2009, 2011b), especially when certain antipsychotics (e.g., clozapine, olanzapine, quetiapine) are used. A paper published jointly by the European Psychiatric Association, the European Society of Cardiology and the European Association for the Study of Diabetes included an algorithm for the risk management of cardiovascular disease in patients with severe mental illness (De Hert et al. 2009). According to this publication, the following steps are necessary before initiating a therapy with antipsychotics: an assessment of family history for cardiovascular and metabolic diseases or early death, smoking history, and exercise and dietary habits and other treatments which may increase the risk is the first step in screening for these risk factors. Furthermore, blood pressure, body weight, waist circumference and body mass index have to be screened. Then, baseline measures of fasting glucose and fasting lipids, total cholesterol, LDL, HDL and triglyceride levels must be collected (De Hert et al. 2009). These measures have to be repeated in weeks 6 and 12 following the beginning of treatment and then repeated annually. Weight and waist circumference should be measured after 1 month and then repeated every 3 months. A weight gain $> 7\%$ than baseline occurring within a few months must alert the psychiatrist and relatives. Specific recommendations and the management of special cases have been published elsewhere (De Hert et al. 2009).

This is in line with the recommendations from the APA/ADA consensus development conference on antipsychotic drugs and obesity and diabetes, which demands baseline screening and ongoing monitoring of metabolic parameters during treatment with antipsychotics (APA 2004). The ADA/APA consensus paper recommends screening at baseline, at weeks 4, 8 and 12, and then annually (APA 2004). Furthermore, the following statement should have great priority in the management of metabolic side effects: "Clinicians should also encourage patients to monitor and chart their own weight. It is particularly important to monitor any alteration in weight following a medication change. The patients' psychiatric illness should not discourage clinicians from addressing the metabolic complications for which these patients are at increased risk" (APA 2004). Patients and their carers should be informed about the metabolic syndrome and the symptoms of diabetes, and patients should be monitored at regular intervals for the criteria of metabolic syndrome (see Alberti et al. 2009). The risks and consequences of metabolic syndrome and

diabetes have to be weighed against the control of psychotic symptoms if switching to another agent with an assumed lower risk of diabetes is considered. This paragraph shows that there is a variance of recommendations and diagnostic algorithms regarding this important topic across guidelines. However, special attention should be paid to the *regular* monitoring of metabolic side effects (Table II).

Other side effects

Cardiovascular side effects (see Table VIII)

Management strategies for orthostatic hypotension include decreasing or dividing doses of antipsychotic, or switching to an antipsychotic without antiadrenergic effects. Patients who experience severe postural hypotension must be cautioned against getting up quickly and without assistance as falls can result in hip fractures and other cardiovascular or cerebrovascular accidents, particularly in elderly patients. Gradual dose titration, starting with a low dose, and monitoring of orthostatic signs minimises the risk of complications due to orthostatic hypotension. Supportive measures include the use of support stockings, increased dietary salt and advising patients who experience severe postural hypotension to avoid getting up quickly and without assistance. Tachycardia due to anticholinergic effects without hypotension can be managed with low doses of a peripherally acting beta-blocker (Miller 2000).

All antipsychotics may cause (dose-dependent) cardiac side effects, at varying rates. Of the FGAs, this predominantly applies to tricyclic neuroleptic agents of the phenothiazine type (e.g., chlorpromazine, promethazine, perazine and, especially, thioridazine) and to pimozide. Of the SGAs, sertindole and ziprasidone were found to lengthen the QT interval in a significant manner. QTc prolongation (QTc intervals above 450/470–500 ms or change from baseline more than 30–60 ms, dependent on publication and textbook) is associated with an increased risk of torsade de pointes and transition to ventricular fibrillation (Glassman and Bigger 2001; Roden 2004; Sumic et al. 2007; Semple and Smyth 2009; Nielsen et al. 2011). If this occurs under antipsychotic 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). A dose-dependent association for QTc prolongation has been detected for most antipsychotics. A combined treatment with other drugs which increase QTc time has to be avoided (detailed lists can be found in textbooks of psychiatry and internal medicine or at http://www.qtdrugs.org/) and the QT interval should be checked regularly (see Table III).

Clozapine is associated with a risk of myocarditis in 1 per 500 to 1 per 10,000 treated patients. If the diagnosis is probable (typical symptoms can be: chest pain, palpitations, dyspnea, reduced general condition, fever, symptoms of right-heart overload like edema or respiratory distress), clozapine should be stopped immediately and the patient referred urgently to a specialist for internal medicine (Marder et al. 2004).

Table VIII. Therapeutic options to manage antipsychotic side effects III (cardiovascular and haematological side effects). For categories of evidence see main text.

Side effect	Prevention	Treatment
Orthostatic hypotension	• Starting with low dose, increase dose slowly and stepwise • Selecting antipsychotic with low α-adrenergic receptor-blocking profile	• Physical activity • Switch to another antipsychotic with another receptor profile (for details see main text) • (Application of oral dihydroergotamine (max. 6 mg/day) or etilefrine (20–60 mg/day))
QTc prolongation	• Selecting antipsychotic with low risk of QTc prolongation • Evaluation of cardiac risk factors • Control for pharmacological interactions • Control of ECG • Avoid combining drugs with a known risk for QTc prolongation	• If QTc is >450/470–500 ms or has increased more than 30–60 ms switching to another antipsychotic is indicated
Leukopenia	• Controlling white blood cell count (WBC)	• In case of agranulocytosis (<1000 granulocytes) immediately stopping antipsychotic treatment • Cooperate with a haematologist • Prevent infections, monitoring WBC • In some cases application of GM-CSF/G-CSF • Clozapine treatment has to be stopped if leukocytes are <3500 or granulocytes are <1500

Haematological side effects (see Table VIII)

This part remains unchanged and is in accordance with the previous version of these guidelines. Agranulocytosis is the most severe side effect of clozapine and some other FGAs (e.g., chlorprothixen). In some cases, however, the condition may also occur in association with other antipsychotic medications. During clozapine treatment, a white blood-cell (WBC) count $<2000/mm^3$ or absolute neutrophil count (ANC) $<1000/mm^3$ indicates impending or current agranulocytosis; the clinician should stop clozapine treatment immediately, check WBC and differential counts daily, monitor for signs of infection, and consider bone marrow aspiration and protective isolation if granulopoiesis is deficient. A WBC count of $2000–3000/mm^3$ or ANC of $1000–1500/mm^3$ indicates a high risk of agranulocytosis, and the clinician should stop clozapine treatment immediately, check the WBC and differential counts daily, and monitor for signs of infection. If the subsequent WBC count is $3000–3500/mm^3$ and the ANC is $>1500/mm^3$, the WBC count has to be repeated with a differential count twice a week until the WBC count is $>3500/mm^3$.

Hyperprolactinaemia and sexual dysfunction (see Table IX)

If hyperprolactinaemia is suspected in a schizophrenia patient, prolactin levels should be measured and the cause, if not explained by the use of neuroleptic medication, should be determined (e.g., exclusion of a pituitary tumour) especially when the level is higher than 5 times the normal range (Marder et al. 2004). When antipsychotic-induced hyperprolactinaemia is associated with menstrual and sexual dysfunction, consideration should be given to changing the medication to a prolactin-sparing agent. If the signs and symptoms disappear and the prolactin level decreases, an endocrine workup can be avoided. Osteoporosis should be considered as another important long-term consequence of hyperprolactinemia (Holt and Peveler 2011).

Switching from a prolactin-elevating antipsychotic (e.g., risperidone, sulpiride) to a non-prolactin-elevating antipsychotic (e.g., aripiprazole; quetiapine, olanzapine) seems to be a promising treatment (Kim et al. 2002; Casey et al. 2003; Kaneda et al. 2004; Kinon et al. 2006; Lee et al. 2006; Potkin et al. 2006; Shim et al. 2007; Lu et al. 2008). However, we could not detect a switching study for the prolactin-elevating SGA amisulpride. Switching from a prolactin-elevating antipsychotic to a non-prolactin-elevating antipsychotic is a method of treating hyperprolactinaemia *(Category of evidence C, Recommendation grade 4)*, but the known risks of relapse and/or symptom worsening following switching antipsychotics should be taken into consideration.

Another treatment option is the addition of the dopamine-agonist bromocriptin to the antipsychotic treatment (Matsuoka et al. 1986; Bliesener et al. 2004; Miller and Sebastian 2005; Lee et al. 2010) *(Category of evidence C, Recommendation grade 4)*, although double-blind RCTs are lacking and an increased risk of psychotic relapse can be assumed. The evidence for the dopamine agonist cabergoline is limited to the findings of one study with 19 patients (Cavallaro et al. 2004). In one randomized crossover comparison, the herbal preparation Peony-Glycyrrhiza Decoction was not inferior to bromocriptine in the treatment of risperidone-induced hyperprolactinemia (Yuan et al. 2008).

Table IX. Therapeutic options to manage antipsychotic side effects IV (other side effects).

Side effect	Prevention	Treatment
Dry mouth	• Prescribing low doses • Selecting antipsychotic with other receptor profile and lower risk	• Drinking small amounts frequently • Using sugar-free drops or chewing gum • Dose reduction
Sialorrhea	• Selecting antipsychotic with other receptor profile and lower risk	• Application of pirenzepine 25–50 mg/day • Dose reduction (e.g., of clozapine)
Sexual dysfunction	• Selecting antipsychotic with no or minimal prolactin elevation • Evaluating prolactin level	• Switching to another antipsychotic with lower risk of prolactin elevation
Constipation	• Selecting antipsychotic with lower risk • Auscultation, palpation and percussion	• Dietary supplementation, physical activity • Lactulose 5–0 g/day, or macrogol 13–40 g/day, or natriumpicosulfat 5–10 mg/day • Pay attention to a adequate fluid intake by the patient
Urinary retention	• Selecting antipsychotic with low anticholinergic side effects	• Dose reduction • Switching to another antipsychotic • Application of carbachol 1–4 mg/day orally; if necessary 0.25 mg i.m. or s.c. • Application of distigmine 2.5–5 mg/day orally

Combining aripiprazole with either risperidone or quetiapine in one multicentre, double-blind, 16-week, placebo-controlled study with 323 schizophrenia or schizoaffective patients 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).

The authors of the PORT guidelines reviewed different treatments for antipsychotic-induced sexual dysfunctions and did not find enough evidence for a treatment recommendation (Buchanan et al. 2010). However, some minimal evidence, based on open-label studies or small double-blind RCTs, exists suggesting that drugs for the treatment of erectile dysfunctions (sildenafil, vardenafil) might be effective for the treatment of antipsychotic-induced sexual dysfunction, but good evidence is still lacking. (Buchanan et al. 2010) *(Category of evidence C, Recommendation grade 4)*.

Others (see Table IX)

Apart from a statement regarding constipation, this part remains unchanged and is in accordance with the previous version of these guidelines. Sialorrhea and drooling occur relatively frequently with clozapine treatment and are most likely due to decreased saliva clearance related to impaired swallowing mechanisms, or possibly to muscarinic cholinergic antagonist activity at the M4 receptor or to alpha-adrenergic agonist activity (Rabinowitz et al. 2001). Therapeutic options for sialorrhea include the application of pirenzepine 25–50 mg/day and dose reduction of clozapine, if possible. Allergic and dermatological effects, including photosensitivity, occur infrequently but are most common with low-potency phenothiazine medications. Patients should be instructed to avoid excessive sunlight and use sunscreen (Lehman et al. 2004). Hepatic effects, such as elevated hepatic enzymes, may be triggered by a number of antipsychotic medications, whereby this is usually asymptomatic. Direct hepatotoxicity or cholestatic jaundice occur extremely rarely and are particularly associated with low-potency phenothiazines (APA 2004; Lehman et al. 2004).

Ophthalmological effects due to pigment accumulation in the lens and cornea, retinopathies, corneal oedema, accommodation disturbances and glaucoma have also been described as side effects of antipsychotic medication. To prevent pigmentary retinopathies, corneal opacities and cataracts, patients maintained on thioridazine and chlorpromazine should have periodic ophthalmological examinations (approximately every 2 years for patients with a cumulative treatment of more than 10 years); 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).

Urinary tract problems such as urinary retention and urinary incontinence may be particularly provoked by antipsychotic medications with marked anticholinergic components such as phenothiazines and those with cholinergic effects. Acute urinary retention problems may be treated with low-dose e.g. carbachol.

Dry mouth and eyes, and constipation may result from adrenergic and anticholinergic stimulation, often described during treatment with FGAs. Patients may be advised to use sugar free chewing gum or drops against dry mouth. Usually patients mostly suffer from the described autonomic side effects when antipsychotic treatment is introduced or doses are increased.

To treat constipation, patients should be advised to drink more, and in some cases administration of lactulose may be useful. However, constipation seems to be a frequent side effect (see Part 1 of this updated guideline) and changing antipsychotics might be discussed in severe cases. Constipation should be identified early to prevent paralytic ileus, bowel obstruction, faecal impaction, bowel perforation and other severe complications (De Hert et al. 2010).

Conclusion

This update of the WFSBP guidelines for the long-term biological treatment of schizophrenia and the management of side effects summarizes the available publications in this field and proves evidence-based treatment recommendations.

For the clinical psychiatrist, knowledge about the efficacy of different antipsychotic drugs in the long-term treatment and the management of antipsychotic-induced side effects is of particular importance. For long-term treatment especially, a good balance between efficacy, side effects and compliance must be achieved. Clinicians must keep in mind that most patients are likely to require life-long treatment and this determines treatment strategies with the optimal balance between efficacy and tolerability. Both FGAs and SGAs are effective in relapse prevention. SGAs do have some advantages with regard to motor side effects and relapse prevention. This could favour certain SGAs (as outlined in these guidelines) in the long-term treatment of schizophrenia.

The management of neurological side effects, especially tardive dyskinesia, and metabolic side effects is the greatest challenge for psychiatry. Before the introduction of the SGAs, schizophrenia patients suffered from severe neurological side effects and nobody wants these times back. However, nobody wants a future in which young schizophrenia patients suffer from obesity, metabolic syndrome, diabetes and coronary heart disease. Solving this problem is the challenge of the future.

Antipsychotics with the best balance between these side effects may have a benefit in the long-term treatment, but there is not enough evidence-based data to make a conclusive statement. Even today, there is unsatisfying evidence relating to different questions in the long-term treatment of schizophrenia and these questions need to be addressed in large well-designed clinical trials. In recent years, some important trials have been published, but each of them has important methodological limitations.

Several aspects, such as the well-known link between sponsorship and study outcome, the use 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. Nevertheless, there is a need for evidence-based national and international treatment recommendations and clinical psychiatrists and researches need to re-evaluate their knowledge and their treatment strategies regularly to provide the best possible treatment for the patient.

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